

Evolution of Translational Omics: Lessons Learned and the Path Forward

IOM Committee on
Omics-based Predictive Tests

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On Behalf of the IOM Committee:

Chair; Gilbert Omenn, MD, PhD



INSTITUTE OF MEDICINE
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Advising the nation / Improving health

Disclosure Information:

ASCO Annual Meeting 2012

Name of Speaker: Daniel F. Hayes

I have the following financial relationships to disclose:

Employee: University of Michigan

Board of Directors: American Society of Clinical Oncology

Consultant for (Scientific Advisory Board): OncoImmune

Speaker's Bureau for: None

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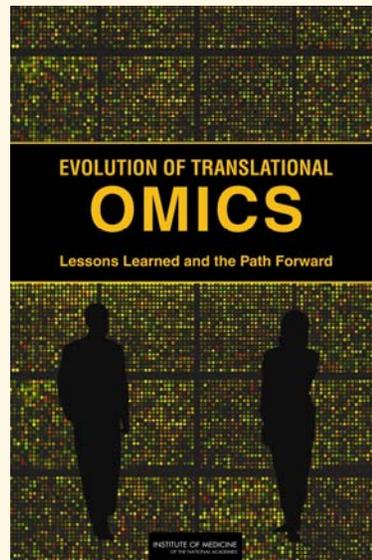
Stockholder in: OncoImmune

Honoraria from: None

Patents Pending: 2, related to discovery and analysis of circulating tumor cells

**X I will not discuss off label use and/or
investigational use in my presentation.**

Overview



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
 - 2009 publication by Baggerly and Coombes:
 - Numerous errors in test development
 - Inconsistencies between primary data and data used in articles
 - Failure to reproduce results

- Criticisms rebuffed for 4 years while:
 - Hundreds of publications cited papers in question
 - 2 companies launched
 - Clinical trials initiated in 2007, using tests to direct patient care

- Trials scrutinized by NCI statistical staff, but apparently not by funders or general oncologic scientific community

- 2010 letter to director of NCI, signed by more than 30 bioinformaticians and statisticians, urged suspension of trials

Problems Identified by Baggerly and Coombes

- First identified in letters to the authors and the journals
- Extensively documented in Annals of Applied Statistics in 2009
- Revealed a series of errors in a number of articles, including:
 - Reversal of “sensitive/resistant” labels in training data
 - Errors in test data, such as:
 - Only 84/122 test samples were distinct
 - Some samples labeled as both “sensitive” and “resistant”
 - “Off by one” errors led to erroneous gene lists
 - Some genes cited as evidence for biological plausibility were not output by software; 2 were not even on the arrays used.
 - Heatmap published in one paper corresponded to data from a different paper.
 - Rejected by lead authors and committees as a “squabble among statisticians”; later acknowledged as “numerous missed signals”

Duke: Retracted Publications

- Key retracted papers by Nevins and Potti:
 - 2006 *Nature Medicine* (Potti et al.)
 - Cited 306 times
 - 2006 *New England Journal of Medicine* (Potti et al.)
 - Cited 350 times
 - 2007 *Lancet Oncology* (Bonnefoi et al.)
 - Cited 95 times
 - 2007 *Journal of Clinical Oncology* (Dressman et al.; Hsu et al.)
 - Cited 111 times, 60 times
- Duke leadership identified 40 papers with Potti as co-author
 - Two thirds will be partially or fully retracted
 - Others may still be valid; pending evaluation (as of 8/11)
 - Surveyed 162 co-investigators
- **NCI asked IOM to review situation and provide guidance for field**

IOM Committee Composition

20 member committee with expertise in:

Clinical medicine

Ethics

Clinical pathology

Patient advocacy

Biomarker test development

FDA oversight

Biostatistics and bioinformatics

Scientific publication

Molecular biology

University administration

Clinical trial design, conduct, and analysis

Discovery and development of omics-based technologies and tests

IOM Committee

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Committee Charge

1. **Develop evaluation criteria** 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.

Lessons from the Duke Case

Importance of:

- Data provenance and data management
- Locking down the computational model
- Making data, code, and other information publicly available
- Independent confirmation of the test
- Test validation
- Effective multidisciplinary collaboration
- Institutional and laboratory culture
- Institutional oversight, including fresh review of the science when serious criticisms are raised or clinical trials or spinoff companies are proposed
- Consultation with FDA and submission of IDE

Limitations of:

- Peer review
- Ability of funders and journals to address scientific controversies
- Ability of institutions to objectively review work of their faculty

Overview of Report

Chapter 1: Overview of the statement of task and scope

Chapter 2: Science, technology, and **discovery process** for omics-based tests

Chapter 3: Test development and **analytical and clinical/biological validation**

Chapter 4: Evaluation of tests **in clinical trials** and ultimately for **clinical use**

Chapter 5: Roles of investigators, institutions, journals, funders, and FDA

Chapter 6: Overview of **lessons learned** from the **case studies**

Appendix A: Summary of **8 case studies**

Appendix B: Summary of the **Duke** University omics-based tests



Omics

- Encompasses multiple molecular disciplines
- **Omics-based Test:** composed or derived from multiple molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result

Omics Characteristics

- Complex, high dimensional data
- Many more variables than samples
- High risk that computational models will overfit data

Test Development Semantics

Analytical Validity: Accuracy, reproducibility, reliability of the test

Clinical/Biological Validity: The test separates the population into at least two separate groups with different biologic properties or clinical outcomes

