A Day in the Life of a Breast Cancer Doctor: Integrating Omics to Optimize Patient Outcomes

March 17-18, 2015
New York, NY

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Moderator:

Otis Webb Brawley, MD, FACP, Chief Medical and Scientific Officer, Executive Vice President, Research, American Cancer Society

Panelists:

- *Brad Gray*, President & CEO, NanoString Technologies, Inc.
- *Amy Krie, MD*, Medical Oncology and Hematology, Avera Cancer Institute
- *Manfred Lehnert, MD*, VP and Head, Innovation, Oncology Therapeutic Area Unit, Takeda Pharmaceuticals International Co.
- *Brian Leyland-Jones, MB BS, PhD*, VP, Molecular and Experimental Medicine, Avera Cancer Institute
- *John J. Sninsky, PhD*, Chief Scientific Officer, CareDX

Challenges and Opportunities for Patient Access: Regulation and Reimbursement

John J. Sninsky

Cancer Progress
Defined Health
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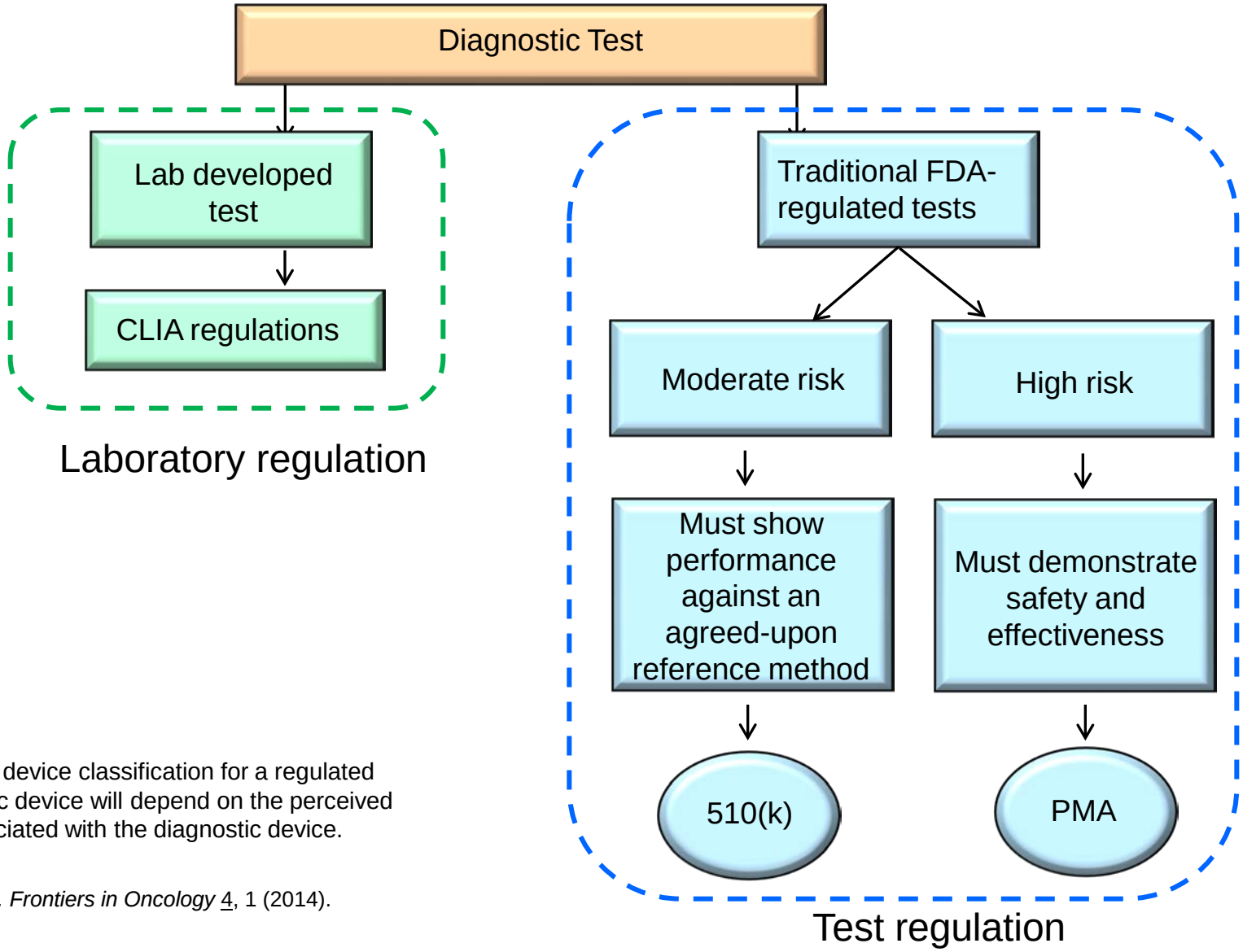
Outline

- Two paths to patient access (CLIA and FDA)
- FDA proposed oversight of CLIA tests (LDTs)
- Stages of diagnostic test development
- Reimbursement rather than regulatory oversight as gating issue
- ‘Adaptive’ versus binary regulatory/reimbursement approval
- IVD and CLIA cancer test examples
  - Metastatic melanoma (FDA IVD)
  - Lung cancer (CLIA)

Two paths for regulatory oversight



The FDA device classification for a regulated diagnostic device will depend on the perceived risk associated with the diagnostic device.

