Free Executive Summary

Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment

Committee on Developing Biomarker-Based Tools for Cancer Screening, Diagnosis, and Treatment, Sharyl J. Nass and Harold L. Moses, Editors

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Summary

Biomedical scientists have long sought to identify ways to diagnose cancers at an early, curable stage or to select the optimal therapy for individual patients. Many cancer patients are diagnosed at a stage in which the cancer is too far advanced to be cured, and most cancer treatments are effective in only a minority of patients undergoing therapy. Thus, there is tremendous opportunity to improve the outcome for people with cancer by enhancing detection and treatment approaches. Biomarkers will be instrumental in making that transition.

Because of the heterogeneity among diseases and patients, recharacterization of disease in pathophysiological terms via biomarkers is key to the future of medicine. A biomarker is defined as any characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response to a therapeutic intervention. These indicators could include a broad range of biochemical entities, such as nucleic acids, proteins, sugars, lipids, and small metabolites, as well as whole cells or biophysical characteristics of tissues. Detection of biomarkers, either individually or as larger sets or patterns, can be accomplished by a wide variety of methods, ranging from biochemical analysis of blood or tissue samples to biomedical imaging. The primary focus of this report is in vitro diagnostic[1] tests. Although many of the challenges in bio-

[1]In this report, "diagnostic" is often used synonymously with "biomarker test." These terms refer to any laboratory-based test that can be used in drug discovery and development as well as in patient care and clinical decision making.

marker development are relevant to both biomedical imaging and in vitro diagnostics, in vivo imaging also entails a set of unique considerations, in part because it often requires administration of chemical agents, and thus has some similarity with drug development. Biomedical imaging will be addressed in a forthcoming workshop of the National Cancer Policy Forum, as this topic was beyond the scope of this report.

In recent decades, knowledge about the basic biology and biochemical pathways underlying cancers has increased tremendously, but translation of that knowledge to more effective patient care and better outcomes remains a challenge. Recent technological advances that enable examination of many potential biomarkers have fueled renewed interest in and optimism for developing biomarkers, and it is widely believed that biomarkers can and will be used to improve cancer screening and detection, to improve the drug development process, and to enhance the effectiveness and safety

BOX S-1 Summary of Recommendations to Develop Biomarker-Based Tools for Cancer

Methods, Tools, and Resources Needed to Discover and Develop Biomarkers (Chapter 2)

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 (Chapter 3)

6. Government agencies and other stakeholders should develop a transparent process to create well-defined consensus standards and

of cancer care by allowing physicians to tailor treatment for individual patients—an approach known as personalized medicine. Some promising strides have been made in classifying tumors at the molecular level and in selecting patients who are more likely to respond to some targeted therapies. However, progress overall has been slow, despite considerable effort and investment, and there are still many challenges and obstacles to overcome before this paradigm shift in oncology can become a reality.

The committee was asked 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 could potentially be overcome through policy changes. The committee identified a number of challenges in biomarker research, development, and implementation and proposed 12 recommendations to foster progress in the field, as outlined in Box S-1. These recommendations fall into three general

guidelines for biomarker development, validation, qualification, and use.

7. The Food and Drug Administration and industry should work together to facilitate the codevelopment and approval of diagnostic-therapeutic combinations.

8. The Food and Drug Administration should clearly delineate and standardize its oversight of biomarker tests used in clinical decision making.

9. The Centers for Medicare & Medicaid Services should develop a specialty area for molecular diagnostics under the Clinical Laboratory Improvement Amendments.

Methods and Processes Needed for Clinical Evaluation and Adoption (Chapter 4)

10. The Centers for Medicare and Medicaid Services should revise and modernize its coding and pricing system for diagnostic tests.

11. The Centers for Medicare and Medicaid Services, as well as 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.

categories: (1) methods, tools, and resources needed to discover and develop biomarkers; (2) guidelines, standards, and oversight needed for biomarker development; and (3) methods and processes needed for clinical evaluation and adoption. Although this report is focused on biomarkers for cancers, implementing these recommendations could have a broad positive effect on the development of biomarkers in general, thereby aiding progress in other areas of biomedical research and reducing the burden of other diseases as well. A great deal of work remains to be done, and keeping in mind the opportunity cost of investing in different areas of biomedical research, the committee's recommendations aim to streamline the biomarker discovery and development process, to make effective use of the available resources, and to develop a pathway for success that balances the need to encourage innovation while also ensuring that adequate standards for validation and qualification are met.

