FDA-NIH Biomarker Working Group

BEST (Biomarkers, EndpointS, and other Tools) Resource

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Food and Drug Administration (US)
Silver Spring (MD)

National Institutes of Health (US)
Bethesda (MD)

Food and Drug Administration (US), Silver Spring (MD)
National Institutes of Health (US), Bethesda (MD)

The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) are joint sponsors of the BEST (Biomarkers, EndpointS, and other Tools) Resource.

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Effective, unambiguous communication is essential for efficient translation of promising scientific discoveries into approved medical products. Unclear definitions and inconsistent use of key terms can hinder the evaluation and interpretation of scientific evidence and may pose significant obstacles to medical product development programs. Lack of clarity and consistency is also problematic in other scientific areas where FDA oversees product safety (e.g., foods and tobacco) to promote public health interests.

In the spring of 2015 the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to study endpoints and biomarkers. Working together with the goals of improving communication, aligning expectations, and improving scientific understanding, the two agencies developed the BEST (Biomarkers, EndpointS, and other Tools) Resource. The first phase of BEST comprises a glossary that clarifies important definitions and describes some of the hierarchical relationships, connections, and dependencies among the terms it contains.

The BEST glossary aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical research, clinical practice, medical product development, and in the regulation of products by FDA. Because the glossary is intended to be broadly applicable to multiple communities of users and stakeholders, its definitions address nuances of usage and interpretation for a wide variety of terms currently in use. Further, based on differing stakeholder needs, it has built in flexibility, when possible and appropriate, to accommodate those interests. NIH and FDA intend to use the definitions included in this glossary when communicating on topics related to its contents (e.g., biomarkers) to ensure a consistent use of the terms and therefore, a common understanding of the issues.

The BEST glossary is meant to be a "living" resource that will be periodically updated with additional terms and clarifying information. We welcome feedback, including specific proposed edits with rationale, from all stakeholders, including the scientific and medical communities, patients, providers, industry, and regulators, so that as we refine and elaborate on these terms, they will remain relevant, thus fostering consistent usage and ultimately help to accelerate development and refinement of medical products which lead to improvements in health outcomes. Suggested revisions will be considered on a regular basis.

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Contents of a Biomarker Description

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The biomarker description is a succinct but comprehensive summary intended to correctly identify the biomarker, its biologic plausibility (i.e., relevance to the disease or condition), and its measurement method. While not exhaustive, these key features of a biomarker's description convey important information to assess information from multiple sources (e.g., evaluating results and conclusions from data published by different laboratories). The description may include multiple important concepts as detailed below:

Biomarker Identity (name, unique identifier, acronym, source and type)

The name of the biomarker includes the specific analyte (e.g., fibrinogen), anatomic feature (e.g., joint angle), or physiological characteristic (e.g., blood pressure) that is measured. If applicable (e.g., molecular biomarkers), the unique identifier for the biomarker[1] and the commonly used acronym are useful information to ensure that two or more resources are referring to the same analyte. The specific source for the biomarker's assessment (e.g., urine, liver biopsy, chest radiograph, pulmonary function test) provides important context (e.g., reference ranges may vary depending on the source materials). The biomarker source also determines the biomarker type (e.g., molecular, histologic, radiographic, digital, or physiologic).

Biologic Plausibility

Providing a brief summary of the biological, physiological, or pathological pathway for the association of the biomarker with the disease or condition of interest provides a contextual linkage between a biomarker and its intended use. In addition, this information helps to delineate how multiple biomarkers may interplay as part of a common use (e.g., shared biochemical pathways leading to a common biologic or clinical phenotype).

Measurement Method

The measurement method (e.g., in vitro diagnostic platform [e.g., ELISA], MRI, echocardiogram) that will be used to measure, image, or otherwise quantify the biomarker and the units of quantification is critical information when comparing information from independent platforms. This information is helpful throughout biomarker development, including early discovery. Sufficient detail should be included to facilitate the interpretation of the results across multiple resources.

Example:

Biomarker Name	Kidney Injury Molecule 1[2]
Acronym	KIM-1
Unique Identifier	Uniprot: Q96D42
Source	Urine
Type	Molecular
Biologic Plausibility	Has been observed to increase in the presence of drug-induced acute tubular kidney injury
Measurement Method	ELISA
Units of Measurement	pg/ml

[1] Where relevant, the molecular identification, formal chemical name or, if listed in a library or other resource, the correct name or unique identifier, referencing the resource and version; such as from UniProt (http://uniprot.org/), HUGO Gene Nomenclature Committee (http://genenames.org), Protein Data Bank (http://rcsb.org/pdb/home/home.do), or Enzyme Commission (http://enzyme.expasy.org) or other curated, standardized resource.

[2] KIM-1 was qualified as a part of a panel. For a composite or panel of biomarkers, please include information for each member in the composite score or panel, including the accompanying biomarker description details for each.

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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Monitoring Biomarker

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Definition

A biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

Examples

- Hepatitis C virus ribonucleic acid (HCV-RNA) level may be used as a monitoring biomarker when assessing treatment response in patients with chronic hepatitis C (AASLD and IDSA 2016, July; AASLD and IDSA 2016, September).
- International normalized ratio (INR) or prothrombin time (PT) may be used as monitoring biomarkers for assessing whether the desired effect of anticoagulation has been attained in patients on warfarin (Holbrook et al. 2012).
- Monoclonal protein (M protein) level in blood may be used as a monitoring biomarker to evaluate whether individuals diagnosed with monoclonal gammopathy of undetermined significance (MGUS) are showing signs of progressing to other disorders, including some types of blood cancer which may require treatment (Kyle et al. 2002).
- Prostate-specific antigen (PSA) may be used as a monitoring biomarker when assessing disease status or burden in patients with prostate cancer (Freedland and Moul 2007; Sandler and Eisenberger 2007; Thompson et al. 2007).
- Cancer antigen 125 (CA 125) may be used as a monitoring biomarker when assessing disease status or burden during and after treatment in patients with ovarian cancer (Gundogdu et al. 2011; Rustin et al. 2001).
- HIV-RNA may be used as a monitoring biomarker to measure and guide treatment with antiretroviral therapy (ART) (AIDSinfo 2007).
- B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) may be used as monitoring biomarkers during follow-up to supplement clinical decision making in pediatric patients with pulmonary hypertension (Kheyfets et al. 2015; ten Kate et al. 2015).
- Blood concentrations of an addictive drug may be used as monitoring biomarkers in drug addiction prevention and treatment trials to measure abstinence and compliance (ASAM 2001).
- Serial measurements of symphysis-fundal height during pregnancy can be used during antenatal screening to detect fetal growth disturbances (Papageorghiou et al. 2016).
- Urinary concentration of tobacco specific nitrosamines (TSNAs) (e.g., total N-Nitrosonornicotine (NNN) and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) may be used as monitoring biomarkers for assessing exposure to tobacco and tobacco smoke (Yalcin and de la Monte 2016; Hecht 2002; IARC 2007; Hecht et al. 2008; Mallery et al. 2014; Park et al. 2015; Schick et al. 2017).

Explanation

A biomarker that is assessed repeatedly over time is called a monitoring biomarker and can be used to assess:

- Disease progression, including the occurrence of new disease effects, worsening of previously existing abnormalities, or change in disease severity or specific abnormalities
- Response of a disease or condition to a treatment, either favorable or unfavorable.

The scope includes biomarkers in a wide range of categories described in the BEST Resource (e.g., safety biomarkers, pharmacodynamic/response biomarkers, prognostic biomarkers). Biomarkers are usually assessed

repeatedly when there is interest in not only the measured value of the biomarker, but also in the rate of change over time, the magnitude of change, the relation of changes to individual or patient (e.g., genotype or demographic), or disease-related characteristics (e.g., disease severity, disease duration, and specific disease).

In clinical care settings or in the context of a clinical trial, monitoring biomarkers may be measured during one or more periods of a patient's clinical course – e.g., following diagnosis of a disease or condition and prior to intervention (e.g., to establish baseline characteristics, assess pre-treatment rate of progression), during the period in which an intervention is being delivered, or after delivery of the intervention has been completed. When assessed repeatedly, biomarker measurements may sometimes detect signs of disease or condition worsening, which may indicate deteriorating prognosis or a need for intervention. Biomarker monitoring during the course of an intervention can serve several purposes, including to determine how a drug is metabolized by a patient by monitoring drug concentration, to detect therapeutic effect or disease progression while on or following treatment, or to detect toxicity. Examples of these uses include measurement of PT and partial thromboplastin time (PTT) values to maintain warfarin or heparin levels within therapeutic range for patients undergoing anticoagulation treatment and monitoring of HCV-RNA levels to assess both the presence of hepatitis C infection that would benefit from treatment and evidence of response or non-response to treatment. Patients undergoing leflunomide and methotrexate therapy for rheumatoid arthritis are routinely assessed for evidence of liver toxicity by periodic measurement of liver enzymes. Serial imaging studies are used routinely for monitoring disease status in patients with solid tumors to detect regression or progression during or after therapy, or to detect recurrence after disease-free status is achieved with initial therapy.

