TUMOR-BIOMARKER DIAGNOSTICS

Breaking a Vicious Cycle

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Despite prodigious advances in tumor biology research, few tumor-biomarker tests have been adopted as standard clinical practice. This lack of reliable tests stems from a vicious cycle of undervaluation, resulting from inconsistent regulatory standards and reimbursement, as well as insufficient investment in research and development, scrutiny of biomarker publications by journals, and evidence of analytical validity and clinical utility. We offer recommendations designed to serve as a roadmap to break this vicious cycle and call for a national dialogue, as changes in regulation, reimbursement, investment, peer review, and guidelines development require the participation of all stakeholders.

The promise of personalized medicine looms large in the oncology field. However, cancer biomarker–test development and adoption into clinical use has lagged far behind advances in therapy (1). Here, we delineate a series of critical but underappreciated issues that have led to the undervaluation of cancer-biomarker tests and propose recommendations to enhance the impact of these powerful diagnostic tools. A biomarker is a biological indicator that objectively measures or evaluates physiological or pathophysiological processes or pharmacological responses to a therapeutic intervention. A tumor-biomarker test is used to detect and quantitate the biomarker (1). These tests may be used to determine risk of or to screen for new cancers, inform differential diagnosis of established malignancy, estimate prognosis, select optimal therapy, and monitor patients to determine the status of their cancers. Prognostic factors, such as regional lymph node status, provide an indication of the likely course of a patient’s disease in the context of previously applied treatment (such as surgery), whereas predictive factors (also called treatment-response modifiers) provide an indication of whether a given treatment being considered will have a beneficial effect. Serial measurement of tumor biomarkers can monitor ongoing therapeutic benefit or emergence of a new event, such as cancer recurrence or progression (2). Pharmacogenetic biomarkers measure risk of toxicity or odds of benefit from anticancer drugs (3).

GETTING READY FOR PRIME TIME

In order to define when a tumor-biomarker test is ready to be used to guide patient management, we adopt and endorse several conventions and frameworks. First, we use the terminology proposed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (www.egappreviews.org/workingrp.htm) for “analytical performance”—how accurately and reliably the test detects the analyte(s) of interest; “clinical validity”—how well the test relates to the clinical outcome of interest (such as survival or response to therapy); and “clinical utility”—whether the results of the test provide information that contributes to and improves current optimal management of the patient’s disease (4). We also refer to evidence levels [ranging from 1 (best) to 5 (worst)] required to demonstrate clinical utility for a specific use, which was first proposed by the American Society of Clinical Oncology (ASCO) and revised by others (5, 6).

Last, we endorse the Institute of Medicine (IOM) pathway for development of new omics-based biomarker tests (fig. S1 (7), which involves three steps: (i) discovery of a biomarker of potential biological or clinical interest, (ii) development of a biomarker test that has both analytical validity and at least clinical and biological validity, and (iii) evaluation of clinical utility for a specific contextual use (4). Strategies proposed by IOM to generate the evidence necessary to demonstrate clinical utility include either using previously archived specimens or conduct of prospective clinical trials. If one chooses to generate sufficient evidence for clinical utility with archived specimens, investigators should ideally conduct prospective retrospective studies using trial-quality methodologies (6). If adequate archived specimens are not available, the clinical utility of a tumor-biomarker test must be studied in prospective trials in which the biomarker-test result either is used to direct patient management in the trial or is prospectively determined to be the primary objective of the trial.

UNDERVALUED ASSETS

A tumor-biomarker test has two component values: clinical and financial. Clinical value stems from improvements in patient care achieved through use of the test. A tumor-biomarker test with established clinical utility provides an indication of whether a cancer patient is likely to benefit from a given treatment. This information allows the patient’s treating physicians to prescribe an effective therapeutic regimen or refrain from prescribing an apparently futile one, thus avoiding needless toxicity.

