

**EVIDENTIARY STANDARDS FOR DETERMINING
THE CLINICAL UTILITY OF
GENOMICS-BASED DIAGNOSTIC TESTS**

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EGAPP Working Group

(Teutsch et al, Genet Med, 2008)

- “Of most concern, the number and quality of studies are limited. Test applications are being proposed and marketed based on descriptive evidence and pathophysiologic reasoning, often lacking well-designed clinical trials or observational studies to establish validity and utility, but advocated by industry and patient interest groups”

The CER/PCOR Hypothesis

- Gaps in evidence will be reduced through greater engagement of decision makers (patients, clinicians, payers) in:
 - Selecting and refining research questions
 - Developing study protocols

Molecular Basis of Uncertainty

- ★ Low affinity receptors for decision makers
- Low affinity receptors for evidence

INTELLECTUAL
CURIOSITY

CLINICAL
RESEARCH
ENTERPRISE

Defective
Transport

Defective
transport

GAPS IN
EVIDENCE

KT3

KT1

Slow Diffusion

PUBLISHED
EVIDENCE

DECISION
MAKERS

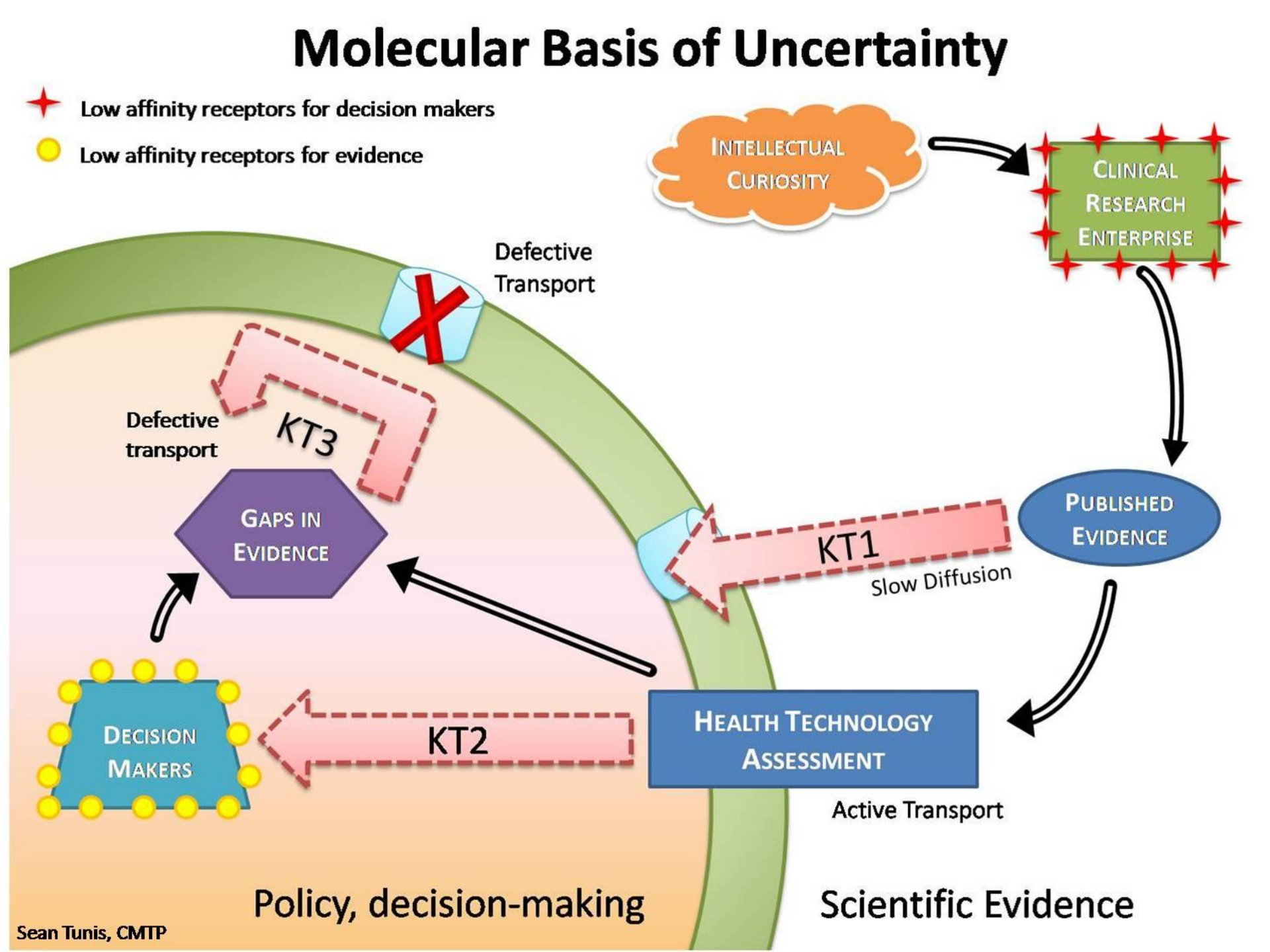
KT2

HEALTH TECHNOLOGY
ASSESSMENT

Active Transport

Policy, decision-making

Scientific Evidence



FDA Regulation of IVD

- reasonable assurance that the probable benefits outweigh any probable risks
 - 21CFR860.7(d)(1)
- reasonable assurance that the use of the device will provide clinically significant results
 - 21CFR860.7(e)(1)

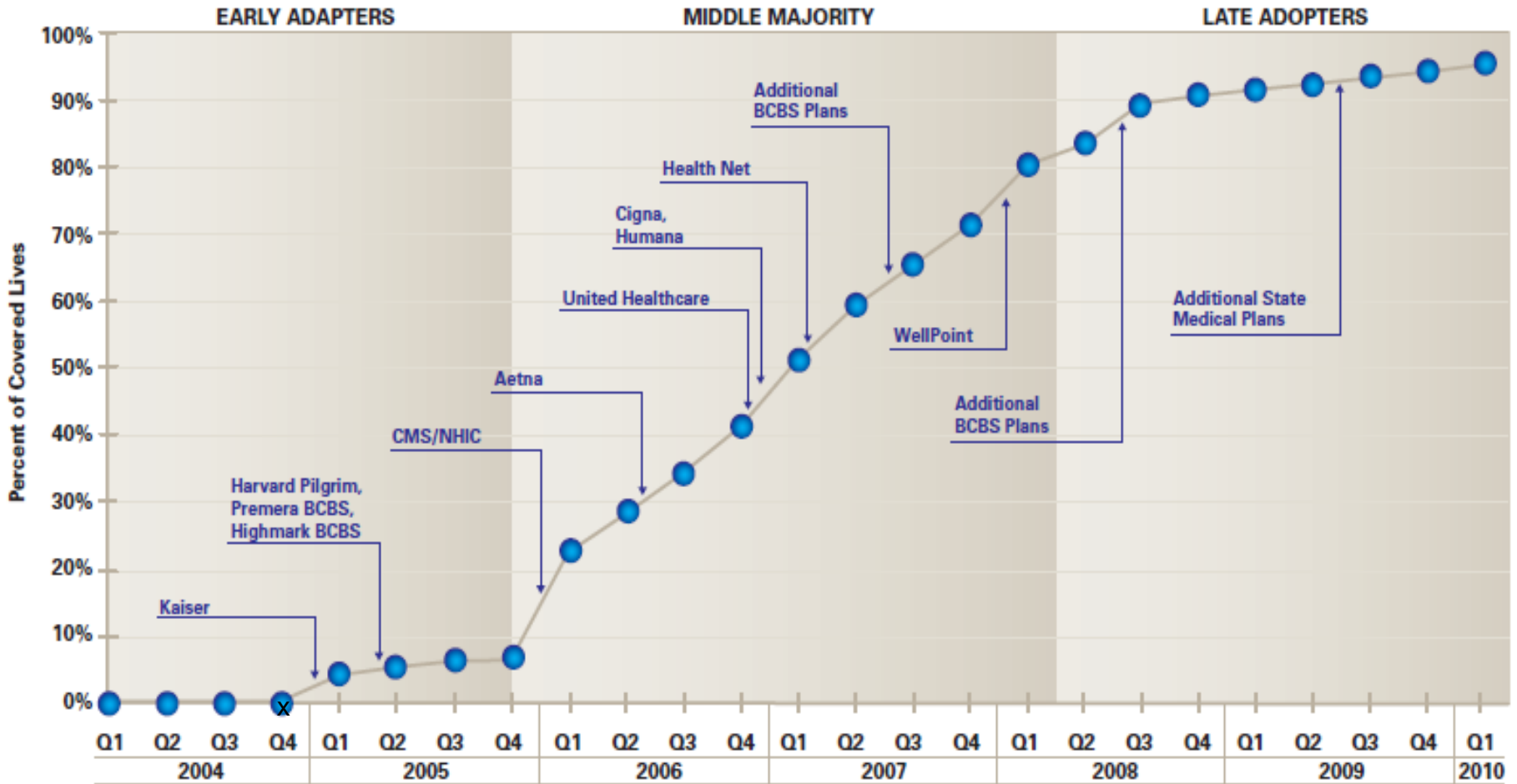
Medicare guidelines for evaluation of dx tests (clinical utility)

