Evolution of Translational Omics:
Lessons Learned and the Path Forward

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for the
Omics-based Test Committee of the IOM

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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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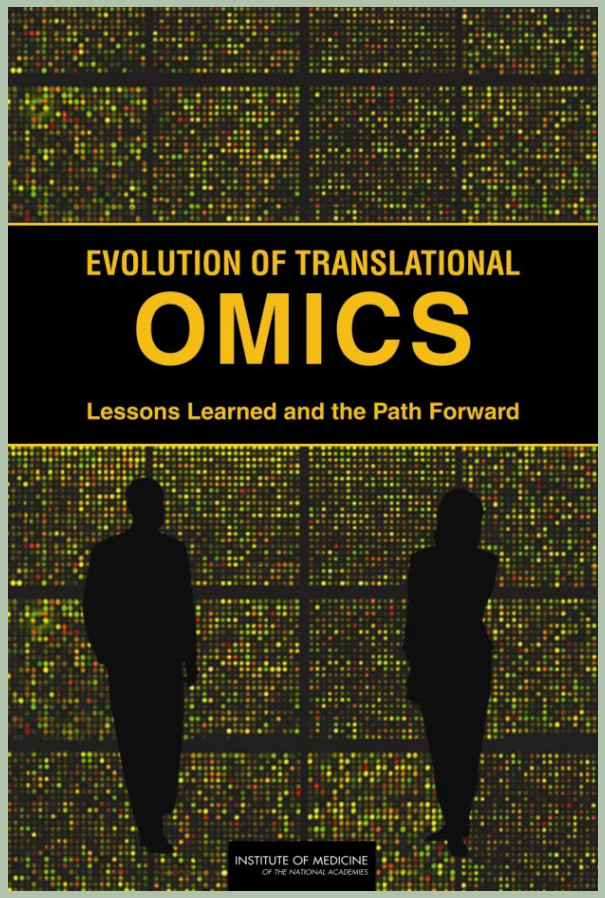

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Study Funders

National Cancer Institute
Food and Drug Administration
Centers for Disease Control and Prevention
U.S. Department of Veterans Affairs
American Society for Clinical Pathology
College of American Pathologists.

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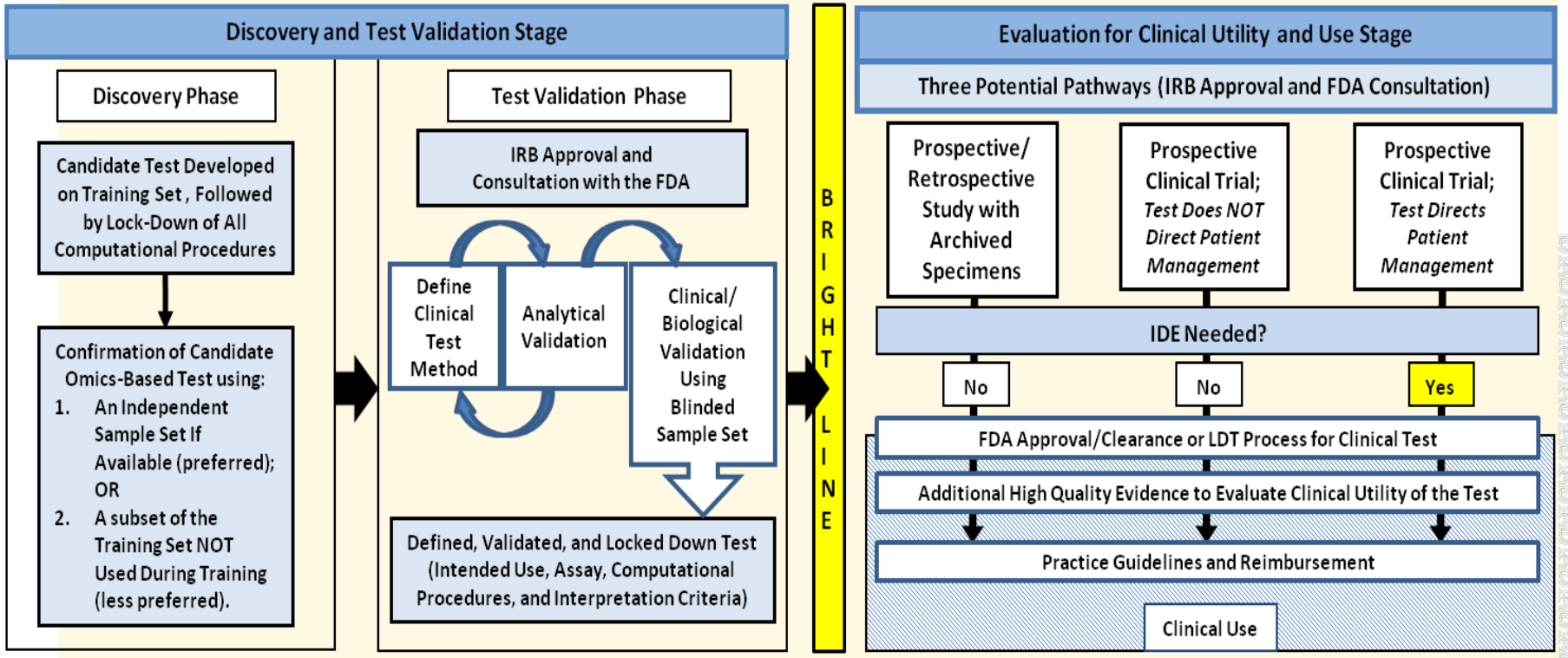
Definition of an Omics Tests

