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Nonhuman Primate Models in Biomedical Research

State of the Science and Future Needs

Kenneth S. Ramos, Autumn Downey, and Olivia C. Yost, *Editors*

Committee on the State of the Science and Future Needs for Nonhuman Primate Model Systems

Board on Health Sciences Policy

Health and Medicine Division

Institute for Laboratory Animal Research

Division on Earth and Life Studies

Consensus Study Report

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions of this report nor did they see

the final draft before its release. The review of this report was overseen by **ELI Y. ADASHI,** Brown University and **BARBARA A. SCHAAL,** Washington University in St. Louis. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

Biomedical research provides insights into the underlying biologic processes that define health and disease. The information generated by these scientific investigations is in turn used to develop interventions designed to prevent, diagnose, and treat human disease and to promote the well-being of humans and other living creatures. Undeniably, the advances made possible by biomedical research have saved countless human lives.

In a perfect world, biomedical research questions across varied research domains would be tested in humans; however, a number of ethical, logistical, and ancillary challenges often call for the use of alternative model systems that can best reproduce the human condition. A primary challenge, then, is to identify the model(s) or model system(s) best suited to answering the scientific question(s) at hand. In several areas of biomedical research, nonhuman primates (NHPs) are regarded as the best available model to reproduce the human condition.

For the past year, at the request of the National Institutes of Health (NIH) and in response to a congressional mandate, our committee explored the current landscape of biomedical research using NHP models and their future roles in NIH-supported research, while also considering the research and development status of new approach methodologies, such as in vitro and in silico models, that may complement and/or reduce reliance on NHP models. Although at the outset the task appeared straightforward, the committee quickly learned that the landscape of NHP research is exceedingly complex, and that evaluation of the current and future status of this research can be challenging given the current limitations of the available data on NHP use in NIH-funded research. While the committee was not asked to make recommendations or to prioritize research domains that currently benefit from the use of NHP models and are likely to do so in the future, our hope is that the landscape analysis and conclusions presented in this report will inform decision makers as they consider strategies for supporting the mission of NIH going forward. To this end, the committee emphasizes the critical importance of investments in domestic NHP resources and tools and strategies that can enhance research using NHP models, as well as qualification and/or validation efforts needed to realize the future potential of new approach methodologies. Finally, we hope that this report will stimulate efforts to create more opportunities for researchers working with

NHPs and those developing and using non-NHP models to collaborate around the common goals of advancing human health and reducing human suffering. The national dialogue on NHPs and alternative methodologies is far too often framed using an opportunity cost model that advances a false dichotomy and that may lose sight of the critical scientific and societal issues that drive decision making. In reality, future advances in human health will require approaches that leverage the complementarity of in vitro and in silico methodologies and NHPs and other animal models for the foreseeable future. Overcoming the silos created and reinforced by current funding mechanisms will be vital to advancing the nation's biomedical research agenda.

The committee would like to thank NIH for sponsoring and supporting this important study, particularly Lyric Jorgenson and Jessica Creery, who served as our points of contact. We are deeply appreciative of their efforts to coordinate and gather responses to the committee's requests for information on NIH programs and priorities. We are also grateful to the many experts who gave presentations and participated in discussions with the committee during its public meetings. The information they shared was invaluable as we undertook our landscape analysis. We also wish to acknowledge the thousands of members of the public who informed our efforts by taking the time to share their perspectives on NHP research with us. Those too informed the committee's efforts and provided essential perspectives to the committee.

The committee's work over the last year was supported by the dedicated project staff at the National Academies of Sciences, Engineering, and Medicine—Autumn Downey, Olivia Yost, Kyle Cavagnini, Kelsey Babik, Lydia Teferra, Aparna Cheran, Bradford Chaney, Susana Rodriguez, and Corrine Lutz. We are deeply appreciative of their tireless and outstanding efforts to keep us on track and facilitate the study's completion. The committee is also grateful for the science writing contributions of Lauren Tobias and for the editing of this report performed by Rona Briere and her talented team, particularly Allie Boman.

Finally, as committee chair, I would like to thank and acknowledge my fellow committee members who generously gave their time and shared their expertise and perspectives, all of which were essential to addressing our task. I have appreciated your passion and engagement and the opportunity to learn from you as we navigated the process of deliberating on the challenging issues inherent in this topic. I am confident that this report and its conclusions will guide strategic decision making for years to come, and I thank you for your outstanding contributions.

It is now time for the nation's leaders to take the action necessary to ensure that the United States maintains its scientific leadership and that biomedical investigators nationwide have the tools necessary to advance vital NIH-supported biomedical research. Indeed, patients are waiting.

Kenneth S. Ramos, *Chair*
Committee on the State of the Science and Future
Needs for Nonhuman Primate Model Systems

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[1] Supplemental materials are available at https://nap.nationalacademies.org/26857.

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Acronyms and Abbreviations

2D	two dimensional
3D	three dimensional
AAV	adeno-associated virus
ACP	Animal Care Policy
ACD	Advisory Committee to the Director
AD	Alzheimer's disease
AI	artificial intelligence
AIDS	acquired immunodeficiency syndrome
ALS	amyotrophic lateral sclerosis
APHIS	Animal and Plant Health Inspection Service
ARRIVE	Animal Research: Reporting of In Vivo Experiments
ART	antiretroviral therapy
ATSC	adult human tissue stem cell
AWA	Animal Welfare Act
AWAR	Animal Welfare Act and Animal Welfare Regulations
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies
CARES	Coronavirus Aid, Relief, and Economic Security (Act)
CAR-T	chimeric antigen receptor T cell
CDC	Centers for Disease Control and Prevention
CFTR	cystic fibrosis transmembrane conductance regulator
CiPA	Comprehensive in vitro Proarrhythmia Assay
CITES	Convention on International Trade in Endangered Species of Wild Fauna and Flora
COU	context of use
CoVTEN	Coronavirus Vaccine and Therapeutic Evaluation Network

CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRO	contract research organization
CT	computed tomography
DART	developmental and reproductive toxicity
DBS	deep brain stimulation
EU	European Union
FDA	U.S. Food and Drug Administration
FY	fiscal year
HDN	hemolytic disease of the newborn
hiPSC-CM	human iPSC–derived cardiomyocytes
HIV	human immunodeficiency virus
HREA	Health Research Extension Act
HSC	hematopoietic stem cell
IACUC	institutional animal care and use committee
ICOs	institutes, centers, and offices
ILAR	Institute for Laboratory Animal Research
IMPC	International Mouse Phenotyping Consortium
iPSC	human induced pluripotent stem cell
ISTAND	Innovative Science and Technology Approaches for New Drugs
IUCN	International Union for Conservation of Nature
mAbs	monoclonal antibodies
MERS	Middle East respiratory syndrome
mCODE	minimal common oncology data elements
mGAP	macaque Genotype and Phenotype
MHC	major histocompatibility complex
ML	machine learning
MPS	microphysiological systems
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHP	nonhuman primate
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development

NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIMH	National Institute of Mental Health
NPRC	National Primate Research Center
OAR	Office of AIDS Research
OLAW	Office of Laboratory Animal Welfare
ORIP	Office of Research Infrastructure Programs
PAR	protease-activated receptor
PCTS	precision-cut tissue slices
PD	pharmacodynamic
PERV	porcine endogenous retrovirus
PET	positron emission tomography
PHS	Public Health Service
PI	principal investigator
PK	pharmacokinetic
RFA	request for applications
RhoGAM	anti-Rh immunoglobulin
SCD	sickle cell disease
SIV	simian immunodeficiency virus
SPECT	single photon emission computed tomography
SPF	specific pathogen free
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
XR	extended reality

Summary[1]

Society relies on biomedical research supported by the National Institutes of Health (NIH) to mitigate disease, prevent the spread of infectious agents, advance technologies to help those with disabilities, and promote health and wellness, among other objectives. Studies aimed at accomplishing these objectives often rely on animal, cellular, and in silico models, with the appropriate choice of a model system being dictated by the question(s) being asked.

Nonhuman primates (NHPs) represent a small proportion—an estimated one-half of 1 percent—of the animals used in biomedical research. NHPs are useful because their similarities to humans with respect to genetic makeup, anatomy, physiology, and behavior make it possible to approximate the human condition. Indeed, remarkable biomedical breakthroughs—including successful treatments for Parkinson's and sickle cell disease, drugs to prevent transplant rejection, and COVID-19 vaccines—have been enabled by fundamental basic and translational research using NHP models. Nonetheless, the use of NHP models is not without controversy or challenge. Policy makers, animal advocates, researchers, and the public continue to raise questions as to whether and how nonanimal models can be used to answer scientific questions for which NHPs have historically been regarded as fit for purpose, questions that apply as well to animal models more broadly. Additionally, a worsening shortage of NHPs, exacerbated by the COVID-19 pandemic and recent restrictions on their exportation and transportation, has had negative impacts on NIH-funded research necessary for both public health and national security. In this context, and at the direction of the U.S. Congress, NIH asked the National Academies of Sciences, Engineering, and Medicine to convene an expert committee to conduct a landscape analysis focused on describing the state of the science of NHP model systems and exploring their current and future role in NIH-funded biomedical research.

[1] This summary does not include references. Citations for the discussion presented in the summary appear in the subsequent report chapters.

STUDY ORIGIN, STATEMENT OF TASK, AND SCOPE

In its Consolidated Appropriations Act of 2021,[2] the U.S. Congress directed NIH to commission an independent National Academies study to explore the current and future use of NHPs in intramural NIH research, as well as existing and anticipated future opportunities for alternatives to reduce NIH's reliance on NHP models. As directed by NIH, the committee's Statement of Task (Box S-1) expanded the scope of the study beyond that described in the congressional language to include both intramural and extramural biomedical research using NHPs. The Statement of Task also charged the committee with determining the status of research, development, and validation efforts for new approach methodologies. The term "new approach methodologies" is often used to refer specifically to potential alternatives to animal models. In this report, new approach methodologies are defined broadly to include in vitro and in silico technologies and approaches that can be used to complement NHP studies or reduce reliance on NHPs in biomedical research.[3] Complementary approaches can be used to fill gaps by answering research questions not fully answered by NHP models, extend understanding of the research conducted using NHPs, or confirm results from that research. Complementary approaches may or may not reduce reliance on NHPs, which can be achieved by substituting alternative models or decreasing the numbers of NHPs used in biomedical research.

The following aspects of NHP research were beyond the scope of this study, as clarified as needed during discussions with NIH representatives at the committee's first meeting:

- NHP research funded by sponsors other than NIH. Based on this exclusion, this report does not include an in-depth analysis of the use of NHPs in industry-sponsored pharmaceutical safety and efficacy testing conducted as part of regulatory approval processes; however, indirect contributions of NIH-funded research to advances in available vaccines and treatments were considered within the study scope. In its assessment of gaps in NHP availability, the committee also considered the constraints imposed on NIH-funded biomedical research using NHP models by competing demands from other sponsors of NHP research (federal and nonfederal).
- Evaluation of the impact of biomedical research on NHP populations in the wild.
- The use of chimpanzees, other great apes, and non-NHP animal species as research models.
- Examination of ethical standards and principles that underlie NHP research, or current ethical issues and disputes relevant to this research. This report rests on the foundational assumption that biomedical research with NHPs can be conducted ethically when an NHP is the appropriate research model to address the aims of the research; when studies are well designed and conducted; and when the research and the housing and care of the animals afford requisite attention to their welfare.
- The development of recommendations with criteria for determining when it is scientifically necessary to use NHPs. Such a task would have substantially altered the committee's composition and its approach, and its exclusion distinguishes the

[2] The complete congressional language requesting this consensus study can be found in Division H of the Joint Explanatory Statement that accompanied H.R. 133, the Consolidated Appropriations Act, 2021 (P.L. 116-260) on PDF page 69 here: https://www.appropriations.senate.gov/imo/media/doc/Division%20H%20-%20Labor%20H%20Statement%20FY21.pdf (accessed September 13, 2022).

[3] Of note, approaches that employ other species of animals as models (e.g., transgenic animals) to replace NHPs were beyond the scope of the committee's charge and are not included within the committee's definition of new approach methodologies.

BOX S-1 STATEMENT OF TASK

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will examine the current role of and future needs for nonhuman primates in biomedical research funded by the National Institutes of Health (NIH).

To inform its examination of the current role of nonhuman primates in NIH-funded research, the committee will:

- Examine the present state of biomedical research studies relying on nonhuman primate models, including:
  - A landscape analysis of scientific opportunities and contributions to human health advancements; and
  - Analysis to augment the 2018 Office of Research Infrastructure Programs study *Nonhuman Primate Evaluation and Analysis* to identify gaps in nonhuman primate availability (i.e., the new demand related to COVID-19 as well as the general importance of aspects such as genetic variability, species type, transportation limitations, and colony size).

To inform its exploration of the future role of nonhuman primates in NIH-funded research, the committee will:

- Explore future needs, opportunities to improve human health, and challenges for biomedical research involving nonhuman primates, including identifying
  - Areas of emerging science that may benefit from nonhuman primate research models;
  - Opportunities for new approach methodologies to complement or reduce reliance on research with nonhuman primates;
  - Status of research, development, and validation efforts into new approach methodologies; and
  - Ways to increase coordination and collaboration between researchers who use nonhuman primates and those who use new approach methodologies to enhance the value of all methods and tools.

Based on its review of the literature and other expert input, the committee will develop a report with its findings and conclusions related to the current and future roles of nonhuman primates in NIH-funded research. This will include the committee's findings related to gaps in research and resources, including those related to nonhuman primate availability and transportation needs.

present study from other studies of the National Academies on the use of large animals—specifically, chimpanzees and dogs—as models in biomedical research.

- Prioritization of research disciplines in terms of their relative importance or the value of NHP models to each field of research.

In accordance with its Statement of Task, the committee presents in this report its findings and conclusions based on a landscape analysis of NIH-supported biomedical research. The committee's analysis included a survey of the various scientific disciplines in which NHPs are currently used and may be used in the future, considering the scientific opportunities, public health needs, and development status with respect to alternative and complementary model systems.

CURRENT LANDSCAPE OF USE OF NONHUMAN PRIMATES FOR NIH-SUPPORTED BIOMEDICAL RESEARCH

Contribution of NHP Models to Advances in Human Health

NHPs serve as models across many biomedical research areas, including infectious disease; immunology; social, cognitive, and behavioral research; reproduction; regenerative medicine; aging; and neuroscience research. No model, animal or otherwise, can fully mimic the complexities of the human body; all have limitations, but that does not negate their usefulness. There remain research questions that currently cannot be answered outside of the context of a living organism, and in some cases, NHPs may be the most translationally relevant animal model available.

Although NHPs represent a small fraction of animals used in biomedical research, their critical importance is evident in the number of medical advances that have relied on their use as models of human disease and disability. Through an iterative combination of fundamental basic and translational biomedical research, NHPs have contributed to and continue to inform the development of numerous medical products, including vaccines, therapeutics, and other treatment strategies, that have improved and preserved the quality of life in the United States and beyond. While it is not feasible for this report to provide a complete cataloging of human health advances enabled through NHP research, illustrative examples include the development of deep brain stimulation as a treatment for Parkinson's disease; vaccines for polio, measles, Ebola, and COVID-19; treatments for human immunodeficiency virus (HIV) and sickle cell disease; and monoclonal antibodies that reduce graft rejection in transplant patients. In each of these cases, NHPs played an essential role because

- vital elements of the research could not be conducted in humans for ethical or logistical reasons;
- nonanimal models (in vitro and in silico) could not fully recapitulate the integrative systems biology required in these specific contexts to demonstrate the effectiveness and safety of the preventive or therapeutic approach;
- other animal models lacked necessary anatomical, physiological, and/or biomolecular structures and processes required to model the human disease condition reliably; and
- the predictive validity of the NHP model was high because of its ability to recapitulate key aspects of the human disease.

Based on this assessment, the committee reached the following conclusions:

Conclusion 2-1: Nonhuman primates have contributed to numerous human health advances that have improved and preserved countless lives, demonstrating a track record of unique predictive relevance critical for supporting ongoing fundamental basic and translational research missions of the National Institutes of Health.

Conclusion 2-2: Nonhuman primate research resources continue to be vital to the nation's ability to respond to public health emergencies, such as the recent COVID-19 pandemic.

Current Use and Availability of NHPs for NIH-Supported Biomedical Research

In examining the state of NHP use in NIH-supported biomedical research, the committee used as a starting point the 2018 report of the NIH Office of Research Infrastructure Programs (ORIP), *Nonhuman Primate Evaluation and Analysis*. The ORIP report provides a snapshot of NHP research priorities and NHP supply and demand from fiscal years 2013 to 2017. A key finding in that report is that the availability of NHPs at the time was insufficient to meet the projected demand for NIH-sponsored biomedical research. Those challenges related to NHP supply and demand have since been exacerbated by external events—the COVID-19 pandemic, which spurred a significant increase in demand for NHPs to support the development of vaccines and treatments for SARS-CoV-2, and a ban by China on all exports of NHPs.[4] These challenges have been magnified by persistent inaction on addressing long-recognized NHP supply-and-demand issues. Consequently, this report addresses the need to reevaluate the state of NHP resources and their ability to support current and future priorities for NIH-funded research.

To inform its landscape analysis of current NHP use and availability, the committee collected information from NIH, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the seven National Primate Research Centers (NPRCs), seven other institutions that receive NIH support for NHP breeding colonies,[5] and more than 200 NIH-supported NHP investigators who responded to a committee-generated survey. Based on these data, the committee found that the NHP shortage projected in the 2018 ORIP report has been exceeded, and that its current severity limits not only immediate research capabilities but also the nation's ability to conduct critical public health research years into the future. This threat is evidenced by the following findings from the committee's assessment:

- The absolute numbers of NHPs held or used for research purposes have decreased over the past decade.
- A more than 20 percent reduction in cynomolgus macaque imports was reported in 2020 following China's export ban, highlighting the vulnerability of NHP research caused by undue reliance on imported NHPs subject to geopolitical pressures and logistical constraints that jeopardize reliable access.
- Approximately 64 percent of respondents to the committee's survey reported challenges with obtaining NHPs for their currently funded NIH awards. For greater than half of all active NIH awards reported by survey respondents, fewer NHPs were enrolled than originally planned.
- In 2021, two-thirds of investigator requests for research-naïve macaques could not be met by the NPRCs because of a shortage of these animals.
- Impacts of NHP shortages have included increased wait times for NHP enrollment in studies and skyrocketing costs of individual NHPs (a 10–200 percent increase depending on the species and source).

[4] In 2019, more than 30,000 NHPs were imported into the United States, and approximately 60 percent of those animals were imported from China (data from the Centers for Disease Control and Prevention, Quarantine and Border Health Services).

[5] Data were collected from the seven NPRCs and the four ORIP-recognized National Resources (the Michale Keeling Center at MD Anderson Cancer Center, The Johns Hopkins University, Wake Forest University, and the Caribbean Primate Research Center). Information was also collected from three additional research facilities with NIH awards supporting NHP breeding (the New Iberia Research Center, Alpha Genesis Inc., and the University of Pittsburgh). Together, these NIH-supported institutions provide NHPs to the NIH extramural and intramural research community.

While NIH and the NPRCs have taken initial steps to ameliorate the impacts of a limited supply of NHPs on NIH-supported biomedical research, these incomplete efforts represent only stopgap measures, not the sustained commitment of resources to existing NHP research infrastructure that is warranted by the current shortage. NPRCs and other institutions with NIH resource grants are the primary sources of NHPs for NIH-supported researchers. Accounting for inflation, funding in the form of base grants (P51 and P40 awards) for these institutions has generally declined over time, and increased supplemental funding provided by ORIP following its 2018 report and in 2020 through the Coronavirus Aid, Relief, and Economic Security (CARES) Act have not been sufficient to compensate for the decline. As a result of these budgetary shortfalls, these institutions have limited ability to expand breeding programs and infrastructure to meet domestic needs.

Based on this evaluation, the committee reached the following conclusions:

Conclusion 3-1: The shortage of nonhuman primate resources for National Institutes of Health (NIH)–supported biomedical research has continued to worsen, extending beyond concerns raised in the 2018 report of the NIH Office of Research Infrastructure Programs. This resource shortage has been exacerbated by export and transportation restrictions and global public health emergencies.

Conclusion 3-2: Without decisive action and a national commitment to a comprehensive plan for nonhuman primate (NHP) availability, the ability of National Institutes of Health (NIH)–supported extramural program investigators to conduct studies requiring the use of an NHP model will become a function more of access to NHPs than of a concerted response to national public health priorities. The core tenet of NIH that the most meritorious research should receive the highest priority will thereby be threatened.

Conclusion 3-3: Inadequate nonhuman primate (NHP), physical, financial, and human resources, along with the high costs of NHPs, severely limit the ability of National Institutes of Health–supported research programs to respond adequately to public health emergencies, as well as to carry out high-impact biomedical research requiring NHP models.

Conclusion 3-4: Biomedical and public health research in the United States is threatened by dependence on imported nonhuman primates (NHPs). This reliance on external resources is unsustainable and undermines the security of the U.S. biomedical research enterprise. To ensure that NHP resources are available to respond to public health threats, the United States needs to prioritize expansion of domestic NHP breeding programs.

Conclusion 3-5: The National Institutes of Health (NIH) has no central data management or reporting structure across its intramural and extramural programs to provide accurate tracking of the numbers of nonhuman primates (NHPs) required to meet current and future research needs. NIH thus has no way to collect the quantitative data needed to implement a comprehensive strategic management plan for its NHP research and resource portfolio.

Conclusion 3-6: Inadequate coordination of nonhuman primate (NHP) resources and research programs at the national level contributes to missed opportunities and diminished opportunities for efficient use of limited NHP resources.

Conclusion 3-7: Although the 2018 report of the National Institutes of Health Office of Research Infrastructure Programs (ORIP) identified a serious shortage of nonhuman primate (NHP) resources that was likely to worsen in the future, support for the ORIP-funded national NHP resource infrastructure remains inadequate.

Conclusion 3-8: Inadequate support for national nonhuman primate (NHP) resources by the National Institutes of Health (NIH) Office of Research Infrastructure Programs represents a major threat to NIH-supported NHP research programs nationwide. Funding will have to address current and future needs and the infrastructure required to support them.

POTENTIAL OF NEW APPROACH METHODOLOGIES TO COMPLEMENT OR REDUCE RELIANCE ON NHP MODELS

Use of NHPs in research comes with many challenges, and investigators using them have been clear about their interest in replacing NHPs with other models as their ability to answer the scientific questions under study can be established. New approach methodologies have been used to answer diverse questions of biomedical relevance, and ongoing research efforts continue to explore their potential to

- improve the translatability of nonclinical research by providing data that optimally reproduce the human condition;
- extend current knowledge of human diseases and provide opportunities to gain additional insights, as well as identify knowledge gaps;
- address shortages in the supply of NHPs by reducing the numbers required for biomedical research; and
- replace the use of NHPs.

Translational relevance, the primary goal for any model system intended to improve understanding of the human condition, is demonstrated through widely accepted qualification and/or validation pathways that establish the reliability and reproducibility of a new technology or approach within a defined context of use.[6] Even when data derived from a new approach methodology is used to address a fundamental research question, in contrast to explicit regulatory decision making, there should be confidence that the approach will produce data that can be reliably used for the intended purpose. The intended purpose will in turn determine the appropriate level of qualification or validation required to provide that confidence in the approach. Notably, the committee found evidence that the Food and Drug Administration is supportive of new approach methodologies and has developed guidance and programs to advance their use in regulatory decision making as in vitro and in silico models are qualified. In the absence of qualification or validation, enthusiasm for new technologies and approaches must be tempered to avoid overpromising their capabilities as valid replacements for necessary and proven experimental systems. It should be emphasized, however, that the value of in vitro and in silico models is not limited to their ability to reduce reliance on NHPs. These models are often used in ways that are complementary to NHP studies and that can help to answer different kinds of scientific questions, including questions that cannot be answered using NHP models.

[6] Context of use denotes the manner and purpose of use for a technology or approach (how and when it will be used).

In Vitro Models

The discovery of human induced pluripotent stem cells (iPSCs) has transformed cell systems and their use by scientists to answer critical human health questions. Under specific differentiation conditions, most human tissue and organ cell types can now be reliably generated from iPSCs. These tractable and renewable cell systems can be used to generate foundational knowledge regarding human gene functions, biochemistry, physiology, and molecular mechanisms. Additionally, iPSCs generated from patients provide unprecedented opportunities for revealing disease-related phenotypes; understanding pathology; identifying disease-specific biomarkers; and screening for potential treatments, including personalized treatment strategies.

Two-dimensional cell cultures are the most simplified cellular model systems. Recent advances in bioengineering have led to the generation of three-dimensional human tissue–specific organoids and microphysiological systems (MPS; commonly referred to as organ or tissue chips) that resemble human tissues/organs in cell-type composition; architecture; and, to a certain extent, function. As such, they represent physiologically relevant in vitro models.

The committee identified numerous ways in which in vitro models are being used to complement NHP research—for example, in the study of pathogen–host interactions—but few concrete examples of a demonstrated role in reducing reliance on NHPs. One of the best examples of reduced reliance is testing to predict cytokine-mediated toxicity associated with biological therapeutics, such as monoclonal antibodies, using in vitro immunoassays. Yet while organoids and MPS have successfully mimicked many aspects of the complex physiology of organs and even interactions among organ systems, they cannot in their current state be used to replicate the full complexity of in vivo systems or to study processes that require systemic regulation. Therefore, these in vitro systems cannot yet be used to answer human health and safety questions that require this level of complexity. Furthermore, certain outcomes, such as behavior, can reliably be studied only using living organisms. Results from studies using in vitro models can, however, be used to inform the design of experiments using NHPs so as to reduce reliance on these animal models. For example, initial drug screening conducted in vitro can identify promising candidates that can then be tested and validated in vivo, ultimately limiting the number of NHPs used to evaluate drug candidates and potentially reducing the likelihood that subsequent testing in NHPs will cause harm.

In Silico Models

Over the years, a wide array of quantitative and computational methods has been used in an attempt to model the properties of biological systems—with greater or lesser degrees of success. Machine learning (ML), a subset of artificial intelligence (AI), has been recognized as having the potential to overcome some of the limitations of other computational modeling tools. AI/ML methods are generally capable of finding patterns in large, complex data sets that can be used to draw inferences about the system being studied. Improvements in both AI/ML methodology and computational speed and power have led to dramatic increases in performance capabilities, enabling improvements in speed and efficiency for in silico drug development and other applications. AI/ML methods have shown their utility in prescreening of large compound libraries to identify high-priority candidates; although these candidates will still need to be tested in a model system such as NHPs, narrowing the field of drug candidates will naturally reduce the use of NHPs in validation experiments. Thus these and other applications of AI/ML have the potential to aid in designing new experimental approaches and in reducing reliance on NHP studies. At the same time, however, all in silico methods

are limited by the available input data, and these methods cannot fully obviate the need for in vitro or in vivo testing.

With adequate high-quality training and validation data and informed knowledge about the limitations of the technology, both AI/ML tools and more well-established computational modeling methods have the potential to learn from past NHP studies and provide additional insights. Through modeling using previously collected data, it may be possible to create virtual NHP control groups that could be used in place of NHPs receiving a placebo. In particular, AI/ML could provide opportunities to develop virtual NHP tissue and organ models to guide drug formulation, design, and dosing regimens and to predict toxicological and efficacy endpoints. In addition to informing NHP studies, these applications could potentially reduce the numbers of animals used in nonclinical studies—an outcome that would both increase the utility of NHP models and make better use of these models at a time when their availability is severely limited.

While such applications are currently aspirational for NHPs, efforts to develop virtual dog tissues are under way, and if successful, could guide similar approaches for NHPs. Implementation of such a strategy will require high-quality training and validation data, investment in education and training, and further methodologic development and validation. One key to the success of AI/ML methods (and indeed any computational methods) would be a commitment to open, reproducible research through a requirement that data, models, and code be shared without restriction in public data archives.

Need for Collaboration

The establishment of collaboration opportunities for investigators developing and using different model systems, including NHP researchers, bioengineers, and computational biologists, could reduce barriers to the adoption of new approach methodologies. Strategies pairing investigators with different ways of approaching the same problems can enhance the complementarity and translatability of the work. Yet the committee found few examples of interaction between research groups developing and using new approach methodologies and NHP researchers. Efforts to facilitate such interactions could enhance awareness among NHP researchers regarding the evolving capabilities of in vitro and in silico systems, and enable improvements in the design of in vitro systems such that they would be better positioned to answer research questions for which NHPs are currently used. Likewise, reciprocal interaction could educate investigators developing new approach methodologies about the needs and priorities of NHP researchers.

Based on its evaluation of the research and development status of new approach methodologies, the committee reached the following conclusions:

Conclusion 4-1: Based on the current state of the science, there are no alternative approaches that can replace nonhuman primate (NHP) models to answer research questions that require complete multiorgan interactions and integrated biology. Thus, NHPs continue to be essential for the conduct of National Institutes of Health–supported biomedical research.

Conclusion 4-2: Select new approach methodologies (in vitro and in silico models) can replicate certain complex cellular interactions and functions. As such, these new approach methodologies may be used to answer specific research questions that contribute to understanding human biology to prevent and treat human disease. Although there currently exist no alternatives that can fully replace nonhuman pri-

mates, it is reasonable to be optimistic that this may change in the years ahead as new approach methodologies continue to advance.

Conclusion 4-3: Furthering the adoption of new approach methodologies (including in vitro and in silico model systems and approaches) with the intent of reducing reliance on nonhuman primate models will require planning and support for studies that can demonstrate adequate performance for specific contexts of use or intended purposes. Expectations for qualification or validation of new approach methodologies depend on the decisions to be made using the data derived from their use and the potential human health consequences of those decisions.

Conclusion 4-4: While nonhuman primates have been regarded as preeminent models for the evaluation of human safety and efficacy, recent guidance demonstrates that the Food and Drug Administration and other regulatory agencies are supportive of the use of new technologies and approaches for regulatory decision making once they have been adequately qualified or validated.

Conclusion 4-5: Efforts to reduce reliance on nonhuman primates (NHPs) in biomedical research will require investment in opportunities to facilitate direct interaction and collaborative research among investigators using NHP models and those developing in vitro and in silico approaches to expand the applicability of new approach methodologies to research questions for which NHPs are currently needed. At present, however, few mechanisms for fostering such interaction and collaborative research are available.

FUTURE NEEDS AND OPPORTUNITIES FOR NHP MODELS IN NIH-SUPPORTED BIOMEDICAL RESEARCH

Pending advances in the capabilities of new approach methodologies to fully recapitulate the physiological and structural complexities of an in vivo system, the committee anticipates that NHPs will remain the best available model for answering many research questions that require access to integrated systems biology to mimic the human condition reliably and reproducibly. Prohibiting the continued use of NHPs in NIH-supported biomedical research or imposing insurmountable barriers to their use could result in significant delays in the discovery and development of effective treatment strategies and interventions for human diseases and increase the potential for harm.

The future needs and opportunities for NHP models in NIH-supported biomedical research will be driven by many of the same factors that have shaped the current landscape. These factors include pressing public health needs; the importance of preparedness for unknown future threats, such as global pandemics; the evolving state of science and public policy; and the availability of NHP research resources and infrastructure. As with any horizon-scanning exercise, however, future predictions need to be undertaken and interpreted with caution commensurate with the numerous scientific and policy uncertainties that will shape the future landscape.

Research Domains for Which the Need for NHPs Is Likely to Grow

Neuroscience and infectious disease are domains of NHP research likely to grow in the future, as reflected in the NIH priorities for NHP research. The complexity of the primate

brain is not adequately modeled by any in silico or in vitro system or other animal species, and the burden of neurologic disease continues to rise as the population ages. Likewise, certain infectious diseases have a pathogenic mechanism seen only in primate species, and the COVID-19 pandemic and Zika, Ebola, and recent epidemics have highlighted the importance of NHP models for understanding novel diseases and testing the safety and efficacy of vaccines and therapeutics.

Other domains of NIH-supported biomedical research using NHPs are likely to see future growth as well. Immunotherapy using cellular-, protein-, or nucleic acid–based therapeutics has emerged as a vital area of NHP research, and the molecular similarity between humans and NHPs is key to understanding the effectiveness of these novel therapies. Another area ripe for future growth is reproductive biology, some aspects of which are primate specific, and the public health, social, and economic burdens associated with infertility and diseases of the reproductive system will continue to drive needs for research using NHPs in this area. Finally, NHP research in the areas of aging and chronic inflammatory diseases is likely to increase given the enormous public health burden associated with such diseases in the United States and the opportunities arising from long-term care that increasingly is being provided to aging NHP research subjects.

Rhesus macaques are likely to remain the predominant NHP species required to support these areas of research, based on input received by the committee from multiple stakeholders, including NIH, the NPRCs and National Resources, and NIH-funded investigators. Marmosets are increasingly being used in NIH-supported research as well, particularly in the area of neuroscience, and in the development of transgenic NHP models.

Conclusion 5-1: Given the nation's most pressing public health needs and the evolving state of the science, specific domains of research—including neuroscience and neurodegenerative disorders, preparedness for unanticipated communicable infectious threats, immunotherapy, reproduction, aging, and chronic inflammatory diseases—are likely to require increased use of nonhuman primates in the future. The species distribution of future need for such research is likely to remain weighted toward macaques (particularly rhesus and cynomolgus), with increased use of marmosets.

Meeting Future NHP Resource Needs

Adequate investment in NHP research resources is necessary to support key strategic priorities for the United States, including maintaining global leadership in biomedical science and safeguarding the nation against unexpected public health threats. It is presently unclear how far into the future the United States will be able to continue importing NHPs for research purposes, and continued reliance on external sources of NHPs is therefore unsustainable. A national commitment and commensurate investment are needed to ensure that NHP research infrastructure, including domestic breeding colonies, supports the projected NHP needs of NIH-funded investigators. A critical window of opportunity now exists during which domestic investments in NHP research resources can be made while NHP species such as cynomolgus macaques, marmosets, and African green monkeys remain accessible from other countries and can be imported to establish breeding stocks. The development of purpose-bred, self-sustaining domestic populations of NHPs also offers the benefits of reducing the impact of increasingly limited options for international transport of imported NHPs and providing assurance of the responsible sourcing of animals. Domestic NHP breeding

can also provide a greater degree of regulatory control over the health and well-being, as well as the social and genetic backgrounds, of NHPs used in research, which in turn can support improved experimental rigor and the quality of the data generated; help prevent misrepresentation of data related to animal origin, age, or prior use; and reduce the impact on wild populations of NHPs in their countries of origin.

Beyond domestic breeding programs, future NHP research will depend on investment in human resources and physical and data infrastructure. Ensuring a scientific workforce with the skills needed to conduct NHP research will require support for training for early-career investigators and the support staff needed for NHP care. Likewise, experience with shortages of laboratory space during the COVID-19 pandemic demonstrated the importance of adequate facilities for NHP research, including biocontainment spaces. Moreover, the expansion of physical infrastructure supporting NHP breeding programs will provide opportunities to ensure optimal housing and husbandry conditions that align with best practices based on the evolving science of animal welfare. Investment in data infrastructure, within NIH and nationally, will be necessary as well to improve tracking of NHP demand and use so as to better support planning and coordination, both of which are essential to guide effective and appropriate use and management of NHP resources going forward. Importantly, such data infrastructure investments will also be integral to future efforts to reduce reliance on NHPs by enabling accurate measurement of the impact of changes in policy and the implementation of nonanimal models.

Given that NHPs are likely to remain a limited and high-cost resource—even with the necessary further investment in domestic breeding to address current shortages—advances in new approach methodologies offer the additional potential benefits of helping to reduce costs and mitigate future NHP shortages. In anticipation of these advances, attention is needed to the development of a strategy on the use of new approach methodologies in conjunction with NHP models to optimize the application of NHP research in the future.

Conclusion 5-2: The 2018 report of the National Institutes of Health (NIH) Office of Research Infrastructure Programs, Nonhuman Primate Evaluation and Analysis, *included recommendations for improving communication and collaboration within the nonhuman primate (NHP) research community, increasing domestic NHP supply capabilities, addressing limitations in NIH funding mechanisms, promoting training in NHP care and research, and enhancing the utility and value of existing NHP resources. These solutions and recommendations have not yet been fully implemented and remain critically important.*

Conclusion 5-3: Addressing the challenges posed for the national research infrastructure by a persistent lack of nonhuman primates (NHPs) will require a commitment and comprehensive national effort focused on expanding domestic NHP resources.

Conclusion 5-4: The creation of a national plan for allocation and expansion of nonhuman primate resources is necessary to optimize the use of this critical scientific resource. Such a plan will require adequate monetary, physical, and personnel resources, as well as a centralized tracking system to match need to investment in a data-driven fashion.

Conclusion 5-5: Continued development and validation of new approach methodologies (in vitro and in silico model systems) is critically important to support further advances in biomedical research. This may reduce the need for nonhuman primate

(NHP) models in the future, and/or enhance their utility. Additionally, this may help to mitigate shortages in NHP supply and the high cost of NHP research.

Enhancing NIH-Supported NHP Research Going Forward

Given the need for continued use of NHPs in NIH-supported biomedical research, it is incumbent on those supporting and conducting such research to ensure that these animal models are used as effectively as possible. NHP resources demand strong stewardship and research conducted in a way that maximizes the knowledge and actionable insights obtained from each individual animal in every study. Technologies and approaches including noninvasive monitoring and imaging approaches (e.g., digital biomarkers such as in home enclosure neural recordings, magnetic resonance imaging), AI/ML, and minimally invasive research procedures (e.g., laparoscopy, positive reinforcement training for voluntary provision of samples) can be applied to increase the impact and rigor of NHP research and improve alignment with processes implemented in the clinical setting. Additional opportunities to enhance NIH-supported NHP research include implementing thoughtful approaches for sample collection and sharing, fostering openness and data sharing, expanding and implementing data-driven NHP care and management practices (e.g., social housing), further characterizing NHP models, and learning from natural variation and disease in NHPs, as well as incentivizing collaboration among NHP and non-NHP research groups.

Conclusion 5-6: Given the limited numbers of nonhuman primates (NHPs) available for research, it is incumbent upon investigators and the National Institutes of Health (NIH) to make the best use of each animal through cooperative efforts, data sharing, purposeful planning, and use of data-driven care and management methods for the long-term care and use of NHPs in research. Examples of successful cooperative efforts from the community of NIH-funded NHP researchers—including collaborative working groups; data-sharing resources for clinical and clinical pathology data, gene expression profiling, and genotype data; and biospecimen repositories—can serve as models for broader adoption.

Conclusion 5-7: A system for consistent reporting is needed to adequately capture the life, scientific, and medical history, including experimental treatments and procedures, of individual nonhuman primates (NHPs). The need for complete NHP life histories further supports the development of increased domestic breeding capacity in the United States to maximize the accurate and complete sharing of clinical and experimental data. Currently, the incentives, mandates, and infrastructure within the National Institutes of Health research enterprise are insufficient to support uniform data management and reporting across all NHP research programs.

Conclusion 5-8: Recent advances in genomics, bioinformatics, imaging, digital biomarkers (e.g., noninvasive home enclosure neural and behavioral recordings), extended reality, and artificial intelligence/machine learning have revealed opportunities to understand normal biology and the mechanisms of disease. Such technologies and approaches have the potential to augment the scientific knowledge that can be gained from individual nonhuman primate (NHP) studies and, in some cases, enable less invasive use of NHPs. Leveraging these opportunities for NHP research will require tracking the genotype, phenotype, and history of each animal used, as well as transdisciplinary interactions.

Conclusion 5-9: Additional investments will be needed to implement, maintain, train, and use current and emerging technologies (such as digital biomarkers, artificial intelligence/machine learning, imaging, extended reality, and laparoscopy), as well as data-driven husbandry practices, with the potential to enhance nonhuman primate research funded by the National Institutes of Health.

1

Introduction

Society relies on biomedical research supported by the National Institutes of Health (NIH) to mitigate disease, prevent the spread of infectious agents, advance technologies to help those with disabilities, and promote health and wellness, among other objectives. Studies aimed at accomplishing these objectives often rely on animal, cellular, and in silico systems to model complex human biological systems and disease processes, with the appropriate choice of a model system being dictated by the question(s) being asked.

Nonhuman primates (NHPs) represent a small proportion—an estimated one-half of 1 percent—of animals used in biomedical research in the United States (Friedman et al., 2017). They are useful because their similarities to humans with respect to genetic makeup, anatomy, physiology, and behavior make it possible to approximate the human condition. Indeed, remarkable biomedical breakthroughs—including successful treatments for Parkinson's and sickle cell disease, drugs to prevent transplant rejection, and vaccines for polio and COVID-19, as well as fundamental discoveries related to vision, motor control, decision making, and memory—have been enabled by research using NHP models. Nonetheless, the use of NHP models is not without controversy or challenge. Policy makers, animal advocates, researchers, and the public continue to raise questions as to whether and how nonanimal models can be used to answer scientific questions for which NHPs have historically been regarded as fit for purpose, questions that apply as well to animal models more broadly. Additionally, limitations in the availability of NHPs, exacerbated by the COVID-19 pandemic and recent restrictions on their exportation and transportation, have had negative impacts on NIH-funded research necessary for both public health and national security (Subbaraman, 2021).

In this context, and at the direction of the U.S. Congress, NIH asked the National Academies of Sciences, Engineering, and Medicine to convene an ad hoc committee of relevant experts to conduct a landscape analysis focused on describing the state of the science of NHP model systems and exploring their current and future role in NIH-funded biomedical research. The committee was also asked to examine opportunities for new approach methodologies to complement or reduce reliance on NIH-supported research using NHPs. The committee's full Statement of Task is presented in Box 1-1.

BOX 1-1 STATEMENT OF TASK

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will examine the current role of and future needs for nonhuman primates in biomedical research funded by the National Institutes of Health (NIH).

To inform its examination of the current role of nonhuman primates in NIH-funded research, the committee will:

- Examine the present state of biomedical research studies relying on nonhuman primate models, including:
  - A landscape analysis of scientific opportunities and contributions to human health advancements; and
  - Analysis to augment the 2018 Office of Research Infrastructure Programs study *Nonhuman Primate Evaluation and Analysis* to identify gaps in nonhuman primate availability (i.e., the new demand related to COVID-19 as well as the general importance of aspects such as genetic variability, species type, transportation limitations, and colony size).

To inform its exploration of the future role of nonhuman primates in NIH-funded research, the committee will:

- Explore future needs, opportunities to improve human health, and challenges for biomedical research involving nonhuman primates, including identifying
  - Areas of emerging science that may benefit from nonhuman primate research models;
  - Opportunities for new approach methodologies to complement or reduce reliance on research with nonhuman primates;
  - Status of research, development, and validation efforts into new approach methodologies; and
  - Ways to increase coordination and collaboration between researchers who use nonhuman primates and those who use new approach methodologies to enhance the value of all methods and tools.

Based on its review of the literature and other expert input, the committee will develop a report with its findings and conclusions related to the current and future roles of nonhuman primates in NIH-funded research. This will include the committee's findings related to gaps in research and resources, including those related to nonhuman primate availability and transportation needs.

STUDY ORIGIN AND SCOPE

In its Consolidated Appropriations Act of 2021,[1] the U.S. Congress directed NIH to commission an independent National Academies study to explore the current and future use of NHPs in intramural NIH research, as well as existing and anticipated future opportunities for alternatives to reduce NIH's reliance on NHP models. As directed by NIH, the committee's Statement of Task (Box 1-1) expanded the scope of the study beyond that described in

[1] The complete congressional language requesting this consensus study can be found in Division H of the Joint Explanatory Statement that accompanied H.R. 133, the Consolidated Appropriations Act, 2021 (P.L. 116-260) on PDF page 69 here: https://www.appropriations.senate.gov/imo/media/doc/Division%20H%20-%20Labor%20H%20Statement%20FY21.pdf (accessed September 13, 2022).

the congressional language to include both intramural and extramural[2] biomedical research using NHPs. While there are differences between the intramural and extramural programs (e.g., scale, funding), many of the elements of the research landscape examined by the committee, including domains of NHP research and NHP availability challenges, are similar across the two programs. Aspects of the study and findings that are specific to NIH's intramural research program are called out as such in the relevant chapters.

Acknowledging that NHPs are used in research in the United States in a broad range of contexts and that such research is supported by federal agencies such as the U.S. Department of Defense and the Food and Drug Administration (FDA), nonprofit organizations, and private industry, NHP research funded by entities other than NIH is beyond the scope of this study. Consequently, this study does not include an in-depth analysis of the use of NHPs in industry-sponsored research, including pharmaceutical safety and efficacy testing as part of regulatory approval processes. At the same time, however, drug and vaccine development builds on a foundation of knowledge derived from fundamental basic, translational, and clinical research (see Chapter 2), and the indirect contributions of NIH-funded research to advances in available vaccines and treatments, though difficult to quantify, were considered to be within the study scope. Additionally, the committee was charged with assessing gaps in NHP availability, and such an assessment cannot ignore the constraints on the system imposed by competing demands from other sponsors of NHP research. Moreover, research supported by different sponsors, both federal and nonfederal, is often complementary. For example, both NIH and the Biomedical Advanced Research and Development Authority may fund research on vaccines and other medical countermeasures in support of eventual product approvals by the FDA (NIH, 2022). NIH provides such support in part through the Small Business Innovation Research and Small Business Technology Transfer award mechanisms (NIGMS, 2023). Thus in some specific contexts, the committee examined how NIH-supported NHP research affects and is affected by NHP research funded by other organizations.

The supply of NHPs for biomedical research in the United States relies in part on the importation of animals from other countries, as discussed in more detail in Chapter 3. Imported NHPs may be bred in other countries and exported for research purposes, or they may be captured from wild populations. The committee was not charged with examining the impacts of biomedical research on wild NHP populations, so no analysis of such impacts is included in this report. Additionally, as of 2015, NIH no longer supports biomedical research with chimpanzees (Collins, 2015). Accordingly, this report does not include consideration of the use of chimpanzees, or other great apes, as research models. Furthermore, approaches that employ non-NHP animal species as alternatives to NHP models were considered to be beyond the scope of this study, although the potential for other animal models (e.g., transgenic animals) to reduce reliance on NHPs is briefly acknowledged in the report where appropriate. A comprehensive assessment of such opportunities would have expanded the study beyond what was feasible given the available time and resources. This represents an important area for future consideration.

The committee recognizes that research utilizing NHPs, like all scientific animal research, must be conducted for ethically appropriate reasons and in ethically appropriate ways. However, as clarified by the sponsor of the study during the committee's first meeting, the charge did not include specific examination of ethical standards and principles that underlie NHP research, or current ethical issues and disputes relevant to this research. This report rests on

[2] Intramural research at NIH is carried out by researchers employed by the federal government, whereas extramural research is carried out by researchers at institutions across the United States and in some foreign countries who have received funding from NIH institutes, centers, and offices (NHGRI, 2015).

the foundational assumption that biomedical research with NHPs can be conducted ethically when an NHP is the appropriate research model to address the aims of the research (a non-NHP model would not achieve the stated aims); when studies are well designed and conducted; and when the research and the housing and care of the animals afford requisite attention to their welfare, including minimization of pain, distress, and discomfort, and appropriate environmental enrichment.

In accordance with the Statement of Task, this report presents the committee's findings and conclusions based on a landscape analysis. As emphasized by NIH during the committee's first public meeting, the analysis was intended to survey the various scientific disciplines in which NHPs are currently used and may be used in the future, considering the scientific opportunities, public health needs, and development status of alternative and complementary model systems. It is important to note that the committee was not asked to prioritize research disciplines in terms of their relative importance or the value of NHP models to each field of research.

Finally, in contrast with other reports of the National Academies on the use of large-animal models—specifically, chimpanzees (IOM, 2011) and dogs (NASEM, 2020)—the committee's charge did not include the provision of conclusions related to parameters intended to guide how and when to use NHPs for biomedical research. Thus, unlike previous reports, the present report does not provide criteria for determining when it is scientifically necessary to use NHPs, a task that would have substantially altered the committee's composition and approach.

KEY TERMINOLOGY

A number of key terms related to research models are used throughout this report. These terms are defined in Box 1-2.

BOX 1-2 KEY TERMINOLOGY USED IN THIS REPORT

New approach methodology: For the purposes of this report, the committee defined new approach methodologies broadly to include in vitro and in silico technologies and approaches that can be used to complement NHP studies or reduce reliance on NHPs in biomedical research. *Complementary approaches* can be used to fill gaps by answering research questions not fully answered by NHP models, extend understanding of the research conducted with NHPs, or confirm results from that research. Complementary approaches may or may not *reduce reliance on NHPs*, which can be achieved by substituting alternative models or decreasing the numbers of NHPs used in biomedical research. Human studies (e.g., clinical trials, population-level epidemiological studies) and approaches that employ other species of animals (e.g., transgenic animals) that may be used as alternatives to NHPs are not included within the committee's definition of new approach methodologies.

Translational relevance: The degree to which findings from research using a model system apply to humans.

Context of use (COU): A term defining the manner and purpose of use for a technology or approach (how and when it will be used) (FDA, 2017).

Validation: The process by which the reliability and relevance of a method, approach, or technology are established for a defined purpose (OECD, 2005).

BOX 1-2 Continued

Model validity: The degree to which a research model resembles the human condition it is intended to model (Varga et al., 2010). Multiple aspects of validity are relevant to discussions of animal and nonanimal research models, including

- *construct validity,* defined as the degree of similarity between the model and human disease in the mechanisms underlying the phenomenon of interest (t' Hart et al., 2018); and
- *predictive validity,* defined as the ability of a model to predict the efficacy of an intervention (t' Hart et al., 2018).

Qualification: The process of confirming that a technology or approach is capable of yielding reproducible results that are suitable for the intended purpose based on the defined COU.

STUDY CONTEXT

NHP Models in the Broader Context of Biomedical and Animal Research

Humankind is plagued by a multitude of diseases, illnesses, and forms of infirmity and disability that shorten or end lives; cause significant pain, distress, fear, anxiety, and sorrow; impair quality of life; and impose substantial economic costs on sufferers and society at large. The steady annual growth in federal expenditures on biomedical research in recent years—the vast majority of which represent investments by NIH (Research!America, 2022)—reflects recognition of the need to address the significant burden on Americans of premature death and disability due to such public health threats as cancer, diabetes, infectious disease, and neurological disorders (see Figure 1-1). For many conditions that threaten the health and quality of life of an aging population, such as Alzheimer's disease, there remains no cure and little understanding of how to prevent or slow their onset or progression (AA, 2022; Eaton and Wishart, 2017). Accordingly, it is incumbent on a society with sufficient resources and scientific expertise to strive to make significant progress in preventing, alleviating, and curing these conditions that are responsible for so much human suffering.

The 21st century has seen numerous technological advances—including high-throughput sequencing, CRISPR-Cas gene editing methodologies, induced pluripotent stem cells, and artificial intelligence—that have revolutionized many areas of biomedical research. Despite this progress, however, some scientific questions cannot be answered outside the context of a living organism (Anderson, 2008; Eaton and Wishart, 2017; Friedman et al., 2017). For many applications, complete biological systems in the form of animal models are needed to study complex biological systems and disease processes and evaluate novel approaches for prevention or treatment when research in humans is unethical or otherwise infeasible. In the study of viral infection, for example, investigation of the interaction between the virus and the cells it infects may be possible in vitro (Rijsbergen et al., 2021), but understanding the body's full immune response requires a living model organism that accurately models the human condition (Baxter and Griffin, 2016; Veenhuis and Zeiss, 2021).

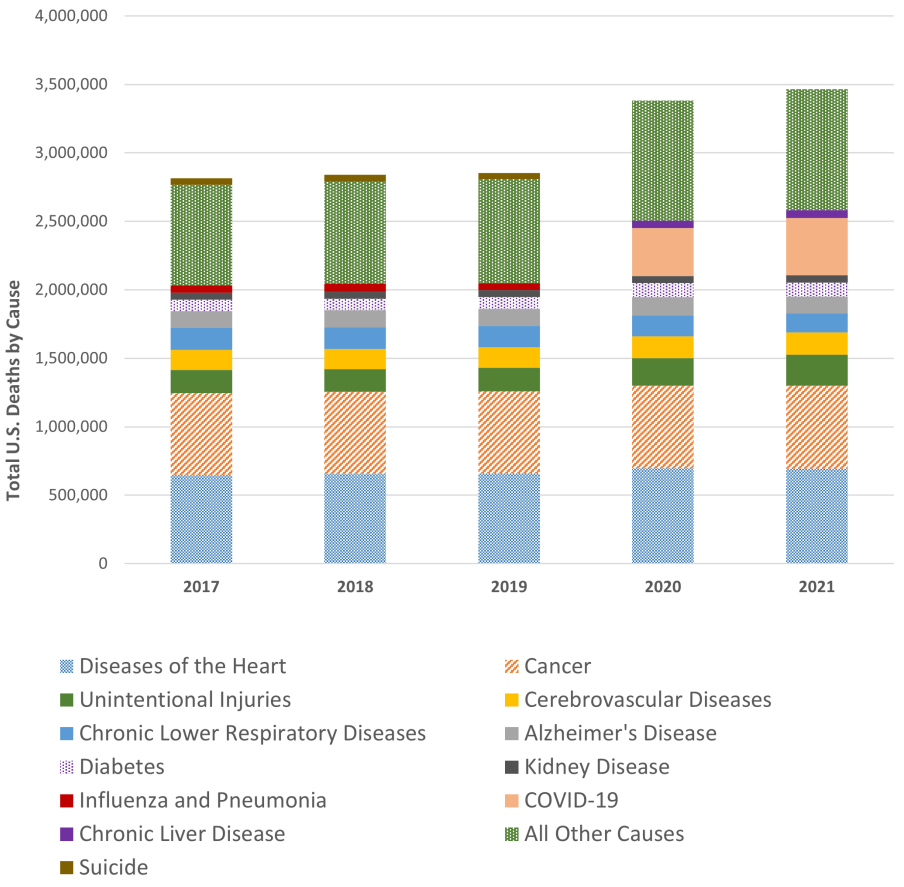

FIGURE 1-1 Leading causes of death in the United States, 2017–2021.
SOURCE: CDC, 2021

As noted earlier, NHPs have been estimated to account for only one-half of 1 percent of all animals used in biomedical research in the United States (Friedman et al., 2017). However, accurate estimation of this figure in the United States is hindered by the absence of requirements to report on subsets of commonly used vertebrate animal models, including rodents and fish, under the Animal Welfare Act of 1966 (AWA),[3] discussed in the section that follows. NHPs, common species of which are listed in Table 1-1, represent approximately 8.6 percent of the nearly 800,000 animals used in research for which the AWA requires reporting to the U.S. Department of Agriculture (USDA) (APHIS, 2021).[4] In the European Union (EU), 93 percent of research is conducted on species not counted under the AWA, with mice accounting for roughly half of the 10.4 million animals used for research in EU member states in 2019 (European Commission, 2022). These EU data have been used to estimate that 14 million vertebrates are used each year in research in the United States (Taylor and Alvarez, 2019),

[3] 7 U.S.C. §§ 2131–2159 (P. L. 89-544), with implementing regulations: 9 C.F.R. § 1(A).

[4] Laboratory mice and rats, fish, and certain other species used in laboratory research are not covered by the AWA and accordingly, their numbers are not reported to USDA; therefore, the relative proportion of NHPs among all laboratory animals is much lower than 8.6 percent (APHIS, 2021).

TABLE 1-1 Nonhuman Primate Species Used in Biomedical Studies

Scientific Name	Common Name	Examples of Applications
Chlorocebus sabaeus	African green monkey	Infectious disease (e.g., COVID-19,[d] HIV/AIDS), neuroscience
Papio spp.	Baboon	Reproduction, neuroscience, hematology, transplantation, COVID-19[d]
Cebus/cebinae	Capuchin	Aging,[b] cognition[e]
Callithrix jacchus	Common marmoset	Reproduction, endocrinology, vision, behavior, COVID-19[d]
Macaca fascicularis	Cynomolgus macaque	Infectious disease (COVID-19,[d] tuberculosis, HIV/AIDS), neuroscience
Macaca fuscata	Japanese macaque	Batten disease,[a] obesity[c]
Aotus spp.	Owl monkey	Vaccine development (e.g., dengue, malaria), behavior, endocrinology, vision
Macaca nemestrina	Pig-tailed macaque	Infectious disease (e.g., COVID-19,[d] HIV/AIDS), reproduction, growth and development, behavior, neuroscience
Macaca mulatta	Rhesus macaque	Infectious disease (e.g., COVID-19,[d] HIV/AIDS, tuberculosis,[g] Ebola,[f] measles[h]), reproduction, growth and development, behavior, neuroscience
Cercocebus atys	Sooty mangabey	HIV/AIDS, leprosy
Saimiri sciureus	Squirrel monkey	Malaria, neuroscience
Callicebinae spp.	Titi monkey	Neuroscience,[i] behavior[j]
Chlorocebus pygerythrus	Vervet	HIV/AIDS, neuroscience

NOTE: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.
SOURCE: Table adapted with permission from Anderson, D.M. 2008. The nonhuman primate as a model for biomedical research. In *Sourcebook of models for biomedical research*. Pp. 251–258. Springer Nature. Additional sources are noted below.

[a] McBride et al., 2018
[b] Williams, 2008
[c] Takahashi et al., 2006
[d] Trichel, 2021
[e] Orkin et al., 2021
[f] Alfson et al., 2021
[g] Peña and Ho, 2015
[h] de Swart, 2009
[i] Bales et al., 2017
[j] Mercier et al., 2020

with NHPs representing approximately 72,000, or 0.5 percent, of those animals in fiscal year (FY) 2021 (APHIS, 2022a). Private industry accounts for just under half of all NHPs reported to USDA (see Appendix B for USDA-reported listings of all research facilities holding and using NHPs in FY2021).

Models are just that—simplified representations of complex systems used to answer specific questions of interest (Denayer et al., 2014; Ferreira et al., 2020). No model, animal or otherwise, can fully recapitulate the unique complexities of the human body and the disease processes that afflict it (even a human is not a perfect model of the health and biology of another human given natural heterogeneity), but that does not negate their usefulness for studying specific aspects of a disease. Given the limitations inherent in all models, the selection of a model depends on the precise question being asked to ensure that the model is fit for purpose. In many cases, a combination of models, each used to address different scientific questions, may better recapitulate the clinical process being studied (Denayer et al., 2014).

The primary determinant of whether NHPs are appropriate and uniquely suited as a model system for answering a specific scientific question is translational relevance (the degree to which findings from research using NHPs applies to humans) and the inability to study the process of interest in other models in a way that is translationally relevant to people. Factors contributing to the translational relevance of NHP models include similarities between the biological (e.g., anatomy and physiology, genetics, epigenetics) and behavioral characteristics of NHPs and humans and the extent to which human diseases are mirrored in NHPs. Also important is predictive validity, or the ability to predict the effect of an intervention (e.g., vaccine, therapeutic) in humans based on the effect observed in the NHP model (Denayer et al., 2014), in terms of both clinical efficacy and safety. A number of factors may affect translational relevance, including the similarity of a given target in disease processes in humans and the animal model. For this reason, limitations in understanding of the underlying biology can pose barriers to selecting an appropriate model.

The use of large-animal models (e.g., NHPs, dogs, pigs) in nonclinical research is generally premised on the greater translational relevance of those models to humans as compared with rodents. The translational relevance of animal models depends to some degree on the evolutionary conservation of biological structures and processes under study. For highly conserved pathways and structures, animals that are more phylogenetically distant from humans (e.g., zebrafish, nematodes, mice) may serve as valuable model systems for the study of human anatomy, physiology, and disease (Bradford et al., 2017; Markaki and Tavernarakis, 2010). Cost, logistics, and ethics are among the considerations that may guide researchers in the decision to use so-called lower-order animals when they can adequately model the system or disease of interest. Yet while mice and other animals that are evolutionarily more distant than NHPs from humans have been invaluable models in biomedical research, they lack certain features unique to primates and may not recapitulate key aspects of human diseases. For example, because of differences in anatomy (especially brain structure) and physiology, rodent models do not represent with fidelity the complete response of human immune and neurological systems across the lifespan (Buffalo et al., 2019; Hutchison and Everling, 2012; Wagar et al., 2018). Concerns regarding a poor rate of translation from bench to bedside have been attributed to such differences (Deutsch et al., 2012; Perlman, 2016). Indeed, one can point to numerous examples of the potential discovery of "cures" for human disease (e.g., cancer) in rodent models that were found not to be clinically relevant in humans (Kerbel, 1998; Mak et al., 2014). Whatever type of model is used, it must sufficiently recapitulate the human disease of interest to increase the likelihood that the data it yields will translate to humans at the clinical trial stage (Ferreira et al., 2020). For biological processes that are unique to primates, NHPs may be the best available model when research cannot be conducted in humans or with human cells or tissues.

That being said, the translatability of even the best available model is not perfect, an observation that has led to questions of whether animal models should be used at all (Pound and Ritskes-Hoitinga, 2018). While NHPs are generally more similar to humans than are mice, species-specific differences still contribute to limitations in predictive validity. For example, the CD28-specific monoclonal antibody TGN1412, which was found to be safe in nonclinical toxicity testing using NHPs, in combination with other animal models, caused unexpected morbidity during first-in-human clinical trials (Pallardy and Hünig, 2010; Suntharalingam et al., 2006) owing to human-specific T cell subtype expression of CD28 unknown at the time. This experience highlights the nature of scientific inquiry, in which the process of reconciling results leads to new understanding and medical breakthroughs. Yet despite examples in which predictive validity has been imperfect, there are numerous examples in which NHP models have proven essential when the necessary testing could not be performed

otherwise. Examples of research in which NHP models have provided critical insights into the human condition and contributed to health advances are highlighted in Chapter 2.

Translational relevance, and thus the suitability of NHPs as model systems, varies across different NHP species for different applications (Cauvin et al., 2015). Moreover, it is worth emphasizing that NHPs are not the most appropriate or only large-animal models for studying all human diseases, including some that contribute substantially to the public health burden in the United States. For example, similarities in the anatomy of pigs and humans make pigs suitable large-animal models for studying atherosclerosis (heart disease) (Hamamdzic and Wilensky, 2013), gastrointestinal disease (Sangild et al., 2014), and some aspects of the renal system (Dalgaard, 2015; Gutierrez et al., 2015).

Other factors beyond translational relevance may make an animal model more or less suitable for use in research. For example, experience with a given species may also be a consideration, as the ability to compare data with findings of past studies may add value to the use of a particular model (Singh and Olabisi, 2017). Moreover, the transition to a different species may initially require adjusting the number of animals to meet the need for a fully characterized new model (Golding et al., 2018). At the same time, however, it is important to guard against letting the availability of historical data alone justify the continued use of any animal model (NASEM, 2020).

Aside from suitability, feasibility may be a consideration in the use of a particular model. Feasibility may be affected by such factors as access, cost, and the ability to meet the care needs of the animal (e.g., housing and veterinary services). Such factors are not to be used to justify the use of a less appropriate model. Ultimately, it is important to use the best model or combination of models, whether animal or not, to answer the question at hand.

Oversight of Care and Use of NHPs in Research

When the best model for a given scientific study is an NHP model, the welfare of the animals and the scientific need to use them are addressed by a robust body of laws, regulations, and policies that guide oversight practices from the federal to the local level, as depicted in Figure 1-2.

Evaluation of Scientific Merit

Like all research proposals submitted to NIH, research proposals involving NHP models receive careful and comprehensive evaluation. The process of obtaining NIH funding is highly competitive. Only a small proportion of proposals receive funding following a peer review process that evaluates the project's scientific merit, experimental design, and potential for impact to the field. This process is conducted for intramural proposals by scientific merit committees (Denny, 2022) and for extramural proposals by NIH scientific review groups (also known as study sections) composed of researchers with expertise in the areas under study (NIH, 2021c). Most NIH institutes fund proposals judged to be within the top 20 percent of those submitted, although specific percentile cutoff points vary by institute and year (Fang et al., 2016).

For proposals involving the use of NHPs, Principal Investigators (PIs) are required in a separate "vertebrate animals section" of the grant application to justify their need for an NHP model and the number of NHPs required for the work (NIH, 2021a). They must also specify how any potential animal pain and distress will be minimized throughout the study. Review of this section of the grant application is part of the rigorous scientific and technical merit review conducted by the study section. Given that all animal research projects funded by

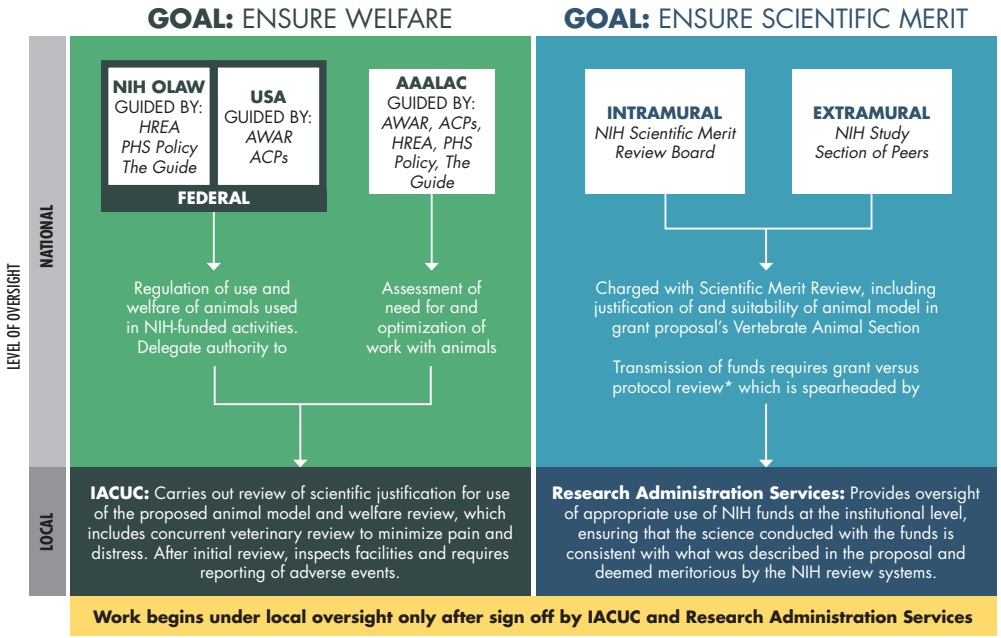

FIGURE 1-2 Elements of oversight of animal research in the United States.