Monitoring biomarkers are also used throughout medical product development, for example, in therapeutic or prevention trials of new drugs, biologics, or devices. Changes in biomarker measurements observed during or after treatment may provide supporting evidence of a pharmacodynamic effect or an early therapeutic response (see pharmacodynamic/response biomarker). A safety biomarker measured repeatedly in early phase clinical trials can be a type of monitoring biomarker for organ toxicity (see safety biomarker). Additionally, biomarkers are sometimes used in therapeutic or prevention trials to assess participant compliance with an assigned intervention. For example, the biomarker might be a blood level of the administered drug or it might be serum level of cotinine (an indicator of use of tobacco products) as part of an interventional trial that aims to prevent smoking. Thus, in addition to guiding clinical care, monitoring biomarkers may help to promote interpretability and credibility of interventional studies.

Monitoring biomarkers may be used for individual or population level surveillance for presence of diseases or medical conditions or risk of developing them. Monitored individuals may have no clinically apparent medical conditions or diseases, or they may have some medical condition or prior exposure that predisposes them to development of some new condition or disease. Healthy adults undergoing annual physical examinations are routinely monitored for levels of biomarkers such as serum cholesterol, blood glucose, and urine creatinine to evaluate risk for, and to detect emergence of, medical conditions such as hypercholesterolemia, diabetes, and impaired kidney function, respectively. The National Health and Nutrition Survey (NHANES)[1] conducts periodic examinations of individuals selected by a complex statistical sampling design from the U.S. population to learn about the health, including tobacco use, and diet of people in the United States. The Air Force Health Study (AFHS) was a congressionally mandated epidemiologic study designed to assess health effects of exposure to herbicides, particularly those with dioxin contaminants, used by Air Force personnel during the Vietnam conflict (Buffler et al. 2011). AFHS participants underwent periodic physical examinations to record clinical outcomes and serial collection of biospecimens, including blood, urine, semen, skin, fat, and stool samples, which could be analyzed for biomarkers of exposures (e.g., serum dioxin levels and epigenetic molecular markers of dioxin exposure) and indicators or risk factors for disease and other medical conditions (e.g., free

[1] http://www.cdc.gov/nchs/nhanes/

immunoglobulin light chains in plasma cell disease, paraoxonase 1 (PON1) in type 2 diabetes and aging, sperm counts in reproductive health) (IOM 2015; National Academies of Sciences, Engineering, and Medicine 2016).

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Pharmacodynamic/Response Biomarker

Created: December 22, 2016.

Definition

A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.

Examples

- Circulating B lymphocytes may be used as a pharmacodynamic/response biomarker when evaluating patients with systemic lupus erythematosus to assess response to a B-lymphocyte stimulator inhibitor (Stohl and Hilbert 2012).
- Blood pressure may be used as a pharmacodynamic/response biomarker when evaluating patients with hypertension, to assess response to an antihypertensive agent or sodium restriction (James et al. 2014).
- Serum LDL cholesterol may be used as a pharmacodynamic/response biomarker when evaluating patients with hypercholesterolemia, to assess response to a lipid-lowering agent or dietary changes (Stone et al. 2014).
- Hemoglobin A1c (HbA1c) may be used as a pharmacodynamic/response biomarker when evaluating patients with diabetes, to assess response to antihyperglycemic agents or lifestyle changes (American Diabetes Association 2016).
- Sweat chloride may be used as a pharmacodynamic/response biomarker when evaluating patients with cystic fibrosis, to assess response to cystic fibrosis transmembrane regulator (CFTR) potentiating agents (Durmowicz et al. 2013; Mayer-Hamblett et al. 2016).
- International normalized ratio (INR) may be used as a pharmacodynamic/response biomarker when evaluating a patient's response to warfarin treatment (Holbrook et al. 2012).
- Viral load may be used as a pharmacodynamic/response biomarker when evaluating response to antiretroviral treatment (AASLD and IDSA 2016, July; AASLD and IDSA 2016, September; DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2016).
- Urinary level of glycosaminoglycans may be used as a pharmacodynamic/response biomarker when evaluating the effect of enzyme replacement therapy for patients with mucopolysaccharidosis type 1 (Jameson et al. 2016).
- Left ventricular ejection fraction may be used as a pharmacodynamic/response biomarker when evaluating the influence of extracorporeal membrane oxygenation (ECMO) on cardiac function (Kimball et al. 1991).
- Standardized uptake value (SUV) as measured by 18FDG-PET/CT may be used as a pharmacodynamics/response biomarker when evaluating cancer patients with diffuse large B-cell lymphoma on treatment with diverse chemotherapeutic and/or molecularly targeted drugs (Kelloff et al. 2005; Wahl et al. 2009).

Explanation

A pharmacodynamic/response biomarker is a biomarker whose level changes in response to an exposure to a medical product or an environmental agent. A change in a pharmacodynamic/response biomarker, such as a circulating small molecule (e.g., serum creatinine, blood sugar) or protein, or a physiologic measure, such as pupil diameter, ejection fraction, heart rate, or QT interval, provides early evidence that a treatment might have an effect on a clinical endpoint of interest or can be used to assess a pharmacologic endpoint related to safety concerns. It can also provide useful information for patient management, e.g., whether to continue treatment or to adjust dose, or for medical product development, e.g., did the drug have the pharmacodynamic effect thought

to be related to clinical effect. Because of the serial nature of their assessment, pharmacodynamic/response biomarkers often fall under the category of monitoring biomarkers.

Pharmacodynamic/response biomarkers do not necessarily reflect the effect of an intervention on a future clinical event, i.e., they may not be accepted surrogate endpoints, but some are accepted in specific contexts: blood pressure, HbA1c, serum potassium, serum creatinine. Pharmacodynamic biomarkers can provide meaningful information about whether an intervention is biologically active, i.e., has the intended pharmacologic effect. Pharmacodynamic biomarkers are very important in the setting of early drug development trials, and can be used to measure the level of response to the intervention (as INR is for coumadin), and to guide clinical dose-response studies.

The main utility of pharmacodynamic/response biomarkers in clinical practice is to guide dosing or continued use of a drug or other intervention. For example, a biomarker like HbA1c is used to evaluate diabetes control following treatment with an antihyperglycemic agent. Such biomarkers may be used to gauge the level of response so that individual drug doses can be altered, or to identify whether therapies need to be added, subtracted or replaced. Pharmacodynamic/response biomarkers allow for more precise dose finding for therapeutic modalities. Biomarkers of coagulation, for example, are used to monitor warfarin therapy and adjust doses so that the biomarkers are kept within specific ranges. Because these biomarkers have been shown to correlate with clinical outcomes in atrial fibrillation, measuring coagulation parameters and adjusting doses can reduce the likelihood of bleeding complications and decrease the likelihood of stroke. In almost all cases in the clinical setting, pharmacodynamic/response biomarkers are monitored because there is, or is thought to be, a link between the biomarker and clinical outcomes.

In a medical product development setting, pharmacodynamic/response biomarkers may be useful to establish proof-of-concept that a drug produces a pharmacologic response in humans thought to be related to clinical benefit, and to guide dose-response studies. It is often very difficult to statistically power an early phase clinical trial to demonstrate a meaningful change in a clinical outcome, and many clinical outcomes require a long period of time before a meaningful change can be demonstrated. In these cases, pharmacodynamic/response biomarkers can provide evidence of target engagement. In addition, these biomarkers can be used in pharmacologic dose-ranging studies to determine which doses should be considered in trials that evaluate a clinical outcome. For example, B-lymphocyte suppression has been used to find doses of anti-CD20 monoclonal antibodies and other B-lymphocyte targeted therapies to determine what dose is required to maximally reduce this cell population, which is presumed to underlie the clinical benefits of these drugs in treating cancer.

