PRECISION MEDICINE

Measure for Measure: Biomarker standards and transparency

Garret A. FitzGerald

Biomarker tests for molecularly targeted therapies might be the key to unlocking the entry gate to precision medicine.

Biomarkers are functional variants or quantitative indices of a biological process that predict or reflect the evolution of or predisposition to a disease or a response to therapy. As such, they may serve to integrate preclinical, translational, and clinical science and are viewed as intrinsic to the pursuit of precision medicine. One focus is the use of biomarkers to guide the prescribing of molecularly targeted therapies in cancer, as exemplified by imatinib (*1*). However, there is big money to be made in a largely unregulated landscape; interventions by the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) to curb the claims of 23andMe (*2*) and Theranos (*3*, *4*) highlight the need for common evidentiary standards relevant to both analytical validity (does the test work?) and clinical utility (does its application influence clinical outcomes?).

In both cases, biomarker testing services were marketed directly to the public, bypassing a mandatory step of professional interpretation. Although this route has the superficial appeal of empowering consumers to reach personal decisions about their health (*5*), problems with variability in data interpretation, sample collection, and analytical reliability prompted intervention by the regulators to warn the manufacturers to curb their practices.

However, problems with interpretation arise even when medical information is provided first to physicians and then to patients. For example, we have only a limited understanding of whether a particular gene variant predicts the development of a disease (penetrance) in an individual patient and whether the presence of the variant dictates action (*6*). This context and the launch of U.S. President Barack Obama's Precision Medicine Initiative (*7*) framed a recent report from the U.S. National Academy of Medicine (NAM) entitled "Biomarker tests for molecularly targeted therapies: Key to unlocking precision medicine" (*8*).

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COMMON EVIDENTIARY STANDARDS

The report highlights the diversity of stakeholders involved, among them patients and their advocates; health care providers; companies that develop, provide, and reimburse such tests; drug manufacturers [exemplified by the linking of drug approval to a diagnostic biomarker (*9*)]; regulators; and policy-makers and other funders who must be encouraged to support the research that underlies the development and application of such tests. The stakeholder pool includes, among others, the U.S. National Institutes of Health (NIH), CMS, the Agency for Healthcare Research and Quality (AHRQ), and the Patient-Centered Outcomes Research Institute (PCORI).

Progress in the biomarker field is held back by interrelated factors—the lack of common evidentiary standards for analytical validity, clinical validity (the accuracy of the test for a specific purpose), and clinical utility (the ability of a test to prevent or ameliorate adverse health outcomes); inconsistent and inefficient standards for regulation and reimbursement; and the lack of an effective framework for the collection of data on patients, tests, treatments, and outcomes as well as approaches for converting such information into new knowledge that will improve patient care and outcomes.

The report calls on the U.S. Department of Health and Human Services (DHHS) to convene one or more public-private stakeholder bodies to establish common evidentiary standards to serve as a basis for regulation and reimbursement. The report also recognizes the inadequacy of the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as a basis for laboratory oversight in an era of continuously evolving genome sequencing technology and of widely varied reimbursement for the same test applied for the same purpose. Intrinsic to the success of this exercise is the recognition of the dynamic nature of the accrual of relevant data, the necessity to capture and interpret such information, and the need to communicate it to diverse stakeholders.

To this end, one of the NAM committee's key recommendations is the introduction of labeling for biomarker tests associated with specific molecularly targeted therapies. These labels should include information about a test described in terms understandable by patients, useful to health care providers, and informative as a basis for reimbursement. For example, in addition to a narrative, a star rating could be applied to specify the test's analytical and clinical validity, and clinical utility. Crucial to this initiative is routine updating of the labeling as new information emerges. For example, the results of a trial measuring clinical outcomes in patients stratified by a biomarker test might upgrade its rating for clinical utility. On the other hand, the apparent "pathogenicity" of a gene variant is often downgraded with the acquisition of larger data sets over time (*6*). Reimbursement might, as an incentive, require ongoing postmarketing data collection and assessment. However, linkage of reimbursement strategies to the updating of labeling information might encourage the provision of new "favorable" information by providers; thus, a monitoring system independent of providers would be necessary to avoid such systematic bias. Last, the strengthening and modernizing of laboratory oversight and accreditation should comply with test labeling requirements.

NATIONAL DATA RESOURCE INITIATIVE

The committee's report calls on manufacturers of electronic health records (EHRs) and laboratory information systems to play a central role in the development of a national data resource for biomarker tests and molecularly targeted therapies. This mandate includes the structuring of information to facilitate data transfer into one or more databases. Such information should include the type, amount, and handling of biomarker specimens; test results and interpretations; what subsequent tests were ordered and treatments prescribed; the influence of the biomarker test results on these decisions; and longitudinal data on clinical outcomes.

To satisfy the interests of diverse stakeholders, EHRs must evolve to be layered for rapid point-of-care data entry with provision of more detailed information before and after a patient visit, to allow for linkage to patient portals that integrate educational materials with labeling information, to incorporate practice guidelines as decision support, and to allow for tracking compliance. Relevant organizations should routinely coordinate information related to their development of clinical guidelines and update data on biomarker tests.