METHODS, TOOLS, AND RESOURCES NEEDED TO DISCOVER AND DEVELOP BIOMARKERS

Despite some notable achievements, only a few biomarkers are routinely used in oncology. Although advances in technology have made it easier to examine many potential biomarkers in a single experiment, discovery efforts are still hampered by the limitations of current technology. In addition, most candidate biomarkers never advance beyond the discovery phase, and the number of biomarkers validated for use in drug development or qualified for clinical applications is still very small. Obstacles to progress could be overcome or minimized by developing different strategies to foster the work, from discovery through development, as outlined in the first five recommendations. These approaches could lead to better biomarkers for the entire spectrum of cancer health care, from chemoprevention, early detection, and disease classification to drug development and treatment planning and monitoring.

Recommendation 1:
Federal agencies including, but not limited to, the National Institutes of Health (NIH) and 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 putative cancer biomarkers and the development of novel technologies.

- A highly directed, contract-based program could be effective in supporting the development of innovative biomarker discovery technologies.
- Extramural experts should be involved in all aspects of program planning, execution, and oversight.
- Successful implementation of this endeavor will require one federal agency to take responsibility for coordinating and overseeing the process.

Rationale

Biomarker discovery efforts to date have been piecemeal and unorganized. In addition, most current biomarker tests use technology that has been available for decades, and the ability to discover and develop new biomarkers is limited by the sensitivity, specificity, and capacity of current technology. Thus, there is a significant need for a more thorough and organized approach to discovery, as well as for new and improved technologies for biomarker discovery, particularly in the field of proteomics, which is more complex and has lagged behind advances in methods for analyzing nucleic acids. Such new technologies also will yield dividends in improved capabilities for understanding fundamental cellular processes in cancers and systems biology in general.

The NIH peer review process generally tends not to favor high-risk projects, and neither broad discovery efforts nor technology development has traditionally been a primary focus of NIH funding. However, that has been slowly changing in recent years, with several directed discovery projects and some recent initiatives by NIH that include the goal of improving technologies for protein detection and characterization. An organized, large-scale approach with a highly directed contract-based program would foster biomarker discovery and technology innovation and also provide incentives to academic researchers to undertake the work, since the career structure and reward system in academia is generally not conducive to technology development or large-scale discovery efforts. The involvement of multiple federal agencies is important, as no single agency is likely to have the needed expertise to address all issues, but it will be important for

one agency to take the lead in organizing intra-institutional efforts. Given NCI's current funding level and recent initiatives and interest in biomarker discovery and development, it may seem an obvious choice for the lead agency for this endeavor, but to date it has not yet developed an adequate overarching leadership strategy.

Recommendation 2:
Industry and other funders of biomedical research should establish international public–private consortia, modeled after the SNP (Single Nucleotide Polymorphism) Consortium (see Box 2-5), to generate and share methods and precompetitive data on the validation and qualification of cancer biomarkers for specific uses.

Rationale

Collaborative, precompetitive projects (most likely unrelated to a particular drug) would be enabling to the field. The costs, uncertainties, and risks of developing biomarkers historically have made this work unappealing to pharmaceutical companies and diagnostic companies alike. Although industry perspectives are slowly changing regarding the strategic value of biomarkers, current business models are neither very viable nor attractive to investors. Furthermore, the quantity of data currently generated by any single company is likely to be inadequate for developing and validating biomarkers, and much duplicative work could be going on without ever being reported, so the process could be greatly improved and streamlined by sharing data and information that is already being generated.

Private companies normally are inclined to protect their data to maintain a competitive edge. However, the willingness of multi-national drug companies to share information via the SNP Consortium to achieve a common goal shows the feasibility of a collaborative approach for fostering precompetitive work that could benefit the entire field. Successful examples of sharing precompetitive data exist outside of biomedical science as well, including SEMATECH (Semiconductor Manufacturing Technology), which helped U.S. semiconductor suppliers develop new production tools and establish industry-wide consensus on product specifications. There is also precedent in the validation of a biomarker; the HIV Surrogate Markers Collaborative Group confirmed the usefulness of HIV RNA as a surrogate marker for testing new anti-HIV drugs. Given the past accomplishments

of consortia, a number of new initiatives have recently been planned or launched with some concentration on biomarker validation, but most do not focus on cancer. One exception is the Oncology Biomarker Qualification Initiative, jointly funded by NCI, FDA, and CMS, which currently has only one project under way. Many more areas of cancer biomarker research could benefit from international public–private collaborations.