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Predictive Biomarker

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Definition

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

Examples

- Squamous differentiation in non-small cell lung cancer may be used as a predictive biomarker to identify patients who should avoid treatment with pemetrexed, on which they are likely to have worse survival or progression-free survival outcome compared to treatment with other standard chemotherapies such as docetaxel or cisplatin in combination with gemcitabine (Scagliotti et al. 2009).
- Certain cystic fibrosis transmembrane conductance regulator (CFTR) mutations may be used as predictive biomarkers in clinical trials evaluating treatment for cystic fibrosis, to select patients more likely to respond to particular treatments (Davies et al. 2013).
- BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as predictive biomarkers when evaluating women with platinum-sensitive ovarian cancer, to identify patients likely to respond to Poly (ADP-ribose) polymerase (PARP) inhibitors (Ledermann et al. 2012).
- Human leukocyte antigen allele (HLA)–B*5701 genotype may be used as a predictive biomarker to evaluate human immunodeficiency virus (HIV) patients before abacavir treatment, to identify patients at risk for severe skin reactions (AIDSinfo 2007).
- Thiopurine methyltransferase (TPMT) genotype or activity may be used as a predictive biomarker when evaluating patients who may be treated with 6-mercaptopurine or azathioprine, to identify those at risk for severe toxicity because of high drug concentrations (PharmGKB 2016; Relling et al. 2011).
- Mutations in the BRCA1/2 genes may be used as predictive biomarkers for sensitivity to ionizing radiation because they may impair the function of the genes' protein products in the repair of double stranded DNA breaks, which are one type of damage induced by ionizing radiation (Pijpe et al. 2012).

Explanation

A predictive biomarker is used to identify individuals who are more likely to respond to exposure to a particular medical product or environmental agent. The response could be a symptomatic benefit, improved survival, or an adverse effect.

A familiar example of use of a predictive biomarker in medical product development is predictive enrichment of the study population for a randomized controlled clinical trial of an investigational therapy, in which the biomarker is used either to select patients for participation or to stratify patients into biomarker positive and biomarker negative groups, with the primary endpoint being the effect in the biomarker positive group (U.S. Food and Drug Administration 2012). If the biomarker is in fact predictive of a favorable outcome, then the effect of the investigational therapy compared to a control therapy (including no therapy) will be greater (or present at all) in patients with the biomarker or some level of the biomarker. When only a small fraction of the patients who receive the investigational therapy are expected to show a meaningful effect, identification of that small group using a predictive biomarker is critical to the feasibility of demonstrating the intervention's effectiveness (Betensky et al. 2002; Maitournam and Simon 2005). The notion of a predictive biomarker applies to a wide variety of interventions, including drugs, biologics, medical devices or procedures, and behavioral or dietary modifications for treatment or prevention of diseases or conditions.

The utility of predictive biomarkers is not limited to a clinical trial setting, as these biomarkers can also assist in informing patient care decisions, such as determining who might benefit from a particular treatment or selecting among multiple interventions. In the latter situation, evidence that a biomarker predicts the comparative effectiveness of an intervention should be accompanied by specification of the alternative interventions involved in the comparison.

Predictive biomarkers for effects of interventions may be characteristics of the individual's biological constitution ("host characteristics") or characteristics of the disease process or other medical condition. Biomarkers representing host characteristics are present irrespective of the individual's disease or medical condition status, such as germline DNA, HLA type or cytochrome P450 enzyme phenotype, renal or hepatic function, or metabolic characteristics. Examples of biomarkers characterizing a disease process or medical condition include protein levels in diseased tissues, mutations in tumors, low or preserved ejection fraction in heart failure, and serum protein levels in pregnancy. Predictive biomarkers for drugs are often chosen initially based on the mechanism of action of the drug and understanding of pathophysiology, but they could also be identified empirically, e.g., based on previous studies. Understanding the impact on outcome of both host and disease or condition characteristics is important for efficient development and optimal application of interventions.

Establishing that a biomarker is predictive for an intervention's effect generally requires a comparison of the intervention to a control treatment in individuals with and without the biomarker, usually in randomized trials. Although studying only biomarker positive patients would establish effectiveness of a particular intervention it does not specifically demonstrate the role of the biomarker. It is therefore generally appropriate to stratify patients in the randomized trial by presence or absence of the biomarker (if dichotomous). Randomization to treatment and control groups is usually important because demonstrating that individuals who are positive for a biomarker and receive an investigational therapy experience a better outcome than those who receive the same therapy but are negative for the biomarker does not establish that the biomarker is predictive. Differences in outcome associated with the biomarker could be due to prognostic abilities of the biomarker and may be present irrespective of the therapy received. The greater differences between treatment and control in the biomarker positive compared to biomarker negative groups are what establish the biomarker as predictive. (See also discussion in *Understanding Prognostic versus Predictive Biomarkers*).

Studies designed to evaluate a predictive biomarker should usually include patients with a range of biomarker values (or positive and negative for binary biomarkers). Sometimes there is sufficient prior evidence to strongly suggest that an investigational therapy will not be effective (or could even be harmful) in a certain subgroup of individuals defined by a biomarker; these circumstances may require excluding patients who are negative for the biomarker from trials of the investigational therapy. When a biomarker identifies a subgroup of patients who will benefit most from an investigational therapy, enrichment of a trial with individuals from that subgroup will provide increased statistical power for detection of the (larger) effect of that therapy; use of such an enrichment strategy will also affect the intended population to receive the therapy after its regulatory approval (U.S. Food and Drug Administration 2012).

The predictive biomarker concept can be extended beyond interventional trials to studies of exposures to environmental toxins, tobacco smoke, nicotine, alcohol, food additives, environmental or occupational radiation, or infectious agents or to studies of the unintended ancillary effects of interventions. In this document, an exposure is distinguished from an intervention in that it may occur passively (e.g., second- hand smoke or exposure to ultraviolet radiation from the sun during outside activities) or without intent to influence an affected system (e.g., kidney toxicity from exposure to aminoglycosides used to treat an infection in another organ). In the exposure setting, a predictive biomarker is one that is associated with increased or decreased likelihood of experiencing a particular outcome of interest when an individual is subjected to the exposure. The predictive biomarker can be used to assess degree of vulnerability to an exposure and can be viewed as an effect modifier.

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Prognostic Biomarker

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Definition

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

Examples

- BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as prognostic biomarkers when evaluating women with breast cancer, to assess the likelihood of a second breast cancer (Basu et al. 2015).
- Chromosome 17p deletions and TP53 mutations may be used as prognostic biomarkers when evaluating patients with chronic lymphocytic leukemia, to assess the likelihood of death (Gonzalez et al. 2011; Shanafelt et al. 2006).
- Increasing prostate-specific antigen (PSA) may be used as a prognostic biomarker when evaluating patients with prostate cancer during follow-up, to assess the likelihood of cancer progression (Roberts et al. 2001).
- Plasma fibrinogen may be used as a prognostic biomarker to select patients with chronic obstructive pulmonary disease at high risk for exacerbation and/or all-cause mortality for inclusion in interventional clinical trials (Miller et al. 2016; U.S. Food and Drug Administration 2016a).
- C-reactive protein (CRP) level may be used as a prognostic biomarker to identify patients with unstable angina or a history of acute myocardial infarction with a greater likelihood of recurrent coronary artery disease events (Ferreiros et al. 1999; Haverkate et al. 1997; Liuzzo et al. 1994; Nakachi et al. 2008; Pearson et al. 2003).
- Gleason score may be used as a prognostic biomarker when evaluating patients with prostate cancer to assess the likelihood of cancer progression (Epstein et al. 2016; Gordetsky and Epstein 2016).
- Total kidney volume may be used as a prognostic biomarker to select patients with autosomal dominant polycystic kidney disease at high risk for progressive decline in renal function for inclusion in interventional clinical trials (Grantham et al. 2006; U.S. Food and Drug Administration 2016b).

Explanation

A prognostic biomarker is one that indicates an increased (or decreased) likelihood of a future clinical event, disease recurrence or progression in an identified population. Prognostic biomarkers are measured at a defined baseline, which may include a background treatment. Many familiar examples of prognostic biomarkers occur in clinical contexts where an individual is diagnosed with a disease or condition and there is interest in assessing the likelihood of a future clinical event. Examples of future events include death, disease progression, disease recurrence, or development of a new medical condition. In oncology, biomarkers such as tumor size, number of lymph nodes positive for tumor cells, and presence of metastasis have traditionally been used to indicate prognosis. Increasingly, molecular indicators or signatures measured on tumors are being used in lieu of, or in addition to, these clinicopathologic characteristics. For patients who have previously suffered a heart attack, elevated blood pressure, evidence of diabetes, elevated LDL cholesterol, and low HDL cholesterol are examples of biomarkers that indicate an increased risk for another heart attack. For individuals with hypertension, concomitant evidence of diabetes is associated with an increased likelihood of cardiovascular events. The prognostic biomarker's association with outcome is present without reference to different interventions (i.e., predicts increased likelihood of an event without an intervention). However, the presence or strength of a prognostic association may vary depending on the specific clinical setting (e.g., background therapy, stage of

disease) and particular endpoint of interest, so it is important that prognostic biomarkers be described in the proper context.