*Grant versus protocol review is a process whereby an institution's Research Administration Services reviews the grant and the protocol side-by-side (often together with IACUC staff) and confirms that everything funded by the grant is approved in the IACUC protocol.

NOTES: ACP = animal care policy; AWAR = Animal Welfare Act and Animal Welfare Regulations; HREA = Health Research Extension Act; IACUC = institutional animal care and use committee; NIH = National Institutes of Health; OLAW = Office of Laboratory Animal Welfare; PHS Policy = *Public Health Service Policy on Humane Care and Use of Laboratory Animals*; the Guide = the National Research Council's *Guide for the Care and Use of Laboratory Animals*; USDA = U.S. Department of Agriculture. Accreditation from AAALAC International, an independent international accrediting agency for animal research facilities, is voluntary.

NIH must be judged by peer reviewers to have strong scientific and technical merit, NIH's funding of a study using NHPs constitutes strong evidence of the likelihood that it will add significant scientific value.

Protection of NHP Welfare

High standards of animal welfare are integral to high-quality science, and multiple layers of oversight are built into the process of ensuring appropriate care and use of NHPs in research. Researchers carrying out work with NHPs, along with animal care staff employed by investigators and research facilities and veterinarians in these facilities, seek to protect and promote the maximum welfare of NHPs.

Before beginning any work involving NHPs (and independently of the project's source of funding), a PI must receive approval from the institution's institutional animal care and use committee (IACUC). IACUCs are legally obligated to apply all relevant laws, regulations, and policies aimed at ensuring that research animals are not subjected to unnecessary pain, distress, or discomfort and are afforded care and housing that is conducive to their comfort

and well-being (NIH, 2021b). IACUC review occurs concurrently with or following input from a veterinarian with experience in the use of NHPs in research, who works closely with the researchers to optimize their protocol so that the animals are handled appropriately, and procedures that may cause pain or distress are minimized and managed effectively. In reviewing research projects involving NHPs and their potential impact on the animals' welfare, IACUCs receive input from all their members, including scientist and veterinarian members, nonscientist members, and members who represent community interests in the proper care and treatment of animals. This review includes application of the 3Rs, described in Box 1-3. In any proposed project involving NHPs funded by NIH, the IACUC must also determine that an NHP model is required to address the questions posed by the project; that no more NHPs will be used than is necessary for addressing these questions; and that all animals receive appropriate housing, care, and environmental enrichment that fosters species-typical behaviors and well-being.

IACUCs receive their authority from federal law, specifically from the AWA and the Health Research Extension Act (HREA) of 1985.[5] Protection of NHP welfare by institutions and investigators is overseen by USDA (pursuant to the AWA); NIH's Office of Laboratory Animal Welfare (OLAW) (pursuant to the HREA); and for a number of research institutions, AAALAC International (AAALAC), an independent international accrediting agency for animal research facilities (AAALAC, n.d.). Institutions can seek accreditation from AAALAC, whose standards of animal care exceed even those of USDA and OLAW. AAALAC accreditation is not compulsory, but OLAW regards it as evidence of the highest standards of care (Na and Diggs, 2021; Newcomer, 2012).

The AWA authorizes and directs USDA to issue and enforce regulations to implement its provisions. These regulations include standards for humane handling, housing, husbandry, veterinary care, and transportation of NHPs and other species covered by the Act. In accordance with the AWA and its associated Animal Welfare Regulations (AWAR) (APHIS, 2022b), all registered institutions must report annually to USDA the number of NHPs being held or used for research purposes. Institutions must also report the number of animals used in research that experienced no pain or distress; the number that received anesthetics, analgesics, or tranquilizers to prevent or relieve potential pain or distress; and the number that experienced unrelieved pain or distress. An explanation of any procedures that cause pain or distress and the reasons such drugs were or were not used must be provided with the report. The AWA and its associated regulations require investigators to prevent or minimize pain and distress whenever possible and to consider alternative procedures to avoid pain and distress. In addition to requiring yearly written updates from the research institution, USDA conducts unannounced inspections of all research facilities at least once yearly, during which inspectors examine the animals' housing environment, the locations where research with the animals is conducted, and the IACUC's processes for providing oversight to ensure that they accord with the AWAR.

Section 495 of the HREA covers all extramural research on vertebrate animals that is funded by NIH or the Public Health Service. Like the AWA, the HREA requires the humane care and treatment of animals used in research that are covered by the Act. The HREA authorizes and directs NIH to issue and enforce standards pursuant to the Act, a mandate that has been delegated to OLAW. OLAW has incorporated into its animal use and care standards the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (U.S. Principles) (Office of Science and Technology Policy, 1985; OLAW, 2018), which were originally adopted by NIH and other federal agencies for

[5] P.L. 99-158.

BOX 1-3 THE 3Rs

The 3Rs were proposed and defined by British scientists W. M. S. Russell and R. L. Burch in their 1959 book *The Principles of Humane Experimental Technique* (Russell and Burch, 1959). They recommended that in designing and conducting animal experiments, investigators employ three general ways of eliminating or minimizing pain, distress, fear, and other significantly unpleasant experiences in experimental animals—refinement, replacement, and reduction.

As originally defined by Russell and Burch, replacement refers to the "substitution for conscious living higher animals of insentient material. Reduction means reduction in the numbers of animals used to obtain information of a given amount and precision. Refinement means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used" (Russell and Burch, 1959, p. 64). Of note, reduction was not defined by Russell and Burch as minimization of numbers of animals used in research, and rather was framed as working with the minimum number of animals needed to provide valid results. Sound experimental design relies on the use of the scientifically appropriate number of animals. While using too many animals might result in more pain, distress, and discomfort than is justified, using too few could render an experiment scientifically unsound and result in unnecessary and, therefore, unjustified pain and distress (Tannenbaum and Bennett, 2015).

In recent years, modifications to the definitions of the 3Rs have gained widespread acceptance. It is now commonplace to define replacement as not using animals in an experiment (Tannenbaum and Bennett, 2015). Revisions of the concept of refinement include providing positive experiences to research animals, as well as preventing or minimizing unpleasant ones. For example, the National Research Council's *Guide for the Care and Use of Laboratory Animals* defines refinement as "modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress" (NRC, 2011, p. 5).

animal research they conduct or require to be conducted by others. OLAW has also incorporated into its animal care standards the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) (OLAW, 2015) and the National Research Council's *Guide for the Care and Use of Laboratory Animals* (the Guide) (NRC, 2011). Although the HREA does not cover research conducted intramurally within NIH itself, NIH has adopted the U.S. Principles, the PHS Policy, and the Guide for its use of NHPs and other vertebrates in intramural research.

Guidance regarding the role of the IACUC, the protocol review process, and how IACUCs should determine whether animal welfare is being protected in a research setting is provided by the AWAR, USDA animal care policies,[6] the U.S. Principles, the PHS Policy, and the Guide, among other documents. Significant deviations from policies and requirements of the HREA and OLAW or from procedures and care and treatment of animals approved by the IACUC must be reported promptly to OLAW, which is authorized to take remedial action, which may include withdrawing funding from a particular research project or prohibiting an investigator or institution from conducting further research using NHPs.

[6] The USDA *Animal Care Policy Manual* is available at https://naldc.nal.usda.gov/catalog/7219640 (accessed January 15, 2023).

The Critical Need for a New Look at the Landscape for NHP Research

In conducting its landscape analysis, the committee benefited from previous efforts to characterize the landscape of NIH-supported research using NHPs; those prior reports (see Box 1-4) provided an invaluable foundation for the committee's work. However, this report differs from past efforts in that it focuses not only on the current and future use of NHPs in biomedical research but also on the opportunities for emerging technologies and innovative approaches to complement such research and/or reduce future reliance on NHPs as model

BOX 1-4 PRIOR ASSESSMENTS OF NHP USE IN NIH-SUPPORTED RESEARCH

- *National Institutes of Health (NIH) Workshop on Ensuring the Continued Responsible Oversight of Research with Non-Human Primates: Final Report* (NIH, 2016)
  Summarizes a workshop conducted in response to a congressional request to NIH to review its ethical policies and processes related to nonhuman primate (NHP) research to ensure that it has appropriate justification for animal research protocols.

- *Nonhuman Primate Evaluation and Analysis Part 1: Analysis of Future Demand and Supply* (ORIP, 2018a)
  Describes supply of and demand for NHPs for fiscal years 2013–2017, including priority research areas identified by a survey of NIH-funded investigators conducting NHP research.

- *Nonhuman Primate Evaluation and Analysis Part 2: Report of the Expert Panel Forum on Challenges in Assessing Nonhuman Primate Needs and Resources for Biomedical Research* (ORIP, 2018b)
  Summarizes the discussions held during an expert panel forum convened to follow up on Part 1 of the report. Topics included institute forecasts, challenges, and emerging technologies and needs in NHP research. Key recommendations from the organizing committee included
  - establishing a trans-NIH NHP working group;
  - increasing funding levels for NHP grants;
  - determining the genetics of all domestic NHP colonies supported by NIH;
  - providing NIH resources to expand existing colonies of rhesus macaques;
  - expanding NIH-sponsored marmoset colonies;
  - establishing domestic breeding colonies of cynomolgus macaques;
  - providing support for the development of species-specific reagents, assays, and technologies; and
  - providing training opportunities for personnel.

  NIH actions taken in response to the recommendations in that report are discussed in Chapter 3 of the present report.

- *Fostering Rigorous Research: Lessons Learned from Non-human Primate Models and Charting the Path Forward* (NIH, 2020)
  Summarizes a workshop focused on enhancing the rigor, transparency, and reproducibility of research with NHPs, including discussions on the importance of rigorous study design, selection of the appropriate model, external factors (environment, husbandry), and data sharing.

systems. Moreover, supply and demand for NHPs for biomedical research have changed dramatically in the past few years, driving a need for a critical evaluation of the state of NHP resources and their ability to support current and future priorities for NIH-funded research.

In 2020, two major related events occurred in rapid succession that drastically altered the landscape for NHP research in the United States and globally. The emergence of SARS-CoV-2 and the subsequent elevation of COVID-19 to pandemic status in early 2020 spurred a significant increase in demand for NHPs as scientists across the globe raced to understand the pathogenesis of the novel coronavirus and to develop treatments and vaccines. Shortly after the emergence of SARS-CoV-2, China, previously the largest supplier of monkeys for research to the United States,[7] banned the export of all NHPs. The export ban, along with existing policies of major airlines prohibiting the transport of NHPs (Grimm, 2018; Wadman, 2012), exacerbated supply issues at a time of heightened demand and necessitated the prioritization of NHPs from other sources for COVID-19 research. As discussed in Chapter 3, these events have impacted the ability of researchers in scientific disciplines apart from COVID-19 research to access NHPs and conduct studies requiring them as models. In this context of increasing external pressures and demand for highly valuable NHP research resources, the present report provides a timely update of previous assessments of the landscape for NHP research, including the status of NHP availability for use in NIH-supported biomedical research.

STUDY APPROACH

Committee Formation

The necessary expertise for a National Academies consensus committee is guided by the study's Statement of Task. To respond to its charge (Box 1-1), the National Academies convened a 16-member committee with expertise in NHP research (including primatology and primate behavior/psychology/welfare in wild and captive contexts), veterinary medicine, pathology, in vitro and in silico models, clinical research, and ethics. Because the committee was charged with analyzing the current and future landscape of continued NHP use, researchers who have used NHPs in their research and are knowledgeable regarding the opportunities and challenges associated with and alternatives to using NHP model systems represented critical areas of expertise for the committee. While it was not feasible to represent every field in which NHPs are used in biomedical research, efforts were made to ensure representation across multiple scientific disciplines (e.g., neuroscience and psychology, infectious disease, reproductive health), phases of the research pipeline (e.g., basic, translational, clinical), and NHP model systems (e.g., macaques, marmosets, baboons, capuchins). Similarly, researchers using different nonanimal models that may be classified as new approach methodologies (e.g., microphysiological systems, organoids, artificial intelligence/machine learning) were sought. Biographical sketches of the committee members can be found in Appendix C.

[7] In 2019, more than 30,000 NHPs were imported into the United States, and approximately 60 percent of those animals were imported from China (based on NHP importation data provided to the committee on February 10, 2023; available by request through the National Academies' Public Access Records Office).

Information Gathering and Public Input

Public Meetings

The committee met and deliberated over a roughly 1-year period (April 2022–April 2023). During this time, the committee held three public information-gathering meetings (April, August, and November 2022). The committee's first public meeting, in April 2022, provided an opportunity to hear the study charge from NIH and to clarify any issues of scope. A public workshop held in conjunction with the August 2022 meeting included sessions on NHP research from the perspective of funders, domestic breeding resources, and investigators. It also included a session on emerging technologies and innovative methodologies with the potential to refine, reduce, and replace the use of NHPs in NIH-supported biomedical research. A public meeting held in November 2022 provided further opportunity for the committee to hear from the NIH Office of Research Infrastructure Programs and representatives of individual NIH institutes, centers, and offices that support NHP research. This meeting also included a session with researchers involved with or having insights on the use of new approach methodologies to complement or reduce reliance on NHP research.

Literature Review

Multiple literature reviews were conducted throughout this study using PubMed and Scopus. These searches guided and provided references for content in this report describing current uses of NHPs in biomedical research and the current state of new approach methodologies. More information on the committee's literature review strategy, including search terms, can be found in Appendix A.

Information Requests and Survey

To supplement the evidence available from the published literature, the committee gathered additional information from stakeholders who support or are engaged in NHP research (detail is provided in Appendix A). Information requests were sent to NIH, FDA, the Centers for Disease Control and Prevention, the National Primate Research Centers (NPRCs), National Resources,[8] and other selected institutions with NIH-supported breeding colonies. Experiences and perspectives of individual investigators with NIH awards supporting NHP research were solicited through an online survey (details on the survey methodology can be found in Appendix A, while a presentation of analyses of data collected by the committee can be found in Appendix B and a copy of the survey with frequency tables can be found in Appendix E).

Public Comments

Members of the public were given an opportunity to submit questions and comments during the committee's first meeting in April 2022 and could also submit comments and documents for the committee's consideration through the project website at any time during the course of the study. The committee received and reviewed more than 4,500 public comments related to its task.

[8] For the purposes of this report, "National Resources" include the four non-NPRC institutions with NHP breeding colonies identified by ORIP: the Michale E. Keeling Center for Comparative Medicine and Research (MD Anderson Cancer Center), The Johns Hopkins University, Wake Forest University, and the Caribbean Primate Research Center (see Chapter 3).

Data Limitations and Challenges Related to Information Gathering

Despite efforts to conduct a comprehensive assessment of the landscape of NHP use in NIH-supported biomedical research, the committee experienced difficulties related to data access. In contrast to the publicly available data systems in the EU for tracking numbers and uses of research animals, centralized data collection on NHPs in the United States is limited to data compiled by USDA, which do not include species-level data or information on specific research applications. While the NIH RePORTER tool[9] provides a mechanism for searching active NIH awards for projects in which NHPs are referenced, limited information is included in the public project descriptions, and not all projects that include references to NHPs involve use of the animals (some may refer to past NHP research, for example). In contrast to the analysis undertaken for the NIH report on NHP supply and demand (ORIP, 2018a), the committee lacked access to internal NIH data systems containing detailed information from NIH award applications (e.g., information on research domain, NHP species, quantity of NHPs planned for use, justification for the choice of model). Much of that information is contained in the vertebrate animals section of the application, which is not included in the information publicly available on NIH RePORTER.

Given the above challenges, an accurate, detailed, quantitative accounting of the use and availability of NHPs in NIH-supported research was not feasible for this study. As a result, the committee included quantitative information in its description of the NHP research landscape only when such data were available and when confidence in the validity of the data was warranted.

ORGANIZATION OF THE REPORT

This report is organized into five chapters. Following this introductory chapter, Chapter 2 provides an overview of the contribution of NHP research to advances in human health. Chapter 3 presents the current landscape of NHP use and availability for NIH-supported intramural and extramural biomedical research. In Chapter 4, the committee examines the status of new approach methodologies with the potential to complement NHP research or reduce reliance on NHP models. Chapter 5 describes the future needs and opportunities for NHPs in NIH-funded biomedical research. Appendix A details the methods used by the committee in conducting this study, while Appendix B provides additional supporting data for the landscape analysis presented in Chapter 3. Biographical sketches of the committee members and disclosures regarding the members' conflicts of interest can be found in Appendixes C and D, respectively. Appendix E includes a copy of the survey provided to NIH-supported NHP researchers and frequency tables of responses.

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[9] RePORTER stands for Research Portfolio Online Reporting Tools (see https://reporter.nih.gov [accessed December 12, 2022]).

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2

Contribution of Nonhuman Primate Models to Advances in Human Health

Scientists' knowledge of human anatomy and physiology, their understanding of the mechanisms of pathogenesis and opportunities for disease prevention and treatment, and the ability to test the safety and efficacy of novel therapeutics and interventions all rely on research using model systems with sufficient complexity and translatability to the human condition, as discussed in Chapter 1. Nonhuman primates (NHPs) are currently used in a small but vital number of biomedical research areas to meet these needs. To address the committee's task of assessing the contributions of NHP models to human health advances and future scientific opportunities (see Box 1-1 in Chapter 1), this chapter provides an overview of NHP use across different stages and scientific disciplines within the biomedical research landscape, focusing specifically on where health advances have been realized. A series of case studies offers detailed examples illustrating how NHPs, often in combination with other model systems and approaches, have contributed to and continue to support significant scientific discoveries and advances in the understanding, prevention, and treatment of human disease, recognizing that all models inherently have limitations and NHP models are no exception. To illustrate the utility of these models, the chapter includes examples that feature opportunities for improving future biomedical research. The chapter ends with the committee's conclusions regarding the current role of NHPs in biomedical research supported by the National Institutes of Health (NIH).

NHP USE ACROSS THE RESEARCH CONTINUUM

Biomedical research, like scientific research generally, is cumulative and iterative in nature. Individual biomedical research studies almost always seek knowledge relating to a narrow aspect of a disease or disability—knowledge that together with the results of other studies will eventually identify or establish the effectiveness of an approach to the prevention, treatment, or cure of a disease. Thus, the advancement of human health through biomedical research is a multiphase process that extends from the laboratory bench to the patient's bed-

side. Rather than being distinct, the phases in this process are best understood as a continuum from basic to clinical research, with those two ends being bridged by and overlapping with translational research. Basic research serves to elucidate fundamental biological processes (NRC, 2005); basic research that is not translational in nature is referred to in this report as fundamental basic research. Translational research itself represents a spectrum of research stages (NCATS, 2021), each of which is characterized by questions with direct application to improving human health (e.g., through the prevention or treatment of human disease) (NCI, 2007; UVA, 2023) and includes research involving safety and efficacy testing for regulatory purposes. Importantly, translational research often builds on the findings of fundamental basic research that may or may not have originally been framed in translational terms, as discussed later in this chapter. Not surprisingly, the overlapping and nonlinear nature of research phases has fostered the adoption of somewhat fluid definitions (Kemp, 2018), which adds complexity to the evaluation of NHP use within the research ecosystem. NIH support for biomedical research encompasses both fundamental basic and translational research, reflecting the dual nature of the agency's mission to "seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability" (NIH, 2015). For the purposes of this report, the committee views NHP use in the context of these two research phases.

When determining the appropriate model for a given scientific question, investigators must consider many factors, including ethical and scientific perspectives. This process includes assessing model validity, which encompasses the strengths and limitations of a model in relation to the scientific question of interest and balanced against the public health issue of concern (see Chapter 1 for discussion of translational relevance and predictive validity in NHP models) (Denayer et al., 2014). As noted previously, all models used across the biomedical research continuum have inherent limitations that impact their value as a translationally relevant research tool. Importantly, no one model—in vivo, in vitro, or in silico—can fully mimic the complexities of the human body or be generalized to the heterogeneity of target patient populations. This limitation is not unique to translational research; scientists face similar challenges in human clinical trials, knowing that trial results may not be reflective of treatment benefit and risk in all patient populations that will be treated in "real world" practice settings.

There remain fundamental basic and translational research questions that cannot be answered outside of the context of a living organism or cannot be studied directly in a human. In some of these cases, NHPs—given their genetic, physiologic, and behavioral similarities to humans (Estes et al., 2018; Phillips et al., 2014)—may be the most translationally relevant animal model available. Yet even when an NHP is the best available model, failures to predict human response can occur. For example, known challenges associated with the use of certain species-specific NHP models for research on biologics include seasonality of reproduction; lack of extensive genomic characterization; high sensitivity; and interanimal variability (e.g., differences in immune system functions and gene sequences across animals sourced from different areas), resulting in phenotypic differences (Cauvin et al., 2015). Importantly, however, failures in research using NHPs can provide opportunities to develop new understanding of model limitations and in some cases, help elucidate new pathways toward discoveries and advances.

NHP Use in Fundamental Basic Biomedical Research

Fundamental basic biomedical research—the foundation upon which translational research is built—is undertaken to generate knowledge of how biological systems function,

information required for developing effective interventions when these systems are not functioning properly (NRC, 2005). Significant time often elapses between discoveries made in fundamental basic research and their impact on biomedical progress, in part because such discoveries often build upon each other, and knowledge accumulates incrementally through the course of the research continuum (Onken et al., 2020; Schor, 2013). Indeed, when fundamental basic research is carried out, there often is no expectation of an immediate or direct practical benefit precisely because the research is aimed at deriving causes and explanations for fundamental processes that are not yet well understood (Schor, 2013). Thus, while the ultimate goal of fundamental basic biomedical research may be to impact clinical outcomes, it is frequently unclear how the findings will impact human health until additional research is carried out, or until investigators can determine how this and additional research can be applied to particular diseases. The process is iterative and incremental and can take years, sometimes decades, as clinical application of fundamental basic research may depend on a future discovery of entirely new and sometimes unexpected or unpredictable knowledge or technologies (Comroe and Dripps, 1976; Tannenbaum, 2017, 2023). The nature and importance of fundamental basic research were emphasized by Dr. Story Landis, former director of the National Institute of Neurologic Disorders and Stroke:

> Fundamental basic research is the engine of discovery; it generates new knowledge, drives innovation, and underlies all past and future breakthroughs. Gaps in our understanding of how the healthy brain and nervous system function can form roadblocks to understanding dysfunction in disease. (Landis, 2014)

More than half of NIH-funded research using NHPs is classified as basic research (Jorgenson, 2022). This fundamental biomedical research using NHPs focuses on advances in understanding of anatomy, physiology, and mechanisms of disease, potentially yielding targets for intervention. NHPs are used in fundamental basic research when the study of the biological structures and processes of interest is not possible in a more phylogenetically distant animal model, and other approaches to discovery are not appropriate or feasible. For example, multiple regions of the human brain that are shared by NHPs do not exist or are less complex in the rodent brain (see the section on research in neurobiology and neurodegenerative disease later in this chapter) (Preuss and Wise, 2022; Wise, 2008). It is important to recognize that discoveries about biological systems resulting from fundamental basic research using NHPs are a starting point for forward translation. Thus the contributions of this work to cutting-edge human health advances are not always obvious. A relevant example is the contribution of fundamental basic research on brain circuitry to advances in brain–machine interface research aimed at helping people living with paralysis regain some motor control using neural prosthetics (Feng et al., 2020), as discussed later in this chapter.

Examples of NHP use in fundamental basic research identified through the committee's Scopus publication analysis (see Appendix A for the methods used in this review) and other high-impact publications suggest that much of this work occurs in the research areas of neuroscience and microbiology and immunology (Burt et al., 2018; Fiebelkorn et al., 2018; Peng et al., 2019; Remington et al., 2018; Russo et al., 2018), fields that require a detailed understanding of complex mechanisms underlying biological processes and their association with health and behavior. Committee-identified examples of topics explored in fundamental basic neuroscience research using NHPs include motor control (Goldring et al., 2022; Yan et al., 2022), mechanisms governing working memory (Brincat et al., 2021), brain activity at rest (Turchi et al., 2018), neural mechanisms of decision making (Okazawa and Kiani, 2023), and facial recognition (Livingstone et al., 2017; Rossion and Taubert, 2019; Tsao, 2014).

Within microbiology and immunology, NHPs have contributed to better understanding of the human microbiome (Edwards et al., 2019; Nagpal et al., 2018) and pathogen-mediated disease mechanisms (Liu et al., 2019). NHPs are also used in fundamental basic research on reproductive biology, such as study of the mechanisms underlying embryo implantation and decidualization (Ochoa-Bernal and Fazleabas, 2020). Further detail on some of the contributions of fundamental basic research using NHPs to human health advances can be found in the case studies of deep brain stimulation (DBS) and endometriosis presented later in this chapter.

NHP Use in Translational Biomedical Research

The goal of translational biomedical research is to move research from the laboratory to clinical practice and from clinical observations back to the laboratory to elucidate new basic research discoveries. Whereas an aim of fundamental basic research is to understand something unknown, translational research is considered "use-inspired," synthesizing basic knowledge to improve on or design novel drugs, devices, diagnostic tools, or other interventions (Kemp, 2018). The process of translation is iterative (Molas-Gallart et al., 2016), so that the first application of a potential new therapy in humans may raise critical questions that can be answered only through the use of animal models.

In translational research, NHP models play a pivotal role in understanding how the integrated functions of complex systems, such as behavior, cognition, anatomy, reproduction, immunology, metabolism, and aging, will likely generalize to humans to inform the development of drugs, biologics, and other medical products aimed at preventing, treating, or curing human disease. NHPs are also used in translational research involving efficacy and safety testing (including that conducted for regulatory purposes) when the use of other animal models may not be scientifically appropriate (such as in the case of some biotherapeutics, when the target is not present in other species). Importantly, the design of preclinical trials in NHPs can be similar to that of the intended future clinical trial in humans because the relatively large physical size of NHPs and their other anatomic similarities to humans facilitate serial sample collection, imaging, and diagnostic testing (Estes et al., 2018; Kennedy et al., 1997; Knechtle et al., 2019; Lemaitre et al., 2021; Phillips et al., 2014; Shou et al., 2021). Models that have been highly successful in predicting clinical outcomes, as is the case for NHPs, are often given preference in translational research because the introduction of new therapeutics in humans needs to be based on the best possible assessment of potential risk and benefit for patients participating in clinical trials to satisfy the important ethical obligations for informed consent.

Thus the unique features of NHP models have firmly positioned them as an invaluable tool in the development of therapies for human diseases that cause extraordinary suffering and impose substantial health care costs and societal burden. At the same time, NHPs are not the best models for translational research in all cases, and several different animal models are often used to study a specific problem. Moreover, scientists are continually making progress toward reducing reliance on NHP models for biomedical research, as discussed further in Chapter 4.

Highly cited articles identified through the committee's Scopus publication analysis and other high-impact, peer-reviewed publications highlight wide-ranging translational research applications of NHP models across multiple areas of human health. Recurring themes across these publications include evaluation of vaccines and therapeutics for the prevention and treatment of high-burden diseases such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (Barouch et al., 2018; Borducchi et al., 2018; Chua et

al., 2018; Cirelli et al., 2019; Gardner et al., 2019; Pardi et al., 2019; Pauthner et al., 2019; Xu et al., 2018), COVID-19, and other viral diseases (Corbett et al., 2020; Erasmus et al., 2020; Mercado et al., 2020; van Doremalen and Munster, 2015; Williamson et al., 2020); tuberculosis (Darrah et al., 2020; Hansen et al., 2018); diabetes (Bochenek et al., 2018; Xie et al., 2018); and cancers (Claus et al., 2019; Nellan et al., 2018). Of note, many of these publications describe the use of multiple animal models, either to draw comparisons or to investigate different aspects of a research question.

EXAMPLES OF NHP USE ACROSS THE RESEARCH LANDSCAPE

The following sections and accompanying case studies are intended to convey the diversity of ways in which NHP models have been used across various phases and domains of the research landscape. The selected case studies—which are not exhaustive and include cases in which no alternative model was available at the time, or NHPs were used in combination with other animal models and approaches—illustrate the role of NHP models in understanding human physiology and mechanisms of disease, as well as in accelerating the development of therapies for prevention and treatment of disease that have improved or saved the lives of millions of patients. The discussion in this section focuses primarily on health advances emerging from the translational research space (e.g., therapeutics and interventions), thereby addressing the committee's task to assess the contributions of NHP models to human health. It is important, however, to acknowledge the vital role of fundamental discoveries that serve as the foundation for this research. Also highlighted in the examples in this section are changes in NHP use over time, with specific attention to how scientific advances have led to reduced need for and reliance on NHP models in some cases, a topic reviewed further in Chapter 4. It should be noted that the discussion here addresses advances related to NHP use broadly; it does not constitute a systematic review of current NHP use and its associated successes and failures in the context of NIH-funded research, as such a review was not feasible given the limited data available to the committee (see Chapter 1).

Contributions of NHP Models to Research in Neurobiology and Neurodegenerative Disease

Neurological and neuropsychiatric disorders have major social and economic impacts on society. The global burden of neurological disease is staggering, and its prevalence continues to rise as the population ages (Riggs, 1998). Major neurological disorders, including stroke, dementia, and Parkinson's disease, are among the leading causes of death and disability worldwide, with stroke being the second leading cause of death globally (Feigin et al., 2020; GBD 2016 Neurology Collaborators, 2019; WHO, 2020a, 2020b). Additionally, neuropsychiatric illnesses—especially depression and anxiety—are increasing, and substance use disorders—such as alcoholism and opioid dependence—are major contributors to the health burden of communities (GBD 2016 Alcohol and Drug Use Collaborators, 2018; GBD 2019 Diseases and Injuries Collaborators, 2020).

Researchers have increasingly turned to NHP models to better understand the functioning of the human brain and develop effective treatments for disease involving the neurologic system. In many instances, selection of an NHP model for this purpose is due to the similarities between NHPs and humans with respect to neuroanatomical and neurophysiological and behavioral characteristics, compared with major differences between the brains of primates and rodents.

The similarities between NHP and human brains are essential for understanding movement control, vision, cognition, and affect. The primate brain is not simply a larger version of the rodent brain, as exemplified by the multiple brain regions that are present in primates but not in rodents (Hutchinson and Everling, 2012). Further, primates share a number of important neural pathways from the periphery to the brain that are either less complex or absent in rodents. For example, 25–30 percent of corticospinal systems in primates originate from areas that are completely absent in the rodent corticospinal system (Strick et al., 2021). An example is the supplementary motor area, which is involved in preparation for voluntary movement and generation of complex movement sequences and is implicated in Parkinson's disease (Cañas et al., 2018; Rahimpour et al., 2022). Additionally, multiple areas in the brain's frontal lobe that control movement, vision, cognition, and affect are present in primates but absent, less complex, or radically underdeveloped in rodents (Hutchinson and Everling, 2012; Laubach et al., 2018; Molnár and Clowry, 2012; Preuss and Wise, 2022). The "failure to translate" treatments developed in rodent models is, in multiple instances, due to these types of brain differences (Azkona and Sanchez-Pernaute, 2022; Buffalo et al., 2019; Scott and Bourne, 2022). For these reasons, NHPs are critical for discovering how to prevent, treat, and cure disorders of the human nervous system.

Many examples of discoveries from fundamental basic research demonstrate the value of NHP models for developing new treatments for human neural dysfunction. For example, understanding of brain anatomy and function through NHP studies has informed treatment strategies for lazy eye in children to reduce the risk of long-term vision problems (Foundation for Biomedical Research, 2022), and has enabled the development of brain–machine interface technology that allows people living with paralysis due to brain injury to operate robotic prosthetics (Feng et al., 2020; Lebedev and Nicolelis, 2017; Yonkovich, 2022). Recent research building upon prior, extensive work using NHP models has demonstrated how neurostimulation can restore arm movement capabilities to patients following a stroke (Barra et al., 2022; Powell et al., 2023). Similarly, advances originating from fundamental basic research using NHPs have led to the use of DBS as a treatment for Parkinson's disease (see Box 2-1), and more recent research suggests that this intervention holds promise for the treatment of amyotrophic lateral sclerosis, spinal cord injury, peripheral neuropathy, stroke, resistant depression, Alzheimer's disease, and obsessive-compulsive disorder (Blomstedt et al., 2013; Elias et al., 2018; Ni and Chen, 2015; Schlaepfer et al., 2013). NHP studies also have enabled clinical trials for optogenetic therapy to restore vision for individuals living with degenerative eye diseases, such as retinitis pigmentosa (Mustari, 2017; Picaud et al., 2019).

NHP models, specifically aging rhesus macaques, are used to investigate Alzheimer's-like pathology, as well as other forms of age-related cognitive decline (Gray and Barnes, 2019; Messaoudi and Ingram, 2012), although there has been little success in the development of effective treatments for dementia and cognitive decline despite research employing a variety of models, including NHPs (Feng et al., 2020). These failures may be attributable in part to the lack of a clear underlying mechanism (Guo et al., 2020), illustrating the interplay between fundamental and translational research that is typical in the development of novel therapeutics.

Similarities in behavior between humans and NHPs also make NHPs good models for the study of neurodevelopmental conditions (including autism) (Aida and Feng, 2020), addiction, and anxiety and depression (Buffalo et al., 2019; Ding and Ko, 2021; Rudebeck et al., 2019; Scott and Bourne, 2022; Willard and Shively, 2012). NHPs have several advantages over other models that have made them instrumental in addiction research, especially their longer life span and ability to carry out drug self-administration procedures that more closely replicate the human experience (Banks et al., 2017; Czoty and Nader, 2015; Huskinson et

BOX 2-1 CASE STUDY: HOW FUNDAMENTAL BASIC RESEARCH CONDUCTED TO UNDERSTAND NEURAL CIRCUITRY LED TO SUCCESSFUL TREATMENT FOR PARKINSON'S DISEASE

As a young physician-scientist, Mahlon DeLong worked in a National Institutes of Health laboratory renowned for developing a technique for recording the activity of single neurons in awake, trained monkeys (Lasker Award Winner Mahlon DeLong, 2014). DeLong became one of the first to record neuron activity in the basal ganglia, a brain region that is impacted in Parkinson's disease (Blandini et al., 2000; DeLong and Wichmann, 2009). This research found that neurons in the basal ganglia were active when the animal was at rest. When the animal made arm movements, it was observed that some neurons within a specific "motor territory" of the basal ganglia changed their activity (DeLong, 1983). DeLong and colleagues used findings from years of fundamental basic research to develop a "wiring diagram" of the basal ganglia that helped to form the foundation for the development of deep brain stimulation (DBS) as a treatment for Parkinson's disease (Gardner, 2013; Wichmann et al., 2018).

A key next step in the development of DBS was the discovery that a neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused symptoms in both humans and nonhuman primates (NHPs) that are similar to those found in older patients with Parkinson's disease (Gardner, 2013; Wichmann et al., 2018). Exposure to MPTP created an NHP model of Parkinsonism that enabled DeLong and his colleagues to define the alterations in basal ganglia activity caused by Parkinsonism (Langston et al., 1984). With this knowledge and their wiring diagram, they showed that a small destructive lesion made in a specific region of the basal ganglia "normalized" its activity and improved the animal's motor behavior (Bergman et al., 1990; Wichmann et al., 2018). The procedure was so effective that the same approach was successfully used to treat patients with Parkinson's disease. Because lesions are irreversible, leaving no room for error, and implantable stimulation devices were by this time available, the French neurosurgeon Alim Louis Benabid and his colleagues developed the use of DBS in the same region of the basal ganglia to produce a comparable blocking effect (Jackson, 2014; Gardner, 2013). While neurostimulation techniques had been used previously, the identification of the mechanism and effective targets were novel (Gardner, 2013).

DBS is now an established, highly effective treatment for the motor symptoms of Parkinson's disease for some individuals and can be used to treat essential tremor, dystonia, and depression (Delaloye and Holtzheimer, 2014; Gardner, 2013; Schlaepfer et al., 2013; Wichmann et al., 2018). Since 1997, more than 150,000 patients have received DBS for treatment of the disease (Sankary et al., 2020). DBS is also being considered as a treatment for multiple neurologic and neuropsychiatric disorders, including addiction, stroke, Alzheimer's disease, severe chronic pain, cluster headache, and obsessive-compulsive disorder (Blomstedt et al., 2013; Elias et al., 2018; Frizon et al., 2020; Luo et al., 2021; Vyas et al., 2019; Wang et al., 2018a).

The development of this treatment depended on three lines of research in NHPs: fundamental basic research into the wiring diagram of the basal ganglia, knowledge of the normal activity of basal ganglia neurons, and recordings in NHPs exposed to MPTP to study how the Parkinson's disease process alters neuron activity. The final step was to use lesions and DBS in the MPTP model to determine whether motor function could be restored (Blesa et al., 2018).

al., 2016; Maguire et al., 2013; Phillips et al., 2014; Wade-Galuska et al., 2011). Moreover, phylogenetic similarities in the brains of NHPs and humans allow for the coordination of behavioral procedures with noninvasive brain imaging techniques (Banks et al., 2017; Bradberry, 2011; Gould et al., 2012; Howell and Murnane, 2008), and phenotypic similarities have provided the ability to study how environmental and lifestyle factors, such as stress and social behavior, influence the effects of drug abuse (Banks et al., 2017; Ewing Corcoran and Howell, 2010; Morgan et al., 2002; Nader et al., 2012).

The creation of novel NHP disease models via genome editing technology has advanced rapidly in the last decade and has been of particular interest in the neuroscience community (Feng et al., 2020; NASEM, 2019; Park and Silva, 2019; Sato and Sasaki, 2018). The simultaneous evolution of understanding of the genetic and epigenetic changes associated with human nervous system disorders (through such investments as the NIH-funded BRAIN [Brain Research Through Advancing Innovative Neurotechnologies] Initiative[1] and the ability to recreate such changes in NHPs through genome editing are generating new opportunities for higher-fidelity modeling of neurodevelopmental conditions, such as autism (Zhao et al., 2018; Zhou et al., 2019), and neurodegenerative disorders, such as Alzheimer's and Huntington's disease (Aron Badin, 2018; Rizzo et al., 2021).

Contributions of NHP Models to Research in Reproductive Health and Fertility Disorders

Infertility affects approximately 10 percent of people of reproductive age in the United States, and is usually diagnosed when they fail to conceive (Stouffer and Woodruff, 2017). The inability to have children has significant societal, emotional, and financial implications. Scientific understanding of infertility is limited in part because of ethical restrictions on research. In this context, research involving use of tissues from early pregnancy, including early embryo implantation, and use of fetal tissues and embryonic stem cells, is either restricted or impermissible (Lo and Parham, 2009; Stouffer and Woodruff, 2017).[2] Given the close phylogenetic relationship between NHPs and humans and similarities in their hormonal, neural, and local control of reproduction, as well as maternal, fetal, and placental interactions during pregnancy, NHPs offer significant advantages as models for research related to reproductive disorders that impact predominantly women.

Old-world primates, primarily rhesus macaques, cynomolgus macaques, and baboons, have been used extensively in reproductive health research. Each of these species has specific advantages and limitations that make it well suited to research addressing different scientific questions (Cauvin et al., 2015). Importantly, all three species have menstrual cycle lengths, ovulation periods, and implantation processes similar to those seen in humans (Carson et al., 2000; Carter et al., 2015; Cauvin et al., 2015; Shimizu, 2008; Siriwardena and Boroviak, 2022; Stouffer and Woodruff, 2017). Baboons in particular offer unique advantages for the study of reproductive biology, some of which include the ability to determine the phase of the menstrual cycle though noninvasive perineal skin monitoring (Bauer, 2015; D'Hooghe, 1997) and access to the uterus transcervically (Stouffer and Woodruff, 2017), which permits endometrial biopsies, embryo transfer, preimplantation embryo flushing, and hysteroscopy (D'Hooghe et al., 2008).

Research using NHPs has yielded significant insights into conditions that can impact fertility and pregnancy, such as polycystic ovarian disease, endometriosis (see Box 2-2), placental dysfunction, preterm labor, and abnormal fetal development (Stouffer and Woodruff, 2017). Spermatogenesis in all species of NHPs is also highly comparable to that in humans, which makes NHP models suitable for studying the male reproductive system (Luetjens et al., 2005). Additionally, NHPs can provide insight into the consequences of mitochondrial DNA transfer, genome editing, and other novel technologies before they are used in humans (Stouffer and Woodruff, 2017). At the same time, however, NHP models have both general and species-specific limitations for reproductive research. Generally, many NHPs have inaccessible early implantation sites (Su and Fazleabas, 2015) and a relatively long gestation

[1] https://braininitiative.nih.gov (accessed March 22, 2023).

[2] In the United States, human embryo research cannot receive federal funding (Matthews and Morali, 2022).

BOX 2-2 CASE STUDY: NHP MODELS UNIQUELY SUITED TO THE DEVELOPMENT OF TREATMENTS TO IMPROVE WOMEN'S REPRODUCTIVE HEALTH BY SLOWING THE PROGRESSION OF ENDOMETRIOSIS

Endometriosis is an increasingly common inflammatory disease characterized by the growth of endometrial tissue outside of the uterine cavity. Approximately 10 percent of women of reproductive age are affected by the disease, which typically causes pelvic pain, extremely painful menstrual cramps, and infertility, among other symptoms. Because its symptoms are nonspecific, endometriosis tends to be undiagnosed or overlooked (Stouffer and Woodruff, 2017), with diagnosis often requiring multiple physician visits and a diagnostic laparoscopy, an invasive procedure (OASH, 2021). Because endometriosis occurs in menstruating nonhuman primates (NHPs), their use to study and advance understanding of this disease holds promise.

One of the greatest barriers to effective treatment of endometriosis is the lack of understanding of the disease process. The predominant mechanism underlying the development of endometriosis is thought to be retrograde menstruation, when some of the menstrual flow, including endometrial tissue, flows into the peritoneal cavity—typically through the fallopian tubes (Halme et al., 1984). Because up to 90 percent of women experience retrograde menstruation (Seli et al., 2003) but only about 10 percent develop the disease, the genetic, epigenetic, and/or environmental factors that predispose individuals to the development of endometriosis remain to be elucidated.

Women with endometriosis have a higher risk for other chronic pain conditions, such as fibromyalgia, rheumatoid arthritis (NICHD, 2002), and migraine (Wu et al., 2022), as well as for other nonmalignant gynecologic diseases, including uterine fibroids (Uimari et al., 2011) and adenomyosis (Gonzales et al., 2012). They are more likely as well to receive subsequent diagnoses of malignancies (Krawczyk et al., 2016), autoimmune diseases (NICHD, 2002), early natural menopause (Thombre Kulkarni et al., 2022), cardiovascular conditions (Okoth et al., 2021), and cerebrovascular conditions, such as stroke (Farland et al., 2022). Endometriosis also has negative impacts on fertility and is often accompanied by chronic pelvic pain, or dysmenorrhea (Bulletti et al., 2010; Tanbo and Fedorcsak, 2017). Approximately 25-50 percent of women with infertility (Bulletti et al., 2010) and more than 70 percent of women with pelvic pain suffer from this disease (Ozawa et al., 2006). It is therefore no surprise that the economic burden of endometriosis in the United States is estimated at $78–119 billion annually (Ellis et al., 2022).

Several NHP species, including Japanese macaques, pig-tailed macaques, rhesus macaques, and baboons, have been used successfully to model endometriosis (Braundmeier and Fazleabas, 2009; Story and Kennedy, 2004). The baboon is viewed as a particularly useful NHP model for studying endometriosis because of its size and the similarity of its reproductive anatomy to that of humans. The menstrual cycle of baboons and humans is similar in both duration and endometrial function, such as changes to the endometrium in preparation for implantation (Hendrickx, 1971). Additionally, baboons demonstrate similar changes in the eutopic endometrium during uterine receptivity, as well as a similar type of placentation (Hendrickx, 1971). In addition to these parallels, baboons can develop spontaneous endometriosis similar to the human disease, resulting in ectopic lesions that resemble those seen in humans (Folse and Stout, 1978; Harirchian et al., 2012; Merrill, 1968).

Studies using baboon models of induced endometriosis have characterized sequential cellular, immunological, and molecular changes in both the uterus and endometriotic lesions during early disease progression, and have provided insight into how the disease contributes to infertility and lesion development (Braundmeier and Fazleabas, 2009; Fazleabas, 2011; Hastings and Fazleabas, 2006). The baboon model has proven useful as well for evaluating the efficacy of novel drug therapies for suppressing lesion development (Stouffer and Woodruff, 2017). Recent studies have evaluated the use of nanoparticle-targeted therapies to eliminate lesions in mice transplanted with endometriotic macaque tissue (Moses et al., 2021; Park et al., 2022). The application of NHP models for evaluating novel therapies for endometriosis is critically important given the current lack of a standard curative treatment for the disease (OASH, 2021) and mixed outcomes seen with the treatment that is provided (Donnez et al., 2003; Lessey, 2000).

period (Silk et al., 1993), and they typically bear a single offspring (Chapman et al., 1990), limiting their use as models for fertility testing. Common marmosets may be an exception, as this species has a higher rate of conception compared with other NHP species (Nubbemeyer et al., 1997), but their translational relevance for reproductive health research is not fully established. Likewise, the use of rhesus macaques in certain aspects of reproductive and developmental research is limited by seasonal variations in reproduction (i.e., fertility limited to 4–5 months per year) (Cauvin et al., 2015).

Contributions of NHP Models to Research in Immunobiology and Host–Pathogen Interaction

The immune system is a large network of cells, organs, antibodies, and chemical messengers that protect the body from such diverse pathogens as bacteria, viruses, parasites, and fungi that cause infection, as well as from cancer cells and foreign material. The immune system can be broadly divided into two categories—innate and adaptive—with the main distinguishing characteristic being how a pathogen is recognized (Vivier and Malissen, 2005). Unlike the innate immune system, whose response does not depend on recognition of specific pathogens, adaptive immunity relies on the development of immune memory that is expressed in the function and frequency of cells that respond to the same or a similar pathogen (Vivier and Malissen, 2005). Immune dysfunction can cause autoimmune disease or cancer or trigger inflammatory disease, and immune cross-regulation with other systems in the body influences many other disease outcomes (e.g., cardiac, metabolic, pulmonary, and neurodegenerative diseases).

Studies of the human immune system are performed primarily using peripheral blood rather than samples from lymph nodes or spleen that drive the immune response (Farber et al., 2014; Park and Kupper, 2015) because of the difficulty and sometimes impossibility of accessing and collecting sufficient tissue to fully characterize the human immune response. As a result, many key advances in immunology have relied on rodent models, whose tissues can be better characterized than those of humans during the development of the immune system and its response to stimuli under controlled conditions. However, the translation of immunologic principles from rodent models to humans has been notoriously difficult (Meyer er al., 2012). Despite considerable similarities between the rodent and human immune systems, there are significant physiological and genetic differences, such as animal size, lifespan, and aging, all of which affect immune function (Mestas and Hughes, 2004; Meyer et al., 2012; Tarantal et al., 2022) and thus are important variables to consider when selecting an appropriate model at each stage of research (Godec et al., 2016; Mestas and Hughes, 2004; Payne and Crooks, 2007; Rivera and Tessarollo, 2008; Seok et al., 2013; Takao and Miyakawa, 2015; von Herrath and Nepom, 2005). Beyond differences in genetics, lifespan, and species–pathogen relationships, environmental factors profoundly influence the immune profile and function in mammals. For example, very "clean" laboratory mice raised under specific pathogen-free conditions do not share the robust, pathogen-educated immune system that is present in NHPs and humans (Masopust et al., 2017). This difference can result in a less stringent immune response, which may result in an over- or underestimation of the therapeutic effects of interventions modeled in mice.

In contrast, the similarities between the innate and adaptive immune systems of NHPs and humans make NHP models advantageous for unraveling the fundamental aspects of immunology, including immune dominance, T cell memory, immune tolerance, and the aging immune system. NHP models have therefore been essential in bridging the gaps in

understanding of how findings in mice might generalize in an immune system with human-like complexity (Hérodin et al., 2005; Messaoudi et al., 2011).

As with all models, understanding the limitations of NHP models is important to guide appropriate model selection and use. For example, many important pathogens have species-specific idiosyncrasies. Viruses, for instance, are exquisitely tailored to their host species. Consequently, viruses that replicate in humans may not replicate in nonprimates or even some NHP species, and when they do, they may not cause human-like disease. Since NHPs are the animals genetically closest to humans, disease progression and host–pathogen responses to viral infections in NHPs are often the most similar to those of humans. Even among NHP species, however, there can be heterogenous responses to infection that must be considered to apply the model appropriately. Understanding the factors influencing host specificity can influence intervention strategies, a notable example being HIV. The discovery of factors that protected NHP species that were natural hosts for the simian immunodeficiency virus (SIV) from disease informed successful antiretroviral treatments for HIV (see Box 2-3).

The utility of NHP models for understanding infectious disease extends beyond viral pathogens to such bacterial and parasitic infections as tuberculosis (Foreman et al., 2017) and malaria, both of which are leading threats to public health (Bourzac, 2014). With an estimated 247 million cases of malaria globally and more than 600,000 deaths from the disease in 2021 (WHO, 2022b), there remains an urgent need to understand the pathogenesis of this parasite. NHPs have a rich history of advancing malaria research to deepen understanding of the overwhelmingly complex host–parasite interactions and chronic infections, relapses, anemia, and immune memory associated with this disease (Galinski, 2022). Systems-based longitudinal studies can be performed in NHPs over the entire course of the disease (i.e., pre- to postinfection scenarios) and in reinfection or coinfection. New techniques using NHP models can be used to characterize immune cell types, niches, and memory recall responses in each of the malaria infection stages. Further progress has been achieved through the integration of multiomic data to address gaps in understanding of the multitude of host–parasite interactions and biological pathways seen with these parasites (Galinski, 2022).

Contributions of NHP Models to Vaccine Development

Vaccines are among the most successful public health interventions in history. NHPs have been used for almost a century in developing vaccines for diseases posing a major public health threat, from polio and measles in the 1950s to COVID-19 today. This section describes the historical and current uses of NHPs for vaccine development, beginning with polio—a historical case in which no alternative model was available at the height of the disease—to the more recent use of NHPs to develop groundbreaking mRNA vaccine technology, which was used in developing multiple vaccines in response to the COVID-19 pandemic. Acknowledging that it is primarily the pharmaceutical industry that is responsible for bringing vaccines to market, it is important to note that research enabling vaccine approval relies and builds on earlier NIH-funded basic and translational research.

Poliomyelitis (commonly referred to as polio) is an ancient disease caused by a highly infectious virus that attacks the nervous system and spreads easily through communities. Before the polio vaccine was developed, the virus infected millions of people, primarily children, around the world (WHO, 2022a). In the early 1950s, it resulted in more than 16,000 paralytic polio cases annually in the United States, and many others worldwide (CDC, 1999). Among those who develop paralysis, 5–10 percent die as a result of the immobilization of their breathing muscles (WHO, 2022c). Today there is still no cure, but the disease has been controlled by

BOX 2-3 CASE STUDY: GROUNDBREAKING ADVANCES IN HIV TREATMENT AND THE ONGOING PURSUIT OF AN EFFECTIVE VACCINE

Globally, 38 million people are living with human immunodeficiency virus (HIV) (CDC, 2022a), an infection that once was considered a death sentence but is now manageable with combination antiretroviral treatments. HIV's path from incurable to what many consider a chronic disease benefited greatly from the study of nonhuman primates (NHPs), in large part because HIV is a direct descendent of a virus that naturally infects chimpanzees (Hatziioannou and Evans, 2012).

In the early 1980s, as cases of an unknown disease affecting the human immune system increased rapidly across the United States, scientists scrambled to identify the cause. Two separate research groups isolated the virus believed to be the cause of the disease, which was named acquired immunodeficiency syndrome (AIDS) by the Centers for Disease Control and Prevention (HIV.gov, 2023). Around the same time that this virus was identified as HIV, researchers recognized a similar disease in captive rhesus macaques (Daniel et al., 1985). Significantly, scientists discovered that when simian immunodeficiency virus (SIV) infected NHP species that were not the virus's natural host, it resulted in CD4 T cell depletion, opportunistic infection, and AIDS-like disease that closely resembles human HIV infection (Chahroudi et al., 2012; Estes et al., 2018; Van Rompay, 2017; Veazey and Lackner, 2017). These similarities positioned NHPs as an important, clinically relevant model for the study of HIV.

In the decades since HIV's discovery, NHPs have been used extensively to understand its origin and pathogenesis and to evaluate prevention and treatment strategies that have changed the trajectory of this global epidemic (Veazey and Lackner, 2017). Because NHP models allow researchers to control variables and collect samples longitudinally, from the point of infection to the development of progressive disease, studies of NHPs have provided a deeper understanding of many host–viral interactions and factors contributing to pathogenesis (Van Rompay, 2017). For example, the discovery that HIV does not replicate in most NHPs led to the identification of several host restriction factors that are now used as drug targets and prevention strategies in humans (Veazey and Lackner, 2017). Notably, the antiviral tenofovir, which has served as a foundation for the potent combination antiviral regimens now widely used in the management of HIV, was first tested and shown to be efficacious in SIV-infected macaques (Veazey and Lackner, 2017). An equally important outcome from NHP models is the development of a better understanding of how antivirals can be used to both treat and prevent infection. NHPs have been used to study the administration of long-term antiretroviral therapy (ART) to reduce viral loads in the blood to undetectable amounts. This research has yielded the development of preexposure prophylaxis strategies, as well as strategies for early ART treatment to prevent infection, resulting in effective postexposure prophylaxis regimens (García-Lerma and Heneine, 2012; Irvine et al., 2015).

NHP models have been invaluable in advancing understanding of HIV/AIDS, and in particular, the development of treatments allowing people to live with HIV (Terrade et al., 2021; Veazey and Lackner, 2017). Still, effective strategies for curing HIV by eliminating latent reservoirs that harbor nonreplicating virus remain to be elucidated (Busman-Sahay et al., 2021). The development of an HIV/AIDS vaccine has proven to be one of the most challenging goals for modern translational medicine. While HIV vaccine candidates evaluated in NHPs have demonstrated varying levels of efficacy (Van Rompay, 2017), knowledge from these studies has contributed to the development of more complex vaccines designed to induce antibodies, cell-mediated immune responses, or a combination of the two (Leggat et al., 2022).

Thus, both the successes and failures in the development of preventive and therapeutic strategies for HIV have yielded important knowledge critical in guiding future studies. Importantly, the body of knowledge resulting from HIV vaccine research in NHPs has cross-pollinated research leading to the development of tools and platforms for success in other diseases (Veazey and Lackner, 2017).

an effective preventive vaccine, whose creation relied on decades of research using NHPs (see Box 2-4). As a result of widespread vaccination campaigns, polio has been nearly eradicated.

Around the same time that the polio vaccine was being developed, NHPs were also being used to study measles. Measles virus is one of the most contagious human pathogens, spread by airborne transmission and responsible for frequent outbreaks with high morbidity and mortality (Morens, 2015; Morens and Taubenberger, 2015; Rota et al., 2016). NHPs were the model of choice for studying measles, as small-animal models are generally not susceptible to infection or do not develop the complex disease pathology seen in primates (de Swart, 2017). Measles virus serially cultured in vitro was studied in NHPs, thus forming the basis for successful live-attenuated measles virus vaccines in the 1960s (de Swart, 2017). While cases continue to occur in unvaccinated individuals, the long incubation period of the measles virus makes it difficult to study early disease pathogenesis. Basic aspects of virus tropism and replication can be studied in cell lines, primary cells, organoids, or tissue culture. However, experimental infection of NHPs with labeled measles virus has made it possible to determine accurately how the virus enters the body, causes disease to develop, and disseminates, as well as the resulting changes in the immune system, which involve many organs and cell types (de Swart, 2009). The findings from research using NHP models have been used to optimize the existing measles vaccine, offer promising new modes of vaccine delivery, and provide a platform on which other vaccines can be developed (de Swart, 2017).

Recent decades have seen waves of severe viral infectious disease epidemics and pandemics, including influenza, severe acute respiratory syndrome, Middle East respiratory syndrome, Ebola and Zika virus disease, and COVID-19, each of which has had devastating impacts on lives and livelihoods around the globe (Baker et al., 2022). Changes in the transmission, infectivity, and pathogenicity of infectious agents continue to generate high demand for ongoing research and the discovery of new therapies. In many cases, there are no validated correlates of protection against these pathogens, necessitating challenge studies for assessment of the efficacy of new vaccines (Klasse and Moore, 2022; Meyer et al., 2021; Triplett et al., 2022). Ethical and safety concerns prohibit human challenge studies with virulent pathogens that are incompletely understood and have no cure or limited treatment options, as in the case of Ebola virus. In such cases, NHP models play an essential role in the conduct of challenge studies.

Vaccine development for pathogens that cannot undergo human challenge studies can be performed in animals under the Food and Drug Administration's (FDA's) Animal Rule regulatory pathway. The Animal Rule states that when human efficacy studies are not ethical and field trials are not feasible for drugs being developed to ameliorate or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic substances, the FDA may grant marketing approval for such drugs based on adequate and well-controlled animal efficacy studies if the results of those studies establish that a drug is reasonably likely to produce clinical benefit in humans (FDA, 2022).

A major breakthrough has been the success of a vaccine for Ebola virus in humans, whose protection was predicted using NHP models (Geisbert, 2017). Ebola causes acute hemorrhagic fever that is fatal in up to 90 percent of cases. While rodent models have been used to develop and test Ebola vaccines, candidates found to be efficacious in these models were not found to be protective when subsequently tested in NHPs. These failures may be due to differences across the animal models (Geisbert et al., 2002), and suggests that protection may require targeting of different mechanisms (Davis et al., 1997; Geisbert et al., 2002; Jaax et al., 1996). NHPs are susceptible to infection and disease caused by the wild-type Ebola virus, with disease pathogenesis—including clinical presentation, chemistry, and hematology values, and ultimately mortality—closely aligning with that in humans (Geisbert et al., 2002; St Claire et al., 2017). Consequently, NHP models are valuable for evaluation of

BOX 2-4 CASE STUDY: THE CRITICAL ROLE OF NHPs IN THE WAR AGAINST POLIO

Throughout the 20th century, polio plagued the United States and developed nations in Europe, becoming increasingly prevalent in the United States by the mid-1900s. At its peak in 1952, 57,000 cases were reported, more than a third of which resulted in paralysis (Breaking the back of polio, 2005). Children were especially at risk, with many being permanently paralyzed and some dying from complications. Thus, the introduction of Jonas Salk's injectable vaccine using inactivated virus in 1955 and the subsequent introduction of Albert Sabin's oral, attenuated live-virus vaccine in 1961 were hailed as remarkable medical breakthroughs (WHO, 2022a).

Polio research using NHP models began decades before the discoveries of Drs. Salk and Sabin, establishing basic, foundational facts about the disease, including its potential to be spread by asymptomatic carriers; the discovery that the virus has three major immunologically distinct strains, all of which can cause irreversible paralysis or even death (Gardner and Luciw, 2008); and the understanding that initial infection occurs in lymphoid tissue of the gastrointestinal tract and that viremia is essential to central nervous system infection (Nathanson, 2005). It is worth noting, however, that some polio research led to erroneous conceptions regarding the mechanism of infection in humans, contributing to unproductive lines of scientific inquiry (Suri, 2022). While Dr. Sabin himself acknowledged the delay resulting from these studies, he was emphatic that studies using nonhuman primates (NHPs) "were necessary to solve many problems before an oral polio-virus vaccine could become a reality," as he wrote in a 1992 letter to the *Winston-Salem Journal* (Speaking of Research, 2011).

Experiments using NHPs were essential in the characterization of polioviruses and the immune responses to infection. Primate research helped determine that antibodies formed endogenously could neutralize the poliovirus, but antibodies against one strain of the virus did not protect against the other strains. The research showed as well that serial passage in tissue culture could weaken the virus, enabling live, attenuated virus to be used as a vaccine (Algorri, 2019; Speaking of Research, 2011).

NHPs also were vital in the final stages of development and testing of polio vaccine, although scientific advances have allowed researchers to reduce reliance on NHPs for vaccine production over time (Gardner and Luciw, 2008). For example, the only option for screening each new batch of the live, attenuated virus used in oral vaccines to ensure that the virus had not reverted to a pathogenic form was the monkey neurovirulence test, which involved administration of vaccine to macaques as a safety screen. More recently, transgenic mouse models and molecular assays have been approved as alternative models for screening for neurovirulence (Fulton and Bailey, 2021; Rubin, 2011). Likewise, advances in cell culture technology in the 20th century enabled the production of virus for the vaccine in continuous cell lines as an alternative to the use of living NHPs or primary monkey kidney cells, thus also enabling production of the vaccine at industrial scale and reducing risks from simian virus contaminants, such as SV40 (van Wezel et al., 1984).

In the first 2 years after the oral polio vaccine was introduced, it is estimated to have prevented nearly 500,000 deaths and 5 million cases of polio globally (Speaking of Research, 2011). The disease was eradicated from North and South America by 1994, and global vaccine programs have been so successful that more than 16 million people worldwide have been saved from paralysis since 1988 (WHO, 2017). Naturally occurring, or wild, poliovirus is now found in only a few countries. Even today, however, there is no treatment for the disease, and it can be carried around the world by travelers from countries where polio continues to circulate. As recently as September 2022, New York State declared a state disaster emergency following the dual indicators of polio infection in an unvaccinated resident (Hochul, 2022) and the discovery of poliovirus in wastewater samples from the New York metropolitan area (Link-Gelles et al., 2022).

Although scientific progress has yielded alternatives to the ongoing use of NHPs to screen and produce polio vaccines, the fact remains that NHPs played a role in one of the greatest public health accomplishments of the 20th century. While largely forgotten in the United States, the threat of reemerging polio serves as a stark reminder of the critical importance of NHP research in the development of effective public health interventions.

Ebola vaccine candidates and drug therapies, as they are considered to have high predictive value (Roozendaal et al., 2020).

To support regulatory submissions and the subsequent licensure of Ebola vaccines, a meta-analysis of NHP control data from multiple Ebola challenge studies was conducted by government sponsors of the studies. This meta-analysis and the supporting dataset were submitted to the FDA as a master file in lieu of the natural history studies from each testing facility (Taylor et al., 2022). This example of a successful strategy for vaccine development has both important scientific and animal welfare implications. First, the data from the meta-analysis can be leveraged to demonstrate the consistency of results obtained by using a standardized animal model for vaccine development instead of conducting separate natural history studies at multiple testing facilities, which allows for more timely vaccine development during a public health emergency. Second, this achievement serves as an important example of reducing the use of NHPs, a strategy that could be applied to other pathogens and that demonstrates the value of partnerships among different groups using NHP models.

The most recent example of the importance of NHPs for vaccine development is COVID-19 (see Box 2-5). Each lead COVID-19 vaccine candidate that progressed to approval for use in humans in the United States was evaluated in NHPs simultaneously with corresponding clinical trials (Jackson et al., 2020; Keech et al., 2020; Sadoff et al., 2021; Walsh et al., 2020). These nonclinical studies using NHPs were used to demonstrate the safety and efficacy of the vaccines (Corbett et al., 2020; Mercado et al., 2020; Tian et al., 2021; Vogel et al., 2021), supporting the FDA's decision to approve Emergency Use Authorization requests.

Contributions of NHP Models to the Development of Therapeutics

The treatment of human disease has historically been dominated by small-molecule drugs. In the last 30 years, however, biologics have become important new therapies. Instead of chemical synthesis, biologic processes are used to create or derive a wide variety of medicinal products, such as blood or blood components, cells, or tissues; gene therapies; and recombinant therapeutic proteins. NHPs have played a pivotal role in the development of biologics used to treat cancer, autoimmune diseases, and heart disease, as well as to protect against infectious disease and prevent organ rejection after transplant (Geisbert et al., 2002; Lu et al., 2020).[3] The importance of NHPs in the development of biologics stems in part from the fact that many such therapeutics are designed to engage their human targets with high specificity and may be effective only in other primates. A classic example is the protease-activated receptors (PARs) that mediate platelet activation in response to thrombin (Hamilton and Trejo, 2017). In mice, PAR-3 and PAR-4, but not PAR-1, reside on platelets. In contrast, primate platelets possess only PAR-1 and PAR-4. As a result, antithrombotic drugs initially developed in mice missed their intended target in humans, highlighting the need for studies in NHPs to validate antithrombotic therapies (Hamilton and Trejo, 2017).

