Prepping Omics for the Clinic

By Rabiya S. Tuma

The much-anticipated Institute of Medicine (IOM) report *Evolution of Translational ‘Omics: Lessons Learned and the Path Forward*, released on March 23, focuses on how scientists can accurately develop omics-based tests for clinical use.

“We describe best practices for the discovery and confirmation of a potential new test in a research lab, validation for the test in a clinical lab, and use of the test in clinical trials—and eventually in clinical practice—to assess its utility in guiding selection of patient therapies,” said Gilbert Omenn, M.D., Ph.D., professor of internal medicine, human genetics, and public health, and director of the Center for Computational Medicine and Bioinformatics at the University of Michigan Medical School in Ann Arbor, who chaired the IOM committee.

The request for the report stemmed from problems at Duke University, where researchers claimed to have developed gene expression signatures that could predict patient responses to therapy and used the tests in patient trials without proper validation (*J. Natl. Cancer Inst.* 2011;103:916–17).

After a little more than a year of work, the committee members developed recommendations aimed at many stakeholders, including investigators, research institutions, journal editors, funding agencies and groups, and the U.S. Food and Drug Administration. The recommendations are not binding, of course, but committee members and observers think the responsible parties have some incentive to follow the report’s guidance.

“I think that academic institutions will pay attention to the report because most institutions are aware of the events at Duke,” said committee member Debra G. B. Leonard, M.D., Ph.D., professor and vice chair for laboratory medicine and director of clinical laboratories at Weill Cornell Medical College in New York, during a press conference announcing the report.

**Transparency and Oversight Are Key**

A main recommendation in the report is a call for increased transparency at multiple levels of the process. For example, investigators developing potential omics-based tests for clinical use should make available the data, computer code, and computational methods they used to develop the test. Such transparency would make replicating, discovering problems with, and building on the work easier for independent researchers.

An additional, but no less important, reason for the transparency is that it can strengthen the value of the work itself, said committee member Nathan D. Price, Ph.D., associate professor at the Institute for Systems Biology in Seattle, during the IOM press conference. Omics-based tests are prone to statistical artifacts because they evaluate many variables (e.g., genes, proteins, or metabolites) on relatively few biological samples. Therefore, true biological signals can be difficult to distinguish from background noise, and conversely, artifacts can be mistaken for biologically meaningful signals.

Those problems, though, diminish as multiple research groups use the same omics signature and methods on different data sets. With such replication, a true biological signal is amplified relative to the noise, according to Price. And that may have good consequences for the field of biomarkers in general, which has not yet fulfilled its promise for personalized medicine.

“There is every reason to think that while up to now in the field most of the studies have been individual, underpowered, and very prone to overfitting, that going forward—as people are open and sharing happens more broadly—these signals will get more robust. It will have a major positive effect on the field,” Price said. (“Overfitting” denotes that the results of a statistical computer analysis fit the data used in the initial analysis but may not work when tested on independent datasets.)

The committee report also emphasizes the need for increased oversight during development process of an omics signature. The report recommends that researchers consult with the FDA long before considering testing their signature in patients. The report also recommends increased oversight at the level of the research institution, felt to be a point of failure during the Duke debacle. In fact, the report states that institutions that either are not willing to conduct or do not have the infrastructure and resources for adequate oversight should not develop omics signatures for clinical use.

“Patient safety is paramount, and public trust is at stake,” Omenn said during the press conference.

**Early Reaction Positive**

At nearly 300 pages, the report is dense. Many experts warn that it will take time for the community to fully digest its contents. Yet early responses are positive. Lisa McShane, Ph.D., the National Cancer Institute biostatistician who helped uncover errors in the Duke signatures, said the committee has set out a rational approach that researchers can follow during development of an omics-based signature for clinical use. According to McShane, it was also...

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important that the committee recognized that much of what happened at Duke might have happened at other places. Some academic researchers developing omics-based tests are stepping into the clinical development arena, without fully understanding the rigors of clinical research, and the committee guidance might mitigate some of the resulting problems. For example, the committee not only emphasized the need for researchers to “lock down” their computational methods and code before validation, but the members also took the time to define what locking it down means.

Keith Baggerly, Ph.D., a biostatistician at the University of Texas M. D. Anderson Cancer Center in Houston, who initially raised concerns about the Duke signatures, is also enthusiastic about the report. “The very existence of the report is recognition that reproducibility is an important problem for the omics-test community. This is a necessary step toward fixing the problem,” he said.

**Moving Forward**

Price acknowledged during the press conference that the committee’s recommendations may increase the hurdles required for any particular omics study. However, on balance, that increased onus on researchers early in the test development process could actually speed uptake of omics-based tests in the clinic by improving the quality of the tests that do make it into clinical validation studies.

“The pace of advancement of what actually makes it to the clinic would be greatly accelerated by adopting rigorous standards such as those put forth in this report,” he said.

The committee’s charge was broad and included a review of what happened at Duke that allowed the faulty signatures to be used in clinical trials even after researchers such as Baggerly expressed concerns about the quality. An appendix to the report describes their findings, which succinctly explain what happened and where errors occurred.

The committee also considered the development processes for eight other tests—seven of which are currently used in the clinic—that can be compared with the Duke case.

The committee, however, did not have major recommendations to manage conflict of interest, either individual or institutional. Committee members acknowledge that the issue is relevant, particularly given the financial value a successful omics test might have, but they deferred specific discussion to others and simply reiterated the need for proper management of conflicts.

As for the erroneous signatures developed at Duke and the investigators involved in those protocols, the most prominent question remains unresolved: The official misconduct investigation is ongoing, and the university spokesperson says there is no indication yet when it will be completed.

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