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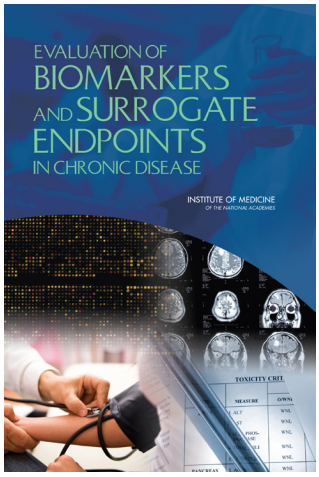
Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease



Doctors, scientists, and other health professionals use biomarkers as tools to obtain information about a person's health status or response to interventions. Defined as characteristics that indicate biological processes, biomarkers are essential for monitoring the health of both individuals and communities. Some biomarkers, called surrogate endpoints, are used as substitutes for actual clinical endpoints such as incidence of disease or death. Surrogate endpoints are intended to predict benefit or harm based on scientific evidence, and they are used in practice when it is difficult to collect data based on clinical endpoints.

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In 2008, the Food and Drug Administration (FDA) asked the Institute of Medicine (IOM) to conduct a study on the evaluation process for biomarkers, focusing on biomarkers and surrogate endpoints in chronic disease. The FDA's Center for Food Safety and Applied Nutrition initiated this study after reviewing dozens of applications for food health claims based on stated effects on biomarkers. The report's authoring committee recommends that the FDA adopt a consistent scientific process and framework for biomarker evaluation in order to achieve a rigorous and transparent process for all stakeholders. The committee tests this framework using case studies of biomarkers and surrogate endpoints in various diseases, such as low-density lipoprotein (LDL) and high-density lipoprotein cholesterol levels in cardiovascular disease.

Significance and Risk of Biomarkers and Surrogate Endpoints

Biomarkers are important in that they can enable faster clinical trials for interventions, improve understanding of healthy dietary choices, assist public health professionals in identifying and tracking health concerns, and help health care practitioners and patients make decisions. Cholesterol levels are among the most widely known examples of biomarkers. However, even though LDL cholesterol level is an excellent biomarker in many situations, it does not always fully predict cardiovascular disease outcomes; in other words, it cannot be assumed to be a surrogate endpoint. No surrogate endpoint is a perfect substitute for a clinical endpoint.

As the gatekeeper for entry of foods, drugs, and many other products into the U.S. marketplace, the FDA examines data and makes decisions about whether biomarkers or surrogate endpoints can be used for regulatory reviews. The FDA sometimes uses surrogate endpoints such as LDL to make decisions about health claims and drugs. When manufacturers present evidence, for example, that a product reduces LDL levels, the FDA considers the evidence in relation to the surrogate endpoint and makes decisions about cardiovascular health claims or drugs based on that evidence.

The use of biomarkers is critical to the regulation of both food and drugs. However, the context in which they are used also is very important, and the science behind their use must be rigorous.

Harmonizing the Scientific Process

The committee recommends that the FDA use the same degree of scientific rigor for evaluating biomarker use across regulatory areas, including drugs, medical devices, biologics, foods, and dietary supplements. Congress may need to strengthen FDA authority to accomplish these goals.

Foods and drugs are regulated differently by the FDA. When the FDA reviews drugs, the safety and efficacy of the entire product is considered; however, when the agency considers foods, the safety of individual ingredients is evaluated rather than the food as a whole. Despite the common perception that foods present fewer risks to consumers than drugs, in fact, food-based public health interventions—for example, supplementing milk with vitamin D and fortifying cereal with iron—may pose greater risks than many drugs because the reach of food is so vast. Even minor risks are significant when the majority of the population is exposed to them.

Just as drugs are expected to impart some benefit, foods are similarly expected to be beneficial and not detrimental to health. Food manufacturers may place claims relating to the health of a food product based on the qualities of a single ingredient. For example, a claim made about a food's ability to lower cholesterol can be made based on just a single component of that food, such as the presence of the fiber found in oats. Further, some claims, such as dietary guidance statements (for example, "dairy products may reduce the risk of osteoporosis"), can be made without any review by the FDA.

Studies show that consumers have trouble assessing the scientific merit of health claims made by manufacturers, and consumers currently do not receive all of the information they need in order to make educated decisions. In addition to the lack of complete information conveyed on labels, consumers also are limited by the FDA's evaluation process. In particular, when surrogate endpoints are used instead of clinical outcomes to explore the health benefits of a food, additional uncertainty about the food's link to clinical outcomes is introduced. For these reasons, the committee concludes that when reviewing the safety of food and supplements and health-related product claims, the FDA should take into account all aspects of a food, including the source of a nutrient or food and any modifying effects of the food

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or supplement that serves as the delivery vehicle. The dietary patterns associated with consumption of the nutrient or food also should be considered.

Adopting a Biomarker Evaluation Framework

The biomarker evaluation process should consist of the following three steps:

1. Analytical validation – Biomarker tests need to be reliable, reproducible across multiple laboratories and clinical settings, and maintain adequate sensitivity and specificity before data based on them can be used in subsequent evaluation steps.
2. Qualification – Qualification requires: (1) evaluation of the nature and strength of evidence regarding whether a biomarker is associated with the disease, and (2) assembly of available evidence demonstrating that interventions targeting the biomarker impact the clinical endpoints of interest.
3. Utilization – Decisions to use biomarkers depend on the specific use proposed in addition to the strength of the available evidence. Strong evidence and a compelling context are needed for the use of a biomarker as a surrogate endpoint.

It is important to emphasize that the steps listed above are interrelated and may not necessarily be separated in time. Conclusions in one step may require revisions or additional work in other steps.

For biomarkers with regulatory impact, the committee recommends that the FDA convene expert panels to evaluate biomarkers and biomarker tests. Initial evaluation of analytical validation and qualification should be conducted separately from a particular context of use. In addition, the expert panels should reevaluate analytical validation, qualification, and utilization on a continual and a case-by-case basis.

Improving Evidence-Based Regulation

The committee recognizes the challenges the FDA faces in accomplishing its mission and therefore recommends that Congress strengthen the FDA's authority to request and enforce post-market surveillance across drugs, devices, and biologics when approvals are initially based on putative surrogate endpoint data. Congress also should grant the FDA authority to request studies and sufficient authority to act on the results of studies on consumer understanding of claims on foods and supplements. Additionally, the U.S. Department of Health and Human Services should facilitate a coordinated, department-wide effort to encourage the collection and sharing of data about biomarkers for all uses, including drugs, biologics, devices, and foods. The FDA, in coordination with

other federal agencies, should build needed data infrastructure and surveillance systems to handle the information necessary to gain sufficient understanding of the effects of biomarker utilization.

Conclusion

Few who are allergic to peanuts, eggs, or shellfish would argue that foods are less risky than drugs. The committee concludes that there is neither rationale nor scientific grounds for basing regulatory decisions on different levels of scientific evidence for different substances—science is science. In the interest of ensuring the public's health, the proposed biomarker evaluation framework recognizes that scientific information is always evolving and yet allows for the introduction of new, life-saving health interventions.

Modern medicine depends on biomarkers. However, without improvements to the way biomarkers in general, and surrogate endpoints specifically, are used, health care practitioners, regulators, and consumers will not be able to collect or assess information about the foods they consume and drugs they use.

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