Prognostic biomarkers are often used as eligibility criteria in clinical trials to identify patients who are more likely to have clinical events or disease progression. Thus, they are widely used as enrichment factors in drug development (U.S. Food and Drug Administration 2012). Many clinical trials of medical interventions have as their endpoint either an event rate or time-to-event. The statistical power for a time-to-event endpoint to assess treatment effect in a controlled clinical trial is driven by the planned effect size (i.e., hazard ratio for a time to event endpoint) and the planned number of events. Enrichment with patients who have a higher likelihood of experiencing an event will therefore increase statistical power. Analogous to this situation is the use of susceptibility/risk biomarkers for enrichment of prevention trial populations. In a treatment setting, prognostic biomarkers can contribute to decisions about whether or how aggressively to intervene with the treatment.

The term prognostic has not been used consistently in the biomedical community. Some have applied the term only in the clinical context of individuals who have already been diagnosed with a disease or other medical condition. Others would include among prognostic biomarkers those that indicate, for apparently healthy individuals, the likelihood of a future diagnosis or disease. This document makes a distinction between **prognostic biomarker** and **susceptibility/risk biomarker,** the latter defined here as applying to individuals *without* clinically apparent disease (or medical condition).

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Reasonably Likely Surrogate Endpoint

Created: September 25, 2017; Updated: September 23, 2020.

Definition

An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices. In the case of accelerated approval for drugs, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on the irreversible morbidity or mortality or other clinical benefit.[1]

Examples

- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis and have supported accelerated approval of drugs to treat tuberculosis.
- Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body and has supported accelerated approval of drugs to treat non-transfusion-dependent thalassemia (NTDT).
- Radiographic evidence of tumor shrinkage (response rate) and progression free survival in certain cancer types have been considered reasonably likely to predict an improvement in overall survival with certain therapies and have supported accelerated approval of drugs to treat these cancer types.
- Biochemical evidence of a clinically significant degree of improvement in alkaline phosphatase (ALP) at 12 months demonstrated in adequate and well controlled studies has been considered reasonably likely to predict decreased risk of liver transplant or death and has supported/ been the basis for evaluating the efficacy for an accelerated approval of a drug to treat adults with primary biliary cirrhosis and an inadequate response to ursodeoxycholic acid (UDCA), or as monotherapy in adults with primary biliary cirrhosis unable to tolerate UDCA.
- Functional serotype-specific antibodies against Streptococcus pneumoniae, as measured by the opsonophagocytic activity (OPA) assay, have been considered reasonably likely to predict prevention of pneumococcal pneumonia and invasive disease, and have supported accelerated approval for a preventive pneumococcal vaccine in adults.

Explanation

This glossary makes a distinction among three categories of endpoints under consideration to serve as surrogate endpoints (i.e., validated surrogate endpoint, reasonably likely surrogate endpoint, and candidate surrogate endpoint). The categories describe use of the endpoints for regulatory decision making in the U.S., based on the level of clinical validation. This discussion considers the use of "reasonably likely surrogate endpoints" in this context.

Randomized clinical trials testing the efficacy of new medical interventions that use as a primary endpoint a measure of clinical benefit provide the highest level of evidence for a clinical benefit, but the time and resources to demonstrate benefit on the endpoint directly are often substantial. Usually effects on surrogate endpoints are appealing because they can be detected far more rapidly or easily, or potentially less invasively, than the effect on a clinical outcome and often with far fewer patients. In situations where there is no effective treatment for a

[1] 21 CFR 314.510

serious illness, use of surrogate endpoints can bring new therapeutics more quickly to those who need them. Effects on surrogate endpoints do not provide direct evidence of a clinical benefit of a therapy. Reasonably likely surrogate endpoints sometimes fail to predict an actual benefit. This limitation underscores the importance of the post-market study to confirm the clinical benefit of the drug.

The accelerated approval of drug and biologic products is governed by the regulations stated in 21 CFR part 314 subpart H, 21 CFR part 601 subpart E and section 506 (c) of the Food, Drug and Cosmetic Act as amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012. The qualifying criteria for a drug (or biologic) to be considered under accelerated approval pathway for marketing in the US are that the drug is intended to treat a serious or life-threatening condition and provides a meaningful therapeutic benefit over available therapies. Approval can then be based on demonstration of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. It is expected that there will be empirical evidence that the observed change in the biomarker after the administration of a drug is likely to predict clinical benefit. This empirical evidence is disease specific and depends on the natural history of the disease. The adequacy of the empirical evidence to support the use of a reasonably likely surrogate endpoint is based on the biologic plausibility of the relationship between the disease and the biomarker and the magnitude of observed change in the biomarker that supports the relationship.

Safety Biomarker

Created: December 22, 2016.

Definition

A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

Examples

- Hepatic aminotransferases and bilirubin may be used as safety biomarkers when evaluating potential hepatotoxicity (Senior 2014).
- Serum creatinine may be used as a safety biomarker when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity (Wasung et al. 2015).
- Serum potassium may be used as a safety biomarker when evaluating patients on diuretics (decreased levels), angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or aldosterone antagonists (increased levels) (James et al. 2014; Roush and Sica 2016).
- Urinary kidney biomarkers (Kim-1, Albumin, Total Protein, β2 Microglobulin, Urinary Clusterin, Urinary Trefoil Factor 3 and Urinary Cystatin C) may be used as safety biomarkers in animal studies for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement (U.S. Food and Drug Administration 2009, U.S. Food and Drug Administration 2010).
- Neutrophil count may be used as a safety biomarker when evaluating patients on cytotoxic chemotherapy to adjust dose, determine the need to interrupt therapy, or consider the use of growth factors (Rizzo et al. 2010; Smith et al. 2015).
- Corrected QT interval (QTc) may be used as a safety biomarker to assess the potential for drugs to induce torsades de pointes (International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 2015; U.S. Food and Drug Administration 2005).
- HLA-B*1502 allele may be used as a safety biomarker to screen patients prior to initiating carbamazepine treatment, as those with the allele are at increased risk of serious and fatal skin reactions. HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk (Chung et al. 2004).

Explanation

Medical interventions and environmental exposures may have undesirable, potentially harmful, or overtly toxic effects. Common to all safety biomarkers is the ability to detect or predict these adverse drug or exposure effects. In some cases, the toxicity is signaled by the detection of or change in a biomarker, allowing dose modification or treatment interruption before toxicity becomes severe, e.g., measuring granulocyte count while using clozapine or serum potassium while using a diuretic (see monitoring biomarker). In other cases the safety biomarker can indicate needed treatment, e.g., hypokalemia with a diuretic can indicate need for potassium supplementation, and hyperkalemia with an aldosterone antagonist can indicate need for dose adjustment or increase in loop diuretics. Periodic monitoring of such biomarkers is required for many drugs to ensure that their potential toxicity is detected and managed. Ideally, a safety biomarker would signal developing toxicity, e.g., drug induced organ injury, prior to clinical signs and before any irreversible damage occurs. Examples include monitoring creatinine phosphokinase for drugs that can cause muscle damage, serum creatinine for potentially nephrotoxic drugs, and transaminases for potentially hepatotoxic drugs. Sometimes effects on biomarkers indicate potential serious (even if rare) toxicity. Observation of even a few patients with elevated transaminases

accompanied by elevated bilirubin predicts the occurrence of serious liver injury (i.e., "Hy's Law"), an unacceptable risk for most drugs.

In addition, safety biomarkers can be used to identify patients for whom particular therapies should not be initiated because of significant safety risks. For example, deficiencies of metabolizing enzymes can identify individuals at risk for toxicity unless drug dose is decreased or identify patients who will not respond to a critical treatment because they cannot make the active metabolite (e.g., thiopurine methyltransferase (TPMT) genotype is used to identify patients who should not be given 6-mercaptopurine or azathioprine because severe toxicity due to high drug concentrations may occur; patients with HLA-B*5701 should not be given abacavir due to hypersensitivity reactions).

At a population level, biomarker measurements can identify persons affected by exposure to certain environmental agents, prompting public health policies or interventions to control or mitigate risk. For example, serum lead levels may be assessed to detect exposure to lead or urinary cotinine levels may be assessed to detect exposure to nicotine (i.e., cigarette smoke). Results from environmental safety biomarker assessments can initiate a search for the source of the exposure, followed by a public health intervention.