A test has financial value if its use permits the application of expensive therapeutic strategies only in a targeted population of likely responders. Currently, financial value is estimated by combining the cost of discovery and test-validation research and the expense of generating sufficient evidence to determine the precise clinical utility of an intended use (6, 7). Capital investments to develop clinically useful tumor-biomarker tests will only be made if there is a reasonable chance of recovering these costs with future revenues. The marketplace has recognized the value of advances in cancer care that have resulted from the discovery and development of molecularly targeted therapies but not the value of robust new tumor-biomarker tests to guide patient management. As a result, R&D for such tests and their adoption into standard clinical practice have lagged behind R&D and clinical use of therapeutics.

When patient management is contingent on the results of a biomarker test, that test becomes as critical for patient care as a therapeutic agent. If a tumor-biomarker test with poor or uncertain analytical perfor-
mance and clinical-outcomes prediction is used to make decisions about prognosis or selection of a specific therapy, health care is likely to be compromised and costs unnecessarily increased. In contrast, if a tumor-biomarker test reliably identifies the patients most likely to benefit from a therapy and this information is used in clinical decision-making, patient outcomes are optimized and health care costs are decreased.

Unfortunately, stakeholders (Table 1) have not fully recognized the potential value of tumor-biomarker tests; thus, the research, regulatory, clinical-use, and reimbursement standards are not as well defined or as rigorous as those applied to therapeutics. Both the financial resources devoted to and third-party reimbursement for new tumor-biomarker assays have historically been much lower than for new therapeutics (8). These conditions have generated little enthusiasm (or funding) for development of the high levels of evidence needed to support the clinical utility of tumor-biomarker tests, resulting in a vicious cycle of under-valuation of tumor-biomarker tests in both the professional and patient communities (Fig. 1A). This mindset has delayed realization of truly personalized cancer care.

The vicious cycle has resulted in two consequences. First, there are too few tumor-biomarker tests with established clinical utility. Clinical guidelines for tumor biomarkers by panels from both ASCO and the National Cancer Center Network (NCCN) have been quite conservative, mostly because of the lack of sufficient evidence of analytical validity or clinical utility to support adoption into clinical use (9, 10). Of equal concern is the adoption of a few tumor-biomarker tests that direct patient management in the absence of sufficient evidence to validate clinical utility. For example, routine screening for prostate cancer by measuring blood levels of prostate-specific antigen (PSA) in men over the age of 50 was widely adopted in the United States without supporting evidence from prospective clinical trial data. Results from two recent prospective randomized trials suggest very small or no survival benefit for men who undergo PSA screening, and the U.S. Preventive Services Task Force and others now recommended against using PSA tests for prostate cancer screening (11).

There is no single starting point for breaking the vicious cycle (Fig. 1A). At each node, the value of tumor-biomarker tests requires appreciation by many stakeholders (Table 1). Further, R&D of well-validated tumor-biomarker tests may require redistribution of health care dollar expenditures in oncology—including third-party clinical reimbursement and R&D funding—to better align tumor-biomarker test value with that of therapeutics. The relative value of these two components is highly skewed and inconsistent with the importance of diagnostics to health care decision-making. Industry experts have estimated that diagnostics account for <2% of total health care spending but influence 60% of clinical decision-making (8).

CAUSES AND (POTENTIAL) CURES

Below, we offer a set of proposals intended to serve as an introductory roadmap to im-
 prove the landscape for tumor-biomarker test R&D, regulation, reimbursement, and clinical use (Table 2). The following concepts are key to our proposals: For any tumor-biomarker test, consistent and predictable regulatory and recommendation standards must be coupled with third-party reimbursement that is commensurate with the value of the test. “Value” should be based on the test’s demonstrated impact on public-health outcomes and health care costs. Our proposals initially may be perceived as creating added burden and cost to tumor-biomarker research and clinical care. However, the provision of adequate funding would ensure that investigators and entrepreneurs enter the tumor-biomarker field with properly calibrated expectations and enthusiasm similar to those that now exist for new therapeutics.

**Cause 1.** Inconsistent regulatory standards for clinical data needed to approve tumor-biomarker tests. There are two regulatory pathways in the United States for bringing a tumor-biomarker test (classified as an in vitro diagnostic device) onto the market for clinical use: application for U.S. Food and Drug Administration (FDA) approval or clearance under premarket approval (PMA) or substantial equivalence (510K) mechanisms, respectively.