Clinical Utility: The test should be used to direct routine clinical management

*Modified from EGAPP initiative;
Teutsch, S. M., et al.; Genet Med; 2009.*

Goals of Committee's Recommendations

GOAL I: Define best practices for discovery and translation of an omics-based test into a clinical trial.
[Recommendations 1-3]

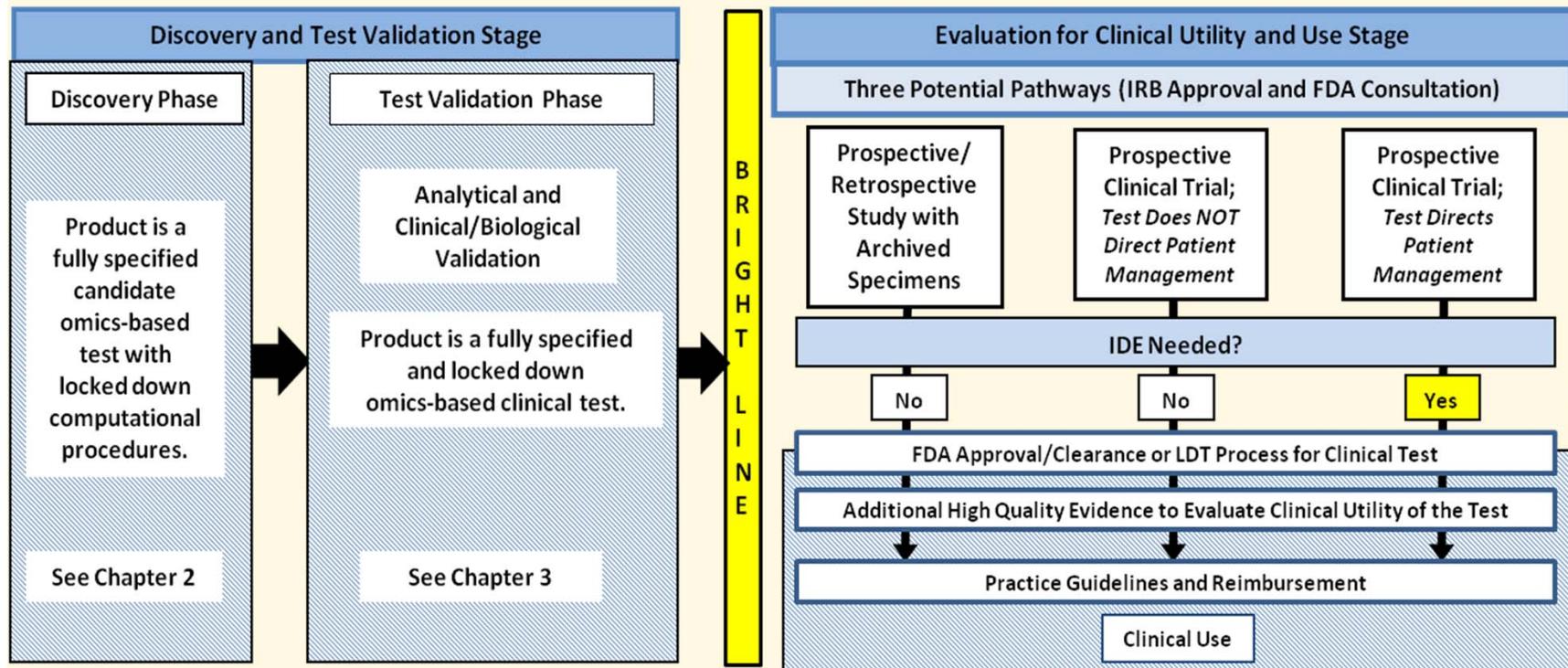
GOAL II: Recommend actions to ensure adoption of and adherence to the development and evaluation process.
[Recommendations 4-7]



Three Stages of Omics Test Development

1. Discovery
2. Test Validation
3. Evaluation for Clinical Utility and Use

Omics-Based Test Development Framework



Three Stages of Omics Test Development

- 1. Discovery**
2. Test Validation
3. Evaluation for Clinical Utility and Use



How are Omics Tests Different?

