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Diagnostic Biomarker

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Definition

A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

Examples

- Sweat chloride may be used as a diagnostic biomarker to confirm cystic fibrosis (Farrell et al. 2008).
- Certain cystic fibrosis transmembrane conductance regulator (CFTR) mutations may be used as diagnostic biomarkers in clinical trials evaluating treatment for cystic fibrosis, to select patients more likely to respond to particular treatments (i.e., to serve as a predictive biomarker) (Davies et al. 2013).
- Galactomannan may be used as a diagnostic biomarker to classify patients as having probable invasive aspergillosis for enrollment into clinical trials of antifungal agents for treatment of invasive aspergillosis (Marr 2016; U.S. Food and Drug Administration 2015).
- Blood sugar or hemoglobin A1c (HbA1c) may be used as a diagnostic biomarker to identify patients with Type 2 diabetes mellitus (DM) (U.S. Preventive Services Task Force 2016a).
- Repeated blood pressure readings obtained outside the clinical setting in adults 18 years and older may be used as a diagnostic biomarker to identify those with essential hypertension (U.S. Preventive Services Task Force 2016b).
- Glomerular filtration rate (GFR) may be used as a diagnostic biomarker to identify patients with chronic kidney disease (National Kidney Foundation 2002).
- Ejection fraction may be used as a diagnostic biomarker in patients with heart failure to identify patients with a subset of disease (those with low ejection fraction or preserved ejection fraction) (Yancy et al. 2013).
- Gene expression profiling may be used as a diagnostic biomarker to segregate patients with diffuse large B-cell lymphoma into subgroups with different tumor cell of origin signatures (Scott et al. 2014).

Explanation

Medical practice requires accurate diagnosis of diseases and conditions. Diagnostic biomarkers are used for the critical determination of whether a patient has a particular medical condition for which treatment may be indicated or whether an individual should be enrolled in a clinical trial studying a particular disease. As is becoming increasingly appreciated, many diseases have subtypes with markedly different prognoses or responses to a specific treatment. Various genetic markers, for example, can predict the likelihood of breast cancer recurrence after surgical tumor removal, i.e., they are prognostic biomarkers. Pathophysiologic markers, such as decreased or preserved ejection fraction in heart failure, can predict who will respond to specific treatments; i.e.,

it is a predictive biomarker. Genetic markers are often used to distinguish responders and non-responders to cancer treatments. Diagnostic biomarkers that identify disease subtypes thus often play critical roles when the results of diagnostic classification can be used as prognostic biomarkers and predictive biomarkers.

The importance of accurate diagnosis warrants assessment of the clinical performance of diagnostic biomarker tests. Typically, a test is evaluated against a reference diagnosis to calculate clinical sensitivity, i.e., the fraction of people with disease who test positive, and specificity, i.e., the fraction of people without the disease who test negative. For a perfect diagnostic biomarker test, all patients with the disease or disease subset would be detected (100% sensitivity) and no patients without the disease would be diagnosed with the disease (100% specificity). In practice, no biomarker test has perfect clinical and analytical performance.

It is important to characterize the expected performance of a diagnostic biomarker test under the defined conditions of use. This involves attention to the intent-to-diagnose population and the manner in which the test is applied to that population. For example, a single blood pressure measurement may not accurately diagnose hypertension, as the results of measurements can vary depending on the conditions under which measurements are taken (e.g., supine vs. erect, resting vs. exercise, home vs. clinical setting) as well as the current state of the patient (e.g., underlying disease state, hydration status, medications, comorbidities, stress). The intent-to-diagnose population, and particularly the prevalence of the disease or condition that the test aims to diagnose or detect in that population, is a major determinant of test performance as reflected in the metrics positive predictive value (PPV, i.e., the proportion of those who tested positive who actually have the disease or condition) and negative predictive value (NPV, i.e., the proportion of those who tested negative who actually do not have the disease or condition). PPV and NPV depend on the test sensitivity and specificity as well as the population prevalence of the disease or condition. If the prevalence in the intent-to-diagnose population is low, it is difficult to achieve high PPV; analogously, if the prevalence is very high, it is difficult to achieve high NPV.

Acceptable tradeoffs among performance characteristics such as sensitivity, specificity, PPV, and NPV will depend on the relative potential harms of false positive and false negative results. For example, if a diagnostic test is used for screening an asymptomatic apparently healthy population where prevalence of the target disease is very low, one generally favors tests with high specificity and PPV to avoid generating large numbers of false positive results that may trigger unnecessary medical interventions and possibly psychological harms. In contrast, if a test is used as part of a diagnostic workup for individuals at high risk of a disease for which early intervention has proven clinical benefit, then greater emphasis might be placed on a test's sensitivity and NPV.

In addition to clinical performance, robust analytical performance would be expected before a biomarker test can be considered acceptable as a clinical diagnostic. For example, qualified sites and operators running the same diagnostic biomarker test should obtain highly concordant results. Exceedingly poor analytical performance will necessarily diminish a diagnostic test's clinical performance.

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