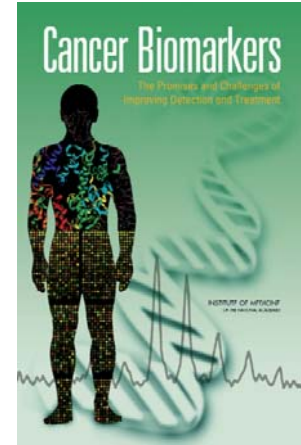


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CANCER BIOMARKERS: THE PROMISES AND CHALLENGES OF IMPROVING DETECTION AND TREATMENT

Advances in biotechnology and genomics have given cancer patients and doctors hope for a different approach to detecting and treating cancer. “Personalized medicine” matches the drug to the person. Since genetic and disease profiles differ from person to person, allowing physicians to tailor treatment for the individual would enhance the effectiveness and safety of cancer care. Biomarkers will play an increasingly important role in designing new drugs and improving the detection and treatment of cancer.

A biomarker is any characteristic that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or of pharmacological response to a therapeutic intervention. A well-known example is the estrogen receptor (ER), which has been used successfully for decades, although concerns remain regarding the accuracy of test results (see Box 1). Biomarkers serve a variety of functions, so applicability to a specific purpose should be fully tested and confirmed before use (see Table 1).



Box 1. Estrogen Receptor—The Classic Cancer Biomarker

For many decades the estrogen receptor (ER) has been used as a prognostic factor and as a predictor of response to endocrine therapies for breast cancer. As such, accurate and reliable assessment of ER status is paramount for optimal breast cancer care. The usefulness of ER as a predictor of therapeutic response was first noted by retrospective review of patient data from many clinical trials conducted around the world. The results indicated that 55 to 60 percent of patients positive for ER responded to endocrine therapy, while those who were negative for ER had virtually no chance of responding.

A semi-quantitative test based on immunohistochemistry (IHC) has become the method of choice for determining ER status, but there is concern that the variability and inaccuracy of the test and interpretation of the results may lead to an unacceptably high error rate. The positive predictive value of ER tests is estimated to be in the range of 60 to 80 percent. The ER IHC test is not standardized, and many laboratories use FDA-approved reagents in different ways. In addition, there is no universal consensus on a scoring system for interpreting the results. A number of suggestions have been made to improve the reliability of the test results, including further improving and standardizing test kit reagents and controls, staining procedures, and scoring methods.

The situation is likely to become even more complex as newer methods have been developed to measure ER mRNA rather than protein. However, these methods are not yet widely used, in part because most labs are not equipped to conduct the tests, and they also are not fully standardized. Furthermore, new endocrine therapies, including aromatase inhibitors, are now available to treat breast cancer, and emerging evidence suggests that optimal response to a particular endocrine therapy depends on the level of ER expression, not just whether it is positive or negative.

SOURCES: McGuire, 1975; Fitzgibbons et al., 2000; Ross, 2005; Diaz and Sneige, 2005.

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Unfortunately, progress for biomarkers has been slow, despite considerable effort and investment. This prompted the Institute of Medicine (IOM) to examine questions regarding the discovery, development, adoption, and use of biomarkers for cancer screening, diagnosis, and treatment, with the goal of identifying obstacles to progress that might be overcome through policy changes. The resulting IOM report, *Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment*, makes 12 recommendations (See Box 2).

Federal agencies and other funders should sponsor demonstration projects focused on a single disease or pathway to discover and develop biomarkers that can predict safety and efficacy in individual patients for drugs already on the market, both as a proof of principle and to establish a model for biomarker development.