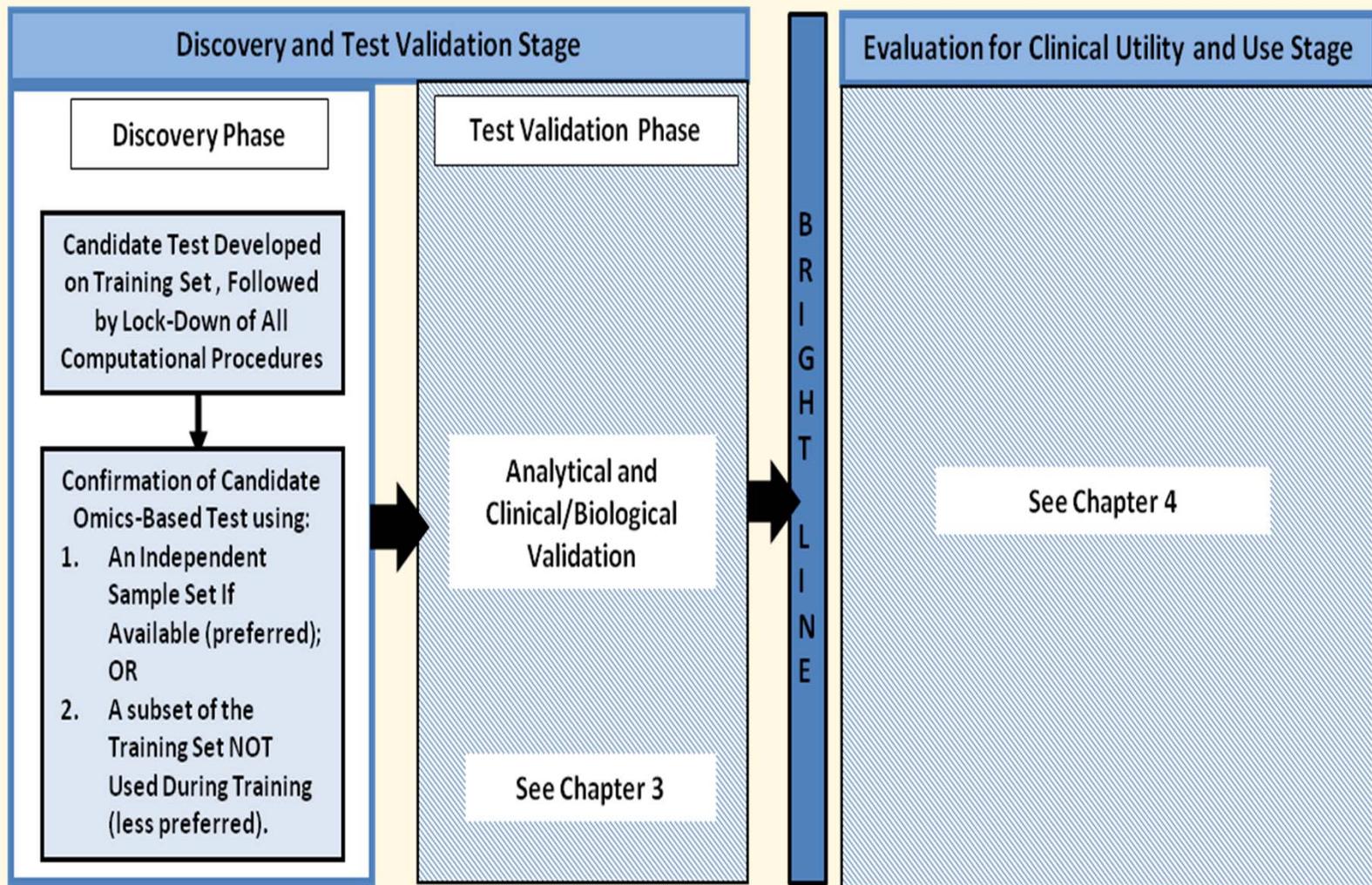
- Difficulty in defining the **biological rationale** underpinning a test
 - Biological rationale behind single-analyte tests is often evident
 - ▶▶▶ Examples: HER2, LDL
 - Biological rationale for an omics-based test is often not well defined
- Challenges in **data provenance and sharing**
 - Large, complex datasets used to create computational models
 - Simple data management errors can easily occur
 - Sharing of data and code is not routine
 - Difficult for other scientists to replicate and verify findings



How are Omics Tests Different?

- Need for individuals with **expertise in multiple disciplines**
 - Biologists, geneticists, statisticians, bioinformaticians, clinical pathologists
 - Responsibility for omics-based test is shared among many investigators, regulatory agencies, funders, and institutions
 - No single investigator has breadth of expertise needed to fully understand all aspects of test development
- **High hope** in omics-enabled medical care, but slow progress thus far
 - Heterogeneity of patients with a given diagnosis
 - Expensive and uncertain development pathway
 - No widely accepted process for translation of omics test into clinics
 - Omics is still an evolving field
 - Lack of carefully annotated tissue archives from trials with outcome information

Discovery Phase



Discovery Phase

- **Candidate test is developed on training set, and locked down.**
- This **candidate test is evaluated** on an independent sample set.
- » **Statistics and bioinformatics validation** occurs throughout the discovery and test validation stage.

Discovery Phase

- **Step 1: Data quality control**
 - ✧ Quality control performed computationally
 - ✧ Need to assess reproducibility from run to run
 - ✧ Sample run date, machine characteristics may confound analysis
- **Step 2: Computational model development**
 - ✧ Overfitting is a major concern
 - ✧ Training set / test set or cross-validation must be used
 - ✧ Model is locked down before proceeding to Step 3
- **Step 3: Confirmation with an independent sample set**
- **Step 4: Release data, code, and full computational models**

Discovery Phase

RECOMMENDATION 1:

If candidate omics-based tests are intended for clinical development:

- a. The tests should be **confirmed using an independent set** of samples*.
- b. **Data, code, and metadata** should be **made available**.
- c. Candidate test should be **defined precisely**:
 - Molecular measurements
 - Computational procedures
 - Intended clinical use