Therapeutic antibodies lead the biologics category of drug development. Remarkably, in just 25 years, monoclonal antibodies (mAbs) have become the dominant treatment for a range of diseases (Grilo and Mantalaris, 2019; Lu et al., 2020). Behind their development is more than 50 years of foundational research combining what was learned from cells in culture, rodents, and NHPs. mAbs are engineered in the laboratory to mimic antibodies, or protective proteins, that the body produces naturally as part of an immune response. In silico and in vitro studies, as well as data from knockout/knockin rodents, can be used to predict

[3] The examples in this section highlight the contributions of these therapeutics brought to market by industry, but often were built upon earlier NIH-funded basic and translational research.

BOX 2-5 CASE STUDY: ACCELERATING VACCINE DEVELOPMENT DURING THE GLOBAL COVID-19 PANDEMIC

The SARS-CoV-2 virus emerged in December 2019 in China's Wuhan Province and quickly evolved into a pandemic of historic proportions (Yang et al., 2020). This novel coronavirus caused a new disease, COVID-19, to which humans had no immunity. Given an early case fatality rate of 5 percent in Wuhan (Yang et al., 2020) and up to 14 percent in other countries (Mathieu et al., 2020), the rapid development of a vaccine and/or treatment became critical. By December 2020, roughly a year after the virus had been discovered, the U.S. Food and Drug Administration had approved two vaccines for emergency use (Fortner and Schumacher, 2021)—an extraordinary pace of development and approval accelerated by use of NHP models (Corbett et al., 2020; Vogel et al., 2021).

Prior to the COVID-19 pandemic, extensive work had been conducted on coronaviruses and messenger RNA (mRNA) vaccine technology. Researchers were able to build upon this knowledge to expedite the groundbreaking strategy of mRNA-based COVID-19 vaccine candidates. Researchers had already proven successful mRNA vaccine delivery (Lindsay et al., 2019) and tested mRNA vaccines against influenza (Bahl et al., 2017) and Zika (Pardi et al., 2017) in nonhuman primates (NHPs). Research on other coronaviruses, such as the virus that causes Middle East respiratory syndrome (MERS), using NHPs demonstrated that targeting different antigenic sites on the spike protein of MERS-CoV could aid antigen design for future vaccine development (Wang et al., 2018b).

The COVID-19 pandemic spurred an international effort to identify and develop models for understanding the pathogenesis of and developing vaccines and therapies for SARS-CoV-2 (Muñoz-Fontela et al., 2020). In March 2020, the International Coalition of Medicines Regulatory Authorities, with representatives from over 20 medical regulatory bodies and experts from the World Health Organization and the European Commission, agreed, among other positions, that animal models would be necessary for evaluating the immune response to vaccine candidates (ICMRA, 2020).

Early in the pandemic, scientists found that macaques recapitulated disease consistent with human infection—a mild to moderate self-limiting respiratory disease (Albrecht et al., 2021). Notable characteristics were high virus loads in the upper and lower respiratory tracts and acute viral interstitial pneumonia, among other similarities in host responses (Hu et al., 2021). Within weeks of being defined, an NHP model for COVID-19 was used to evaluate the safety and efficacy of several vaccines and therapies. This work led to key discoveries: that mRNA vaccines expressing spike proteins and monoclonal antibodies targeting those proteins could prevent lung damage associated with SARS-CoV-2 infection (Corbett et al., 2021; Loo et al., 2022). In September 2020, pharmaceutical companies Pfizer and BioNTech announced that their vaccine protected rhesus macaques against severe COVID-19 disease (Pfizer, 2020). The macaque model also showed that although deep lung replication was controlled with the vaccine (Vogel et al., 2021), virus replication in the upper respiratory tract was not eliminated. This observation correlates well with the finding that vaccinated humans are protected from severe COVID-19 but still shed virus from the upper respiratory tract (Singanayagam et al., 2022).

Equally important, NHP models showed that antibody titers generated by vaccines could be correlated with protection against severe disease in a macaque model, with lower antibody titers being sufficient for viral control in the lower respiratory tract, while a more robust response was needed to reduce viral replication in upper airways and transmission (Corbett et al., 2021; McMahan et al., 2021). Furthermore, these studies found that cell-mediated immunity played a role in disease control in the absence of a potent immune response (McMahan et al., 2021).

As of August 2022, just 2.5 years after the introduction of a novel virus and disease, four different vaccines were available in the United States to protect against COVID-19 (HHS, n.d.). These vaccines have greatly reduced severe disease in vaccinated individuals and have had a profound global impact, thanks in part to the use of NHPs. In the first year alone following authorization of the first COVID-19 vaccine, immunizations prevented more than 19 million deaths worldwide, thus altering the course of the pandemic (Watson et al., 2022).

adverse events with mAbs. These models can limit the use of NHPs in routine safety and efficacy studies for standard immunoglobulin G–based mAbs. However, the use of rodent models does not easily extend to development that involves novel targets, mechanisms of action, or mAb scaffold and structures, which is where much of the pharmacology is unknown and unpredictable (Brennan et al., 2018). NHP and human antibodies are so similar that they often cross-react (Bjornson-Hooper et al., 2022), so the exact human drugs and assays under evaluation can be used directly with NHPs. NHPs are often the only relevant model for mAb testing because of the high species specificity of most immune receptors targeted by mAbs (Chapman et al., 2009). Therefore, this application of NHP modeling also demonstrates the need for careful understanding of species-related differences if the data derived from the modeling are to be properly interpreted.

NHPs have meaningfully informed mAb development and have predicted the efficacy, safety, and limitations of numerous new therapeutic strategies. Such NHP research has resulted in cancer-targeted mAbs—including Herceptin to treat HER2-positive breast cancer (Lewis Phillips et al., 2022) and rituximab for non-Hodgkin's lymphoma (Maloney et al., 1994; Pierpont et al., 2018)—that have fundamentally improved cancer therapy to dramatically improve quality of life and survival in circumstances previously considered untreatable or terminal (Zahavi and Weiner, 2020). Anti-inflammatory mAbs have revolutionized treatment for immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, ulcerative colitis, and other inflammatory disorders (Lisa et al., 2017; Tanaka et al., 2014; Voge and Alvarez, 2019), and more recently have proven to be some of the most effective COVID-19 treatments (Marovich et al., 2020; Taylor et al., 2021).

Blood products have become such a mainstay of clinical medicine that someone in the United States needs blood or platelets every 2 seconds (American Red Cross, 2023). These products are used to treat patients with life-threatening inherited disorders such as hemophilia or immune deficiency and acquired conditions such as cancer or trauma, to support complex surgical procedures, and to address maternal health. In 1940, the Rh blood group system was identified—named after the rhesus monkey blood cells used in making the discovery—and was recognized as the cause of dangerous transfusion reactions to blood products and incompatibility between mother and fetus, a condition that can cause fertility issues, fetal death, and hemolytic disease of the newborn (HDN) (Treichel, 1987). By examining NHP species such as rhesus macaques, which are one of four NHP species that do not develop HDN, researchers discovered that newborn red cells survive because of differences in the level and binding ability of maternal antibodies (Treichel, 1987). Based on this observation, anti-Rh immunoglobulin (rhoGAM) was developed. It is used to stop the generation of antibodies that attack Rh-positive cells (Kedrion Biopharma, 2023), which mirrors the natural protective mechanism in NHP species that do not develop HDN. As a result, this disease, which once killed 10,000 newborns a year and caused brain damage, has now been nearly eradicated (Neighbor, 2018).

Considering the value of NHPs in transfusion medicine, it is no surprise that they also have a place of prime importance in cell and tissue transplantation (Fitch et al., 2019; Kirk, 1999, 2003). More than 40,000 organ and tissue transplants (grafts) are performed each year in the United States as treatment for most end-stage organ diseases (OPTN, 2022). Graft and patient outcomes have steadily improved over the decades because of improved understanding of donor and recipient factors that affect transplant outcomes and the ability to manipulate the immune system more effectively. The major determinant of acceptance or rejection is the magnitude of the response to the graft by the host's immune system. Chronic immunosuppression strategies are used in patients to prevent graft rejection, and the development of increasingly potent immunosuppressive agents has been a major factor in longer graft survival. Safety and

efficacy evaluations of certain immunosuppressive agents, such as humanized mAbs, can be performed only in NHP models in which antibodies cross-react between primates (see Box 2-6).

BOX 2-6 CASE STUDY: THE DEVELOPMENT OF BREAKTHROUGH BIOLOGICS FOR ORGAN TRANSPLANTATION

The ability of modern science to replace a damaged human organ improves and in many cases, extends lives. Approximately 106,000 people in the United States today are on waitlists for organ transplantation (HRSA, 2022). The first human organ to be transplanted successfully was a kidney in 1954, and various organ transplantations, or grafts, followed. In September 2022, the United States reached the milestone of 1 million organ transplants (UNOS, 2023). This achievement was possible only through the use of nonhuman primates (NHPs) to evaluate new therapies for preventing rejection and prolonging allograft survival, therapies that have translated successfully into the management of human organ transplant patients.

Antibodies are proteins produced by the immune system that attach to substances recognized as foreign to help neutralize or eliminate the perceived threat they pose. Therapeutic antibodies can be engineered to regulate the body's immune response or directed against a particular pathogen. Production of this biologic is carried out in laboratory cultures either by using clones of several different immune cells (for polyclonal antibodies) or by using identical cells (for monoclonal antibodies [mAbs]). These therapeutic antibodies have been used to target cancer cells and improve treatment for such immune-mediated diseases as rheumatoid arthritis, psoriasis, and Crohn's disease (Ritchlin and Krueger, 2016; Tamilarasan et al., 2019; Tanaka et al., 2014; Zahavi and Weiner, 2020). They are capable of suppressing the body's natural immune response to reject a "foreign" organ in transplant patients and thus dramatically improve organ survival and function (Sablinski et al., 1991; Yetmar et al., 2021).

Because the immune system of NHPs is more like the human immune system compared with any other animal model, NHPs have been highly accurate in representing the physiology of the transplant patient (Dehoux and Gianello, 2007). They are often the only animal model used to inform disease treatments that rely on a molecule that is produced exclusively by primates and would be destroyed by the immune system of other species. For this reason, NHPs have played critical roles in the safety and efficacy testing of most approved mAbs (Brennan et al., 2018). Many promising immunomodulating therapies in rodent transplant models do not translate successfully to NHPs or humans (Cosimi, 1999; Knechtle et al., 2019). Such mAbs as LFA-1 blockade, sphingosine-1-phosphate agonists/antagonists, and IL-15 blockade were successful in mice but failed in a more rigorous NHP model (Fitch et al., 2019), and futile or potentially harmful human testing was thereby avoided. The fully educated immune system of the NHP has therefore been indispensable for bridging from promising studies in rodents to humans (Cosimi, 1999). For example, CTLA4-Ig mAb, which is used to treat rheumatoid arthritis, was highly effective in preventing graft rejection in mice but not NHPs (Crepeau and Ford, 2017). The NHP model was used to optimize a high-affinity CTLA4-Ig mAb, resulting in the successful clinical translation of the more potent belatacept for preventing transplant rejection. Favorable results in NHPs are the major driver of clinically successful transplant regimens with mAbs, including antilymphocyte antigen CD52, IL-6R, blockade TNF-inhibition, and anti-CD40/CD154 (Knechtle et al., 2019).

Continued improvements in NHP models, along with other scientific and technological advances, including imaging, cell tracking, and single-cell analytics, hold great promise for enhancing understanding of immune response and biological therapeutics so that more can be learned using fewer animal studies in the future. In vitro immunoassays are reducing reliance on NHPs for toxicity testing of mAbs, as discussed further in Chapter 4. However, given that in vitro studies with human cells have failed to predict the response to mAbs in a whole-animal system (Brennan et al., 2018), the application of in vitro technologies for safety assessment of these therapeutics will likely need to be case dependent, and NHPs will continue to play a critical role in the development of mAbs for organ transplantation in the near term.

Likewise, NHP studies can combine existing drugs used in clinical transplantation in novel ways alongside cutting-edge reagents and strategies to show proof of concept before clinical trials are initiated in human patients (Anderson and Kirk, 2013; McDaid et al., 2015). In transplant recipients, lifelong immunosuppression comes with an increased likelihood of cancer, infection, and premature death (Claeys and Vermeire, 2019), so the goal in transplantation research continues to be minimizing or eliminating immunosuppression. Strategies to this end involve inducing immune tolerance by conditioning the immune system to be unresponsive to specific antigens (Alpdogan and van den Brink, 2012). In transplantation, this means that the immune system does not respond to the transplanted tissue even as it maintains important responses against infection or malignancies. Studies in NHPs are considered a scientific and ethical requirement before any such tolerance-inducing strategies are tested in humans (Knechtle et al., 2019), given the enormous consequences of graft loss in a patient after complete withdrawal of immunosuppression that might otherwise be successful under the standard of care. NHP models cannot fully recapitulate the human condition. Nonetheless, the similarity of NHPs to humans in environmental exposures, size, effects of drugs, and long lifespan makes them the most stringent, informative, and predictive nonclinical model for transplantation (Kirk, 2003), as is demonstrated by new immunosuppressive drugs and regimens that have been successfully translated from NHPs to the clinic, including alemtuzumab, belatacept, and regimens promoting immune tolerance (Fitch et al., 2019; Knechtle et al., 2019).

Even with these important advances, the shortage of organ donors leaves more than 100,000 patients on the waiting list annually, and many die from their condition before receiving a donor organ (HRSA, 2022). To address this critical organ shortage, grafts derived from domesticated animals—specifically pigs (i.e., xenografts)—are a novel source of replacements for failed organs. Pig-to-NHP xenograft modeling has allowed researchers to gain a deeper understanding of the key biological differences between pigs and primates that affect graft rejection, and to identify targets for gene editing as a strategy for intervention (Lu et al., 2019; Niu et al., 2021; Sykes and Sachs, 2022). This same model has also demonstrated that conventional immunosuppression is insufficient in the xenograft context, and that an alternative immunosuppressive approach (blockade of the CD40-CD154 costimulatory pathway) is a highly effective strategy for preventing rejection of xenograft cells and organs (Coe et al., 2020; Cooper et al., 2021; Graham et al., 2022). While the pig-to-NHP model can inform many aspects of xenograft safety, scientists have extensively characterized the model to determine when it is not informative (Denner and Graham, 2015; Graham and Schuurman, 2013; Wijkstrom et al., 2013). These efforts have shown that while NHPs are an excellent overall model for screening for zoonotic infection risk, this model cannot be used to evaluate the risk around transmission of porcine endogenous retrovirus (PERV) since the PERV receptor in NHPs is not fully functional (Denner, 2018). Nonetheless, decades of research using the pig-to-NHP model has advanced clinical xenotransplantation to a reality (Choi and Han, 2022; Griffith et al., 2022; Längin et al., 2018).

Stem cell therapy is another approach for replacing tissues damaged by disease. Stem cells can adapt and differentiate into different cell types in the body. Similar to conventional transplant modeling, NHP models have been critical in developing and evaluating the therapeutic efficacy of induced pluripotent stem cell–based therapies (Li et al., 2019), most prominently for treatment of myocardial infarction, Parkinson's disease, and type 1 diabetes. Modeling of myocardial infarction in NHPs has been used to evaluate the regenerative capacity of stem cell–derived cardiomyocytes in the heart (Blin et al., 2010; Chong et al., 2014). Parkinson's disease models in NHPs have been used to study the differences between autologous and allogeneic stem cell–derived neural cells, innervation, differentiation profile, and safety and efficacy to support Phase 1 clinical trials (Daadi et al., 2012; Doi et al.,

2012; Emborg et al., 2013a,b; Kefalopoulou et al., 2014; Kriks et al., 2011; Morizane et al., 2013; Takagi et al., 2005). The most advanced stem cell–based strategy is pancreatic islet cell replacement, an effective therapy for patients with type 1 diabetes that is difficult to control (Ricordi and Strom, 2004; Shapiro et al., 2000). The use of cell-derived islets has created an unprecedented opportunity to mass-produce insulin-producing cells and to overcome the challenges of a limited donor supply, which is a main barrier to the widespread use of islet transplantation as a therapy (Verhoeff et al., 2021). The first beta cell transplants to determine whether stem cell therapy can successfully produce insulin in people with type 1 diabetes are currently under way (Markmann et al., 2022; Ramzy et al., 2021; Shapiro et al., 2021). Persistent challenges in optimizing dose, control over immune response, and delivery (Butler and Gale, 2022) will likely require NHP modeling that facilitates longitudinal studies of transplant function and risk.

Gene therapy, another approach to treating human disease, entails replacement of a missing gene, addition of genes to help treat a disease, or deletion or correction of mutations in genes that contribute to a disease. Gene therapy offers the potential to develop treatments for rare genetic diseases, more than 7,000 of which currently affect 30 million Americans (Genetic and Rare Diseases Center, n.d.). Box 2-7 describes how this approach

BOX 2-7 CASE STUDY: USE OF NHP MODELS TO GUIDE A GENE THERAPY APPROACH TO SICKLE CELL DISEASE

Sickle cell disease (SCD) is an inherited blood disorder that impacts approximately 100,000 people in the United States and millions globally (Duncombe, 2020), reducing life expectancy by up to 20 years (CDC, 2022b). The disease is minimally treatable, and for some patients, the only cure is a blood and bone marrow transplant. For this reason, there has been a long-standing need for novel treatments to improve quality of life and preserve the life expectancy of those affected. Nonhuman primate (NHP) models have been invaluable in evaluating gene therapy strategies to address this need.

SCD is caused by the inheritance of two copies of the β-globin (also known as beta globin) gene containing a single nucleotide mutation that results in abnormal hemoglobin, a protein in the blood that carries oxygen throughout the body (NHLBI, 2022). SCD causes red blood cells to have a crescent shape (like a sickle) rather than their typical disc shape, and this sickling results in cells that are less effective in carrying oxygen. The misshapen cells can block circulation and cause extreme pain, anemia, and organ damage (Duncombe, 2020).

For many years, the standard treatment protocol for SCD involved primarily pain management (Duncombe, 2020); it was not until 1998 that the first drug, hydroxyurea, specifically targeting SCD rather than management of its symptoms was approved (Agrawal et al., 2014; Eisenstein, 2021). Hydroxyurea promotes fetal hemoglobin induction and helps reduce red blood cell sickling, but it was initially approved only for adults and has shown variable therapeutic benefit for patients (Bridges et al., 1996; Uchida et al., 2021).

Since the 1980s, bone marrow stem cell transplants using both allogeneic and autologous methods have been explored as potential curative treatments for SCD (Ashorobi and Bhatt, 2022). Allogeneic transplants entail infusing patients with hematopoietic, or blood-producing, stem cells (HSCs) from a matching donor (Duncombe, 2020; Uchida et al., 2021). This procedure has demonstrated efficacy in reversing severe cases of SCD, as shown in a 2014 study in which 26 of 30 participants were successfully treated (Hsieh et al., 2014); however, only about 10 percent of patients can find suitable donors (Duncombe, 2020; Uchida et al., 2019).

Autologous methods, on the other hand, circumvent the challenge of finding matching donors by modifying the patient's own bone marrow cells using gene therapy. Patients are treated with

has led to a treatment for sickle cell disease. NHP modeling has supported multiple gene therapy treatments now approved for human use (Day et al., 2021; Mendell et al., 2021; Weed et al., 2019). It has been especially valuable in understanding factors affecting sustained therapeutic gene expression from adeno-associated virus (AAV) vectors that carry the replacement gene (transgene), including immune responses to the vector and transgene product and the stability of the vector genome (Herzog et al., 2011). Like humans, NHPs are naturally infected with AAV, and so can be used to model how preexisting AAV antibodies affect safety and efficacy in humans with variable antibody expression (Hurlbut et al., 2010). NHPs have also been used to understand outcomes observed in clinical trials, such as the cause of death of a patient in a gene therapy trial. In this case, the treatment of NHPs with high dosages of AAV—similar to those used in the human trial—revealed massive cytokine release related to the protein coat of the vector (Stephenson, 2001). Similarly, an NHP model was used to understand cytokine release syndrome and neurotoxicity associated with chimeric antigen receptor (CAR) T cell immunotherapy in the clinic (Taraseviciute et al., 2018). CAR-T cell–based gene therapy has revolutionized the treatment of leukemia and lymphoma, and enabling the discovery of interventions that could prevent adverse outcomes is key to extending its utility.

drugs that stimulate the circulation of HSCs, and these cells are subsequently harvested and genetically modified to correct the mutation before being transplanted back into the patient, who undergoes chemotherapy to reduce the existing, pathogenic versions of the cells (Duncombe, 2020; Eisenstein, 2021). Research on autologous HSC transplants has been conducted in NHP models (Hayakawa et al., 2009; Uchida et al., 2019). The approach has demonstrated efficacy in clinical trials over the years, with patients experiencing improved sickle cell symptoms and requiring fewer hospital visits (Duncombe, 2020; Eisenstein, 2021).

The genetic similarities between NHPs and humans explain why NHPs are particularly well suited to research on the safety and efficacy of gene therapies. NHP models are useful for studying the treatment of hemoglobinopathies such as SCD for several reasons. Because NHP HSCs express cell surface markers that are homologous to those of humans, many of the reagents used in the clinical setting, such as recombinant growth factors and antibodies, are cross-reactive with NHPs. In addition, NHPs and human patients require the collection and transplant of similar numbers of cells and have comparable hematopoietic demand. Finally, it is possible to follow the differentiation of transplanted HSCs into hemoglobin-producing red blood cells in NHPs (Humbert et al., 2018).

Researchers have established mouse transplantation models for gene therapy designed to treat SCD, but the mice must be severely immunodeficient for transplanted human cells to be engrafted (Uchida et al., 2021). This may explain why previous studies have overestimated the engraftment of genetically modified human cells in mice compared with NHP transplantation models (Uchida et al., 2021). Given these limitations in the predictive value of xenograft mouse transplantation for human cell engraftment, translational research using NHPs can offer meaningful insights that can advance these gene therapy approaches (Uchida et al., 2021).

SCD is a lifelong illness that reduces quality of life for thousands of Americans and for which a cure remains elusive. As gene therapies mature, however, researchers remain hopeful that scientific study will yield breakthrough treatments and perhaps a cure. NHP models will have an essential role in ensuring that any approaches are both safe and effective for humans.

CONCLUSIONS

This chapter has examined the vital role of NHPs in biomedical research designed to enhance understanding of the human body and the progression of disease, discover new targets for disease prevention and treatment, and maximize the safety and efficacy of novel therapeutics. Although NHPs make up a very small fraction of animals used in biomedical research, their critical importance is evident in the number of modern medical advances that have relied on the use of NHP models. Based on this evaluation of the current landscape for NHP research, the committee reached the following conclusions:

Conclusion 2-1: Nonhuman primates have contributed to numerous human health advances that have improved and preserved countless lives, demonstrating a track record of unique predictive relevance critical for supporting ongoing fundamental basic and translational research missions of the National Institutes of Health.

Conclusion 2-2: Nonhuman primate research resources continue to be vital to the nation's ability to respond to public health emergencies, such as the recent COVID-19 pandemic.

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3

Current Landscape of Use and Availability of Nonhuman Primates for NIH-Supported Biomedical Research

The committee was charged with examining the current landscape of use and availability of nonhuman primates (NHPs) for National Institutes of Health (NIH)–supported biomedical research. In carrying out this task, the committee built on the 2018 NIH Office of Research Infrastructure Programs (ORIP) report *Nonhuman Primate Evaluation and Analysis* (ORIP report), which provides a snapshot of research priorities and supply and demand for NHPs in the United States during fiscal years (FY) 2013–2017 (ORIP, 2018a,b). As discussed in Chapter 1, recent events, including the COVID-19 pandemic and a ban on NHP exportation by China, have dramatically altered the landscape of NHP use in biomedical research in the United States (Ackley et al., 2023). In this chapter, the committee describes the current state of NIH-supported NHP research, as well as the impacts of NHP shortages on the nation's ability to meet patient needs for biomedical advances and respond to future public health emergencies. Data presented in this chapter demonstrate the worsening shortage of NHPs available for NIH-supported research, the vulnerabilities of current importation practices, and the need for investment in data and research infrastructure to optimize efficient use and ensure future availability of critical NHP resources in the United States.

OVERVIEW OF NIH-SUPPORTED NHP RESEARCH

This section provides an overview of NIH's role in advancing biomedical research in the United States, a description of the complex landscape for NHP acquisition and use in the context of NIH-supported research, and an overview of stakeholders involved in the supply and use of NHP resources. In accordance with the committee's charge, the emphasis of this review of the NHP research landscape is on NIH and its extramural and intramural research programs; however, other stakeholders are briefly referenced within the context of the broader landscape of suppliers and users of NHP resources.

NIH Support for Biomedical Research Using NHP Models

NIH is the largest public source of funding for biomedical research in the United States, directing significant investments to advance both basic fundamental and translational research (NIH, 2015). Guided by the research priorities identified by the 27 individual NIH institutes and centers (NIH, n.d.), funds are distributed through a variety of established mechanisms, including grants, cooperative agreements, and contracts. Different funding mechanisms provide support for distinct components of the research enterprise, including research projects, operations, construction and physical infrastructure improvements, and workforce training, among others. Table 3-1 provides brief descriptions of the primary funding mechanisms used by NIH institutes, centers, and offices (ICOs), as well as examples of commonly used activity codes.

Most NIH funds for research activities support extramural research programs—that is, research conducted at academic centers and other institutions external to NIH. In FY2021, across its entire research portfolio, NIH awarded more than $24.3 billion in research project grants, which provide direct support for research projects led by extramural principal investigators (NIH, 2023). In addition to extramural research funding, ICOs can direct funds

TABLE 3-1 Overview of Common National Institutes of Health (NIH) Funding Mechanisms

Mechanism	Description	Common Activity Codes*
Research Project Grants	NIH-solicited or investigator-initiated awards for extramural health-related research projects or innovation research based on the mission of NIH	R01, R21, R34, U01, U19
Research Center Grants	Funds for large, multiproject efforts that include a diverse array of research activities	P20, P30, P40, P50, P51
Resource Grants	Grant programs that provide research-related support or access to resources	R24, R45, X01
Training, Fellowship, and Career Grants	Funding programs that provide opportunities for training and career growth	T01, F30, F31, F32, K01, K08, K24, R25, T32, U18, U24, K99/R00
Research and Development Contracts	Contracts between NIH and a contractor that are used to support research in high-priority areas and to further progress toward a research goal	N01
Small Business Program Grants	Awards through the Small Business Innovation Research and Small Business Technology Transfer programs that provide funds to small businesses	R42, R44
Research Construction Programs	Support for construction or major remodeling to create new research facilities	C06
Cooperative Agreements	Funding mechanism that acts as a hybrid of the grant and contract mechanisms, used when substantial involvement of NIH programs or scientific staff is required in an area of high research priority	U42, U01, U18, U24
Intramural Research	Funds supporting internal research programs within NIH institutes, centers, and offices	ZIA, ZIC

*Activity codes can serve multiple functions at the discretion of NIH and may be applied to more than one funding mechanism. Common codes are provided in this column but are not listed exhaustively.
SOURCE: NIH, 2022c.

toward intramural biomedical research conducted at NIH federal laboratories, some of which involves the use of NHPs. The intramural research program makes up approximately 10 percent of the overall NIH budget (NIH, 2022d) and functions to advance NIH's broader research mission.

NIH provides support for NHP research within both its intramural and extramural research programs, as well as support for the production and maintenance of NHP resources. In FY2017, NIH-supported research involving the use of NHP models accounted for approximately 1.5 percent of all NIH awards (ORIP, 2018a). As of this writing, 12 and 19 ICOs, respectively, reported support of intramural and extramural research involving NHP models (NIH, 2022a).[1] Research project grants and research center grants are the primary funding mechanisms used by NIH to support the research infrastructure that provides NHPs for NIH-supported research programs.

Research center awards (e.g., P51, P40) provide funding to the National Primate Research Centers (NPRCs); National Resources with NHP breeding colonies;[2] and some large, multi-project research efforts that enroll NHPs. NHP research resources supported by NIH—specifically, through NPRC and National Resource grants—are funded and managed by ORIP as part of its mission. The majority of the funding for these resources comprises both "base" funding (value of the primary grant) and "supplemental" funding (value of additional funds provided to expand existing awards).[3] Base and supplemental funding provided through the P51 award mechanism—used exclusively for the operation of the seven NPRCs to support personnel, specialized facilities, and breeding colonies—increased by 12 percent between FY2018 and FY2022, while funding for National Resources over the same period through the P40 award mechanism increased by 6 percent (NIH Reporter, 2023b).[4] The 12 percent increase in funding for the NPRCs reflects increases in both base and supplemental funding aimed at addressing concerns raised in the 2018 ORIP report related to insufficient support for the maintenance of existing research infrastructure at NPRCs, as well as Coronavirus Aid, Relief, and Economic Security (CARES) Act funding allocated for the COVID-19 response. CARES Act funds accounted for more than half of P51 supplemental funding distributed between 2020 and 2022 (NIH RePORTER, 2023a). After accounting for inflation,[5] however, the committee found that total award funding for NPRCs (P51 awards) between 2012 and 2022 decreased by more than 23 percent (approximately $20,000,000 total decrease) and inflation-adjusted P40 funding for National Resources over the same time period decreased by

[1] ICOs reporting intramural research activities using NHPs include the National Institute of Neurological Disorders and Stroke (NINDS); the National Institute of Mental Health (NIMH); the National Institute on Deafness and Other Communication Disorders (NIDCD); the National Institute on Drug Abuse (NIDA); the National Institute of Allergy and Infectious Diseases (NIAID); the National Institute on Alcohol Abuse and Alcoholism (NIAAA); the National Institute on Aging (NIA); the National Heart, Lung, and Blood Institute (NHLBI); the National Eye Institute (NEI); the National Cancer Institute (NCI); the National Center for Advancing Translational Sciences (NCATS); and the NIH Clinical Center. ICOs reporting extramural research activities using NHPs include the Office of AIDS Research, NINDS, NIMH, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Dental and Craniofacial Research, NIDCD, NIDA, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Biomedical Imaging and Bioengineering, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAID, NIAAA, NIA, NHLBI, the National Human Genome Research Institute, NEI, NCI, the National Center for Complementary and Integrative Health, and NCATS.

[2] While P40 awards are used to fund National Resources with NHP breeding colonies, other activity codes can be used to support entities that may perform activities similar to those carried out by institutions with P40 National Resource awards (e.g., N01, R24, U42).

[3] Awards other than this base and supplemental funding may also be provided via other mechanisms on a limited basis for research infrastructure (e.g., awards for construction of NHP housing) (NIH RePORTER, 2023a).

[4] The Johns Hopkins University (one of the four National Resources) stopped receiving P40 funding after 2016.

[5] Inflation calculated based on the Consumer Price Index for all urban consumers (BLS, 2023).

8.5 percent (approximately $390,000 total decrease) (BLS, 2023; NIH RePORTER, 2023a,b). For additional details, see the section on physical research infrastructure later in this chapter.

Complexity of the NHP Research Landscape

Describing the supply and use of NHPs in NIH-supported research quantitatively is challenging because of the complexity of the NHP research landscape, inadequacies of data tracking systems, and current limitations of data integration/harmonization.

The broad landscape of NHP research in the United States involves many different stakeholders who are active in both the supply and use of NHPs in biomedical research, which makes it difficult to develop a clear understanding of NHP supply and demand. Understanding the NIH-supported NHP research landscape specifically is further complicated at the stakeholder level by the complexities of contracts and awards from federal and nonfederal funders for the production and use of NHPs. An ICO-owned NHP breeding colony used for intramural research, for example, may be managed by a private contract research organization (CRO) that also conducts contracted research using CRO-owned NHPs held onsite for pharmaceutical companies. This CRO may also supply domestically produced NHPs for the commercial market, which may involve investigators seeking to purchase NHPs for their NIH award. In a different scenario, an academic institution holding an NIH award to support the management of an onsite breeding colony of rhesus macaques may also hold an active contract with a for-profit entity to provide rhesus macaques and marmosets from its institutionally owned colonies. In both of these cases, the organizations will have records of the overall number of NHPs in their care, which are reported to the U.S. Department of Agriculture (USDA) annually, but the numbers and species used specifically for NIH research cannot be determined with certainty.

Related challenges to describing the NHP research landscape include the lack of a common database or tracking system providing quantitative data on the supply and use of NHPs specifically for extramural and intramural NIH research. While some existing data sources can help in contextualizing the overall scope of the NHP research landscape, these sources are insufficient for assessing NHP supply and use at the level of NIH support. Data from USDA, for example, provide exact numbers of NHPs held and used for research purposes[6] at individual research facilities (see Appendix B for these USDA data for FY2021). However, these data include no additional information about the origin of these NHPs, whether they came from an NIH-supported breeding site, or whether they were ultimately used in NIH-supported research (see Appendix A for a description of data limitations associated with USDA annual report data).

NIH RePORTER, the publicly accessible repository of NIH-funded projects, also cannot be used to obtain an accurate representation of the NIH-supported NHP research landscape because it is not designed to search awards by research model type (NIH RePORTER, 2023c). The vertebrate animals section of the full NIH application record for each award gives specific details about any animal model(s) the investigator plans to use during the course of the proposed research project, as well as consideration given to alternative models (OLAW, 2021), and could be used to quantify the number of NHPs planned for use in any given

[6] USDA reports include information on the total number of NHPs held, which describes the "number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes" (USDA, 2021). These reports also provide information on the total number of NHPs used, which describes the "number of animals upon which teaching, research, experiments, or tests were conducted," regardless of whether pain was inflicted. This number does not include those animals held, bred, or conditioned for research but not yet used (USDA, 2021).

project. This approach was in fact used to collect data for analysis in the ORIP report in 2018. However, open access to these data is limited because the vertebrate animals section is not included in the publicly available information that can be collected from NIH RePORTER. To inform its analysis of the current landscape of NIH-supported NHP research, the committee requested records of all active NIH awards involving NHPs, including the vertebrate animals sections of those awards, but was unable to access these internal NIH records.

For NHPs used in intramural NIH research, USDA data provide the number of NHPs held and used by NIH, but do not include data from individual ICOs except for the National Institute of Allergy and Infectious Diseases (NIAID). Importantly, these data do not capture those animals involved in NIH intramural research that are held or used at third-party sites.

Major Stakeholders Involved in the Supply and Use of NHP Resources for NIH-Supported Research

As noted in the previous section, describing and quantifying NHP supply and use is complex, and the available data are insufficient to parse out, in a detailed manner, NHP production and use within the context of NIH-supported biomedical research. One aspect of this complex landscape is the diversity of stakeholders with key roles in the support and/or conduct of NIH-funded NHP research. Several of these stakeholders, specifically the NIH-supported intramural NHP resources and ORIP-supported NPRCs and National Resources, constitute NIH's long-established NHP research infrastructure, which is dedicated to supporting NIH-funded NHP research in the United States. These stakeholders and others are described in the sections that follow.

NIH Intramural Research Facilities

NIH ICOs are actively involved in both supporting the supply of NHPs for intramural research activities and the use of NHPs in research. USDA data from FY2021 show that 7,328 NHPs were reportedly held or used for research purposes at NIH ICO facilities supporting intramural programs (USDA, 2021) (see Table B-2 in Appendix B). [7] NIH support for intramural NHP resources involves several different acquisition pathways, although publicly available details are limited and complicated by complex funding and contracting processes. Several ICOs own breeding colonies for intramural research use, some of which are managed by third parties (Florence, 2022). ICOs may also have agreements with other ICOs to provide animals for use in intramural research. In addition, ICOs may access NHPs from NPRCs and National Resources, other academic centers with breeding colonies, or international and domestic suppliers. It should be noted that these suppliers do not contract exclusively with NIH ICOs and may also supply NHPs for their own use or for sale to other research institutions.

National Primate Research Centers

First established in the 1960s as regional primate research centers (Gibson, 1994), NPRCs are awarded competitively by NIH and hosted at research universities and institutions throughout the United States (see Figure 3-1). NPRCs complement and enable the missions of NIH ICOs by maintaining NHP breeding colonies and providing investigators with central-

[7] With the exception of NIAID, NIH reporting to USDA does not specify individual ICOs holding or using NHPs for intramural research. The NIH-wide USDA record on NHP holding and use of NHPs for FY2021 is assigned to the NIH Office of Animal Care and Use.

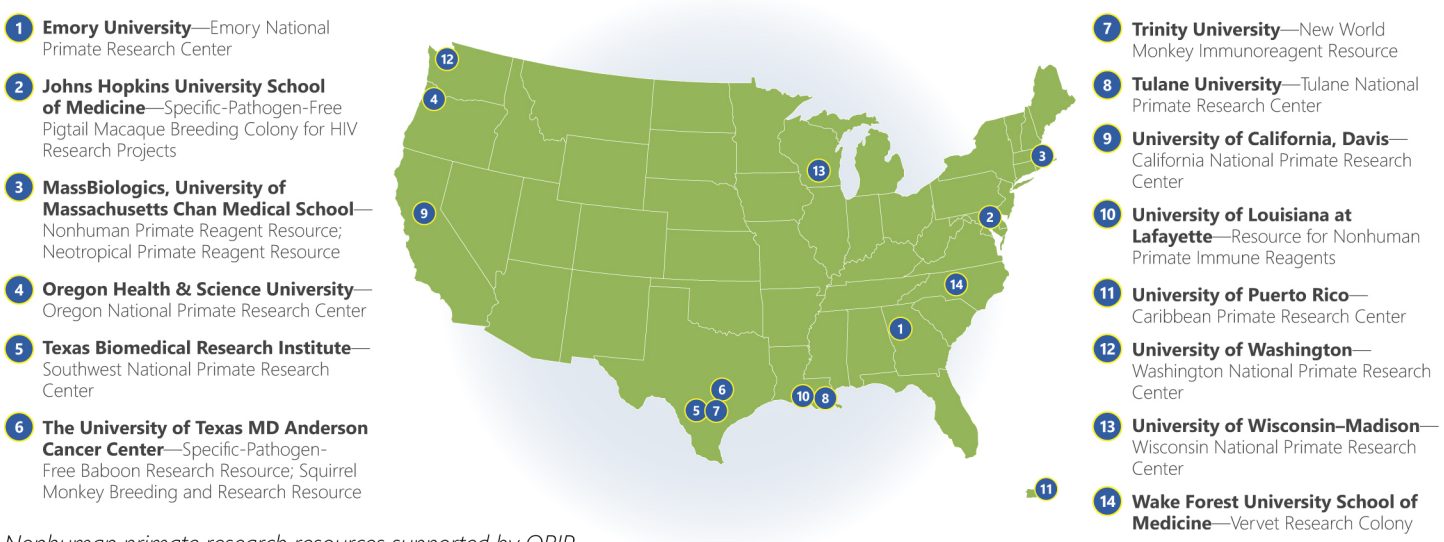

FIGURE 3-1 National Primate Research Centers and other nonhuman primate research resources supported by the Office of Research Infrastructure Programs (ORIP) at the National Institutes of Health.
NOTES: In addition to the seven National Primate Research Centers, ORIP provides support via P40 awards and/or other funding mechanisms to four National Resources with nonhuman primate breeding colonies—University of Texas MD Anderson Cancer Center, Caribbean Primate Research Center at the University of Puerto Rico, Wake Forest University School of Medicine, and The Johns Hopkins University School of Medicine—and three Reagent Resources—MassBiologics at the University of Massachusetts Chan Medical School, Trinity University, and University of Louisiana at Lafayette. HIV = human immunodeficiency virus.
SOURCE: Image provided courtesy of the NIH Office of Research Infrastructure Programs (ORIP). Developed by The Scientific Consulting Group.

ized expertise and resources (e.g., clinical laboratories, staffed cores for collecting samples, development of NHP models). Thus, these facilities fulfill essential functions for the domestic production of NHPs in addition to being active in the conduct of specialized research programs using NHPs. NPRCs receive funding from the Division of Comparative Medicine within ORIP via P51 Primate Research Center Grants (NIH, 2020), along with supplemental awards, to perform their dual functions of NHP resource production and research.

While much of the work of NPRCs is focused on NIH-supported research projects carried out by investigators internal and external to the center, NRPCs do not supply NHPs exclusively to NIH-supported investigators or carry out only NIH-supported research. The seven NIH-supported NPRCs accounted for nearly 24 percent (27,067) of all NHPs reported to USDA in FY2021 (USDA, 2021); however, the exact number of NHPs used by the NPRCs for NIH-supported research projects is unknown because of the aforementioned data limitations.

Individual NPRCs establish their own administrative processes for reviewing investigator requests for animals and services. However, these requests are generally prioritized in the following order based on funding source, as specified by NIH (NIH, 2020): (1) NIH extramural grants, (2) NIH intramural funding, (3) other federal agency funding, (4) not-for-profit funding, and (5) for-profit funding. Other factors considered within the context of this prioritization structure include primary research domain, funding mechanism, scientific justification, and logistical issues such as transportation (NPRC Information Request, 2022[8]).

The seven NPRCs carry out coordinated activities under the auspices of the NPRC Consortium, an important component of the NIH-supported NHP research infrastructure. These Consortium-based activities are NPRC-driven and include the sharing of best practices, protocols, and data to "enhance the resources of the program and promote cost savings by standardizing common activities across all of the NPRCs" (NIH, 2020). Working groups within the Consortium (e.g., Breeding Colony Management, Genetics and Genomics, Behavioral Management, Occupational Health and Safety, Pathology) are formed in consultation with ORIP staff, and their members are appointed by NPRC directors.

Non-NPRC National Resources

Four institutions receive ORIP support to serve as National Resources for domestic breeding colonies of NHPs (see Figure 3-1).[9] NHPs reported by these four National Resources accounted for just over 7 percent (8,112) of all NHPs reported to USDA as held or used for research purposes in FY2021 (USDA, 2021). As with NPRCs and other stakeholders, however, the proportion of this population that was associated with NIH-supported research is unknown, as National Resources may receive funds from other federal and private entities to breed and supply NHPs (e.g., NIH directly supports the maintenance of a squirrel monkey colony at the MD Anderson Cancer Center but not the rhesus macaque colony at the same site, even though all of these animals may be used for NIH-supported research projects). Investigators at National Resources also actively conduct NHP research, some of which may be funded by NIH, and may purchase supplemental animals from the commercial market to

[8] This reference refers to written responses to a committee information request received from each of the seven NPRCs (Washington NPRC, Oregon NPRC, California NPRC, Tulane NPRC, Emory NPRC, Wisconsin NPRC, and Southwest NPRC). Individual responses to the committee's information request can be found in the committee's public access file.

[9] For the purposes of this report, "National Resources" include the four non-NPRC institutions with NHP breeding colonies identified by ORIP: the Michale E. Keeling Center for Comparative Medicine and Research (MD Anderson Cancer Center), The Johns Hopkins University, Wake Forest University, and the Caribbean Primate Research Center. Reagent Resources supported by ORIP (see Figure 3-1) are not included in references to "National Resources" throughout this report.

meet their research needs. In addition to National Resources supplying NHPs for research use, ORIP supports three Reagent Resources (Figure 3-1) that do not maintain ORIP-funded NHP breeding colonies but serve as resources for primate-specific immune reagents (Grieder, 2023; ORIP, 2022). In contrast with the loosely centralized coordination efforts of the NPRC Consortium, the National Resources set priorities and operate independently, with no formal or informal coordinating structure, although they are often invited to participate in NPRC working groups.

Contract Research Organizations and Other Commercial NHP Suppliers

CROs provide an array of contracted research services within their facilities, often using CRO-owned NHP colonies for drug and product development activities. Some CROs and other commercial organizations also act as suppliers of NHPs and make animals from their onsite populations available for purchase; they also may arrange for importation of NHPs (Harding, 2017; ORIP, 2018a). Cumulatively, NHPs reported by these entities accounted for greater than 42 percent (approximately 48,400) of all NHPs reported to USDA as held or used for research purposes in FY2021 (see the listing of research facilities in Tables B-2 and B-3 in Appendix B) (USDA, 2021). It is not known what proportion of these NHPs were supplied for or used in NIH-supported research.

Several CROs and commercial suppliers have relationships with NIH ICOs through cooperative agreements and contracts to manage NIH-owned breeding colonies or to supply animals for extramural or intramural research purposes from colonies owned and/or managed by third parties. The NHP breeding colony on Morgan Island, South Carolina, for example, is owned by NIH for intramural research purposes but is managed by the CRO Charles River Laboratories, which in turn leases the land from the State of South Carolina (GovTribe, 2022; McCombs, 2021).

Private Pharmaceutical and Biotechnology Companies

Pharmaceutical and biotechnology companies also use NHPs to support their research programs in the United States, accounting for 2.7 percent of NHPs reported to USDA in 2021 (see the listing of pharmaceutical and biotechnology companies in Tables B-2 and B-3 in Appendix B) (USDA, 2021). This small percentage does not represent the totality of industry-sponsored NHP research, as these companies frequently use CROs to carry out research activities offsite (Harding, 2017). These companies may manage their own NHP colonies, procure NHPs from international or domestic suppliers, or contract with CROs to carry out NHP research activities. While rarely associated directly with NIH-supported research using NHPs, industry-sponsored NHP research activities can impact the balance of supply, demand, and prices for NHP resources across the broader research landscape. Increases in NHP demand by pharmaceutical and biotechnology companies that cannot be met by importation or industry-owned colonies—a situation experienced during the COVID-19 pandemic—can result in increased competition and cost increases for the limited domestic NHP resources sought after by other stakeholders (Zhang, 2020).

NHP Investigators at Non-NPRC and Non–National Resource Academic Institutions

An assessment of USDA NHP use data shows that academic institutions—outside of NPRCs and National Resources—reported using more than 16,000 NHPs in FY2021, with 31 percent of these facilities reporting use of fewer than 20 NHPs (USDA, 2021). In total,

these academic institutions account for just over 14 percent of all NHPs reported to USDA in 2021, but nearly 47 percent of all research facilities conducting research using NHPs. NIH RePORTER records indicate that many of these institutions hold active awards from NIH to carry out research using NHP models. The finding that many institutions report the use of small numbers of NHPs suggests that much of the NIH-supported, investigator-initiated research in the United States may involve small numbers of NHPs used by individual NIH grantees. These findings have implications for the tracking of investigator demand and strategies for ensuring access to NHP resources.

NHP SUPPLY AND DEMAND

The worsening shortage of NHPs for biomedical research, highlighted in the 2018 ORIP report (ORIP, 2018a,b), represents an increasingly serious threat to national security because of the critical importance of NHP models in responding to ongoing and emerging public health threats. Absent response, this shortage also stands to impede progress toward meeting other pressing medical and public health challenges. Actions taken by NIH in response to some of the concerns raised in the 2018 ORIP report (see Box 3-1) have been insufficient to bolster NHP supply to the levels required to meet research demands. This section documents the nature and extent of the NHP shortage and its impacts on NIH-supported biomedical research within the United States and identifies areas for targeted action. The data presented here were obtained from responses to the committee's information requests[10] and a survey of 273 NIH-funded investigators carried out by the committee. Collectively, these data aid in understanding recent importation trends, domestic breeding capacity, investigator demand, and the impacts of NHP availability issues on NIH-supported research (see Appendix A for additional detail on these information-gathering activities of the committee, Appendix B for additional analyses of data collected by the committee, and Appendix E for a listing of survey questions and aggregated responses).

Availability of NHP Resources

The availability of NHPs for biomedical research in the United States has been a longstanding challenge (NIH, 1978), dating as far back as the war on polio in the early 20th century (Suri, 2022). As discussed previously, NHPs used in biomedical research are either produced at domestic breeding facilities or imported from suppliers. While the available supply of this research resource has always been limited because of high demand, recent geopolitical events and public health emergencies have directly impacted these dual pathways for the supply of NHPs and exacerbated the existing challenges of scarce NHP research resources. As discussed further in the sections that follow and in Appendix B, key findings[11] related to NHP availability for NIH-supported extramural and intramural research include the following:

- The absolute number of NHPs held or used for research purposes decreased over the past decade by more than 2,100 animals. The total number of NHPs held but not yet used for research purposes declined by 11 percent over this period.
- The importation of NHPs, particularly cynomolgus macaques but also other species, is vulnerable to geopolitical pressures and logistical constraints (e.g., air transportation) that jeopardize reliable access to these animals.

[10] Summaries of these responses to the information requests can be found in Appendix B. Original responses of information requests are available upon request via the National Academies' Public Access Records Office.

[11] Supporting data and references for these findings can be found in the text sections that follow this bulleted list.

BOX 3-1 ACTIONS TAKEN BY NIH SINCE PUBLICATION OF THE 2018 ORIP REPORT TO ADDRESS NHP SUPPLY-AND-DEMAND CHALLENGES

The 2018 Office of Research Infrastructure Programs (ORIP) report was commissioned to give the National Institutes of Health (NIH) and the broader research community a better understanding of the supply of and demand for NHPs in the United States. Part II of the report provides an expert panel's recommendations to NIH for addressing NHP resource needs and ensuring the availability of this critical resource for future research and public health emergencies (ORIP, 2018b). Recommendations from the expert panel include

- the establishment of a trans-NIH NHP working group;
- increased funding for existing NHP research resources and other related awards (e.g., P51, P40, U42, R24 awards);
- the planning and implementation of genetic analysis on all NHPs in colonies supported by NIH awards;
- the provision of resources for the expansion of NIH-supported rhesus macaque and marmoset breeding colonies, specifically;
- the establishment of domestic cynomolgus macaque breeding colonies;
- financial support directed to the development of species-specific reagents, assays, and technologies for multiple NHP species; and
- the implementation of additional training opportunities for NHP researchers, support staff, and other professionals in the field.

Since the report's publication in 2018, NIH has taken several steps to respond to some of the report's recommendations. These efforts have included the establishment of a trans-NIH NHP resource planning working group with representation from 20 institutes, centers, and offices (ICOs) that meets monthly to increase collaboration within NIH around NHP resource management. The working group is charged with developing strategies for implementing the ORIP report's recommendations, and determining whether and how to address recommendations of future commissioned NIH-sponsored expert panels. This group's responsibilities related to NHP research also include performing ongoing assessment of the use of NIH-funded resources, addressing challenges in the NHP resource planning process, coordinating management and funding of NHP resources, avoiding research duplication, planning for long-term research resource needs, and promoting data sharing practices (Shaw, 2022).

Following its formation in 2019, the trans-NIH NHP resource planning working group created five subcommittees addressing different aspects of the ORIP report's recommendations. These subcommittees deliberated on future resource needs and opportunities, and in April 2020 presented their conclusions and recommendations to NIH leadership (Shaw, 2022). Several actions were taken in response, including the establishment of two new breeding centers and a coordination center for marmosets, expanded resources for rhesus macaques (under the Coronavirus Aid, Relief, and Economic Security [CARES] Act in response to COVID-19 pressures), awards of funding to support additional career-development opportunities for NHP researchers, and the provision of construction funding for both human immunodeficiency virus (HIV) and non-HIV research activities (Grieder, 2022).

As reported by NIH representatives at the November 2022 public session held by the committee, attention was diverted from the implementation of working group recommendations toward the demand for domestic NHP resources required for the COVID-19 response, and many of the recommendations in the 2018 ORIP report have yet to be fully implemented. Indeed, the committee heard from stakeholders that the steps NIH has taken to date in response to the ORIP report's recommendations are insufficient to address the needs of NHP researchers or those of the National Primate Research Centers and National Resources for maintaining NHP resources to support NIH-funded investigators (Flynn, 2022; Morrison et al., 2022).

- Changes in patterns of importation (e.g., a nearly 23 percent reduction in cynomolgus macaque imports in FY2020 as compared to FY2019 levels), as seen following the Chinese export ban and during the COVID-19 pandemic, have serious, secondary effects on demand for the limited supply of domestically produced NHPs.
- Macaques and marmosets represent current and future domestic breeding priorities. Existing breeding programs for these species cannot meet current investigator demand. Interest in transgenic NHP models, particularly transgenic marmosets for use in neuroscience research, is creating new demands that are likely to increase.

NHP Trends in the United States

Analysis of USDA-reported data on NHPs held and used in all research facilities in the United States over the last decade suggests that usage is outpacing the supply of NHPs held but not used for research purposes (e.g., animals reserved for breeding and held while maturing to ages suitable for use in research). As shown in Figure 3-2, the total number of NHPs actively used for research protocols in the United States annually—not just those used in NIH-supported research—has fluctuated over time, but was roughly the same in FY2021 as FY2008 (just over 70,000). However, the number of NHPs held or bred but not yet used for research purposes has declined overall. As a result, the absolute number of NHPs—those held but not used in research and those actively used—has decreased over the past decade (2011–2021) by more than 2,100 and has shown only minor year-to-year fluctuations (USDA, 2021, 2022). The decline in animals reserved for domestic breeding, if not addressed through targeted action, has implications for the future availability of NHPs to meet research needs.

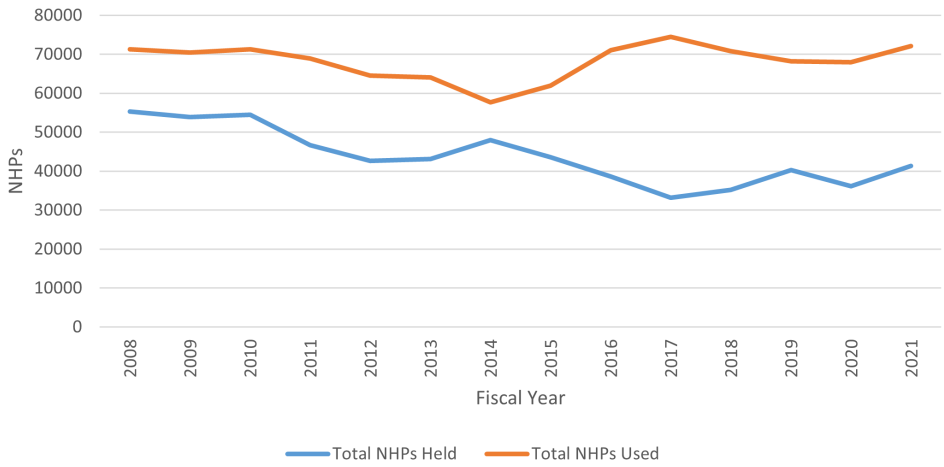

FIGURE 3-2 Nonhuman primates (NHPs) held or used for research purposes annually in the United States for fiscal years 2008–2021, based on data collected by the U.S. Department of Agriculture.
NOTES: These data include all NHPs held and used in the United States and are not restricted to NHPs held or used as part of National Institutes of Health–supported research. The total number of NHPs held describes the "number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes," and the total number of NHPs used describes the "number of animals upon which teaching, research, experiments, or tests were conducted" (USDA, 2021).
SOURCE: USDA, 2021, 2022.

NHP Importation

Based on information gathered by the committee on the species of NHPs used by NIH-supported investigators and the predominant NHP species imported into the United States (discussed below), it is likely that the majority of imported NHPs are intended for use by private industry, while a lesser proportion is used for NIH-supported research purposes. However, the Centers for Disease Control and Prevention (CDC), which tracks the importation of NHPs into the United States, does not collect data on the ultimate destination and use of NHPs after their arrival (CDC, 2022); therefore, the number of imported NHPs eventually used in NIH-funded research cannot be accurately determined. These data issues limited the committee's ability to assess the role of imported NHPs in NIH-supported research.

Between FY2012 and FY2017, more than 90 percent of the NHPs imported into the United States were cynomolgus macaques (ORIP, 2018a); from FY2019 to FY2022, this species accounted for a yearly average of 95 percent of all NHP imports (CDC, 2023). Data collected by the committee show that low numbers of cynomolgus macaques are held and used by NPRCs and National Resources, which instead report high levels of use of rhesus macaques (National Resources Information Request, 2022[12]; NPRC Information Request, 2022). Similarly, data collected from the committee's survey of NIH-supported NHP investigators found high levels of use of rhesus compared with cynomolgus macaques (see Table B-16 in Appendix B) (NHP Investigators Survey, 2022). These data suggest that imported cynomolgus macaques are used largely by private industry (e.g., CROs and pharmaceutical and biotechnology companies), a finding consistent with previous accounts (Grimm, 2022). Domestic resources of cynomolgus macaques have been slow to develop because importing the NHPs (primarily from China) has been deemed more cost-effective than developing U.S. breeding colonies (ORIP, 2018b).

As discussed previously, unexpected and rapidly implemented export restrictions established by China in early 2020 included a total ban on exports of NHPs. This restriction had the effect of reducing the total number of NHPs imported into the United States in FY2020 by more than 20 percent compared with FY2019 and increasing demand for domestic NHP resources (CDC, 2023). Such dramatic shifts in importation create secondary demand for commercially available domestic populations of NHPs, which are also used by NIH-supported investigators, and place further pressure on NPRCs and National Resources to fulfill the needs of these investigators.

As shown in Table 3-2, the total number of NHPs imported into the United States had recovered by FY2021, largely through increased importation of cynomolgus macaques from Asian countries other than China—primarily Cambodia, Vietnam, and Mauritius (see Appendix B for importation data by country of origin). These alternative sources of imported NHPs are not assured, however, as these nations could choose to end exportation of NHPs at any time (see the discussion of Indian NHP exportation below). Additionally, anecdotal reports indicate that China is competing with the United States for the purchase of NHPs from Southeast Asian countries—over which China holds significant geopolitical influence—as it endeavors to expand its own domestic NHP research programs (see Box 3-2) (Einhorn and Lew, 2022).

In 2022, a further threat to importation of NHPs was highlighted following the apparent illegal exportation of wild-caught cynomolgus macaques from Cambodia that were falsely labeled as captive bred, drawing international concern (Grimm, 2022) and scrutiny of exports by both Cambodia and the United States. Relatedly, the importation of NHPs also raises concerns about the conditions in which NHPs are bred and housed in nations with less stringent animal welfare regulations prior to their export (Mitchell et al., 2021). Beyond serious animal welfare considerations, poor conditions prior to export could impact the future suitability of

[12] This citation refers to written responses to a committee information request received from each of the four ORIP-supported National Resources. Individual responses to the committee's information request can be found in the committee's public access file.

TABLE 3-2 Number of Nonhuman Primates Imported to the United States, by Species and Fiscal Year (FY)

Species	FY2019	FY2020	FY2021
Cynomolgus macaque	32,273	24,879	30,649
Rhesus macaque	964	724	80
African green monkey	328	720	711
Common marmoset	195	326	284
Squirrel monkey	30	34	68
Capuchin	15	0	40
Other*	13	45	12
Total	33,818	26,728	31,844

* Other imported species varied by year but included colobus monkeys, siamangs, DeBrazza's monkeys, geladas, saki monkeys, spider monkeys, emperor tamarins, bushbabies, and orangutans.
NOTE: Due to data limitations, these numbers represent NHPs imported for a variety of purposes and do not represent animals imported exclusively for biomedical research use.
SOURCE: CDC, 2023.

BOX 3-2 IMPLICATIONS OF CHINESE EXPANSION OF NHP RESEARCH

China is investing heavily in nonhuman primate (NHP) research for the advancement of biomedical research and development. The China Brain Project, with an estimated budget of $746 million allocated over a 5-year period for neuroscience research, is a notable example of China's targeted investment in accelerating NHP research. China's investment in its NHP research capabilities includes the expansion of domestic breeding capacity, which represents a costly but long-term investment in its national biomedical research programs. As of 2022, the Kunming Institute of Zoology was completing construction on a facility with capacity to hold up to 5,000 NHPs—the largest such facility in the country. A decade from now, however, the numbers of NHPs being held could be exponentially larger: a research and breeding center in the Hainan province may eventually hold up to 20,000 NHPs, close to the total number housed by the seven U.S. National Primate Research Centers (NPRCs) (Normile, 2022). With the growth of China's pharmaceutical industry, the for-profit monkey-breeding business has also experienced increased expansion. WuXi AppTec Co., for example, purchased a Guangdong-based breeder holding approximately 20,000 NHPs in 2019, and other Chinese-based companies are following suit (Einhorn and Lew, 2022).

The Chinese biomedical research landscape differs from that of the United States and the European Union in the relative absence of anti–animal research activism (Normile, 2022). In addition to China's virtual absence of concentrated opposition from animal rights groups, investigators may be encouraged to move their NHP research to China by the greater availability of and access to NHPs, with some noting that less time is required to initiate preclinical trials for new drugs and medical devices using NHPs in China compared with the United States (Einhorn and Lew, 2022). The implications of this include intellectual property and national security concerns.

Like those of all nations, however, China's biomedical research enterprise has been impacted negatively by the COVID-19 pandemic. Beijing's temporary ban on the trading of live animals, for example, stalled research using cynomolgus macaques, as this species is not native to China and must be imported from Southeast Asia (Einhorn and Lew, 2022). Now that this ban has been lifted (in contrast to China's export ban, which remains in place), China's involvement in these other markets, to which the United States has turned since China's export ban was instituted, could heighten the global competition for access to NHPs, increasing the vulnerability of international NHP sources used by the United States and, by extension, heightening demand for limited domestic NHP supply.

the animals for research. Having purpose-bred, self-sustaining domestic populations of NHPs would likely allow for a greater degree of regulatory control over the health and well-being of NHPs used in research, as well as tracing of their social and genetic backgrounds, which in turn would support improved experimental rigor and the quality of the data generated.

The above recent experiences, together with the possible future risk of additional export restrictions instituted by countries attempting to prevent the exportation of wild-caught animals, suggest that importation is not an assured long-term solution for sourcing of cynomolgus macaques and other NHPs for research use in the United States. Failure to reduce reliance on foreign sources for these critical research resources exposes U.S. biomedical research programs to preventable supply chain vulnerabilities and impedes the nation's ability to prepare for future public health threats.

The vulnerabilities associated with reliance on China for the majority of imported NHPs, specifically cynomolgus macaques, are highlighted in the 2018 ORIP report, which notes that between FY2013 and FY2017, the majority of cynomolgus macaques imported to the United States were supplied by China (ORIP, 2018a). The report further emphasizes that a disruption in this supply—upon which the device and therapeutics development industry relies—would likely result in increased demand for domestic macaque populations by industry and a reduction in the number of domestic animals available for use by academic investigators supported by NIH grants, as well as dramatically increased costs of animals for all stakeholders (ORIP, 2018a,b). As described previously, these vulnerabilities associated with dependence on foreign sources of NHPs were realized in 2020 with China's export ban and were further intensified by NIH's prioritization of domestic populations of NHPs for COVID-19 research.

It is unclear how far into the future the United States will be able to continue importing NHPs for research purposes. The elimination of NHP exportation by foreign nations is not a novel occurrence, and the expectation of a reversal of exportation policy at some point in the future is not an appropriate strategy for ensuring a sustainable supply of NHPs for biomedical research. India, for example, reduced its NHP exportations over a 5-year period before instituting a complete ban (NIH, 1978), which allowed the United States time to procure Indian-origin rhesus macaques and establish domestic breeding populations. India has not reversed this policy in the decades since. The recent experience with China serves as a stark reminder that access to imported NHP species could be cut off with no advance notice in the future.

There now exists a critical window of opportunity during which domestic investments in NHP research resources can be made while NHP species such as cynomolgus macaques, marmosets, and African green monkeys remain accessible from other countries and can be imported to establish ethically sourced breeding stocks. The development of purpose-bred, self-sustaining, and diverse U.S. populations of NHPs also would provide a greater degree of regulatory control over the health and well-being of the animals; prevent misrepresentation of animal origin, age, or prior use; and reduce the impact on wild populations of NHPs in their countries of origin. The latter benefit is particularly important given how classification of NHP species as endangered will drastically impact research using those species, leading to lost opportunities for scientific and medical breakthrough discoveries (discussed in Box 3-3).

Domestic Breeding of NHP Resources

The seven NPRCs and four National Resources together constitute a long-established network of highly specialized research facilities that are responsible for providing domestically produced NHPs for NIH-supported extramural research purposes (see Table 3-3 for a

BOX 3-3 POTENTIAL IMPACT OF CHANGES IN WILD MACAQUE POPULATIONS ON BIOMEDICAL RESEARCH

A species' global population status (e.g., threatened, endangered) is established by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), an intergovernmental collaboration. CITES lists each endangered species within one of three different appendixes to the Convention articles (Appendix I, II, or III) based on the species' level of endangerment and the degree of protection from international trade believed necessary. Those species listed in Appendix I are considered to be threatened with extinction, and trade in them is prohibited apart from exceptional circumstances (CITES, n.d.). Other organizations also track and publish data on the status of wild populations. In 2022, the International Union for Conservation of Nature (IUCN) designated both the long-tailed or cynomolgus macaque (*Macaca fascicularis*) and the pig-tailed macaque (*Macaca nemestrina*) as endangered species, one step up from their previous designation as "vulnerable" (IUCN, 2022a,b), although they are not listed as such in CITES Appendix I. This decision was prompted by an effort to promote the species' survival in their natural habitats in Southeast Asia (Robitzski, 2022).

Both species have proven to be instrumental in the development of disease models in biomedical research with which to study and design treatments for viruses such as human immunodeficiency virus (HIV) and, most recently, SARS-CoV-2 (Robitzski, 2022). Cynomolgus macaques have been captured from the wild for use in biomedical research since the 1960s, with approximately 450,000 animals having been traded between 2008 and 2019 (Hansen et al., 2021); it is unclear what percentage of these animals were intended for research use.