TABLE 1. Use of Cancer Biomarkers in Patient Care

Clinical Biomarker Use	Clinical Objective
Risk stratification	Assess the likelihood that cancers will develop (or recur)
Chemoprevention	Target mechanisms of carcinogenesis in precancerous tissues
Screening	Detect early-stage cancers in the asymptomatic population
Diagnosis	Definitively establish the presence of cancer
Classification	Classify patients by disease subset
Prognosis	Predict the probable outcome of cancer regardless of therapy
Prediction/treatment stratification	Predict response to particular therapies; choose the drug mostly likely to yield a favorable response in a given patient
Risk management	Identify patients with high probability of adverse drug effects
Therapy monitoring	Determine whether a therapy is having the intended effect on a disease and whether adverse effects arise
Posttreatment surveillance	Early detection and treatment of recurrent disease

DISCOVERING BIOMARKERS—A UNITED EFFORT

Biomarker discovery efforts to date have been piecemeal and unorganized. Most candidate biomarkers never advance beyond the discovery phase, and the number of biomarkers approved for clinical use is still very small.

Multiple federal agencies must be involved in these efforts, as no single agency is likely to have enough expertise to address all the issues. However, one agency should take the lead in organizing inter-institutional efforts. Therefore, the IOM committee recommends that federal agencies such as the National Institutes of Health (NIH), the National Cancer Institute (NCI), the Food and Drug Administration (FDA), and the National Institute of Standards and Technology (NIST) should take a more organized, comprehensive approach to the discovery of potential cancer biomarkers and the development of new technologies. Given the challenge and expense of developing biomarkers, it may be difficult or impossible for any single company or organization to successfully undertake the work alone. Sponsors of biomedical research should establish international public-private consortia, modeled after the SNP (Single Nucleotide Polymorphism) Consortium, to generate and share methods and precompetitive data.

GUIDELINES FOR BIOMARKER DEVELOPMENT

Oversight, strategy, and ownership of the biomarker development process are key to its success, but no federal agency currently takes responsibility for ensuring the clinical validity or utility of biomarkers. Government agencies (e.g., NIH, FDA, Centers for Medicare and Medicaid Services [CMS], and NIST) and non-government stakeholders (e.g., academia, the pharmaceutical and diagnostics industry, and health care payors) should work together to create well-defined consensus standards and guidelines for biomarker development, validation, qualification, and use, to reduce the uncertainty in the process. An appropriate federal agency should take responsibility in providing a leadership role in the process to coordinate and oversee interagency activities.

Coordinated development of diagnostics and therapeutics could help companies choose the most promising drug leads, optimize clinical trial designs, and facilitate rapid and effective adoption into clinical practice. Timing is important to the release and marketing of a diagnostic test linked to a drug, but often there is a rush to develop the diagnostic near the end of a drug's development. The FDA and industry should work together to facilitate the co-development of drugs and diagnostic tests.

Previously the FDA has claimed legal authority over diagnostic tests, but generally it has chosen to limit oversight, which is most likely due to resource constraints. Unpredictability in FDA oversight can reduce interest and investment in developing innovative diagnostics. The FDA should clarify its authority and then establish and consistently apply clear guidelines for oversight. In addition, the appropriate federal agency (e.g., the FDA or the Federal Trade Commission) should monitor marketing claims.

DEVELOPING THE BEST BIOMARKERS FOR MULTIPLE USES

Markers that can identify biochemical pathways altered in cancers are more likely to be applicable to the development of a new drug that targets an essential pathway. Pathway biomarkers allow for a “systems” approach to diagnosis, treatment, and surveillance by recognizing that signaling pathways operate as interconnected networks. These biomarkers will have the broadest applicability (e.g., across different tumor types, diseases, and drugs).

Selecting the appropriate target populations for oncology drugs already approved by FDA would improve treatment outcomes for patients, and would also catalyze the biomarker field. Federal agencies and other funders should sponsor demonstration projects focused on a single disease or pathway to discover and develop biomarkers that can predict safety and efficacy in individual patients for drugs already on the market, both as a proof of principle and to establish a model for biomarker development.