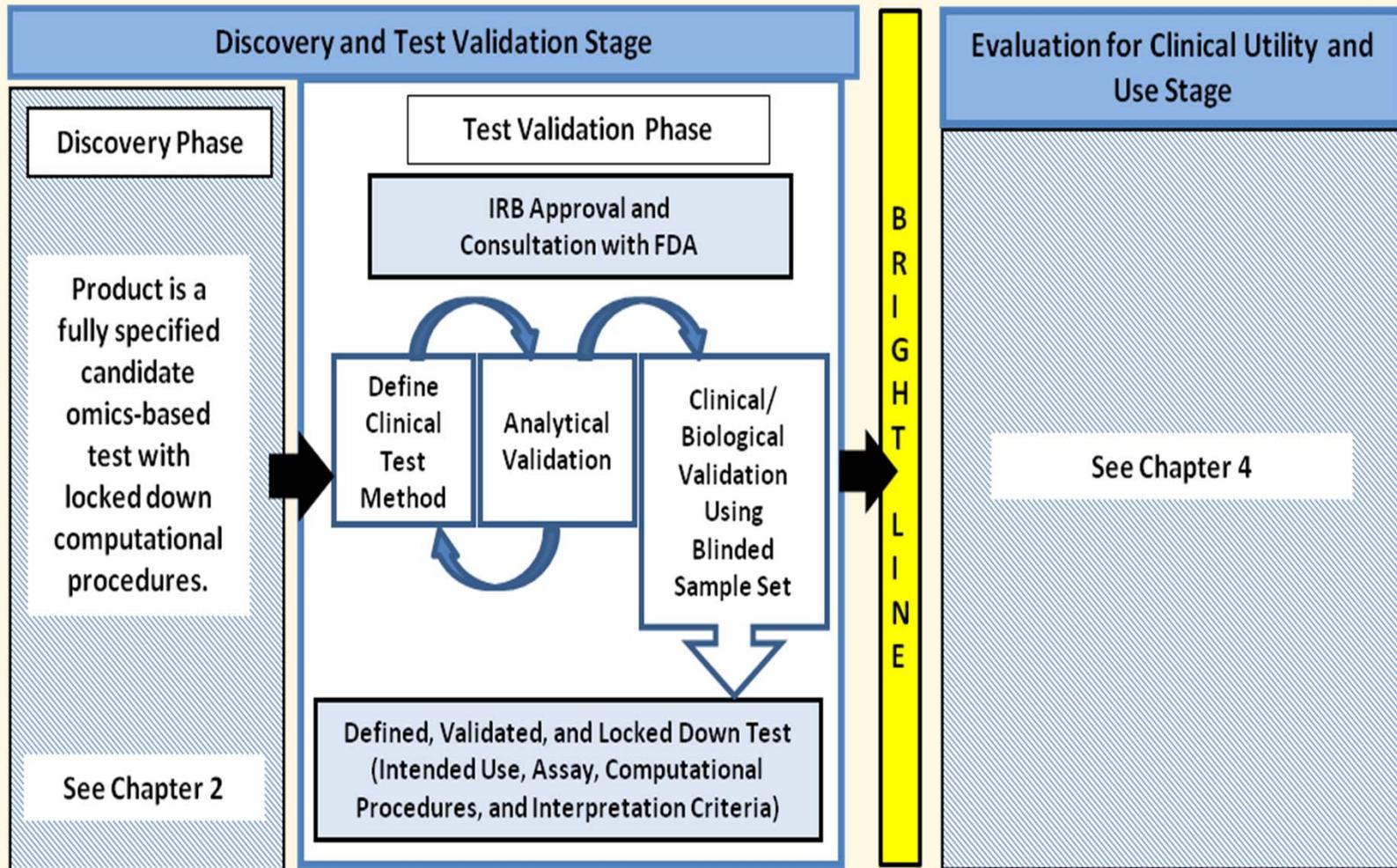
*In some cases (e.g. tests developed using preclinical models or data generated in early clinical trials, independent data sets may not exist)

Three Stages of Omics Test Development

1. Discovery
- 2. Test Validation**
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Test Validation Phase



Test Validation Phase

An omics-based test consists of both the data-generating assay and the fully specified computational model.

Both components should be validated.

Recommendations apply to both development pathways:

- FDA approval or clearance as a device
- Development of an LDT, as defined by the FDA

How are Omics Tests Different?

- **Regulatory oversight** for omics tests differs from drug development
- Two paths for bringing a test to clinical use:
 1. Via FDA review
 2. Via validation in a CLIA-certified lab as a Laboratory Developed Test (LDT)
- LDT Pathway:
 - FDA hasn't yet clearly defined a regulatory framework for review
 - Academic medical centers can move omics tests from discovery to clinical use without external regulatory review
 - Academic centers may be unprepared for such oversight responsibility

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 lab 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.