- **Question 1: *Is the evidence adequate to determine whether the test provides more accurate diagnostic information?***
- **Question 2: *If the test changes accuracy, is the evidence adequate to determine how the changed accuracy affects health outcomes?***

BCBSA Criteria

- **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**
 - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals.
 - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

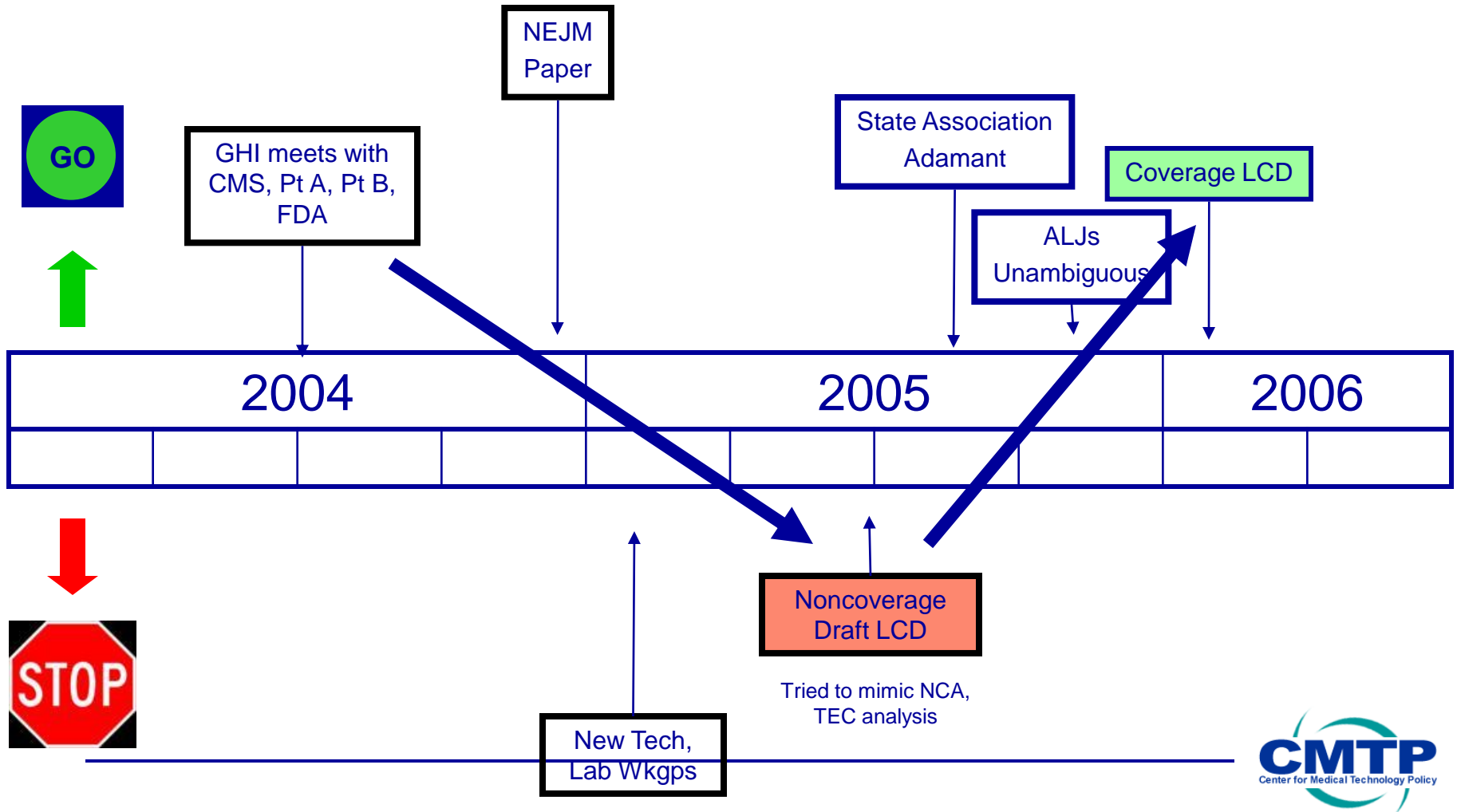
FIGURE 7: ONCOTYPE DX COVERAGE TIMELINE
 Positive coverage as percent of total US covered lives over time