Compliance with FDA regulations for in vitro diagnostic devices is required for approval or clearance of tumor-biomarker tests that will be marketed and distributed as kits to multiple laboratories. However, FDA clearance or approval of a tumor-biomarker test does not imply or require demonstration of clinical utility. FDA has not adopted the precise EGAPP or Clinical Assay Development Program terminology but does require analytical validation of a new test and evidence that the test performance is aligned with the claims, or intended use, of the manufacturer—including demonstration of clinical and statistical significance of the result in the test population. Nonetheless, the statute and regulations on which FDA operates, in most cases, does not allow FDA to require the high levels of evidence needed to show that use of the test improves clinical outcome (that is, clinical utility) (4).

Laboratory-developed diagnostic tests (LDTs) are produced and characterized within an individual laboratory following practices described under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. An LDT is used exclusively by the laboratory that developed and validated it. Laboratories that perform LDTs must either make their own reagents or purchase analyte-specific reagents that are regulated by FDA. However, CLIA has no requirement that, or a review process to determine whether, individual tests have either clinical validity or utility, and LDT review processes are not universally required for all laboratories performing LDTs. Because FDA has historically exercised enforcement discretion toward most LDTs, they do not require premarket review.

Approval of a new therapeutic agent in the absence of proven clinical utility or use of a new therapeutic without FDA approval is not permitted. The same should be true for a tumor-biomarker test that is used to guide patient management. In the current regulatory environment, many tumor-biomarker tests enter the market with analytical and clinical validity but insufficient information to establish their impact on health care outcomes. Thus, few of these tests are included in evidence-based guidelines, leaving health care professionals or third-party payers unsure of whether and how to use the tests or how much to pay for them, respectively (causes 2 and 5). Indeed, some commercial entities have circumvented FDA oversight by providing proprietary testing under CLIA within their own laboratories. FDA is currently considering internal and external discussion regarding this policy and has signaled its intention to begin regulating high-risk LDTs.

The uncertain regulatory environment also has a negative impact on domestic capital investment in the field. In a report from an IOM workshop on genome-based diagnostics, a venture capital expert pointed out that “creating a company to develop and fully commercialize an LDT can take up to $100 million dollars to get to a break-even point. … Even though some regulations may be tougher [outside the United States], they are clearer and [companies] know how to get reimbursed. Here in the [United] States, it is not clear that we can get reimbursed for molecular diagnostic tests. So better predictability and increased efficiency [is needed] because without clarity we cannot assess the risk of knowing when to invest or when not to invest” (12).

**Recommendation 1.** Reform regulatory review of tumor-biomarker tests. The same regulatory requirements that pertain to new therapeutics should apply to tumor-biomarker tests because they are used to direct therapy. We suggest four components, some of which can be implemented at the discretion of FDA, whereas others require congressional input (Table 1).

(i) FDA should reorganize review of all oncology products, including biomarkers and therapeutics, into an oncologic product line that is reviewed jointly by the Office of Hematology and Oncology Products (OHOP) in the Center for Drug Evaluation and Research (CDER) and the Office of In Vitro Diagnostics (OIVD) in the Center for Devices and Radiological Health (CDRH).

(ii) Currently, tumor-biomarker tests are principally reviewed by CDRH, which is responsible for a broad range of therapeutic and diagnostic devices, whereas cancer therapeutics are reviewed by CDER. Although these offices communicate, the focus of each center on its respective expertise is not optimal for regulation of new products designed to be used in concert for management of the same disease, such as cancer. The organization of oncological products, whether they are diagnostic or therapeutic, into a single administrative structure would combine the specialized expertise of each center and provide a broader “corporate memory” regarding tumor-biomarker test evaluation.

(ii) Do not adopt the EGAPP definitions [endorsed by the National Cancer Institute (NCI) and IOM] of analytical and clinical validity and clinical use are required. We recommend that (i) FDA adopt the EGAPP definitions [endorsed by the National Cancer Institute (NCI) and IOM] of analytical and clinical validity and clinical use are required. We recommend that (i) FDA adopt the EGAPP definitions [endorsed by the National Cancer Institute (NCI) and IOM] of analytical and clinical validity and clinical use are required.
utility and (ii) tumor-biomarker tests, like drugs, receive FDA approval or clearance only if level 1 evidence generated either in prospective clinical trials or in prospective-retrospective studies exists to support both analytical validity and clinical utility.