Moreover, tumor samples have been collected and stored in repositories for many years, but there is much variability in methods, data elements, and quality, and the ability to maintain a repository may be lost when funding for a particular study comes to an end. NIH, NCI, and others should initiate and sustain funding for high-quality and accessible biorepositories of patient samples. NCI should actively facilitate interaction among all interested biomarker developers and groups involved in clinical research, including therapeutic, screening, prevention, and cohort studies, to enable the collection of high-quality patient samples for validating biomarkers.

EVALUATION AND ADOPTION OF BIOMARKERS

Many experts argue that the reimbursement levels for diagnostics set by CMS do not adequately reflect their actual cost or clinical value, with some reimbursement rates being too high relative to value, and others being too low. Fair pricing would foster innovation by enabling developers to better predict the return on investment. Seeking input from outside experts, as FDA does in evaluating new drug and device applications, would greatly improve the process. CMS should modernize the process for evaluating, coding, and pricing diagnostic tests, and use their longitudinal data to assess the value of such tests.

Conditional coverage by CMS could provide a means of collecting important data on the use, effectiveness, and value of biomarker tests before they are broadly adopted. CMS and other health care payors, including private insurers, should develop criteria for temporary, conditional coverage of new biomarker tests to facilitate controlled use of a diagnostic until sufficient evidence can be gathered for an informed decision about permanent, non-provisional coverage. In this risk-sharing approach, payors would agree to cover new tests under the condition that, in the interim, data on the tests would be collected to assess their clinical utility and value.

Biomarkers will be clinically valuable if they encourage appropriate selective use of treatments or identify cancers at a stage that is easier and less costly to treat. If conditional coverage is applied, the cost-effectiveness of biomarkers should be studied by independent research entities, in addition to assessments of the technology accuracy and clinical effectiveness.

CONCLUSION

Despite considerable effort and investment, the biomarker discovery and development process has been slow. The committee concluded that improved methods, tools, and resources are necessary for the discovery and development of biomarkers, as well as better guidelines, standards, and oversight. Implementing the report’s recommendations could have a broad impact on the development of biomarkers and other areas of biomedical research, and reduce the burden of diseases. The recommendations focus on streamlining the biomarker discovery and development process to make effective use of the available resources and create a pathway for success that balances the need to encourage innovation with adequate standards for validation and qualification.

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BOX 2. Summary of Recommendations to Develop Biomarker-Based Tools for Cancer

Methods, Tools, and Resources Needed to Discover and Develop Biomarkers

1. Federal agencies should develop an organized, comprehensive approach to biomarker discovery, and foster development of novel technologies.
2. Industry and other funders should establish international consortia to generate and share precompetitive data on the validation and qualification of biomarkers.
3. Funders should place a major emphasis on developing quantitative pathway biomarkers to broaden applicability.
4. Funders should sponsor demonstration projects to develop biomarkers that can predict efficacy and safety in patients for drugs already on the market.
5. Government agencies and other funders should sustain support for high-quality biorepositories of prospectively collected samples.

Guidelines, Standards, Oversight, and Incentives Needed for Biomarker Development

6. Government agencies and other stakeholders should develop a transparent process to create well-defined consensus standards and guidelines for biomarker development, validation, qualification, and use.
7. The FDA and industry should work together to facilitate the codevelopment and approval of diagnostic-therapeutic combinations.
8. The FDA should clearly delineate and standardize its oversight of biomarker tests used in clinical decision-making.
9. CMS should develop a specialty area for molecular diagnostics under the Clinical Laboratory Improvement Amendments.

Methods and Processes Needed for Clinical Evaluation and Adoption

10. CMS should revise its coding and pricing system for diagnostic tests.
11. CMS and other payors should develop criteria for conditional coverage of new biomarker tests.
12. As a component of conditional coverage, establish procedures for high-quality population-based assessments of efficacy and cost-effectiveness of biomarker tests.

FOR MORE INFORMATION...

Copies of *Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment*, are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, <http://www.nap.edu>. The full text of this report is available at <http://www.nap.edu>.

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