Three Stages of Omics Test Development

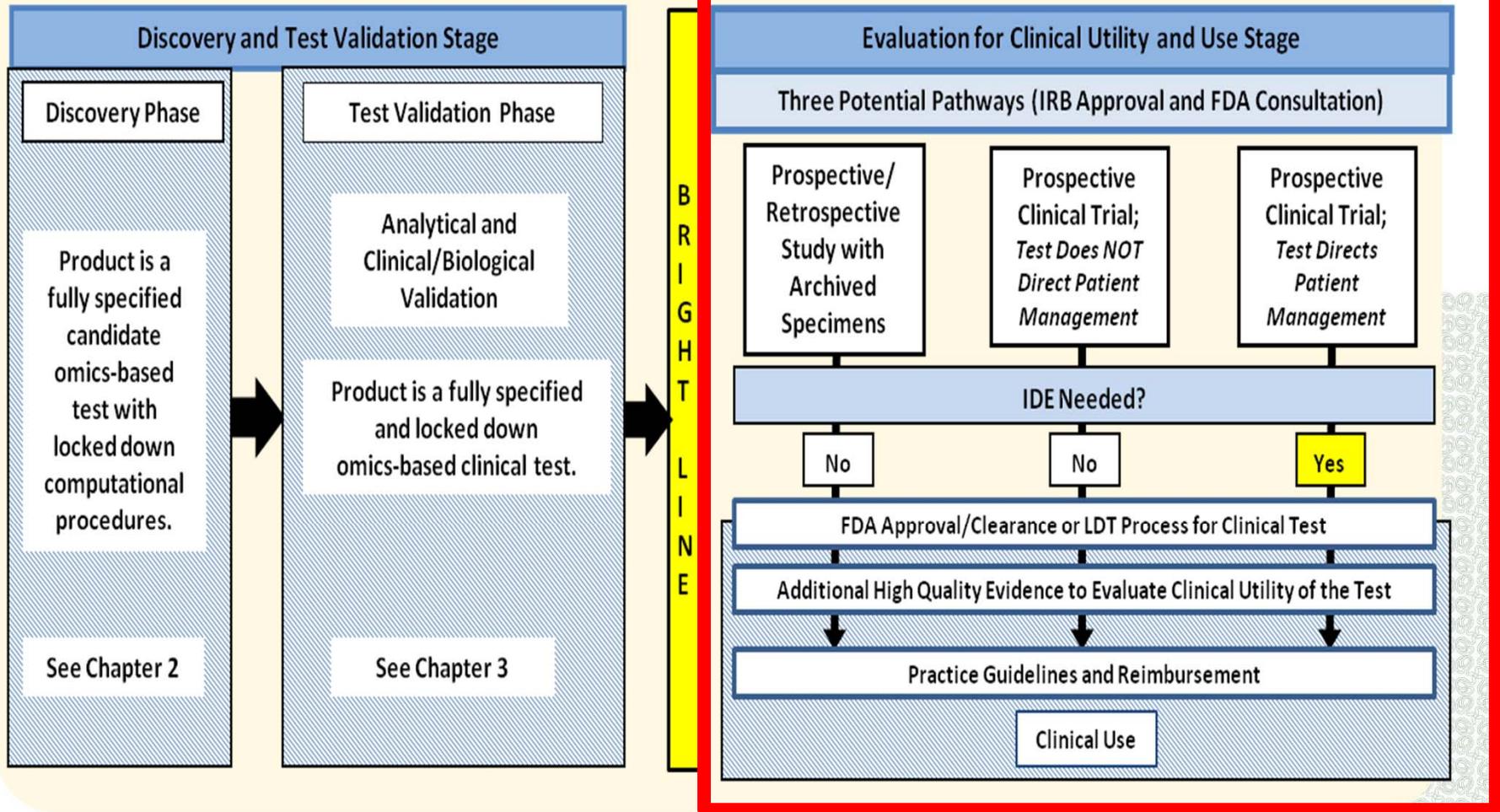
1. Discovery
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- 3. Evaluation for Clinical Utility and Use**



Evaluation for Clinical Utility and Use

- **Clinical Utility:** “Evidence of improved measurable clinical outcomes . . . compared with current management without [omics] testing.”
- Clinical utility is not assessed by FDA or in the LDT process
- Lack of FDA review does not mean lack of clinical utility
- Process of gathering evidence to support clinical use should begin before test is introduced into clinical practice

Evaluation for Clinical Utility and Use



Evaluation for Clinical Utility and Use

Three pathways:

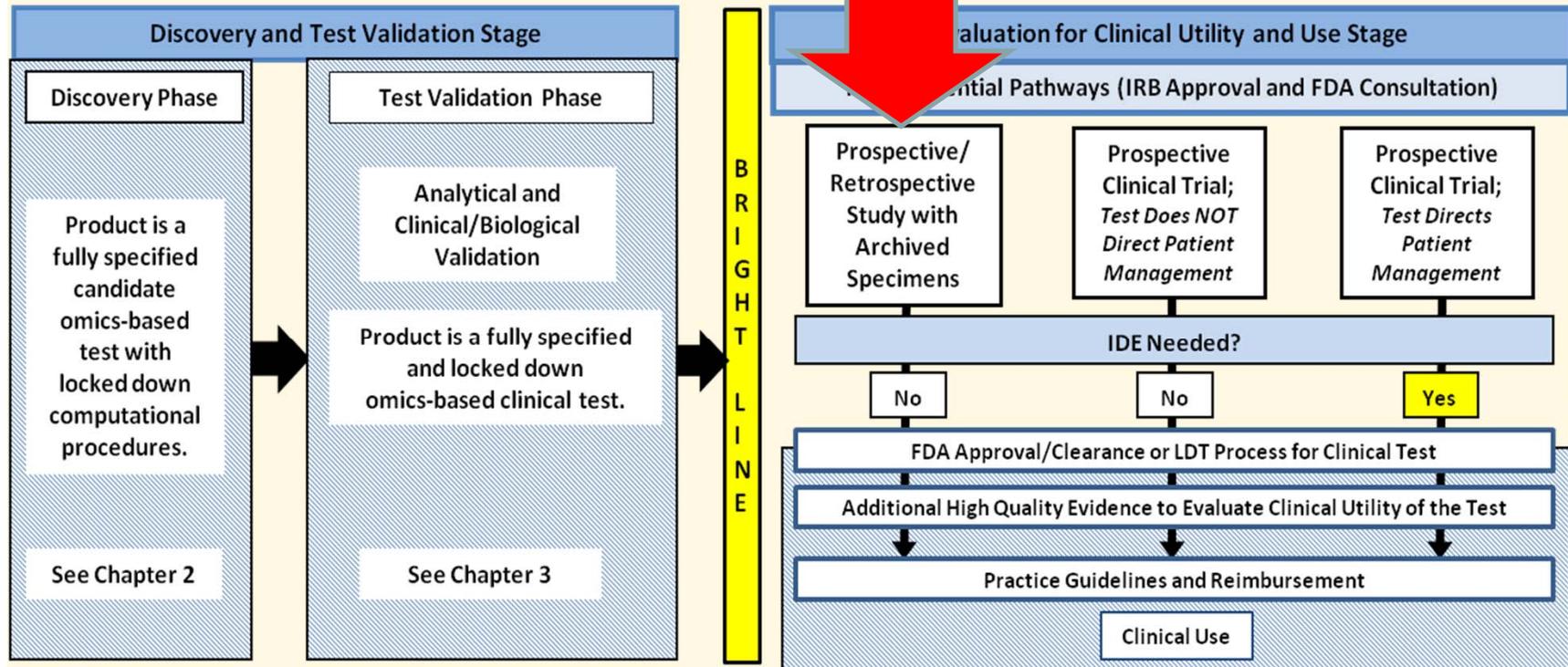
- **Prospective–retrospective studies** using archived specimens from previously conducted clinical trials.
- **Prospective clinical trials** that directly address the utility of the omics-based test, where either
 - ✧ The test **does not direct** patient management, or
 - ✧ The test **does direct** patient management.