The IUCN has classified use in laboratory research as one of the primary threats facing macaques (Robitzski, 2022), and investigators are concerned about how this classification will impact biomedical research, a concern that further highlights the need for expanded domestic breeding capacity. Although this classification does not have immediate consequences for ongoing nonhuman primate (NHP) research, it could potentially impact future research (Robitzski, 2022). The IUCN's decision could sway other influential institutions, such as CITES or the U.S. Fish and Wildlife Service, to take similar action, which would have a much greater impact on investigators conducting research with these animals in the United States (Robitzski, 2022). If CITES were to list these macaque species in Appendix I, that action would limit future research and development relying on these animals, given that the Endangered Species Act of 1973* prohibits importing, exporting, possessing taking, selling, and transporting endangered wildlife species with limited exceptions. These potential scenarios contribute to the many uncertainties surrounding the future of biomedical research using NHP models.

**Endangered Species Act of 1973*, P.L. 93-205, 16 U.S.C.35 § 1531

listing of the species bred as reported by NPRCs and National Resources). In FY2021, these resource programs reported producing approximately 5,000 NHPs across 11 different species (see Tables B-11 and B-12 in Appendix B); the lack of historical data on domestic breeding levels makes it impossible to know whether this reported production represents an increase over recent years. As discussed previously, other academic research facilities (such as the New Iberia Research Center) and commercial entities (such as Alpha Genesis, Inc.) also breed NHPs domestically under contracts and cooperative agreements with federal agencies and others. In some cases, academic and other institutions with breeding colonies (e.g., the Keeling Center at the MD Anderson Cancer Center and Wake Forest University) may maintain colonies supported by both NIH and other sources.

TABLE 3-3 Species of Nonhuman Primates Bred by Domestic National Institutes of Health (NIH)–Supported National Primate Research Centers (NPRCs) and National Resources, Fiscal Year (FY) 2017 versus FY2021

	NPRCs and National Resources	
Species	**FY2021**	**FY2017**
African Green, Vervet, or Grivet *Chlorocebus spp.*	Wake Forest University	Wake Forest University
Baboon *Papio spp.*	Southwest NPRC MD Anderson Cancer Center	Southwest NPRC MD Anderson Cancer Center
Squirrel Monkey *Saimiri spp.*	MD Anderson Cancer Center	MD Anderson Cancer Center
Owl Monkey *Aotus spp.*	MD Anderson Cancer Center*	MD Anderson Cancer Center*
Common Marmoset *Callithrix jacchus*	Southwest NPRC Wisconsin NPRC Johns Hopkins University MD Anderson Cancer Center	Southwest NPRC Wisconsin NPRC Johns Hopkins University*
Macaque—Cynomolgus, Crab Eating, or Longtailed *Macaca fascicularis*	Wisconsin NPRC	
Macaque—Japanese *Macaca fuscata*	Oregon NPRC	Oregon NPRC
Macaque—Pig-tailed *Macaca nemestrina*	Johns Hopkins University Washington NPRC	Johns Hopkins University Washington NPRC
Macaque—Rhesus *Macaca mulatta*	California NPRC Emory NPRC Oregon NPRC Southwest NPRC Tulane NPRC Wisconsin NPRC Caribbean Primate Research Center Johns Hopkins University* MD Anderson Cancer Center*	California NPRC Emory NPRC Oregon NPRC Southwest NPRC Tulane NPRC Wisconsin NPRC Caribbean Primate Research Center Johns Hopkins University* MD Anderson Cancer Center*
Titi Monkey *Callicebus spp.*	California NPRC	California NPRC
Sooty Mangabey *Cercocebus atys*	Emory NPRC	Emory NPRC

*Breeding colony is not NIH sponsored.
NOTES: The institutions listed may maintain breeding colonies that are not supported by NIH. National Resource data include information from Wake Forest University, MD Anderson Cancer Center, The Johns Hopkins University, and the Caribbean Primate Research Center.
SOURCES: National Resources Information Request, 2022; NPRC Information Request 2022; ORIP, 2018a.

Rhesus macaques continue to be the most commonly bred species at NPRCs and National Resources (more than 4,000 bred in FY2021), and nearly all NIH-supported stakeholders engaged by the committee predicted increases in demand for this species given its widespread use as a model. Of the 517 active NIH awards using NHPs reported by investigators surveyed by the committee, and for which data on NHP species were provided, nearly 71 percent involve the use of rhesus macaques (NHP Investigators Survey, 2022). In contrast with other NHP species, for which only a few institutions maintain breeding colonies, most NPRCs and National Resources report breeding rhesus macaques, as do other stakeholders

with NIH agreements for breeding services (National Resources Information Request, 2022; NPRC Information Request, 2022). Still, the current production of rhesus macaques at these domestic facilities remains insufficient to meet the demand of investigators (as discussed further in the section below on investigator demand).

The 2018 ORIP report also cites marmosets as a high-demand species for biomedical research (ORIP 2018a,b), and interest in using this model continues to grow among both extramural and intramural investigators, particularly in the areas of behavioral and systems neuroscience, molecular neuroscience, neurodegenerative disorders, and visual systems research. Just 6 percent of active awards captured in the committee's survey of NIH-supported NHP researchers for which species data were provided involved the use of marmosets. However, more than 11 percent of responding investigators indicated that they planned to use marmosets for future research (see Table B-28 in Appendix B) (NHP Investigators Survey, 2022). The potential of transgenic marmoset models to advance research on neurodevelopmental conditions, such as autism (Zhao et al., 2018), and neurodegenerative disorders, such as Alzheimer's disease (Rizzo et al., 2021), is further increasing interest in this species.

In FY2021, 194 marmosets were produced at NPRCs and National Resources (National Resources Information Request, 2022; NPRC Information Request, 2022). In 2019, concerns related to extramural investigators' increasingly limited access to marmosets for neuroscience research spurred several ICOs to cofund a request for applications (RFA) through the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative to support the creation of a Marmoset Coordinating Center to facilitate data sharing and coordination of marmoset distribution and breeding efforts (NIH, 2019). This U24 cooperative agreement was eventually awarded to the Oregon Health & Sciences University in collaboration with the Wisconsin NPRC and Southwest NPRC for oversight of the Coordinating Center's functions (OHSU, 2021; Robinson, 2020). Additionally, in 2020, a U24 grant was awarded to The Johns Hopkins University, in collaboration with the University of California, San Diego, to establish the Bicoastal Marmoset Breeding Center (NIH RePORTER, 2022), which will support two breeding colonies to supply research programs with marmosets. Information provided to the committee by NIH-funded investigators and NIH ICOs indicates that these current breeding colonies remain small and continue to be outpaced by demand, although it should be noted that the shorter biological development periods of marmosets versus other NHPs, especially sexual maturity and gestation period, do provide advantages with respect to the time required to expand breeding colonies (NASEM, 2019).

Although, as discussed above, cynomolgus macaques are less commonly used than rhesus macaques in NIH-supported extramural research, they are critical resources frequently used in research sponsored by the pharmaceutical industry[13] and increasingly in some areas of NIH extramural research (ORIP, 2018a). Responses of investigators surveyed both by ORIP for the 2018 report and by this committee indicate that demand for this model has remained stable since 2018—just over 20 percent of responding investigators reported planned future use of cynomolgus macaques in both 2018 and in 2022 (NHP Investigators Survey, 2022; ORIP, 2018a). As mentioned earlier, the ease of importing cynomolgus macaques in the past has served as a disincentive for the creation of domestic breeding colonies (ORIP, 2018a). However, establishment of such colonies is a key recommendation of the 2018 ORIP report, and efforts were subsequently undertaken to establish a breeding population at the Wisconsin NPRC (NPRC Information Request, 2022). A breeding colony at the New Iberia Research Center was also established under an NIH cooperative agreement (HHS, 2021). However,

[13] Industry stakeholders may own private breeding colonies of cynomolgus macaques for the conduct of in-house research.

the annual production of animals at these domestic facilities remains low (e.g., 102 reported bred at the Wisconsin NPRC in FY2021), numbers that are insufficient to meet the current demands of NIH-supported investigators.

Given the predictions of NPRCs and National Resources that investigator demand for NHPs for use in NIH-supported research—specifically for rhesus and cynomolgus macaques and marmosets—will increase, efforts and investment to further expand existing breeding programs at NPRCs and National Resources are needed. Among the 258 NIH-supported investigators who responded to the committee's survey question about future demand for NHPs and reported expected NHP species needs for future NIH awards, rhesus macaques were overwhelmingly identified as the preferred NHP species (82 percent), followed by cynomolgus macaques (22 percent), common marmosets (11 percent), and baboons (11 percent) (see Table B-28 in Appendix B) (NHP Investigators Survey, 2022).

Meeting the anticipated future demand for NHPs is possible given the nation's past investment in establishing a strong network of research infrastructure and expertise at NPRCs and National Resources, which currently support much of NIH-funded NHP research. However, ensuring that these essential stakeholders have the capacity to meet the demands of the U.S. biomedical research enterprise, particularly if the nation seeks to move away from its reliance on foreign sources of NHPs, will require dedicated, long-term investments. These investments include dedicated funds to support the update and expansion of physical infrastructure for breeding facilities; their maintenance to remain in regulatory compliance; and their operation, since the process of expanding domestic breeding colonies is inherently lengthy (see the section below on research infrastructure). Additionally, meeting anticipated demand will likely require an up-front decrease in the number of animals allocated by NPRCs and National Resources for use in study protocols, as more animals will need to be held for breeding purposes. Both the 2018 ORIP report and testimony given to the committee described these facilities as being close to or at capacity, and highlighted the need to accommodate more animals and acquire additional personnel to provide for their care (NPRC Information Request, 2022; ORIP, 2018b). In establishing breeding programs to secure the domestic NHP supply, it will be important to consider geographic separation of breeding sites, in much the same way as the NPRCs were separated across the United States, which will help mitigate risks from the collapse of a single colony as the result of a natural disaster (Hutchinson, 2022). Also important is providing a means of enhancing genetic diversity (which can improve colony health and help avoid genetic confounding in population studies) (ORIP, 2018b).

Availability of NHP Resources for Intramural Research Programs

NHPs used for NIH intramural research are procured from several different sources, including ICO-owned colonies and facilities contracted to provide the animals. Whereas multiple ICOs reported concerns in 2021 with respect to the availability of NHPs for intramural research, NIAID, which holds its own established breeding colonies, reported minimal issues with acquiring rhesus macaques, highlighting the value of these long-term investments in securing a stable supply of NHPs (NIH, 2022a).

NPRCs and National Resources are not major providers of NHPs for intramural research but do supply some specific species (ORIP, 2018a,b). At the committee's August 2022 public workshop, representatives of the NIH intramural research program reported that approximately 66 percent of the roughly 800 animals acquired for use in intramural research in each year had come from NIH-owned colonies, such as the rhesus macaque colony on Morgan

Island in South Carolina, while 33 percent had been purchased from private-sector suppliers (Denny, 2022). The remaining animals had been obtained from other outside sources.[14]

Meeting Investigator Demand

The shortfall in NHP supply to meet current NIH-supported research needs is reflected in a statement by NIH accompanying the Biden administration's FY2022 budget request: "There are not enough NHPs at present to support both pandemic research and all the existing NIH research for which NHPs are necessary" (NIH, 2021). This shortfall is unsurprising given the findings of the 2018 ORIP report, as summarized above, and the inadequate investment in infrastructure and domestic NHP resources in the years leading up to the pandemic. This section elaborates on the committee's assessment of investigator demand for NHPs from domestic NIH-supported sources; barriers to meeting that demand that could be targeted to address NHP supply issues, including access challenges; and the related impacts on research quality and timeliness. Key findings[15] from the committee's assessment include the following:

- The current demand of investigators for NHP models is not met by existing NHP resources, as reported to the committee by multiple stakeholders. This shortfall is particularly acute for certain high-demand species, such as rhesus macaques and marmosets. About 64 percent of respondents to the committee's survey reported issues with obtaining NHPs for their current awards, regardless of the source of the animals or the type of research facility in which the research was being conducted. In 2021, two-thirds of investigator requests for research-naïve macaques could not be met at NPRCs because of a shortage of these animals.
- The accessibility of NHP models for NIH-supported investigators has decreased, as reflected in long wait times and increased costs for the animals. More than half (57 percent) of active NIH awards reported by survey respondents ultimately enrolled fewer NHPs than originally planned.
- The prioritization of NHPs for use in COVID-19 research exacerbated shortages in other research domains.
- Neuroscience and related disorders and infectious diseases and immunology remain areas of high demand for NHP models. NHP models are increasingly of value in research related to the development and testing of gene therapies.

Investigator Demand and Access Challenges

Timely access to NHP models is a concern widely reported by NIH-supported investigators and the ICOs for both extramural and intramural research (NIH, 2022a; NHP Investigators Survey, 2022). Among the NIH-supported NHP investigators responding to the committee's survey (n = 273), about 64 percent reported issues with obtaining NHPs for their current awards, regardless of the source of the animals (e.g., NPRC, importer, other domestic supplier) or the type of research facility in which the research was being conducted (NHP

[14] The committee was unable to obtain complete numbers for NIH intramural breeding programs. The numbers reported in this section are based on remarks provided to the committee at its August 2022 public workshop. Regarding numbers of animals coming from contracted and subcontracted breeding facilities, NIH indicated that these data are not considered part of the NIH intramural program because such contracts are procured and managed through individual ICOs rather than the intramural program itself.

[15] Supporting data and references for these findings can be found in the text sections that follow this bulleted list.

Investigators Survey, 2022). This percentage represents an increase since the ORIP report was published in 2018; 50 percent of the extramural investigators surveyed at that time reported issues related to access to NHPs or related research services (ORIP, 2018a).

Additionally, three of the seven NPRCs reported being unable to fulfill on average 10 to 25 percent of investigator requests for NHPs between 2018 and 2021, and one NPRC was unable to fulfill more than half of requests during that time (see Table 3-4) (NPRC Information Request, 2022). NIH-supported investigators' access to NHPs from NPRCs varies relative to the intended research location. Overall, the provision of NHPs to investigators who planned to carry out the research at an external institution (e.g., researchers not employed by an NPRC who wished to conduct research at their home institution using animals sourced from NPRCs) declined by more than half in FY2020 and FY2021 relative to FY2019, although individual NPRCs varied substantially in the number of NHPs provided for research at external facilities during FY2018–2021. The number of animals provided to external investigators for research being carried out at the NPRCs increased in FY2021 following declines the previous 2 years (NPRC Information Request, 2022) (see Tables B-18 and B-19 in Appendix B). These shifts may be related to prioritization of NPRC research efforts carried out during the COVID-19 pandemic or to other logistical barriers limiting access to these resources.

Challenges in securing NHP resources for intramural research activities were reported by the National Institute of Mental Health (NIMH); the National Eye Institute (NEI); the National Institute on Drug Abuse (NIDA); the National Heart, Lung, and Blood Institute (NHLBI); the National Cancer Institute (NCI); and NIAID (NIH, 2022a). Difficulties with timely access to NHPs, particularly macaques and animals of a specific sex or age, on the commercial market were emphasized as barriers to conducting research (NIH, 2022b). As with NIH-supported extramural research, intramural research has faced project delays, long wait times for animals, and modifications to study designs to accommodate reduced numbers of NHPs (NIH, 2022a).

Among investigators who responded to the committee's survey and reported specific challenges with accessing NHPs for any of their NIH awards, the factors associated with these access challenges included a lack of animals that met specific demographic criteria required for the research (e.g., age, sex) (72 percent of respondents), the increasingly high cost of animals (43 percent of respondents), and the unavailability of NHPs with specific genotypes or genetic diversity (15 percent of respondents) (see Table B-24 in Appendix B) (NHP Investigators Survey, 2022). These findings indicate not only that there are insufficient supplies of NHPs, but also that those animals that are available do not necessarily have characteristics that align with the needs of investigators. For example, investigators may be

TABLE 3-4 Proportion of National Institutes of Health–Supported Investigator Requests Not Met by National Primate Research Centers (NPRCs), Fiscal Years 2018–2021

Proportion of Requests for Which Fulfillment Was Not Possible	Number of Reporting NPRCs (N = 7)
Less than 10%	2
Greater than 10% but less than 25%	3
Greater than 50%	1
None	1

SOURCE: NPRC Information Request, 2022.

unable to access female NHPs that would be needed to study sex differences as part of their study design because females may be held for use in breeding colonies.

High demand for and limited supplies of NHPs have also resulted in research projects enrolling fewer animals than originally planned. A description of the number of animals planned for use in a study is recorded in the NIH award application and reviewed to confirm that studies are sufficiently powered and properly designed. Reducing the number of animals enrolled in a study may negatively impact the quality of the research and the conclusions drawn from it. Thus, initiation of studies for which funding has been received may need to be delayed until adequate numbers of NHPs become available. More than 57 percent of active NIH awards reported by survey respondents ultimately enrolled fewer NHPs than originally planned (see Table 3-5). The most common factor reportedly contributing to lower-than-planned enrollment of NHPs for awards was lack of access to NHPs (57 percent of awards for which fewer NHPs were used than planned) (see Table 3-6) (NHP Investigators Survey, 2022). NIH ICOs also have recently raised concerns about lower-than-planned enrollment by extramural projects. In a case reported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the project in question was able to obtain only 8 of the 12 requested macaques because of severe shortages (NIH, 2022a).

Related to challenges in obtaining the requested number of NHPs to carry out studies funded by NIH awards, both NIH ICOs and committee-surveyed investigators reported long wait times for receipt of animals, a pattern identified as a barrier to the conduct of high-quality research. Because animals at NPRCs and National Resources are often committed several years in advance, investigators must wait for existing animals to become ready for use in their respective protocols. For example, the committee learned that specific-pathogen-free (SPF) baboons at the MD Anderson Cancer Center have already been committed for the next 2 years (Hopkins, 2022). Of the 475 awards reported by investigators responding to the committee survey question on enrollment times, 41 percent received NHPs after the desired date of enrollment. For awards reporting the use of rhesus macaques (n = 351), late enrollment increased to 44 percent of all awards (see Table 3-7) (NHP Investigators Survey, 2022). While it is impossible to compare changes in wait times since 2018 because of a lack

TABLE 3-5 Nonhuman Primates (NHPs) Planned versus Used, by Source

NHP Source	Total Unique NIH Awards Reported by Survey Respondents	Percentage of Awards for Which Respondents Reported Use of Fewer NHPs Than Planned (%)	Percentage of Awards for Which Respondents Reported Use of More NHPs Than Planned (%)
All Sources	491	57	4
Respondent's Institution	108	65	2
NPRC	238	65	5
Domestic Breeder	109	58	3
Imported	58	55	7
Other	81	43	5

NOTES: The "Other" category includes animals already onsite (n = 17); other institutions, including those of collaborators or subawardees (n = 16); National Primate Research Centers (NPRCs) and other, non-NPRC NIH sources (n = 13); contract research organizations (n = 6); domestic suppliers (n = 6); and studies using existing tissues or data (n = 5). This table was generated from award information provided by investigators responding to questions 6, 7, and 11 on the NHP Investigators Survey. NIH = National Institutes of Health.
SOURCE: NHP Investigators Survey, 2022.

TABLE 3-6 Factors Contributing to Decreased Enrollment of Nonhuman Primates (NHPs), by Source

NHP Source	Total Awards Using Fewer NHPs Than Planned (N=288)	Percentage of Awards for Which a Change in Study Design Was a Contributing Factor (%)	Percentage of Awards for Which Lack of NHP Availability Was a Contributing Factor (%)	Percentage of Awards for Which the Cost of NHPs Was a Contributing Factor (%)	Percentage of Awards for Which Respondents Indicated Not Applicable (N/A) (%)	Percentage of Awards for Which Respondents Reported Other Contributing Factors (%)
All Sources	288	18	57	22	10	35
Respondent's Institution	72	17	58	19	15	29
NPRC	159	19	59	21	9	38
Domestic Breeder	65	14	68	28	3	32
Imported	33	12	70	30	6	27
Other	35	17	63	26	11	26

NOTES: Columns do not add to 100 percent because (1) some respondents reported more than one source of NHPs, and (2) 75 respondents did not provide data on the source of NHPs. Respondents were able to select more than one factor. This table was generated from award information provided by investigators responding to questions 8, 11, and 12 on the NHP Investigators Survey. NPRC = National Primate Research Center.
SOURCE: NHP Investigators Survey, 2022.

of historical data on this variable, five of the seven NPRCs reported an average wait time of more than 3 but less than 6 months for fulfilling a given NHP request (not species specific) (see Table 3-8). Extended wait times for access to NHPs can have significant effects on the success as well as the timeliness of a research project, depending on the nature of the study

TABLE 3-7 Wait Times for Nonhuman Primates (NHPs) Reported by National Institutes of Health–Supported Survey Respondents

Awards for Which NHP Enrollment Time Was Reported	Number of Awards for Which On-Time Enrollment Was Reported	Number of Awards for Which Late Enrollment Was Reported	Percentage of Awards for Which On-Time Enrollment Was Reported (%)*	Percentage of Awards for Which Late Enrollment Was Reported (%)*
All awards (N = 475)	280	195	59	41
Awards using rhesus macaques (N = 351)	186	145	56	44

* Denominator includes only those survey respondents reporting enrollment time.
NOTES: On-time enrollment includes NHPs received by the date requested or earlier. Late enrollment includes any award receiving NHPs after the planned enrollment date. This table was generated from award information provided by investigators responding to questions 5, 9, and 10 on the NHP Investigators Survey.
SOURCE: NHP Investigators Survey, 2022.

TABLE 3-8 Average Wait Times for Nonhuman Primates (NHPs), Fiscal Years 2018–2021

Average Wait Time for NHPs	Number of Reporting National Primate Research Centers (N = 7)	Number of Reporting National Resources (N = 4)
Less than 3 months	1	1
More than 3 months but less than 6 months	5	2
More than 6 months but less than a year	1	0
Greater than a year	0	1

SOURCES: National Resources Information Request, 2022; NPRC Information Request, 2022.

and its funding requirements (e.g., need for a no-cost extension or return of funds) and on the advancement of biomedical research in general. Such delays can be extremely costly given the urgency of emergent needs at times of crisis. Moreover, delays in nonclinical studies can prolong the time to initiate clinical trials for potential disease treatments, delays that are particularly significant for rapidly progressing, terminal conditions such as amyotrophic lateral sclerosis (ALS).

NPRCs reported that species, age, genotype, and sex are common factors likely to cause delays for those requests that can be fulfilled, corroborating experiences with unmet demand reported by NHP investigators and NIH ICOs (see Table B-22 in Appendix B) (NPRC Information Request, 2022). For this reason, requests for certain high-demand species, such as rhesus macaques, are more likely not to be fulfilled or to require longer wait times. For example, NPRCs were able to fulfill only one-third of the 5,300 investigator requests received in FY2021 for research-naïve macaques (including pig-tailed, cynomolgus, and rhesus macaques) (Johnson, 2022). In another example provided to the committee, Wake Forest University, which is a National Resource, reported that it was able to fulfill just one-third of requests for African green monkeys during the height of the COVID-19 pandemic (Jorgensen, 2022).

These recent data indicate that barriers to NHP access have persisted and in fact have worsened since publication of the 2018 ORIP report, which at that time acknowledged similar investigator challenges related to meeting demand for NHPs, increased wait times, and the need to stagger delivery of animals over the course of studies. In summary, although NHP models continue to be necessary to carry out NIH-supported research, data collected from NPRCs, National Resources, and NIH-supported investigators indicate that demand for NHPs (rhesus and cynomolgus macaques and marmosets in particular) cannot be met by the existing supply chain.

Demand for NHP Resources by Research Domain: Extramural Research

Data collected from NPRCs, National Resources, ICOs, and NIH-supported investigators demonstrate several overlapping areas of NHP use across the current biomedical research landscape. Stakeholders cited research in neuroscience and neurological disorders as well as in infectious diseases and immunology (including human immunodeficiency virus [HIV]/acquired immune deficiency syndrome [AIDS]) as priority areas for current NHP research (National Resources Information Request, 2022; NIH, 2022b; NHP Investigators Survey, 2022; NPRC Information Request, 2022). These same priority NHP research areas are identified in the ORIP report (ORIP, 2018a). Emerging trends include the use of NHPs in develop-

ing and testing gene therapies (see Appendix B for data on current research priorities across different stakeholders).

ICOs widely reported infectious disease and immunology research as a priority for NHP use in extramural research for FY2021 (Eisinger, 2022). Figures on the number of NHPs reprioritized for research on the pathogenesis of COVID-19 and for supporting the development and testing of vaccines and therapeutics are not available. Nonetheless, stakeholders described the impacts of this prioritization as a factor exacerbating the inadequate supply of NHPs for use in other areas of infectious disease research, as well as increasing costs of the limited pool of available animals (NIH, 2022a; Ross, 2022).

Information on active extramural research provided by multiple ICOs, including NIAID, NIDA, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Office of AIDS Research (OAR), indicates that the demand for NHPs for research in the area of HIV/AIDS has remained high in recent years. ICOs described HIV/AIDS research as encompassing a broad range of activities, from the development of treatments and cures to the exploration of other body systems and associated complications in the context of HIV infection (NIH, 2022a). Surveyed investigators likewise cited HIV/AIDS as a highly active area of NHP research, accounting for 36 percent of all NHPs reported as being used by responding investigators (see Table B-27 in Appendix B for information on priority research domains for NIH-supported researchers) (NHP Investigators Survey, 2022).

Multiple stakeholders identified research in neuroscience and neurological disorders as continuing to represent a major priority for NHP research. Respondents to the committee's survey highlighted projects in behavioral and systems neuroscience in particular as a major domain for current NHP use, accounting for the highest number of individual awards reported for a single domain—155 of 482 unique awards (note that respondents were able to select more than one research domain to describe the focus of an active NIH award) (see Figure B-1 in Appendix B) (NHP Investigators Survey, 2022). ICOs provided several examples of active extramural research projects in this domain, providing a sense of the scope of neuroscience research conducted using NHPs. Among these examples are collaborative research on neural circuitry through the BRAIN Initiative, the development of therapies for neurodegenerative diseases, and exploration of the brain–computer interface (NIH, 2022a).

The data collected by the committee on current demand for NHPs indicate that priority areas for NHP research remain similar to those identified in the 2018 ORIP report. However, data provided by ICOs regarding their current priority investment areas for extramural research show an increasing focus on NHP use for studies of genetic disorders and for the development and testing of gene therapies (NIH, 2022a)—research areas also reported by NPRCs and National Resources (National Resources Information Request, 2022; NPRC Information Request, 2022).

Demand for NHP Resources by Research Domain and Species: Intramural Research

Information on demand for NHP models within the NIH intramural research program, based on current intramural research activities, shows overall concordance with high-demand domains in extramural research—including neuroscience and neurological disorders, and infectious disease and immunology (Denny, 2022). These domains for the intramural program also align with past trends described in the 2018 ORIP report (ORIP, 2018a).

ICOs provided several examples of intramural research activities requiring the use of NHPs within these high-priority research domains. In the domain of neuroscience and

neurological disorders, the National Institute of Neurological Disorders and Stroke (NINDS) highlighted investment in research using NHPs to better understand the pathogenesis of such neurodegenerative diseases as multiple sclerosis, Alzheimer's disease, and ALS. NIMH cited the need for NHPs to study brain–behavior relationships to better understand the dysregulation of cognition and emotion in psychiatric disease and how neural circuit manipulations can ameliorate such dysfunction. The National Institute on Deafness and Other Communication Disorders (NIDCD) highlighted the use of NHPs for gene therapy work to advance its efforts to develop treatments for hearing loss and balance issues (NIH, 2022a).

There is significant demand for NHPs in intramural research in the domain of infectious disease and immunology, with much of this research being carried out by NIAID. This work focuses on the development and testing of therapeutics and vaccines for such high-consequence microbial threats as Ebola, Nipah, Hendra, Marburg, Lassa, and other viral agents (NIH, 2022a).

Additionally, the National Institute on Aging (NIA) reported active NHP use for research in the domain of aging and age-related disease. Specifically, this work is focused on understanding the pathogenesis of and the development of translational models of aging and age-related disease. The provision of NHP resources for investigators was noted as a priority for NIA's intramural program (NIH, 2022a).

As with extramural research, multiple ICOs with intramural research programs noted that COVID-19 research efforts significantly altered use patterns for NHPs and resulted in unmet demand for NHPs for some research activities within these programs (NIH, 2022a). NINDS, for example, reported a 3-year hiatus from macaque use, while NHLBI had to delay promising studies on stem cell transplantation and gene therapy (NIH, 2022a).

Compared with the extramural research program, the NIH intramural research program relies on fewer NHP species. Data provided by ICOs that carry out intramural research using NHPs show that macaques account for 75 percent of all NHPs used (Denny, 2022), a proportion consistent with that described in the 2018 ORIP report. Marmosets account for much of the remainder of NHP use, with squirrel and African green monkeys being used in some limited instances for neuroscience and infectious disease research (NIH, 2022a).

Costs of NHPs

The increased demand for NHPs caused by the COVID-19 pandemic exacerbated the existing shortage of NHPs described in the 2018 ORIP report, which in turn resulted in a rapid and substantial rise in the cost of NHPs. These skyrocketing costs have had direct implications for the conduct of both extramural and intramural NIH-supported biomedical research by limiting the number of NHPs that can be procured and the number of NHP studies that can be performed. Increases in the average price of NHPs—not species specific—since 2019 as reported by individual NPRCs range from 10 percent to 22 percent (NPRC Information Request, 2022).[16] National Resources reported that the price of animals increased by 25–35 percent during the same period (National Resources Information Request, 2022).

The costs of animals from other sources, such as commercial suppliers, have been reported as vastly surpassing cost increases at NIH-supported resources, and the price increases for high-demand species, such as rhesus and cynomolgus macaques, have been especially steep. NINDS conveyed to the committee the concerns raised by its awardees with respect to the costs of rhesus macaques, which had risen from $8,000 to $24,000—a 200 percent increase (NIH, 2022a). Compounding these difficulties related to NHP costs, rising

[16] Emory NPRC is projecting a 31 percent increase for FY2023.

inflation has resulted in increased costs for personnel and husbandry programs associated with NHP care (NIH, 2022b).

Intramural research programs have experienced similar cost pressures. ICOs reported that since 2018, all costs related to intramural NHP research infrastructure, procurement, and care have increased dramatically, primarily as a result of the scarcity of NHPs, the Chinese export ban, and rising inflation (NIH, 2022b). NEI and others reported that the cost of NHPs has increased two to five times compared with recent years. NIAID indicated that the price of cynomolgus macaques, the supply of which was strongly impacted by the Chinese export ban, had increased by 500 percent. Cost increases apply to all NHP species used in intramural research, even those for which demand is not typically high and whose supply was largely unaffected by the knock-on effects of shortages of macaques, as seen with the doubling in price of African green monkeys. NCI reported that the severe shortage of NHPs has resulted in the need to procure young animals and house them until they are mature enough to be used in NCI research protocols, a process that incurs a substantial additional cost over the life of the animals for their housing and care and limits the physical capacity of the institute to carry out research at its anticipated pace (NIH, 2022a).

These cost increases have a particularly detrimental impact on NIH-supported extramural NHP research because of the inflexibility of NIH direct funding caps, which the 2018 ORIP report cites as a challenge for investigators (ORIP, 2018b). These funding caps have not been raised for many years and currently are fixed at $500,000 per year for direct costs (ORIP, 2018a). ICOs described approaches used to address the increased costs, including provision of supplemental funding for the purchase of animals from alternative suppliers, reallocation of contract funds, and recycling of animals where possible (NIH, 2022a). However, these approaches are not always available and do not adequately address the rapidly rising costs of NHPs and overall increases in the cost of conducting NHP research. How frequently exemptions to funding caps are granted and other approaches are used to address the rising costs of NHPs remain unknown.

Transportation and NHP Accessibility

Importation challenges resulting from recent changes in international export policy (discussed earlier) have been compounded by increasingly strict transportation policies that affect NHP availability. In addition to the international and domestic regulations for NHP transport (NRC, 2006), commercial transporters have enacted their own policies that have resulted in operational and logistical barriers to the transportation of NHPs for biomedical research purposes, both internationally and within the borders of the United States (ORIP, 2018a,b). The most significant of these corporate policy decisions is the cessation of air transportation of NHPs by major commercial air carriers, with most noncharter carriers being influenced by public pressure to restrict NHP transport (Abbott, 2014; AviationPros, 2013; Grimm, 2018; Wadman, 2012). Added in 2022 to this list of carriers were Egypt Air; Kenya Airways; and Air France, the last major carrier to provide international air transport for NHPs (Daley, 2022; O'Grady, 2022; Roscoe, 2022). Alternative international transportation options, such as transit by sea, are not permitted because of the deleterious effects of the long journey on the animals' health (Wadman, 2012).

These changes in policies have impacted the availability of and access to NHPs by U.S.-based investigators both directly, with investigators increasingly being unable to import animals because of transportation barriers, and indirectly, because of increased demand and cost for domestically produced primates. Four of seven NPRCs reported that transportation issues limit their ability to meet investigator demand; transportation issues were also cited

as a barrier by National Resources (National Resources Information Request, 2022; NPRC Information Request, 2022). Among NHP investigators who responded to the committee's survey noting specific challenges with accessing NHPs for their research (n = 175), 18 percent attributed these challenges to transportation issues (see Table B-24 in Appendix B) (NHP Investigators Survey, 2022).

Domestically, U.S.-based NHP research is increasingly relying on ground transportation in response to the lack of air travel options. This shift in transportation mode has various implications for both investigators' access to animals and the animals' health and safety (Prescott and Jennings, 2004), as well as that of the public (Elmore, 2008), during transport. For example, the vast majority of the NPRCs and National Resources are located along a coastline and investigators requiring animals may experience difficulties in transporting animals to their home institutions or in traveling to an NPRC to carry out their research. One significant concern with long-duration transportation of NHPs is the increased risk of accidents. In 2020, for example, a truck transporting NHPs caught on fire in New Jersey (Tarrazi, 2020), and in 2022, a collision between a dump truck and a truck carrying a trailer with NHPs in Pennsylvania resulted in the euthanasia of multiple animals (AP, 2022). Increased travel times increase the risk of illness in the animals, as well as their degree of stress (Elmore, 2008; Prescott and Jennings, 2004), as indicated by elevated levels of cortisol (Nehete et al., 2017) and weight loss (Málaga et al., 1991). Some animals may be unable to stabilize once resettled in their new locations. Outwardly sick and/or injured NHPs cannot be used in research, compounding an already limited and insufficient NHP supply.

Short-Term Efforts by Stakeholders to Address Impacts of Unmet Investigator Demand

Both NIH and NPRCs have actively undertaken measures to ameliorate the impacts of limited NHP supply on biomedical research (Eisinger, 2022), although the NPRCs emphasized that these efforts, while beneficial, are only short-term measures, and that long-term solutions are needed to address the persistent shortfall in supply, including increased and continued investment in domestic breeding of animals, infrastructure, and personnel (Morrison et al., 2022). Recent measures to address NHP supply constraints have involved coordinated action around specific public health threats to prevent duplication of research across multiple centers and enhance complementary work, thereby reducing the total number of NHPs needed to carry out the proposed research. Additionally, the reuse of animals is prioritized where possible (NIH, 2022a), although not all NHPs will be fit for reuse based on prior research interventions.

There have been strategic efforts to maximize the usefulness of the NHPs that are available. In response to the exacerbation of the shortage of animals during the COVID-19 pandemic, for example, NIH provided funding to build a partnership across the seven NPRCs called the Coronavirus Vaccine and Therapeutic Evaluation Network (CoVTEN). This coordinated NPRC effort, led by the Tulane NPRC, was aimed at standardizing research protocols and methods, collecting and disseminating preliminary data, and reducing numbers of NHPs needed by using a single control group across multiple studies (NASEM, 2021; Rappaport, 2022; Tate, 2021). Other efforts undertaken to maximize the limited supply of NHPs included policy changes by NIH that allowed for SPF colony repurposing, as well as ORIP's publication of a notice of limited availability of research NHPs in March 2021 (Eisinger, 2022). This notice formalized the prioritization of NHPs at NPRCs and National Resources to conserve their use for research that is "urgently required to save human lives or shorten the COVID-19 pandemic" (HHS, 2021).

Impacts on Research from Unmet Demand

The inability of NIH-supported NPRCs, National Resources, and other suppliers to fulfill the demand for NHPs by NIH-supported investigators has direct implications for biomedical research both now and in the future. Concerns about NHP supply and the impacts of not meeting investigator demand are also noted in the 2018 ORIP report (ORIP, 2018a,b), but information gathered by the committee suggests that these same issues now impact a growing proportion of investigators. Among the 64 percent of NIH-supported investigators who responded to the committee's survey and reported experiencing challenges with obtaining NHPs, reported impacts on research projects included significant delays in planned research activities (91 percent), alterations to study design driven by operational constraints rather than scientific need (e.g., reduction in sample size) (53 percent), and loss of grant funding or study termination (3 percent). Some investigators who were able to obtain animals reported that they accepted animals not considered ideal for their purposes (e.g., change of species, use of a single sex) (NHP Investigators Survey, 2022).

Experiences with extended research delays were also reported by multiple ICOs, including NIAID, NIA, NCI, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), NIMH, NIDDK, NIDCD, NHLBI, and the NIAAA, among others. Additionally, ICOs noted cases in which investigators were unable to access NHPs with specific characteristics (e.g., seronegative status for adeno-associated viral vectors), which caused significant delays, posed a risk to the completion of critical research, or required the alteration of study designs. In an example provided by NIDA, a study had to be modified because male marmosets were not available for germ cell studies. In another example, provided by NIAID, an extramural research team developing a triage device for radiation emergencies had to request a second no-cost extension because they were waiting for NHPs to be available (NIH, 2022a).

As noted previously, another concern expressed was that biomedical research, like the microchip industry, will continue to relocate overseas, thus ceding scientific leadership to China and other countries (Einhorn and Lew, 2022; ORIP, 2018b). Already, cutting-edge biomedical research is increasingly being conducted in China, as reflected in its growing share of high-impact research publications (see Figure 3-3) (Conroy and Plackett, 2022; Makris et al., 2009).

STATE OF CURRENT NHP RESEARCH INFRASTRUCTURE: GAPS AND NEEDS

Physical Research Infrastructure

In response to concerns related to the difficulties of NPRCs and National Resources in continuing to provide adequate numbers of NHPs for NIH-supported research and the need to invest in the maintenance of existing NHP research resource infrastructure, the 2018 ORIP report includes a recommendation that ORIP provide greater support for NHP research resources that support NIH's extramural grant programs (ORIP, 2018b). After accounting for inflation, however, the committee found that ORIP support for NPRCs decreased from 2012 to 2022 (see Figure 3-4). There also has been no sustained increase in P40 grant support for National Resources (after adjusting for inflation) over that same period (see Figure 3-5). It is noteworthy that some additional support has been provided through grant supplements in recent years. Neither increased supplemental funding for NPRCs and National Resources awarded by ORIP immediately after the 2018 report was published as part of an effort to address the report's recommendations nor increased supplemental funding provided dur-

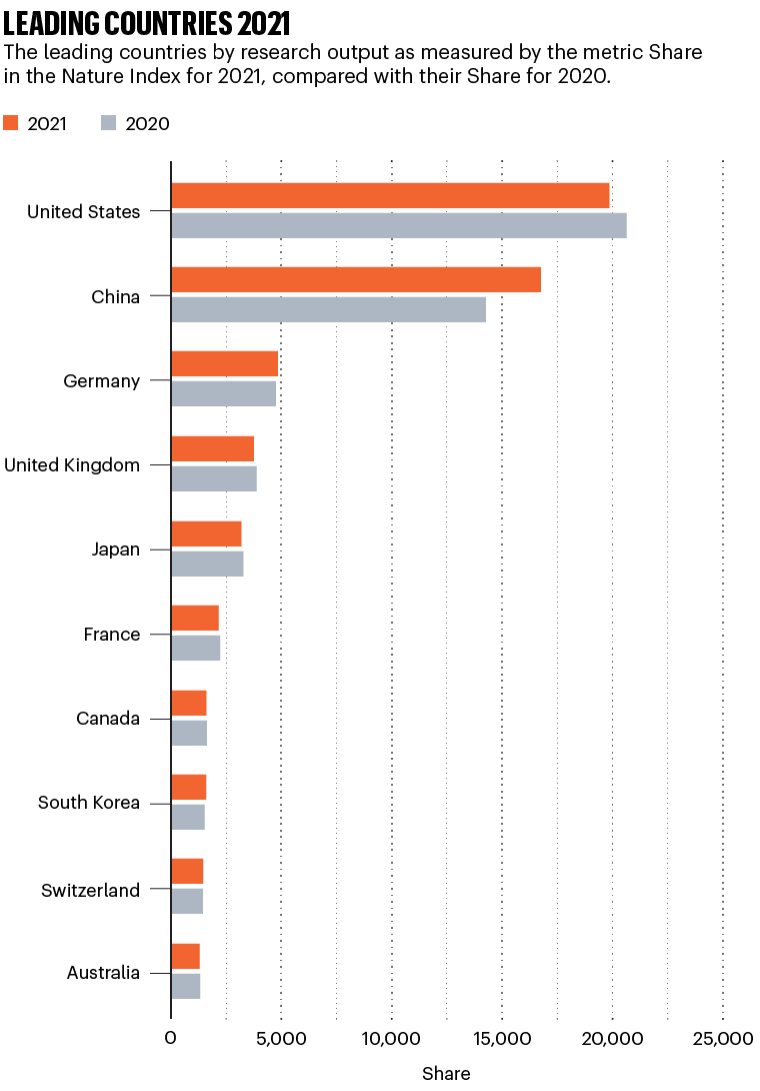

FIGURE 3-3 Performance of leading science nations on the Nature Index.
NOTE: China's adjusted ranking in 2021 increased by more than 14 percent from 2020, whereas the U.S. ranking decreased by more than 6 percent over the same period.
SOURCE: Image reproduced with permission from Conroy, G., and B. Plackett. 2022. Nature index annual tables 2022: China's research spending pays off. Springer Nature.

ing the COVID-19 pandemic (Eisinger, 2022; Grieder, 2022; Subbaraman, 2021) has been sustained. This persistent budgetary shortfall limits the ability of NPRCs to carry out their critical dual role as both major providers of NHP resources and physical centers of biomedical research services and expertise as they attempt to meet increasing demand for NHP resources.

Both the NPRCs and National Resources emphasized that consistent and adequate funding for operational expenses—both day-to-day operational requirements and the maintenance and expansion of aging physical infrastructure—is essential if they are to continue to provide

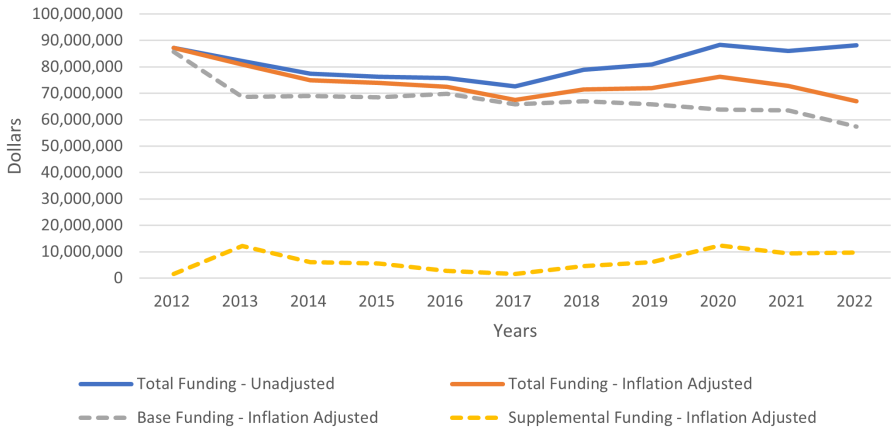

FIGURE 3-4 P51 National Primate Research Center awards, fiscal years 2012–2022, adjusted for inflation.
NOTES: Dollar amounts are presented both as nominal dollars (blue line) and inflation-adjusted dollars (orange line) as calculated by the Consumer Price Index for all urban consumers. Inflation adjustments were made using the Bureau of Labor Statistics calculator, placing all dollar amounts in 2012 dollars and then computing the difference between the projected 2012 dollar value and the annual award value.
SOURCE: NIH RePORTER, 2023a.

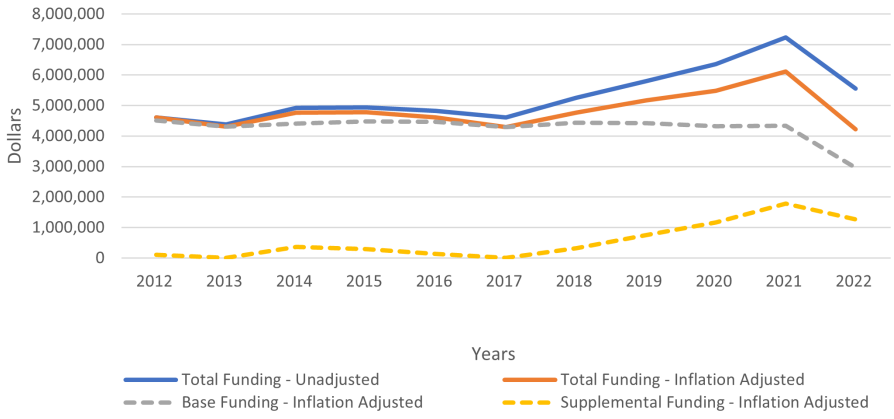

FIGURE 3-5 P40 research center awards for National Resources, fiscal years 2012–2022, adjusted for inflation.
NOTES: Dollar amounts are presented both as nominal dollars (blue line) and inflation-adjusted dollars (orange line) as calculated by the Consumer Price Index for all urban consumers. Inflation adjustments were made using the Bureau of Labor Statistics calculator, placing all dollar amounts in 2012 dollars and then computing the difference between the projected 2012 dollar value and the annual award value. The P40 mechanism is not the exclusive funding tool used by the National Institutes of Health for Office of Research Infrastructure Programs–supported National Resources. The Johns Hopkins University does not currently receive support through the P40 funding mechanism.
SOURCE: NIH RePORTER, 2023b.

research services and ensure animal welfare and to meet current and future demand for high-quality NHPs while reducing reliance on imported animals (Hutchinson, 2022; Morrison et al., 2022; Rappaport, 2022). ORIP frequently offers competitive supplemental awards for the NPRC P51 grants, which are awarded on a year-to-year basis and provide an important mechanism for addressing unanticipated non-recurring costs. As emphasized by the NPRCs, however, these supplemental awards tend to be short term (they can decrease or completely stop from one year to the next) and narrowly focused (e.g., dedicated to a specific type of renovation, replacement of research equipment, or a singular research area), often cannot be used for overhead or operational expenses, and are insufficient to expand center-wide infrastructure to meet increasing demand (Morrison et al., 2022). Investment in existing NHP infrastructure to build capacity that can meet biomedical research needs cannot be piecemeal or short term. The successful expansion or establishment of domestic breeding programs with the capacity to generate 1,000 NHPs annually, for example, would incur up-front costs and require an extended start-up time before any NHPs would be available for use by investigators (Subbaraman, 2021). The NPRCs noted that these requirements do not fit into the typical 5-year duration of research grants or the NPRCs' P51 base grants (Morrison et al., 2022).

As stated previously, these centers have little financial flexibility to expand the production of key NHP species to address unmet investigator demand and ensure the capacity to respond to future public health emergencies. For several ORIP-supported stakeholders in recent years, breeding expansion plans and renovation of aging infrastructure have been postponed or halted as a result of changing priorities for the use of funds during the COVID-19 response and increased costs of building materials resulting from supply chain issues during the pandemic (Rappaport, 2022). The 2020 CARES Act allowed NIH to invest in colony infrastructure at NPRCs, with the goal of expanding rhesus macaque breeding capabilities (NIH, 2022b). Eighteen P51 supplemental awards were funded using CARES Act funding between 2020 and 2022, accounting for more than half of all P51 supplemental awards during this period (NIH RePORTER, 2023a). The NPRCs noted, however, that while this supplemental funding helped them meet critical needs during the COVID-19 pandemic, both base and supplemental funding levels have remained insufficient to address the larger infrastructure issues that limit their ability to meet investigator needs. These shortfalls in operational budgets have also been felt by NHP investigators at academic institutions with their own NHP resources, who have experienced shortages of space or NHP housing that have resulted in research delays and higher daily operational costs. Ultimately, dedicated, consistent funding for existing research infrastructure would limit the strain on NHP resources and allow for recovery and planning for future public health needs.

Data Infrastructure

A critical aspect of ensuring that NHPs are available for future NIH-supported biomedical research is the capacity of stakeholders to collect accurate data with which to track NHP use so that future needs can be forecast (Contreras et al., 2021). As discussed previously, however, there presently is no comprehensive mechanism for tracking NHPs used for biomedical research in the United States or for NIH-supported research specifically, and the systems that do exist have limited capabilities or are largely inaccessible to the public, to NHP researchers, to NPRC and National Resource leadership, and even to NIH administrators. For example, while USDA data provide up-to-date, annual information on the numbers of NHPs reported in research facilities nationally, including facilities used in NIH-supported intramural and extramural research programs, no information is available on the origin or species of the animals, the type of research funding, or the animals' use over time. Similarly, no public-

facing data system exists with which to quantify the number of animals produced domestically, or the number used each year by NIH-supported investigators. Thus, it is impossible to quantify NHP supply and demand accurately so that proactive, evidence-based measures can be implemented to support NHP resource management decisions at the national level.

While recognizing that forecasting of future NHP resource needs is an ongoing challenge, NIH itself provides no funding for comprehensive programs with which to track animals involved in NIH-supported research activities, nor does it actively track those animals in extramural research facilities or their use by researchers. NIH views tracking of NHPs within extramural facilities as the responsibility of its grantees and asserts that any mandatory data collection would impose a significant burden on both facilities and researchers (NIH, 2022b). In lieu of collecting quantitative data on NHP supply and demand across its sponsored research activities, NIH engages in meetings with stakeholders it regards as having greater expertise in NHP inventory planning (e.g., NPRCs), in addition to commissioning ad hoc studies (e.g., the 2018 ORIP report).

Comprehensive tracking of NHP resources in the intramural program is also limited. However, each individual ICO holding or using NHPs for intramural research purposes tracks the number of animals and NHP species held to assess its own NHP resource maintenance and infrastructure needs, to monitor colony health, and to determine per diem cost allocations (NIH, 2022b). Yet it is unclear whether or how these data are used to coordinate intramural program resources or to forecast future needs for the broader landscape of NIH-supported biomedical research.

NHP Research Workforce

NPRCs and National Resources view staffing and training concerns as a significant barrier to meeting demand for NHPs from their facilities. NPRCs, National Resources, and other stakeholders point to the lack of access to supplementary funding with overhead funds for hiring and keeping personnel, an insufficient pipeline of early-career professionals entering the field, and rampant staff burnout during the COVID-19 pandemic as the main factors in these concerns.

As a barrier to maintaining a fully staffed workforce, NPRCs noted that the supplementary funding provided by NIH to cover infrastructure expansion does not always cover the personnel requirements associated with maintaining expanded breeding colonies or research facilities. These centers also face issues with recruiting a skilled workforce (Morrison et al., 2022). Stakeholders, including NIH, noted that the pipeline of professionals entering this line of work appears to be decreasing and that those professionals are increasingly recruited by private companies. These barriers limit the feasibility of hiring and retaining well-trained staff across all levels of training and all backgrounds (National Resources Information Request, 2022; NIH, 2022b; NPRC Information Request, 2022). There is an ongoing need for animal care staff, veterinary nurses/technicians, behavioral managers, veterinarians, and pathologists. In testimony given to the committee, stakeholders pointed to the value of training grants (Hopkins, 2022; Hutchinson, 2022), which are limited in number, as a tool for helping to develop and retain this talent (e.g., R25 for veterinarian and veterinary tech training and T32 and K awards for early-stage investigator support).

These staffing challenges, previously noted in the 2018 ORIP report, were exacerbated by the COVID-19 pandemic. Representatives from multiple NPRCs and National Resources at the committee's August 2022 workshop cited high turnover of trained personnel and considerable staff fatigue as an ongoing challenge made worse by the pandemic (Haigwood, 2022; Hopkins, 2022; Hutchinson, 2022; Martinez, 2022). The heightened demand for NHPs during the pandemic also led to an increase in the number of trained staff needed to man-

age the care and use of NHPs. For example, the pandemic resulted in a higher demand for biocontainment laboratory spaces required for conducting research on SARS-CoV-2, which in turn required additional skilled personnel to work in these settings, along with specialized training to ensure their safety (Hild et al., 2021).

Funding shortages, along with the many uncertainties surrounding NHP availability, also create challenges to encouraging students or junior scholars to pursue NHP research in the future. The perception of NHP research as an increasingly risky profession to pursue could potentially change the profile of investigators willing to enter this field (Basso, 2022), ultimately reducing the strength and diversity of the workforce. Thus, it is essential to address the staffing challenges outlined above not only to maintain the caliber of research currently being carried out, but to also meet the needs of NIH-supported NHP research for the future.

CONCLUSIONS

The committee's assessment of the current state of the NIH-supported research landscape since the publication of the 2018 ORIP report showed that NHP resources remain insufficient to meet the demands of the NIH-supported biomedical research ecosystem. The committee found that this shortage is worsening as a result of a combination of inadequate action following publication of the 2018 ORIP report and the pressures posed by external events (e.g., the Chinese ban on the export of NHPs, the COVID-19 pandemic). In turn, domestic resources struggle to meet increasing demand for NHPs by intramural and extramural investigators. Other pressures on the NHP landscape, such as transportation restrictions, rising research and NHP costs, and workforce limitations, have exacerbated the inability of investigators to access NHPs and carry out their research, and this situation is likely to persist into the future absent targeted intervention. Underlying these issues is a critical lack of comprehensive data systems that can be shared across stakeholders to provide essential information on current NHP use. Such databases are needed to develop evidence-based forecasts of future use and anticipated research needs.

Considered cumulatively, the research landscape would benefit from a unified response—such as a national plan for NHP research resources (discussed further in Chapter 5)—to proactively assess, track, and evaluate stakeholder needs and system barriers and ensure that the United States is able to carry out critical biomedical research using NHPs when appropriate, including in response to future public health emergencies. The committee's conclusions, presented below, build on its findings regarding NHP resources and NIH-supported biomedical research using NHP models, as well as future needs for NHP resources.

Conclusion 3-1: The shortage of nonhuman primate resources for National Institutes of Health (NIH)–supported biomedical research has continued to worsen, extending beyond concerns raised in the 2018 report of the NIH Office of Research Infrastructure Programs. This resource shortage has been exacerbated by export and transportation restrictions and global public health emergencies.

Conclusion 3-2: Without decisive action and a national commitment to a comprehensive plan for nonhuman primate (NHP) availability, the ability of National Institutes of Health (NIH)–supported extramural program investigators to conduct studies requiring the use of an NHP model will become a function more of access to NHPs than of a concerted response to national public health priorities. The core tenet of NIH that the most meritorious research should receive the highest priority will thereby be threatened.

Conclusion 3-3: Inadequate nonhuman primate (NHP), physical, financial, and human resources, along with the high costs of NHPs, severely limit the ability of National Institutes of Health–supported research programs to respond adequately to public health emergencies, as well as to carry out high-impact biomedical research requiring NHP models.

Conclusion 3-4: Biomedical and public health research in the United States is threatened by dependence on imported nonhuman primates (NHPs). This reliance on external resources is unsustainable and undermines the security of the U.S. biomedical research enterprise. To ensure that NHP resources are available to respond to public health threats, the United States needs to prioritize expansion of domestic NHP breeding programs.

Conclusion 3-5: The National Institutes of Health (NIH) has no central data management or reporting structure across its intramural and extramural programs to provide accurate tracking of the numbers of nonhuman primates (NHPs) required to meet current and future research needs. NIH thus has no way to collect the quantitative data needed to implement a comprehensive strategic management plan for its NHP research and resource portfolio.

Conclusion 3-6: Inadequate coordination of nonhuman primate (NHP) resources and research programs at the national level contributes to missed opportunities and diminished opportunities for efficient use of limited NHP resources.

Conclusion 3-7: Although the 2018 report of the National Institutes of Health Office of Research Infrastructure Programs (ORIP) identified a serious shortage of nonhuman primate (NHP) resources that was likely to worsen in the future, support for the ORIP-funded national NHP resource infrastructure remains inadequate.

Conclusion 3-8: Inadequate support for national nonhuman primate (NHP) resources by the National Institutes of Health (NIH) Office of Research Infrastructure Programs represents a major threat to NIH-supported NHP research programs nationwide. Funding will have to address current and future needs and the infrastructure required to support them.

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4

The Landscape of New Approach Methodologies

There are numerous motivations—economic, logistical, social, and strategic—for transitioning away from nonhuman primates (NHPs) as research models when doing so is scientifically feasible. The COVID-19 pandemic, for example, demonstrated the importance of NHPs in biomedical research, but also the risks and challenges associated with dependence on NHPs as research models, such as bottlenecks in the development of countermeasures for public health threats that result from finite NHP resources and the lack of suitable alternatives (Hewitt et al., 2020). Accordingly, investigators using NHPs have been clear about their interest in replacing NHPs with other models if the ability of these models to answer the scientific questions under study can be established. New approach methodologies have been used to answer diverse questions of biomedical relevance, and ongoing research efforts continue to explore their potential to

- improve the translatability of nonclinical research by providing data that optimally reproduce the human condition;
- extend current knowledge of human diseases and provide opportunities to gain additional insights, as well as identify knowledge gaps;
- address shortages in the supply of NHPs by reducing the numbers required for biomedical research; and
- replace the use of NHPs in biomedical research.

In the context of this report, the term "new approach methodology" encompasses in vitro and in silico technologies and approaches that can be used to *complement* NHP studies or *reduce reliance on* NHPs in biomedical research (see Box 1-2 in Chapter 1). A technology or approach may complement NHP research, for example, if it provides additional insight into human physiology or disease. Complementary approaches may or may not help reduce reliance on NHPs, which can be achieved by substituting alternative models or decreasing the numbers of NHPs used in research. An example is the current practice of screening therapeutic candidates with new approach methodologies before progressing to an NHP

model to answer questions that only such a model can answer, thereby directly reducing the number of studies conducted using NHPs and potentially reducing the likelihood that subsequent testing in NHPs will cause harm. The ability to substitute a different model to answer a specific research question does not negate the need for NHP models altogether.

Importantly, the value of in vitro and in silico models is not limited to their ability to reduce reliance on NHPs, as this is rarely the intended purpose for the development of such technologies and approaches. In fact, the committee did not identify any specific examples of studies conducted with the explicit objective of demonstrating that a new approach methodology was an effective substitute for NHPs. While there are examples discussed later in this chapter showing the potential for new approach methodologies to reduce reliance on NHPs, in vitro and in silico models are often used in ways that are complementary to NHP studies and that can help to answer different kinds of scientific questions, including those that cannot be answered using NHP models.

It is important to note that scientists conducting research are always expected to seek out nonanimal or non-NHP methods wherever feasible, and to determine that research using NHPs is the most appropriate (or only) means of answering the scientific question at hand before seeking to use them. Indeed, for proposals responding to NIH funding opportunities that involve the use of NHPs, consideration of alternatives and justification of the use of NHPs are required elements of a separate vertebrate animals section of the grant application. It should also be acknowledged that some technologies and approaches used in NHP research—such as minimally invasive and noninvasive methodologies for the collection of data (e.g., digital biomarkers, including in home enclosure recording) and samples (e.g., laparoscopy, positive reinforcement training of NHPs to voluntarily provide samples) and assays that provide results with samples of decreasing volume/size—can also contribute to reducing the numbers of NHPs used in research. Such technologies and approaches are not considered new approach methodologies for the purposes of this report but are discussed separately in Chapter 5.

As science advances and new technologies and approaches become available, the biomedical research enterprise needs to be prepared to integrate these new approach methodologies into the armamentarium available for addressing research questions related to the nation's most pressing public health and medical needs. Research investments in exploring opportunities to accelerate the adoption of new approach methodologies are therefore important, and this chapter begins by describing a pathway for adoption of a new technology or approach. The chapter goes on to describe examples of new approach methodologies that can complement or reduce reliance on NHP models for some research questions while explaining why full replacement of NHP models is not yet feasible. The discussion turns next to recent changes in the regulatory landscape that are shaping the use of NHPs and alternatives for studies involving human safety, and then examines the needs and opportunities for facilitating collaboration between NHP researchers and those who develop and use new approach methodologies. The chapter ends with the committee's conclusions regarding the status of new approach methodologies and the steps needed to further their adoption so as to reduce reliance on NHPs.

A PATHWAY FOR ADOPTION OF NEW APPROACH METHODOLOGIES

Translational relevance[1] is the anchor for any nonclinical model system, animal or otherwise, that is intended to help understand, prevent, or treat a human condition. The principles

[1] As defined in Chapter 1 (Box 1-2), translational relevance in this context is the degree to which findings from research using NHPs apply to humans.

that define translational relevance include replication of human physiology and pathophysiology (organ responses or disease state/pathogenesis), genetics, epigenetics, and/or other aspects of the biology of human cells. New approach methodologies are expected to meet translational expectations if they are to be broadly adopted to decrease reliance on NHPs in biomedical research. Attaining sufficient legitimacy based on its performance (track record) is key to successful adoption of a new approach methodology by scientists and organizations (Eckert et al., 2020; Marx et al., 2020; van der Zalm et al., 2022). Once a new approach methodology has demonstrated that it is equivalent or superior to other models for predicting or explaining human conditions or outcomes, it may be adopted as a model of choice (FDA, 2022b). Ultimately, the performance of a technology or approach determines whether it can be used to answer a specific research question. Although performance uncertainty is inherent in all new technologies and approaches, resource investments that can reduce that uncertainty are required to accelerate their adoption. This requirement is framed in the sections that follow as mapping out a pathway to adoption for a new technology or approach.

Key Terminology

Important terminology used to describe the components of a pathway to adoption for promising new approach methodologies include

- context of use,
- qualification,
- validation, and
- benchmarking.

These terms are defined here to support and provide guidance for those seeking to determine the status and credibility of an emerging technology or innovative approach for an intended use. More detailed discussion of these terms can be found elsewhere (Fabre et al., 2020; FDA, 2017; FDA and NIH, 2016; Patterson et al., 2021; Steger-Hartmann and Raschke, 2020; Tadenev and Burgess, 2019).

Context of Use

Context of use (COU) defines the manner and purpose of use for a technology or approach (how and when it will be used) (Baran et al., 2022; FDA, 2017, 2020). This term can generally be applied for any intended use of a methodology. COU elements include

- what is measured and in what form, and
- the purpose of the technology or approach in the testing of hypotheses or decision making/action.

The term "fit for purpose" is occasionally used synonymously with COU. However, a fit for purpose statement is meant to communicate that the intended use of a technology or approach is supported by validation/qualification information (FDA and NIH, 2016).

Qualification

Qualification is the process of confirming that a methodology is capable of yielding reproducible results that are suitable for the intended purpose based on the defined COU

(Kennett, 2010). A technology or approach that is qualified for a specific COU can be relied upon to have a specific interpretation and application (FDA, 2017, 2020; FDA and NIH, 2016). The pathway for qualification of a new approach methodology is depicted in Figure 4-1, which shows that specifying the COU is a first step and defines the needs for the subsequent steps (Parish et al., 2020).

Validation

Validation is the process by which the reliability and relevance of a technology or approach is established for a defined purpose using specific criteria (OECD, 2005). The process includes assessments of the methodology's sensitivity, specificity, precision, robustness, reproducibility, and stability. Formal validation can involve intensive and costly processes that may not be necessary for all uses of a new approach methodology (FDA, 2017; ICCVAM, 2018); expectations may vary depending on the particular technology or approach.

Qualification versus Validation

Qualification and validation of a methodology denote the means used to demonstrate its suitability for its intended purpose (FDA, 2017; FDA and NIH, 2016). One way to describe the difference between the two terms is that they differ as to the extent and robustness of the parameters evaluated and the number of replicates performed for each. The extent to which a technology or approach needs to be qualified or validated depends on the decisions to be made with the data it generates, including the interpretation of the data and subsequent actions to be taken for a given outcome. For example, are the data intended for regulatory use, or to advance understanding and guide subsequent investigations? COU and assay qualification are intended to help decrease barriers to adoption by highlighting data that confirm a level of validation appropriate for the intended use of the methodology (FDA, 2017).

Benchmarking

Benchmarking entails rigorous comparison of the performance of different technologies or approaches to determine the strengths of each or to provide recommendations regarding their suitability for the purpose at hand (Weber et al., 2019). Benchmarking has several ben-

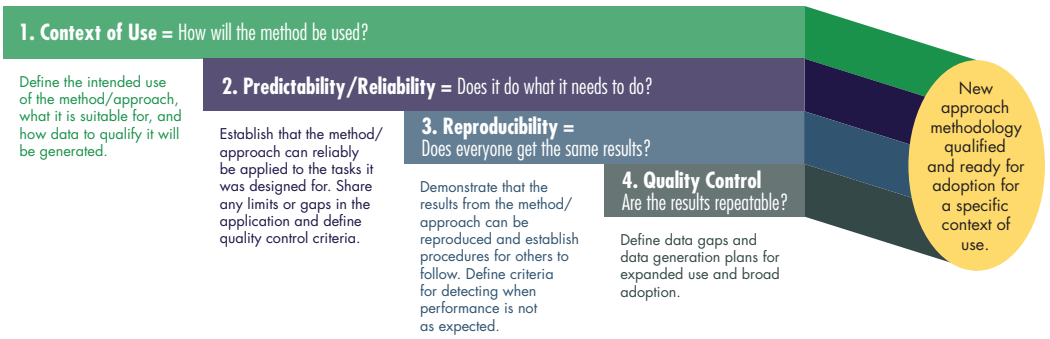

FIGURE 4-1 Pathway for qualification of the performance of a new approach methodology for a specific context of use.

efits, including increasing awareness of emerging technologies and approaches (NIH, 2023) and understanding how the performance of a new approach methodology compares with that of in vivo approaches. Benchmarking is also appropriate for comparing new approach methodologies relative to the same or different intended uses for a model, allowing for identification of the most appropriate technologies and approaches for specific COUs (Mangul et al., 2019; Wu et al., 2023).