- 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

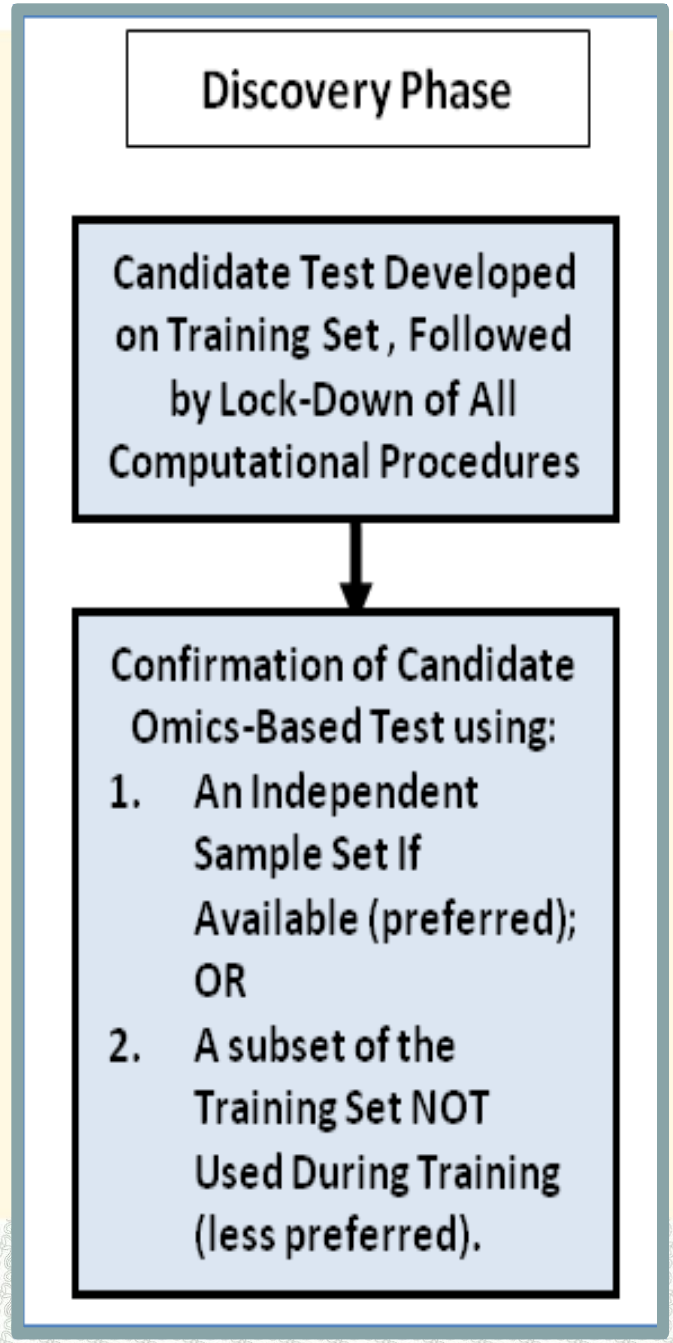
Omics Test Characteristics

- 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 Phase of Omics Test Development (Research Laboratory Setting)