Recommendation 3:
Funders should place a major emphasis on research to develop quantifiable biomarkers of cell signaling pathways that will have the broadest applicability (e.g., across different tumor types and drugs, as well as other diseases).

Rationale

This approach could reduce the risk inherent in the biomarker development process by increasing their applicability. Biomarkers that are exclusively focused on a particular drug could become obsolete if the drug fails to gain FDA approval, or if therapy guidelines change. In contrast, markers that can identify biochemical pathways that are altered in cancers are more likely to be applicable to the development of any new drug that targets an essential pathway. For example, signaling pathway biomarkers that are validated in common cancers potentially could also be useful in rarer forms of cancer that are more difficult to study and would offer smaller returns to developers. Furthermore, pathway biomarkers could also be useful for early detection of multiple cancer types. Pathway biomarkers would also allow for a "systems" approach to diagnosis, treatment, and surveillance, recognizing that signaling pathways operate in the context of interconnected networks.

Recommendation 4:
Federal agencies and other funders should sponsor adequately powered demonstration projects focused on a single disease or pathway to discover and develop biomarkers that can predict safety and efficacy in individual patients (and thus select appropriate target populations) for drugs already on the market, as proof of principle and to establish a paradigm for biomarker development.

Rationale

The purpose of such demonstration projects would be to identify patient populations likely to respond to a drug, those likely to have resistance to a drug, and those likely to experience adverse reactions to a drug. A high-impact finding would not only improve treatment outcomes for patients, but could also define the biomarker field and catalyze the diagnostics and pharmaceutical industries and academia to undertake such studies for many cancers and therapeutics by establishing a viable route to market and by delineating a viable business strategy. Questions about how best to conduct such studies will need to be addressed early on. In particular, the studies must be well designed and adequately powered, but since patients are already taking the drugs, it should not be difficult to accrue participants for a study.

Recommendation 5:
NIH, NCI, and other funders should initiate and sustain funding for high-quality and highly accessible biorepositories of patient samples prospectively collected in conjunction with large cohort studies and clinical trials, and use of these prospectively collected samples should be encouraged for validating biomarkers. NCI should actively encourage and facilitate interaction among all interested biomarker developers and groups involved in clinical research, including therapeutic, screening, prevention, and cohort studies, to enable the prospective collection of high-quality patient samples that are intended to test specific hypotheses. The following would be important to ensure the quality and value of repositories:

- Providing sufficient funding to cover all essential biorepository components and activities, including:
  - — Involvement of pathologists to assess sample quality and confirm diagnosis
  - — Optimized sample collection and preparation
  - — Capturing and consistently annotating clinical patient records
  - — Medical informatics and database management
  - — General administrative and maintenance costs.
- Adhering to standard operating procedures.

- Developing consensus on common data elements.
- Developing strategies for prioritizing and maximizing access to samples (including procedures for handling intellectual property issues).
- Developing strategies to ensure patient rights and privacy without impeding research, such as:
  - Reassessing the Privacy Rule established under the Health Insurance Portability and Accountability Act and promoting uniformity across states and institutions
  - Promoting interagency harmonization on informed consent to maximize the use and value of collected samples
  - Ensuring broad representation of extramural experts on oversight committees.
- Supporting biorepositories through public–private consortia in the long term, as proposed in Recommendation 2.

Rationale

Tumor samples have been collected and stored in repositories for many years, but there is substantial variability in methods, data elements, and quality. In addition, access to samples may be highly restrictive, and there is no central clearinghouse in which researchers can search for or obtain access to samples. When clinical trials end or funding for cohort studies is not renewed, the ability to maintain the biorepositories created in conjunction with the study is often lost. The samples collected in these prospective studies may be highly valuable for biomarker research and development, and NIH should consider continued funding for biorepository maintenance, even if the original study itself is not continued.

There are numerous examples of ongoing activities that could be instructive in this undertaking. For instance, the Multiple Myeloma Research Consortium Tissue and Data Banks provide an excellent model for the collection and use of patient samples for cancer research. Several NCI initiatives are also noteworthy, including the Early Detection Research Network's Informatics Infrastructure, which provides a model for defining common data elements and sharing information among researchers and institutions. The new Office of Biorepositories and Biospecimen Research is developing guidelines to optimize and unify operational, legal, and ethical policies and procedures for NCI-supported biorepositories, and it has launched a pilot study to test implementation of those guidelines.