(iii) FDA should reconsider enforcement discretion currently being applied to tumor-biomarker LDTs and ensure they are subject to FDA regulatory controls.

This proposal would require that FDA establish a risk-based review process for all tests no matter their source of manufacture and commercialization strategy. This strategy should be flexible and balance the need for both innovation and patient safety, and equivalent standards should be applied uniformly across all tests. We propose that FDA, at the very least, review new biomarker tests to determine whether the test has analytical validity and sufficient level 1 evidence to support clinical utility.

(iv) FDA should recommend that all new drug registration trials be accompanied by an appropriate biospecimen bank that is collected and archived with support from the sponsoring pharmaceutical company.

FDA has recently proposed a policy that recommends that development of a companion diagnostic be performed in concert with clinical development of a new therapeutic if the test is required to ensure safety and efficacy of the therapeutic (13). However, for many therapeutics, the precise target is not yet fully delineated, or the test is not yet developed at the time the clinical trial is conducted. Archived specimens from the registered clinical trial would permit prospective-retrospective studies to generate high levels of evidence data that support clinical utility for a subsequently generated predictive tumor biomarker (6). Preferably, biospecimen banks should be maintained by an “honest-broker” committee of clinical, translational, and statistical scientists. We suggest that the sponsoring company should have input regarding use of these specimens but should not have final say or veto power. This proposal would require development of new intellectual property models, entailing legal co-rights for the sponsoring pharmaceutical company to any new products that are developed. This initiative might be accompanied by innovative tax credit accounting, so that pharmaceutical manufacturers are rewarded financially for developing, maintaining, and using valuable biospecimen banks derived from therapeutic clinical trials. Such considerations were addressed in a recently published American Association for Cancer Research (AACR)-FDA-NCI Cancer Biomarkers Collaborative Consensus Report (1).

### Table 2. Proposals to enhance adoption of tumor-biomarker test results into the clinic.

1. **Reform regulatory review of tumor-biomarker tests.**
   
   FDA should:
   
   a. Consider reorganization of review of all oncology products, including biomarkers and therapeutics, into an “Oncologic Product Line” that is reviewed jointly in a matrix consisting of the OHOP in CDER and OIVD in CDRH.
   
   b. Revise criteria for tumor-biomarker test approval, so that both analytical validity and clinical utility are required.
   
   c. Reconsider enforcement discretion currently being applied to tumor-biomarker LDTs and ensure that these tests are subject to all appropriate FDA regulatory controls.
   
   d. Consider that all new drug registration trials be accompanied by an appropriate biospecimen bank for which specimens are collected and archived with support from the sponsoring pharmaceutical company.

2. **Increase reimbursement for tumor-biomarker tests that have clinical utility.**
   
   a. Reimbursement should be value-based for a tumor-biomarker test with level 1 evidence that demonstrates clinical utility.

3. **Increase investment for tumor-biomarker research commensurate with that for therapeutics.**
   
   NCI and other cancer research–funding entities should:
   
   a. Support studies that are designed to determine the clinical utility of tumor-biomarker tests, in a manner similar to support provided for therapeutics.
   
   b. Provide adequate per capita (per patient) funding for clinical trials of tumor-biomarker tests that are commensurate with that provided for therapeutic studies.
   
   c. Provide adequate funding for proper collection, processing, and analysis of biospecimens in all clinical trials.
   
   d. Provide adequate funding for, or provision of, the tests required to conduct prospective clinical trials of new tumor-biomarker tests.
   
   e. Establish a system for collaborative research of tumor-biomarker tests similar to the CRADA system now in place for cancer therapeutics.

4. **Increase rigor for tumor-biomarker publication peer review and endorse and enforce reporting guidelines.**
   
   a. Journal editors should more widely adopt and more rigorously enforce BRIQ, REMARK, and other similar reporting formats for biomarker test studies by incorporating checklists in submission requirements.
   
   b. Be as eager to accept for publication studies of analytical validation and ones with negative results that refute previously published data as they are for highly positive, speculative results.