Pant *et al. Frontiers in Oncology* 4, 1 (2014).

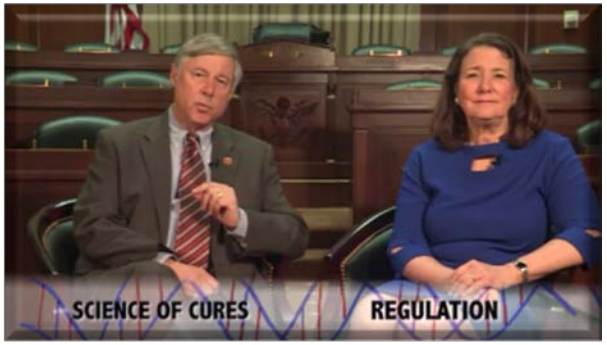
Improvements in CLIA and FDA IVD are needed

- Neither CLIA nor IVD products satisfactorily address present clinical needs
- FDA IVD products
  - IVD too slow to accommodate pace of accumulated evidence
    - Content and technology
  - IVD lacks incentives for continued improvement
  - FDA NGS discussion paper proposes ‘boundary’ subset validation
- CLIA/CAP services
  - LDTs perceived of in need of additional oversight
  - Some may be unaware of rigor of laboratory regulations
    - For example, proficiency testing required by CLIA (493.901 and 493.2), NYS Standards, and CAP accreditation
  - NGS proficiency testing standards and plans in place
    - National Institute of Standards and Technology (NIST) plans to create NIST Reference Materials from these genomes (Genome-in-a-Bottle (GIAB))
    - NY State guidelines for NGS testing
    - Horizon Discovery reference standards

https://sites.stanford.edu/abms/giab
http://www.wadsworth.org/labcert/TestApproval/forms/NextGenSeq_ONCO_Guidelines.pdf
http://www.horizondx.com/

FDA oversight of CLIA tests (LDTs)

- Many stakeholders have serious concerns
  - result in substantial limitations on physician and patient access to life altering health information
  - markedly delay the translation of innovation in diagnostic procedures and new information
  - result in significant increases in healthcare costs but review path will not permit estimates to be determined
- Draft guidance is not predictable, reasonable or transparent and there are alternative proposals to address perceived regulatory gaps and stakeholder concerns through modernization of CLIA regulations
- Runs counter to the Congressional 21st Century Cures Initiative to accelerate patient care



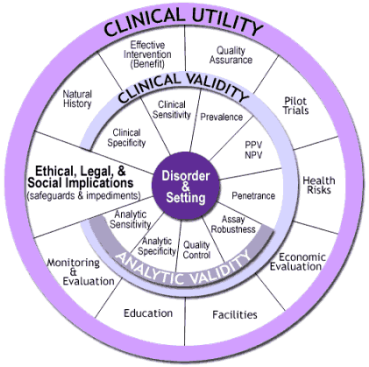
CAP http://www.cap.org/apps/docs/membership/fda-ldt-plan-webinar.pdf September 3, 2014
AACC http://www.aacc.org/events/meetings/Pages/9087.aspx# September 10, 2014
AMP http://www.amp.org/Webinars/2014.cfm September 16, 2014

Staged metrics for diagnostic testing

- **Analytical validity** refers to how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent?

- **Clinical validity** refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.

- **Clinical utility** refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.



With recent coding changes and decisions by most payors, reimbursement requires clinical utility

LDT	IVD	Payors
√	√	√
Inferred by CLIA[1,2] Included in CAP	√[3]	√
Not required	Not required	√