Applying Translational Principles and Qualification/Validation of New Approach Methodologies on a Path to Reducing Reliance on NHPs

When properly qualified or validated, new approach methodologies present great potential to address specific research questions, particularly when intended to decrease reliance on NHPs in biomedical research. In considering the adoption of new approach methodologies to reduce reliance on the use of NHPs in biomedical research, it is reasonable to adopt principles of translational relevance to define qualification and/or validation pathways and to establish a well-defined COU (Low et al., 2021). Qualification schemes for emerging technologies and approaches are highly dependent on the complexity of the questions (or mechanistic hypotheses) of interest and the pathophysiology necessary to answer those questions (Ekert et al., 2020; Hargrove-Grimes et al., 2022; van der Zalm et al., 2022). Even when use of the data derived from a new technology or approach is intended to address a fundamental research question rather than to inform explicit regulatory decision making, there should be confidence that the approach can yield reliable data for its intended purpose. For example, if a new approach methodology is expected to reduce reliance on an NHP model of pulmonary fibrosis, that approach or technology would be expected to recapitulate the underlying molecular and cellular mechanisms that are present and relevant in NHP or human disease. Similarly, the use of new approach methodologies for investigational research in pharma is not defined or restricted by regulatory guidance, and many new approach methodologies are being used now in this context. In contrast, the adoption and integration of a new approach methodology to determine whether a candidate is sufficiently safe to be used in clinical trials needs to be based on proven robustness and a high level of confidence in the technology or approach (Pognan et al., 2023). The level of robustness and confidence required is often afforded by appropriately rigorous qualification and validation and ultimately determined by the intended use of the data.

Specifically, expectations for the stringency of the qualification or validation process relate to the decisions the data will inform and the potential consequences of those decisions for human health. The expectations for stringency may differ when, for example, the COU is the safety evaluation of a novel drug rather than a basic biology application, such as understanding host–pathogen interactions.

NEW APPROACH METHODOLOGIES WITH THE POTENTIAL TO COMPLEMENT OR REDUCE RELIANCE ON NHP MODELS IN BIOMEDICAL RESEARCH

This section describes new approach methodologies with the potential to complement or reduce reliance on NHP models in biomedical research. These examples are intended to be illustrative and do not represent a comprehensive cataloging of all possible new approach methodologies. Although some of these technologies and approaches have shown promise in specific applications, those applications cannot necessarily be generalized to other

COUs. Rather, each COU will pose specific requirements that must be addressed when any technology or approach is intended to complement or decrease reliance on NHP models. No data set can support a summary of the validation state of new approach methodologies as a whole.

As discussed in Chapter 1, the committee did not include animal models within its definition of new approach methodologies, but with the advancement of genome editing technologies and cell/tissue transplant approaches, it should be acknowledged that engineered animal models also have the potential to complement and reduce reliance on NHP models in biomedical research.

In Vitro Cell Culture Models

The sections below provide examples of in vitro assays as well as two-dimensional (2D) and three-dimensional (3D) human cell culture models with great potential to complement NHP research and, in some cases, reduce reliance on NHPs.

In Vitro Immunoassays

In vitro immunoassays that use cultured human cells, such as assays that predict the risk of cytokine release syndrome,[2] provide a clear example of how in vitro models can address a question related to human safety (Finco et al., 2014). Cytokine release syndrome is an acute systemic inflammatory syndrome that may be triggered by biologic therapeutics, such as monoclonal antibodies (Eastwood et al., 2010), including those used to treat COVID-19. There are several validated methods for assessing the potential risk that immune-modulating drugs or other treatments will trigger exaggerated levels of cytokine release in vivo (Vessillier et al., 2020). Use of in vitro cytokine release assays can aid in the prediction of human physiological responses (Joubert et al., 2016), thus reducing reliance on NHPs for this purpose.

2D and 3D Stem Cell–Based Cell Culture Models

Cell culture models may use immortalized cell lines or primary cells isolated from animals, and both sources have been used to create in vitro models for biomedical research. Given that the use of NHPs in research is driven mainly by their translational relevance to humans, this section focuses primarily on stem cell–based 2D and 3D cellular models with completely human genomes. These 2D and 3D models offer opportunities for translational relevance and may be used in specific contexts to complement or reduce reliance on NHP models, particularly if they are qualified for use and can be relied upon for reproducible results of high quality. While the committee distinguishes between 2D and 3D cell culture models for the descriptions found in this section, appropriate spatial organization and replication of organ functions are important features for both.

The discovery of human induced pluripotent stem cells (iPSCs) in 2006 by Dr. Shinya Yamanaka (2012) transformed cell culture systems and their use to answer critical human health questions. These cells are generated by introducing the Yamanaka factors (Oct3/4, Sox2, Klf4, and c-Myc) into skin fibroblasts or peripheral blood mononuclear cells, resulting in cells that can be differentiated into various cell types (Lam and Wu, 2021). Under specific differentiation conditions, most tissue/organ cell types can now be reliably generated from human iPSCs. Whereas iPSCs have the potential to generate all cell types in a human body,

[2] Of note, not all in vitro cytokine release assays involve the culturing of human cells.

adult human tissue stem cells (ATSCs) have a more limited differentiation capacity (Chang et al., 2019). These tractable and renewable cell systems contain the complete human genome and can be used to study human gene functions, biochemistry, physiology, and molecular mechanisms. Both iPSCs and ATSCs can be derived from individuals of various genetic and ethnic backgrounds, offering unique advantages in understanding genetic and molecular mechanisms governing human cell biology and physiology. Moreover, iPSCs and ATSCs can be generated from patients, providing unprecedented opportunities for revealing disease-related phenotypes; understanding pathology; identifying disease-specific biomarkers; and screening for potential treatments, including personalized treatment strategies (Chang et al., 2019; Moradi et al., 2019; Son et al., 2017).

2D cell cultures are the most simplified cellular model systems. They are composed of a single or a few cell types and lack the molecular and cellular complexity and interactions of human organs under physiological conditions (Jensen and Tang, 2020). In contrast, in vitro systems that contain multiple cell types representing cells from various organs are used in attempts to recapitulate human organs and are being connected to represent multiple organs. However, since an organ is a functional entity with a need for specific structural context, formally defining an in vitro system as an organ requires that functionality and structure be recapitulated to some extent. Multiple cell types have been placed together in elegantly engineered platforms to form "organ-like" structures, and a few have recapitulated functionalities and structural context to some extent (Hofer and Lutolf, 2021; Huh et al., 2011). For example, with the application of tissue-patterning factors and self-organization capabilities, human tissue–specific 3D organoids can be generated from iPSCs (as depicted in Figure 4-2), as well as some ATSCs (Artegiani and Clevers, 2018). Organoids may be phenotypically similar to human tissues/organs in cell-type composition; architecture; and, to a certain degree, function. In general, ATSC-derived organoids specialize in mimicking the physiology of functionally more mature organs, whereas iPSC-derived organoids are useful for modeling organogenesis in a developmental context (Schutgens and Clevers, 2020).

While recreating a whole organ or human body (which contains 78 organs) in vitro is appreciated as a futuristic goal, in the past decade human organoids with endoderm, mesoderm, and ectoderm origins have been generated that represent complex organs, including brain, liver, lung, airway, kidney, intestine, and sensory organs, among others (Artegiani and Clevers, 2018; Ho et al., 2018; Schutgens and Clevers, 2020). Compared with 2D cell culture models, human organoids are in general more complex and, in many cases, more physiologically relevant because they preserve or reconstitute the cell-type diversity of the organs in vivo. In some cases, they also maintain similarity to human organs at the molecular, cellular, and functional levels (Artegiani and Clevers, 2018; Schutgens and Clevers, 2020). Certain cells, such as milk-producing mammary gland cells, function as in vivo counterparts only when cultured under 3D conditions (Barcellos-Hoff et al., 1989). Patterned, self-assembled 3D organoids contain major cell types from the same lineage; cell types originating from different lineages, such as mesenchymal cells, vasculature cells, or immune cells, are usually not present (Ho et al., 2018; Qian et al., 2019).

Advances in 3D culture technology, microfluidics,[3] and bioengineering have led to the generation of more complex microphysiological systems (MPS). MPS are in vitro platforms composed of 3D constructs (including spheroids, organoids, bioprinted tissue constructs, and

[3] One of the technological advances driving the development of MPS platforms, particularly for drug-testing applications, is the effort to use inert plastic- or glass-based materials for fabricating chips. Materials that have traditionally been used for microfluidic devices (such as polydimethylsiloxane [PDMS]) suffer from drug and drug metabolite losses due to adsorption to device surfaces and absorption into the device material (Berthier et al., 2012; Hargrove-Grimes et al., 2022).

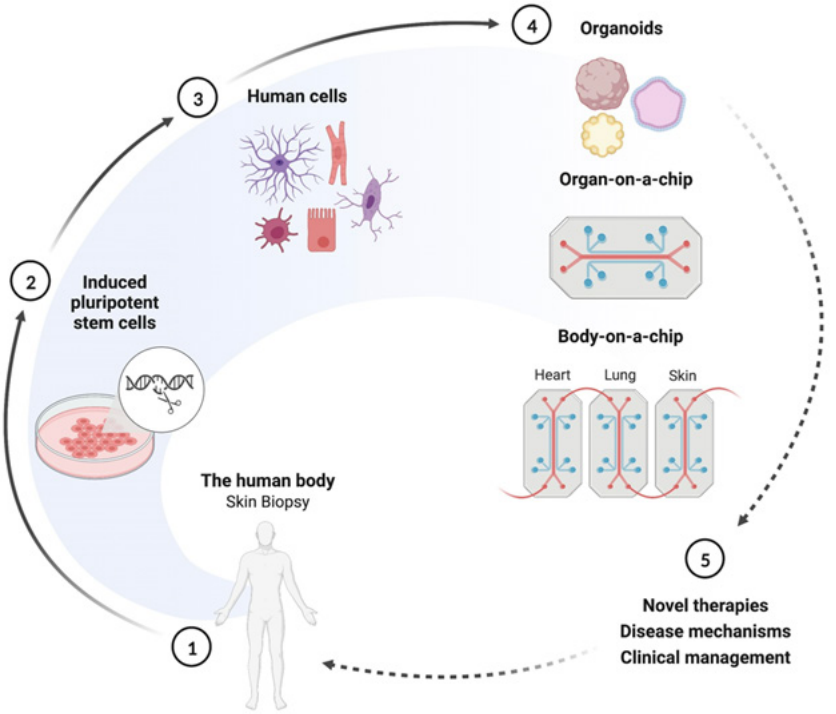

FIGURE 4-2 Generation and differentiation of induced pluripotent stem cells.
SOURCE: Image reproduced with permission from Ashutosh Agarwal and created with BioRender.com.

tissue/organs-on-chips) of human or animal origin that mimic the biochemical, electrical, and/or mechanical properties of organ or tissue function. The design of MPS platforms allows researchers to control the composition of the tissue and its architecture using cellular and extracellular cues—molecular, structural, and mechanical—found within the human organ system (Hargrove-Grimes et al., 2021). Vasculature or immune cells, for example, can be cocultured with various types of organoids (Sun et al., 2022; Trujillo and Muotri, 2018; Yu, 2021). More complex models can be created by fusing different types of organoids generated separately to create assembloids that reconstitute the interaction of multiple tissues (Kanton and Paşca, 2022; Paşca, 2019; Paşca et al., 2022). For example, brain, spinal cord, and muscle organoids have been assembled together to model the motor control from brain to muscle (Andersen et al., 2020). Through the integration of organoids and microfluidic chips, MPS enable the engineering of a more physiologically relevant in vitro model and permit closer control over cell–cell and cell–matrix interactions, biomechanical cues, nutrient delivery, and waste removal (Huh et al., 2011; Ingber, 2022). Box 4-1 describes biomedical applications for tissue-specific organoids and MPS.

The real power of MPS technology lies in the capacity of singular organ chips to reveal not only drug effects or biological response on primary human organs but also secondary effects stemming from organ–organ interactions. Therefore, multiorgan MPS are being designed to be as physiologically realistic as possible by connecting individual organ chips in a modular fashion (Ronaldson et al., 2022; Sung et al., 2019); factoring in functional organ scaling in the human body; and replicating those scaling parameters, such as organ volumes, volumetric

perfusion rates, and fluid-to-cell ratios (Malik et al., 2021). While multiorgan MPS with as many as 10 organ-specific components have been generated as proof of concept (Novak et al., 2020), MPS models being used in biomedical research are generally less complex. For example, since liver is the primary site for human metabolism, several "liver–other tissue" (e.g., liver–gut, liver–heart, liver–skin, liver–kidney, liver–muscle, liver–bone marrow–tumor tissue) MPS platforms have been developed to study potential side effects of both the parent compound and its metabolites on multiple downstream organs (Chang et al., 2017; Edington et al., 2018; Maschmeyer et al., 2015; McAleer et al., 2019; Sung et al., 2010; Tsamandouras et al., 2017; Vernetti et al., 2017; Wagner et al., 2013). Outside of the drug development space, multiorgan MPS are also being used to better understand human physiology and disease mechanisms. For example, a multiorgan MPS with liver, gut, and cerebral components has been used to gain insight into pathogenic mechanisms for Parkinson's disease (Trapecar et al., 2021). Another notable example of a complex multiorgan MPS is the EVATAR system, which includes separate organ modules for the ovary, fallopian tube, uterus, cervix, and liver within a microfluidic system to simulate the in vivo female reproductive tract. The system includes endocrine loops with a sustained circulating flow between all tissues and has demonstrated that the human female menstrual cycle can be modeled in vitro (Xiao et al., 2017).

Several scientifically rich hurdles remain. Finding an in vitro blood substitute that could perfuse all organ chips and regulation of the blood surrogate volume to mimic physiological levels are critical to obtain precise concentrations of drug/hormone/chemical metabolites in the blood surrogate volume (Malik et al., 2021; Herland et al., 2020). It is also important to build organ-specific endothelial barriers so that nutrients, oxygen, drugs, and other solutes must circulate through a common vascular conduit (Herland et al., 2020; Ronaldson et al., 2022). Ideally, each chip also requires on-chip analytical technologies so that effective functional readouts (in addition to viability and morphological analyses) can be carried out to assess the cellular responses to a specific challenge (Jalili-Firoozinezhad et al., 2019; Kujala et al., 2016; Odijk et al., 2015; van der Helm et al., 2019). If these technical challenges can be addressed, multiorgan MPS technology is poised to offer useful, cost-effective guidance in the early determination of drug toxicity and efficacy, response to hormones and endogenous metabolites, and modeling of human disease. Ultimately, the goal of multiorgan MPS efforts is not to build a perfect replicate of the human body but to provide a predictive model that is superior to animal models, including NHPs.

Cultured Tissue Slice Models

Cultured human tissue explants,[4] such as precision-cut-tissue slices (PCTS), offer some advantages over the 3D stem cell–based MPS models described above in that the natural architecture of the human tissue/organ is retained, all cell types found in the tissue are present and in their original tissue–matrix configuration, and tissue- or organ-specific functions (e.g., metabolic and some aspects of immunologic activity) are preserved to a certain extent (Liu et al., 2019; Majorova et al., 2021). While tissue slices have been used in biomedical research for decades, technological advances over the years that have enabled precision cutting of slices and extended cell viability during culture have increased the utility of this model system for answering specific research questions (Alsafadi et al., 2020). PCTS models can be generated from healthy or diseased human tissues (e.g., liver, kidney, brain, lung), enabling their use in understanding fundamental human anatomy and physiology, as well as disease modeling.

[4] While some may refer to tissue slices as ex vivo models, for the purposes of this report, tissue slices that are cultured are classified as in vitro systems.

BOX 4-1 BIOMEDICAL APPLICATIONS OF TISSUE-SPECIFIC ORGANOIDS AND MPS

Brain. The brain is the most complex organ in the human body. Intractable neurodegenerative diseases (such as Huntington's disease and Alzheimer's disease) present a unique challenge for drug discovery efforts, as well as a strong motivation for the development of human-relevant complex in vitro models. The self-organizing capacity of brain organoids can be used to perform developmental studies and to gain a better understanding of brain physiology, although they cannot fully recapitulate the complex processes of the human brain. Brain microphysiological systems (MPS) are now beginning to combine brain organoids with different methods for measuring electrophysiological readouts (Forro et al., 2021), which potentially can be implemented on a chip. As organoid technology matures in accurately replicating the intricate connection pathways between neurons, as well as communication with nonneuronal cells such as astrocytes and microglia (Forro et al., 2021; Smirnova et al., 2023), electrophysiological mesh sensors that can penetrate the organoids and collect live functional readouts from their core are also being developed (Li et al., 2019).

Retina. Retinal diseases, such as macular degeneration (the incidence of which is increasing with an aging population), diabetic retinopathies (the incidence of which is increasing because of increases in diabetes), and retinitis pigmentosa, are among the leading causes of vision loss in humans (CDC, 2022; Cross et al., 2022; NEI, 2021). The establishment of complex human tissue–based in vitro retina models is poised to impact ophthalmologic drug development. Much of the excitement is driven by the discovery of self-forming retinal organoids derived from human pluripotent stem cell sources that model the complex stratified retinal tissue in a human-relevant manner (Habibey et al., 2022). However, several challenges remain in culturing the inner and outer retina as one compartment self-organized from pluripotent stem cells (Singh et al., 2018). Quantitative psychophysical and electrophysiological tests have increased understanding of retinal function, development, physiology, and disease (Holder, 2001; Leinonen and Tanila, 2018). Therefore, incorporating such tests within an MPS can be a valuable addition.

Neuromuscular junction. The ability to combine microfluidics and stem cell technologies has opened up new opportunities for in vitro investigation of molecular and cellular phenotypes of devastating neuromuscular junction diseases such as amyotrophic lateral sclerosis, Charcot–Marie–Tooth disease, Duchenne muscular dystrophy, myasthenia gravis, and spinal muscular atrophy. Spinal cord neurospheres derived from engineered stem cells are often combined with skeletal muscle tissue to establish functional neuromuscular junctions in vitro (Natarajan et

Their ability to closely recapitulate in vivo conditions and enable the study of interactions at the molecular, cellular, and extracellular levels has made PCTS useful human-relevant models for research related to drug discovery, toxicology, and host–pathogen interactions, among other purposes (Alsafadi et al., 2020; Majorova et al., 2021). However, finite culture viability and limited accessibility of qualified human tissue constrain the scalability of this approach.

Examples Demonstrating Potential to Complement or Reduce Reliance on NHP Models

This section provides examples of the application of 2D and 3D human cellular models in research areas in which NHPs are commonly used. These examples include research

earlier are being implemented on a chip to stimulate neurons electrically in order to improve muscle maturation into myotubes (Yamamoto et al., 2021).

Liver. Liver organoids and MPS are rapidly maturing and are poised to benefit drug toxicity screening (Ewart et al., 2022; Jang et al., 2019). The liver plays an important role in metabolism of drugs after intake. Compared with typical liver MPS that incorporate monolayer cultures of hepatocytes and endothelial cells, liver organoids include higher complexity and form more in vivo–like structures (Gough et al., 2021; Harrison et al., 2021). Platforms are used to generate liver organoids out of human pluripotent stem cells. With the use of perfusion, the formation of three-dimensional (3D) human hepatic organoids is facilitated (Schepers et al., 2016; Wang et al., 2020). Liver MPS can also be used in series with other specialized tissue chips to track toxicity on other tissues after metabolism. Since the liver has an important role in drug degradation in the human body, it is often part of multiorgan systems. One such system was developed to screen for hepatic modification of drug-induced cardiotoxicity (Yin et al., 2021).

Intestine. Several intestinal organoid MPS have recently been established that form 3D villi in vitro, although these villi are difficult to analyze in live culture. As a result, platforms typically have been used to culture these 3D structures on a membrane. A common technique employs the widely used MPS motif, consisting of two layers separated by a porous silicone channel (Kim et al., 2012), to recapitulate and assess the complex structure of the epithelial cells (Kasendra et al., 2018; Workman et al., 2018). In the future, one can envision personalized intestine-on-a-chip models populated using patient-derived blood and intestinal tissue biopsies that feature "patient-specific immune, vascular, and intestinal cells in coculture with microbiome isolated from the patient's stool" (Donkers et al., 2021, pg. 10). Discovery of lead compounds on these personalized platforms could then be used for clinical management of patients.

Kidney. Kidney MPS technologies that include individual components of the nephron, including the glomerulus, proximal tubule, and distal tubule/medullary collecting duct, have been successfully developed (Li et al., 2017; Musah et al., 2017; Weber et al., 2016). Importantly, recapitulating the perfusion flow of the kidney results in enhancement of tissue maturity, vascularization, and development of perfusable lumens in kidney organoid MPS (Homan et al., 2019). These platforms will advance drug toxicity testing—for kidney alone or in combination with other tissue MPS (Vernetti et al., 2017)—and eventually may augment renal replacement therapies.

aimed at generating fundamental knowledge regarding normal human biology and translational research focused on understanding disease mechanisms, identifying potential therapeutic targets, and evaluating drug and vaccine candidates. Note that these examples are intended to be illustrative and do not represent a comprehensive cataloging of ways in which these models have complemented NHP research or reduced reliance on NHPs. Note also that, while the examples focus primarily on human cell culture models, animal cell–based models have a role in informing the development of and building confidence in human cell–based MPS, as well as in assisting in the interpretation of existing animal model data and refining the use of future animal models (NASEM, 2021).

As detailed in Chapter 2, NHPs are widely used for research on infectious diseases such as COVID-19, Zika, and malaria to understand pathogen tropism (i.e., the types of cells the

pathogen infects), immune responses, and pathological outcomes, as well as for vaccine and drug testing (Doritchamou et al., 2017; Galinski, 2022; Haese et al., 2021; Liang et al., 2021; Miner and Diamond, 2017; Osuna and Whitney, 2017; Rutkai et al., 2022). With rapid advances in human stem cell research, many 2D and 3D human cell culture systems have been applied to address similar questions.

The COVID-19 pandemic in particular spurred collaborative efforts to develop and apply human cellular models to address the urgent need to understand SARS-CoV-2 pathogenesis and to develop effective therapeutic and prophylactic products (Kleinstreuer and Holmes, 2021). In the past 3 years, many studies have reported on the use of such models to elucidate cellular tropism, to study immune responses to SARS-CoV-2 and the pathology in different tissue and organs, and to facilitate drug development for COVID-19 (Busquet et al., 2020; Clevers, 2020; Monteil et al., 2020). Examples include cardiac cells recapitulating patient cardiac cytopathic features (Perez-Bermejo et al., 2021); examining immune responses in lung lineage cells (Huang et al., 2020; Youk et al., 2020); demonstrating infection and viral replication within the intestinal epithelium using intestinal organoids (Lamers et al., 2020); and studying neurotropism identified in brain organoids (Jacob et al., 2020; Samudyata et al., 2022; Wang et al., 2021). Si and colleagues (2021) demonstrated the utility of an MPS model (human airway chip) for screening antiviral therapeutics for SARS-CoV-2 and the potential to accelerate the identification of drugs previously approved for other indications that have repurposing potential.

In research on Zika virus, human brain organoids were used to suggest the causality of infection and microcephaly (Qian et al., 2016). Human iPSC–derived 2D neural cultures and 3D brain organoids were used to identify the neurotropism and pathogenesis of Zika virus infection (Qian et al., 2016; Tang et al., 2016) and to screen protective treatments (Xu et al., 2016). The Centers for Disease Control and Prevention used human stem cell–based in vitro findings, along with evidence from animal models and clinical and epidemiological evidence in humans, to conclude that Zika virus causes microcephaly (Rasmussen et al., 2016). Importantly, neural progenitor cells were found to be one of the main cellular targets in vitro (Tang et al., 2016), a finding that has been replicated in many animal models, including NHP models.

Human brain organoids are also being applied to study human immunodeficiency virus (HIV) infection of the central nervous system, including neuropathology and the establishment of viral reservoirs (dos Reis et al., 2020; Premeaux et al., 2021). Understanding of latent reservoirs is important to the development of effective curative strategies, which have remained elusive despite successes in the development of HIV therapeutics, as discussed in Chapter 2 (see Box 2-3). Findings from such in vitro human model systems can be used to better inform the design of experiments in NHP models for questions that cannot be addressed in vitro.

The complementarity of in vitro and NHP models has also been a critical component of the study of neurological disorders. The brain is the most evolutionarily advanced organ and is difficult to model in vitro because of its complex circuitry and ongoing development in response to experience. Compared with other conventional animal models, NHPs exhibit greater similarity to humans in brain structure and complexity, and as discussed in Chapter 2, research using NHP models therefore provides valuable insights into brain function and neurological disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and stroke, many of which remain untreatable. To date, many iPSC lines have been established from patients with neuropsychiatric (Levy and Pasca, 2023; Zhang et al., 2023) and neurodegenerative disorders. Brain cells or organoids have been generated from these lines to examine the molecular and cellular changes potentially linked to disease (Mertens et al.,

2018) (see also Box 4-2) and to enable "initial rapid, high-throughput screens (genetic or pharmacological) to define and characterize putative targets" (Outeiro et al., 2021, p. 835).

While brain organoids are enabling improved understanding of neurodevelopmental processes and diseases (Andrews and Kriegstein, 2022), these models currently have limited

BOX 4-2 POTENTIAL OF HUMAN CELLULAR MODELS TO YIELD INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF ALZHEIMER'S DISEASE

Two main hypotheses proposed to explain the pathogenic mechanisms of Alzheimer's disease (AD) are the amyloid cascade hypothesis and the tau hyperphosphorylation hypothesis. Amyloid-β plaques were originally proposed by Paul Blocq and George Mannesco after discovering "circular accumulation in the brains of elderly patients" in 1892 (Fan et al., 2019). The pathological description of AD was first provided by Alois Alzheimer in 1907 (Alzheimer, 1907; Strassnig and Ganguli, 2005). After almost a century of research, "beta-amyloid" was isolated from the meningeal vessels of Alzheimer's cases and the peptide sequence was partially identified (Fan et al., 2019; Glenner and Wong, 1984). A pivotal discovery in AD research was that AD could be inherited in an autosomal-dominant fashion through a mutation in the gene coding for APP, the protein from which the amyloid-β peptide is excised via sequential scission by the β-APP cleaving enzyme and γ-secretase (Chow et al., 2010; Ringman et al., 2014). That mutations in the tau gene could cause autosomal-dominant frontotemporal lobe dementia and parkinsonism linked to chromosome 17 was another critical discovery (Hutton et al., 1998). These authors identified those mutations, showing that tau pathology alone is sufficient to cause progressive neurodegeneration (Wolfe, 2012). The tau pathology in frontotemporal dementia is similar to that found in AD, but without the appearance of amyloid-β plaques (Karran et al., 2011). The precise temporal and mechanistic relationships between amyloid-β deposition and tau pathology remain to be resolved. While a small proportion of AD cases are inherited (familial), most are sporadic, and heterogeneous genetic and molecular processes are thought to underlie the risk for developing the disease (Bali et al., 2012). This incomplete understanding of the disease has impeded efforts to bring effective treatments to the market.

Despite their biological closeness to humans, nonhuman primates (NHPs) do not appear to develop naturally occurring AD. While efforts are under way to develop more translationally relevant NHP models through genome editing (as discussed in Chapter 2), animal models in general have to date demonstrated poor predictive power in the evaluation of potential AD therapeutics (Veening-Griffioen et al., 2019). If questions related to amyloid and tau interactions and processing can be addressed by new approach methodologies, therapies designed to engage mechanisms targeting these interactions may represent a context of use for a new technology or approach, although such a methodology, like NHP models, might not recapitulate the full disease pathogenesis. For example, Bowles and colleagues (2021) describe cerebral organoids that elucidate early events in the pathogenesis of frontotemporal dementia arising from microtubule-associated protein tau mutations. By 6 months, tau-V337M organoids show the distinct loss of glutamatergic neurons, which has been observed among patients with frontotemporal dementia. Mutant neurons are susceptible to glutamate toxicity, which can be addressed pharmacologically by the PIKfyve kinase inhibitor apilimod (Bowles et al., 2021).

The development of new approach methodologies for AD and related dementias is an active area of investment by the National Institute on Aging, which supports efforts related to modeling disease complexity and all stages of drug development, from target identification to Phase 3 clinical trials (NIA, 2022). Induced pluripotent stem cells (iPSCs) collected from AD patients provide unique opportunities to capture the heterogeneity in genetic and other (some as yet unknown) risk factors for this complex disease. iPSC-based platforms (e.g., organoids, microphysiological systems) also offer the potential for personalized medicine approaches to screening therapeutics.

applicability to the study of experience-related refinement of neural circuitry (e.g., changes in response to visual cues or other postnatal stimuli) and neurological conditions that are emergent from the activity of neural networks (Andrews and Kriegstein, 2022; Jalink and Caiazzo, 2021; Trujillo and Muotri, 2018). Brain organoids cannot yet recapitulate the full complexity of the spatial organization of a human brain, have limited cellular diversity and connectivity between different brain regions (Arlotta and Gage, 2023), and demonstrate several shortcomings with respect to studying the development of neurodegenerative disorders that develop over long periods of time (Jalink and Caiazzo, 2021; Kim et al., 2021; Qian et al., 2019; Shou et al., 2020; Sun et al., 2021; Wang, 2018). Animal models, including NHPs, are needed to test mechanistic hypotheses for the development of typical symptoms and to test therapeutic strategies at the organism level (Outeiro et al., 2021). From these studies, it is clear that certain pathologic features are conserved in both in vitro and NHP models, which thus complement each other.

Given their similarities to humans, NHPs are important models in the area of reproductive biology and have contributed to improved understanding of endometriosis, as discussed in Chapter 2. Recently, complex, multicellular endometrial organoids have been developed that provide an in vitro model for the study of endometrial physiology (e.g., molecular and cellular regulation of dynamic cyclic tissue remodeling) and pathology (e.g., endometriosis), highlighting the opportunities for organoid models to contribute to both basic and translational research (Song and Fazleabas, 2021).

NHP research plays an important role in the development of safe and effective treatments that are translatable to humans. Given the relatively low cost and high throughput of in vitro culture systems, initial drug screening using disease-relevant human cellular models may significantly reduce the number of NHPs required for drug development research by advancing only promising candidates to NHP studies (Prior et al., 2017; SCHEER, 2017). The Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative, for example, which began following a 2013 workshop hosted by the Food and Drug Administration (FDA) (CiPA Initiative, 2019), resulted in validation of the use of human iPSC–derived cardiomyocytes (hiPSC-CM) to determine the risk of drugs inducing torsade des pointes tachyarrhythmias in a clinical setting (Blinova et al., 2018). The use of iPSC-derived cardiac myocytes in the CiPA initiative is one example, specifically in toxicology, of a successful approach to clearly demonstrating the utility of a 2D hiPSC-CM system for detecting drug-induced proarrhythmic effects and reducing the use of animals, including NHPs, in such research (Pang et al., 2019). In another example, Kerns and colleagues (2021) showed that a MPS could recapitulate antibody-mediated lung toxicities observed in cynomolgus macaques, demonstrating the value of the model for evaluating translation of animal findings to human cellular models, and raising the potential for a reduction in reliance on NHP-based safety assessments.

Other Applications of In Vitro Cell Culture Models

As emphasized earlier in this chapter, the usefulness of new approach methodologies extends beyond opportunities to reduce reliance on NHPs; 2D and 3D cell culture models have many valuable applications, particularly when good animal models for human disease are lacking. For example, iPSCs derived from patients suffering from familial cancers can be used to identify the mechanisms underlying the onset of pediatric cancer and to detect some familial mutations, making it possible for these cells to serve as a valuable prognostic tool (Marin Navarro et al., 2018). Disease causality for several genetic polymorphisms in long QT syndrome and aortic valve disease were demonstrated by combining the use of cardiomyocytes differentiated from iPSCs with multiomics technologies (Evans et al., 2022).

Similarly, causality was established between a specific gene mutation and disease-associated phenotype using cortical neurons differentiated from iPSCs from patients with major mental disorders and genome editing (Wen et al., 2014).

A notable area of application for in vitro cell culture models is personalized medicine. In the past decade, innovative 3D culture approaches have resulted in successful derivation and cultivation of tumor organoids, including colon, breast, liver, lung, pancreas, ovary, bladder, esophagus, and brain cancer organoids. These tumor organoids have shown some similarity in drug responses to the responses of patients, making them a valuable tool for studying personalized disease progression and therapies (Veninga and Voest, 2021). In a recent example, Schuster and colleagues (2020) developed a microfluidic platform to study pancreatic tumor organoids. Using this system, hundreds of patient-derived cultures were treated with combinations of drug treatments, and an automated, high-throughput analysis of the microfluidic 3D organoids enabled the identification of potentially effective treatments for individual patients, demonstrating the potential of these culture systems to support personalized precision medicine. Importantly, the results showed significant differences in drug response among different patients, a feature that cannot be studied using NHPs. In another example, human rectal organoids from cystic fibrosis patients were used to predict drug response, enabling the identification of responders to *CFTR*-modulating drug therapy even for those patients with very rare genetic mutations in the *CFTR* gene (Dekkers et al., 2016).

Advantages and Limitations of In Vitro Models

Significant advances have been made in deriving and culturing human cells, tissues, and organs from stem cells to study basic biology and certain disease-related cellular pathologies. For example, the molecular mechanisms underlying cortical layer formation were delineated using brain organoids involving Wnt signaling, which is disrupted by a psychiatric disorder–associated genetic mutation in brain organoids derived from patient iPSCs (Qian et al., 2020). In another example, human iPSC–derived neural cells were used to identify the fundamental molecular and cellular mechanisms underlying human neoteny (Iwata et al., 2023; Linker et al., 2022).

The ability to derive ATSCs and iPSCs from patients, combined with targeted differentiation into disease-relevant cell types, enables use of these cellular models to reveal disease-related phenotypes, understand pathology, and identify potential biomarkers. The more complex cell models, such as organoids and MPS, allow better understanding of disease pathology and mechanisms using relevant human cell and tissue types, as well as physiologic niches important for disease development and progression, especially in hereditary diseases. ATSCs and iPSCs also are amenable to CRISPR/Cas-based genetic editing, thus making it possible to understand the functional contribution of specific genes involved in normal function or under diseased conditions, and to establish a causal relationship between genotype and phenotype (Evans et al., 2022; Wen et al., 2014).

However, not all human cell types can be isolated or generated from ATSCs or iPSCs, and the integrity of the cells (e.g., low rate of genotype discordance between parent cell and iPSC cell DNA, genomic structural integrity, and transcriptomic similarity between the derived cell type and the cells that reside in tissues in vivo) must be confirmed before the cells can be used reliably (Assou et al., 2018; Kammers et al., 2017; Kanchan et al., 2020). As with all models, predictivity and validation principles must be established. For translational purposes, qualification and a well-defined COU for these model systems are essential (Hargrove-Grimes et al., 2021, 2022; Ingber, 2022; Low et al., 2021) and can significantly expand the types of critical human health–related questions they can be used to explore.

While organoids and MPS have successfully mimicked many aspects of the complex physiology of human organs, 3D culture systems in their current state cannot replicate all of the complex interactions that occur in vivo (Low et al., 2021; Marx et al., 2020), nor can they be used to study processes that require systemic regulation. Therefore, for human health and safety questions that require this level of complexity, these in vitro systems cannot replace NHPs. The use of in vitro systems to study surgical interventions is limited as well (Ruspi et al., 2019). Furthermore, certain outcomes, such as behavior, can be studied only in the full context that is present in vivo. However, results from studies using in vitro models can inform improvements in the design of experiments using NHPs to reduce reliance on these animal models, such as with drug screening, as discussed earlier in this chapter.

In Silico Models

Over the years, researchers have attempted to use a wide array of quantitative and computational methods to model the properties of biological systems, including their response to perturbations, with greater or lesser degrees of success. Statistical modeling can be used to associate a relatively small number of variables with defined endpoints and can provide robust estimation of the effects of a number of parameters in inferring properties of a system. Differential equations can be fit to temporal data sets to model the response of a biological system to a perturbation and to predict responses to related challenges (Daun et al., 2008). Bayesian and Boolean networks and Markov models can be used to capture the complex interactions among parameters that characterize a biological system and to predict the responses to stimuli that alter those parameters (Chen et al., 2016; Li et al., 2007; Trairatphisan et al., 2013; Yoon, 2009). While there are many examples of the use of these and other quantitative methods in the analysis of data from biological systems, each has limitations for applications involving capturing the complexity of behavioral, biochemical, or other responses of NHPs to external stimuli.

For example, statistical inference requires that one start with a set of "outcomes" for the system under study. An underlying model can be created that is based on the variables believed to influence the outcomes, and sampling of a population can be used to estimate parameters that relate the variables to the observed outcomes; the parameterized model can then be used to infer the outcome state for new measurements on the system under study. Indeed, statistical inference can take advantage of scientists' ability to control variability and measure a more comprehensive set of relevant parameters in NHPs as compared with other systems. The resulting models can be used to make accurate predictions across a number of readouts. However, the small number of NHPs available for use in a given study often prevents a sufficient number of measurements for the creation of statistical models with more than a few parameters, and these models would likely carry a great deal of uncertainty. Further, even if data were available for larger numbers of animals, it is unlikely that a statistical model would be able to estimate response to a system-perturbing stimulus that would be sufficiently different from responses already observed. Similarly, a differential equations model requires that one start with a predefined collection of supposed interactions that govern the evolution of the system and sufficient time-course measurements to estimate what can quickly become a large number of model parameters (Daun et al., 2008). Consequently, most models cannot capture the full complexity of NHP models and extend predictions to human systems.

Machine learning (ML), a subset of artificial intelligence (AI), has been recognized as having the potential to overcome some of the limitations of other computational modeling tools. AI/ML methods are generally capable of finding patterns in large, complex data sets

that can be used to draw inferences about the system being studied (Bzdok et al., 2017; Paul et al., 2021). Improvements in both AI/ML methodology and computational speed and power have led to dramatic increases in performance capabilities (by some estimates, performance doubles every 3 months [Saran, 2019]). Over the last decade, AI/ML has been a major contributor to improvements in the speed and efficiency of in silico drug development (Jayatunga et al., 2022; Patel and Shah, 2022; Vo et al., 2020; Walden et al., 2021), with applications including molecule design (Paul et al., 2021) and the application of knowledge graphs to understand target biology (Alshahrani et al., 2022). As documented by Jayatunga and colleagues (2022), several companies have advanced molecules to clinical trials based on AI drug discovery. AI-enabled programs have been able to complete the discovery and preclinical phases within 4 years, compared with historical timelines of 5–6 years (Jayatunga et al., 2022). In particular, AI/ML has shown utility in prescreening large compound libraries to identify high-priority candidates (Dreiman et al., 2021). Although these compounds must still be tested in a model system such as NHPs, narrowing the field of drug candidates will naturally reduce the use of NHPs in validation experiments.

AI/ML methods rely on having large bodies of "training data" that can enable AI/ML models to learn rules for predicting outcomes of interest (Vo et al., 2020). For example, one might use the chemical structures of small molecules and a particular response of cell lines treated with those compounds, such as growth arrest, to train AI/ML models to recognize structural features that are predictive of the response and its magnitude. The AI/ML models thus trained could be used to evaluate thousands of structurally defined compounds in order to identify candidates that might be more effective than existing compounds or might have fewer side effects. Yet while this methodology can speed drug development by guiding the search for new agents and help design and reduce reliance on NHP studies, it does not obviate the need for in vitro or in vivo testing.

AI/ML has also seen increased applications in many areas of health care and pharmaceutical and chemical research by enabling predictions (Luechtefeld and Hartung, 2017; Luechtefeld et al., 2018), the creation of synthetic data to fill data gaps, and the extraction of complex and nonlinear relationships between input data and desired outcomes (Walden et al., 2021). With access to ever-greater amounts of digitized historical experimental data, data-driven supervised AI/ML algorithms have proven effective in a number of applications (Maharao et al., 2020; Walden et al., 2021). To improve model performance with smaller or relatively limited (sparse) data sets, ML researchers have developed new computational methods that include AI/transfer learning; one-shot, zero-shot learning; and Bayesian-based optimization methods (Walden et al., 2021). They have also developed hybrid methods that integrate mechanistic modeling with more conventional ML as a way of increasing the interpretability of AI/ML models (Antontsev et al., 2021)—something that is necessary if these models are to be used to derive biologic insight into the systems being modeled.

Potential to Complement and Reduce Reliance on NHPs

As touched on briefly in the previous section, the ability of AI/ML methods to learn from data depends on both the quantity and appropriateness of the training and validation data employed. In many instances, AI/ML tools have the potential to learn from historical NHP data and could provide insights beyond those extracted using conventional tools (Steger-Hartmann et al., 2020). Doing so with appropriate data could allow the creation of virtual NHP control groups. These arms would be modeled using previously collected data and used in place of NHPs receiving a placebo, thereby reducing the number of NHPs used in nonclinical studies—an outcome that would both increase the utility of NHP

models and make better use of these models at a time when NHP availability is severely limited. This approach would require careful design of the control and treatment arms in the relevant studies to ensure that robust conclusions can be drawn (Steger-Hartmann et al., 2020; Wright et al., 2023). A hybrid approach, combining mechanistic modeling and ML (Antontsev et al., 2021), also provides an opportunity to develop virtual NHP tissue and organ models to inform formulation, design, and dosing regimens and predict toxicological and efficacy endpoints, thus enabling the execution of more informed, refined NHP studies with the potential to reduce the numbers of NHPs required. Efforts to develop virtual dog organs and tissues to model toxicologic endpoints for new drugs are currently under way (NC3RS, 2021) and if successful, could guide similar approaches for NHPs. Such efforts rely on the accumulation of mechanistic knowledge through animal studies. In many instances, however, the mechanistic models of drug metabolism and drug effects are incomplete, so the implementation of such a strategy would require additional methodologic development and validation.

It has been suggested that combining systems biology with AI/ML can help better translate data from animal (including NHP) studies to clinical research (Brubaker and Lauffenburger, 2020). This approach would overcome some of the limitations inherent in the assumption that orthologs (evolutionarily related genes in different species that carry out the same basic function) influence cellular or organismal phenotypes in the same way. Instead, the hope is that by incorporating higher-order associations among genes, RNAs, proteins, and metabolites, together with mechanistic models, AI/ML models can be developed to better predict human responses relative to those in animal models, thus helping to improve the translational relevance of data from NHP studies. Such an approach is being used in vaccine development for HIV. Building on efforts to identify correlates of protection against HIV and simian immunodeficiency virus infection (Ehrenberg et al., 2019; Fourati et al., 2019), ML models are aiding in the discovery of latent variables from NHP vaccine data that are most predictive of efficacy in human trials. By identifying biologic pathways predictive of clinical trial outcomes, such data can guide the development and evaluation of future vaccine candidates (Lauffenburger, 2022). In the area of drug development, Singh and Shah (2017) demonstrate the impact of NHP pharmacokinetic (PK) and efficacy data using multiscale PK/pharmacodynamic (PD) modeling to predict the efficacy of an antibody–drug conjugate, trastuzumab emtansine, for breast cancer in humans.

Even in these advanced settings, however, AI/ML is limited by the data available to train the models, as it cannot learn far beyond the realm of the data inputs. For example, with enough data on the observed mutations of the SARS-CoV-2 virus spike protein and information about transmissibility or disease severity, AI/ML models might be able to predict the severity of a new variant. Such models, however, would likely not be of value in predicting the transmissibility of another virus for which the structure of the capsid proteins was radically different or one with distinct modes of infection or transmission. Nor would models trained on data relevant to modeling transmission of the virus likely be of use in solving a different problem, such as the development of a new antiviral agent to fight COVID-19. The use of NHP models adds another layer of complexity to considering both how AI/ML models will be trained and validated (given the small numbers of animals available) and how those models will be used. While these problems are not insurmountable, their consideration is essential if AI/ML methods are to affect the use and utility of NHP models. Consequently, AI/ML methods are viewed as complementary to the use of NHPs and other in vitro and animal models, and in this context are recognized primarily as tools with the potential to extract additional insights from NHP studies. The application of AI/ML methods to extract insights from NHP studies is discussed further in Chapter 5.

Challenges for Adoption of AI/ML Models

A number of limitations have slowed the adoption of AI/ML models. Any computational model—and indeed any analytical model—will be limited by the ability to characterize the biological or pathophysiological phenotype of the model systems under study and to relate this information to the relevant human phenotype. While it may be easy to distinguish tumor from normal tissue, even cancers have continuous phenotypes with respect to molecular characteristics and the gross phenotype, and may have different effects in different species; most chronic diseases are even more difficult to characterize and translate between models.

Scientists conduct experiments to answer a specific question, such as what factors explain the properties of the biologic system under study. Although AI/ML methods can do an outstanding job of identifying experimental groups or classifying new samples into known groups, they often fail to provide a clear picture of how particular assignments are made. AI/ML methods work by iteratively combining multiple data elements and weighting them at each stage to arrive at the prediction of some "outcome" that is captured in the data. The result is a model that is highly nonlinear, meaning that the data elements being combined and their respective weights in the final model are often obscured from the user and impossible to extract, which in turn leads to difficulties in explaining and interpreting AI outcomes and gives rise to the "black box" character of these methods (Mathews, 2019). Consequently, some scientists remain skeptical of the results derived with these models (Baran and Henstock, 2023).

Research into creating explainable AI models is ongoing, and good results have been obtained with hybrid methods that integrate AI/ML and mechanistic modeling (Antontsev et al., 2021), but the work done in this area thus far has not made it possible to explain every output and identify sources of error. Lack of repeatability, replicability, and reproducibility may still be observed during AI/ML learning because of different software versions, implementation variations, hardware differences, and unrecognized biases in the data (Haibe-Kains et al., 2020). However, these challenges can be addressed by the identification of appropriate COUs and the application of appropriate qualification, validation, and benchmarking criteria (Baran and Henstock, 2023; FDA, 2017; Kennett, 2010; NIH, 2023; OECD, 2014; Wu et al., 2023). Also important is having both representative training and validation data sets and appropriate design for the training and validation phases of model development. There are countless examples in the literature of computational methods trained and validated using data from, for example, largely Caucasian populations when the intended application is in a population that is more diverse (Parikh et al., 2019). Other studies have mixed training and validation data sets in ways that bias the results and ultimately limit their applicability. This challenge has been widely recognized, and many publications address it, describing validation criteria and approaches for identifying and selecting training and validation data (Lin and Chou, 2022; Lu et al., 2018; Maharao et al., 2020; OECD, 2014; Sprous et al., 2010; Tropsha, 2010; Vo et al., 2020).

Lack of AI/ML expertise, training, and education has led to nonspecific use of these methods and false expectations about their applicability. Further, users often fail to recognize critical aspects of AI/ML model development, including the importance of representative, high-quality training and validation data (de Hond et al., 2022). In NHP research, a fragmented knowledge landscape, lack of data harmonization, lack of data digitization and digitalization, and limited access to NHP and human data of sufficient quality and quantity can result in poor system training and overfitting, which in turn leads to poor-quality model performance. Moreover, inadequate reporting of experimental conditions from NHP research can make it difficult to identify comparable data sets with which to train or validate AI/ML models. Advances in ML, such as those based on continuous learning techniques, along with

focusing of the questions being asked, can aid in filling data gaps with accurate synthetic data in a specific COU.

Effective use of AI/ML requires careful planning of experiments to generate appropriate data. With AI/ML tools, one must identify a specific and focused question and a design that will allow collection of the appropriate data. Thus there may be many investigations that could be conducted in NHPs that would not feasibly be replaced by AI/ML modeling. In some experiments, for example, NHPs are exposed to a particular compound or agent, and a readout is obtained from various organs and systems. Such a broad question with an unknown agent whose mechanism of action is unknown would not be amenable to AI/ML analyses.

It is important to note that AI/ML has the potential to introduce new research cybersecurity requirements. At a time when life science organizations are increasingly targeted by cyberattacks (Guttieres et al., 2019), effective AI/ML development and use requires that data remain secure against unauthorized access while remaining readily accessible to peers and collaborators. The potential for obtaining NHP study data, such as video, through the Freedom of Information Act and the subsequent potential for misrepresentation also needs to be considered and addressed.

Finally, advancing the use of AI/ML models to complement and reduce reliance on NHP models will require a strong commitment to open science and data sharing—including the sharing of training data sets, computational models, and software code. The value of any such AI/ML model will be strongly driven by the data used to train and validate it, while the community's confidence in the model's results will depend on the transparency and understanding of the model so it can be tested and validated (Haibe-Kains et al., 2020).

REGULATORY GUIDANCE ON TECHNOLOGIES AND APPROACHES TO COMPLEMENT OR REDUCE RELIANCE ON NHP MODELS

The National Institutes of Health (NIH) has supported a few programmatic efforts with the expressed intent of enabling investigational new drug applications (INDs) (see, for example, the Bridging Interventional Development Gaps program supported by the National Center for Advancing Translational Sciences [NIH, 2022]). These efforts represent a very small percentage of the total resource allocation of the NIH institutes and centers, and do not necessarily involve research conducted with NHPs. With this in mind, this section provides some relevant information about the regulatory landscape for new approach methodologies. Notably, the regulatory views included in this section are not relevant to the use of NHPs in basic disease research and are focused on informing human safety.

In general practice, NHPs are used to answer questions about human safety when it is scientifically demonstrated and clear that NHPs are the most relevant species for human translation, and no other approach is appropriate for the purpose of the study (SCHEER, 2017). Scientific demonstration "may include metabolic, pharmacokinetic, and pharmacologic similarities to humans as well as sensitivity to particular types of toxicity, among other factors" (FDA, 2022c, p.3). The committee found evidence that the FDA and other regulatory agencies are supportive of new approach methodologies and have communicated strategies that are being considered to put this acceptance into practice (FDA, 2021a, 2022a). To this end, the FDA formed an Alternative Methods Working Group[5] focused on the advancement of both new and existing

[5] A recent and detailed source for the views of the FDA on alternative methods can be found here: https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda (accessed January 16, 2023). A current list of FDA guidance that includes use of alternative methods can be found here: https://www.fda.gov/science-research/about-science-research-fda/regulatory-guidances-list-alternative-methods (accessed January 16, 2023).

models to support regulatory decision making in toxicology. The working group also facilitates interactions with global regulatory bodies that are considering the application of alternative methodologies in toxicology (FDA, 2022a). This effort and others are focused on ensuring that the data generated will be comparable and of the highest quality, and that studies using these models and the data generated from them will be robust, reproducible, relevant, and fit for purpose. In response to the 21st Century Cures Act of 2016,[6] the FDA also launched its Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program, which is designed to support the development and, in some cases, qualification of novel approaches to drug development—including MPS and AI/ML-based algorithms—for use in regulatory decision making (FDA, 2021c). All of these efforts have culminated in the FDA Modernization Act 2.0,[7] enacted in December 2022, which amended the Federal Food, Drug, and Cosmetic Act to explicitly permit the use of new approach methodologies, including in vitro and in silico methods, as alternatives to in vivo nonclinical testing. Taken together with the efforts already implemented at the FDA, this new law encourages the application of new approach methodologies and documents policy efforts to facilitate their use as they are qualified and/or validated.

New FDA guidance with direct relevance to the reliance on NHPs for conducting nonclinical toxicity assessments is included in *Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic* (FDA, 2022c). The FDA provided this guidance to address challenges related to the limited NHP supply resulting from the pandemic. The guidance states: "FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method is adequate to meet the regulatory need." Although this guidance was prompted by the COVID-19 pandemic, the core issue was the reduction in the already limited NHP supply available for nonclinical toxicity assessments, together with the simultaneous increase in demand for NHPs for evaluating candidate COVID-19 treatments and vaccines. In response, the FDA acknowledged the restricted availability of NHPs for other pharmaceutical development programs and potential delays in the development of new medications for diseases that currently lack any effective treatment options. Specifically, this guidance discourages "the use of NHPs for the general toxicology assessment of small molecule drugs unless the sponsor can provide a scientifically compelling reason why NHPs must be used." The guidance also states:

- "If the biological product is active in other nonrodent species, the sponsor should conduct any warranted general toxicity studies in a nonrodent species other than the NHP, whenever scientifically justified."
- "On a case-by-case basis, if the biological product is active in a rodent and acts on a well-characterized target (e.g., vascular endothelial growth factor, or its receptor), it may be scientifically appropriate for sponsors to conduct warranted general toxicity studies only in the rodent."
- "Sponsors should not use sexually mature NHPs in toxicity studies designed specifically to assess fertility by histopathological examination when fertility parameters can be assessed in rodents."
- "Consistent with current FDA guidance on the assessment of developmental and reproductive toxicity (DART), FDA considers NHPs to be a nonroutine test species for the DART assessment of small molecule drugs. FDA strongly discourages spon-

[6] P.L. 114–255.

[7] *FDA Modernization Act 2.0*, 117th Congress (December 29, 2022).

sors from using NHPs for assessing DART endpoints for their small molecule drug development programs."

- "Consistent with current FDA guidance, sponsors should only use NHPs for the DART assessment of biological products if they are the only relevant species. For the duration of the COVID-19-related disruption in the supply of NHPs, sponsors should also consider the following when planning approaches to address DART for biological products that are pharmacologically inactive in non-primates: […] while the supply of NHPs is disrupted, we strongly encourage the use of appropriate alternative models for assessing DART endpoints (e.g., species-specific surrogates in rodents, genetically modified rodents) when scientifically justified." (FDA, 2022c).

In general, this guidance provides many approaches that can be considered to reduce reliance on NHPs even after the end of the COVID-19 public health crisis.

Another relevant FDA source is *Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science* (FDA, 2021b). The section of this document on "Novel Technologies to Improve Predictivity of Non-clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing" (p. 31) describes the FDA's intention "to replace, reduce, and refine (the 3 Rs) dependence on animal studies by advancing development of, and evaluating new, fit-for-purpose nonclinical tools, standards, and approaches that may someday improve predictability." In the document, it is recognized that in silico modeling, such as using "available information in computational science approaches to predict safety issues, can be used to supplement and may potentially replace some risk analyses that are currently based on animal data." Of note, the document also expresses that these advances will depend on the development of performance criteria for the realistic assessment of the potential use of these new tools for safety and efficacy testing, and the conduct of "large multilaboratory studies to assess the reliability, sensitivity, specificity, and reproducibility of in vitro alternatives to in vivo assays (e.g., to assess the potency of certain vaccines)."

NEED FOR COLLABORATION BETWEEN NHP RESEARCHERS AND THOSE DEVELOPING AND USING NEW APPROACH METHODOLOGIES

The establishment of collaborations between developers of new approach methodologies and those who currently use NHPs may reduce barriers to the adoption of new approach methodologies (ICCVAM, 2018). These collaborations might entail training NHP researchers to implement new technologies and approaches in their own laboratories or creating a partnership whereby research with different model systems would be conducted in different laboratories. Effective collaborations involving multiple laboratories with expertise in different model systems are facilitated by supportive funding mechanisms. For example, the Collaborative Research in Computational Neuroscience program—a joint program of the National Science Foundation and NIH—supports collaborative research projects in theoretical and experimental neuroscience that involve multiple investigators using both animal models (including NHPs) and computational models (Flanders, 2022). Coordination within NIH—for example, between programs supporting NHP research and those developing MPS for Alzheimer's disease research—could facilitate the pursuit of promising research goals in this space. Additionally, the inclusion of experts in new approach methodologies in the review process for NIH research proposals involving NHP models (including review of the consideration of alternatives in the vertebrate animals section of the proposal) could help identify opportunities for collaborative research that might complement the proposed NHP study or reduce the need for NHPs.

At present, interactions between research groups developing and using new approach methodologies and those using NHP models are limited. Such interactions could help raise awareness among NHP researchers regarding the evolving capabilities of in vitro and in silico systems, and could educate investigators developing new approach methodologies on the needs and priorities of NHP researchers, thereby enabling improvements in the design of in vitro systems such that they would be better suited to answering research questions for which NHPs are currently used. For example, this approach could be used to define COUs to ensure that systems would be designed to be fit for purpose. Accordingly, there is an urgent need for mechanisms that can facilitate such direct interaction and collaboration, including

- multilaboratory funding opportunities, such as those supported by the Collaborative Research in Computational Neuroscience program;
- challenge programs that encourage cross-sector collaborations, such as that supporting the application of data from experimental dog studies to the development of a virtual "second species" for toxicology studies;
- cross-training programs; and
- conferences, symposiums, and other events designed to provide opportunities for interaction between those investigators with expertise in the evolving capabilities of new approach methodologies and those using animal models, and to catalyze collaborations.

CONCLUSIONS

In its examination of new approach methodologies, the committee identified numerous ways in which in vitro and in silico models are being used to complement NHP research, but few concrete examples of a demonstrated role for those models in reducing reliance on NHPs. While references to replacement of NHPs are aspirational at this time, the committee envisions the potential for new approach methodologies to reduce reliance on NHPs in the future, especially as technology and science continue to advance, and as investments are made in the development of fit-for-purpose model systems and in their validation and qualification. In the absence of validation, enthusiasm for new technologies and approaches must be tempered to avoid overpromising their capabilities as valid replacements for necessary and proven experimental systems. Based on its evaluation of the research and development status of new approach methodologies, the committee reached the following conclusions:

Conclusion 4-1: Based on the current state of the science, there are no alternative approaches that can replace nonhuman primate (NHP) models to answer research questions that require complete multiorgan interactions and integrated biology. Thus, NHPs continue to be essential for the conduct of National Institutes of Health–supported biomedical research.

Conclusion 4-2: Select new approach methodologies (in vitro and in silico models) can replicate certain complex cellular interactions and functions. As such, these new approach methodologies may be used to answer specific research questions that contribute to understanding human biology to prevent and treat human disease. Although there currently exist no alternatives that can fully replace nonhuman primates, it is reasonable to be optimistic that this may change in the years ahead as new approach methodologies continue to advance.

Conclusion 4-3: Furthering the adoption of new approach methodologies (including in vitro and in silico model systems and approaches) with the intent of reducing reliance on nonhuman primate models will require planning and support for studies that can demonstrate adequate performance for specific contexts of use or intended purposes. Expectations for qualification or validation of new approach methodologies depend on the decisions to be made using the data derived from their use and the potential human health consequences of those decisions.

Conclusion 4-4: While nonhuman primates have been regarded as preeminent models for the evaluation of human safety and efficacy, recent guidance demonstrates that the Food and Drug Administration and other regulatory agencies are supportive of the use of new technologies and approaches for regulatory decision making once they have been adequately qualified or validated.

Conclusion 4-5: Efforts to reduce reliance on nonhuman primates (NHPs) in biomedical research will require investment in opportunities to facilitate direct interaction and collaborative research among investigators using NHP models and those developing in vitro and in silico approaches to expand the applicability of new approach methodologies to research questions for which NHPs are currently needed. At present, however, few mechanisms for fostering such interaction and collaborative research are available.

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5

Future Needs and Opportunities for Nonhuman Primate Models in Biomedical Research

The committee was charged with examining the current and future roles of nonhuman primates (NHPs) in research supported by the National Institutes of Health (NIH). As described in Chapter 2, NHPs play an essential role in advancing scientific research that continues to improve and preserve countless lives by, for example, enabling the development of safe and effective vaccines against infectious agents, the development of methods that are improving the success of organ transplantation, and the introduction of new treatments for diseases such as Parkinson's and sickle cell disease. While great progress has been made toward developing in vitro and in silico technologies and approaches for answering questions of biomedical relevance (see Chapter 4), these new approach methodologies are as yet unable to recapitulate the complexity of many human biological systems and diseases, and have not yet been validated for many applications. Consequently, the committee concluded that NHPs will remain critical models in multiple areas of biomedical research for years to come. Scientific progress in future years will determine the extent to which reliance on NHPs can be reduced. For now, however, given the need for continued use of NHPs in NIH-supported biomedical research, it is critical to ensure that these animal models are used as effectively as possible, particularly given the ongoing shortage of NHPs available for research, as highlighted in Chapter 3. Research should be conducted humanely with respect to the well-being of the animals under study and at the highest level of scientific integrity and rigor.

Building on its assessment of the current landscape (Chapters 2, 3, and 4), this chapter describes the committee's perspective on the future role of NHPs in NIH-supported biomedical research. The chapter begins with an overview of the factors that will influence the future need for NHPs in biomedical research, which is followed by a discussion of research domains in which the need for NHPs is likely to grow. After touching briefly on future needs for specific NHP species, the chapter explores opportunities to enhance the efficiency and translational relevance of NIH-supported research with NHPs, before ending with the committee's conclusions regarding the future of NHP research.

FACTORS INFLUENCING THE FUTURE NEED FOR NHPs IN BIOMEDICAL RESEARCH

The future need for NHP models in NIH-supported biomedical research will be driven by many of the same factors that have shaped the current landscape, including pressing current public health needs and preparedness for future threats to public health. Other factors include scientific advances, national policies, and the availability of NHP research resources and infrastructure. Each of these factors is explored below.

Pressing Public Health Needs

The use of NHPs in biomedical research is driven by the imperative to reduce human suffering and improve the quality of human life (Friedman et al., 2017; Harding 2017). Public health threats that currently contribute to significant morbidity and mortality in the United States are likely to continue to guide priority areas for NIH-supported NHP research. These threats to public health include chronic diseases and aging-related conditions that impose a tremendous and growing societal and economic burden, but for which few effective interventions for prevention and treatment are presently available. Some diseases, such as amyotrophic lateral sclerosis (ALS), can be fatal within a few years of diagnosis, underscoring the importance of advancing biomedical research as quickly as possible using the best available models, which in many cases are NHPs (Uchida et al., 2012). As emphasized by one participant in a public meeting held for this study, patients are waiting (Murry, 2022).

The lack of progress with clinical translation of research on these public health threats often reflects a lack of foundational knowledge regarding underlying mechanisms or disease processes. This knowledge gap underscores the importance of continued investment in fundamental basic and early translational research to enhance understanding of human biology and pathophysiological processes and to identify targets for intervention. As an illustrative example, the number of U.S. adults with Alzheimer's disease is projected to more than double in the next 40 years, reaching nearly 14 million (AA, 2022) (see Figure 5-1). The enormous public health and economic impacts of Alzheimer's disease are influenced not only by its increasing prevalence but also by its long duration. In 2022, the health care and long-term care costs for Alzheimer's disease and related dementias were estimated at $321 billion (Skaria, 2022). Yet while scientists' knowledge of the pathophysiology underlying Alzheimer's disease has advanced tremendously over the last three decades, the translation of those insights into clinical gains has been limited (King, 2018).

Clinical progress on Alzheimer's disease has been hampered in part by the absence of a naturally occurring animal model for this disease and an overreliance on rodent models (Drummond and Wisniewski, 2017; Van Dam and De Deyn, 2011). Transgenic mice that developed hallmark plaques and signs of cognitive deficits associated with the disease were engineered starting in the 1990s, contributing to a better understanding of disease mechanisms. However, treatments shown to clear plaques in mouse models failed to benefit human patients in clinical trials, indicating that these animal models were not fully recapitulating the human condition. Therefore, NHP models in which Alzheimer's disease phenotypes are induced and three-dimensional human brain organoids are being pursued as complementary models for nonclinical drug testing (Arnsten et al., 2019; Beckman et al., 2019, 2021; King, 2018). In vitro models are well suited for high-throughput drug screening and continued investigation of pathogenesis at the cellular and molecular levels but cannot be used to evaluate the cognitive outcomes of treatments. NHP models, by contrast, enable evaluation of putative therapeutics in the context of complete biological systems that closely mimic those of humans in such areas as lifespan and cognitive function (Lear et al., 2022; Mattison and Vaughn 2017).

