Evolution of Translational Omics: Lessons Learned and the Path Forward

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for the
Oomics-based Test Committee of the IOM
Origin of the Task

- Omics tests developed at Duke to predict sensitivity to chemoRx
  - Papers suggested major advance in directing therapy
  - Concerns about accuracy and validity raised immediately
  - Clinical trials initiated in 2007, using tests to direct patient care
  - 2009 publication by Baggerly and Coombes:
    - Numerous errors
    - Inconsistencies in data
    - Failure to reproduce results

- 2010 letter to director of NCI, signed by more than 30 bioinformaticians and statisticians, urged suspension of trials
- NCI investigation of test and computational models
- NCI asked IOM to review situation and provide guidance for field
Committee Charge

1. Recommend an evaluation process to determine when omics-based tests are fit for use in a clinical trial.

2. Apply these criteria to omics-based tests used in three cancer clinical trials conducted by Duke investigators.

3. Recommend ways to ensure adherence to the development framework.
Committee Appointment

IOM appointed a 20 member committee with expertise in:

- Clinical medicine
- Clinical pathology
- Biomarker test development
- Biostatistics and bioinformatics
- Molecular biology
- Clinical trial design, conduct, and analysis
- Discovery and development of omics-based technologies and tests
- Ethics
- Patient advocacy
- FDA oversight
- Scientific publication
- University administration
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Definition of an Omics Tests

• Composed or derived from multiple molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result
• Genomics, transcriptomics, proteomics, epigenomics, etc.
• NOT single gene or non-complex testing

Omics Test Characteristics
• Complex, high dimensional data sets
• Interpretation by a computational model
• High risk that computational model will overfit data
Recommended Framework for Evaluation of Omics Tests from Discovery to Clinical Use

Discovery and Test Validation Stage

- **Discovery Phase**
  - Candidate Test Developed on Training Set, Followed by Lock-Down of All Computational Procedures
  - Confirmation of Candidate Omics-Based Test using:
    1. An Independent Sample Set if Available (preferred); OR
    2. A subset of the Training Set NOT Used During Training (less preferred).

- **Test Validation Phase**
  - Define Clinical Test Method
  - Analytical Validation
  - Clinical/Biological Validation Using Blinded Sample Set
  - Defined, Validated, and Locked Down Test (Intended Use, Assay, Computational Procedures, and Interpretation Criteria)

Evaluation for Clinical Utility and Use Stage

Three Potential Pathways (IRB Approval and FDA Consultation)

- Prospective/Retrospective Study with Archived Specimens
- Prospective Clinical Trial; Test Does NOT Direct Patient Management
- Prospective Clinical Trial; Test Directs Patient Management

IDE Needed?

- No
- No
- Yes

- FDA Approval/Clearance or LDT Process for Clinical Test
- Additional High Quality Evidence to Evaluate Clinical Utility of the Test
  - Practice Guidelines and Reimbursement
  - Clinical Use

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Discovery Phase of Omics Test Development (Research Laboratory Setting)

Discovery Phase

Candidate Test Developed on Training Set, Followed by Lock-Down of All Computational Procedures

Confirmation of Candidate Omics-Based Test using:
1. An Independent Sample Set If Available (preferred); OR
2. A subset of the Training Set NOT Used During Training (less preferred).
Recommendation 1: Discovery Phase

If candidate omics-based discoveries are intended for clinical development & use:

a. The tests should be confirmed using an independent set of samples from the discovery sample set.

b. Data, code, and metadata should be made available.

c. Candidate test should be defined precisely:
   - Intended clinical use
   - Molecular measurements
   - Computational procedures
Test Validation Phase

- IRB Approval and Consultation with FDA
- Define Clinical Test Method
- Analytical Validation
- Clinical/Biological Validation Using Blinded Sample Set
- Defined, Validated, and Locked Down Test (Intended Use, Assay, Computational Procedures, and Interpretation Criteria)
Recommendation 2: Test Validation

- Test should be discussed with FDA prior to validation studies.

- Test development and validation should be performed in a CLIA-certified clinical laboratory.
  - CLIA-accredited Laboratory if test result used for patient care
  - Research Lab okay if test not used for patient care, but not ideal if want to translate to clinical use

- CLIA laboratory should design, optimize, validate, and implement the test under current clinical laboratory standards.

- Analytical validation and CLIA requirements should be met by each laboratory in which test will be performed for clinical trial.
Evaluation for Clinical Utility and Use Stage

- Clinical utility is not assessed by FDA or in the LDT process
- Lack of FDA review does not mean the test lacks clinical utility
- Process of gathering evidence to support clinical use should begin before test is introduced into clinical practice
- Approaches:
  - Prospective / Retrospective Study
  - Prospective Clinical Trial
Evaluation for Clinical Utility and Use Stage

Three pathways:

- **Prospective/Retrospective studies** using archived specimens from previously conducted clinical trials

- **Prospective clinical trials** that directly address the utility of the omics-based test, where either
  - The test **does not direct** patient management, or
  - The test **does direct** patient management.
Recommendation 3: Evaluation for Clinical Utility and Use Stage

For investigators conducting a clinical trial to assess the clinical utility and use of an omics-based test that has been confirmed and validated as described in Recommendations 1-2, the committee recommends that:

a. Investigators should communicate early with the FDA regarding the Investigational Device Exemption (IDE) process and requirements.

b. Omics-based tests should not be changed during the clinical trial without a protocol amendment and discussion with the FDA. A substantive change to the test may require restarting the study.
Omics Report: A Personal Perspective

- While report focuses on omics tests for any disease, the pathway is relevant to any test development process (simple; oncology)
- Test development pathway is segmented into different groups who do not understand impact of their work on the next translational steps
- IOM Report defines best practices so everyone can understand the entire interrelated process with best practices at each step
- Barriers to use of the recommended pathway are complex and not addressed by the IOM Committee, and include:
  - Lack of funding for translational studies for test development
  - Lack of availability & access to annotated specimen/data sets
  - No process for establishing payment and level of payment
  - No teeth, only recommendations; but it is from the IOM
Report Released
March 23, 2012

To download or read the report:
www.nap.edu