GUIDELINES, STANDARDS, OVERSIGHT, AND INCENTIVES NEEDED FOR BIOMARKER DEVELOPMENT

The discovery of putative biomarkers is often reported in scientific journals, but validation of those potential markers for specific uses requires a great deal of additional investigation and study, which is often not undertaken because of the cost and complexity of the work. When these studies are undertaken, the standards used to demonstrate validity vary considerably, in part because there is no overarching leadership in the field of biomarkers to set uniform, consensus standards for biomarker development. The FDA and CMS have some authority over diagnostic tests, but oversight has been variable and unpredictable, and in many cases inadequate to ensure the safety, effectiveness, and value of tests on the market. Oversight by federal agencies has been evolving recently, with greater scrutiny of some tests by the FDA, and with CMS taking a greater interest in diagnostic tests. The FDA in particular has taken initial positive steps with the recent development of draft guidance documents. However, there is still a need for clarification, uniformity, and leadership in this area. The next four recommendations strive to improve the process of biomarker development and evaluation by making it more transparent, consistent, and effective.

Recommendation 6:
Government agencies (e.g., NIH, FDA, CMS, NIST) and nongovernment stakeholders (e.g., academia, the pharmaceutical and diagnostics industry, and health care payors) should work together to develop a transparent process for creating well-defined consensus standards and guidelines for biomarker development, validation, qualification, and use to reduce the uncertainty in the process of development and adoption. The appropriate federal agency should take responsibility to provide a leadership role in the process, coordinating and overseeing interagency activities.

- Different sets of guidelines will probably need to be developed for different applications, including the various stages of drug development and different types of clinical applications (e.g., prevention, screening, diagnosis, treatment planning, response monitoring, and surrogate endpoints), for different technologies, and for single biomarkers versus biomarker panels or patterns.

- A dynamic process will be needed so that guidelines can be revised as technologies or evidence change.
- Federal funding should stipulate adherence to publication guidelines.
- FDA, CMS, and industry should work together to develop guidelines for clinical study designs that will enable sponsors to run a single study (or a minimal number of studies) to generate adequate clinical data for review by both agencies.
- Postmarket surveillance will be needed to ensure quality and accuracy.

Rationale

Oversight, strategy, and ownership of the biomarker development process are key to success, but no federal agency currently takes responsibility for ensuring the clinical validity or utility of biomarkers. NIST has had a limited role in the biomedical sciences to date, but it has the appropriate experience to play a broader role in the establishment of standards for biomarkers, given adequate funding.

Professional organizations and other groups have developed numerous guidelines for publication of data or for clinical use of biomarkers; however, most are nonbinding. This piecemeal approach has created a patchwork of standards, with many gaps as well as some overlap, which can lead to conflict and confusion. Uniform consensus guidelines that cover the entire continuum are needed.

Currently developers often determine their own standards each time they consider a new biomarker, and competition to reach the market quickly creates an incentive to lower those standards. Variability in evidence standards applied by the FDA, CMS, and other health care payors can have a major impact on the cost of development and product revenue, so uniform standards would reduce the risk of development and make it easier to predict return on investment. Optimizing clinical study design will shorten the time to market, reduce cost and risk, and strengthen the evidence base for evaluation. It is important to strike a balance between fostering innovation and ensuring the validity and usefulness of tests.

Improved postmarket surveillance will be important to maintain high-quality standards because CMS oversight via the Clinical Laboratory Improvement Amendments (CLIA) appears not to be sufficient to ensure the accuracy of current biomarker tests. Accuracy problems with

well-established clinical tests (e.g., immunohistochemistry for HER2 and estrogen receptor) underscore the need for greater postmarket oversight.

Recommendation 7:
The FDA and industry should work together to facilitate the codevelopment of diagnostic-therapeutic combinations.

- The FDA should more clearly delineate the expectations and requirements for diagnostic-therapeutic combination approval, and approval of the therapeutic and diagnostic should be linked, such that one is contingent on the other.
- Companies need to better integrate basic and clinical research, and emphasize the search for patient subpopulations based on theoretical and empirical evidence prior to phase III trials.
- Because more than one FDA center will be involved in the approval/clearance decisions for diagnostic-therapeutic combinations, the agency should clarify the roles of each center and focus on ensuring coordination among the centers to facilitate the review and approval process.
- The FDA should develop more dynamic ways of changing drug labels when new data for selecting appropriate target populations emerge.