X

X

NHIC / CMS Policy on Oncotype Dx



SACGHS recommendation

- “Information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions.”
- “HHS should create a public private entity of stakeholders to....establish evidentiary standards and levels of certainty required for different situations”

Guidance for Comparative Effectiveness

- Recommendations for study design reflecting information needs of patients, clinicians, payers
 - Analogous to FDA-guidance
 - Specific to a define class of interventions
- Targeted to public/private sector clinical researchers
- Describe study designs that provide “reasonable confidence of improved health outcomes”
- Balance validity with relevance, feasibility, timeliness
- “Effectiveness Guidance Documents”

Example: PROs in off-label studies of oncology drugs

- Include the following 14 patient-reported symptoms (“core symptom set”) in all research designs for post-market cancer clinical trials: anorexia, anxiety, constipation, depression, diarrhea, dyspnea, fatigue, insomnia, mucositis-oral, nausea, pain, sensory neuropathy, rash, and vomiting.

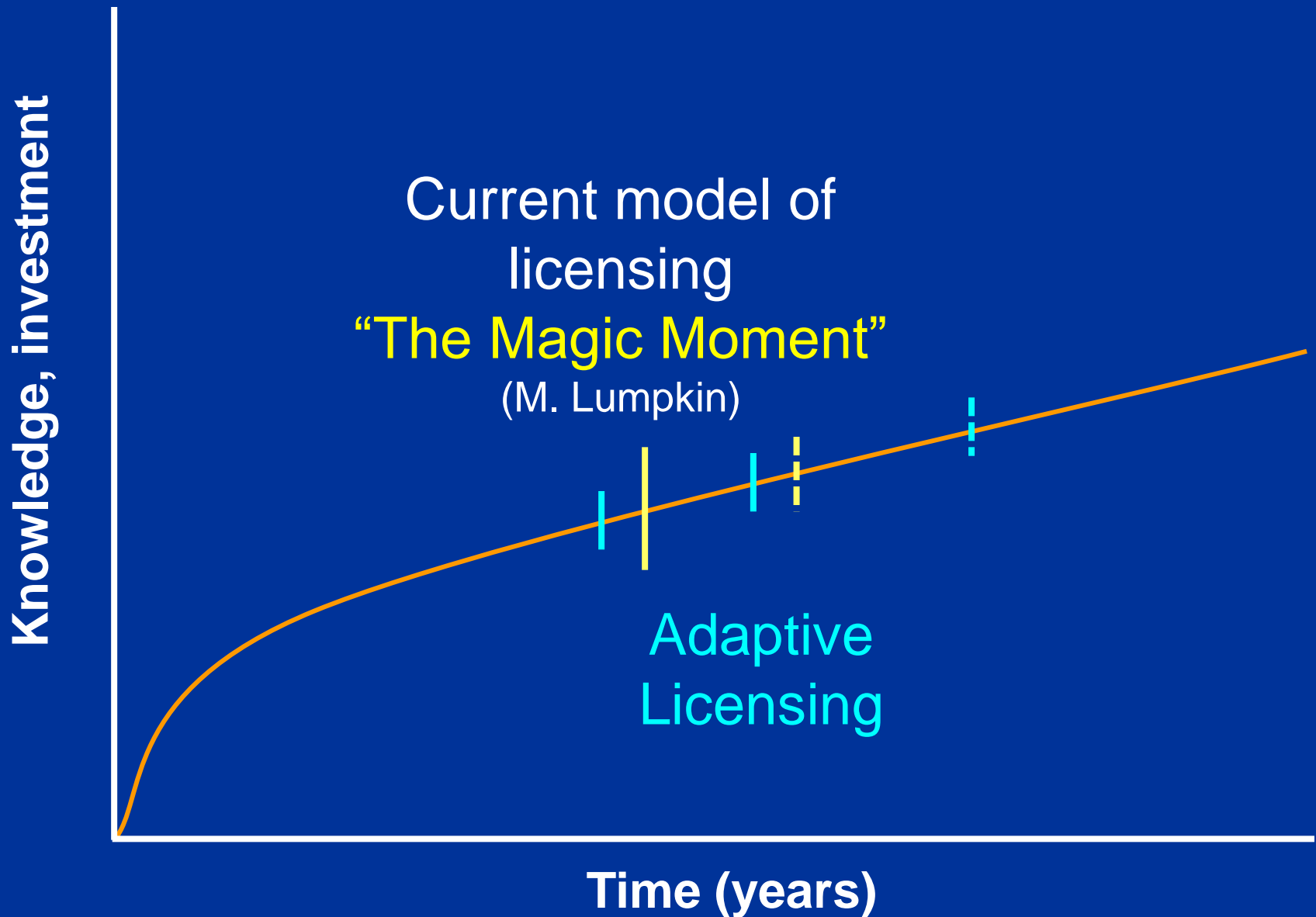
Technical Working Group on Clinical Utility of MDx in Oncology

TWG Member Name	Stakeholder Category	Affiliation
Linda Bradley	Geneticist/Lab Director	Women & Children's Hospital of Rhode Island
Louis Jacques	Payer	Center for Medicare & Medicaid Services
Gary Lyman	Clinician	Duke University
Howard McLeod	Researcher	UNC Institute PGx & Individualized Therapy
David Nelson	Industry	Epic Sciences
David Parkinson	Industry	Nodality
TBD	FDA	FDA Representative