5. **Guidelines bodies should adhere to evidence-based recommendations for tumor-biomarker test use.**

Cause 2. Poor reimbursement levels for tumor-biomarker tests with established clinical utility. Pharmaceutical companies continue to pursue novel therapeutics because, historically, “blockbuster” agents result in sales that make up for the long and expensive R&D process (14, 15). In contrast, tumor-biomarker tests are not expected to yield the same level of financial return on the investment because revenues are lower for diagnostics than for therapeutics. The most successful commercial tumor-biomarker tests, such as the 21-gene recurrence score for breast cancer (OncomineDx, Genomics Health, Inc), may generate only $50 to $200 million per year (form 10-K; filed 11 March 2011; www.sec.gov/Archives/edgar/data/1131324/00009501231124832/ f58029e10vk.htm), and annual revenues for the majority of such tests on the market today are <$50 million (16).

Current reimbursement for LDTs is based on the laboratory resources necessary to produce the tumor-biomarker test rather than its clinical value. Because laboratories are not required to produce evidence supporting clinical utility, clinicians have determined whether a test is useful by using it. Furthermore, LDTs are rarely patented because the laboratories do not intend to...
commercialize the tests, and thus, LDTs are easily copied.

In the current U.S. reimbursement environment, it is impractical to require the level of clinically relevant scientific rigor for adoption of a new tumor-biomarker test that is necessary for approving therapeutics because the commercial entity cannot recoup its investment during the patent life of the product. Furthermore, although difficult to document, it is likely that the use of LDTs that mimic commercially available devices erode the market for the latter. However, inappropriate validation and use of tumor-biomarker tests lead to equally inappropriate application of therapeutics. In the absence of an accurate and reliable tumor-biomarker test, effective therapies may be withheld from patients who could have benefited most, or—much more commonly in oncology—a therapy, with all of its associated toxicities and cost, is administered to a large group of patients, among which only a few will benefit.

Recommendation 2. Increase reimbursement for tumor-biomarker tests that have clinical utility. Adoption of this recommendation requires assessment of evidence that shows that clinical use of a tumor-biomarker test improves patient outcomes (7). This requirement will raise the cost of translating a tumor-biomarker test to clinic. Thus, reimbursement for a tumor-biomarker test should permit recovery of R&D costs with a reasonable profit margin if level 1 evidence supports clinical utility; this will stimulate more investigators and entrepreneurs to both enter the field and conduct rigorous studies to address clinical utility, rather than just clinical validity, of a tumor-biomarker test.

A tumor-biomarker test with clinical utility is one that identifies patients who will not benefit from a given therapy (either because of a very favorable prognosis or an unfavorable prediction of response to therapy) or who are no longer benefiting from a specific therapeutic strategy (determined on the bases of serial monitoring). Given the enormous expense of targeted anticancer therapies, the identification of patients whose chance of benefit is so small that they would forego the treatment to avoid the toxicities will save money that is now spent on futile treatments. This concept needs to be demonstrated by rigorous studies of clinical utility so as to determine the impacts on patient outcomes and costs of therapy.

Reimbursement of a few thousand dollars, considered high for a diagnostic test, is minimal when compared to the $50,000 to $100,000 per-year cost of many anticancer regimens (17). For example, reimbursement for cetuximab is approximately $110,000 per year. Median overall survival benefit for cetuximab versus nil is 1.5 months for an unselected population with metastatic colorectal cancer, but there is no benefit if the cancer contains KRAS mutations versus a 4.7-month benefit for those with wild-type KRAS tumors (18). Thus, focusing therapy on those patients with wild-type KRAS cancers saves millions of dollars, while ensuring that those most likely to benefit are treated.

A corollary to this recommendation is that third-party payers, while being asked to provide reimbursement for tumor-biomarker tests, would be justified in not reimbursing for treatments of patients for whom tumor-biomarker test results suggest that the therapy would be of little or no benefit. Cost- and clinical-effectiveness analyses must be conducted for each tumor-biomarker test for specific intended uses and clinical situations, and the ratio of the number of patients who must be tested in order to identify those who will not benefit from a drug will influence the extent of savings. Some of this increased efficiency should be used to reward investigators and commercial entities that engage in rigorous development and assessment of the biomarker test.