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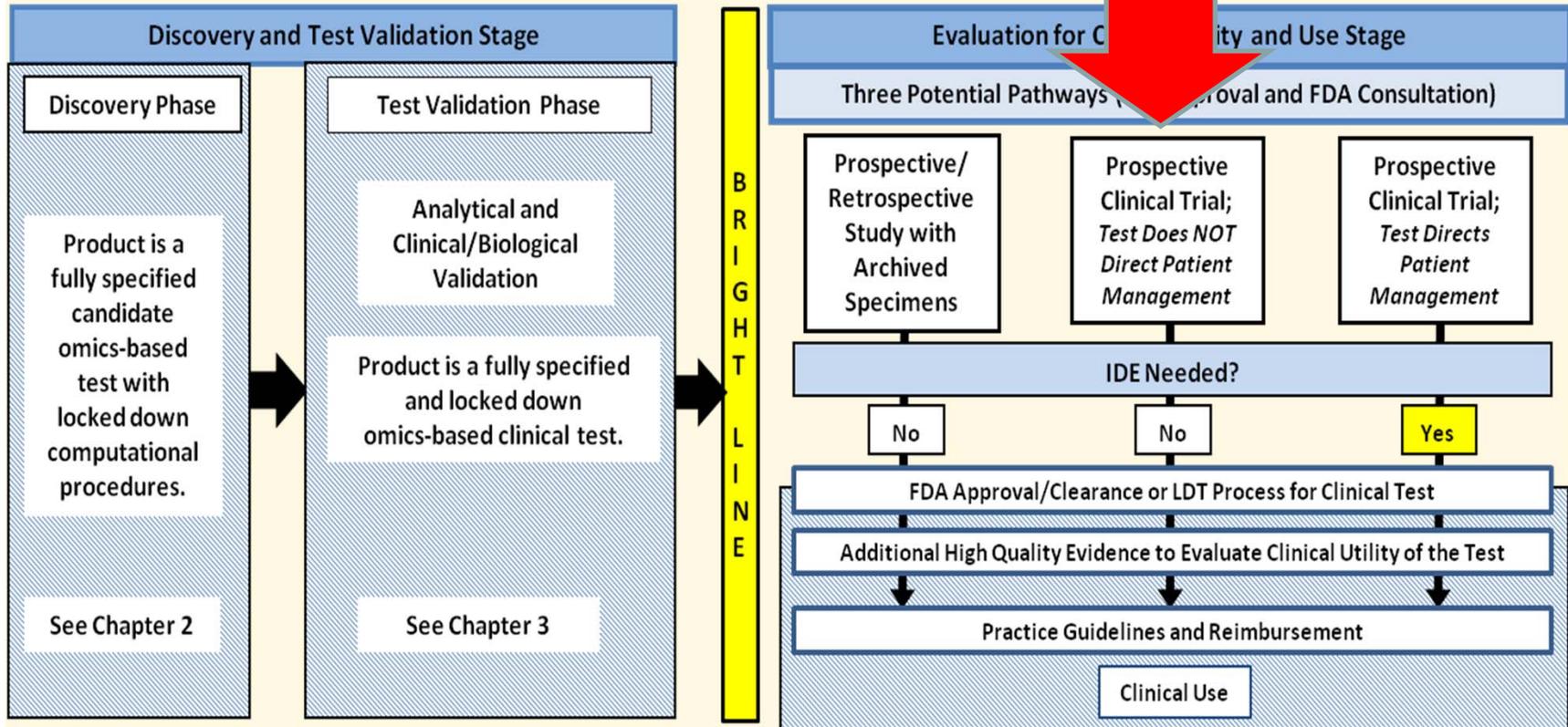
Simon, R. M., et al.; *J Natl Cancer Inst*; 2009.

