Evolution of Translational Omics
Lessons Learned and the Path Forward

Sequencing the human genome opened a new era in biomedical science. Researchers have begun to untangle the complex roles of biology and genetics in specific diseases, and now better understand why particular therapies do or do not work in individual patients. New technologies have made it feasible to measure an enormous number of molecules within a tissue or cell; for example, genomics investigates thousands of DNA sequences, and proteomics examines large numbers of proteins. Collectively, these technologies are referred to as omics.

Patients look to the scientific community to develop innovative omics-based tests to more reliably detect disease and to predict their likelihood of responding to specific drugs. However, transforming the great promise of these new technologies into clinical laboratory tests that can help patients directly has happened more slowly than anticipated.

The process to translate omics-based discoveries into clinically useful tests is much more demanding than has been widely recognized. For example, verification of the complex computational procedures used to develop omics-based tests requires adequate access to the data, computer code, and computational steps used to develop that test. Also, regulatory oversight of clinical laboratory tests differs from that of drugs. Thus far, the Food and Drug Administration (FDA) has chosen not to review most of these clinical tests.

These challenges converged during a recent case involving premature use of omics-based tests in clinical trials at Duke University. Flawed gene-expression tests developed by cancer researchers at Duke were used in three clinical trials to determine which chemotherapy treatment patients with lung or breast cancer would receive. For three years, the Duke investigators rebuffed...
external criticisms about publications describing their tests. But in July 2010, more than 30 outside scientists raised concerns about the validity of the tests and asked the National Cancer Institute (NCI) to intervene and suspend the trials until the gene-expression tests could be reviewed adequately.

The episode led the NCI to request that the Institute of Medicine (IOM) establish a committee to recommend ways to strengthen omics-based test development and evaluation. While lessons were drawn from several case studies of omics-based test development, including at Duke University, investigating allegations of scientific misconduct at Duke was outside the scope of the IOM study.

**Best Practices for Future Research and Development**

In its report *Evolution of Translational Omics: Lessons Learned and the Path Forward*, the IOM committee identifies best practices to enhance development, evaluation, and translation of omics-based tests while simultaneously strengthening steps to be taken to ensure that these tests are appropriately assessed for scientific validity before they are used to guide patient treatment in clinical trials. (See Figure.)

The committee’s recommendations speak to the many parties responsible for discovery and development of omics-based tests, including investigators, their institutions, sponsors of research, the FDA, and scientific journals. The committee’s test development process guides the actions of these key players at every milestone, as omics-based tests make their way from the laboratory into clinical trials to assess their usefulness in guiding medical decisions for patients.

Because omics research relies on the analysis of very large datasets, the use of rigorous methods in statistics, bioinformatics, and data management are essential. Inappropriate methods yield computational procedures that are accurate for the samples used in the initial discovery but are inaccurate for any other samples.

Accordingly, the committee recommends that all information needed to verify the test discovery process be disclosed through publication or patent application. In addition, the computational procedures must be “locked down” (recorded and no longer changed) and then confirmed with a new set of samples not used in the initial discovery. If the locked-down test is not confirmed at this stage, it is much more likely to fail in subsequent steps. Investigators should complete this confirmation without prior knowledge of the clinical information linked to specimens that are being analyzed.

At the end of the discovery phase, a candidate omics-based test should be precisely defined, including the molecular measurements, locked-down computational procedures, and intended clinical use.

Next, the candidate omics-based test moves to the validation phase so that its ability to generate accurate and consistent measurements as well as its ability to accurately and reliably predict the clinical condition of interest can be assessed. Any clinical laboratory that reports tests for use in guiding patient care falls under the purview of the Clinical Laboratory Improvement Act (CLIA), which provides oversight for the quality of laboratory operations. For this reason, test validation should be performed in a CLIA-certified laboratory, which should design, optimize, validate, and implement the omics-based test under current clinical laboratory standards.

Once the performance of the clinical laboratory test is deemed acceptable, the candidate test is ready for use in a clinical trial to assess its usefulness in guiding medical decisions for patients. The committee strongly urges that investigators consult with the FDA prior to beginning a clinical trial. If decisions about patient care will be guided by omics-based test findings in a clinical trial, this consultation is a legal requirement.
engaging in research to develop omics-based tests intended for clinical use.

To avoid adding new barriers to innovation in this promising field, the committee is not recommending creating a brand new system of oversight. Rather, its recommendations focus on existing responsibilities of institutions to ensure the integrity of the scientific process. For example, although nearly all institutions have policies and procedures to disclose and mitigate financial conflicts of interest for individuals, there is often less clarity when handling institutional conflicts of interest—both financial and non-financial. In certain instances, an outside body should be asked to investigate when an institution might appear too conflicted.

Lessons From the Duke Case

Because many published papers describing the omics-based tests developed at Duke University now have been retracted, it is widely accepted that those particular tests were not scientifically valid. Unfortunately, the usual systems to ensure the integrity and rigor of the scientific and translational process failed to prevent those invalid tests from being used in clinical trials.

This failure stemmed from problems that may exist at other institutions: unclear lines of accountability, lack of consistently strong data management, lack of independent confirmation of the omics discovery, failure to lock down the specific test methods, inadequate validation of the omics-based test prior to commencing clinical

Institutional Policies and Procedures to Support Scientific Integrity

The investigators involved in omics research and test development, often working in interdisciplinary teams, bear the greatest responsibility and accountability for the scientific rigor and transparency of omics research. They need to foster a culture of scientific integrity through the discovery and development process.

Academic institutions, other non-profit research organizations, and for-profit companies that support development of omics-based tests also are responsible for ensuring proper oversight of the omics research conducted and reported by their respective staffs.

An institution’s overarching role is to develop policies and procedures that promote scientific integrity, and—when circumstances warrant—to investigate allegations of incorrect or improper research and reporting practices.

The committee stresses the importance of institutional awareness and oversight when developing tests for use in clinical trials, in part because FDA oversight traditionally has not been a central component of clinical laboratory test development. Lack of FDA oversight places an often unrecognized demand on academic institutions to provide proper oversight for omics-based test development, validation, and clinical use.

The committee suggests that institutions lacking the infrastructure or capability to follow all elements of the recommended test development and evaluation process should consider not engaging in research to develop omics-based tests intended for clinical use.
Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials

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Food and Drug Administration
Centers for Disease Control and Prevention
U.S. Department of Veterans Affairs
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Conclusion

New omics-based tools have the potential to truly revolutionize patient care, but as with any great promise, they come with great responsibility. The recommendations outlined in this report define best practices and provide a guide along the entire pathway for developing omics-based tests—from discovery to clinical trials—to assist the many parties contributing to this important translational research. These guidelines, if adopted, can ensure that progress in omics-based test development is grounded in sound scientific practice and is reproducible, resulting not only in improved health care but also—and perhaps equally important—in continued public trust.

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**FIGURE: Omics-Based Test Development Process**

NOTE: The computational procedures are locked down in the discovery phase, meaning they are recorded and no longer changed in the subsequent development steps. A clinical test should be fully defined, validated, and locked down before crossing the bright line to enter the stage in which the test undergoes evaluation for its intended clinical use. (FDA is the Food and Drug Administration, IDE is an investigational device exemption, IRB is an Institutional Review Board, and LDT is a laboratory-developed test.)