Cause 3. Insufficient investment for tumor-biomarker test development and clinical research. We maintain that the relative undervaluation of tumor-biomarker tests contributes to the great disparity in the degree of public and private/commercial support for therapeutics versus tumor-biomarker studies that assess clinical utility. More consideration must be given to enhancing support for the generation of high-level data on the clinical utility of tumor-biomarker tests outlined in the IOM report on omics-based tests (6, 7, 19, 20). However, if more stringent criteria for regulatory approval are implemented in the absence of resources in order to support the necessary research and to reward commercial entities that comply, then the vicious cycle (Fig. 1A) will be perpetuated, and even fewer new tests will be developed.

Areas of progress. Only a few clinical trials designed to prospectively address the specific clinical utility of a tumor-biomarker test have been conducted in the NCI-sponsored North American cooperative groups (21–23). Although NCI has provided funding for collection and archiving of biospecimens from patients enrolled in cooperative-group therapeutic trials, far too many clinical trials, especially those supported by industry, do not prospectively collect and bank biospecimens. Therefore, although prospective-retrospective studies are expedient, the biospecimens needed to conduct them properly may not be available [recommendation 1 (iv), above]. NCI has generated several other encouraging initiatives that are directly or indirectly designed to stimulate tumor-biomarker research (table S2). These efforts should provide the impetus to design and conduct prospective trials to investigate the clinical utility of a cancer biomarker test, but they remain insufficient when compared with the existing infrastructure to support therapeutic research.

Recommendation 3. Increase investment for tumor-biomarker research commensurate with that for therapeutics. Although these subproposals are directed mainly toward studies funded by NIH or private foundations, they are applicable to pharmaceutical industry–sponsored studies as well. Public, private, and commercial cancer-research funding entities should:

(i) Support studies that are designed to determine the clinical utility of tumor-biomarker tests.

(ii) Provide adequate per capita (per patient) funding for clinical trials of tumor-biomarker tests commensurate with that provided for therapeutic studies.

(iii) Provide adequate funding for patient accrual and for proper collection, processing, and analysis of biospecimens in all clinical trials. The overall NCI-sponsored cancer clinical trial system is underfunded (24). However, clinical investigators currently are provided even less per capita support for accrual to a tumor-biomarker test study than for a therapeutic trial, even though if properly conducted, the workload is the same or even higher, given the requirement for collection, processing, and mailing of biospecimens.

(iv) Provide adequate funding for, or provision of, the tests required to conduct prospective clinical trials of new tumor biomarker tests. Although the Biomarker, Imaging and Quality of Life Studies Funding Program is exciting, its funding is inadequate and only represents a fraction of the support for therapeutic trials.

(v) Establish a system for collaborative research of tumor-biomarker tests similar to the Cooperative Research and Development Agreement (CRADA) system now in place.
for cancer therapeutics. Using the CRADA process, pharmaceutical companies establish private-public partnerships to provide drugs for clinical trials conducted within the cooperative groups, sponsored by NIH (http://oig.hhs.gov/oei/reports/oei-01-92-01100.pdf).

**Cause 4. Insufficient scrutiny by peer-reviewed journals for tumor-biomarker research publications.** Criteria for peer-reviewed publication of tumor-biomarker test results have generally been less rigorous and less well defined than those for clinical trial research reports, resulting in a multitude of substandard studies that suggest clinical validity but very few studies that address clinical utility at a high level of evidence.

**Areas of progress.** Most major journals have accepted and endorsed criteria that strengthen reporting of clinical trial results for novel therapeutic strategies, including the requirement that a clinical trial be prospectively registered (clinicaltrials.gov) and that the manuscript methods clearly provide details regarding patient eligibility and ineligibility, primary and secondary end points, prespecified hypotheses, the statistical/analytical plan, and description of patient flow through the study (the CONSORT criteria) (25). Initiatives to provide more rigorous and transparent criteria for publication of tumor-biomarker studies include the REMARK criteria (26) and the Biospecimen Reporting for Improved Study Quality criteria (BRISQ) for more transparent reporting of preanalytical issues (27, 28). A tumor-biomarker test study registry similar to clinicaltrials.gov was recently established (29). However, a review of published tumor-biomarker test results in selected major journals in years subsequent to these endorsements suggests that fewer than half of the authors adhered to or cited the REMARK criteria (30). Such documentation should be an essential component for publication in high-impact journals of biomarker data that are purported to support clinical utility.