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Evaluation for Clinical Utility and Use Stage



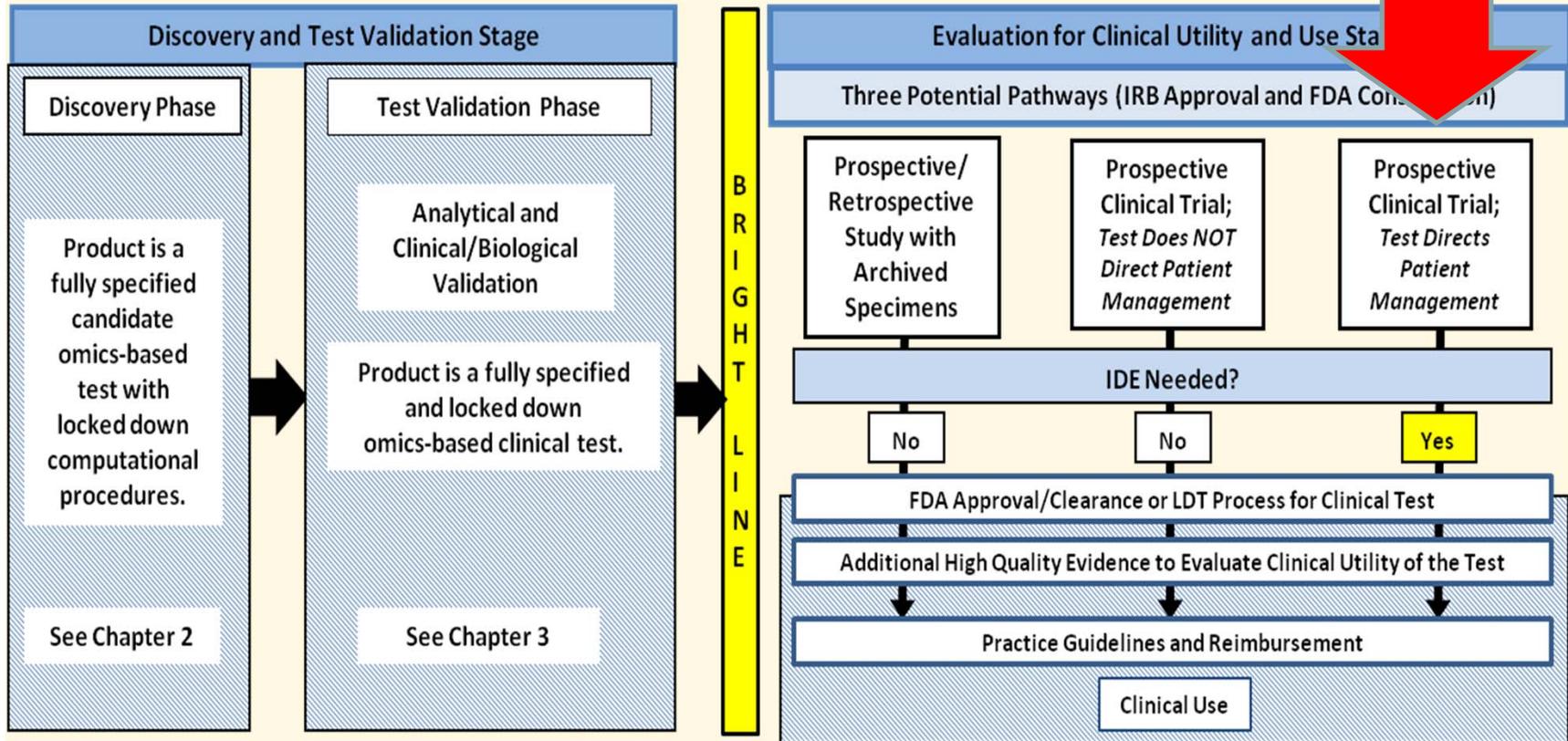
- ✧ *Sargent, D. J., et al.; J Clin Oncol; 2005.*
- ✧ *Freidlin, B., et al.; J Natl Cancer Inst; 2010*