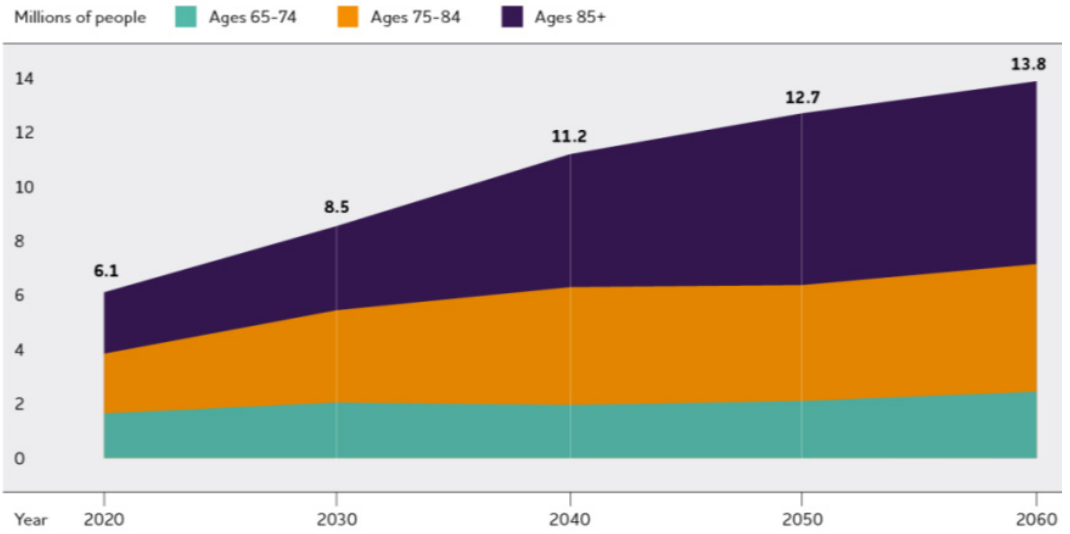

FIGURE 5-1 Projected number of people aged 65 and older in the U.S. population with Alzheimer's dementia, 2020–2060.
SOURCE: Image from the 2022 Alzheimer's Disease Facts and Figures report was reproduced with permission from the Alzheimer's Association.

Preparedness for Future Threats to Public Health

Investments in biomedical research are generally based on the most prevalent diseases imposing the greatest health burden. However, this investment must be balanced with preparedness for unknown future threats. Chapter 4 explores ways in which the use of NHPs could be reduced or complemented by new approach methodologies without a substantial negative effect on critical research areas in the United States, but it is important as well to consider the opportunity cost of not having access to NHPs. A tool commonly used in risk assessment is the Johari Window, which quantifies awareness of the state of knowledge about the situation at hand (Beach, 1982; Ha, 2019; Luft and Ingham, 1955). The most difficult challenges to prepare for are those described as "unknown unknowns." In 2020, the world faced an unanticipated challenge in the form of an infectious disease—the emergence of the SARS-CoV-2 virus and the COVID-19 pandemic. As documented in this report, having access to NHPs was essential for the development of vaccines and therapies for this new threat, and, as noted during the committee's August 2022 public workshop, shortages of NHP resources hindered the development of some products (Bailey, 2022). In the context of the unanticipated need for NHP models for COVID-19 research, NHP resources were conserved for COVID-19 research at a cost to progress in other important research domains (NIH, 2022d). It may not be possible to meet future unexpected public health needs even with similar resource reallocation strategies if action is not taken to address the ongoing shortage in NHP supply. This possibility highlights the importance of maintaining an adequate reserve of NHPs to respond to the challenges of new infectious diseases (Carlson et al., 2022; Howard and Fletcher, 2012); chemical, biological, or radiological warfare threats (DiCarlo et al., 2011; Singh and Olabisi, 2017); or other unanticipated threats as an essential component of U.S. national security and competitiveness.

The disruption to the biomedical research enterprise and ongoing NHP research that occurred during the COVID-19 pandemic demonstrated the importance of planning and preparing for public health emergencies, a process that needs to include the development of a framework for prioritization of NHP resources and biocontainment facilities in emergency scenarios. As demand for NHPs surged early in the pandemic, NIH assembled an expert panel of subject matter experts to provide input to the Office of Research Infrastructure Programs (ORIP) on the urgency of each of the funded studies and its potential public health impact. The panel's recommendations were then conveyed to the National Primate Research Centers (NPRCs) and other ORIP-supported NHP facilities (HHS, 2021), and used by NIH and the NPRCs to guide the development of mechanisms for the prioritization of scarce NHP resources during the pandemic. This experience provides an opportunity to learn about what did and did not work well to inform the development of a framework for future public health emergencies.

Scientific Advances

Scientific knowledge is constantly advancing, and as a result, short- and long-term needs for NHP research will differ. The latter can be challenging to predict because science does not advance in a linear fashion (NRC, 2007). Rather, scientific progress can be characterized by turning points and sharp departures in lines of inquiry, and a great deal of uncertainty surrounds which of numerous discoveries emerging at a given point in time will be informative for future research and how findings may ultimately be used.

The maturity of new approach methodologies continues to advance at a rapid pace, and accordingly, in vitro and in silico models are being applied to answer an increasingly diverse set of biomedical research questions. As described in Chapter 4, the data provided by new approach methodologies are expanding scientists' knowledge of disease pathways, helping to contextualize evidence from other sources, and enabling cost-effective screening, among other applications. In combination with other approaches, in vitro and in silico models make valuable contributions to the overall weight of scientific evidence. Given the range of possible interactions within even a single organ—much less within the entire human body—and the physiologic and structural complexity required of new approach methodologies to fully recapitulate an in vivo system, it is unlikely that the prediction of all in vivo outcomes is an imminent reality. The committee is optimistic, however, about the potential for new approach methodologies to reduce reliance on NHPs in the future as technology and science advance. Given that NHPs are likely to remain a limited and high-cost resource—even with further investments in domestic breeding to address current shortages—advances in new approach methodologies offer the potential benefit of helping to reduce costs and mitigate future NHP shortages. In anticipation of this, attention is needed to the development of a strategy for the advancement of new approach methodologies that can be used in conjunction with NHP models to optimize the application of NHP research and to answer pressing biomedical research questions in the future. One consideration for such a strategy is the inclusion of new approach methodology experts in the review process for NIH research proposals involving NHP models.

While some areas of advancing science, such as new approach methodologies, may reduce the future need for NHPs, others, such as genetic engineering, may create new demands for NHP models that can better replicate the human condition and address biomedical and societal priorities (NASEM, 2019; Sato and Sasaki, 2018). As with new approach methodologies, whether research using transgenic NHPs will achieve the antici-

pated improvements in translation to human health benefits relative to traditional models is not yet clear (Prescott, 2020). The use of genetically engineered NHPs is relatively limited in scope at the present time, and the technology has yet to mature to the point of readiness to assess its value and impact. As the efficiency of genome editing technologies improves and current challenges are addressed (Aida and Feng, 2020; Park and Silva, 2019), and as more laboratories develop the capabilities to establish these model systems, the committee anticipates acceleration of transgenic NHP models in the future.

While neither engineered (e.g., transgenic, transplant) non-NHP animal models nor human studies were included in the committee's definition of new approach methodologies and consequently not focus areas for this report, it is important to acknowledge that scientific advances in both areas may play a role in reducing reliance on NHPs going forward. Transgenic animal models (e.g., rodents, pigs) are increasingly being used to understand the function of human genes and genetic disease–related pathology. Relevant examples include the ACE2 (angiotensin-converting enzyme 2) expressing transgenic mice used for COVID-19 research (Winkler et al., 2020) and mice expressing human genes linked to Alzheimer's disease (Baglietto-Vargas et al., 2021). Transplant of human cells and tissues (for example, bone marrow or thymus) into mice has enabled the creation of mouse models with elements of human immune systems that have been useful in understanding some aspects of human immunodeficiency virus (HIV) pathogenesis and evaluation of the efficacy of antiretroviral therapies (Hassounah et al., 2016), as well as study of cancer immunology and immunotherapy (Tian et al., 2020).

Nonclinical NHP studies may be precursors to human studies when there are concerns regarding human safety risks associated with research protocols. For example, nonclinical studies using NHPs may be undertaken prior to Phase 1 clinical trials. Advances in technologies, such as those used for imaging (Prescott and Poirier, 2021; SCHEER, 2017), and evolving approaches to clinical trials, including human challenge studies and Phase 0 microdose studies (Burt et al., 2017, 2018; Palacios and Shah, 2019; SCHEER, 2017), are opening new opportunities to conduct ethical biomedical research in human volunteers. With respect to the opportunities to reduce reliance on NHPs through human studies, however, attention needs to be focused on widely recognized challenges in achieving adequate clinical trial enrollments (Briel et al., 2021; IOM, 2012; Unger et al., 2016) and ensuring that risks are not borne disproportionately by groups that may be more likely to enroll in "first-in-human" trials, particularly disadvantaged populations (Kalbaugh et al., 2021).

National Policy

Policy decisions have enormous potential to influence the future of NIH-supported NHP research. The committee understands the continued emphasis of policy makers on the development and implementation of new approach methodologies with the potential to reduce reliance on NHPs and other animal models. Critically, however, policy needs to be informed by the state of the science. Legislation that prohibits or imposes insurmountable barriers to NHP research in the absence of validated alternative models can potentially put human lives at risk, increase economic costs, spur relocation of U.S. research programs to other countries, and compromise U.S. global leadership in public health and biomedical research.

The use of NHPs in federally funded research has been the focus of ongoing congressional attention. In the Further Consolidated Appropriations Act of 2020, Congress placed restrictions on the use of NHPs (as well as dogs and cats) in research funded by the U.S.

Department of Veterans Affairs (VA).[1] The Act directed the VA to develop plans for reducing or eliminating NHP research (Grimm, 2019). This legislation, along with another bill introduced but not enacted,[2] demonstrates the potential for future legislation to place constraints on NIH-supported NHP research.

Policy actions may also catalyze the continued development of new approach methodologies with the potential to reduce reliance on NHPs. In response to a congressional directive to accelerate efforts to identify and implement nonanimal alternatives for biomedical research,[3] NIH launched a new working group on Novel Alternative Methods under the auspices of the NIH Advisory Committee to the Director (ACD) in November 2022 (Chang and Jorgenson, 2022). The charge to the new ACD working group is to identify high-priority areas for NIH investment in the development and use of novel alternative methods that can (1) advance understanding of biologic processes or states, and (2) complement and/or potentially replace traditional models used in biomedical research (NIH, 2022a). As discussed in Chapter 4, the Food and Drug Administration (FDA) has also established an Alternative Methods Working Group and undertaken other initiatives focused on identifying and advancing opportunities to incorporate new approach methodologies into the regulatory pathway (FDA, 2021a,b), a process that is further encouraged by the FDA Modernization Act 2.0[4] enacted in December 2022 (see Chapter 4). The FDA may also continue to use regulatory guidance, such as the 2022 guidance on mitigating NHP supply constraints arising from the COVID-19 pandemic (FDA, 2022), to identify opportunities to reduce reliance on NHPs. The 2022 guidance encourages sponsors to use NHPs only when there is no other relevant model.

Availability of NHP Research Resources and Infrastructure

Resources necessary for the continued study of NHPs in the United States have declined in the face of growing needs for the use of NHPs to advance scientific knowledge and protect human health, as described in Chapter 3. Shortages have resulted from overreliance on foreign sources for NHPs and the failure to develop adequate resources for domestic breeding (NASEM, 2021; O'Grady, 2022; Subbaraman, 2021). The challenges associated with availability of NHPs will likely continue to influence their use in the future as efforts to increase supply fall short of the needs created by surges in demand, such as was experienced during the COVID-19 pandemic. Ensuring a supply of NHPs that can meet the needs of the nation's biomedical research enterprise will require a commitment to supplying NIH-supported investigators from domestic resources.

The development and implementation of a national plan for NHP research resources would help ensure the availability of NHPs to meet the nation's public health needs. Operational and programmatic elements that need to be considered for such a plan include but are not limited to the

- allocation of scarce NHP resources to priority research areas;
- coordination of domestic breeding plans and the welfare of the animals;
- monitoring and evaluation of changing resource needs across the biomedical research landscape;

[1] Further Consolidated Appropriations Act, 2020 (P.L. 116-94, 116th Congress) (December 20, 2019).

[2] The Primate Protection and Research Modernization Act was introduced in December 2018 but was not enacted. See https://www.congress.gov/bill/115th-congress/senate-bill/3773/all-info (accessed November 7, 2022).

[3] Further Consolidated Appropriations Act, 2022, Committee Print of the Committee on Appropriations U.S. House of Representatives: Legislative Text and Explanatory Statement, P.L. 117-103, 117th Congress, (April 2022).

[4] FDA Modernization Act 2.0 (S. 5002 — 117th Congress [2021–2022]).

- implementation of centralized tracking systems for NHP resources,
- formalization of collaborative research and training opportunities for the study of NHP models and new approach methodologies; and
- implementation of other data sharing opportunities.

Investigative teams in the private sector—major users of NHPs in the United States—have the financial means to acquire and study NHPs. But research conducted under private-sector sponsorship is generally not shared unless such sharing is advantageous to the sponsor. For example, data generated in the FDA drug approval process are not disclosed unless the sponsor elects to do so.[5] There have been instances of public–private data sharing, such as the Early Detection Research Network (Srivastava and Wagner, 2020), but in general, data that impact the intellectual property rights or future development plans of private companies are kept private, even after major findings have been published (Hopkins et al., 2018; Modi et al., 2022). In contrast, the findings of NIH-sponsored research must be disclosed openly (NIH, 2022e), and a data sharing plan is a required part of grant applications (NIH, 2023b). Without increased NIH support for domestic production of NHPs, NHP research would likely move increasingly into the private sector, where funding is more abundant, priorities are market driven, and disclosure is limited. Another likely outcome of limitations on NHP research infrastructure in the United States is for research programs to move to countries such as China, where government investment in NHP research is substantial (Einhorn and Lew, 2022; Normile, 2022).

RESEARCH DOMAINS IN WHICH THE NEED FOR NHPs IS LIKELY TO GROW

There are specific domains of scientific inquiry for which research using NHPs is currently indispensable, and the committee anticipates that the need for NHPs in these domains will continue to grow. These domains and the committee's rationale for anticipating this continued growth are described in Table 5-1. The committee identified these domains after considering the nation's most pressing public health needs and the evolving state of the science, discussed earlier in this chapter, as well as the findings presented in previous chapters of this report regarding research domains in which NHPs are contributing to advances in human health (Chapter 2), current and future anticipated demand for NHPs (Chapter 3), and the current and future potential of new approach methodologies to reduce reliance on NHPs (Chapter 4).

Neuroscience and infectious disease are research domains likely to grow in the future, as reflected in NIH priorities for NHP research (Eisinger, 2022). The complexity of the primate brain is not adequately modeled by any in silico or in vitro system or other animal species (Feng et al., 2020; Hutchison and Everling, 2012; Roelfsema and Treue, 2014), and the burden of neurologic disease will continue to rise as the population ages (Riggs, 1998). Certain infectious diseases have a pathogenic mechanism seen only in primate species, and the COVID-19, Zika, Ebola, and other recent epidemics demonstrate the importance of NHP models to understanding novel diseases and testing the safety and efficacy of vaccines and therapeutics. Immunotherapy using cellular-, protein-, or nucleic acid–based therapeutics has emerged as another vital area of NHP research that is likely to continue to grow (Lisa et al., 2017; Tanaka et al., 2014; Voge and Alvarez, 2019), and the degree of molecular similarity between humans and NHPs is key to understanding the effectiveness of these novel thera-

[5] Investigational New Drug Application (21 C.F.R. § 312.130).

TABLE 5-1 Research Domains in Which the Need for Nonhuman Primates (NHPs) Is Likely to Grow

Research Domain	Rationale
Basic and applied research in behavior and neuroscience	Many approaches for monitoring and manipulating structures and processes within the brain are invasive and rarely can be carried out in healthy human volunteers. Functional imaging in humans has allowed analysis of the normal and diseased brain in ways not previously possible. The insights gained from imaging in humans are complemented and expanded by imaging in NHPs, which also provides the opportunity to explore the actual neural activity that generates the imaging signals. In addition, movement, cognition, and affect are emergent properties that are a consequence of the activity of large networks of neurons with precise interconnections. The complex interconnections between neurons in these networks are a result of detailed genetic programs and experience. These factors are not easily recreated by tissue culture and organoids. Key brain regions and connections important to normal motor, cognitive, and affective function in humans are absent in rodents but present in NHPs. Genetic engineering of NHPs is creating new opportunities to study neurological disorders.
Infectious diseases, including those that are emerging or feature primate-specific pathogenesis or susceptibility	Emerging infectious diseases—both novel agents, such as SARS-CoV-2, and reemerging threats, such as multidrug-resistant tuberculosis and polio—have the potential to abruptly increase needs for NHP research. Pandemics and epidemics create urgent requirements for model systems that can recapitulate the course and outcomes of human disease and support the safety and efficacy testing of vaccines and therapeutics. NHPs are invaluable as models for emerging infectious diseases because of their anatomical, physiological, and immunological similarities to humans and their susceptibility to many human pathogens.
Genetics	The close genetic similarities between humans and NHPs provide an opportunity to understand the evolution and function of gene sequences involved in health and disease. Increasing computational capacity to study gene sequence data will allow the study of not only single-mutation diseases but also complex polygenic disorders and epigenetic regulation of gene expression. Gene therapies, including both somatic cell modification in individual patients and heritable germline modification, hold enormous promise for treatment of currently untreatable genetic disorders with severe consequences for affected humans.
Development of therapies requiring a primate-specific target	Many biologic therapeutics are designed to engage human targets with high specificity that may manifest their intended pharmacological activity only in other primates. Examples include protease-activated receptors that mediate platelet activation and monoclonal antibodies. As a result of their specificity, therapeutics developed using mice or other nonprimate models may miss their intended target in humans, necessitating studies in NHPs. Stem cell–based therapies, like gene therapies, have generated a great deal of excitement, but safety and feasibility studies in NHPs continue to be critical. In the case of countermeasures that cannot be evaluated for efficacy through human challenge studies, animal studies, including NHP studies when scientifically justified, provide a pathway for regulatory approval under the Food and Drug Administration's Animal Rule.
Reproductive biology	Getting pregnant and carrying a pregnancy to term are complicated processes during which something can go wrong, leading to challenges with fertility. Implications of factors that can contribute to the inability of a woman to conceive, such as aging, failure to ovulate, oocyte maturity, implantation failure, and gynecological diseases and infections, can be modeled in NHPs to address questions directly relevant to human female reproduction.
Aging, obesity, and inflammatory disease	Chronic inflammation is a major factor in age-related diseases. The adaptive immune system deteriorates with advancing age, but the impact of aging on specific immune cells and their role in inflammation remain incompletely understood. NHPs are invaluable as models for these processes because of their anatomical, physiological, and immunological similarities to humans, as well as their susceptibility to spontaneous obesity, insulin resistance, and related cardiometabolic comorbidities. Some cancers also arise spontaneously in aging NHPs and are remarkably similar to those seen in humans with regard to incidence, risk factors, and progression to metastasis. Effects of environment, activity, diet, and exposure to medications can be strictly controlled for NHPs and evaluated longitudinally, something that cannot be achieved in humans in an uncontrolled setting.

	Example Research Topics
	• Basic brain biology (such as neural pathways, brain regions, and brain connections) • Pathogenesis of and treatments for neurodegenerative disorders (such as Parkinson's and Alzheimer's disease and age-related cognitive decline) • Brain injury and new methods for promoting recovery of function following stroke and spinal cord injury • Addiction and substance abuse • Social/behavioral effects on health • New approaches to preventing and treating neurodevelopmental disorders • New methods for preventing blindness and restoring vision
	• Human immunodeficiency virus • Coronaviruses • Viruses targeted for eradication, such as measles and polio viruses • Filoviruses, such as Ebola • Tuberculosis • Malaria • The next novel pandemic virus
	• Genetic disorders with a high level of sequence identity or homology between NHPs and humans (e.g., colorectal cancer, retinitis pigmentosa, epidermolysis bullosa) • Gene therapy • Gene editing • Monogenic and polygenic diseases • Genetic modification of NHPs to model diseases caused by specific gene polymorphisms
	• Immunotherapies • Gene therapies • Cellular therapies • Medical countermeasures against radiation, chemical, or biological hazards
	• Fertility • Endometriosis • Polycystic ovarian syndrome
	• Cardiovascular disease • Type 2 diabetes • Kidney disease • Depression • Dementia • Osteoporosis • Anemia • Osteoarthritis • Sarcopenia • Multimorbidity patterns of aging • Determinants of frailty and resilience • Naturally occurring cancers, such as breast, colon, cervical, and lymphoma cancers

pies. Likewise, some aspects of reproductive biology are primate specific and, in the case of reproductive health in women, understudied (Metz, 2022; Slawson, 2019); the public health, social, and economic burdens associated with infertility and diseases of the reproductive system will continue to drive needs for NHPs in research in this area. Finally, NHP research in aging and chronic inflammatory diseases is likely to increase given the enormous public health burden associated with such diseases in the United States and the opportunities to study them in the context of the long-term care increasingly being provided to aging NHP research subjects (Verdier et al., 2015). Of note, increased numbers of long-term NHP studies undertaken in the context of aging research also provide new opportunities to study naturally occurring cancers that arise spontaneously in aging NHPs (Deycmar et al., 2023). Treatment of such cancers may inform new tumor-targeting strategies, an advance that not only has high relevance to human disease but also may benefit the NHPs themselves.

FUTURE NEEDS FOR SPECIFIC NHP SPECIES

While multiple macaque species continue to be used in and contribute knowledge to different domains of biomedical research (e.g., neuroscience, infectious disease), rhesus macaques (*Macaca mulatta*) are likely to remain the predominant species under study based on the abundance of data characterizing this species—including the first and most-studied NHP genome (Gibbs et al., 2007; Rogers, 2022)—and the increasing availability of immunologic reagents, as well as their current widespread use in research funded by NIH (NHP Investigators Survey, 2022; NPRC Information Request, 2022[6]; ORIP, 2018) and globally. These NHPs play a key role in both HIV research (Cooper et al., 2022; Rogers, 2022) and the study of outbreaks, such as Zika virus infection (Dudley et al., 2019; Haese et al., 2021), Ebola (Geisbert, 2017), and COVID-19 (Albrecht et al., 2021; Hild et al., 2021). These animals develop type 2 diabetes mellitus (Havel et al., 2017) and naturally occurring cancers of the colon (Ozirmak Lermi et al., 2022), breast (Wood et al., 2006), and cervix (Wood et al., 2007), with mechanisms of disease pathogenesis nearly identical to those of humans. They are abundant and are not endangered, or even threatened, in the wild (CITES, 2023; Singh et al., 2020).

Use of the common marmoset (*Callithrix jacchus*) is likely to increase because this small species is the best characterized and most widely used of the New World NHP species (Colman et al., 2020; Han et al., 2022a; Malukiewicz et al., 2020). These NHPs are increasingly used for studies of neurodevelopment and neurodegenerative diseases. Their shorter lifespan relative to other NHPs allows for lifetime studies in a relatively short period of time. They are a tractable species, and they reproduce well under laboratory housing conditions, typically producing twins or triplets and thus allowing for studies of gene–environment interactions. The first representative marmoset genome was sequenced in 2014 (Worley et al., 2014), and transgenic marmosets have been generated (Sasaki et al., 2009).

Some other species will likely continue to be studied to answer specific research questions. For example, both vervet monkeys (*Chlorocebus aethiops*) and squirrel monkeys (*Saimiri sciureus*) provide unique insights into neurodegenerative diseases such as Alzheimer's disease (Frye et al., 2021; Patel et al., 2021), and owl monkeys (*Aotus spp.*) continue to be used in malaria research (Sharma et al., 2022).

[6] This reference refers to written responses to a committee information request from each of the seven NPRCs (Washington NPRC, Oregon NPRC, California NPRC, Tulane NPRC, Emory NPRC, Wisconsin NPRC, and Southwest NPRC). Individual responses to the committee's information request can be found in the committee's public access file.

OPPORTUNITIES FOR ENHANCING NIH-SUPPORTED RESEARCH WITH NHPs

NHPs are precious resources demanding robust stewardship and the conduct of rigorous research that maximizes the knowledge and actionable insight obtained from each individual animal and study. Opportunities to use NHP resources more effectively include using thoughtful approaches for sample collection and sharing, fostering openness and data sharing, learning from natural disease in NHPs, and incentivizing collaboration among NHP research groups. Tools and technologies, including noninvasive monitoring and imaging approaches, artificial intelligence/machine learning (AI/ML), extended reality (XR), and laparoscopy, can be applied to increase the impact and rigor of NHP research, dissect natural disease behavior, reduce or refine sample collection, and improve alignment with processes being implemented in clinical settings. Each of these interrelated approaches to enhancing the use of NHPs in NIH-supported biomedical research, many of which have been noted previously by other expert groups (Bliss-Moreau et al., 2021a; NIH, 2020; ORIP, 2018), is discussed below.

Centralized Tracking and Stewardship of NIH NHP Resources

No clear or complete accounting of domestic NHP populations maintained through NIH funding was provided to the committee. NIH institutes, centers, and offices contract for NHPs as needed with contract research organizations and universities. However, the process used for allocating available NHP resources to researchers in need of NHP models did not appear fully transparent to the committee or consistent across resources, making it difficult to assess equitability for different researchers and disciplines or the research community at large. Given the unique value of NHPs to the research community, there is an opportunity to enhance NIH-supported NHP research through more formalized, centralized, digitized and digitalized, and comprehensive national management and tracking of NHPs maintained and used by NIH's intramural and extramural programs. The NHP animal locator service based at the Washington NPRC is an invaluable resource for investigators nationwide (NHPRC, 2023; WaNPRC, 2023); expansion of this service and designation of NIH staff to support that effort would improve transparency regarding the availability of scarce NHP resources and allow their more efficient utilization.

Increasing Use of Data-Driven Noninvasive or Minimally Invasive Technologies

This section describes noninvasive or minimally invasive technologies with the potential to enhance biomedical research conducted using NHP models. Examples of these technologies include digital biomarkers, XR, laparoscopy, and imaging; also discussed is the use of computational methods, including AI/ML and computer vision. Some of these technologies, such as laparoscopy and imaging, are already used in NHP studies to some degree (Association of Primate Veterinarians, 2019; Basso et al., 2021; Milham et al., 2018; Prescott and Poirier, 2021). Digital biomarkers and XR technologies have been used with NHPs on a limited basis (Davis et al., 2021; Usher et al., 2018) but are used more commonly with rodent species (Baran et al., 2020, 2021; Venkatesan et al., 2021). These technologies have been implemented within clinical phase drug development and even health care (Crawshaw et al., 2015; FDA, 2020; Mori et al., 2022). Leveraging technologies and approaches that

are non- or minimally invasive offers many potential benefits for NHP research, including enabling

- longitudinal assessment of disease progression that allows each animal to serve as its own baseline control, leading to increased sensitivity and reducing variability and numbers of animals needed for the research; and
- improved measurements of drug safety, tolerability, and efficacy through the incorporation of drug distribution measurements in real time.

The sections that follow provide further descriptions of the potential uses and benefits of non- or minimally invasive technologies in the context of NHP research. Note that the benefits described under each technology-specific subsection are intended to be illustrative and do not represent a comprehensive cataloging. It should be noted as well that current grant mechanisms offer little support for the development of novel, less invasive procedures for NHP research, despite the potential of these approaches and technologies to benefit animal welfare and data quality and reduce the numbers of animals used.

Digital Biomarkers

A digital biomarker refers to a characteristic or set of characteristics, collected from digital technologies, that are measured as an indicator of normal biological processes; pathogenic processes; or responses to an exposure or intervention, including therapeutic interventions (Vasudevan et al., 2022). Digital biomarker data can be collected continuously from freely moving NHPs in their home environment (Prescott et al., 2021) using a variety of digital monitoring technologies, including internal (e.g., injectable, implantable, or ingestible) and external (e.g., wearable, camera, or electromagnetic field detector) devices (Baran et al., 2022; Brattain et al., 2016; Koizumi et al., 2021; Ma et al., 2020; Prescott et al., 2021). Examples of the use of digital biomarkers in NHP research include detection and tracking of experimentally induced or naturally occurring diseases (NIH and HHS, 2020), including subclinical (mild) disease that may cause NHPs to be distressed without showing observable clinical signs (Davis et al., 2021). Other applications include the study of social behavior and cognition using micro-electrocorticogram recordings (Xu et al., 2022). Approaches using digital biomarkers have also been assessed for their utility in managing Alzheimer's disease in human patients (Harms et al., 2022) and, more commonly, in research using rodent models across a range of diseases (Baran et al., 2020, 2021; Defensor et al., 2019; Do et al., 2020; Geuther et al., 2022; Golini et al., 2020; Hobson et al., 2020; Wotton et al., 2020).

Use of digital biomarkers enables the collection of objective, quantifiable, and clinically relevant measures of physiological and behavioral response to disease progression or therapeutic intervention (Motahari-Nezhad et al., 2021; Traverso et al., 2015). Increased accuracy of experimental observations may be achieved by eliminating the subjectivity that results from inconsistency in human observations, as well as the influences of human intervention when recordings are made (Baran et al., 2022). Collection of digital biomarker data may also improve the planning, design, and execution of NHP studies by identifying outliers before a study begins.

NHP data collection and study outcomes can be influenced by routine handling or in-room observations that impact NHPs' physiology and behavior (Clarke et al., 1988, 1994; Pomerantz et al., 2022). Digital biomarker technologies have the potential to enhance the quality of research by decreasing the data variability that results from stress and alteration of the basal physiology and behavior of NHPs associated with in-person checks or handling.

Similar effects are observed in the clinical setting when outcomes of patients' physiological and behavioral assessments are impacted by stress and drive for higher performance in a clinic versus at home (Drawz et al., 2012; Mallick et al., 2009). Thus, another potential benefit of biomarker collection is increased precision and sensitivity for detecting significant pharmacologic or toxicologic changes, as well as enhanced study reproducibility.

Digital biomarker technologies have the potential to provide a more holistic assessment and view of NHPs because they offer continuous monitoring instead of the snapshot derived from traditional assessments. Continuous collection of digital biomarkers has the potential to enhance current NHP approaches by providing unbiased longitudinal monitoring of behavioral and physiological function for various research domains, from aging to neurological diseases to safety testing. In NHP research, standard techniques for quantifying biological age and the progression of aging are challenging to implement reproducibly and longitudinally in cohorts within and/or between research laboratories (Baran et al., 2021; Shively et al., 2021). The ability to conduct longitudinal disease characterization and tracking may be especially useful in diseases with variable onset and rates of progression, as well as when the health of NHPs may decline rapidly without obvious warning signs or so slowly that change is difficult to assess (Baran et al., 2022). Use of digital biomarker technologies not only provides an opportunity to align with clinical approaches and provide a higher-resolution picture of NHP health or disease state, but also has the potential, noted earlier, to reduce the number of NHPs required as NHPs on longitudinal studies can serve as their own controls.

Digital biomarkers may also reduce reliance on traditional measurements, such as blood collection under sedation or some types of neurobehavioral recordings collected from restrained NHPs, which require handling the animals (Prescott et al., 2021) and may necessitate removing them from family groups. In addition, the potential replacement of histopathology endpoints, which require euthanasia, with digital biomarkers in specific contexts of use may reduce the number of NHPs needed in a study. In some cases, moreover, digital biomarkers may be able to show modest therapeutic improvement that is clinically relevant but that traditional measures are not sensitive enough to detect (Baran et al., 2022).

Overall, continued development and broader implementation of digital biomarker approaches for NHP studies provides an important opportunity to enhance NHP research through assessments that are objective (not impacted by perceptual biases), have high resolution (collected continuously), and are realistic (collected within the home environment of NHPs) (Baran et al., 2022).

Extended Reality, Including Virtual and Augmented Reality

XR technology, including virtual and augmented reality, can be used for NHP management, staff training, and clinical assessments (AALAS, 2020). Use of this technology is just now emerging within the life sciences. While it is not yet widely applied to the handling and care of NHPs, experience in other veterinary and research settings (McCool et al., 2019; Tang et al., 2020) suggests that XR technology has the potential to

- increase the efficiency of NHP clinical assessments and veterinary training, such as by enabling staff who are assessing an NHP to share observations with the veterinary team in real time while accessing health and study records;
- reduce NHP stress and potentially morbidity and mortality by allowing staff to make decisions in real time;
- provide access to NHP subject matter experts and researchers on- and offsite;

- reduce the number of personnel entering the facility, thereby reducing the risk of contamination;
- standardize the collection and reporting of clinical and pathology outcomes; and
- augment training of personnel and researchers by allowing access to immersive training prior to in-person training (McCool et al., 2019), making the latter more effective with less disruption of and impact on NHPs and reducing the number of animals required.

Minimally Invasive Surgical Techniques

Laparoscopic surgery, also referred to as minimally invasive surgery of the abdomen, has become the gold standard in human medicine for many abdominal surgical procedures, and multiple publications have described its benefits in NHP research (Chai, 2015; Hutz et al., 1988; Kumar et al., 2011; Liao et al., 2004; Rippy et al., 1996), indicating the value of expanding future use of this technique when possible. As in the clinical context, laparoscopic surgery results in less postoperative pain, inflammation, and infection, and NHPs therefore require less time to recover as compared with laparotomy (open surgery). Additionally, the laparoscopic approach allows for repeated visualization of the site, biopsy collection, and intervention within the same NHP. This capability minimizes interanimal variability and facilitates longitudinal studies of disease progression within the same animal in lieu of relying on postmortem samples collected from replicates (Baran et al., 2011). Wider implementation of laparoscopy thus has the potential to enhance animal well-being and reduce the variability of research data while increasing precision and sensitivity.

Imaging

Imaging technologies, such as optical imaging, magnetic resonance imaging (MRI), ultrasonography, computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), can be used to facilitate longitudinal monitoring of disease progression and biological responses over time (Bercovich and Javitt, 2018). CT, including contrast-enhanced CT, can be used for quantitative assessment of body composition (using, for example, tissue density to distinguish healthy from diseased tissue) (Troschel et al., 2020). In a recent example, a combination of CT and fluorine-18 fluorodesoxyglucose (18F-FDG) PET imaging was used to collect additional data on COVID-19 pathogenesis in the lung and to evaluate therapies in NHPs (Naninck et al., 2022). MRI has been particularly useful in neuroscience, enabling study of NHPs' affective states, brain evolution, and face processing, among other topics (Prescott and Poirier, 2021). Insights regarding normal and diseased brain states gained from functional imaging using PET and MRI in humans are complemented and expanded by imaging in NHPs, in which exploration of the neural activity that generates the imaging signals is possible. For some studies, the potential decrease in variability achieved by using as the control values the baseline measurements obtained with imaging of the same animal (as opposed to separate control animals) may also reduce the number of animals required for detecting a change in response to a physiological perturbation.

Computational Methods, Including AI/ML and Computer Vision

AI/ML methods and applications are described in Chapter 4 in the context of approaches for complementing or reducing reliance on NHP models. AI/ML can also assist with the analysis of NHP experimental data to obtain information on and insight into the systems being studied. Through AI/ML analyses, one can obtain both real-time and accelerated access

to insights that can expedite decision making, which in turn may reduce the length of a study or enable faster intervention if needed.

Computer vision, a subcategory of AI, has been used in the analysis of video data collected during studies of NHP behavior and physiology (Bala et al., 2020; Brattain et al., 2016). Deep learning, another AI subcategory, has been used to count NHP retinal ganglion cell axons in optic nerve tissue images, outperforming manual counts (Ritch et al., 2020). In the analysis of histological imaging data, AI/ML methods can be trained to recognize specific features in imaging data, and once validated, can be used to examine other images to identify relevant features; such methods are already having an impact in radiology and tumor histology. AI/ML methods can also be used to analyze complex patterns in imaging or video data and, given appropriate training data, draw inferences about NHPs' behavior and psychology (Bala et al., 2020; Berger et al., 2020; Yao et al., 2023) in the same way that AI/ML systems are being trained to recognize changes in human psychology (e.g., cognitive decline). Such systems could also be used to identify neurodegenerative disorders or symptoms and to monitor their progression or potential response to therapies.

The behavioral and neuroscience fields offer additional examples of AI/ML applied in NHP research to increase data processing efficiency, extract additional knowledge and insights from available data, and provide predictions. These examples include behavioral evaluations (Lauer et al., 2022), identification of predictors of neurodegeneration, imaging genetics and genomics, classification of electrocorticograms, and preprocessing and automating MRI analysis (Bogdan et al., 2017; Choi et al., 2021; Hadj-Bouziane et al., 2003; Neff, 2020; Pilkiw and Takehara-Nishiuchi, 2018; Teil et al., 2021).

Outside of neuroscience, AI/ML methods have been used to better understand the humoral immune responses of vaccine candidates by identifying the features of humoral immunity that distinguish protective from nonprotective responses (Ackerman et al., 2017). Within cardiovascular pathology, these methods have been used for histopathology diagnosis (Glass et al., 2022). These computational tools can also expedite NHP biomarker discovery and indicators of disease outcomes (Marino et al., 2016). Hybrid approaches may involve integrating AI/ML with system biology (Antontsev et al., 2021) and can allow for translation of computational models across species (NHPs and humans) (Brubaker and Lauffenburger, 2020).

Ultimately, the successful deployment of any computational methods and their effective use in NHP studies will require sharing the data, computational models, and software code. Such sharing will help ensure that the data are used to maximum effect and that the results from each study are reproducible (or falsifiable).

Increasing Impact by Combining Technologies

While each of the above technologies may have a positive impact on NHP research, combining them holds the potential for greater impact (EY, 2018). For example, combining digital biomarker data collected continuously from freely moving animals in their home environment with AI/ML extraction (such as computer vision) could enable the development of digital NHP twins for specific applications, as seen in the behavioral sciences (Baran et al., 2022), given sufficient and relevant training data for the task at hand. Such a system could also facilitate the identification of subtle behavioral changes that would enable earlier detection of the effects of experimental treatment (Davis et al., 2021), which in turn might allow investigators to intervene sooner, thereby improving NHP care. Such predictive models would require substantial validation before they could be widely used or the results from such studies could be fully trusted. Still, the noninvasive nature of digital biomarkers means

that such approaches could be developed at relatively low cost and without undue stress or risk to NHPs.

Combining NHP training (Graham et al., 2012) (see the section on Data-Driven Advances in NHP Care and Management that follows) with digital biomarker technologies may achieve a combinatorial effect that goes beyond what a single technology can provide, as both approaches reduce stress on NHPs and decrease the variability of research data. Incorporating laparoscopic, imaging, and digital biomarker technologies for longitudinal assessment of disease progression, when appropriate, also has the potential for achieving a combinatorial effect.

Data-Driven Advances in NHP Care and Management

In NHP research, the iterative scientific process is often focused on questions related to human health, but the process also applies to other aspects of NHP research, including standard management practices for NHP care. The data generated from NHP research are inexorably linked to the conditions in which the animals exist in the laboratory, even if this link is not always explicitly recognized. For example, social conditions in which infant monkeys are born and reared have lasting impacts on their psychosocial development (Harlow et al., 1965), neurobiology (Martin et al., 1991; Sánchez et al., 1998; Struble and Riesen, 1978), and programing of the immune system (Capitanio, 1998; Hawkley et al., 2012; Lubach et al., 1995). Furthermore, social housing in adulthood prevents the development of and reduces existing deleterious behaviors (Baker et al., 2012; Gottlieb et al., 2015; Schapiro et al., 1996). Accordingly, a federal mandate requires housing NHPs in social contexts,[7] although exemptions to this rule are allowed for scientific reasons.

The impact of social context is likely greater than was previously thought. A growing body of literature demonstrates that the adult monkey's social context (even when the animal has been reared to adulthood in social groups) impacts the data generated by translational NHP models for the study of human health. Such impacts have been observed, for example, in studies related to mood disorders—influenced by variability in access to social partners (Charbonneau et al., 2022), and variability in the number and strength of close relationships (Bliss-Moreau et al., 2021b)—and immune function (Capitanio and Cole, 2015; Castell et al., 2022; Guerrero-Martin et al., 2021).

Little funding is available with which to test specific hypotheses related to social context, leaving many open questions. Nonetheless, these findings suggest that the best NHP models for studying human health are NHPs living in social contexts—and preferably specific types of social contexts that include full access to partners in stable relationships. Similarly, research has shown that providing NHPs with control over their environment by training them to participate actively in research studies, such that they are cooperative during drug administration or blood sampling reduces stress, decreases the variability of research data, and more accurately models diabetes in a macaque model (Graham et al., 2012). This finding is perhaps not surprising, as it mirrors the voluntary provision of samples by human patients. Additionally, both providing social housing and training NHPs to cooperate in studies have been found to reduce the variability of the data produced by macaque models for the study of infectious and metabolic diseases (Graham et al., 2012; Guerrero-Martin et al., 2021), a finding with important implications for the number of animals necessary to conduct a meaningful study (less-variable data requires fewer animals to draw conclusions), as well as for reproducibility. As with social housing, however, acclimating or training animals to par-

[7] Housing Facilities, General (9 C.F.R. § 3.75).

ticipate actively in studies requires significant resources, including personnel with expertise and time.

Although it is becoming increasingly apparent that the methods used with NHPs influence the data they generate, various factors impede the ability to fully comprehend that relationship. Peer-reviewed articles often do not report important methodological details (e.g., housing conditions, including whether the animals were pair-housed and what environmental enhancements were provided; handling techniques, such as acclimation and training strategies). Best practices intended to guide researchers in including such details in the methods sections of their manuscripts (Bliss-Moreau et al., 2021a; Percie du Sert et al., 2020; Pomerantz et al., 2022) are often neglected because of lack of awareness, or the desire of the author or the journal to adhere to word count limits. In fact, the authorship guidelines of many top journals actively encourage researchers to truncate their methods sections. This practice presents a challenge not only to researchers who wish to replicate published studies but also to the research community's efforts to assess how widespread different practices are.

It is also important to note that NIH specifically does not fund research focused on the effect of housing conditions or handling techniques on animal models unless the research is framed in a directly translational fashion (e.g., the effect of social stability on the immune response), and non-NIH sources of funding for such studies are few and limited with respect to the amount of funds available. Details about care conditions that could dramatically impact data outcomes are often very minimal or not included in grant applications, mirroring their lack of inclusion in publications and making it difficult to evaluate whether future research will address these issues. As a result, researchers and grant application evaluators face challenges in determining how changes in housing or handling will impact the data generated. This lack of information on care conditions also presents a challenge for leveraging current scientific insights to speed both scientific discovery and future improvements in NHP science. This gap needs to be addressed through explicit recognition of the importance of these factors and matched by strategic investments in determining their effect on research outcomes. Such investments would ensure that these factors are addressed in scientific practice, detailed in the reporting of scientific discoveries, and ultimately leveraged to ensure the well-being of NHPs and maximum benefit from future NHP research.

Facilitation of Intergroup Collaboration and Information Sharing

Facilitating Collaboration among NHP Researchers

While examples of collaborative NHP research can be found within and among research institutions, including NPRCs (Messinger et al., 2021; Yee et al., 2022), increasing collaboration across NHP research groups would have several potential benefits, including more efficient use of individual animals, facilitation of data and knowledge sharing, and improvements in the rigor of research. Collaborative approaches could provide an opportunity for, and reduce barriers to, incorporating novel technologies, including new approach methodologies, into research using NHPs.

Regardless of whether collaborations would be established within a single research institution or across multiple facilities where NHPs are being used, plans for each upcoming NHP study would be shared among participating researchers so additional samples could be taken or data collected from the same NHP cohort for use by multiple research groups. For example, one uninfected (control) cohort could serve as a control for multiple unrelated research questions, as long as appropriate samples and data were collected from those animals. Such efforts would require extensive preplanning, harmonization of protocols, and

ongoing communication, as well as the resources for collection and storage of samples and the digitization and digitalization of data. Also important would be cultural climates that foster collaboration and mechanisms and regulatory flexibility for multiple researchers to be mapped to a single group of animals.

Promoting intergroup collaborations will require (1) investigator-driven efforts—an example of which is ManyPrimates, which employs a "crowd-sourced" method of cooperation and data sharing dedicated to accelerating research on primate cognition (Altschul et al., 2019); and (2) explicit NIH funding opportunities (see Box 5-1). Collaborative opportunities could further be realized through screening for common diseases enzootic in captive NHP breeding colonies/populations, such as genital papillomavirus infections; screening for early cancer detection; and multicenter studies of common morbidities, such as osteoarthritis and metabolic disease, that involve banking of samples and data from affected animals in a central resource for community analysis.

Effective interinstitutional collaborations require tools and strategies that allow for acquiring and storing data in harmonized and digital formats, sharing records, and integrating clinical and research data. The Zika research group at the Wisconsin NPRC (Dudley et al., 2019), for example, made its data public early in the Zika virus pandemic via LabKey—an electronic tool that allows data to be anonymized and published in a public forum (Butler, 2016)—which led to collaborations across NPRCs. These collaborations allowed researchers at the centers to pool data and generate discoveries that would have taken significantly more time and resources had the centers' teams been isolated from one another (Dudley et al., 2018; Raasch et al., 2022).

Efforts to promote collaboration among NHP research groups are not without challenges. One of the most persistent barriers to large-scale collaboration has been funding limitations. NIH funding mechanisms are often not designed for intergroup collaboration, contributing

BOX 5-1 EXAMPLES OF NIH SUPPORT FOR COLLABORATIVE NHP RESEARCH

For more than a decade, the National Institutes of Health (NIH) has supported collaboration in nonhuman primate (NHP) research through the multicenter Nonhuman Primate Transplantation Tolerance Cooperative Study Group program. The goals of this program are to evaluate the safety and efficacy of existing and novel immune tolerance induction regimens in preclinical transplantation studies (kidney, pancreatic islet, heart, and lung transplantation) and to identify mechanisms associated with the induction, maintenance, and/or loss of tolerance in NHP models. NIH support for the initiative includes access to a dedicated colony of NHPs that have been selected for specific characteristics, such as major histocompatibility complex (MHC) profile, age, and sex. Ultimately, the program aims to support the development and evaluation of immune tolerance induction regimens that enhance long-term graft survival in human transplantation patients (NIH, 2016).

More recently, the Coronavirus Vaccine and Therapeutic Evaluation Network (COVTEN), a partnership among the seven National Primate Research Centers, was established with the aim of advancing COVID-19 vaccine research and development (NASEM, 2021; Tate, 2021). The objective of this partnership was to standardize data collection procedures across centers, share data and best practices, and reduce the number of NHPs in use by sharing single control groups across numerous studies (NASEM, 2021; Tate, 2021). This unique collaborative effort allowed for the pooling of resources and harmonization of data among multiple organizations tackling similar research questions, thereby helping to limit resource duplication and accelerate research findings.

to the creation of silos in research (ORIP, 2018). Other challenges include the potential loss of intellectual property or misattribution of credit for academic career advancement (NIH, 2020) and, in cases of international collaboration, differences in the regulations guiding the use of NHPs in research across countries (Mitchell et al., 2021). Funders and other relevant parties will need to address these barriers if the potential of collaboration for the advancement of NHP research is to be realized.

Promoting Quality, Openness, and Data Sharing in NHP Research

The past decade has witnessed a surge of interest in improving the quality of science, born out of notable failures to replicate scientific findings across studies, laboratories, or species (Errington et al., 2021; Open Science Collaboration, 2015; Owens, 2018). The result has been increased focus on developing methods and reporting structures that will allow for the evaluation and improvement of scientific rigor and reproducibility (Bliss-Moreau et al., 2021a; Hewitt et al., 2017). The expectation is that increasing the transparency of experimental design and data analysis, along with data sharing, will enhance the ability of scientists to evaluate the quality of published scientific studies and replicate their findings, although it should be noted that, while replication of findings is often viewed as a gold standard for high-quality research (Collins and Tabak, 2014), a study can be repeatable without being rigorous or translationally relevant.

Replication is rare in NHP science because of the scarcity and critical importance of NHP resources. Only 26.5 percent of the 264 NIH-supported investigators who responded to the questions on this topic in a committee-generated survey reported carrying out any kind of replication of existing studies (NHP Investigators Survey, 2022). Still, practices that allow for evaluation and improvement of the rigor and scientific impact of existing research offer a means of promoting quality in NHP studies. They include the adoption of good practices for documentation, digitization and digitalization, and data reporting and the sharing of experimental materials and data, which are discussed in more detail below. Wider adoption of such practices, however, will require systems of accountability and mechanisms for addressing the real and perceived barriers to their implementation.

Facilitating Data Sharing

Data sharing is a key means of assessing and promoting rigor in NHP research and can also help reduce redundant research by enabling investigators to access existing data sets instead of having to replicate existing ones using additional animals. As discussed previously, moreover, large, curated data sets are required for training and validation of computational tools (Alharbi and Rashid, 2022; Yao et al., 2023). For these reasons, it is important to promote data sharing opportunities by developing and maintaining a robust infrastructure that can accommodate the large quantities and types of data generated within the diverse NHP research ecosystem, including all relevant metadata (e.g., genetic characteristics and origins of the animals, clinical data, how the animals were housed and handled [Pomerantz et al., 2022]; other specifics of the study design), without which the value of shared data can be limited, potentially leading to biased interpretations.

The genomics field has been a leader in data sharing, providing an example of the potential benefits of open access. It is common practice for researchers to deposit raw genomic data before or upon publication (NIH, 2020). At present, two databases developed by the NPRCs in collaboration with the University of California, Santa Cruz, enable sharing of NHP genomic and annotated phenotypic data (NIH, 2020). In addition, the Gene Expres-

sion Omnibus database, which includes gene expression data from NHPs, serves as a public transcriptomics data repository (Han et al., 2022b; NCBI, 2021).

Other examples of NHP data sharing include the National Institute on Aging (NIA)–supported Primate Aging Database[8] (Kemnitz, 2019) at the Wisconsin NPRC, which captures biological variables relevant to aging, and an effort led by the California NPRC to facilitate access to longitudinal behavioral, clinical, and other data generated as part of its Biobehavioral Assessment Program. In the latter example, which was recently described in a review by Capitanio (2021), infant monkeys at the California NPRC underwent comprehensive behavioral and immunophenotyping shown to have significant predictive capacity for a variety of behavioral and disease-related processes (Baxter et al., 2021; Kinnally et al., 2019; Myers et al., 2021). These data are made available via the California NPRC colony records, allowing researchers to select animals based on early temperament and physiology, and also serving as a valuable resource for the identification and characterization of naturally occurring animal models, most recently yielding a naturally occurring macaque model for the study of autism (Myers et al., 2021).

The cultural shift toward increased data sharing is far broader than the NHP research enterprise and continues to evolve (NIH, 2023a). The need remains, however, to encourage data sharing among qualified investigators and to provide the resources necessary to sustain large data sharing efforts. In the committee's survey of NIH-funded NHP researchers, many researchers self-reported sharing their data via trusted repositories (80 percent of 264 respondents), with fewer sharing data analytic methods (code) in such repositories (50 percent) (NHP Investigators Survey, 2022). Beyond the concerns that have impeded data sharing in science more generally, including those related to intellectual property and data security (Alter and Vardigan, 2015), additional concerns and barriers related to the sharing of NHP data in particular were identified. In responses to the committee's survey, lack of sufficient resources was a recurring theme, with additional concerns including a lack of "trusted repositories," storage space for data, and personnel to manage shared data, along with limited funding to support these ventures. Some respondents stated that NHP data are precious, expensive, nuanced resources often used for many projects in any given laboratory and supporting multiple trainees. Respondents indicated that sharing in this context reduces the laboratories' ability to use data for their own purposes, opens up opportunities to be "scooped," and creates intellectual property issues. The sensitivity and complexity of NHP research were also cited as barriers to sharing, with concerns in this regard including how shared data would be interpreted and limited quality control regarding which data would be shared. Expressed as well was the possibility that animal rights groups would use the data and expose the laboratory to information requests under the Freedom of Information Act and state public records laws, which vary from state to state and to which public universities are subject (NHP Investigators Survey, 2022). It is important to note here that different kinds of data have different risk levels; for example, the risk is greater with video data than with omics data.

Improving the Consistency of Health and Research Record Documentation for NHPs

For various reasons, information on the life, health, and experimental history of NHPs is often not communicated across laboratories or in publications. Clinical records are in different formats in different laboratories, while experimental data are usually separate from medical records and may be unavailable because of blinded study designs or intellectual

[8] See https://primatedatabase.org/ (accessed November 19, 2022).

property concerns. Currently, some of these health and experimental records are required by funders, but there are no consistent criteria for their collection, digitization, and digitalization. Furthermore, NIH typically funds projects for 5 years at a time, and the maintenance of experimental data may be discontinued when funding ends—a particular concern for long-lived species such as NHPs.

Even among those tracking these data, the types of information captured vary (Bliss-Moreau et al., 2021a; NIH, 2020). Inconsistent tracking of lifelong health and experimental data for NHPs has the potential to impact both research outcomes and animal welfare. Previous housing or husbandry conditions, social interactions or isolation, health conditions (including infection status for non–specific pathogen free [SPF] NHPs), and experimental and clinical histories may affect experimental outcomes in unpredictable ways, potentially obscuring the impact of experimental manipulations (ARRIVE, n.d.). Thus, a mechanism is needed for collecting and sharing in a consistent format across research groups a minimum set of experimental, medical, and life history data for NHPs used in NIH-supported biomedical research.

Consistent assessments and health screening criteria would not only improve scientific rigor and guide NHP health management but also facilitate more consistent reporting across investigative teams and provide a means of better matching NHPs with future studies, particularly if information on available NHPs at NPRCs were accessible to the broader research community (as discussed earlier in the context of the California NPRC's Biobehavioral Assessment Program). Lessons from the advancement of personalized medicine may be applicable to NHP characterization and research, particularly in the context of population stratification and diagnostics. However, this level of characterization is most likely to occur in domestically bred NHPs, providing further rationale for investment in domestic resources to reduce reliance on imported animals. In the long term, standardized record systems could be pursued, but given the burden associated with the development and maintenance of such systems, mechanisms that foster the harmonization and adoption of good documentation practices provide a path to more immediate benefit.

A number of examples of useful record systems from the clinical realm could be adapted for NHP research. They include, for example, electronic health records; clinical trial–like case report forms; and standard data models, such as Cancer mCODE (Minimal Common Oncology Data Elements) (MITRE, 2022) and the Standard for Exchange of Nonclinical Data (SEND), which is used for submission of nonclinical study data to the FDA (Choudhary et al., 2018). At a minimum, record systems need to be digital, searchable, and interoperable while also complying with the FAIR (Findability, Accessibility, Interoperability, and Reuse) Guiding Principles (Wilkinson et al., 2016).[9] The development and implementation of such systems will require resources including but not limited to standardized information systems and the personnel needed to manage the records and facilitate their use by investigators.

Development of Genetic and Genotype–Phenotype Resources

Progress has been made in the genomic sequencing of select NHP species commonly used in research, including rhesus macaques (Gibbs et al., 2007), vervets (Warren et al., 2015), and marmosets (Worley et al., 2014). The macaque Genotype and Phenotype (mGAP) resource[10] is notable in that it is the first public website providing for macaques searchable, annotated gene variant data, along with disease phenotype data, enabling the linking

[9] See https://www.go-fair.org/fair-principles/ (accessed November 19, 2022).
[10] See https://mgap.ohsu.edu/ (accessed November 19, 2022).

of variants to specific disorders (Bimber et al., 2019). Gene–disease associations based on this unique resource have been reported for such serious diseases as retinitis pigmentosa (Peterson et al., 2019), epidermolysis bullosa (Johnson et al., 2020), and the hypomyelination disorder Pelizaeus-Merzbacher disease (Sherman et al., 2021). Understanding of the substantial genetic variability within and across NHP species is increasing and can be leveraged for discovery and interpretation (Cheng et al., 2022).

Major histocompatibility complex (MHC) typing in acquired immunodeficiency syndrome (AIDS) research is another example of progress in model characterization. Specific MHC haplotypes have been linked to specific outcomes in simian immunodeficiency virus (SIV)–infected macaques, most notably natural suppression of viral replication and protection against progression to a neuro-AIDS phenotype (Sauermann et al., 2008). Characterization of the MHC haplotypes of macaques has become commonplace, and attempts to review the haplotypes before individual macaques are selected for a study have proven valuable in allowing researchers to select animals best suited to the research questions at hand.

Much work remains, however, before the characterization of NHP models is as extensive as that of murine models, which benefit from an International Mouse Phenotyping Consortium (IMPC).[11] The IMPC is focused on systematically characterizing mouse strains and models using a standardized battery of methods aimed at revealing disease manifestations across multiple body systems (Muñoz-Fuentes et al., 2018). The results of these tests are then made widely available through the IMPC website, with clear reference to their potential translational value, as are the mice themselves. A similar system could be established to ensure optimal characterization of NHPs at NPRCs and facilitate the sharing of tissues, animals, and data across institutions.

A key complement to the development of NHP genomic resources is the development and expansion of NHP phenotyping resources. Pathology resources are a required component of all NRPCs, but they are constrained by limited funding and the variability of necropsy procedures and reporting protocols across institutions. While all NRPCs and National Resources queried by the committee reported performing necropsies (ranging from 75 percent to 100 percent of decedent NHPs), the types of examination performed vary, ranging from the conduct of both gross and histological necropsy examinations on all decedents to gross examinations only, depending on the study protocol (National Resources Information Request, 2022[12]; NPRC Information Request, 2022). Tissue storage and sharing practices also vary with respect to how long samples are stored and with whom they are shared. Examples of focused collaborative efforts to standardize the collection and reporting of pathology outcomes include studies of hypertrophic cardiomyopathy (Reader et al., 2016), the development of standards for examination of the brain (Pardo et al., 2012), and the International Harmonization of Nomenclature and Diagnostic Criteria project (Colman et al., 2021). Notably, the latter project was a grassroots collaboration among pathologists in the private sector (pharmaceutical companies and contract research organizations), academia, and NIH, accomplished largely on a volunteer basis. NIH support for disease phenotyping of NHPs could have a transformative impact on the research landscape.

As NHP models are further characterized, it will be important to have agreed-upon standardized terminology for communicating such information as genetic background and phenotype. An example of the development of such standardized nomenclature is the work

[11] See https://www.mousephenotype.org/ (accessed November 19, 2022).

[12] This reference refers to written responses to a committee information request from each of the four ORIP-supported National Resources. Individual responses to the committee's information request can be found in the committee's public access file.

of the International Committee on Standardized Genetic Nomenclature for Mice (MGI, 2022); that nomenclature is now required by major journal publishers that adhere to the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines (Percie du Sert et al., 2020). The strain, source, and genetic modifications of different mouse models have profound effects on the data produced by these animals. Thus, it is essential to have a clear way to communicate these types of details for NHP data so the data can be interpreted appropriately, and the utility of prior research can be realized. Subdisciplines within the NHP research enterprise currently suffer from a lack of such standardized nomenclature to facilitate communication and could benefit from the use of an approach similar to that used for mice. Given the broad scope of professionals who work with NHPs across the conservation, zoological, anthropology, primatology, and biomedical fields, such an effort would need to be cross-disciplinary to have maximum impact and would benefit from federal sponsorship.

Improvement of NHP Research Infrastructure

Resources for Biobanking

Biobanking of samples collected from individual animals used in research studies represents an important opportunity to optimize and share NHP resources going forward, and potentially to reduce the number of NHPs needed to address scientific questions. Biobanking, an area of growing interest and support within NIH, requires appropriate structure and funding, and a thoughtful approach to sample collection for biobanking requires anticipating potential future data needs and considering costs. Additionally, biobanked samples have little value if they are sequestered and unavailable to researchers, but the opportunities available for NHP researchers to access biobanks are currently limited.

Compared with biobanks for other types of animals, primate biobanks contain more diverse and less-standardized samples, with frequent changes in availability (Witham and Wells, 2022). In addition, samples are often taken sporadically over long periods of time by different people (Witham and Wells, 2022). The development of active processes for maintaining and sharing biobanked samples will be critical to maximizing the utilization of NHP resources.

There are several useful examples of successful biobanking both within (NIA, 2022) and outside of the NHP research ecosystem (MAF, 2022; NNTC, 2022). The Golden Retriever Lifetime Study, conducted by the Morris Animal Foundation, is an example outside of the NHP research world that involves the crowdsourced collection of genetic and other samples throughout the life of individual dogs, submitted voluntarily by owners using standardized collection protocols (MAF, 2022). NIA's Nonhuman Primate Tissue Bank serves as a repository of tissue for researchers conducting aging studies funded by NIH or other government institutions at no cost to the researchers (NIA, 2022). And digital pathology resources, such as the Primate Pathology Image Database at the Oregon NPRC, make it possible to share experimental and natural disease findings without repeating work and wasting resources (NIH, 2010).

Physical Infrastructure

Expansion of the physical infrastructure supporting NHP programs offers opportunities to ensure that housing and husbandry conditions align with best practices based on the evolving science of animal welfare. Experience with shortages of laboratory space during the COVID-19 pandemic demonstrated the importance of building adequate facilities for

NHP research, including biocontainment spaces (Animal Biosafety Level 3 or 4) adjacent to facilities housing NHPs (Hild et al., 2021; NASEM, 2021). Physical infrastructure to support expanded breeding colonies may include animal support facilities such as veterinary hospital space, quarantine areas, transition facilities for moving animals into and out of breeding colonies, and staff support facilities. The recent infrastructure funding opportunities offered by the Coronavirus Aid, Relief, and Economic Security (CARES) Act in 2021[13] and ORIP in 2019, 2020, and 2022 have provided much-needed support in this domain.

Information Technology Infrastructure

Investment in data infrastructure is necessary to improve the tracking of NHP demand and use to better support planning and coordination, both of which are necessary to guide effective and appropriate use of NHP resources going forward. As described in Chapter 3, past tracking efforts in the United States have been ad hoc, and existing data systems have been fragmented and largely inaccessible to the scientific community. Systems for tracking animal use for scientific purposes in the European Union, such as the ALURES Statistical EU Database,[14,15] provide useful models for investment in data infrastructure and support openness in animal research. Importantly, such investments will also be integral to future efforts to reduce reliance on NHPs by enabling accurate measurement of the impact of such measures as changes in policy and implementation of nonanimal models. Improved information technology infrastructure is also critical for storing data and meeting new NIH data sharing requirements (NIH, 2023a).

Training the Next Generation of NHP Research and Care Professionals

NHP research has been affected by shortfalls in critical human resources (Hild et al., 2021), as detailed in Chapter 3. The future of NHP research will depend on training and ongoing support for investigators, care staff, and veterinary professionals so they have the knowledge and skills required to work productively and appropriately with NHP research subjects. Furthermore, progress will be facilitated by enhanced attention to workforce diversity, broadly defined not only in terms of the sociopolitical features of identity already recognized as important by NIH (2019), but also with respect to training backgrounds and trajectories (including but not limited to conscious integration of trainees with expertise in new approach methodologies). Diversity in the scientific workforce is critical for many reasons, not the least of which is that it improves scientific outcomes and speeds discovery (Freeman and Huang, 2014; Medin and Lee, 2012; Nielsen et al., 2017). Initiatives to train the next-generation workforce and to support current professionals from diverse backgrounds rely in turn on the availability of training support for early-career scientists and for people in staff positions who may or may not be in formalized training programs (e.g., animal care technicians). Existing opportunities to support the professional development of NHP researchers include the ORIP T35 and T32 pipeline for veterinary researchers and public–private partnerships for training (such as the Boehringer Ingelheim program for veterinary

[13] Coronavirus Aid, Relief, and Economic Security Act (P.L. 116-136, 116th Congress), (March 27, 2020).

[14] Regulation (EU) 2019/1010 of the European Parliament and of the Council (OJ L 170/115, 25.6.2019).

[15] Available at https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm (accessed November 7, 2022).

scholars) (BIVSP, 2022; NIH, 2022b, 2022c). However, there are impediments to ensuring the human resources needed to support NHP research, including

- a limited number of funded positions at institutions with the ability to train PhD, DVM, and MD researchers for work with NHPs;
- the lack of programs for recruiting and training non-PhD support professionals, including research technologists, animal care technicians, veterinary technicians, and behaviorists, deficits that exacerbate the current shortage of workers at NHP facilities and limit the ability of well-trained researchers to complete their studies; and
- societal misperceptions of and stigma directed at NHP research, which can be a barrier to recruiting scientists and support staff to the field and, at times, their retention.

Ensuring a diverse scientific workforce with the skills at all levels needed to conduct rigorous NHP research will require coordinated outreach at earlier stages of education. It will also require more opportunities for the public and scientists to gain an appreciation of the actuality of the work conducted at NHP facilities and the rationale for and benefits of the research.

CONCLUSIONS

This chapter has described the results of a forward-looking evaluation undertaken by the committee to address the aspects of its charge related to exploring the future role of NHPs in biomedical research supported by NIH. The committee began this effort by acknowledging that any activity involving future predictions should be undertaken with caution given the numerous scientific and policy uncertainties that shape the future landscape. With this caution in mind, the committee provides the following conclusions regarding the NHP research and resources that will be vital to supporting the mission and priorities of NIH going forward.

Conclusion 5-1: Given the nation's most pressing public health needs and the evolving state of the science, specific domains of research—including neuroscience and neurodegenerative disorders, preparedness for unanticipated communicable infectious threats, immunotherapy, reproduction, aging, and chronic inflammatory diseases—are likely to require increased use of nonhuman primates in the future. The species distribution of future need for such research is likely to remain weighted toward macaques (particularly rhesus and cynomolgus), with increased use of marmosets.

Conclusion 5-2: The 2018 report of the National Institutes of Health (NIH) Office of Research Infrastructure Programs, Nonhuman Primate Evaluation and Analysis, *included recommendations for improving communication and collaboration within the nonhuman primate (NHP) research community, increasing domestic NHP supply capabilities, addressing limitations in NIH funding mechanisms, promoting training in NHP care and research, and enhancing the utility and value of existing NHP resources. These solutions and recommendations have not yet been fully implemented and remain critically important.*

Conclusion 5-3: Addressing the challenges posed for the national research infrastructure by a persistent lack of nonhuman primates (NHPs) will require a commitment and comprehensive national effort focused on expanding domestic NHP resources.