Intrinsically linked to this initiative is the NAM report's call for DHHS to convene a task

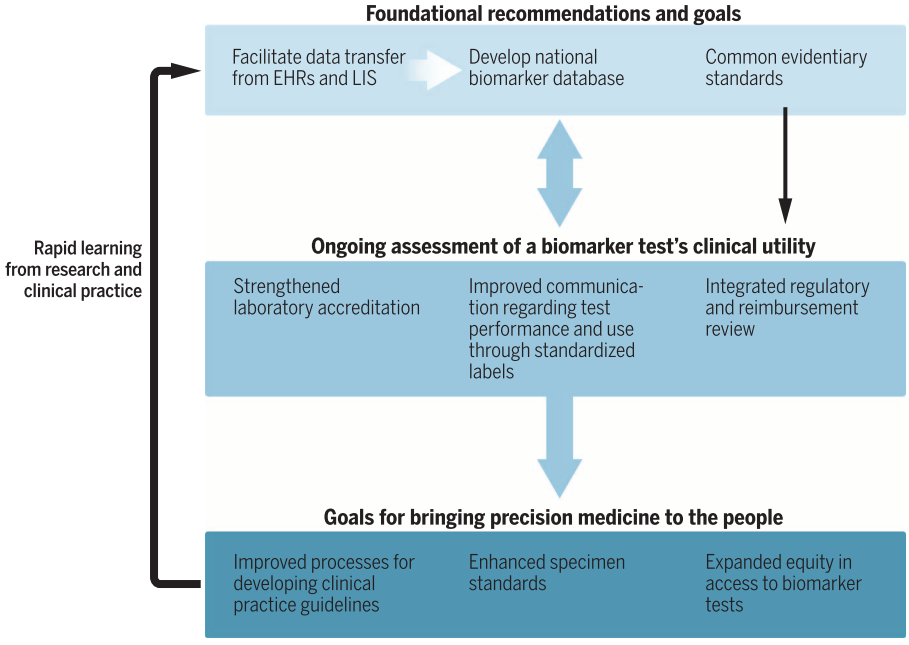

Fig. 1. "What's mine is yours, and what is yours is mine."* Synthesis of many people's research and clinical data can pinpoint truly beneficial biomarkers and drive precision medicine. The schematic illustrates NAM's vision for finding, validating, and continuously improving biomarkers for clinical use. Row 1, fundamental goals; Row 2, perpetual assessment to improve biomarker tests; Row 3, goals for bringing precision medicine to the people. *From *Measure for Measure* by William Shakespeare.

force of FDA scientists and potential funders charged with developing an appendable national database for scientific, regulatory, and clinical information that would be updated and sustained. This database would then develop over time as an accumulating resource for interpretation of the clinical utility of biomarker tests for molecularly targeted therapies in a disease-agnostic fashion. The committee emphasized that strategies should be developed to incentivize health care professionals and researchers to enter their data into such a secure and compliant open-access repository.

A RAPID LEARNING SYSTEM

NAM's strategy for using biomarkers and targeted therapies to drive precision medicine rests on a rapid learning system whereby data derived from scientific research and clinical practice continuously refine the national data resource and, potentially, the evidentiary standards (Fig. 1). Development of a rapid learning system for health care requires educational initiatives at many levels but especially for patients and health care providers. Particular emphasis is placed on strategies for thwarting health or disease disparities—a fundamental goal for realizing the promise of precision medicine—be they regional, socioeconomic, or reflective of the rarity or nature of a disease. Given the pitch of recreational genetic analysis to the affluent and worried well (*2*), it is vital that treatment refinements and enhancement of clinical outcomes promised by the efficient linkage of biomarker tests to molecularly targeted therapies not be restricted to particular patient groups.

The development of broad evidentiary standards and cumulative acquisition of data on clinical utility will drive decisions to prescribe specific drugs only for those patients in whom the therapeutic might reasonably be expected to yield improved health outcomes. Successful precision medicine strategies provide a rationale for reimbursement, continued innovation, and broad coverage unrestrained by a patient's distinct circumstances.

REFERENCES

1. B. J. Druker, N. B. Lydon, Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. *J. Clin. Invest.* **105**, 3–7 (2000).
2. G. J. Annas, S. Elias, 23andMe and the FDA. *N. Engl. J. Med.* **370**, 985–988 (2014).
3. B. A. Kidd, G. Hoffman, N. Zimmerman, L. Li, J. W. Morgan, P. K. Glowe, G. J. Botwin, S. Parekh, N. Babic, M. W. Doust, G. B. Stock, E. E. Schadt, J. T. Dudley, Evaluation of direct-to-consumer low-volume lab tests in healthy adults. *J. Clin. Invest.* **126**, 1734–1744 (2016).
4. D. Crow, "Blood simple: Theranos technology under fire," *Financial Times*, 9 April 2016.
5. E. Topol, *The Patient Will See You Now. The Future of Medicine Is in Your Hands* (Basic Books, New York, 2015), p. 384.
6. A. K. Manrai, J. P. Ioannidis, I. S. Kohane, Clinical genomics: From pathogenicity claims to quantitative risk estimates. *JAMA* **315**, 1233–1234 (2016).
7. E. A. Ashley, The Precision Medicine Initiative: A new national effort. *JAMA* **313**, 2119–2120 (2015).
8. Biomarker tests for molecularly targeted therapies: Key to unlocking precision medicine. Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies, Board on Health Care Services, Institute of Medicine, U.S. National Academies of Sciences, Engineering, and Medicine; L. A. Graig, J. K. Phillips, H. L. Moses, Eds. (National Academies Press, Washington, DC, 2016).
9. S. L. Martiniano, S. D. Sagel, E. T. Zemanick, Cystic fibrosis: A model system for precision medicine. *Curr. Opin. Pediatr.* **28**, 312–317 (2016).

10.1126/scitranslmed.aaf8590

Citation: G. A. FitzGerald, Measure for Measure: Biomarker standards and transparency. *Sci. Transl. Med.* **8**, 343fs10 (2016).

Science Translational Medicine

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Sci Transl Med **8**, 343fs10343fs10.
DOI: 10.1126/scitranslmed.aaf8590