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Susceptibility/Risk Biomarker

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Definition

A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

Examples

- BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer (Struewing et al. 1997; Thorlacius et al. 1998).
- Factor V Leiden may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop deep vein thrombosis (DVT) (Kujovich 2011).
- Apolipoprotein E (APOE) gene variations may be used as susceptibility/risk biomarkers to identify individuals with a predisposition to develop Alzheimer's disease (Chartier-Harlin et al. 1994; Genin et al. 2011).
- Infection with certain human papillomavirus (HPV) subtypes may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop cervical cancer (Khan et al. 2005; Schiffman et al. 2011).
- C-reactive protein (CRP) level may be used as a susceptibility/risk biomarker to identify adult patients with a greater likelihood of incident coronary disease (Greenland et al. 2010; Pearson et al. 2003; Ridker et al. 2007; Ridker et al. 2008).
- Urinary concentration of tobacco specific nitrosamines (TSNAs) (e.g., total N-Nitrosonornicotine (total NNN) and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)) may be used as susceptibility/risk biomarkers to identify those at greater likelihood of cancer development (Hecht 2002; Hecht et al. 2008; Khariwala et al. 2013; Yuan et al. 2011; Park et al. 2015; Nilsson 2011; U.S. Department of Health and Human Services 2014, Yalcin and de la Monte 2016).

Explanation

A susceptibility/risk biomarker is a biomarker that is associated with an increased, or in some cases, decreased chance of developing a disease or medical condition in an individual who, from a clinical standpoint, does not yet have that disease or medical condition. An example of a susceptibility/risk biomarker is a genetic biomarker that indicates whether an individual has an increased likelihood of developing cancer later in life. This is in contrast to prognostic biomarkers, which indicate an increased likelihood of a specific clinical event in an individual already diagnosed with a disease or medical condition, and diagnostic biomarkers, which may confirm whether a disease is actually present. Susceptibility/risk biomarkers may be detected many years – in some cases decades – before the appearance of clinical signs and symptoms. Susceptibility/risk biomarkers do not describe a relationship to any specific treatment.

A familiar example of a susceptibility/risk biomarker is elevated low-density lipoprotein (LDL) cholesterol levels, which identify an increased risk of coronary artery disease. Virtually all cardiovascular risk models include LDL cholesterol to estimate the likelihood of having a cardiovascular event by some future time point. Additional factors such as high-density lipoprotein cholesterol levels, diabetes, age, sex, smoking status, and family history are also routinely considered in models of risk to improve the accuracy of the predictions.

The main utility of susceptibility/risk biomarkers in clinical practice is to guide preventive strategies. A susceptibility/risk biomarker like BRCA1/2 mutation is used to evaluate the likelihood of developing breast and

ovarian cancers. Such biomarkers may be used to determine whether lifestyle, nutritional, or other preventive interventions are indicated. Susceptibility/risk biomarkers may also identify individuals for whom more aggressive surveillance for the presence of disease is needed, such as more frequent colonoscopy or mammography to screen for cancers. The utility of a susceptibility/risk biomarker depends in part on whether there are interventions available to modify risk of disease.

In a medical product development setting, susceptibility/risk biomarkers may be useful for clinical trial enrichment, in the same way that prognostic biomarkers would be used. Often, in a primary prevention setting, it is very difficult to accrue enough clinical events to make clinical trials feasible. Enriching preventive clinical trials for those patients who are most likely to develop a particular disease may therefore be necessary, particularly for the evaluation of chemoprevention therapies or targeted use of vaccines. This allows for 1) the trial to be feasibly conducted by enriching for a population that may be more likely to develop the disease or medical condition and 2) preventive interventions with potential side effects to be appropriately targeted to strike the right balance of benefit and risk.

Susceptibility/risk biomarkers share many properties with prognostic biomarkers insofar as they indicate risk for some future occurrence of a disease-related event. However, the main distinction is that prognostic biomarkers are used in individuals who already have been diagnosed with a particular disease, while susceptibility/risk biomarkers could be used in individuals who otherwise appear healthy. The line distinguishing these types of biomarkers may not be so clear in some instances. For example, a susceptibility/risk biomarker and a prognostic biomarker could forecast the same event, i.e., a myocardial infarction. However, in this example, atherosclerosis begins to develop early in life. The point at which an individual is "diagnosed" as having a disease is more a function of developing clinically overt signs and symptoms (e.g., angina). Regardless, the screening or intervention strategies could differ between someone who appears healthy and someone who has established coronary artery disease.

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Understanding Prognostic versus Predictive Biomarkers

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A variety of factors influence a patient's clinical outcome, including intrinsic characteristics of the patient, disease, or medical condition, and the effects of any treatments that the patient receives. Some of the intrinsic characteristics may be reflected as prognostic biomarkers, i.e., biomarkers used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest, and others as predictive biomarkers, i.e., biomarkers used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent. Prognostic biomarkers and predictive biomarkers cannot generally be distinguished when only patients who have received a particular therapy are studied. Some biomarkers are both prognostic and predictive. Prognostic biomarkers are often identified from observational data and are regularly used to identify patients more likely to have a particular outcome.

To identify a predictive biomarker, there generally should be a comparison of a treatment to a control in patients with and without the biomarker. However, there are circumstances in which preclinical and early clinical data provide such compelling evidence that a new treatment will not work in patients without the biomarker that definitive clinical trials are performed only in populations enriched for the putative predictive biomarker. An illustration of such a situation was the development of the BRAF inhibitor vemurafenib for treatment of patients with late-stage melanoma that is positive for the BRAF V600E mutation.

Distinguishing prognostic biomarkers and predictive biomarkers can be difficult, as the following examples illustrate. Considering a simple example involving a survival outcome and binary biomarker, Figure 1A illustrates how a difference in survival distribution associated with biomarker status for patients who received an experimental therapy might be misinterpreted as evidence that patients who are biomarker positive receive greater benefit from that therapy, in the absence of survival curves for patients receiving standard or no therapy. In this and subsequent figures, assume that patients have been randomized to receive either the experimental or standard therapy. Superimposing onto the survival curves in Figure 1A a new pair of survival curves reflecting the outcomes of patients who received a standard therapy reveals that the same survival differences according to biomarker status exist with standard therapy (Figure 1B). Therefore, the biomarker illustrated in Figures 1A and 1B is prognostic but not predictive and will not be helpful in choosing between standard and experimental therapy. In contrast, Figure 2A illustrates a scenario in which the biomarker might at first appear to not provide information useful in deciding whether to administer the experimental therapy, but with full analysis the biomarker is predictive. The biomarker is a negative prognostic biomarker as seen in the poorer survival in Figure 2B in patients who are positive for the biomarker and are given standard treatment. Figure 2B leads to the correct conclusion that the biomarker is indeed predictive because patients who are biomarker positive (and do worse on standard therapy) have a clear benefit from the experimental therapy and do as well as biomarker negative patients on that therapy. There is no difference in survival on the two treatments for patients who are biomarker negative.

Additional considerations may apply when evaluating the clinical utility of a predictive biomarker for selecting between two therapy options. Figure 3 depicts a situation in which the experimental therapy leads to better survival for both the biomarker positive and negative patients, albeit with different magnitude of benefit. Unless toxicity or other costs overshadow the survival benefits experienced in one of the subgroups, it is likely that the experimental therapy would be preferred over the standard therapy for all patients and the biomarker might not be useful for selecting between these two treatments. In statistical terms, Figure 3 conveys the concept of a quantitative treatment-by-biomarker interaction. Figure 4 illustrates an ideal type of predictive biomarker in which there is a clear benefit of the experimental treatment in one biomarker subgroup (positive) but a clear lack of benefit, or potentially even slight harm, from the experimental therapy in the other biomarker subgroup

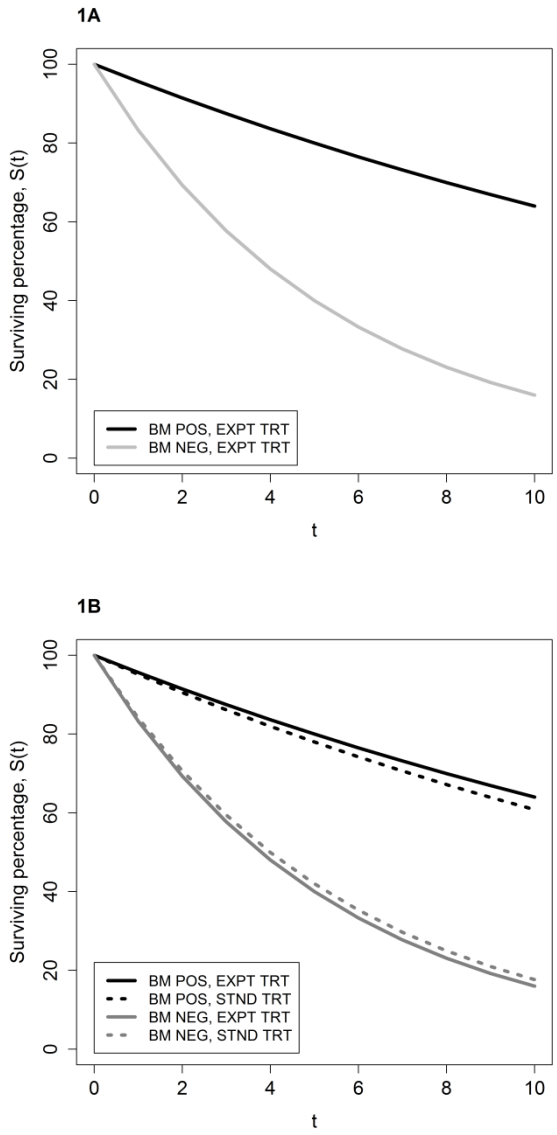

Figure 1. Example of a biomarker that is prognostic but not predictive. Assume that patients have been randomized to the experimental and standard therapies. A) For patients receiving the experimental therapy, those who are positive for the biomarker (black curve) survive longer than those who are negative for the biomarker (gray curve). B) The biomarker is associated with the same difference in survival for those patients receiving the standard therapy (black dashed curve versus gray dashed curve); therefore, it is prognostic. The biomarker is not predictive for benefit of the experimental therapy (solid curves) relative to the standard therapy (dashed curves) because within each biomarker subgroup the survival distribution is the same regardless of treatment received.