Conclusion 5-4: The creation of a national plan for allocation and expansion of nonhuman primate resources is necessary to optimize the use of this critical scientific resource. Such a plan will require adequate monetary, physical, and personnel resources, as well as a centralized tracking system to match need to investment in a data-driven fashion.

Conclusion 5-5: Continued development and validation of new approach methodologies (in vitro and in silico model systems) is critically important to support further advances in biomedical research. This may reduce the need for nonhuman primate (NHP) models in the future, and/or enhance their utility. Additionally, this may help to mitigate shortages in NHP supply and the high cost of NHP research.

Conclusion 5-6: Given the limited numbers of nonhuman primates (NHPs) available for research, it is incumbent upon investigators and the National Institutes of Health (NIH) to make the best use of each animal through cooperative efforts, data sharing, purposeful planning, and use of data-driven care and management methods for the long-term care and use of NHPs in research. Examples of successful cooperative efforts from the community of NIH-funded NHP researchers—including collaborative working groups; data-sharing resources for clinical and clinical pathology data, gene expression profiling, and genotype data; and biospecimen repositories—can serve as models for broader adoption.

Conclusion 5-7: A system for consistent reporting is needed to adequately capture the life, scientific, and medical history, including experimental treatments and procedures, of individual nonhuman primates (NHPs). The need for complete NHP life histories further supports the development of increased domestic breeding capacity in the United States to maximize the accurate and complete sharing of clinical and experimental data. Currently, the incentives, mandates, and infrastructure within the National Institutes of Health research enterprise are insufficient to support uniform data management and reporting across all NHP research programs.

Conclusion 5-8: Recent advances in genomics, bioinformatics, imaging, digital biomarkers (e.g., noninvasive home enclosure neural and behavioral recordings), extended reality, and artificial intelligence/machine learning have revealed opportunities to understand normal biology and the mechanisms of disease. Such technologies and approaches have the potential to augment the scientific knowledge that can be gained from individual nonhuman primate (NHP) studies and, in some cases, enable less invasive use of NHPs. Leveraging these opportunities for NHP research will require tracking the genotype, phenotype, and history of each animal used, as well as transdisciplinary interactions.

Conclusion 5-9: Additional investments will be needed to implement, maintain, train, and use current and emerging technologies (such as digital biomarkers, artificial intelligence/machine learning, imaging, extended reality, and laparoscopy), as well as data-driven husbandry practices, with the potential to enhance nonhuman primate research funded by the National Institutes of Health.

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A

Study Approach and Methods

In response to a request by the National Institutes of Health (NIH), the National Academies of Sciences, Engineering, and Medicine (National Academies) convened the Committee on the State of the Science and Future Needs for Nonhuman Primate Model Systems. This committee was charged with conducting a landscape analysis to describe the state of the science on nonhuman primate (NHP) model systems, including exploring their current and future roles in biomedical research funded by NIH. As part of its landscape analysis, the committee was also asked to assess opportunities for new approach methodologies to complement or reduce reliance on NHP models in NIH-supported research. This appendix describes the approach and methods used by the committee in conducting its landscape analysis.

STAKEHOLDER ENGAGEMENT AND INFORMATION GATHERING

The committee deliberated from April 2022 to March 2023, during which time it held seven meetings, three of which were open to the public. The April, August, and November 2022 meetings included portions that were open sessions (see agendas below). During the April 2022 meeting, the committee received the charge from NIH and provided opportunity for public questions regarding the study. A 2-day workshop in August 2022 included sessions with federal funders of NHP research, representatives from domestic NHP breeding resources, investigators using NHP models, and stakeholders involved with the development and application of new approach methodologies. A third public meeting was held in November 2022 and included representatives from the NIH Office of Research Infrastructure Programs (ORIP) and individual NIH institutes, centers, and offices (ICOs) that support NHP research, as well as researchers involved with the use of new approach methodologies for complementing or reducing reliance on NHP research. The remainder of the committee meetings were held in closed session.

To inform its deliberations, the committee used several additional mechanisms to gather information, including (1) information requests and a survey of NHP researchers; (2) reviews

of the published literature and publicly available data; and (3) a review of public comments received over the course of the committee's deliberations. These are discussed further in the sections below.

RESEARCH METHODS

The committee gathered data from many different sources to address its charge and to inform its findings and conclusions. Building upon the 2018 report published by ORIP on NHP supply and demand,[1] the committee sought to mirror some of the data-collection methods used in that report to evaluate current use of and future priorities for the use of NHPs. These efforts included the collection and analysis of publicly available data from the U.S. Department of Agriculture's (USDA's) Animal and Plant Health Inspection Service (APHIS) and NIH; a survey of experiences and perspectives of NIH-supported principal investigators (PIs) using NHPs in their research; and information requests to federal agencies (NIH, Food and Drug Administration [FDA], Centers for Disease Control and Prevention [CDC]), the National Primate Research Centers (NPRCs), and seven institutions that receive NIH support for breeding colonies or colony management. In addition to these data-collection efforts, the committee conducted a series of literature searches of peer-reviewed and gray literature (e.g., federal agency reports, working papers). This section describes each of these activities and how the resulting data were used in the report.

Information Requests

The committee sent formal information requests to several federal agencies and other stakeholder organizations to collect information that was not publicly available (see Table A-1). Copies of these written requests and their complete responses can be requested from the committee's public access file. The nature of these requests and descriptions of how the resulting information was used in this report are included below.

CDC

The committee requested up-to-date information from the CDC Quarantine and Border Health Services branch on NHP importation from 2019 to 2022 to assess changes in recent NHP importation levels. Data requested included number of NHPs imported, countries of origin, and species. These data were used in the report to assess importation trends from 2018 to 2022, including species imported and country of origin.

FDA

The committee requested data from FDA on the use of NHPs, as well as in vitro and in silico methods that have been used as alternatives to animal-based models, in regulatory approval processes. While quantitative data were unavailable, examples provided by FDA

[1] ORIP. 2018. *Nonhuman primate evaluation and analysis Part 1: Analysis of future demand and supply.* National Institutes of Health. https://orip.nih.gov/about-orip/research-highlights/nonhuman-primate-evaluation-and-analysis-part-1-analysis-future (accessed March 21, 2023); ORIP. 2018b. *Nonhuman primate evaluation and analysis Part 2: Report of the expert panel forum on challenges in asssessing the nonhuman primate needs and resources for biomedical research.* National Institutes of Health. https://orip.nih.gov/sites/default/files/NHP%20Evaluation%20and%20Analysis%20Final%20%20Report%20-%20Part%202%20Final%20508%2021Dec2018_002.pdf (accessed March 3, 2023).

TABLE A-1 Overview of Committee Information Requests to Federal Agencies and Other Stakeholder Organizations

Agency/Organization	Information Request Description*
Centers for Disease Control and Prevention	Nonhuman primate (NHP) importation data, 2019–2022
Food and Drug Administration	Data on nonanimal methods successfully used in regulatory approvals
National Primate Research Centers	Information on recent NHP use trends and experiences
National Resources and select research facilities supported by the National Institutes of Health	Information on recent NHP use trends and experiences
National Institutes of Health (NIH)	Information on active NIH awards using NHPs (e.g., research domains, species used, number of animals used), priorities for NHP use in extramural and intramural research, supply-and-demand experiences, and data on intramural NHP breeding at NIH-owned or -sponsored colonies

*In some cases, more than one information request was submitted as additional data needs were identified by the committee.

informed the committee's evaluation of the landscape of NHP research and new approach methodologies.

NPRCs

Information requests were sent to the center directors at each of the seven NPRCs through an Alchemer survey form. Information requested to characterize current use trends and experiences included (1) species bred and used, (2) number of NHPs on-site, (3) annual production from breeding colonies, (4) number of NHPs enrolled in active research protocols, (5) capacity to meet recent investigator requests, and (6) current challenges experienced in meeting demand for NHPs. Additionally, to describe predictions of future needs for NHP models, NPRCs were asked to provide their predictions for future priority research areas, changes in demand for NHP models, and their ability to meet future demand for NHPs. All seven NPRCs completed the written information request, and these data were used to describe trends in NHP use by species, capacity to meet research needs, research priorities, and future challenges and opportunities for these institutions.

National Resources and Selected NIH-Supported Research Facilities

Information requests were sent to points of contact at select research facilities receiving NIH support to maintain breeding colonies. These included ORIP-supported National Resources—MD Anderson Cancer Center (Keeling Center), The Johns Hopkins University, Caribbean Primate Research Center, and Wake Forest University.[2] Additionally, identical information requests were sent to institutions with NIH P40 and N01 awards used to support breeding colonies but not identified by ORIP as National Resources. These included the University of Pittsburgh; University of Louisiana at Lafayette (New Iberia Research Center);

[2] The three national NHP reagent resources supported by ORIP—University of Massachusetts, University of Louisiana at Lafayette, and Trinity University—were not asked to complete this information request because they do not host National Resource NHP breeding colonies.

and Alpha Genesis, Inc. Requested information included (1) species currently bred and used, (2) number of NHPs on-site, (3) annual production from breeding colonies, (4) number of NHPs enrolled in active research protocols, (5) recent capacity to meet investigator requests, and (6) current challenges experienced. The form also asked the research facilities to provide predictions for future priority research areas, changes in demand for NHP models, and their ability to meet future demand for NHPs. All seven facilities completed the written request, and these data were used to describe trends in NHP use by species, capacity to meet research needs, current NHP use in research, and future priorities and needs for these facilities.

NIH

In addition to the participation of NIH ICOs in the committee's public information-gathering sessions, the committee sent several information requests to NIH in efforts to gather quantitative and qualitative data on NHP use in extramural and intramural research projects, challenges related to supply and demand, and NIH-supported and -owned breeding colonies. Quantitative data from internal NIH data systems were not available to the committee because of privacy concerns by NIH about accessing internal records, and because no automated methods are in place for collecting the requested data. Thus, this lack of quantitative data on NHP use in NIH-supported research limited the committee's ability to evaluate the NHP research landscape quantitatively. However, 21 ICOs provided brief summaries of current extramural and intramural research priorities for NHP research, NHP availability concerns, and areas of investment, as applicable. Additionally, NIH provided written responses to committee questions in advance of the November 2022 public meeting. These responses provided additional details about NHP research funding, priorities, and collaboration efforts.

Literature Reviews and Publication Analysis

Multiple literature searches, carried out in PubMed and Scopus, were conducted throughout the study as research needs evolved. These searches were used to guide and provide references for report content describing current uses of NHPs in biomedical research and the current state of new approach methodologies.

Scopus Publication Analysis

In addition to literature searches, the committee commissioned the National Academies Research Center to conduct a literature review and series of publication analyses in Scopus, which provided additional context and evidentiary support for the description of the current use of NHPs in NIH-funded biomedical research in Chapter 2. This review was restricted to research published since 2018 and supported by NIH funding. Because the intent of this effort was to understand the distribution of NHP research and, importantly, identify examples of NHP use and types of research, the committee targeted a nonrandom selection of highly cited articles. Relevant articles were used in the committee's description of the landscape of NHP research and the contribution of NHPs to advances in human health (Chapter 2).

In addition to the Scopus publication analysis carried out for recent NHP research, two literature reviews were also conducted in Scopus for recently published reviews on in vitro and in silico approaches. These searches were not restricted to NIH-funded projects. The results were used to broadly evaluate the scope of impactful new approach methodologies. Additionally, the results of these two Scopus searches were narrowed to recently published reviews, the abstracts of which were assessed by a committee member to determine whether

these reviews provided detail on how new approach methodologies could complement or reduce reliance on NHP models in biomedical research. These review articles were used to contextualize the contents of Chapter 4.

Search Terms

KEY(monkey* or primate* or aotus or owl-monkey* or callithrix or marmoset or cebus-capucinus or cercocebus or mangabey or sabaeus or african-green or chlorocebus-pygerythrus or vervet or erythrocebus-patas or patas-monkey or macaca-mulatta or m-mulatta or macaca-fascicularis or m-fascicularis or macaca-nemestrina or m-nemestrina or rhesus-macaque or cynomolgus or pigtail-macque or papio or baboon* or saguinus or tamarin or saimiri or saimiri-boliviensis or saimiri-oerstedii or saimiri-sciureus or saimiri-ustus or saimiri-vanzolinii or squirrel-monkey) AND PUBYEAR > 2017 AND (LIMIT-TO (FUND-SPONSOR,"National Institutes of Health") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Allergy and Infectious Diseases") OR LIMIT-TO (FUND-SPONSOR,"NIH Office of the Director") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Mental Health") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Neurological Disorders and Stroke") OR LIMIT-TO (FUND-SPONSOR,"National Eye Institute") OR LIMIT-TO (FUND-SPONSOR,"Eunice Kennedy Shriver National Institute of Child Health and Human Development") OR LIMIT-TO (FUND-SPONSOR,"National Cancer Institute") OR LIMIT-TO (FUND-SPONSOR,"National Institute on Aging") OR LIMIT-TO (FUND-SPONSOR,"National Institute on Drug Abuse") OR LIMIT-TO (FUND-SPONSOR,"National Heart, Lung, and Blood Institute") OR LIMIT-TO (FUND-SPONSOR,"National Center for Advancing Translational Sciences") OR LIMIT-TO (FUND-SPONSOR,"Office of Research Infrastructure Programs, National Institutes of Health") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Diabetes and Digestive and Kidney Diseases") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Child Health and Human Development") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Biomedical Imaging and Bioengineering") OR LIMIT-TO (FUND-SPONSOR,"National Institute on Deafness and Other Communication Disorders") OR LIMIT-TO (FUND-SPONSOR,"Division of Intramural Research, National Institute of Allergy and Infectious Diseases") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Dental and Craniofacial Research") OR LIMIT-TO (FUND-SPONSOR,"National Institute of Environmental Health Sciences") OR LIMIT-TO (FUND-SPONSOR,"National Human Genome Research Institute") OR LIMIT-TO (FUND-SPONSOR,"Foundation for the National Institutes of Health"))

TITLE(2D-cell-culture-model* or 2D-cell-culture-system* OR 2-dimensional-cell-culture-model* OR 2-dimensional-cell-culture-system* or two-dimensional-cell-culture-model* or two-dimensional-cell-culture-system* or 2D-cellular-model* or 2D-cellular-system* or 3D-cell-culture-model* or 3D-cell-culture-system* or 3-dimensional-cell-culture-model* or 3-dimensional-cell-culture-system* or three-dimensional-cell-culture-system* or three-dimensional-cell-culture-model* or spheroid* or organotypic-culture* or tissue-slice* or explant-culture* or primary-culture* or microtissue* or 3D-bioprint* or stem-cell* or 3D-cellular-model* or 3D-cellular-system* or organoid* or organ-on-a-chip or human-on-a-chip or liver-on-a-chip or skin-on-a-chip or kidney-on-a-chip or microphysiological-system* or microphysiological-device* or new-approach-method* or new-approach-methodology or in-vitro-complex-model* or microfluidic-model* or biomechanical-cue*) OR KEY(2D-cell-culture-model* or 2D-cell-culture-system* OR 2-dimensional-cell-culture-model* OR 2-dimensional-cell-culture-system* or two-dimensional-cell-culture-model* or two-dimensional-cell-culture-system* or 2D-cellular-model* or 2D-cellular-system* or 3D-cell-culture-model* or 3D-cell-culture-

system* or 3-dimensional-cell-culture-model* or 3-dimensional-cell-culture-system* or three-dimensional-cell-culture-system* or three-dimensional-cell-culture-model* or spheroid* or organotypic-culture* or tissue-slice* or explant-culture* or primary-culture* or microtissue* or 3D-bioprint* or stem-cell* or 3D-cellular-model* or 3D-cellular-system* or organoid* or organ-on-a-chip or human-on-a-chip or liver-on-a-chip or skin-on-a-chip or kidney-on-a-chip or microphysiological-system* or microphysiological-device* or new-approach-method* or new-approach-methodology or in-vitro-complex-model* or microfluidic-model* or biomechanical-cue*) AND PUBYEAR > 2017

TITLE(virtual-human* or digital-twin* or QSAR-model* or quantitative-structure-activity-relationship* or systems-toxicology-modeling or IVIVE-model* or in-vitro-to-in-vivo-extrapolation or PBPK-model* or physiologically-based-pharmokinetic-model* or human-patient-simulator* or avatar* or quantitative-systems-pharmacology or computational-model* or computational-model-systems or computational-method* or computational-approach* or artificial-intelligence* or machine-learning) OR KEY(virtual-human* or digital-twin* or QSAR-model* or quantitative-structure-activity-relationship* or systems-toxicology-modeling or IVIVE-model* or in-vitro-to-in-vivo-extrapolation or PBPK-model* or physiologically-based-pharmokinetic-model* or human-patient-simulator* or avatar* or quantitative-systems-pharmacology or computational-model* or computational-model-systems or computational-method* or computational-approach* or artificial-intelligence* or machine-learning) AND PUBYEAR > 2017

Data Collection from Federal Sources

NIH RePORTER

The committee mined NIH RePORTER, a publicly accessible database of NIH awards, to collect data on NIH funding for P51 and P40 award mechanisms from fiscal years 2012 to 2022. This included funding provided via the primary awards (often referred to as "base grants"), as well as via administrative and competitive supplemental awards to each P51 and P40.

While the NIH RePORTER database represents a comprehensive record of NIH-supported biomedical research, it does not feature a mechanism for identifying projects using NHP models (generally, or specific species) as part of their methodologies. Keyword searches using NHP terminology did not provide a complete listing of active awards using NHPs. Unlike the prior review of NHP supply and use published by ORIP in 2018, the committee did not have access to internal NIH data systems to provide detailed information on current NHP use (e.g., information on research domain, species, quantity of NHPs planned for use, justification for the choice of model). This lack of access to complete quantitative and descriptive data limited the detail that could be provided regarding the landscape of extramural and intramural NHP research.

USDA

Annual data on NHP use in research facilities was collected from USDA's APHIS Animal Care Public Search Tool. This tool provides a listing of the number of animals held, bred, or used for research purposes by registered institutions in the United States as required by the Animal Welfare Act,[3] and represents the most comprehensive listing of the number of NHPs used

[3] 7 U.S.C. §§ 2131–2159 (P.L. 89-544), with implementing regulations: 9 C.F.R. § 1(A)

in research by year. However, this tool reports at an institutional level and does not include detail on the species used, specifics on the research domain in which NHPs were used, or source of the animals (e.g., imported or domestically sourced). Additionally, these annual reports by facilities do not provide information on individual animals over time, which limits understanding of how NHPs are used in these facilities over multiple years. For example, some facilities may host several long-term studies or run breeding colonies where the same animals are recorded on-site over multiple years. Conversely, other facilities may have animals enrolled in termination studies or may transport many NHPs out to other facilities, which in turn may impact how numbers are reported to USDA or may result in duplicative counting of animals moved across facilities, respectively. While these data have limitations, these annual reports are the only quantitative sources of information about NHP use at research facilities in the United States. Annual reports by research facilities reporting NHP holdings and use[4] to APHIS were collected by year, 2018–2021, and were used to analyze NHP holdings and use over time and to identify the types of stakeholders involved in NHP research.

Survey of NIH-Supported Researchers Using NHPs

Given the paucity of publicly available, detailed information on the experiences of investigators engaged in NIH-supported NHP research, original data collection was undertaken by the committee in the form of a survey of NIH-supported researchers using NHPs in active NIH awards. This survey sought to (1) describe the landscape of NIH-funded extramural research using NHP models and (2) capture researcher experiences with limitations and challenges related to the access and use of NHPs in biomedical research, and predictions on future areas of value and infrastructure needs in this space. The protocol for these data-collection efforts was submitted to the Committee to Review Human Subjects, which acts as the National Academies' Institutional Review Board (IRB) (#IRB00000281), and received an exemption from IRB review, under category 2 (subcategory i) of the Common Rule.[5] A copy of the survey sent to investigators, including frequency tables by survey question, can be found in Appendix E.

Participant Recruitment

Because the committee was unable to access a comprehensive list of active, NIH-supported projects using NHPs, the committee used NIH RePORTER to identify all active NIH-sponsored extramural research projects likely to involve the use of NHPs by searching project abstracts, titles, and keywords. This database search was carried out by National Academies staff using such generic keywords as "primate" and "monkey," as well as the scientific and common names for NHPs currently used in biomedical research (see search terms in the section above on NIH RePORTER). No restrictions were made in terms of research type (e.g., fundamental basic, translational) or area (e.g., immunology, psychology, neuroscience). The search was restricted to active project-driven research grants as categorized on NIH RePORTER as funding mechanisms for "Research Projects." It should be noted that this search of NIH RePORTER captured projects that did not use NHP models, such as those projects that used a search term in the abstract in reference to prior research using NHPs, and likely missed some projects that did use NHPs, such as those that did not include a keyword in

[4] APHIS annual reports from research facilities provide information on the number of animals held, bred, or conditioned for research use and the number used for research purposes.

[5] 45 C.F.R. 46, Part A § 46.104

the abstract that allowed it to be captured by the search. Investigators who responded to the committee survey but who did not use NHP models for their active award(s) were excluded. Because all investigators in the population of interest were contacted, no random sample was generated.

Inclusion criteria:

1. Principal investigator on an active, research-driven, extramural NIH award
2. Research involving the likely planned use of NHP models as part of the research methodology

Exclusion criteria:

1. Principal investigators with infrastructure or resource awards only
2. Intramural NIH investigators
3. Studies that do not use NHP models as part of the planned research methodology
4. Contact information not publicly available

National Academies staff manually collected emails for all PIs identified via the NIH RePORTER search of awards. In cases where the award was a multi-investigator grant, only the contact PI was contacted. After collecting this contact information, invitations to participate in the survey were sent by email by National Academies staff to each investigator identified (1,431 investigators after deduplication) with a description of the National Academies committee, its Statement of Task, the purpose of the survey, and a link to the survey form. All participants were given 3 weeks to complete the survey. For those who had not completed the survey, reminder emails were sent after the first and second weeks.

Because of the lack of information available about those respondents who did not choose to respond to the survey, no analysis of the representativeness of the respondents or the awards for which they reported information could be performed. Therefore, it is not known whether a higher or lower portion of researchers from a specific research domain, for example, responded to the survey as compared with the entire population of NIH-supported investigators using NHPs. Summaries of the survey responses, along with information on response rate and demographics, can be found in Appendix B.

Survey Composition

Survey questions were developed by the committee—specifically, the committee chair and appropriate content experts, including those with expertise in survey methodology. Because this National Academies committee built upon the work of the previously published 2018 ORIP report, which included a survey of a similar population of participants, this survey adopted similar methods, structure, and wording of questions. Prior to sending the survey, five investigators were selected to complete the survey and asked to provide preliminary feedback on the wording and content of the questions as a pilot phase.

The online survey began with a description of the purpose of the National Academies study, the voluntary nature of participation, and a description of noncompensation. The page also described how answers provided through the survey would be used and presented in the committee's report (e.g., data would be deidentified and only aggregate data would be reported), as well as a description of how the data would be stored and managed. Participants were required to confirm that they read this material and that they agreed (or disagreed) to participate before they could proceed to the survey questions. After submitting their answers to the survey, each participant was thanked for their input and redirected to the study webpage.

Data Storage and Analysis

Each survey submission was collected and stored by the survey platform, Alchemer. After the time period for responding expired (3 weeks from invitation), a copy of the survey data file was downloaded to an Excel file. The identifiable survey data file was stored on the private drive of a National Academies study staff member whose laptop was password protected and required a personal identification number and VPN application to access.

Any identifying information, including NIH grant numbers, was anonymized and the code key deleted. No identifiable survey data were shared with any committee members and only aggregate data were made available to the full committee. Deidentified data were shared with a committee member with expertise in data analysis, who assisted staff in performing data analyses. Following publication of the report, all digital copies of the deidentified data were deleted. The original survey data file was archived until the final version of the report was published in June 2023, and then deleted permanently.

Data processing, including calculating of summary statistics and generating frequency tables, was carried out in R using the anonymized data.[6] Survey data were subset into researcher- and award-level groups for analyses. Researcher-level analysis assessed questions on participants' experiences with NHP research in general. Award-level analysis assessed questions on individual awards held by participants. Award-level responses were excluded in six cases because the respondent did not fill in any information for the award. For the eight instances in which multiple respondents provided information on the same award for a multi-PI grant, the responses provided by the contact PI were used for seven of the awards with multiple responses. The eighth award lacked a contact PI respondent, so responses from the self-identified core director were used. Because of the small sample size, statistical analysis could not be applied to assess the strength of differences between groups (e.g., differences in availability of certain NHP species by research domain). Responses to open-ended survey questions on current challenges and opportunities for NIH-supported NHP research were reviewed to identify key themes, which were found to mirror findings from closed-ended and multiple-choice questions.

PUBLIC SESSION AGENDAS

First Committee Meeting

PUBLIC SESSION MEETING AGENDA
Tuesday April 5, 2022
11:30am–1:00pm (ET)
Zoom

Session I	**Open (Public) Session** **PRESENTATION OF THE CHARGE – DISCUSSION OF THE SCOPE AND STUDY CONTEXT**
Objective:	To present and clarify as needed the charge to the committee.

[6] R Core Team. 2022. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. See https://www.R-project.org.

11:30 a.m.	**Welcome and Introductions for the Session** Kenneth Ramos, *Committee Chair* Texas A&M University
11:40 a.m.	**Presentation of the Charge to the Committee** Lyric Jorgenson Acting Director, Office of Science Policy National Institutes of Health
12:00 p.m.	**Clarifying Questions on the Statement of Task**
12:45 p.m.	**Committee Discussion of Comments and Questions from the Public**
1:00 p.m.	**Adjourn Open Session**

Third Committee Meeting (Public Workshop)

Public Session Agenda
August 25, 2022
8:30 am–5:30 pm (ET)

	Open Session
8:30 am	**Welcome and Opening Remarks** Kenneth Ramos, *Committee Chair* Texas A&M University
Session I	**LANDSCAPE ANALYSIS AND FUTURE PROJECTIONS FOR NONHUMAN PRIMATE USE IN RESEARCH TO ADVANCE HUMAN HEALTH AND SAFETY**
Purpose:	• Explore current strengths and weaknesses of NIH-supported biomedical research using NHPs, current and future research priorities, and opportunities to improve human health. • Consider the current state of NHP availability and implications for biomedical research and public health. • Reflect on the infrastructure investments that are needed to address current challenges and pursue future opportunities related to NHP research, including supply issues.
8:45 a.m.	**Opening Panel Session Remarks from Committee Moderator** Eliza Bliss-Moreau, Committee Member University of California, Davis
8:50 a.m.	**Panel 1: NIH Perspectives** Robert Eisinger Acting Director of the Division of Program Coordination, Planning, and Strategic Initiatives

National Institutes of Health
RICHARD WYATT
Deputy Director, Office of Intramural Research
National Institutes of Health

STEPHEN DENNY
Director, Office of Animal Care and Use
Office of Intramural Research
National Institutes of Health

9:10 a.m. **Committee Q&A**

9:30 a.m. **Panel 2: Other Federal Agency Perspectives**

Perspective from FDA
NAMANDJÉ BUMPUS
Chief Scientist
Food and Drug Administration

Perspective from ASPR/BARDA
APRIL BRYS
Director of Nonclinical Development
Biomedical Advanced Research & Development Authority
Administration for Strategic Preparedness and Response

9:45 a.m. **Committee Q&A**

10:05 a.m. **Panel 3: Industry and Research Advocacy Organization Perspectives**
SEAN MAGUIRE
Comparative & Translational Sciences Director & Associate Fellow
GlaxoSmithKline
3Rs Translational and Predictive Sciences Leadership Group
International Consortium for Innovation and Quality in Pharmaceutical Development

JOEL PERLMUTTER
Elliot Stein Family Professor of Neurology
Head of Movement Disorders
Professor of Radiology, Neuroscience, Physical Therapy and Occupational Therapy
Washington University in St. Louis
Scientific Director, Dystonia Medical Research Foundation

MATTHEW BAILEY
President
National Association for Biomedical Research

10:25 a.m. **Committee Q&A**

10:45 a.m. **Break**

Session II **PERSPECTIVES FROM NATIONAL PRIMATE RESOURCES**

Purpose:
- Reflect on the strengths, opportunities, and challenges of NHP research from the perspective of the National Primate Resource Centers.
- Explore priorities driving the investments in NHP research and infra structure at these centers.
- Discuss approaches to overcoming NHP supply issues (overall NHP numbers, species type, genetic variability) and other challenges.

10:55 a.m. **Opening Panel Session Remarks from Committee Moderator**
Ricardo Carrion Jr., Committee Member
Texas Biomedical Research Institute

11:00 a.m. **Panel 1: National Primate Research Center Perspectives (Moderated Discussion)**
Michele A. Basso
Director, Washington National Primate Research Center

Nancy Haigwood
Director, Oregon National Primate Research Center

Paul Johnson
Director, Yerkes National Primate Research Center

Jon Levine
Director, Wisconsin National Primate Research Center

John Morrison
Director, California National Primate Research Center

Jay Rappaport
Director, Tulane National Primate Research Center

Corinna Ross
Associate Director of Research, Southwest National Primate Research Center

11:45 a.m. **Panel 2: Perspective from Other National Nonhuman Primate Resource Centers (Moderated Discussion)**
William Hopkins
Director, Michale E. Keeling Center for Comparative Medicine and Research
MD Anderson Cancer Center

Eric Hutchinson
Director of Research Animal Resources
Johns Hopkins University School of Medicine

MATTHEW JORGENSEN
Director, Wake Forest Vervet Research Colony

MELWEEN MARTINEZ
Director, Caribbean Primate Research Center

FRANCOIS VILLINGER
Director, New Iberia Research Center

GREG WESTERGAARD
President and CEO, Alpha Genesis Inc.

BILL YATES
Vice Chancellor of Research Protections, University of Pittsburgh

12:30 p.m. **Lunch Break**

Session III **VALIDATION AND TRANSLATABILITY OF EMERGING TECHNOLOGIES AND INNOVATIVE METHODOLOGIES**

Purpose:
- Explore the potential for emerging technologies and innovative applications of existing methods to refine, reduce, and replace NHPs in NIH-supported biomedical research.
- Discuss the validation and benchmarking needs for such technologies for specific contexts of use.
- Consider the opportunities for collaboration between NHP researchers and those developing emerging technologies.

1:30 p.m. **Opening Panel Session Remarks from Committee Moderator**
MYRTLE DAVIS, Committee Member
Bristol Myers Squibb

1:35 p.m. **Panel 1 Presentations: Emerging Technologies and Innovative Applications of Existing Methodologies**

Cell-Based Models
JOSEPH WU
Director, Stanford Cardiovascular Institute

Artificial Intelligence and Machine Learning, from Behavioral to Neuroimaging
JAN ZIMMERMANN
Assistant Professor, Department of Neuroscience
University of Minnesota Medical School

Genetic Engineering and Imaging
AFONSO SILVA
Endowed Chair Professor of Translational Neuroimaging and Neurobiology
University of Pittsburgh

Behavioral Management
MARK PRESCOTT
Director of Policy and Outreach
National Centre for the Replacement, Refinement and Reduction of Animals in Research

2:25 p.m. **Panel 2 Presentations: Translatability and Validation of Models to Refine, Reduce, and Replace NHPs in NIH-Supported Biomedical Research**

FDA Perspective
NAKISSA SADRIEH
Associate Director for New Alternative Methods, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

European Experiences
SONJA BEKEN
Non-clinical Working Party
European Medicines Agency

2:45 p.m. **Committee Q&A with Panels**

3:30 p.m. **Break**

Session IV **NONHUMAN PRIMATE RESEARCHER PERSPECTIVES ON THE RESEARCH LANDSCAPE AND EMERGING TECHNOLOGIES**

Purpose:
- Explore areas of emerging science that may benefit from NHP research.
- Discuss opportunities to promote rigorous science and to maximize the potential of NHP models.
- Discuss the impact of NHP availability on future NHP research in the field.
- Consider the opportunities for collaboration between NHP researchers and those developing emerging technologies that may contribute to the 3Rs.

3:40 p.m. **Opening Panel Session Remarks from Committee Moderator**
KELLY METCALF PATE, Committee Member
Massachusetts Institute of Technology

3:45 pm **Perspectives from NHP Researchers (Moderated Discussion)**

NHP Use in Infectious Disease Research
DAN BAROUCH
Director, Center for Virology and Vaccine Research
Beth Israel Deaconess Medical Center
Professor of Medicine
Harvard Medical School

JOANNE FLYNN
Department of Microbiology and Molecular Genetics
University of Pittsburgh School of Medicine

NHP Use in Transplantation Research
CHRISTIAN LARSEN
Professor of Surgery, Division of Transplantation, Department of Surgery
Emory University School of Medicine

NORMA SUE KENYON
Professor of Surgery, Microbiology & Immunology, Biomedical Engineering, Biochemistry & Molecular Biology
Diabetes Research Institute
Miller School of Medicine
University of Miami

NHP Use in Neuroscience and Aging Research
GUOPING FENG
Poitras Professor of Neuroscience
McGovern Institute for Brain Research
Massachusetts Institute of Technology

CAROL BARNES
Regents' Professor of Psychology, Neurology and Neuroscience
Director, Evelyn F. McKnight Brain Institute
University of Arizona

NHP Use in Reproductive Health Research
SHAWN CHAVEZ
Associate Professor
Division of Reproductive & Developmental Sciences
Oregon National Primate Research Center
Departments of Obstetrics & Gynecology and Molecular & Medical Genetics
Oregon Health & Science University

Session V **REFLECTIONS ON FUTURE NEEDS RELATED TO NHPs IN BIOMEDICAL RESEARCH**

Purpose:
- Reflect on future needs and priorities for NHPs in light of opportunities and challenges discussed throughout the day.

4:45 p.m. **Opening Panel Session Remarks from Session V Moderator**
KENNETH RAMOS, *Committee Chair*
Texas A&M University

Session Highlights from Previous Session Moderators
ELIZA BLISS-MOREAU, Committee Member
University of California, Davis

Ricardo Carrion Jr., Committee Member
Texas Biomedical Research Institute

Myrtle Davis, Committee Member
Bristol Myers Squibb

Kelly Metcalf Pate, Committee Member
Massachusetts Institute of Technology

Reflections from Invited Participants

5:25 pm **Wrap-Up Discussion and Closing Remarks**
Kenneth Ramos, *Committee Chair*
Texas A&M University

5:30 pm **Adjourn**

Fifth Committee Meeting

Public Session Agenda
November 21, 2022
9:30 am–1:00 pm (ET)

Open Session

9:30 am **Welcome and Opening Remarks**
Kenneth Ramos, *Committee Chair*
Texas A&M University

Session I **DISCUSSION WITH NIH INSTITUTES, CENTERS, AND OFFICES**

Purpose:

- Explore efforts undertaken in response to the challenges and recommendations included in the 2018 ORIP report, *Nonhuman Primate Evaluation and Analysis*.
- Discuss future priority areas for NIH-supported NHP research based on public health needs and evolving science.
- Explore opportunities for facilitating collaboration across researchers, including with researchers working with new approach methodologies that may be complementary, increase the value of models used, or reduce future reliance on NHP models.

9:45 a.m. **Updates since the 2018 NIH ORIP Report, *Nonhuman Primate Evaluation and Analysis***
Franziska Grieder
NIH Office of Research Infrastructure Programs

Julia Shaw
National Institute of Allergy and Infectious Diseases
Co-chair, NHP Resource Planning Working Group

9:55 a.m. **Q&A**

10:15 a.m. **Opening Remarks from Representatives from NIH Institutes**
Julia Shaw (*Speaker*)
Marisa St. Claire, Nancy Miller, and Clint Florence (*Discussants*)
National Institute of Allergy and Infectious Diseases

Bettina Buhring
National Institute of Child Health and Human Development

Daofen Chen
National Institute of Neurological Disorders and Stroke

Greg Farber
National Institute of Mental Health

Martha Flanders
National Eye Institute

Manuel Moro
National Institute on Aging

John Tisdale (*Speaker*) and Sogun Hong (*Discussant*)
National Heart, Lung, and Blood Institute

10:40 a.m. **Moderated Discussion with NIH Panelists**

11:35 a.m. **Break**

Session II **OPPORTUNITIES FOR COMPLEMENTARY AND COLLABORATIVE RESEARCH**

Purpose:
- Identify examples of, or opportunities for, new approach methodologies (in vitro and in silico methods) to complement and/or reduce reliance on NHP research.
- Explore the scientific, operational, and financial considerations for expanding collaborative work and how this work could be supported or incentivized at a larger scale.

11:45 a.m. **Speaker Presentations**
Charles Murry
Conner Chair and Professor of Laboratory Medicine & Pathology,
Bioengineering and Medicine/Cardiology
Director, Institute for Stem Cell and Regenerative Medicine
University of Washington

Julie Kim
Susy Y. Hung Professor of Obstetrics and Gynecology
Codirector of Center of Reproductive Science
Director of Cancer Biology Cluster
Northwestern University

Frank Verreck and Anne-Marie Zeeman
Biomedical Primate Research Centre, Netherlands

Douglas Lauffenburger
Ford Professor of Engineering
Massachusetts Institute of Technology

12:15 p.m. **Committee Q&A**

12:45 p.m. **WRAP-UP DISCUSSION AND CLOSING REMARKS**
Kenneth Ramos, Committee Chair
Texas A&M University

1:00 pm **Adjourn**

B

Data on Nonhuman Primate Use in NIH-Supported Biomedical Research

This appendix serves as an accompanying resource to the major findings presented in the body of the report, specifically Chapter 3, on the current landscape of intramural and extramural research using nonhuman primates (NHPs) supported by the National Institutes of Health (NIH). It summarizes data from various stakeholders on NHP supply, investigator demand, impacts of NHP shortages, and future priorities for NHP models in NIH-supported biomedical research. The data presented below are grouped topically, where applicable. Appendix A provides an accounting of the committee's data-collection methodology.

RESEARCH FACILITIES REPORTING NHP USE IN 2021

U.S. Department of Agriculture (USDA) data compiled from reports submitted annually by research facilities in the United States were the most complete data available to the committee on NHP use, although these data do not provide information on funding source (e.g., whether the research using NHPs was NIH supported), number of studies, species, research domain, or origin and ultimate destination of animals. Therefore, these data should be reviewed with the understanding that the numbers presented do not reflect NHP holding and use in the specific context of NIH-supported research. Despite these limitations, the USDA data provide a foundation for understanding the general distribution of NHP holdings and use in the United States over time, and these data can be categorized by stakeholders, some of which are largely or entirely supported by NIH (e.g., National Primate Research Centers [NPRCs]).

Table B-1 shows the distribution of NHPs across major stakeholders[1] in fiscal year (FY) 2021 and is grouped by stakeholder type. The 34 facilities listed account for nearly 93 percent of the 113,502 NHPs reported as held or used to USDA in FY2021. This table shows the

[1] For the purposes of this report, major research facilities include facilities reporting 400 or more NHPs held and used in FY2021. A similar cutoff was used in the 2018 report by the NIH Office of Research Infrastructure Programs (ORIP, 2018).

major commercial entities—including pharmaceutical and biotechnology companies, contract research organizations (CROs), and private-sector breeders/suppliers of animals for research—that account for over 43 percent of all NHPs reported to USDA in FY2021. As described in greater detail in Chapter 3, CROs and other facilities that breed and supply animals for research use can play a role in supplying NHPs for NIH-supported extramural and intramural research through direct sales to investigators or through awarded contracts or agreements with NIH.

Table B-1 also shows that intramural research facilities account for a much smaller proportion of NHPs held or used each year, although these figures do not include NHPs held or used off-site at CROs or in other stakeholder facilities using NIH funds (i.e., these off-site animals would be included in the counts of animals at the non-NIH research facility). Lastly, while the users listed in the table account for nearly 93 percent of NHPs reported to USDA in 2021, these facilities represent just under 23 percent of all research facilities holding or using NHPs. Table B-2 shows the numbers of NHPs held or used at major research facilities with 400 or more total NHPs on-site, ordered from highest to lowest total NHPs. This table breaks down the number of NHPs used for research purposes from those held but not yet used for research purposes. This latter category may include animals in breeding colonies.

TABLE B-1 Research Facilities with 400 or More Nonhuman Primates (NHPs) On-Site in Fiscal Year 2021, by Stakeholder Type

National Primate Research Centers (NPRCs)[a] 27,067 NHPs
California NPRC Emory NPRC Oregon NPRC Southwest NPRC Tulane NPRC Wisconsin NPRC Washington NPRC
National Resources Supported by the National Institutes of Health (NIH) Office of Research Infrastructure Programs[b] 8,112 NHPs
The Johns Hopkins University Michale E. Keeling Center for Comparative Medicine and Research at MD Anderson Cancer Center University of Puerto Rico (Caribbean NPRC) Wake Forest University
Other Academic Centers 11,815 NHPs
University of Louisiana at Lafayette (New Iberia Research Center) University of Pittsburgh University of Texas Medical Branch
Contract Research Organizations and Other Commercial NHP Suppliers 47,169 NHPs
Alpha Genesis, Inc. Altasciences Preclinical Battelle Memorial Institute Bioanalytical Systems, Inc. Biomere BIOQUAL, Inc. Charles River Laboratories Labcorp Early Development Laboratories Inc. Lovelace Biomedical Research Institute The Mannheimer Foundation, Inc. Northern Biomedical Research Inc. Primate Products, LLC. Valley Biosystems

TABLE B-1 Continued

Pharmaceutical and Biotechnology Companies 2,769 NHPs
AbbVie Bristol Myers Squibb Merck Pfizer
Federal Laboratories Intramural Research Programs 8,416 NHPs
National Institute of Allergy and Infectious Diseases – Morgan Island National Institutes of Health – Office of Animal Care and Use U.S. Army Medical Research Institute of Infectious Diseases

NOTES: These facilities are listed in alphabetic order within their respective stakeholder categories and represent those research facilities that reported 400 or more NHPs held or used in fiscal year (FY) 2021. The Children's Hospital of Philadelphia reported more than 400 NHPs onsite in FY2021 but is not included on this table as it does not fit into these major stakeholder categories. These 34 facilities account for nearly 93 percent of all NHPs held or used for research purposes in the United States in FY2021 (113,502 NHPs).

[a] These facilities hold NIH awards that involve the holding or use of NHPs for NIH intramural or extramural research purposes.

[b] These facilities host an NIH-supported breeding colony. In some cases, not all NHPs reported to USDA by the facility are supported by NIH funds, as these facilities also receive funding for domestic breeding and research from other sources.
SOURCE: USDA, 2021.

TABLE B-2 U.S. Department of Agriculture (USDA) Annual Report Holding and Use Data from All Facilities with 400 or More Nonhuman Primates (NHPs)

Facility	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
Charles River Laboratories**	2,258	17,105	19,363
University of Louisiana at Lafayette*	7,997	2,443	10,440
Labcorp Early Development Laboratories Inc.**	1,016	7,588	8,604
Tulane University (Tulane National Primate Research Center [NPRC])	4,945	881	5,826
Oregon Health & Sciences University (Oregon NPRC)	4,278	1,382	5,660
University of California, Davis (California NPRC)	2,652	2,357	5,009
The Mannheimer Foundation, Inc.**	4,285	323	4,608
Altasciences Preclinical**	1,114	3,371	4,485
University of Puerto Rico (National Resource)	0	4,172	4,172
Emory University (Emory NPRC)	2,798	1,143	3,941
National Institutes of Health	692	3,127	3,819
BIOQUAL, Inc.**	0	3,657	3,657
National Institute of Allergy and Infectious Diseases – Morgan Island	3,509	0	3,509

continued

TABLE B-2 Continued

Facility	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
Texas Biomedical Research Institute (Southwest NPRC)	1,841	1,119	2,960
University of Texas, M.D. Anderson Cancer Center (National Resource)	24	2,595	2,619
University of Wisconsin (Wisconsin NPRC)	896	1,511	2,407
Biomere**	0	1,284	1,284
University of Washington (Washington NPRC)	762	502	1,264
U.S. Army Medical Research Institute of Infectious Diseases	14	1,074	1,088
Bioanalytical Systems, Inc.**	271	750	1,021
Merck	106	878	984
Lovelace Biomedical Research Institute**	0	923	923
Wake Forest University (National Resource)	0	903	903
Primate Products LLC**	0	887	887
Pfizer	0	815	815
University of Pittsburgh*	9	804	813
Northern Biomedical Research Inc.**	0	661	661
Battelle Memorial Institute**	0	662	622
Alpha Genesis, Inc.**	0	572	572
Bristol Myers Squibb	25	544	569
University of Texas Medical Branch*	61	501	562
Valley Biosystems**	279	203	482
Children's Hospital of Philadelphia	0	434	434
The Johns Hopkins University (National Resource)	191	227	418
AbbVie	85	316	401
Total	40,108	65,674	105,782

NOTE: This table includes the 35 facilities holding or using 400 or more NHPs per fiscal year; facilities are listed from most to least total NHPs reported to USDA.

[a] "Total NHPs held" describes the number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes (USDA, 2021).

[b] "Total NHPs used" describes the number of animals upon which teaching, research, experiments, or tests were conducted, regardless of whether or not pain was inflicted. This number does not include those animals held, bred, or conditioned for research but not yet used (USDA, 2021).

[c] "Total NHPs" describes the number of NHPs reported to be held, bred, or conditioned for research purposes but not yet used, and the number of NHPs used for research purposes in the identified fiscal year.

* Denotes an academic institution (excluding NPRCs and National Resources).

** Denotes a contract research organization or commercial NHP supplier.

SOURCE: USDA, 2021.

Table B-3 lists all facilities reporting fewer than 400 NHPs to USDA in 2021 and the number of animals held versus used for research purposes. Unlike Table B-2, which lists the major research facilities with 400 or more total NHPs reported to USDA and includes many CROs, suppliers of NHPs, and pharmaceutical and biotechnology companies, the research facilities listed in Table B-3 represent a higher proportion of academic institutions with most using a small number of NHPs. The 67 academic institutions in this table make up nearly 45 percent of all facilities reporting NHP use to USDA, but report just 3.7 percent of all NHPs held or used. Because of the limitations of available databases, the proportion of these academic institutions with investigators holding active NIH awards for NHP research is unknown.

TABLE B-3 U.S. Department of Agriculture Annual Report Holding and Use Data from Facilities with Fewer than 400 Nonhuman Primates (NHPs)

Facility or Organization	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
General Hospital Corporation	0	370	370
Massachusetts Institute of Technology*	133	234	367
Columbia University*	13	210	223
Southern Research Institute**	37	180	217
DuMond Conservancy for Primates & Tropical Forests	13	198	211
Frontage Laboratories**	0	204	204
IIT Research Institute**	4	196	200
University of Pennsylvania*	0	192	192
Duke University*	3	182	185
Centers for Disease Control and Prevention	68	117	185
University of Nebraska–Lincoln*	0	185	185
Boston University*	3	165	168
University of Texas at San Antonio*	0	164	164
Glaxo SmithKline	31	128	159
Envigo Global Services Inc.**	105	51	156
Center for Biologics Evaluation and Research	0	155	155
U.S. Army Medical Research Institute of Diseases Chemical Defense Commander	22	126	148
University of Illinois Chicago*	29	119	148
Broad Institute*	55	92	147
Yale University*	77	66	143
Salk Institute for Biological Studies*	50	91	141
McLean Hospital Corporation	0	132	132
Walter Reed Army Institute of Research	34	98	132
Vanderbilt University Medical Center*	43	85	128
University of Rochester*	53	67	120

continued

TABLE B-3 Continued

Facility or Organization	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
University of Texas at Austin*	44	57	101
University of Nebraska–Omaha*	2	99	101
University of Maryland, Baltimore*	0	100	100
University of Mississippi Medical Center*	0	98	98
University of Alabama at Birmingham*	0	93	93
Food and Drug Administration/National Center for Toxicological Research	38	52	90
MRIGlobal	0	87	87
The Rockefeller University*	0	82	82
State University of New York, Brooklyn*	2	79	81
Sinclair Research Center, LLC**	20	60	80
Boehringer Ingelheim Pharmaceuticals Inc	0	76	76
BTS Research**	30	43	73
University of Houston*	0	71	71
AmplifyBio, LLC**	0	68	68
Washington University*	0	65	65
University of Kentucky*	0	60	60
University of Oklahoma*	0	60	60
University of California, San Diego*	25	34	59
BASi Gaithersburg**	0	54	54
Bucknell University*	0	52	52
Stanford University*	24	27	51
Lemur Conservation Foundation	0	51	51
State University of New York, Syracuse*	44	5	49
Harvard Medical School*	0	48	48
University of Nebraska Medical Center*	0	47	47
University of Utah*	30	16	46
Georgia State University*	0	46	46
Alcon Research	45	0	45
The University of Chicago*	0	44	44
Eastern Virginia Medical School*	8	31	39
Battelle National Biodefense Institute, LLC	0	39	39
Gibbon Conservation Center	0	37	37
Alamogordo Primate Facility	37	0	37
Weill Cornell Medicine*	0	36	36
Fort Worth Zoological Park	35	0	35
University of California, Berkeley*	7	25	32

TABLE B-3 Continued

Facility or Organization	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
Carnegie Mellon University*	0	28	28
Augusta University*	0	28	28
Brown University*	0	26	26
State University of New York College of Optometry*	19	7	26
Nathan S. Kline Institute for Psychiatric Research	0	24	24
California Institute of Technology*	3	21	24
Louisiana State University System*	0	24	24
SRI International**	0	22	22
University of Massachusetts Amherst*	0	21	21
East Carolina University*	0	20	20
The University of Arizona*	0	20	20
Air Force Research Laboratory	11	9	20
Barton's West End Farms Inc.**	1	18	19
University of Massachusetts Medical School*	0	17	17
Princeton University*	0	17	17
Northwestern University*	0	17	17
Arizona State University*	11	6	17
Georgetown University*	0	16	16
University of Texas at Houston*	0	16	16
New York State Psychiatric Institute	0	16	16
Franklin & Marshall College*	0	15	15
Memorial Sloan Kettering Cancer Center	8	7	15
Albert Einstein College of Medicine*	6	9	15
Neuralink	0	15	15
The Ohio State University*	0	14	14
Calvert Laboratories, Inc.**	0	14	14
Loyola University Chicago*	2	12	14
Cleveland Clinic Foundation	0	12	12
University of Miami*	0	12	12
Legacy Health	0	12	12
The Methodist Hospital Research Institute	0	12	12
University of California, Los Angeles*	0	11	11
University of California, San Francisco*	0	10	10
Toxikon Corporation**	2	6	8
Florida Institute of Technology*	0	8	8
Smithsonian Institution	0	7	7
Ape Cognition and Conservation Initiative	0	7	7

continued

TABLE B-3 Continued

Facility or Organization	Total NHPs Held Fiscal Year (FY) 2021[a]	Total NHPs Used FY2021[b]	Total NHPs[c]
State University of New York College of Technology*	0	6	6
Montana State University*	3	3	6
University of Kansas Medical Center*	2	4	6
Carleton College*	0	6	6
Experimur, LLC**	5	1	6
Rutgers Biomedical and Health Sciences New Jersey Medical School*	0	6	6
The Research Institute at Nationwide Children's Hospital	0	5	5
University of North Carolina*	0	4	4
The Austin Savanna, LLC	0	4	4
Mount Sinai School of Medicine*	3	0	3
University of Southern California*	0	2	0
Kyle Taitt	0	1	1
4 facility reports with no name listed	0	233	233
Total	1,240	6,480	7,720

NOTE: This table includes the 114 research facilities reporting fewer than 400 NHPs in FY2021 and is ordered by facility from greatest to fewest total NHPs.

[a] "Total NHPs held" describes the number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes (USDA, 2021).

[b] "Total NHPs used" describes the number of animals upon which teaching, research, experiments, or tests were conducted, regardless of whether or not pain was inflicted. This number does not include those animals held, bred, or conditioned for research but not yet used (USDA, 2021).

[c] "Total NHPs" describes the number of NHPs reported to be held, bred, or conditioned for research purposes but not yet used and the number of NHPs used for research purposes in the identified fiscal year.

* Denotes an academic institution.

** Denotes a contract research organization or commercial NHP supplier.

SOURCE: USDA, 2021.

NHP RESOURCES FOR BIOMEDICAL RESEARCH

The following tables and figures support content in the section on NHP availability in Chapter 3. It should be noted that the supporting data presented do not focus exclusively on the supply of animals available and used only for NIH-supported research, as noted in the sections that follow.

NHP Importation

The Centers for Disease Control and Prevention (CDC) tracks all NHPs imported into the United States, regardless of whether they are being transported for use in research or for nonresearch use. Therefore, while the numbers presented below include all NHPs imported into the United States for research use, they may also include a minority of NHPs brought in for other purposes (e.g., for zoos or wildlife parks). The CDC does not maintain a database

tracking the purpose of each importation (CDC, 2022), so the exact proportion of imported NHPs intended for use in biomedical research could not be calculated.

Table B-4 shows the number of NHPs imported between FY2019 and FY2022, and illustrates the 21 percent decrease in total imported NHPs in FY2020 (following the start of the Chinese ban of NHP exportation) as compared with FY2019 levels. NHP imports in FY2021 were only 6 percent less than the FY2019 level.

Table B-5 reports NHP imports from FY2019 to FY2022 by species, showing that the importation of cynomolgus macaques in FY2020 was greatly impacted by the Chinese export ban, although the importation numbers for this species largely recovered the following year. In contrast, the importation of rhesus macaques has not returned to the FY2019 level. Importation of other species—African green monkeys, marmosets, squirrel monkeys, and capuchins—was higher in FY2021 as compared with FY2019 levels. These shifts in importation have secondary impacts on demand for domestically produced animals, as detailed in Chapter 3.

TABLE B-4 Total Nonhuman Primates Imported into the United States, by Fiscal Year (FY)

FY (Dates)	Total Nonhuman Primates Imported (all species)	Percent Change from Previous Year
FY2019 (Oct 1, 2018–Sept 31, 2019)	33,818	N/A
FY2020 (Oct 1, 2019–Sept 31, 2020)	26,728*	–21.0%
FY2021 (Oct 1, 2020–Sept 31, 2021)	31,844	19.1%
FY2022 (Oct 1, 2021–Sept 31, 2022)	32,811	3%

*Includes one smuggled spider monkey.
NOTE: Due to data limitations, these numbers represent NHPs imported for a variety of purposes and do not represent animals imported exclusively for biomedical research use.
SOURCE: CDC, 2023.

TABLE B-5 Number of Nonhuman Primates Imported, by Species and Fiscal Year (FY)

	Number of Nonhuman Primates Imported			
Nonhuman Primate Species	FY2019	FY2020	FY2021	FY2022
Cynomolgus macaque	32,273	24,879	30,649	31,617
Rhesus macaque	964	724	80	0
African green monkey	328	720	711	808
Common marmoset	195	326	284	172
Squirrel monkey	30	34	68	60
Capuchin	15	0	40	86
Other*	13	45	12	68
Total	33,818	26,728	31,844	32,811

*Other imported species varied by year but included colobus monkeys, siamangs, DeBrazza's monkeys, geladas, saki monkeys, spider monkeys, emperor tamarins, bushbabies, and orangutans.
NOTE: Due to data limitations these numbers represent NHPs imported for a variety of purposes and do not represent animals imported exclusively for biomedical research use.
SOURCE: CDC, 2023.

Tables B-6 and B-7 detail importation trends by country of origin and species by country of origin, respectively, and illustrate the major shift in countries supplying NHPs to stakeholders in the United States. Table B-6 shows a sharp increase in animals imported from Cambodia and Mauritius, which corresponds with the sudden decrease in animals originating from China. Table B-7 details these trends at a species level. These data show that the countries of origin for imported cynomolgus macaques have shifted since FY2020. Although China was previously a major supplier of cynomolgus macaques to the United States, following the Chinese exportation ban in early 2020 the number of cynomolgus and rhesus macaques imported from China dropped to zero. In FY2021, imports of cynomolgus macaques originating from Cambodia, Vietnam, and Mauritius greatly increased. As compared to FY2020, FY2021 also saw increases in importation of capuchin and squirrel monkeys from Guyana. Chapter 3 describes the impacts of these changes in importation patterns and risks associated with the reliance of biomedical research on imported NHPs.

TABLE B-6 Number of Nonhuman Primates Imported, by Country and Fiscal Year (FY)

Country of Origin	FY2019	FY2020	FY2021	FY2022	Net Change FY2019–2021
Argentina	1	0	0	0	–1
Barbados	0	192	144	361	+144
Cambodia	8,571	15,664	18,870	19,618	+10,299
Canada	17	40	80	0	+63
China	20,270	3,723	0	0	–20,270
Czech Republic	0	4	0	0	0
France	0	0	0	12	0
Germany	39	4	0	0	–39
Guyana	52	40	101	187	+49
Indonesia	0	0	120	600	+120
Mauritius	3,540	5,032	10,069	8,312	+6,529
Mexico*	0	1	2	3	+2
Philippines	0	700	350	355	+350
South Africa	160	320	240	180	+80
St. Kitts	328	528	567	447	+239
Suriname	0	0	17	0	+17
United Kingdom	0	0	44	4	+44
Vietnam	840	480	1,240	2,732	+400
Total	33,818	26,728	31,844	32,811	–1,974

*Smuggled spider monkeys seized at the U.S.-Mexico border.
NOTE: Due to data limitations these numbers represent NHPs imported for a variety of purposes and do not represent animals imported exclusively for biomedical research use.
SOURCE: CDC, 2023.

TABLE B-7 Number of Nonhuman Primates Imported by Species, Country, and Fiscal Year (FY)

Nonhuman Primate Species	Country of Origin	FY2019	FY2020	FY2021	FY2022
African green monkey	Barbados St. Kitts	0 328	192 528	144 567	361 447
Capuchin	Guyana Suriname	15 0	0 0	38 2	86 0
Cynomolgus macaque	Cambodia China Indonesia Mauritius Philippines Vietnam	8,571 19,322 0 3,540 0 840	15,664 3,003 0 5,032 700 480	18,870 0 120 10,069 350 1,240	19,618 0 600 8,312 355 2,732
Common marmoset	France South Africa United Kingdom Germany Guyana	0 160 0 35 0	0 320 0 0 6	0 240 44 0 0	12 160 0 0 0
Rhesus macaque	Canada China Germany	16 948 0	0 720 4	80 0 0	0 0 0
Squirrel monkey	Guyana Suriname	30 0	34 0	63 5	60 0
Other**	Canada Argentina Czech Republic Mexico* Guyana Germany South Africa Suriname United Kingdom	1 1 0 0 7 4 0 0 0	40 0 4 1 0 0 0 0 0	0 0 0 1 0 0 0 10 0	0 0 0 3 41 0 20 0 4
Total		33,818	26,728	31,844	32,811

*Smuggled spider moneys seized at the U.S.–Mexico border.

**Other imported species varied by year but commonly included colobus monkeys, siamangs, DeBrzazz's monkeys, geladas, saki monkeys, spider monkeys, emperor tamarins, bushbabies, and orangutans.

NOTE: Due to data limitations these numbers represent NHPs imported for a variety of purposes and do not represent animals imported exclusively for biomedical research use.

SOURCE: CDC, 2023.

NHP Resources at NPRCs and National Resources

As described in Chapter 3, NPRCs and National Resources receive funding from NIH's Office of Research Infrastructure Programs (ORIP) to maintain NHP resources for NIH-supported biomedical research. These facilities house a range of NHP species, some of which are actively bred in domestic breeding colonies. The data presented in the tables that follow originate from information provided by the seven NPRCs and four National Resources following a committee request for information, as well as from USDA (see Appendix A).

Table B-8 shows the change in the number of NHPs reported held or used by the seven NPRCs to USDA between FY2015 and FY2021. When reviewing changes across all NPRCs, the total number of NHPs reported to USDA increased by just over 3 percent between FY2015 and FY2021, while the number of NHPs held but not used for research increased by

TABLE B-8 Comparison of Fiscal Year (FY) 2015 and FY2021 Nonhuman Primate (NHP) Holdings and Usage Data Reported by National Primate Research Centers (NPRCs) to the U.S. Department of Agriculture (USDA)

Center	Total Nonhuman Primates (NHPs) Reported to USDA, FY2015	Total NHPs Held in FY2015	Total NHPs Used in FY2015	Total NHPs Reported to USDA, FY2021	Total NHPs Held in FY2021	Total NHPs Used in FY2021	Percent Change in Total NHPs Reported to USDA FY2015 vs. FY2021	Percent Change in NHPs Held FY2015 vs. FY2021	Percent Change in NHPs Used FY2015 vs. FY2021
California NPRC	6,078	3,359	2,719	5,009	2,652	2,357	–17.6	–21.0	–13.3
Tulane NPRC	4,709	3,953	756	5,826	4,945	881	23.7	25.1	16.5
Wisconsin NPRC	2,513	1,124	1,389	2,407	896	1,511	–4.2	–20.3	8.8
Washington NPRC	1,316	554	762	1,264	762	502	–4.0	37.5	–34.1
Emory NPRC	3,604	1,598	2,006	3,941	2,798	1,143	9.4	75.1	–43.0
Southwest NPRC	3,502	1,521	1,981	2,960	1,841	1,119	–15.5	21.0	–43.5
Oregon NPRC	4,459	2,111	2,348	5,660	4,278	1,382	26.9	102.7	–41.1
Total	26,181	14,220	11,961	27,067	18,172	8,895	3.4	27.8	–25.6

SOURCE: USDA, 2015, 2021.

nearly 28 percent, and the number of NHPs used for research purposes decreased by over 25 percent over the same time. However, when examining the data at the center level, there is no clear pattern of change. The data reported by the Wisconsin NPRC show a decline in the number of NHPs held and an increase in the number of NHPs used in research over this 6-year period. While the actual reasons for these shifts are not known, it is possible that NHPs originally included in breeding colonies had been shifted to research use. The reported values from the California NPRC showed a decrease in the number of NHPs held and in the number of NHPs used over these 6 years, although the reasons for these dual reductions are not clear, nor is it clear which change came first based on the data available. Lastly, the Tulane, Southwest, Oregon, Washington, and Emory NPRCs each showed an increase in the number of NHPs held; however, the Tulane and Oregon NPRCs reported an increase in the number of NHPs ultimately used in research, while the Southwest, Washington, and Emory NPRCs recorded a decrease in NHPs used over the same period. Again, because of limitations in the data available from USDA, the context underlying these changes is unknown.

Based on information provided by the NPRCs as summarized in Table B-9, 12 species of NHPs are currently held or used at NPRC facilities. Of these, rhesus and cynomolgus macaques are reported to be held or used at every center. Other species were reported by a smaller number of sites (1–3 NPRCs), suggesting that they are models used for fewer areas of research. Table B-10 shows the seven species reported as currently held or used by the four ORIP-supported National Resources. These tables do not report which species are being bred in colonies at NPRCs and National Resources.

TABLE B-9 Nonhuman Primate Species Held or Used at National Primate Research Centers (NPRCs), Fiscal Year 2021

Nonhuman Primate Species	California NPRC	Oregon NPRC	Southwest NPRC	Tulane NPRC	Washington NPRC	Wisconsin NPRC	Emory NPRC
African green, vervet, grivet			X	X			
Baboon		X	X				
All capuchin species			X				
Common marmoset			X			X	
Titi monkey	X						
Cynomolgus macaque	X	X	X	X	X	X	X
Japanese macaque		X					
Pig-tailed macaque				X	X		
Rhesus macaque	X	X	X	X	X	X	X
Sooty mangabey				X			X
Squirrel monkey		X			X		X
White-capped mangabey				X			

SOURCE: NPRC Information Request, 2022.

TABLE B-10 Nonhuman Primate Species Held or Used at National Resources Supported by the National Institutes of Health Office of Research Infrastructure Programs, Fiscal Year 2021

Nonhuman Primate Species	MD Anderson Cancer Center	The Johns Hopkins University	Caribbean Primate Research Center	Wake Forest University
African green, vervet, grivet				X
Baboon	X	X		
Common marmoset	X	X		
Pig-tailed macaque		X		
Rhesus macaque	X	X	X	
Squirrel monkey	X			
All owl monkey species	X			

NOTES: These data may include NHPs not directly supported by Office of Research Infrastructure Programs funding. Additionally, these facilities may also hold or use other NHP species that were not reported in the facilities' responses to the committee's information request.
SOURCE: National Resources Information Request, 2022.

Annual Production from Breeding by Species

NPRCs and National Resources receive NIH support to maintain domestic colonies of NHPs for biomedical research use. Table B-11 shows the eight species with annual production from domestic breeding, as reported by the NPRCs to the committee. More than 3,500 NHPs were produced from breeding colonies at NPRCs in FY2021, and of these, nearly 85 percent were rhesus macaques. The corresponding data from National Resources can be found in Table B-12 and show that more than 1,300 NHPs were produced in FY2021 from breeding colonies managed by National Resources. As with the data reported by the NPRCs, most (76 percent) of the NHPs bred by National Resources were rhesus macaques.

TABLE B-11 Reported Number of Nonhuman Primates Produced Annually at National Primate Research Centers, by Species, Fiscal Year 2021

Nonhuman Primate Species	Annual Production from Breeding
African green, vervet, or grivet	0
Baboon	100
Squirrel monkey	0
Titi monkey	7
White-capped mangabey	0
All owl monkey species	0
All capuchin species	0

TABLE B-11 Continued

Nonhuman Primate Species	Annual Production from Breeding
Common marmoset	158
Macaque—crab eating, cynomolgus, or longtailed	102
Macaque—Japanese	50
Macaque—pig-tailed	120
Macaque—rhesus	3,003
Sooty mangabey	6
Other (chimpanzee)	0
Total	3,546

SOURCE: NPRC Information Request, 2022.