Rationale

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. However, diagnostics and therapeutics are currently developed separately, often by different entities. Timing is key for corelease and marketing of a diagnostic linked to a drug, but often there is a rush near the end of drug development to develop the diagnostic. As a result, the diagnostic may not be scrutinized as thoroughly. New strategies, methods, and infrastructure are needed to leverage and integrate the available data to better inform the biology.

The cost and risks of diagnostic development and validation are great when clinical validity and utility must be established, and they add substantially to the existing high cost of drug development. Companies may

be unwilling to invest in diagnostic development in the earlier phases of testing when approval of the drug is so uncertain, because without drug approval, there may be no market for the diagnostic. Thus, devising strategies to share and minimize the costs and risks of codevelopment would foster this work.

Recommendation 8:
The FDA should clarify its authority over biomarker tests linked to clinical decision making and then establish and consistently apply clear guidelines for the oversight of those tests. In addition, the appropriate federal agency (e.g., the FDA or the Federal Trade Commission) should monitor and enforce marketing claims made about molecular diagnostics.

- A coherent strategy is needed to define and clarify the rules and their enforcement to make the process more transparent, to remove inconsistency and uncertainty, and to elevate standards and oversight.
- The FDA needs a dynamic process for updatating regulations to adapt to rapid changes in technology.
- The FDA needs additional resources if it is to make meaningful changes in this field.

Rationale

The FDA previously has claimed legal authority to assert jurisdiction over diagnostic tests, but generally it has chosen to limit oversight, most likely due to resource constraints. Recently, the FDA appears to be trying to create clarification and precedent on a case-by-case basis regarding molecular diagnostics, through warning letters and untitled letters and via nonbinding guidance documents. However, variability and unpredictability in FDA oversight can reduce interest and investment in developing innovative diagnostics. Moreover, inadequate evaluation and oversight could lead to harm for patients and unnecessary cost burden for society.

The Federal Trade Commission prohibits false or misleading advertising and has claimed it will take action against such advertising of genetic tests. But the agency's limited resources appear to be preventing it from following through on its commitment. To date, it has not exercised authority to enforce accurate marketing claims for molecular diagnostic tests.

Recommendation 9:
CMS should develop a specialty area for molecular diagnostics under CLIA.

Rationale

The minimum generic standards set by CMS under CLIA are not adequately tailored to the complexities of molecular diagnostics, and private-sector accreditation is voluntary and limited in scope. For most "high-complexity" tests, CMS has created specialty areas under CLIA, mandating, among other requirements, participation in specified proficiency testing programs. Molecular diagnostics are high-complexity tests, but CMS has not created a specialty area for these tests. In 2000, the Secretary's Advisory Committee on Genetic Testing concluded that oversight of genetics tests was insufficient to ensure their safety, accuracy, and clinical validity and recommended that CMS should develop a specialty area for genetic testing under CLIA. That recommendation has not been implemented and CMS recently asserted that there is insufficient "criticality" to warrant rule making for genetic testing.

METHODS AND PROCESSES NEEDED FOR CLINICAL EVALUATION AND ADOPTION

Diagnostic tests historically have been adopted into clinical practice with relatively little assessment of their value to patients and clinicians. That is slowly changing, as health care payors are beginning to demand more evidence of effectiveness when making coverage and reimbursement decisions. Appropriate clinical use of diagnostic tests requires assessments of the clinical risks and benefits, but the studies needed to make those assessments can be costly, lengthy, and difficult, making it hard for sponsoring companies to undertake them. New approaches to gathering data on effectiveness, cost, and value are needed to strike the necessary balance between encouraging innovation and ensuring that patients and providers have accurate and reliable tests. The final three recommendations suggest strategies to facilitate collection of needed data while also fostering expedient access to the market, and appropriate pricing of tests.

Recommendation 10:
CMS should modernize the process for evaluating, coding, and pricing diagnostic tests, and use the power of their longitudinal data to assess the value of tests.

- As previously recommended by an Institute of Medicine report (2000), Medicare ought to have "a single national, rational fee schedule" for clinical laboratory tests.
- Reimbursement policies should be clarified and the decision process should be made more uniform and transparent.
- CMS should convene stakeholders to develop consensus guidance on how to assess diagnostics to make coverage and reimbursement decisions.
- Expert panels should review new tests and reach consensus on coverage and pricing.

Rationale

Pricing of diagnostics is very different from that of drugs. For diagnostics, CMS uses "gap filling" and "cross-walking" to establish prices based on comparisons with tests and procedures already in use. Federal legislation also specifies national limitation amounts and links price increases to the consumer price index, whose rate of growth is below the rate of medical inflation. As a result, 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 too high relative to value, while others are too low.