**Recommendation 4. Increase rigor for tumor-biomarker publication peer review, and endorse and enforce reporting guidelines.** Journal editors should (i) more widely adopt and more rigorously enforce BRISQ, REMARK, and other similar reporting formats for biomarker-test studies by incorporating checklists in submission requirements and (ii) be as eager to accept for publication studies of analytical validation and negative studies that refute previously published results as they are for positive speculative results.

**Cause 5. Poor availability of high levels of evidence for tumor-biomarker test clinical utility to support recommendations for clinical use.** The absence of definitive federal regulatory review of tumor-biomarker test clinical utility has led professional guideline panels and third-party technical assessment committees to provide guidance for clinical use of tumor-biomarker tests. However, causative factors 2 to 4 have dampened enthusiasm to conduct the type of clinical research needed to generate high levels of evidence to support clinical utility of tumor-biomarker tests. In spite of the thousands of publications on cancer biomarkers in the peer-reviewed literature, only a few tumor-biomarker tests have gained sufficient levels of evidence to be recommended for clinical use (5, 6, 9). The data to support clinical utility of other potentially useful tumor-biomarker tests are simply insufficient for evidence-based guidelines committees to make firm recommendations.

**Recommendation 5. Guidelines bodies should adhere to evidence-based recommendations for tumor-biomarker test use, insisting on high-level evidence to do so.** The corollary to this recommendation is that clinicians should only order tumor-biomarker tests for which high-level evidence to document clinical utility exists. Furthermore, they should not order tests on which they will not rely for clinical decision-making, and third-party payers would be justified in denying reimbursement for such tests. This recommendation does not mean that a clinician must adhere to a clinical pathway dictated by a tumor-biomarker test in all instances. An approved therapy may not always work or may have unexpected toxicities, and therefore, clinicians must use judgment to decide whether to continue that treatment for individual patients. Nonetheless, if the clinician has high confidence in the clinical utility of a tumor-biomarker test, he or she is more likely to be comfortable acting on the results.

A vicious cycle (Fig. 1A) has prevented widespread adoption of robust tumor-biomarker tests and, just as importantly, has introduced poorly validated tests into clinical practice, thus impeding the advance of personalized medicine. We propose reform of (i) the perception, design, conduct, and funding of tumor-biomarker research and (ii) regulatory oversight, criteria for clinical utility (4, 31), reimbursement practices, and peer-reviewed publication policies to raise the value of tumor-biomarker tests to that of therapeutics. If adopted, these ambitious but critical reforms should result in a virtuous cycle in which tumor biomarkers are properly valued by all stakeholders (Fig. 1B). We call for a national dialogue among all the key stakeholders (Table 1) to reach a consensus referendum on tumor-biomarker test R&D so that such tests can be rapidly introduced into routine patient care.

**SUPPLEMENTARY MATERIALS**

www.sciencetranslationalmedicine.org/cgi/content/full/5/196/196cm6/DC1

Table S1. NCI initiatives to stimulate tumor-biomarker research. Fig. S1. Tumor-biomarker test development process.

**REFERENCES AND NOTES**

COMMENTARY


Competing interests: D. F. H. is a consultant for Oncimmune LLC, Inbiomotion, and Biomarker Strategies; has received research funding from Novartis, Veridex (Johnson & Johnson), and Janssen R&D, LLC (Johnson & Johnson); is a co-inventor on U.S. Patent No. 05725638.0-1223-US2005008602, which described a method for predicting progression-free and overall survival in metastatic breast cancer patients using circulating tumor cells; and has applied for patents for a test for diagnosis and treatment of breast cancer (U.S. Provisional Patent Application. Original Application No. 61/079,642) and for Circulating Tumor Cell Capturing Techniques and Devices (U.S. Provisional Patent Application No. 61/593,092). None of the other authors declare that they have competing interests.