(negative). This reflects the statistical concept of a qualitative treatment-by-biomarker interaction; such biomarkers may be particularly useful for treatment selection.

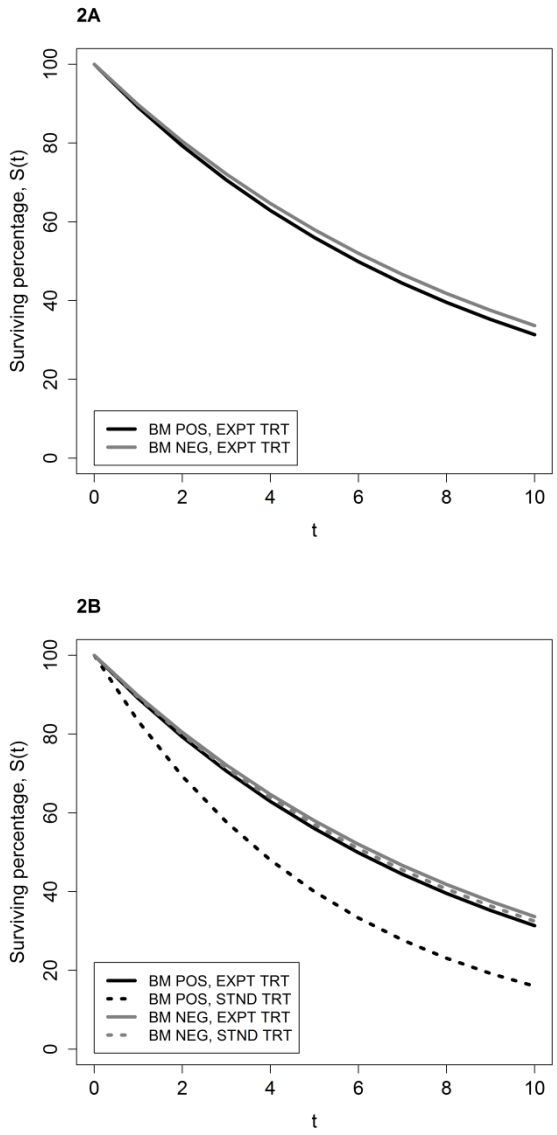

Figure 2. Example of a biomarker that is both prognostic (negatively) and predictive. Assume that patients have been randomized to the experimental and standard therapies. A) For patients receiving the experimental therapy, those who are positive for the biomarker (black curve) have survival similar to those who are negative for the biomarker (gray curve). B) For patients receiving the standard therapy, those who are positive for the biomarker have shorter survival (black dashed curve) compared to those who are negative for the biomarker (gray dashed curve); therefore, the biomarker is negatively prognostic. The biomarker is also predictive for benefit of the experimental therapy (solid curves) relative to the standard therapy (dashed curves) because survival for patients who are positive for the biomarker is substantially longer for those receiving the experimental therapy (black solid curve) compared to standard therapy (black dashed curve); whereas, for patients who are negative for the biomarker (gray curves) the survival distribution is the same regardless of treatment received.

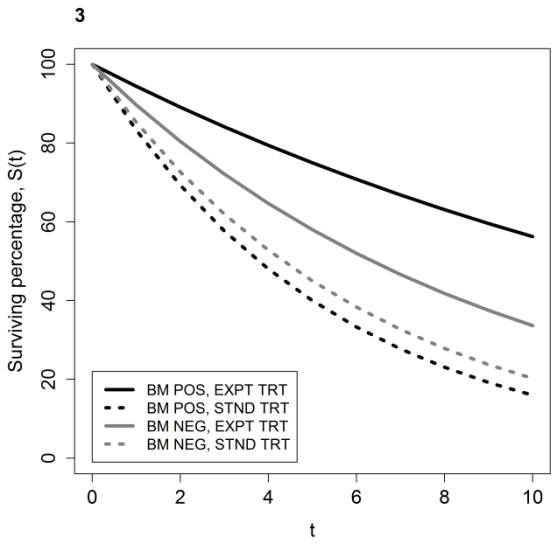

Figure 3. Example of a predictive biomarker that exhibits a quantitative treatment-by-biomarker statistical interaction. Assume that patients have been randomized to the experimental and standard therapies. Within each biomarker subgroup (black curves for biomarker positive and gray curves for biomarker negative), survival is substantially longer for patients who receive the experimental therapy (solid curves) compared to standard therapy (dashed curves). The magnitude of the increase in survival for those receiving experimental therapy compared to standard therapy is numerically larger for those who are positive for the biomarker than for those who are negative for the biomarker.

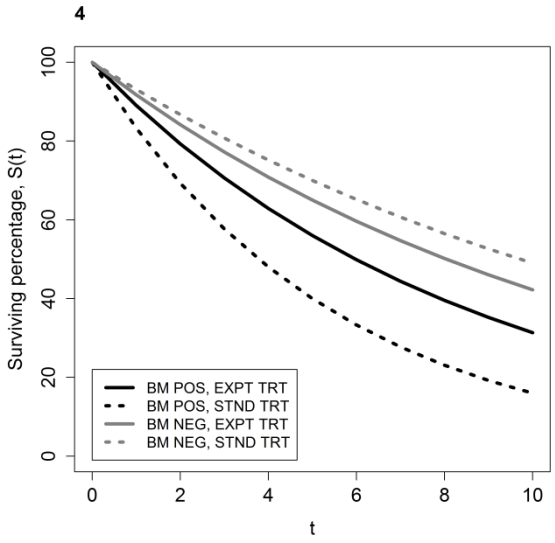

Figure 4. Example of a predictive biomarker that exhibits a qualitative treatment-by-biomarker statistical interaction. Assume that patients have been randomized to the experimental and standard therapies. For patients who are positive for the biomarker (black curves), survival is substantially longer for patients who receive the experimental therapy (solid black curve) compared to standard therapy (dashed black curve); whereas, for patients who are negative for the biomarker (gray curves), survival is about the same or slightly shorter for patients who receive the experimental therapy (solid gray curve) compared to standard therapy (dashed gray curve).

Validated Surrogate Endpoint

Created: September 25, 2017; Updated: November 13, 2020.

Definition

An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit. A validated surrogate endpoint can be used to support marketing approval of a medical or tobacco product in a defined context without the need for additional studies to demonstrate the clinical benefit directly. Although the term has been used in a conceptually broader way, from a U.S. regulatory standpoint, a validated surrogate endpoint almost always refers to a biomarker.

Examples

- Hemoglobin A1c (HbA1c) reduction is a validated surrogate endpoint for reduction of microvascular complications associated with diabetes mellitus and has been used as the basis for approval of drugs intended to treat diabetes mellitus.
- HIV-RNA reduction is a validated surrogate endpoint for human immunodeficiency virus (HIV) clinical disease control and has been used as the basis for approval of drugs intended to treat HIV.
- Low-density lipoprotein (LDL) cholesterol reduction is a validated surrogate endpoint for reduction of cardiovascular events and has been used as the basis for approval of statins and other LDL-lowering drugs such as PCSK9 inhibitors and ezetimibe.
- Blood pressure reduction is a validated surrogate endpoint for reduction in rates of stroke, myocardial infarction, and mortality and has been used as the basis for the approval of drugs and in pivotal trials of medical devices intended to treat hypertension.
- Serum uric acid reduction is a validated surrogate endpoint for improvement of gout symptoms and has been used as the basis for approval of drugs to treat gout.
- Anti-Hepatitis B surface antigen antibody level is a validated surrogate endpoint that predicts protection against primary hepatitis B infection and has been used as the basis for approval of vaccines used to prevent hepatitis B infection.