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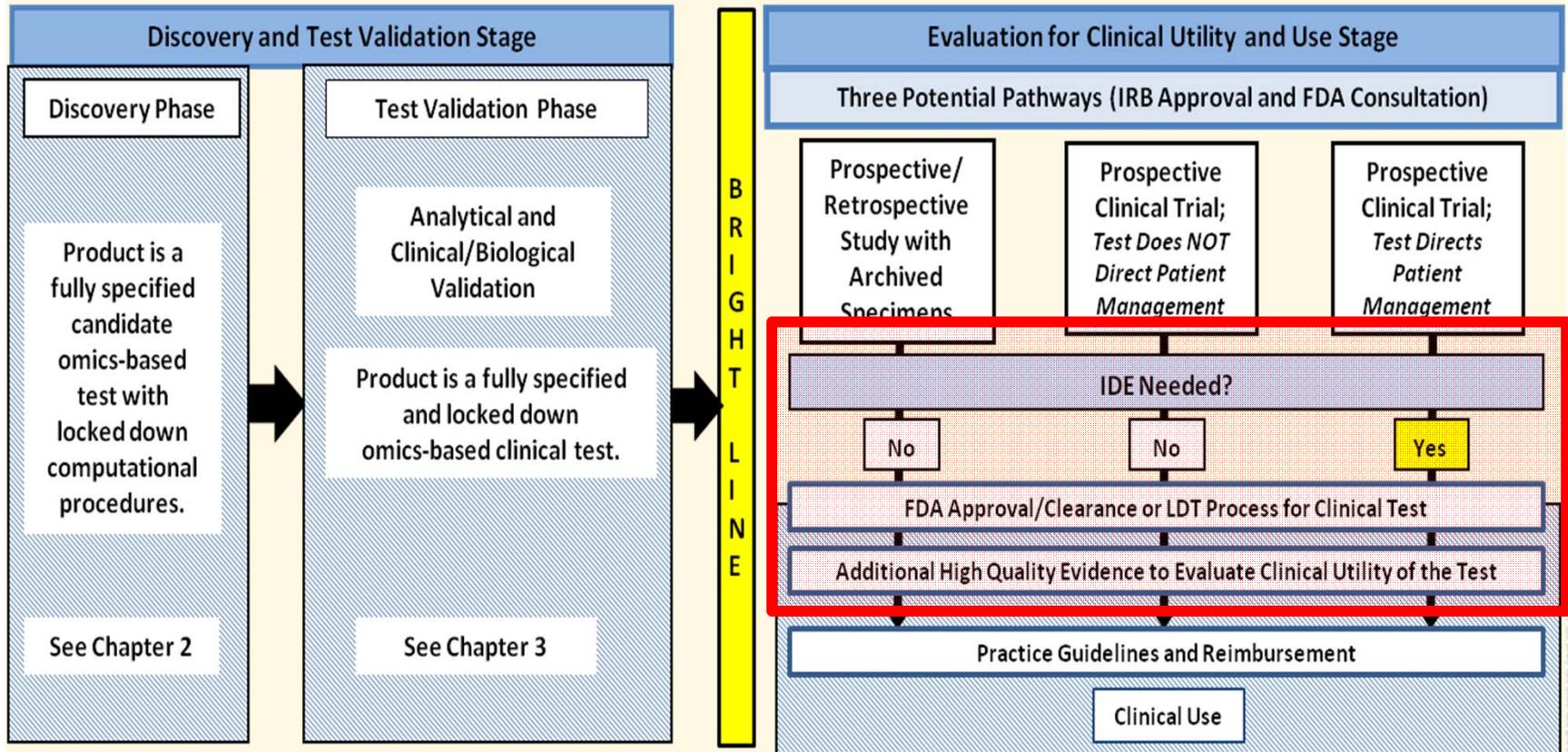
- ✧ Sargent, D. J., et al.; *J Clin Oncol*; 2005.
- ✧ Freidlin, B., et al.; *J Natl Cancer Inst*; 2010

Evaluation for Clinical Utility and Use

RECOMMENDATION 3:

- a. Investigators should **communicate early with the FDA** regarding Investigational Device Exemption (IDE) process.
- 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 study.

Evaluation for Clinical Utility and Use Stage



- ◇ *Simon, R. M., et al.; J Natl Cancer Inst; 2009*
- ◇ *Sargent, D. J., et al.; J Clin Oncol; 2005*
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Goals of Committee's Recommendations

GOAL II:

Recommendations to ensure adoption of and adherence to the development and evaluation process

Recommendations: Institutions

Recommendation 4:

4a: Institutions are responsible for establishing, supporting, and overseeing the infrastructure and research processes for omics-based test development and evaluation.

Recommendations: Institutions

Recommendation 4:

4b: Institutional leaders should provide oversight and promote a culture of integrity and transparency by designating officials responsible for:

- i. **IDE and IND requirements**
- ii. **management of financial and non-financial conflicts of interest (individual and institutional)**
- iii. a **system for preventing, reporting, adjudicating lapses in integrity**
- iv. establishing **clear procedures for response to inquiries**

Recommendations: Institutions

Recommendation 4:

4c: Institutions should **ensure that individuals who collaborate** on omics research and test development are:

- i. Treated as **equal co-investigators** and co-owners of responsibility
- ii. **Represented on** relevant review and **oversight bodies**
- iii. **Intellectually independent**

Recommendations: Funders

Recommendation 5:

5a: All funders of omics-based translational research should:

- i. **Require investigators to make data**, prespecified analysis plans, code, and computational models **publicly available**
- ii. **Provide continuing support for independent repositories** to guarantee ongoing access to omics and clinical data
- iii. **Support test validation** in a CLIA-certified laboratory and the independent **confirmation** of a candidate omics-based
- iv. **Alert the institutional leadership** about serious questions
- v. Establish lines of **communication with other funders** to be used when serious problems arise

5b: Federal funders of omics-based research should **have authority to investigate** research being conducted by a funding recipient.

Recommendations: FDA

Recommendation 6:

6a: FDA should develop and finalize a risk-based guidance or a regulation on:

- i. Bringing omics-based tests to the FDA for review
- ii. Oversight of LDTs

6b: FDA should communicate IDE requirements for use of omics-based tests in clinical trials to OHRP, IRBs, and others.

Recommendations: Journals

Recommendation 7: Journal editors should:

7a: Require authors describing clinical evaluations of omics-based tests to:

- i. **Register all clinical trials**
- ii. **Make data**, metadata, analysis plans, code, and fully specified computational models **publicly available**
- iii. Provide relevant sections of the **research protocol**
- iv. Require authors to state roles and attest to study integrity
- v. Use appropriate **reporting guidelines**

7b: Develop mechanisms to **resolve possible serious errors**

7c: Alert the institutional leadership and all authors when a serious question of accuracy or integrity has been raised

Examples of Reporting Standards

System	Date	Study Type
REMARK	2005, 2012	Tumor marker prognostic studies
CONSORT	2001 (updated in 2010)	Randomized controlled trials
MIAME	2001	Microarray-based gene expression experiments
BRISQ	2011	Studies that use human biospecimens
STARD	2003	Diagnostic accuracy
MONITOR	2013	Circulating tumor biomarkers to monitor clinical course

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