Current pricing methods are particularly problematic for insurers with regard to homebrew tests. It is easier for payors to evaluate and control the use and the reimbursement rate of an FDA-approved test kit, which has its own individual Current Procedural Terminology (CPT) code. But for homebrew tests, a laboratory breaks down what they do into specific methods and analytes used, each with its own CPT code. Thus, a single test could entail 10–15 different codes, making it difficult to identify and evaluate appropriate use of the test.

Fair and rational 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. Although CMS is prohibited from using clinical value as a criterion for reimbursement, assessing the clinical value of tests would aid clinical decision making.

Recommendation 11:
CMS (and other health care payors, including private insurers) should develop criteria for temporary, conditional coverage of new biomarker tests in certain circumstances to facilitate controlled and limited use of a diagnostic with a therapeutic and, even more importantly, a screening biomarker test, until sufficient evidence can be gathered to make an informed decision about standard (permanent, nonprovisional) coverage. Using this risk-sharing approach, payors would agree to provisionally cover new tests in specified circumstances with the proviso that, in the interim, data would be collected in conjunction with use of the test, to assess its clinical utility and value.

Rationale

Biomarker tests often enter the market with little assessment or evidence of patient benefit, so payors may have to make coverage decisions with very little information. But premature adoption of inaccurate or ineffective biomarkers could be more costly to society than paying for conditional coverage, because, once provided, coverage is rarely retracted. Several national health care plans in Europe have high standards for evidence in coverage decisions, but they also commonly share some of the costs and risks of evidence development with technology sponsors. Coverage under Evidence Development (CED) is already being used by CMS in some cases (e.g., positron emission tomography imaging for cancer diagnosis, staging, and monitoring, as well as off-label uses of four drugs approved for colorectal cancer), demonstrating the feasibility of this approach. Thus, 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. Private insurers may experience some difficulty in implementing conditional coverage because they are required to administer benefits according to the terms of their benefit plans, which often exclude experimental or investigational items, but it would be beneficial to examine and overcome these challenges. Because Medicare primarily covers patients who are older than 65, private insurers could make a very important contribution by col-

lecting data on younger patient populations for whom cancer screening tests may yield the greatest gains in survival and reduced morbidity.

The conditional coverage approach would be especially useful for testing biomarkers for screening due to the very large populations needed to evaluate them. Companies do not have the financial means or incentives to undertake the very large, lengthy, and costly studies to assess a screening test. Most tests enter the market as a diagnostic but may then be adopted for screening, in the absence of adequate evaluation, via off-label use. Once adopted in such a fashion, it may be difficult or impossible to adequately assess the risks, benefits, and value of a screening test.

Recommendation 12:
When conditional coverage is applied, the cost-effectiveness of biomarkers should be studied by independent research entities, in conjunction with the assessment of technology accuracy and clinical effectiveness. This issue is particularly important for screening biomarkers due to the costs and potential morbidity of false positive tests.

- Optimal study designs are needed for high-quality population-based assessments of efficacy and cost-effectiveness of biomarker tests.
- To maximize the cost-effectiveness of diagnostics and therapeutics, it will be necessary to account for heterogeneity in patient populations, including risk, benefit, and behavior (e.g., patterns of use and self-selection).
- A structure and transparent process is needed for sharing information among laboratory test manufacturers, clinical laboratories, and health care payors. The format of the Academy of Managed Care Pharmacy evidence-based evaluation of drugs could be instructive in this regard.

Rationale

CMS is prohibited from using cost-effectiveness in coverage decisions, and currently, evidence for the application and utility of laboratory tests is often quite limited. However, demand for such evidence is increasing, so new methods and approaches are needed. The rapidly increasing costs of medical care are a common concern and are often attributed in part to

adoption of new technologies. Although diagnostics account for only 1.6 percent of total Medicare costs, they influence the majority of downstream treatment decisions, so there is a need to assess potential indirect downstream risk and costs. In oncology, the cost of new targeted therapies can be an order of magnitude higher than traditional cancer treatments, and often only a fraction of patients benefit significantly from the treatments. Screening an entire asymptomatic population is also costly and can lead to harm as well as benefit. 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.

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclu-

sions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Melvin Worth, MD,** Scholar-in-Residence at the Institute of Medicine, and **Gilbert S. Omenn, MD, PhD,** University of Michigan Medical School. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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