Margaret Piper	Payer	Blue Cross Blue Shield Tech Assessment
Richard Simon	Methodologist	National Cancer Institute
Mary Lou Smith	Patients & Consumers	Research Advocacy Network
Plus 2-4 Additional Members		

EGD Development Process

- Review regulatory guidance and systematic reviews / clinical guidelines to identify gaps
- Content experts generate initial draft recommendations
- Technical working group refines draft recs
- Mutely-disciplinary methods symposium to discuss key methods controversies
- Revised recs circulated for public comment
- Final methods recommendations posted

A better model for drug-licensing?



CED and Genomic Diagnostics

- CED provides coverage contingent on participation in a clinical study (clinical trial, registry, etc)
 - For diagnostic tests, evidence of impact on health outcomes may not be feasible for initial coverage
 - However, unconditional coverage significantly reduces incentives to confirm health impacts
 - Optimal public health benefits from genomic diagnostics may be achieved through initial coverage at clinical validity, studies of clinical utility under CED

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PCORI Methods Committee View

JAMA. 2012;307(15):1636-1640

- “Engagement of patients at every step of the research process is viewed as essential, including in the selection of research questions, study design, conduct, analysis, and implementation of findings.”
- “As such, the Methodology Committee is engaged in developing standards to support the validity and generalizability of research, as well as patient-centeredness.”