Recommendation 1: Discovery Phase

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

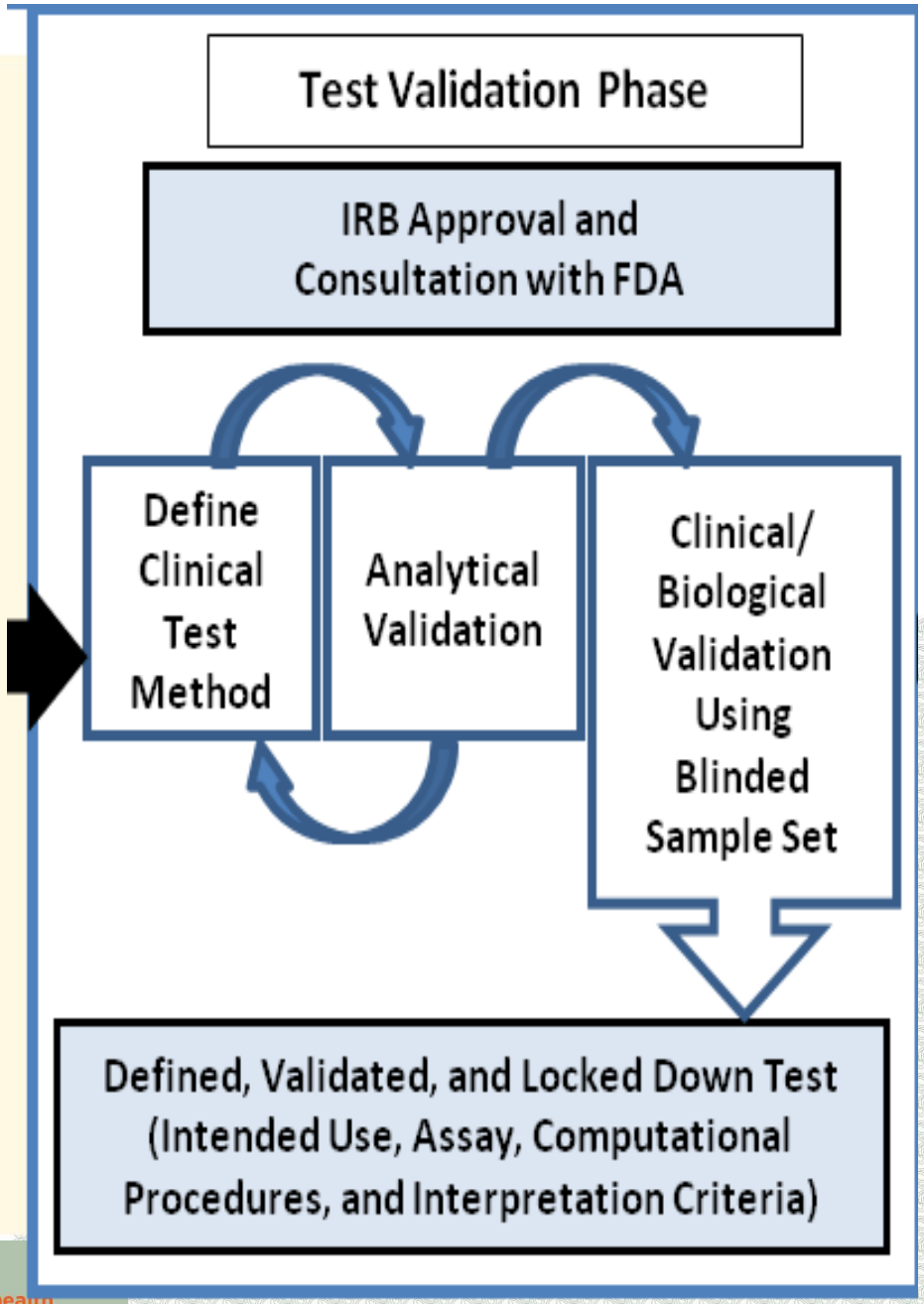
a. The tests should be **confirmed using an independent set** of samples from the discovery sample set.