Explanation

This glossary makes a distinction among three categories of endpoints under consideration to serve as surrogate endpoints (i.e., validated surrogate endpoint, reasonably likely surrogate endpoint, and candidate surrogate endpoint). The categories describe use of the endpoints for regulatory decision making in the U.S., based on the level of clinical validation. This discussion considers the use of "validated surrogate endpoints" in this context.

Randomized clinical trials testing the efficacy of new medical interventions that use as a primary endpoint a measure of clinical benefit provide the highest level of evidence for a clinical benefit, but the time and resources to demonstrate benefit on the endpoint directly are often substantial. Usually effects on surrogate endpoints are appealing because they can be detected far more rapidly or easily, or potentially less invasively, than the effect on a clinical outcome and often with far fewer patients. In situations where there is no effective treatment for a serious illness, use of surrogate endpoints can bring new therapeutics more quickly to those who need them. Validated surrogates have also proven useful for evaluation of new drugs in established drug classes, such as anti-hypertensives, diabetic treatment medications, and HMGCoA reductase inhibitors, where outcome studies against placebo would be unethical and non-inferiority studies with certain clinical outcomes would be very long, costly and potentially infeasible. In addition, validated surrogate endpoints have been used to assess harm (e.g., Hy's Law as a predictor of hepatic toxicity or QTc prolongation as a predictor of TdP arrhythmias).

Biomarkers provide a rich pool of candidate alternative endpoints, but in order for a biomarker to be considered a validated surrogate endpoint in a specific clinical context, there must be evidence to demonstrate that an effect on the surrogate endpoint reliably predicts the clinical effectiveness of a medical product. This is important in a regulatory setting, as a validated surrogate endpoint can be used as the basis for approval of a medical product without the need for additional studies to demonstrate the clinical benefit. Generally, required evidence includes a combination of a clear mechanistic rationale and in most cases, data from multiple randomized clinical trials showing that the effect on the surrogate endpoint predicts the effect on the clinical outcome of primary interest. Observational studies can provide supportive data for the surrogate endpoint's validation, but cannot prove etiology, causation, or mechanism and therefore generally cannot alone validate a surrogate endpoint.

Historically there have been examples of mechanistically plausible surrogate endpoints supported by epidemiologic findings that have not predicted a clinical benefit in controlled clinical trials. For example, after an acute myocardial infarction, a number of ventricular premature beats per hour greater than 10 is a strong predictor of an increased risk of sudden death. The Cardiac Arrhythmia Suppression Trials (CAST 1 and 2) used the drugs encainide, flecainide, and ethmozine to substantially lower ventricular premature beats (VPB) rates, but the three drugs markedly increased mortality. This example illustrates that correlation between a biomarker and the endpoint intended to assess clinical benefit across individuals (i.e., the biomarker is a "correlate") is necessary but not sufficient to conclude that the biomarker is a validated surrogate endpoint that can be used as a replacement for the endpoint intended to assess clinical benefit in clinical trials (i.e., the biomarker is a "trial-level" surrogate endpoint). This phenomenon might occur because therapies have multiple mechanisms of action or have unanticipated, or "off-target," effects that have different impacts on various endpoints.

There are, however, some cases in which the biomarker is directly in the disease pathway or is the disease itself. In such circumstances, the surrogate endpoint may be considered a validated surrogate endpoint, sometimes even without extensive empirical clinical evidence.

1. Declining kidney function manifests as elevated serum creatinine and decreased glomerular filtration rate and is often progressive. When this occurs in renal disease due to conditions such as diabetes, hypertension or autoimmune disease, reduction in the decline of renal function has been accepted as a validated surrogate endpoint for evaluation of treatments intended to slow the rate of decline of renal function. Two angiotensin receptor blockers, losartan and irbesartan were shown to have such an effect. In the studies that showed this effect, longer follow up also showed a reduction in the rate of end stage renal disease.
2. In the treatment of hepatitis C, because progression of liver disease occurs over a long period of time, clinicians use sustained virologic response (SVR) to determine treatment success and it is considered a virologic cure. Sustained virologic response 12 weeks after treatment (SVR12) has been considered a validated surrogate and is used as the primary endpoint in clinical trials based on numerous observational cohorts showing strong correlations between SVR assessed at earlier and later time points and multiple clinically important outcomes.

Validation

Created: November 14, 2017; Updated: November 16, 2020.

For biomarkers and clinical outcome assessments (COAs) alike, adequate validation is important for ensuring that a test, tool, or instrument is adequate for its proposed use.

For biomarkers, it is critical to establish that the test measures what it was intended to measure (i.e., analytical validation) and that the biomarker (through its test) has the ability to predict or measure the relevant clinical concept (i.e., clinical validation). By establishing whether biomarkers (and the tests used to assess them) are fit-for-purpose, validation informs essentially any potential use of a biomarker in all the biomarker categories.

For COAs, it is critical to establish that the test, tool, or instrument measures the clinical outcome it is intended to measure and that the performance of the COA (through its test, tool, or instrument) can be relied upon to provide a given interpretation in the specified context of use (i.e., it is fit-for-purpose). COA validation includes evaluation of evidence supporting that the performance of the COA meeting multiple prespecified criteria, including whether all of the important aspects of the concept (e.g., disease-related symptoms or physical functioning) are reflected in the test, tool, or instrument; whether the COA's measurements are sufficiently sensitive to reflect changes in the concept; and whether those changes can be interpreted to reflect clinically meaningful changes in the concept).

The importance of validation is shown in the following uses:

- A prognostic biomarker may be used to enrich for patients with unfavorable prognosis in order to increase the statistical power of a clinical trial. Use of an analytically invalid test or non-informative prognostic biomarker could lead to failure to show a treatment effect because of insufficient enrichment for patients having higher likelihood of events which could result in inadequate statistical power.
- A predictive biomarker may be used to identify patients who are likely to respond to the treatment. However, the use of an analytically invalid test or non-informative predictive biomarker could lead to an underpowered trial due to smaller than expected treatment effect.
- A COA may be used for an outcome assessment in a medical product development program.
    - The use of a COA with insufficient sensitivity to detect change could result in clinical trials that fail to detect a treatment effect when one exists.
    - The use of a COA that assesses only a subset of key symptoms of a disease, but purports to assess all the key symptoms of a disease, could lead to erroneous interpretation of a medical product's clinical benefit.

Certain practices are essential to any validation effort. First is specifying the biomarker or clinical outcome of interest and specifying the particular test, tool or instrument that is the object for validation. Next is stating clearly the purpose, including the setting, for which the test, tool, or instrument will be used and understanding the potential benefits and risks associated with that use. The benefits and risks of using the biomarker or COA for the stated purpose inform the kind and amount of evidence needed and the criteria for concluding that the test, tool, or instrument is fit-for-purpose. For example, using a biomarker as a surrogate endpoint as the basis for approval has implications that differ from using a biomarker for prognostic enrichment in a trial, because the degree of uncertainty would differ between these two use cases. For examples of how one may validate a surrogate endpoint, see discussion of the term "validated surrogate endpoint".

Typically, data from exploratory and discovery studies are not sufficient for biomarker validation. Instead, a process for collecting and analyzing information about the analytical and clinical performance of the test, tool, or instrument is devised and carried out.

COA validation evaluates qualitative and quantitative evidence linking the COA to a clinically meaningful concept of health. For example, qualitative evidence (e.g., evidence derived from input from the relevant

stakeholders) is useful to ensure the COA's content (e.g., items, tasks) reflects all the important aspects related to the concept (e.g., disease-related symptoms or physical functioning) in the given context of use. Quantitative evidence is typically used to evaluate assumptions about the COA's method of generating a score or rating and about sensitivity to clinically meaningful changes in the concept.

It is important to note that validation is a process that is related to a specific intended purpose. Therefore, a biomarker or COA that has been determined to be fit-for-purpose for a non-regulatory use, or a given regulatory purpose, is not necessarily sufficient for another regulatory purpose, such as those needed for marketing approval or qualification.

Glossary

Created: January 28, 2016; Updated: January 25, 2021.

Terms and Definitions

accelerated approval

Regulatory mechanism by which new drugs[1] meant to treat serious, life-threatening diseases and that provide meaningful therapeutic benefit to patients over existing treatments can be approved on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a reasonably likely surrogate endpoint or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (intermediate clinical endpoint). Postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. For more information, see also chapter on Reasonably Likely Surrogate Endpoint.

Relevant Links:

FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

analytical validation

A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness. For more information, see also chapter on Validation.

assay

An analytic procedure for detecting or measuring the presence, amount, state or functional activity of a biomarker. An assay is one component of a test, tool, or instrument.

