Collaborative Development of Evidentiary Standards for Clinical Utility of MDx

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The Potential

- Widespread recognition that genomics, MDx may have transformational impact over next several decades
  - Anticipation of highly target therapies with dramatic improvements in risks, benefits
- Genomic tests and molecular diagnostics currently apply to 2% of population, with potential to rise to 60% (UHC, 2012)
- Life sciences market of $42 billion by 2015, 10% annual growth (PWC, 2011)

Current Reality - According to EGAPP

(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"
  - Translation: "we're not calling it snake oil, but…."

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?***

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BCBSA Criteria

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

Core Premise

- The generation of evidence required to demonstrate the benefits of MDx will depend in part on clear, predictable, consistent standards of evidence by which these technologies will be judged.
- Critical to understand what infrastructure and partnerships are needed
- Essential for investors and entrepreneurs to accurately judge risk and potential ROI

NHIC / CMS Policy on Oncotype Dx

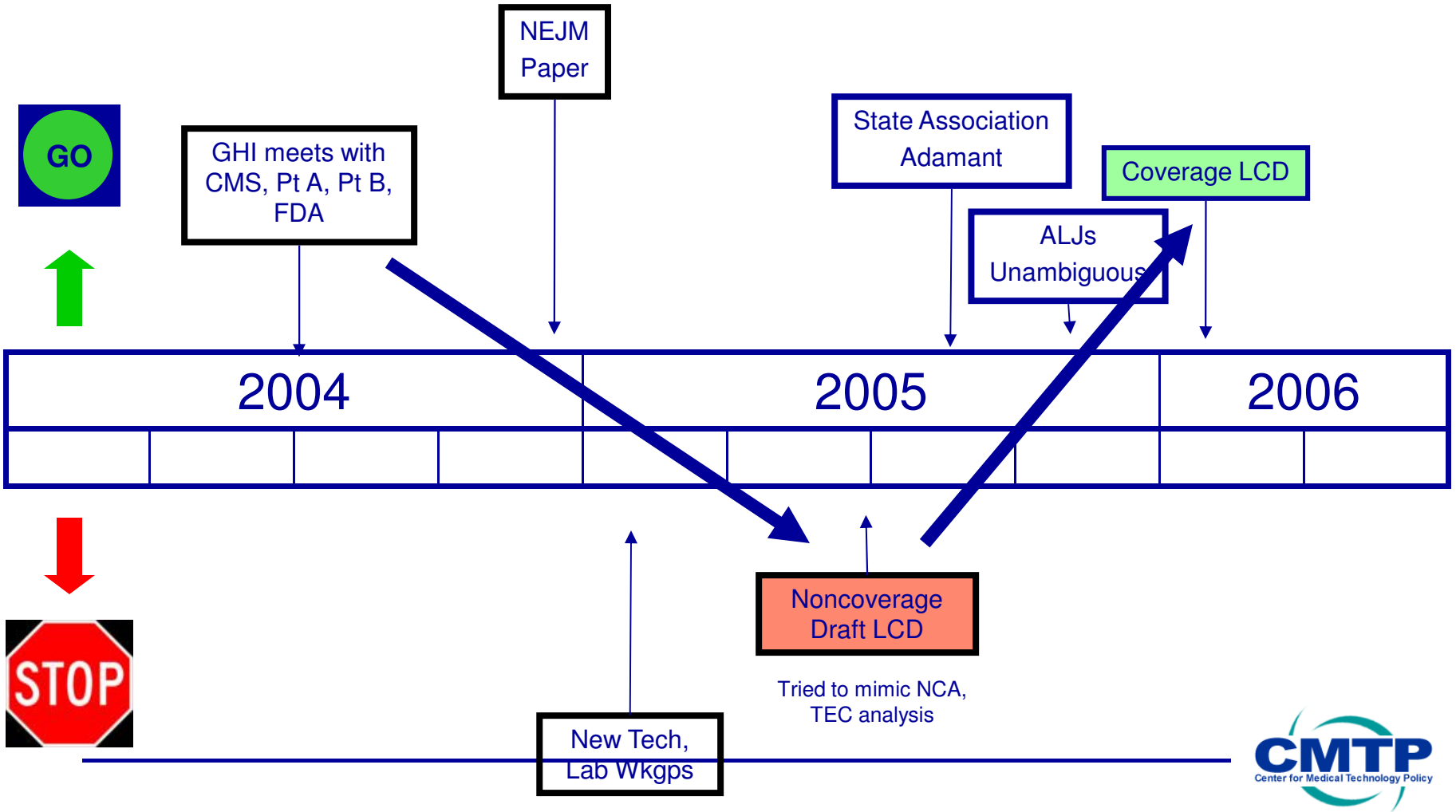
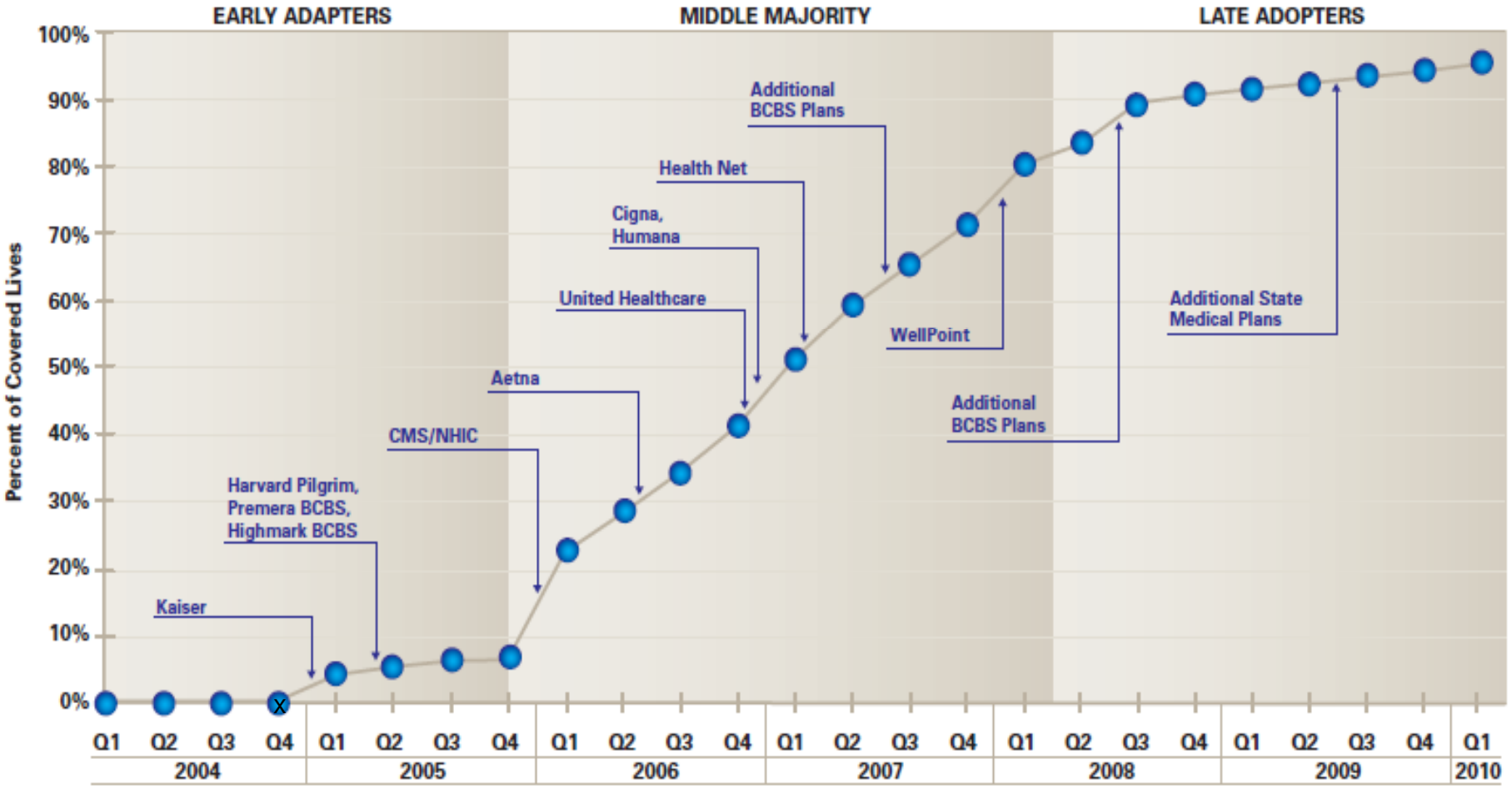


FIGURE 7: ONCO*TYPE* DX COVERAGE TIMELINE

Positive coverage as percent of total US covered lives over time



x

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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"

The Fundamental Trade-offs

- There is an inherent tension between level of certainty about risk-benefit and early access to new technologies (innovation, ROI)
- Not easily determined what is the optimal balance to maximize long-term public health
  - Varies by stakeholder interest and perspectives
- Clarity, consistency and predictability of evidence expectations are essential

Effectiveness Guidance Documents

- Specific recommendations for study design reflecting information needs of patients, clinicians, payers
- Targeted to public/private sector clinical researchers
- Describe study designs that provide "reasonable confidence of improved health outcomes"
- Balance internal validity with generalizability, feasibility, timeliness and cost
- Multi-stakeholder collaborative process

Essential Ingredients to Promote Evidence of Clinical Utility

- Clearly defined evidentiary expectations
- Infrastructure for efficient conduct of studies
- Reimbursement policy that promotes evidence development
- Collaborative forum to support partnerships of test developers, researchers, payers, and other key stakeholders

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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.

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."

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