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



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

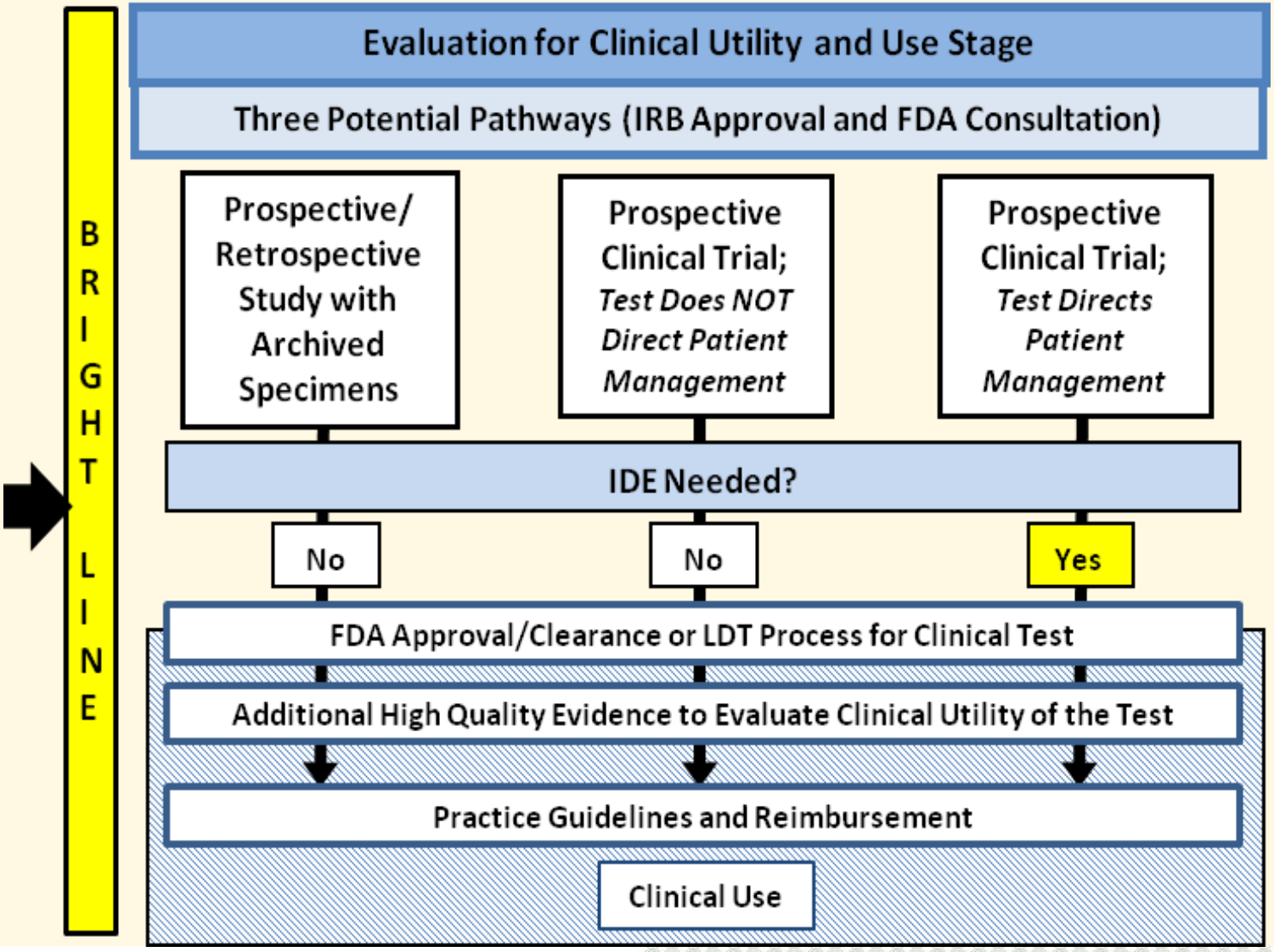
- Clinical utility is not assessed by FDA or in the LDT process
- Lack of FDA review does not mean the test lacks clinical utility
- Process of gathering evidence to support clinical use should begin before test is introduced into clinical practice
- Approaches:
  - Prospective / Retrospective Study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

Evaluation for Clinical Utility and Use Stage



Recommendation 3: Evaluation for Clinical Utility and Use Stage

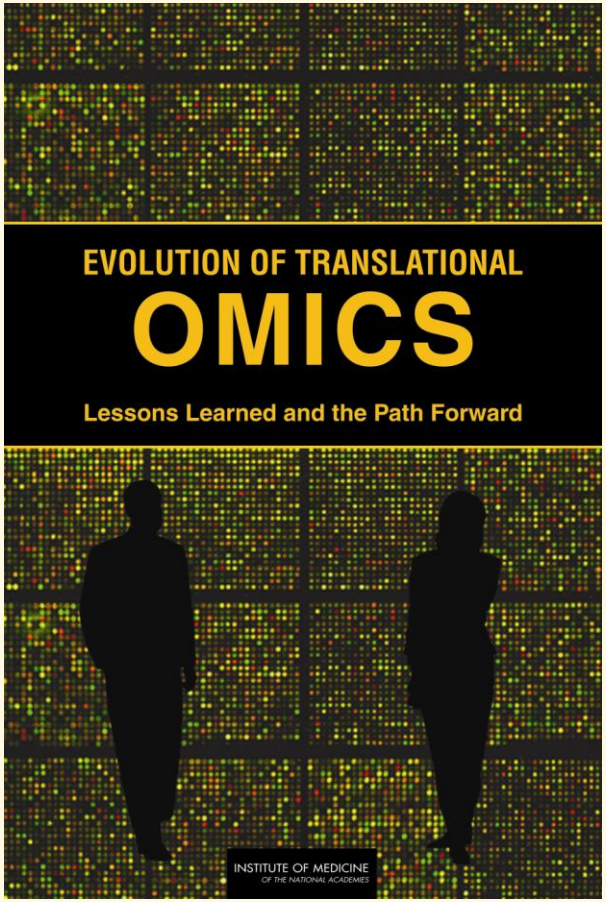
For investigators conducting a clinical trial to assess the clinical utility and use of an omics-based test that has been confirmed and validated as described in Recommendations 1-2, the committee recommends that:

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