TABLE B-12 Reported Number of Nonhuman Primates Produced Annually at the National Resources, by Species, Fiscal Year 2021

Nonhuman Primate Species	Annual Production from Breeding
African green, vervet, or grivet	46
Baboon	98
Squirrel monkey	21
Titi monkey	0
White-capped mangabey	0
All owl monkey species	46
All capuchin species	0
Common marmoset	36
Macaque—crab-eating, cynomolgus, or longtailed	0
Macaque—Japanese	0
Macaque—pig-tailed	70
Macaque—rhesus	1,011
Sooty mangabey	0
Total	1,328

NOTE: These data may include NHPs produced in breeding colonies not directly supported by Office of Research Infrastructure Programs funding.
SOURCE: National Resources Information Request, 2022.

Annual Production from Breeding by Facility

Tables B-13 and B-14 list the number of NHPs produced at the NPRCs and National Resources in FY2021. These numbers do not include all NHPs produced for biomedical research use (they do not include numbers from NIH intramural facilities and breeding colonies outside the seven NPRCs and four ORIP-supported National Resources). As previously noted, NPRCs report an annual production of more than 3,500 NHPs annually, and National Resources report more than 1,300. Of the NPRCs, the Wisconsin NPRC produced the greatest number of NHPs, followed by the California NPRC. The Caribbean Primate Research Center accounts for more than half of NHPs produced by the National Resources in FY2021.

TABLE B-13 Total Number of Nonhuman Primates Produced Annually at National Primate Research Centers (NPRCs), Fiscal Year 2021

NPRC	Annual Production from Breeding
California NPRC	707
Tulane NPRC	606
Wisconsin NPRC	720
Washington NPRC	120
Emory NPRC	513
Southwest NPRC	240
Oregon NPRC	640
Total	3,546

SOURCE: NPRC Information Request, 2022.

TABLE B-14 Total Number of Nonhuman Primates Produced Annually at National Resources, Fiscal Year 2021

National Resource	Annual Production from Breeding
Wake Forest University	46
Caribbean Primate Research Center	732
MD Anderson Cancer Center	365
The Johns Hopkins University	185
Total	1,328

NOTE: These data may include NHPs produced by breeding colonies not directly supported by Office of Research Infrastructure Programs funding.
SOURCE: National Resources Information Request, 2022.

INVESTIGATOR DEMAND FOR NHPs IN NIH-SUPPORTED RESEARCH

The tables and figures in this section support content in the Chapter 3 section on investigator demand for NHP resources. These data were collected from NIH-supported NHP researchers via a survey and from NPRCs, National Resources, and NIH via information requests (see Appendix A for data-collection methodology). The section begins with details on NHP researcher survey responses and subsequently provides data on NHP researcher sourcing practices and demand by research domain and NHP species. A copy of the survey sent to investigators and complete reporting of the frequency of responses by question are included in Appendix E.

NHP Researcher Survey Demographics

A total of 1,431 researchers were contacted with an invitation to complete the committee's survey on NIH-supported investigator perspectives on and experiences with using NHPs in biomedical research. A total of 273 investigators responded (19.1 percent); three of these respondents reported incomplete data regarding their NIH awards (i.e., answered few questions). A total of 535 awards were reported by respondents[2] with an average of two NIH research project grants per investigator (min = 1, max = 9). Institutions in which responding investigators carry out their research can be found in Table B-15. More than half (56 percent) of respondents included in the data analysis reported their affiliation as an "other academic center," which represents facilities that are not an NPRC, a National Resource, or an academic center with an NHP breeding colony. Domains in which responding investigators conduct NHP research can be found in Figure B-1. Behavioral and systems neuroscience was the most reported research domain by responding investigators, followed by HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome), viral infectious disease (non-HIV/AIDS), and visual system research.

TABLE B-15 Responding Investigators by the Primary Institution in Which They Carry Out Their Research

Institution in Which Nonhuman Primate Research Is Carried Out	Number of Survey Respondents
National Primate Research Center	82
National Resource or academic center with breeding colony	23
Other academic center	153
Commercial organization	13
Federal laboratory	1
Total Respondents	272

NOTE: Table generated from responses to Question 113 from the NHP Investigators Survey.
SOURCE: NHP Investigators Survey, 2022.

[2] These reported awards are based on the number of responses received to Question 2 of the survey. Complete information for six awards was not provided by respondents and these awards were excluded from further analysis.

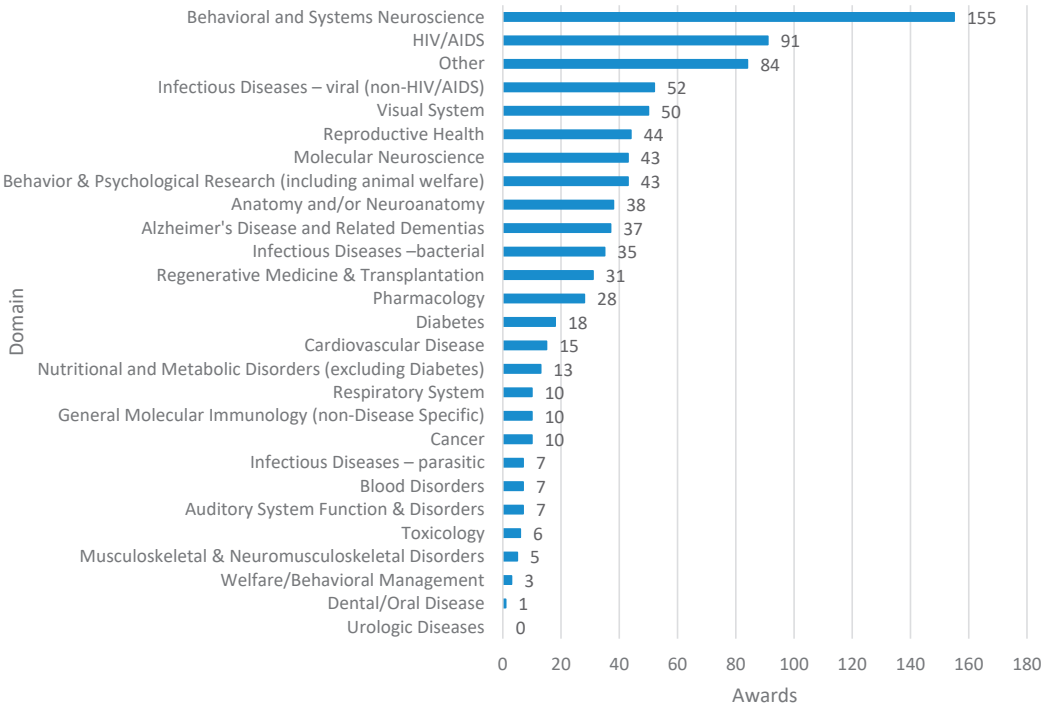

FIGURE B-1 Research domains for responding nonhuman primate researchers across all reported National Institutes of Health awards.
NOTES: Counts add to more than the number of responding investigators (n = 250) as some investigators reported having awards in multiple research domains. "Other" category included neurological disorders, including Parkinson's disease; substance use disorders and addiction; biodefense and radiation effects; pregnancy and fetal programming; and aging, among others. Figure generated from responses to Question 12 from the NHP Investigators Survey.
SOURCE: NHP Investigators Survey, 2022.

Sourcing of NHPs for NIH-Supported Research

Among the active awards reported by responding NIH-supported NHP investigators, just over half used NHPs sourced from NPRCs (see Table B-16). Of those awards that used NHPs obtained from NPRCs, nearly 75 percent used rhesus macaques. NHPs were acquired from importers for approximately 14 percent of awards reported by responding NHP investigators. These data indicate that NPRCs serve as a major source of NHPs for NIH-supported research.

Access to NHP Models for Biomedical Research

Delays in the enrollment of NHPs for NIH-supported research projects were noted in the 2018 ORIP report *Nonhuman Primate Evaluation and Analysis* (ORIP, 2018) as a consequence of persisting NHP shortages. Among awards reported by NHP researchers responding to the committee's survey, NHPs were received after the planned enrollment date for 41 percent of awards using any NHP species and 44 percent of awards using rhesus macaques—the most widely used and in-demand NHP species (see Table B-17).

TABLE B-16 Active National Institutes of Health Awards Using Nonhuman Primates (NHPs) as Reported by NHP Researchers Responding to the Committee's Survey, by Species and Source

NHP Species	Source					Total Awards Using Each Nonhuman Primate Species
	Home Institution	NPRC	Domestic Breeder	Importer	Other	
African green, vervet, or grivet	6	2	0	1	1	10
Baboon	7	15	6	3	7	32
All owl monkey species	0	1	0	0	1	2
All capuchin species	0	0	0	2	1	3
Common marmoset	9	11	4	3	8	30
Macaque—crab-eating, cynomolgus, or longtailed	5	14	29	35	13	75
Macaque—Japanese	1	7	0	0	0	8
Macaque—pig-tailed	7	16	12	1	2	30
Macaque—rhesus	76	195	81	23	59	366
Sooty mangabey	0	0	0	0	0	0
Squirrel monkey	6	0	3	2	1	12
Titi monkey	0	1	0	0	0	1
White-capped mangabey	0	0	0	0	0	0
Other—write in	1	3	0	1	5	10
Total Awards by Nonhuman Primate Source	118	265	135	71	98	

NOTES: Total awards column may not reflect the sum of numbers in each row because some awards obtained the same species of nonhuman primates from multiple sources. Contingency table generated from unique awards (n = 506) reported by respondents to both Questions 5 and 11 from the NHP Investigators Survey. NPRC = National Primate Research Center.
SOURCE: NHP Investigators Survey, 2022.

TABLE B-17 Enrollment Status by Award as Reported by Nonhuman Primate (NHP) Researchers Responding to the Committee's Survey

Awards for Which NHP Enrollment Time Information Was Reported	Number on Time	Number Late	Percent on Time (%)	Percent Late (%)
Overall (number of unique awards, n = 475)	280	195	59	41
Rhesus macaques (number of unique awards, n = 351)	186	145	56	44

NOTES: Late enrollment included any award receiving NHPs after the planned enrollment date. Contingency table generated from award data reported by respondents to both Questions 9 and 10 from the NHP Investigators Survey.
SOURCE: NHP Investigators Survey, 2022.

NPRCs provide animals for use by investigators at their facilities and for use at external research facilities (e.g., an academic center that does not have a breeding colony on-site and requires marmosets for an NIH-funded study). Numbers of NHPs provided to NIH-funded investigators for use at a facility external to the NPRC varied by NPRC and year but generally were lower in FY2020 and FY2021 relative to the FY2018 and FY2019 numbers (Table B-18). The number of NHPs provided to external investigators for research carried out at the NPRC was lower in FY2019 and FY2020 relative to FY2018 numbers but in FY2021 increased above the FY2018 numbers (Table B-19). Data provided by the responding National Resources did not yield any clear trends in the provision of NHPs to external investigators conducting research at the National Resource facility or at a different location (Tables B-20 and B-21). It appears that the distribution of animals by the Caribbean Primate Research Center is the major driver in increasing provision of NHPs for research at external facilities and for a decline in the number of animals made available for use for research conducted within the center.

TABLE B-18 Numbers of Nonhuman Primates Provided by National Primate Research Centers (NPRCs) to National Institutes of Health–Funded Researchers for Research Conducted at an External Facility, Fiscal Years (FY) 2018–2021

NPRC	FY2018	FY2019	FY2020	FY2021
California NPRC	86	160	150	23
Tulane NPRC	13	363	2	241
Wisconsin NPRC	0	7	0	14
Washington NPRC	112	51	44	75
Emory NPRC	0	0	0	22
Southwest NPRC	222	302	69	50
Oregon NPRC	175	217	221	66
Totals	608	1,100	486	491

SOURCE: NPRC Information Request, 2022.

TABLE B-19 Numbers of Nonhuman Primates Provided by National Primate Research Centers (NPRCs) to External National Institutes of Health–Funded Researchers for Research Conducted at the NPRC, Fiscal Years (FY) 2018–2021

NPRC	FY2018	FY2019	FY2020	FY2021
California NPRC	194	189	160	331
Tulane NPRC	145	92	65	112
Wisconsin NPRC	231	168	307	360
Washington NPRC	82	64	66	62
Emory NPRC	74	110	102	214
Southwest NPRC	59	49	18	24
Oregon NPRC	243	318	234	143
Totals	1,028	990	952	1,246

SOURCE: NPRC Information Request, 2022.

TABLE B-20 Numbers of Nonhuman Primates Provided by National Resources to National Institutes of Health–Funded Researchers for Research Conducted at an External Facility, Fiscal Years (FY) 2018–2021

National Resource	FY2018	FY2019	FY2020	FY2021
Wake Forest University	4	8	36	14
Caribbean Primate Research Center	192	103	204	286
MD Anderson Cancer Center	140	118	106	135
The Johns Hopkins University	75	4	69	96
Totals	411	233	415	531

SOURCE: National Resources Information Request, 2022.

TABLE B-21 Numbers of Nonhuman Primates Provided by National Resources to External National Institutes of Health–Funded Researchers for Use in Research Conducted at the National Resource Facility, Fiscal Years (FY) 2018–2021

National Resource	FY2018	FY2019	FY2020	FY2021
Wake Forest University	81	35	11	34
Caribbean Primate Research Center	1,885	1,942	1,694	1,646
MD Anderson Cancer Center	62	64	40	108
The Johns Hopkins University	0	0	0	0
Totals	2,028	2,041	1,745	1,788

SOURCE: National Resources Information Request, 2022.

Needs for specific NHP characteristics, as well as external pressures (e.g., infrastructure and logistical issues), were found to be factors associated with poor accessibility of NHPs by NIH-supported investigators. Certain characteristics of investigators' requests for animals from NPRCs and National Resources were noted by these stakeholders as contributing to longer wait times for animals (Table B-22). Particularly, all NPRCs and National Resources indicated that the need for a specific age of the requested NHPs was associated with longer wait times for animals. Sex and specific genotypes of requested NHPs were also commonly reported by NPRCs and National Resources as factors associated with increased wait times. Factors commonly reported by NPRCs and National Resources as impediments to meeting researcher demands for NHPs (Table B-23) included issues related to NHP housing, sufficiency of funding, and the time required to expand breeding colonies. These factors and challenges are described in Chapter 3.

TABLE B-22 Nonhuman Primate Demographics and Characteristics Associated with Increased Wait Times for Investigators as Reported by National Primate Research Centers (NPRCs) and National Resources

Nonhuman Primate Demographics Reported to Result in Longer Wait Times for Principal Investigators	Number of Reporting NPRCs That Selected the Response (n = 7)	Number of Reporting National Resources That Selected the Response (n = 4)
Age	7	4
Specific genotype	7	2
Sex	6	4
Species	4	2
Other—write in*	4	1

* "Other" characteristics noted as associated with long wait times by responding NPRCs include viral infection status (n = 4), animal size and weight (n = 1), and pregnancy status (n = 1). Among responding National Resources, the single "other" response noted was viral status (n = 1).
SOURCES: NPRC Information Request, 2022; National Resources Information Request, 2022.

TABLE B-23 National Primate Research Center (NPRC) and National Resources Perspectives on Challenges to Meeting Researcher Demand for Nonhuman Primates

Reported Challenges Faced by NPRCs and National Resources in Meeting Changes in Demand for Nonhuman Primates	Number of Reporting NPRCs That Selected the Response (n = 7)	Number of Reporting National Resources That Selected the Response (n = 4)
Housing	7	2
Funding	7	3
Length of time required for breeding colony expansion	7	3
Transportation	4	2
Lack of availability of animals for breeding	3	2
Other—write in*	4	1

*"Other" challenges reported by responding NPRCs included staffing challenges (n = 4) and research infrastructure challenges (research equipment and nonhuman primate caging) (n = 2). Among responding National Resources, the single "other" response noted staffing challenges (n = 1).
SOURCE: National Resources Information Request, 2022; NPRC Information Request, 2022

As indicated earlier, in Table B-17, NIH-supported researchers experienced challenges with timely enrollment of NHPs in their studies. Among investigators responding to the committee's survey and reporting issues with accessing NHPs, 72 percent associated these challenges with shortages of NHPs meeting specific demographics required for their study protocols, and 50 percent faced challenges accessing NHPs from their preferred source (see Table B-24). More detail about these challenges and associated impacts on NIH-supported research can be found in Chapter 3.

TABLE B-24 Challenges Associated with the Timely Enrollment of Nonhuman Primates (NHPs) as Reported by NHP Researchers Responding to the Committee's Survey

Challenges Reported by Survey Respondents with Timely Enrollment of NHPs	Number of Respondents Reporting Specific Challenges Related to Timely Enrollment* (n = 175)	Percentage of Respondents Reporting Specific Challenges Related to Timely Enrollment (%) (n = 175)
Availability of specific demographics of NHPs (e.g., age classes, sex)	126	72
Availability from a preferred source	87	50
Funding and costs associated with obtaining NHPs	76	43
Infrastructure issues (e.g., lack of access to appropriate equipment for conducting research)	50	29
Transportation	32	18
Availability of NHPs with specific genotypes or genetic diversity	27	15
Other—write in*	44	25

* Other issues reported as write-in responses related to challenges with obtaining NHPs were similar to those provided as options for the survey and included lack of availability of nonhuman primates with needed characteristics, delays related to COVID-19, limitations in NIH funding, available space, and staffing issues, among others.
NOTES: Table generated from responses to Question 115 from the NHP Investigators Survey. Respondents were able to select more than one challenge.
SOURCE: NHP Investigators Survey, 2022.

Demand for NHPs by Research Domain and Species

NPRCs, National Resources, NIH-supported investigators, and NIH institutes, centers, and offices were asked to consider areas for future demand for NHPs (see Figure B-2 and Tables B-25 and B-26). The most commonly listed domains generally overlapped across stakeholders and indicated existing and future demand for NHP models in neuroscience research, infectious disease, aging and aging-related diseases (such as Alzheimer's disease and related disorders), and regenerative medicine. More information about priority research domains for current use and future NHP investment across these stakeholders is described in Chapter 3.

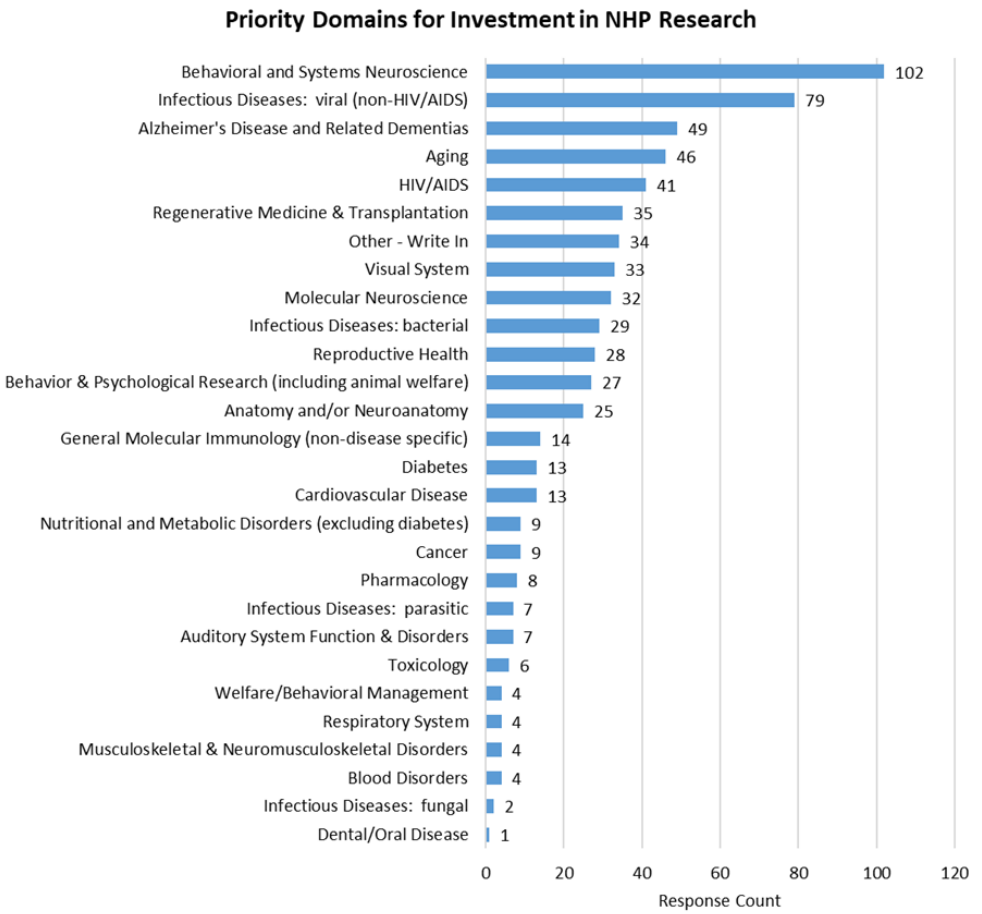

FIGURE B-2 Priority research domains for nonhuman primate research reported by investigators supported by the National Institutes of Health.
NOTES: Figure generated from responses to Question 119 from the NHP Investigators Survey. Respondents were able to select up to three priority research domains. A total of 259 respondents provided input on priority domains. HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.
SOURCE: NHP Investigators Survey, 2022.

TABLE B-25 National Primate Research Center Predicted Future Demand for Nonhuman Primates by Research Domain

Research Domain	Number of Reporting National Primate Research Centers (n = 7)
Immunology and infectious disease	7
Neuroscience	7
Aging	6
Regenerative medicine	6
Metabolism	5
Neonatal disease	5
Reproductive health	5
Women's health	5
Genetics	4
Genomics	4
Nutrition/obesity	4
Stem cells	4
Transplantation	4
Alcohol, drug abuse, addiction	3
Animal welfare	3
Children's health	3
Developmental sciences	3
Heart, lungs, blood	3
Behavior/psychology	2
Vision	2
Cancer	1
Environmental enrichment	1
Psychological well-being	1
Allergy	0
Autoimmune	0
Digestive disorders	0
Endocrine	0
Kidney disease	0
Musculoskeletal	0
Oral/dental	0
Skin	0
Urinary health	0

NOTE: Respondents were able to select multiple priority research domains.
SOURCE: NPRC Information Request, 2022.

TABLE B-26 National Resources Predicted Future Demand for Nonhuman Primates by Research Domain

Research Domain	Number of Reporting National Resources (n = 4)
Immunology and infectious disease	4
Aging	3
Neuroscience	3
Behavior/psychology	3
Alcohol, drug abuse, addiction	2
Genetics	2
Neonatal disease	2
Regenerative medicine	2
Women's health	2
Transplantation	1
Metabolism	1
Nutrition/obesity	1
Vision	1
Autoimmune	1
Cancer	1
Children's health	1
Developmental sciences	1
Genomics	1
Stem cells	1
Animal welfare	1
Psychological well-being	1
Endocrine	0
Heart, lungs, blood	0
Allergy	0
Digestive disorders	0
Environmental enrichment	0
Kidney disease	0
Musculoskeletal	0
Oral/dental	0
Reproductive health	0
Skin	0
Urinary health	0

NOTE: Respondents were able to select multiple priority research domains.
SOURCE: National Resources Information Request, 2022.

No available, comprehensive data sources describe the number of NHPs used in NIH-supported research or how NHPs are used across different research domains. Table B-27 shows the distribution of NHPs used in active NIH awards across research domains as self-identified by investigators who responded to the committee's survey. The greatest number of NHPs used were reported for NIH awards associated with HIV/AIDS, behavioral and systems neuroscience, behavior and psychological research, reproductive health, and viral infectious diseases (besides HIV/AIDS). It should be noted that investigators were able to select more than one domain per

award; therefore, the numbers in the table do not represent the absolute number of NHPs used by investigators responding to the survey. Table B-28 describes the projected future NHP species needs by this same group of investigators and shows investigator interest in using rhesus macaques (82 percent of respondents who anticipate NHP use in the next 5 years), cynomolgus macaques (22 percent), common marmosets (11 percent), and baboons (11 percent).

TABLE B-27 Current Nonhuman Primate (NHP) Use by Research Domain among NHP Researchers Responding to the Committee's Survey

Research Domains of Current National Institutes of Health Awards Reported by Responding Investigators	Number of NHPs Used
HIV/AIDS	6,310
Behavioral and Systems Neuroscience	4,537
Behavior & Psychological Research (including animal welfare)	4,511
Reproductive Health	4,301
Molecular Neuroscience	3,310
Nutritional and Metabolic Disorders (excluding diabetes)	3,177
Anatomy and/or Neuroanatomy	3,025
Welfare/Behavioral Management	2,845
Infectious Diseases—Parasitic	2,359
Visual System	2,306
Dental/Oral Disease	2,300
Alzheimer's Disease and Related Dementias	1,445
Cardiovascular Disease	1,218
Diabetes	1,167
Regenerative Medicine & Transplantation	1,103
Infectious Diseases—Bacterial	899
Cancer	792
Respiratory System	561
Pharmacology	489
General Molecular Immunology (non–disease specific)	416
Blood Disorders	332
Musculoskeletal & Neuromusculoskeletal Disorders	323
Toxicology	217
Auditory System Function & Disorders	71
Infectious Diseases—Fungal	0
Urologic Diseases	0
Other*	2,902

* "Other" category included such write-in responses as Genetics and Genomics (950), Microbiome (400), Aging (391), Biodefense and Radiation Research (333), Neuroanatomy and Neurological Disorders and Injuries (173), Social Effects of Health (170), Substance Abuse and Addiction (134), Pain Research (21), Neuromodulation and Deep Brain Stimulation (12), Gene Therapy and Gene Editing (6).

NOTES: Contingency table generated from award data provided by respondents to both Questions 7 and 12 from the NHP Investigators Survey. Respondents were able to select more than one research domain per award, and NHPs used on an award can be represented in more than one category. The total number of NHPs across all awards reported by respondents to these questions was 17,729.

SOURCE: NHP Investigators Survey, 2022.

TABLE B-28 Projected Future Needs for Nonhuman Primate (NHP) Species among Researchers Responding to the Committee's Survey Who Anticipate Using NHPs in the Next 5 Years

NHP Species Projected for Future Use	Percent of Responding Future NHP Users (%) (n = 258)
Macaque—rhesus	82
Macaque—crab-eating, cynomolgus, or longtailed	22
Common marmoset	11
Baboon	11
Macaque—pig-tailed	8
African green, vervet, or grivet	6
Squirrel monkey	3
Other—write In	2
All capuchin species	2
Macaque—Japanese	2
All owl monkey species	1
Titi monkey	0.4
Sooty mangabey	0
White-capped mangabey	0

NOTES: Table generated from responses to Question 118 from the NHP Investigators Survey. A total of 258 respondents responded to the question and were able to select more than one species in response.
SOURCE: NHP Investigators Survey, 2022.

NPRCs were prompted similarly to provide projections for future increases and decreases in researcher demand for NHP species (Table B-29) and identified high-demand species similar to those identified by the investigators responding to the committee's survey. Six of seven NPRCs indicated that demand for certain species will increase, and of the six NPRCs that responded to this question, all projected increased demand for rhesus macaques.

TABLE B-29 National Primate Research Center (NPRC) Projections for Change in Researcher Demand, by Nonhuman Primate (NHP) Species

NHP Species	Number of NPRCs Reporting Projected Decrease in Demand (n = 7)	Number of NPRCs Reporting Projected Increase in Demand (n = 7)
Baboon	0	2
Common marmoset	0	4
Macaque—crab-eating, cynomolgus, or longtailed	1	3
Macaque—Japanese	1	0
Macaque—pig-tailed	0	1
Macaque—rhesus	0	6

SOURCE: NPRC Information Request, 2022.

Openness Practices in NHP Research

Investigators who responded to the committee's survey were asked to provide their experiences with engaging in various openness practices aimed at improving scientific rigor. Of the 263 researchers who answered the survey question, 81 percent indicated that they were engaged in the sharing of data in its raw or aggregate form upon the submission of a manuscript for publication. Other actions reported by respondents included actions to increase the transparency of study design and analysis (74 percent), the sharing of research materials (60 percent), and sharing of code or other analytic methods (50 percent) (Table B-30). These data suggest that interest in engaging in openness practices for the benefit of rigor are widespread.

TABLE B-30 Openness Practices for Scientific Rigor among Nonhuman Primate Researchers Responding to the Committee's Survey

Openness Practices	Number of Respondents (n = 263)	Percentage of All Respondents (%)
Sharing data (i.e., raw or aggregate data are deposited in trusted repository minimally upon submission or publication of a manuscript)	212	81
Design and analysis transparency (i.e., publications detail sufficient experimental details to recreate experiments, including the use of standardized checklists such as the ARRIVE guidelines, reporting of variables such as social housing conditions of animals, etc.)	194	74
Research materials sharing (i.e., materials required to carry out experiment are deposited in a trusted repository or available via some other publicly known method)	158	60
Analytic methods (code) sharing (i.e., code to run analyses is deposited in a trusted repository)	131	50
Engagement in replicating existing studies	70	27
Meta-analytic or quantitative reviews of existing literature	45	17
Preregistration of studies	21	8
Preregistration of analysis plans	17	6
Other*	21	8

*The "other" responses included the publication of results in peer-reviewed journals, tissue sharing, studies that combine research groups across multiple centers, and the use and sharing of standardized written methods and transparent data documentation, among others.
NOTES: Table generated from responses to Question 122 from the NHP Investigators Survey. A total of 263 unique investigators responded and were able to select more than one response. ARRIVE = Animal Research: Reporting of *In Vivo* Experiments.
SOURCE: NHP Investigators Survey, 2022.

PATHOLOGY, TISSUE ARCHIVES, AND RESOURCE SHARING

The seven NPRCs and four National Resources were asked to provide information on their tissue-archiving and resource-sharing practices. Responses varied across institutions in terms of the proportion of decedent NHPs undergoing necropsy examinations, the types of examinations performed, and the length of time tissues were archived. While all NPRCs

and National Resources performed necropsies (ranging from 75 percent to 100 percent of decedent NHPs), there was variation in the type of examination performed (see Boxes B-1 and B-2).

BOX B-1 TISSUE ARCHIVING AND SHARING PRACTICE AT NATIONAL PRIMATE RESEARCH CENTERS (NPRCS)

1. Proportion of nonhuman primates at NPRCs that undergo necropsy examinations
   a. All decedents (5 NPRCs)
   b. >75 percent (2 NPRCs)
2. Type of necropsy performed (number indicating "Gross" versus "Gross and histologic" or "Other")
   a. Gross and histologic exam (5 NPRCs)
   b. Gross on all animals, histology on selected cases, as well as any project-specific procedures (1 NPRC)
   c. Depends on the study (1 NPRC)
3. Length of time paraffin-embedded tissues are stored
   a. >10 years (4 NPRCs)
   b. 5–10 years (1 NPRC)
   c. Indefinitely (1 NPRC)
   d. Archives never purged (1 NPRC)
4. Proportion of fixed or embedded samples from necropsies available for sharing with federally funded investigators
   a. >75 percent (6 NPRCs)
   b. 25–75 percent (1 NPRC)
5. Length of time frozen tissues from necropsy are stored
   a. >10 years (4 NPRCs)
   b. 5–10 years (1 NPRC)
   c. Indefinitely (1 NPRC)
   d. N/A (1 NPRC)
6. Proportion of frozen samples from necropsies available for sharing with federally funded investigators
   a. >75 percent (3 NPRCs)
   b. 25–75 percent (3 NPRCs)
   c. N/A (1 NPRC)

SOURCE: NPRC Information Request, 2022.

BOX B-2 TISSUE ARCHIVING AND SHARING PRACTICE AT NATIONAL RESOURCES

1. Proportion of nonhuman primates at National Resources that undergo necropsy examinations
   a. All decedents (2 National Resources)
   b. >75 percent (2 National Resources)
2. Type of necropsy performed (number indicating "Gross" versus "Gross and histologic" or "Other")
   a. Gross and histologic exam: (2 National Resources)
   b. Gross exam only (1 National Resource)
   c. Other: Diagnostic necropsies include both gross and histological exam. Experimental necropsies do not unless requested by the PI [principal investigator]. (1 National Resource)
3. Length of time paraffin-embedded tissues are stored
   a. >10 years (3 National Resources)
   b. 5–10 years (1 National Resource)
   c. No policy (none)
4. Proportion of fixed or embedded samples from necropsies available for sharing with federally funded investigators
   a. >75 percent (2 National Resources)
   b. 25–75 percent (1 National Resource)
   c. N/A (1 National Resource)
5. Length of time frozen tissues from necropsy are stored
   a. >10 years (3 National Resources)
   b. 5–10 years (1 National Resource)
   c. No policy (none)
6. Proportion of frozen samples from necropsies available for sharing with federally funded investigators
   a. >75 percent (3 National Resources)
   b. 25–75 percent (1 National Resource)
   c. N/A (none)

SOURCE: National Resources Information Request, 2022.

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Biographical Sketches of Committee Members and Staff

COMMITTEE MEMBERS

Kenneth Ramos, M.D., Ph.D. (NAM) (*Chair*), is professor of translational medical sciences, Alkek chair of medical genetics, executive director of the Institute of Biosciences and Technology, associate vice president for research, and assistant vice chancellor for health services for the Texas A&M University System. He is an accomplished physician-scientist with designations in the National Academy of Medicine (elected member) and National Academy of Sciences (lifetime associate). He is a transformational leader recognized throughout the world for his scientific contributions in the areas of genomics, precision medicine, and toxicology. With formal training in pharmaceutical sciences, chemistry, biochemistry, pharmacology, and medicine, Dr. Ramos is helping to steer the changing landscape of medicine, biotechnology, and health care. In this context, he leads several translational, clinical research, and educational programs that integrate diverse approaches to elucidate genomic mechanisms of disease and to develop novel therapies for several oncologic, pulmonary, and vascular diseases. Dr. Ramos has provided academic, executive, administrative, and scientific leadership in the areas of genetics and genomic medicine and toxicology at various academic institutions, and over the course of his career has positively influenced the career of numerous clinicians and scientists engaged in medical, veterinary, and pharmaceutical practice. He is deeply committed to initiatives that advance modern technological applications to improve the quality of health care and reduce disease burden and health-associated costs.

Christian Abee, D.V.M., M.S., received his D.V.M. from Texas A&M University and subsequently completed a postdoctoral fellowship and training program in comparative medicine at the Wake Forest University School of Medicine. He began his career as a research scientist at Tulane National Primate Research Center (1974–1979). In 1979, he became director of animal health and resources at University of South Alabama College of Medicine, where he later became chair of the Department of Comparative Medicine and distinguished university professor. He moved to the University of Texas MD Anderson Cancer Center in 2005 to

become the Doctor R. Lee Clark professor, chair of the Department of Comparative Medicine, and director of the Michale E. Keeling Center for Comparative Medicine and Research. He served as principal investigator of National Institutes of Health (NIH) grants and contracts and directed several NIH-supported national research resources, including the Squirrel Monkey Breeding and Research Resource, the Owl Monkey Breeding and Research Resource, the Rhesus Monkey Breeding and Research Resource, the Specific-Pathogen-Free Baboon Research Resource, and the National Center for Chimpanzee Care. He served as chair of the NIH Comparative Medicine Review Committee; served on the Institute for Laboratory Animal Research (ILAR) Council, the AAALAC International Council on Accreditation, and the Board of Directors of the National Association for Biomedical Research (NABR). He has served as president of both the American College of Laboratory Animal Medicine and the Association of Primate Veterinarians, and he served on the National Scientific Advisory Boards of four National Primate Research Centers. He was an editor of two editions of *Nonhuman Primates in Biomedical Research*. He is a recipient of the Charles River Prize for his contributions to laboratory animal science and medicine, the Nathan R. Brewer Lifetime Achievement Award for contributions to animals and science, and received an Outstanding Alumnus Award in 2007 from the Texas A&M University College of Veterinary Medicine & Biomedical Sciences. He was awarded an emeritus professorship by the University of Texas MD Anderson Cancer Center in 2020.

Ashutosh Agarwal, Ph.D., is an associate professor of biomedical engineering, and director of engineering and applied physics of the Desai Sethi Urology Institute at the University of Miami. The research mission of his Physiomimetic Microsystems Laboratory is to develop human-relevant organ mimic platforms to replace or significantly reduce animal testing for discovery of therapies and drugs. Organs on chips are also being employed for modeling of disease states, for conducting mechanistic studies, and for differentiation, maturation, and evaluation of human stem cells. The laboratory is supported by multiple consortium grants from the National Institutes of Health (NIH) (National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute). Dr. Agarwal was selected as a Kavli Fellow to participate in the National Academy of Sciences Frontiers of Science symposium in Jerusalem (2019), was a featured speaker at a National Academy of Engineering–National Academy of Medicine Regional Meeting in Miami (2018), and co-organized a National Academies workshop on Microphysiological Systems for Efficacy and Safety Studies, focused on advances in organ-on-a-chip technologies for animals. Dr. Agarwal holds patents related to microphysiological systems and is cofounder of Bio-Vitro LLC, an early-stage startup company established in 2018 with the mission of accelerating development of disease models and novel therapeutics by providing an easy-to-use platform for culture and assessment of 3D cellular constructs. He has also previously received funding from Mallinckrodt Pharmaceuticals related to lung-on-a-chip research.

Szczepan Baran, V.M.D., M.S., is chief scientific officer at VeriSIM Life, a company that has developed and offers pharmaceutical and biotech companies access to an artificial intelligence (AI)–enabled platform that guides preclinical translational drug development by predicting clinical outcomes. A scientist and comparative medicine veterinarian turned "technology geek," he is passionate about transforming the delivery of innovative medicines to patients through digital technologies and data enablement to be more efficient, cost-effective, and environmentally conscious while pushing the scientific envelope and reimagining patient engagement. Prior to joining VeriSIM Life, he was head of emerging technologies within Comparative Medicine at Novartis. In this position, he led an integrated

digital enterprise strategy to modernize and increase the agility of current processes, with a focus on the development and incorporation of patient-relevant AI technologies and digital endpoints. In parallel, Dr. Baran focused on stakeholder engagement to identify adaptation hurdles and develop regulatory qualification pathways for microphysiological systems (MPS) technologies. Dr. Baran has played instrumental roles in establishing and leading the Global Novartis Institutes for BioMedical Research Preclinical Digital Biomarkers and MPS Groups with a vision for strategic alignment and data agility. He has received multiple 3Rs Awards for implementation of emerging technologies, including development of novel in vitro techniques to reduce the use of nonhuman primates (NHPs) in malaria research. He is a graduate of the University of Delaware and the University of Pennsylvania School of Veterinary Medicine. He completed his residency in Laboratory Animal Medicine and received a master of science in comparative medicine from the University of Washington School of Medicine. Dr. Baran began his career at the Fred Hutchinson Cancer Research Center, where he was recruited to develop the first canine embryonic stem cell lines and collaborate on developing novel NHP and canine transplantation protocols to eliminate graft versus host disease. Before joining Novartis, he held multiple startup and faculty positions and served on numerous boards. He is a Medical & Scientific Advisory Board member at the Canines-N-Kids Foundation. He serves as an ad hoc member on the Scientific Advisory Committee on Alternative Toxicological Methods, AAALAC International as an ad hoc specialist, and as a member of the Boston Innovation Advisory Council. In December 2022, Dr. Baran was appointed to a National Institutes of Health advisory committee to the director working group on novel alternative methods.

Eliza Bliss-Moreau, Ph.D., is a professor in the Department of Psychology and a core scientist at the California National Primate Research Center at the University of California, Davis (UC Davis). She was formally trained as a social psychologist (graduate training), as well as a nonhuman primate (NHP) neuroanatomist, behavioral neuroscientist, and primatologist (postdoctoral training). Her multispecies, multimethod, multidisciplinary laboratory was started in 2016 and focuses on how emotions came to be across evolutionary time and come to be across developmental time, carrying out "womb-to-tomb" comparative and translational affective science and often working in the context of neurodevelopmental disease (e.g., fetal Zika virus infection, Alzheimer's disease). Her research team is interested in the fundamental components of mood, what makes individuals (humans, monkeys, agricultural animals, plus a variety of other model species such as aplysia) "well" and how features of the social and physical environment create the contexts for moods to emerge. She works across a variety of settings including the laboratory, field (in India and Malaysia), and agricultural barns. An increasing focus of her laboratory's work is on how to improve NHP science, by increasing transparency to promote evaluation of scientific rigor. Dr. Bliss-Moreau receives research funding from the National Institutes of Health, National Science Foundation, and the University of California. She is a member of the Society for Neuroscience Committee on Animals in Research and participates in the University of California's Animal Research Transparency Working Group. She recently served as a consultant for Biomere, Inc., related to the contract research organization's NHP enrichment and training protocols. Dr. Bliss-Moreau has authored more than 70 publications and received national recognition for her innovative research, including the Association for Psychological Science's "Rising Star" award in 2013, the American Psychological Association Distinguished Scientific Award for Early Career Contributions (in animal learning, cognition) in 2018, and a Fellow of the Association for Psychological Science in 2020. Prior to joining the Department of Psychology, she was a faculty member in the UC Davis School of Veterinary Medicine.

Ricardo Carrion, Jr., Ph.D., is professor and director of maximum containment contract research and program co-lead at the Texas Biomedical Research Institute, and a core scientist at the Southwest National Primate Research Center. Dr. Carrion's research program aims to develop and characterize animal models for biosafety level 4 hemorrhagic fever viruses and other high-consequence pathogens. He was the first to show that the common marmoset faithfully mimics human Ebola virus disease, Marburg virus disease, and Lassa fever, thus providing a novel small nonhuman primate (NHP) model for evaluating countermeasures to these diseases. He has characterized a number of models of virus-induced disease that have been used for advanced preclinical development of vaccines and therapies to support eventual licensure via the animal rule pathway. Several filovirus vaccine platforms and therapeutics were advanced by Dr. Carrion's group using cynomolgus and rhesus Ebola virus macaque models. In addition, his laboratory performed critical preclinical studies for the first approved Ebola antibody therapy. Most recently, Dr. Carrion's lab has supported development of NHP COVID-19 models and has subsequently used these models for advanced preclinical development of several COVID-19 countermeasures, including mRNA vaccines, subunit vaccines, DNA vaccines, and monoclonal antibodies. Dr. Carrion's current research is funded by the National Institutes of Health, Biomedical Advanced Research and Development Authority, Department of Defense, Advanced Technology International, the Medical CBRN Defense Consortium, Novavax Inc., Inovio Pharmaceuticals, and Gilead Sciences.

J. Mark Cline, D.V.M., Ph.D., is an experienced researcher with more than 25 years of continuous National Institutes of Health (NIH) funding and is a board-certified veterinary pathologist specializing in the discovery and development of animal models of cancer and radiation effects. Much of his past work focused on primate studies of hormonal and dietary effects on the pathophysiology of breast and reproductive cancer risk, with comparative work in rodents, and translational studies in human subjects. He is now principal investigator (PI) for the NIH/National Institute of Allergy and Infectious Diseases Wake Forest Primate Radiation Late Effects Program (U01 AI150578). This unique resource is funded from 2007 to 2027, includes long-term clinical assessments of multiple organ systems in male and female primates, and serves a network of more than 50 investigators across the United States. He also served as PI of a recently concluded Department of Defense/Congressionally Directed Medical Research Focused Program designed to assess cardiac, metabolic, immune, and genomic injury in irradiated nonhuman primates. He is program director for an NIH T32 Postdoctoral Training Program in Laboratory Animal and Comparative Medicine, focused on training graduate veterinarians to become independent researchers. More recently, his laboratory has developed the Primate Cancer Initiative, which conducts outreach to primate research facilities nationally to find primates with naturally occurring cancers and treat them, using novel immunotherapy approaches. This work has high translational value and helps to support cancer therapy for nonhuman primates who might not otherwise be treated. His salary is supported primarily by competitively awarded NIH grants, with limited salary support from Roche for immunotherapy studies.

Myrtle Davis, D.V.M., Ph.D., is scientific vice president of discovery toxicology at Bristol Myers Squibb. Previously, she served at the National Cancer Institute as chief of the Toxicology and Pharmacology Branch of the Developmental Therapeutics Program. Dr. Davis has previous experience as a research advisor in the Drug Safety group of Lilly Research Laboratories (Eli Lilly Pharmaceutical company). In both roles, she contributed to the advancement of several drug candidates and to the understanding of toxicological mechanisms. Dr. Davis also has several years of academic experience as an associate professor in the

Department of Pathology in the School of Medicine at the University of Maryland. She is currently responsible for leading scientific efforts in discovery toxicology to provide target and molecular hazard identification. She also leads and oversees the toxicology efforts needed to support mechanistic understanding of the toxicities of potential new drugs during their discovery. A native New Yorker, Dr. Davis completed a postdoctoral fellowship in Toxicologic Pathology at the University of Maryland. She earned a Ph.D. in toxicology from the University of Illinois Urbana-Champaign and obtained her doctor of veterinary medicine degree from Tuskegee University School of Veterinary Medicine. She also completed undergraduate work in chemistry and math at Tuskegee University. Dr. Davis is a Fellow of the Academy of Toxicological Sciences, an active member of the Society of Toxicology (currently serving as vice president), and a member of the Society of Toxicologic Pathology. She is currently serving on the Board of Scientific Councilors of the National Toxicology Program, and she is a reviewer for the Assay Development and Screening Technologies Laboratory of the National Center for Advancing Translational Sciences (NCATS). Dr. Davis served as associate editor for *Toxicological Sciences* and *Toxicologic Pathology*, and as editor-in-chief of the *ILAR Journal*. She has authored several book chapters and coauthored peer-reviewed publications on a range of topics. She has also developed course content and lectures for medical and graduate student education. In December 2022, Dr. Davis was appointed to a National Institutes of Health advisory committee to the director working group on novel alternative methods.

Asgerally Fazleabas, Ph.D., is professor and associate chair of research in the Department of Obstetrics, Gynecology and Reproductive Biology, director of the Center for Women's Health Research, and codirector of the Reproductive and Developmental Sciences Program at Michigan State University. His research is focused on using the baboon as a nonhuman primate (NHP) model to understand early embryo–maternal dialog and implications of implantation failure, and the development of a baboon model for endometriosis to study early events in lesion development and impact on fertility. Dr. Fazleabas's laboratory was the first to conclusively demonstrate that signals from the primate embryo, like those of other species, induce cell-specific changes in uterine gene expression. These changes are thought to play critical roles in establishing a synchrony between the maternal environment and the developing embryo that is a prerequisite for a successful pregnancy. The unique nature of the endometriosis NHP model he has developed, as well as the strong multidisciplinary group that he has established, has led to important and fundamental findings regarding the causative effects of endometriosis on aberrant gene expression in the eutopic endometrium that may contribute to infertility. Furthermore, studies from his laboratory have identified the genes that may be involved with the process of angiogenesis and cell adhesion during the establishment of lesions in the peritoneal environment. Dr. Fazleabas received his B.S. from California State University, Fresno, and his Ph.D. in reproductive physiology from the University of Illinois at Urbana-Champaign. Following his postdoctoral training in reproductive biology/cell and molecular biology at the University of Florida in Gainesville, he joined the Department of Obstetrics and Gynecology at the University of Illinois Chicago where he held the rank of professor and director of women's health and reproduction until October 2009. He has received several awards for his work, including the Carl Hartman Award from the Society for the Study of Reproduction. Dr. Fazleabas is a member of the scientific advisory board of the Oregon National Primate Research Center, serving as an advisor to the Developmental and Reproductive Sciences Division. He receives research funding for work with NHP models from the National Institutes of Health and Comanche Biopharma, a preclinical biopharmaceutical company developing a novel siRNA therapy for the treatment

of preeclampsia. Dr. Fazleabas is also a consultant with Ship of Theseus, a startup company focused on the development of mutated proteins for endometriosis treatment.

Melanie Graham, M.P.H., Ph.D., is a professor in the departments of Surgery, Medical School, where she holds the Robert and Katherine Goodale chair in minimally invasive surgery, and veterinary population medicine in the College of Veterinary Medicine, and is director of the Preclinical Research Center (PCRC) at the University of Minnesota. She was trained in surgical modeling and as an epidemiologist at the University of Minnesota. She completed doctoral training at Utrecht University as a primatologist focused on animal welfare science, with a thesis titled "Working on the 3Rs: Utilization of refinement to enhance the value of translational research in nonhuman primates." Dr. Graham's research focuses on validity in preclinical modeling and refining models of chronic disease to maximize their predictive accuracy to the clinic. She has published extensively in peer-reviewed journals and has presented both nationally and internationally on her work defining model limitations, methods for refining the animal experience to improve well-being, and novel approaches for improving experimental rigor. She is similarly recognized for her deep expertise in the study of metabolic diseases and interventions centered on regenerative medicine, specifically innovative cell-based therapies and immunomodulation. Accordingly, Dr. Graham has integrated this work to lead influential pivotal trials that include the successful demonstration of both long-term diabetes reversal after islet xenotransplant and immunosuppression-free transplantation in primates. She is committed to engaging scientists with the 3Rs (replacement, reduction, and refinement) in the most meaningful way by objectively demonstrating their impact on the scientific value of experimental animal models. Dr. Graham serves on the Academy of Surgical Research Board of Directors and participates in the National Institute of Allergy and Infectious Diseases (NIAID) Nonhuman Primate Transplantation Tolerance Cooperative and the NIAID Immunobiology of Xenotransplantation Cooperative Research Program. She is a board of directors emeritus of the North American 3Rs Consortium, a nonprofit focused on refinement, reduction, and replacement of animal models in scientific research. Dr. Graham is a member of a scientific advisory group convened by the Medical Research Council and Wellcome Trust to conduct a review of the current status of nonhuman primate academic research across funding bodies in the United Kingdom. She is the site investigator for PCRC, and her research is supported by the State of Minnesota, Juvenile Diabetes Research Foundation, Department of Defense, and National Institutes of Health.

Kelly Metcalf Pate, D.V.M, Ph.D., is director of the Division of Comparative Medicine and Dorothy W. Poitras associate professor of biological engineering at the Massachusetts Institute of Technology (MIT). She is a veterinarian-scientist and boarded specialist in laboratory animal medicine with more than 15 years of independent and collaborative expertise in the development and refinement of nonhuman primate and murine models of human disease, especially in the context of host–pathogen interactions. Dr. Metcalf Pate's laboratory focuses on the elucidation of the role of platelets in the immune response to infectious disease, with a focus on the downstream effects of the platelet's interactions with other cells throughout the pathogenesis of human immunodeficiency virus (HIV) and cytomegalovirus infection, and how modulating the response of platelets to infection alters the course of disease. Recent work in her group has expanded to include the influence of environmental factors, especially social stress and the microbiome, on the immune response to viral infection, and on the translational validity and reproducibility of work with animal models. Her research is currently funded by the Department of Defense. Prior to joining MIT, Dr. Metcalf Pate was faculty at the Johns Hopkins School of Medicine, where she facilitated the development and

refinement of animal models of HIV pathogenesis as cochair of the Center for AIDS Research Cure Scientific Working Group, oversaw the research training programs funded by Boehringer Ingelheim and Charles River for veterinarians and veterinary students, and founded the Johns Hopkins University summer Veterinary Scholars Research Program and the summer Laboratory Animal Fellowship. She currently serves as an ad hoc consultant for AAALAC International, vice chair of the Scientific Advisory Committee for the American Association of Laboratory Animal Science, member of the Primate Care Committee of the American Society of Primatologists, member of the Association of Primate Veterinarians, and member of the advisory board for the Center for Alternatives to Animal Testing; previously, she served as chair of the Animal Welfare Advisory Board for the Morris Animal Foundation. Dr. Metcalf Pate is a diplomate of the American College of Laboratory Animal Medicine since 2011. In December 2022, she was appointed to a National Institutes of Health advisory committee to the director working group on novel alternative methods. Dr. Metcalf Pate received her B.A. from Boston University, her D.V.M. from Purdue University School of Veterinary Medicine, and her Ph.D. and comparative medicine fellowship training from Johns Hopkins School of Medicine.

Guo-li Ming, M.D., Ph.D. (NAM), is Perelman Professor of Neuroscience and a member of the Institute of Regenerative Medicine at the University of Pennsylvania School of Medicine. She received her medical training on child and maternal care from Tongji Medical University in China in 1994 and Ph.D. from the University of California, San Diego, in 2002. After her postdoctoral training at the Salk Institute for Biological Studies, Dr. Ming became an assistant professor at The Johns Hopkins University in 2003 and professor in 2011. The research in her laboratory centers on understanding the molecular mechanisms underlying neuronal development and its dysregulation using mouse systems and patient-derived induced pluripotent stem cells. Dr. Ming has received a number of awards, including the Charles E. Culpeper Scholarship in Medical Science in 2003, Alfred P. Sloan research fellowship in 2005, young investigator award from the Society for Neuroscience in 2012, and A. E. Bennett Research Award from the Society of Biological Psychiatry in 2014. She became a member of the National Academy of Medicine in 2019. Dr. Ming is cofounder of and sits on the scientific advisory board of 3Dnamics, a biotechnology company that generates disease-specific and organoid models for preclinical drug screening and efficacy/toxicity testing.

Steven Piantadosi, M.D., Ph.D., is a clinical trials methodologist and senior statistician in the Department of Surgery at Brigham and Women's Hospital, a member of the Dana-Farber Cancer Institute, and professor in residence at Harvard Medical School. He has been associate group chair for strategy and innovation since 2018 in the Alliance National Clinical Trials Network (NCTN) group, one of five cancer clinical trials groups supported by the National Cancer Institute. As of October 2022, Dr. Piantadosi serves as the contact principal investigator for the Alliance NCTN grant. From 2007 to 2017, he was the inaugural director of the Samuel Oschin Cancer Institute at Cedars-Sinai Medical Center and professor at the University of California, Los Angeles. From 2010 to 2017 he was a member of the National Academies National Cancer Policy Forum. Dr. Piantadosi served 20 years as founding division head for Biostatistics and Bioinformatics in the Cancer Center at the Johns Hopkins School of Medicine. His research has been in clinical trials design, methods, and applications in diverse fields including cancer, neurodegenerative disease, and emphysema. Dr. Piantadosi has advised numerous public and commercial entities regarding clinical trials and taught extensively in domestic and international venues for more than 30 years. Dr. Piantadosi holds a consulting contract with Janssen Pharmaceuticals to serve as chair of the data monitoring

board for an international clinical trial for prostate cancer. In addition, he serves as chair of a Data and Safety Monitoring Board for an international retinitis pigmentosa clinical trial sponsored by the National Eye Institute. Dr. Piantadosi serves as consultant to the MITRE Corporation for work related to electronic health record data and is also a consultant for a medical device startup, CrainiUS, focused on the intracranial delivery of drugs for gliomas.

John Quackenbush, Ph.D., is professor of computational biology and bioinformatics and chair of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health, and professor in the Channing Division of Network Medicine at Brigham and Women's Hospital and in the Department of Data Science at the Dana-Farber Cancer Institute. Dr. Quackenbush's Ph.D. was in theoretical physics, but in 1992 he received a fellowship to work on the Human Genome Project. This led him through the Salk Institute, Stanford University, and The Institute for Genomic Research (TIGR), before moving to Harvard in 2005. Dr. Quackenbush's research is funded by the National Institutes of Health and uses massive data to probe how many small effects combine to influence our health and risk of disease. He has published more than 320 scientific papers that have collectively been cited more than 85,000 times; among his honors is recognition in 2013 as a White House Open Science Champion of Change. In 2012, Dr. Quackenbush founded Genospace, a precision medicine software company providing data platforms to hospitals, diagnostic testing labs, and other groups. In 2017, Genospace was purchased by the Hospital Corporation of America. He currently serves on the scientific advisory boards for Caris Life Sciences, Olema Pharmaceuticals, 3x Genomics, Stitch Bio, and RenalytixAI.

Peter L. Strick, Ph.D. (NAS), is Thomas Detre Professor and chair, Department of Neurobiology; scientific director, University of Pittsburgh Brain Institute; director, Systems Neuroscience Center; and codirector, Center for Neuroscience, University of Pittsburgh. Dr. Strick cofounded the Neural Control of Movement Society (1990) and served as its conference cochair, program chair (1990–2007), and president (2007–2010). Dr. Strick has served on many national and international committees. He was elected scientific councilor (1996–2000) and treasurer (1998–2000) of the Society for Neuroscience. He was selected as section editor (1986–1995) and then editor in chief (1995–2002) of the *Journal of Neurophysiology*, and he currently serves as senior editor (since 2003) of *Cerebral Cortex* and on the editorial board (since 2016) of the *Proceedings of the National Academy of Sciences*. Dr. Strick's major awards include the C. J. Herrick Award from the American Association of Anatomists (1979); Javits Neuroscience Investigator Award from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (1986); Established Investigator Award from the National Alliance for Research on Schizophrenia and Depression (1995–1996); President's Award for Excellence and Leadership in Research, State University of New York Upstate Medical Center (1996); Senior Research Career Scientist Award from the Veterans Administration (1987–2015); University Distinguished Professor of Neurobiology (2011); Chancellor's Distinguished Research Award, Senior Scholar (2013); Linne Lecture, Uppsala University, Sweden (2017); Paul D. MacLean Award, American Psychosomatic Society (2018); Carnegie Science Award in the Life Sciences (2018); NIH Director's Transformative Research Award (2018); Krieg Cortical Kudos Discover Award, Cajal Club (2019); and Goldman-Rakic Prize, Brain & Behavior Research Foundation (2022). Dr. Strick was elected to the American Academy of Arts and Sciences (2004) and to the National Academy of Sciences (2012). His research focuses on four major areas: the generation and control of voluntary movement by the motor areas of the cerebral cortex; the motor and cognitive functions of the basal ganglia

and cerebellum; the neural basis for the mind-body connection; and unraveling the complex neural networks that comprise the central nervous system.

Jerrold Tannenbaum, J.D., is an established animal ethicist and lawyer and professor emeritus at the University of California, Davis, School of Veterinary Medicine, where he taught required courses in veterinary ethics and law from 1999 to 2013. Prior to this he taught at Tufts University School of Veterinary Medicine, where he helped found that school's signature program in ethics and values and its M.S. program in animals and public policy. Professor Tannenbaum completed graduate work in philosophy at Rockefeller University and Cornell University, and obtained his J.D. from Harvard Law School. His current primary areas of interest are animal research ethics and animal research law. Professor Tannenbaum has numerous publications in this area, including "Russell and Burch's 3Rs Then and Now: The Need for Clarity in Definition and Purpose" (with B. Taylor Bennett), which appeared in 2015 in the *Journal of the American Association for Laboratory Animal Science*, and "The Pursuit and Advancement of Knowledge as a Justification for the Use of Animals in Research," which appeared in 2019 in the *ILAR Journal*. He is also author of *Veterinary Ethics*, the first comprehensive book on veterinary ethics. Professor Tannenbaum has spoken widely on ethical and legal issues relating to animals to a variety of audiences ranging from veterinary students to humane societies. He is a member of the National Academies Institute for Laboratory Animal Research Standing Committee for the Care and Use of Animals in Research.

NATIONAL ACADEMIES STAFF

Autumn S. Downey, Ph.D. (*Study Director*), is a senior program officer with the Board on Health Sciences Policy. She joined the National Academies of Sciences, Engineering, and Medicine in 2012 and is currently directing a consensus study on nonhuman primate models in biomedical research, as well as a standing committee on personal protective equipment. She was formerly director of the Standing Committee on Medical and Epidemiological Aspects of Air Pollution on U.S. Government Employees and their Families. Other National Academies studies she has worked on include Frameworks for Protecting Workers and the Public from Inhalation Hazards; Meeting the Challenge of Caring for Persons Living with Dementia and Their Care Partners and Caregivers; Evidence-Based Practice for Public Health Emergency Preparedness and Response; Return of Individual-Specific Research Results Generated in Research Laboratories; Preventing Cognitive Decline and Dementia; A National Trauma Care System; Healthy, Resilient, and Sustainable Communities After Disasters; BioWatch PCR Assays; and Advancing Workforce Health at the Department of Homeland Security. Dr. Downey received her Ph.D. in molecular microbiology and immunology from the Johns Hopkins Bloomberg School of Public Health, where she also completed a postdoctoral fellowship at the school's National Center for the Study of Preparedness and Catastrophic Event Response. Prior to joining the National Academies, she was a National Research Council Postdoctoral Fellow at the National Institute of Standards and Technology, where she worked on environmental sampling for biothreat agents and the indoor microbiome.

Olivia C. Yost, M.Sc., is a program officer with the Board on Health Sciences Policy. She has supported multiple consensus study and standing committees related to the topics of laboratory animal research, respiratory protection, and occupational health. Prior to joining the National Academies in 2015, Ms. Yost worked as a research officer for ARCHIVE Global, where she managed evaluation activities for disease control programs in the Caribbean, West

Africa, and South Asia. Ms. Yost received her M.Sc. in the control of infectious diseases from the London School of Hygiene & Tropical Medicine, where her graduate research focused on developing rapid testing methodologies to identify failing wastewater infrastructure. She received her B.A. in history and communications from Franklin University Switzerland.

Susana Rodriguez, Ph.D., is a program officer with the Board on Animal Health Sciences, Conservation, and Research. She supports the Standing Committee for Care and Use of Animals in Research and the Roundtable on Science and Welfare in Laboratory Animal Use. Dr. Rodriguez received her Ph.D. in biological chemistry from the Johns Hopkins University School of Medicine (JHUSOM). Her doctoral research focused on developing chemical-genetic tools to control the spatial and temporal expression of metabolic enzymes involved in regulating lipid metabolism in mammalian cells. For her postdoctoral work, Dr. Rodriguez transferred to the Department of Physiology at JHUSOM to characterize the metabolic functions of a novel and highly conserved family of secreted proteins that are altered by nutritional, metabolic, and disease states.

Kyle Cavagnini, Ph.D., is an associate program officer with the Board on Health Sciences Policy. They currently staff the Forum on Drug Discovery, Development, and Translation. Dr. Cavagnini previously worked with the National Academies Board on Animal Health Sciences, Conservation, and Research, where they supported the Standing Committee for the Care and Use of Animals in Research and workshop committees engaged in the One Health field. Prior to joining the National Academies, Dr. Cavagnini completed a science policy fellowship with the Federation of American Societies for Experimental Biology and was a Fulbright Research Fellow to Norway. They earned their Ph.D. in biological chemistry from the Johns Hopkins University School of Medicine, where their doctoral research focused on genomic contributions to metabolic sensing in the liver and other tissues. They received undergraduate degrees in biochemistry and philosophy from the University of North Carolina at Asheville.

Kelsey R. Babik, M.P.H., is an associate program officer with the Health and Medicine Division at the National Academies of Sciences, Engineering, and Medicine. In addition to this study, she works on projects initiated by the Committee on Personal Protective Equipment for Workplace Safety and Health. This is a standing committee at the National Academies of Sciences, Engineering, and Medicine sponsored by the National Personal Protective Technology Laboratory of the National Institute for Occupational Safety and Health that provides a forum for discussion of scientific and technical issues relevant to the development, certification, deployment, and use of personal protective equipment, standards, and related systems to ensure workplace safety and health. Previously, at the Risk Sciences and Public Policy Institute of the Johns Hopkins Bloomberg School of Public Health, Ms. Babik worked on occupational health risk assessments for first responders. She is currently a part-time doctor of public health student at the University of Illinois Chicago. Ms. Babik has a B.S. in molecular biology from the University of Pittsburgh and an M.P.H. from the University of Maryland.

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Disclosure of Unavoidable Conflicts of Interest

The conflict-of-interest policy of the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/about/institutional-policies-and-procedures/conflict-of-interest-policies-and-procedures) prohibits the appointment of an individual to a committee like the one that authored this Consensus Study Report if the individual has a conflict of interest that is relevant to the task to be performed. An exception to this prohibition is permitted only if the National Academies determine that the conflict is unavoidable and the conflict is promptly and publicly disclosed.

When the committee that authored this report was established, a determination of whether there was a conflict of interest was made for each committee member given the individual's circumstances and the task being undertaken by the committee. A determination that an individual has a conflict of interest is not an assessment of that individual's actual behavior or character or ability to act objectively despite the conflicting interest.

Dr. Ashutosh Agarwal was determined to have a conflict of interest because of his patents related to microphysiological systems and his financial interests in Bio-Vitro LLC, a company that is commercializing organ-on-chip microfluidic devices that are amenable to large-scale manufacturing, with the goal of accelerating the development of disease models and novel therapeutics.

Dr. Szczepan Baran was determined to have a conflict of interest because of his employment as chief scientific officer at VeriSIM Life, a company that is commercializing an artificial intelligence–enabled platform for biosimulations to predict clinical outcomes and improve drug-related research and development.

Dr. Guo-li Ming was determined to have a conflict of interest because of her financial interests in 3Dnamics, a biotechnology company that generates disease-specific organoid models for preclinical drug screening and efficacy/toxicity testing.

In each case, the National Academies determined that the experience and expertise of the individual was needed for the committee to accomplish the task for which it was established. The National Academies could not find other available individuals who had the

equivalent experience and expertise and did not have a conflict of interest. Therefore, the National Academies concluded that the conflicts were unavoidable and publicly disclosed them on its website (www.nationalacademies.org).