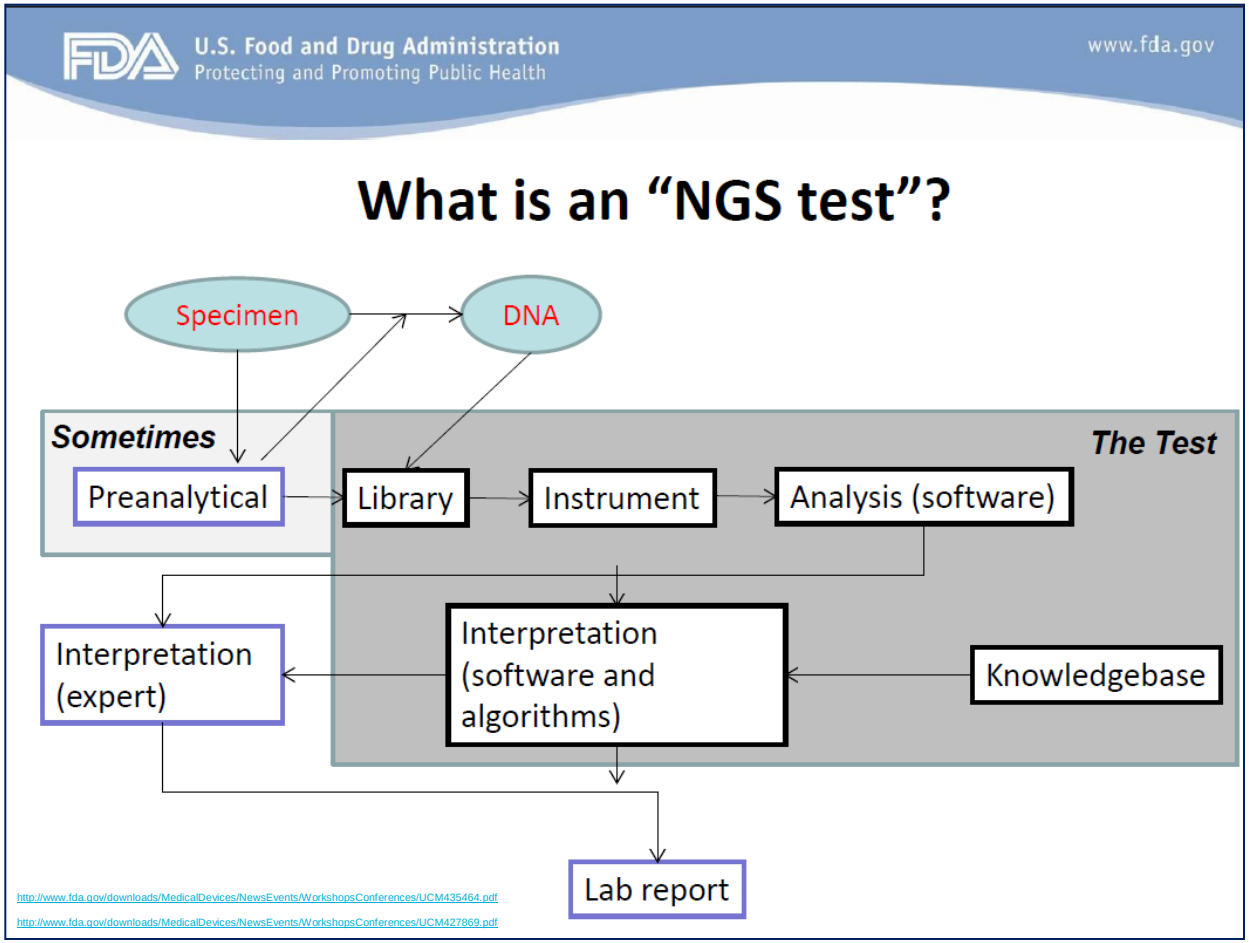
[1] Ferreira-Gonzalez *et al. J Mol Diag* 16, 3 (2014).

[2] mostly peer-reviewed literature but some retrospective analysis of RCT

[3] mostly clinical trials or RCTs but some peer-reviewed literature

http://ghr.nlm.nih.gov/handbook/testing/validtest
http://www.cdc.gov/genomics/gtesting/ACCE

NGS distinct from other reviewed tests



FDA NGS Workshop February 20, 2015 Litwack and FDA Discussion paper

FDA may decide to require analytical and clinical validation and refer to clinical grade databases for interpretation (clinical utility)

Proposal for phased and timely commercialization based on benefit/risk ratio of patients

Conventional	**'Adaptive'**
Single gating licensing decision	Phased licensing decisions
Risk of expanded use	Risk addressed by surveillance and monitoring
RCT only	Adopt new evidence (EMR)
Broad population	Targeted subset of population
Focus on licensing	Focus on patient access
Open utilization	Specified utilization