Assessment

The interpretation or the evaluation of the measurement.

biomarker

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives. Categories of biomarkers include:

- susceptibility/risk biomarker
- diagnostic biomarker
- monitoring biomarker
- prognostic biomarker
- predictive biomarker

[1] References to drugs or drug products include both human drugs and biological drug products regulated by the Food and Drug Administration's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research unless otherwise specified.

- pharmacodynamic/response biomarker
- safety biomarker

For more information, see also chapter on Contents of a Biomarker Description.

Relevant links:

FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

FDA/Center for Drug Evaluation and Research Biomarker Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Drug Development Tools (DDT) Qualification Programs Webpage

FDA/Center for Devices and Radiological Health Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff: Medical Device Development Tools

FDA/Center for Devices and Radiological Health Medical Device Development Tools (MDDT) Webpage

candidate surrogate endpoint

An endpoint still under evaluation for its ability to predict clinical benefit.

clinician-reported outcome

A type of clinical outcome assessment. A measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient. ClinRO measures include:

- Reports of particular clinical findings (e.g., presence of a skin lesion or swollen lymph nodes) or clinical events (stroke, heart attack, death, hospitalization for a particular cause), which can be based on clinical observations together with biomarker data, such as electrocardiogram (ECG) and creatine phosphokinase (CPK) results supporting a myocardial infarction
- Rating scales, such as:
  - Psoriasis Area and Severity Index (PASI) for measurement of severity and extent of a patient's psoriasis
  - Hamilton Depression Rating Scale (HAM-D) for assessment of depression

clinical benefit

A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.

clinical outcome

An outcome that describes or reflects how an individual feels, functions or survives.

clinical outcome assessment

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs.

- clinician-reported outcome
- observer-reported outcome

- patient-reported outcome
- performance outcome

Relevant links:

FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

FDA/Center for Drug Evaluation and Research Clinical Outcome Assessment Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Drug Development Tools (DDT) Qualification Programs Webpage

FDA/Center for Devices and Radiological Health Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff: Medical Device Development Tools

FDA/Center for Devices and Radiological Health Medical Device Development Tools (MDDT) Webpage

clinical utility

The conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.

clinical validation

A process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest. For more information, see also chapter on Validation.

ClinRO

See clinician-reported outcome.

COA

See clinical outcome assessment.

COU

See context of use.

companion diagnostic

A medical device, usually an in vitro diagnostic (IVD) device, that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of a companion diagnostic with a therapeutic product is typically stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.

Relevant links:

FDA/FDA/Center for Devices and Radiological Health Companion Diagnostics Webpage

FDA/FDA/Center for Devices and Radiological Health List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) Webpage

concept

In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture (or reflect).

context of use

A statement that fully and clearly describes the way the medical product development tool is to be used and the regulated product development and review-related purpose of the use.

diagnostic biomarker — 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. For more information, see also chapter on Diagnostic Biomarker.

digital health technology — A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products.

endpoint

A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

expedited access

A voluntary program for certain medical devices that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions. Under the Expedited Access Pathway (EAP) Program, the FDA works with device sponsors to try to reduce the time and cost from development to marketing decision without changing the FDA's standards.

Relevant Links:

FDA/ Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage

fit-for-purpose — A conclusion that the level of validation associated with a biomarker or COA is sufficient to support its proposed use.

intended use

The specific clinical circumstance or purpose for which a medical product or test is being developed. In the regulatory context, "intended use" refers to the objective intent of the persons legally responsible for the labeling of medical products.[2]

[2] 21 CFR 201.128

intermediate clinical endpoint

In a regulatory context, an endpoint measuring a clinical outcome that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) and that is considered reasonably likely to predict the medical product's effect on IMM or other clinical benefit. The intermediate clinical endpoint may be a basis for full approval if the effect on the endpoint is considered clinically meaningful. It may also be a basis for accelerated approval if the IMM effect is considered critical for use of the drug or for expedited access for medical devices intended for unmet medical need for life threatening or irreversibly debilitating diseases or conditions.

- Example: Exercise tolerance has been used as an intermediate clinical endpoint in trials of device treatments for heart failure.
- Example: A treatment for preterm labor was approved based on a demonstration of delay in delivery. Under accelerated approval, the sponsor was required to conduct postmarketing studies to demonstrate improved long-term postnatal outcomes.

Relevant Links:

FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

FDA/Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage

measurement

The obtained value using a test, tool, or instrument.

medical product development tool

Methods, materials, or measurements used to assess the effectiveness, safety, or performance of a medical product. In a regulatory context, examples of MPDTs are clinical outcome assessments, assessments of biomarkers, and non-clinical assessment methods or models.

Relevant links:

FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

FDA/ Center for Drug Evaluation and Research Animal Model Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Biomarker Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Clinical Outcome Assessment Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Drug Development Tools (DDT) Qualification Programs Webpage

FDA/Center for Devices and Radiological Health Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff: Medical Device Development Tools

FDA/Center for Devices and Radiological Health Medical Device Development Tools (MDDT) Webpage

MPDT

See medical product development tool.

monitoring biomarker

A biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent. For more information, see also chapter on Monitoring Biomarker.

observer-reported outcome

A type of clinical outcome assessment. A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants or individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation. ObsRO measures include:

- Rating scales, such as:
  - Acute Otitis Media Severity of Symptoms scale (AOM-SOS), a measure used to assess signs and behaviors related to acute otitis media in infants
  - Face, Legs, Activity, Cry, Consolability scale (FLACC), a measure used to assess signs and behaviors related to pain
- Counts of events (e.g., observer-completed log of seizure episodes)

ObsRO

See observer-reported outcome.

outcome

The measureable characteristic (clinical outcome assessment, biomarker) that is influenced or affected by an individuals' baseline state or an intervention as in a clinical trial or other exposure.

outcome assessment

An assessment of an outcome that results in recorded data point(s) (e.g., for a biomarker or clinical outcome assessment).

patient-reported outcome

A type of clinical outcome assessment. A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. PRO measures include:

- Rating scales (e.g., numeric rating scale of pain intensity or Minnesota Living with Heart Failure Questionnaire for assessing heart failure)
- Counts of events (e.g., patient-completed log of emesis episodes or micturition episodes)

PerfO

See performance outcome.

performance outcome

A type of clinical outcome assessment. A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions. A PerfO assessment may be administered by an appropriately trained individual or completed by the patient independently. PerfO assessments include:

- Measures of gait speed (e.g., timed 25 foot walk test using a stopwatch or using sensors on ankles)
- Measures of memory (e.g., word recall test)

pharmacodynamic/response biomarker

A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent. For more information, see also chapter on Pharmacodynamic/ Response Biomarker.

predictive biomarker

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent. For more information, see also chapters on Predictive Biomarker and Understanding Prognostic versus Predictive Biomarkers.

PRO

See patient-reported outcome.

prognostic biomarker

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. For more information, see also chapters on Prognostic Biomarker and Understanding Prognostic versus Predictive Biomarkers.

qualification

A conclusion, based on a formal regulatory process, that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

Relevant links:

FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

FDA/ Center for Drug Evaluation and Research Animal Model Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Biomarker Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Clinical Outcome Assessment Qualification Program Webpage

FDA/Center for Drug Evaluation and Research Drug Development Tools (DDT) Qualification Programs Webpage

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FDA/Center for Devices and Radiological Health Medical Device Development Tools (MDDT) Webpage

reasonably likely surrogate endpoint

An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices. In the case of accelerated approval for drugs, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.[3] For more information, see also chapter on Reasonably Likely Surrogate Endpoint.

Relevant Links:

FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

safety biomarker

A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect. For more information, see also chapter on Safety Biomarker.

surrogate endpoint

An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation:

- validated surrogate endpoint
- reasonably likely surrogate endpoint
- candidate surrogate endpoint

For more information, see also chapters on Reasonably Likely Surrogate Endpoint and Validated Surrogate Endpoint.

Relevant Links:

FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

FDA/ Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage

[3] 21 CFR 314.510

susceptibility/risk biomarker

A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition. For more information, see also chapter on Susceptibility/Risk Biomarker.

test, tool, or instrument — An assessment system comprising three essential components: 1) materials for measurement; 2) an assay (i.e., for biomarkers) or method or procedure (i.e., for COAs) for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements.

validated surrogate endpoint

An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit. A validated surrogate endpoint can be used to support marketing approval of a medical or tobacco product in a defined context without the need for additional studies to demonstrate the clinical benefit directly. Although the term has been used in a conceptually broader way, from a U.S. regulatory standpoint, a validated surrogate endpoint almost always refers to a biomarker. For more information, see also chapters on Validated Surrogate Endpoint and Validation.

validation

A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. For biomarkers, elements of validation include but are not limited to the following:

- analytical validation
- clinical validation

For more information, see also chapter on Validation.