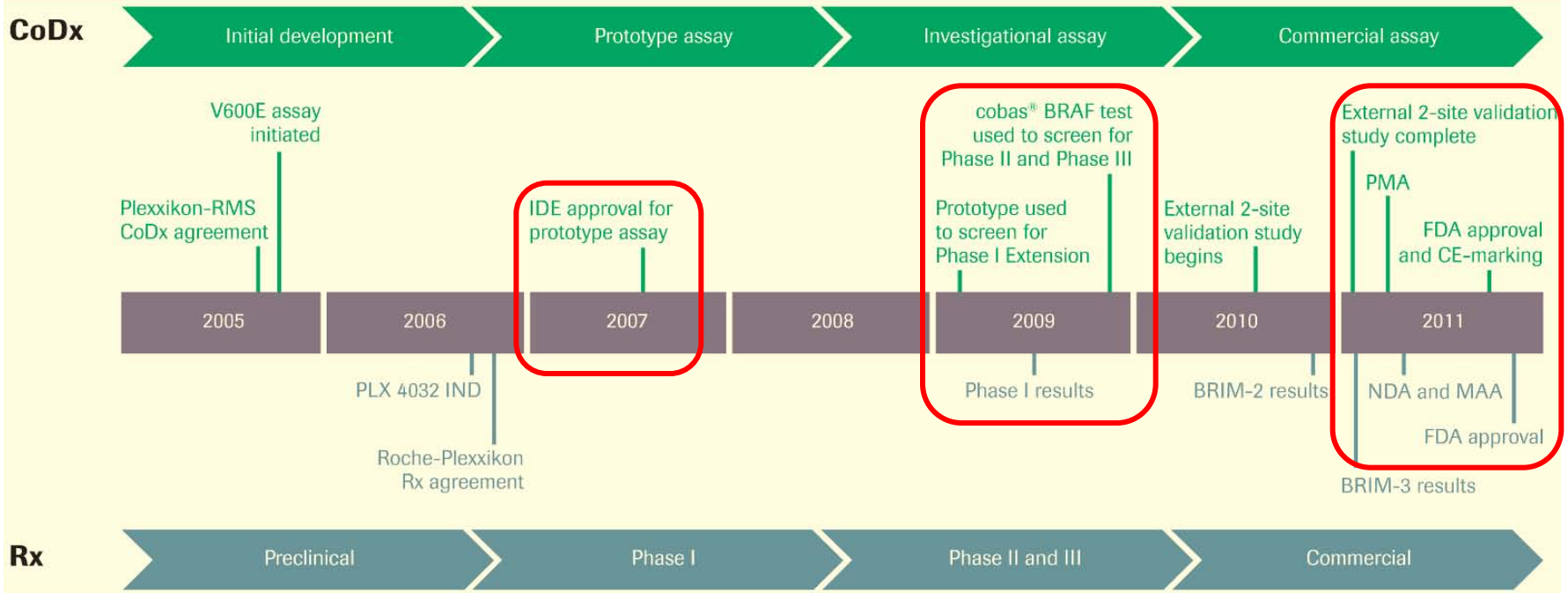
Though proposed for drug approvals, equally applicable to diagnostics and reimbursement

Eichler *et al. Clin Pharm & Ther* 91, 426 (2012).
Baird *et al. Clin Pharm & Ther* 96, 559 (2014).
Eichler *et al. Clin Pharm & Ther* 97, 234 (2015).

European Medicines Agency, MIT Center for Biomedical Innovation with some FDA co-authors

FDA approved BRAF inhibitor test has been eclipsed by 'recent' content and technology

Pant *et al. Frontiers in Oncology* 4, 1 (Article 78) (2014) .



- ~15% of patients who test negative by Cobas V600 carry V600 mutations according to Sanger[1] and NGS[2,3] sequencing
  - Consistent with the Roche BRAF US-IVD package insert (10.8%)
- 92% of V600E2 (12/13) and 34% V600K (13/38) missed by Cobas test
- European Medicines Agency (EMA)[4] approved V600 mutations more broadly than FDA
  - EMA used literature support

[1]Qu *et al*. *J Mol Diagn* 15, 790 (2013).
[2]Siroy et al. J Invest Derm (2014).
[3]Ihle *et al. BMC Cancer* 14, 13 (2014).
[4]da Rocha Dias et al.Eur J Cancer 49, 1654 (2013).

Lung Cancer: accelerated patient access to CLIA NGS

- Published analytic and clinical validation study
  - Frampton *et al. Nature Biotechnology* 31, 1023 (2013).
- MolDx Palmetto Clinical Test Evaluation Process (CTEP) M000096 September 2014
  - If level of evidence is not at least **Prospective Observational Studies (POS)** involving prospectively enrolled patients in a registry, treating according to a defined pathway using the molecular test as an integral part of the care plan, the request will be denied
- Published clinical utility study
  - Drilon *et al. Clin Can Res* Jan 7 Epub (2015).
- NCCN updated clinical practice guidelines (Version 5.2015) for non-small cell lung cancer. The guidelines endorses broad molecular profiling to identify "rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials."
- MolDx Palmetto (CMS) Draft Local Coverage Decision (LCD)

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