Level of Evidence for Adoption of Tumor Markers – A Model for Genomic Companion Diagnostics

"We propose that the Tumor Marker Utility Grading System is a step toward helping to standardize and establish some order in the presently chaotic field of tumor markers." Hayes et al 1996

I. ***Evidence from a single, high-powered, prospective controlled study that is specifically designed to test marker***, or evidence from well-done meta-analysis of level II studies. ***Ideally, the study is a prospective, randomized controlled trial…***

II. Evidence from study in which marker data are determined in relationship to a *prospective* therapeutic trial that is performed to test therapeutic hypothesis ***but not specifically designed to test marker utility***. Specimen collection for marker study and statistical analysis are ***prospectively determined*** in protocol as secondary objectives.

III. Evidence from large but ***retrospective*** studies from which variable numbers of samples are available or selected. Statistical analysis for tumor marker was not dictated prospectively at time of therapeutic trial design.

IV. Evidence from small ***retrospective*** studies that do not have prospectively dictated therapy, follow-up, specimen selection or statistical analysis.

V. Evidence from ***small pilot*** studies designed to determine or estimate distribution of marker levels in sample populations.

Hayes DF, Bast RC, Desch CE et al. JNCI 1996;88:1456–1466

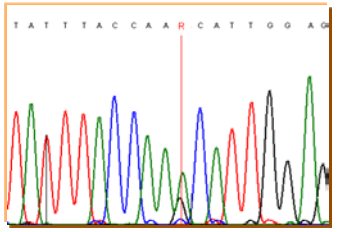
Leveling the Playing Field: Bringing Development of Biomarkers and Molecular Diagnostics Up to the Standards for Drug Development

George Poste, David Carbone, David Parkinson, Jaap Verwiij, Stephen Hewitt and J. Millburn Jessup
***Clin Cancer Res: 18;1515* (2012)**

- The analytical validity of an assay is the primary focus of diagnostic laboratory CLIA accreditation
- For clinical diagnostic tests that guide treatment decisions (eg. companion diagnostics), establishing the clinical validity of the IVD is as important as determining its analytical validity
- Finally, before payors will reimburse for an IVD and clinical practitioners can incorporate it into routine practice, the biomarker and IVD must be shown to have high clinical utility

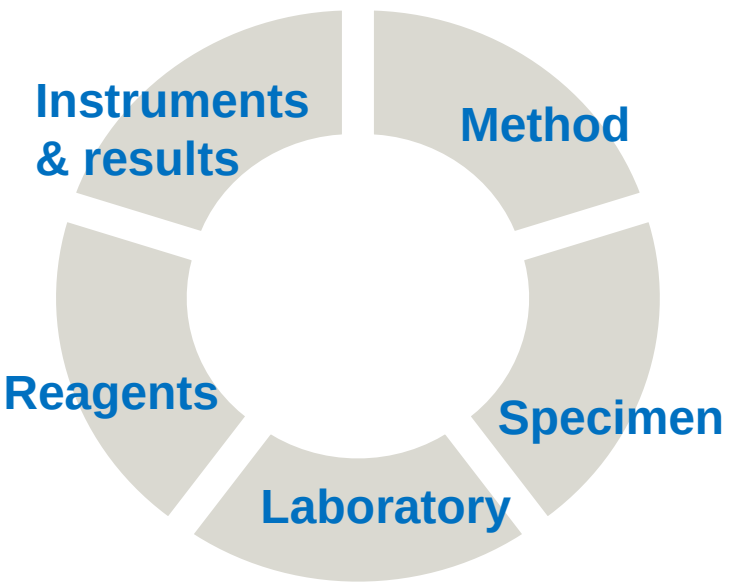
In vitro Diagnostics Vary in Performance

Many sources of variability and potential for error



Manual analysis, interpretation & reporting

Multi-source reagents, lot-to-lot variability



Undefined procedural steps [1,2]

Many technology choices, Lab to lab variability

Variable quality & quantity

[1]Beau-Faller et al *J. Thor. Oncology 2011*
[2]Dequeker et al *Virchows Arch 2011*

Advanced Molecular Tests are not Fungible

*Example: **cobas®** BRAF V600 Test vs. Sanger Sequencing performance*

Metric	cobas®	Sanger[1]	Clinical Implication using Sanger
Invalid rate: No result despite multiple attempts	1 (0.2%)	44 (9.2%)	Patient denied or delayed access to ZELBORAF
False negative: Incorrectly reported as wild type[2]	3 (0.7%)	17 (3.9%)	ZELBORAF inappropriately withheld
False positive: Incorrectly reported as V600E[2]	0 (0%)	2 (0.5%)	Patients inappropriately receive ZELBORAF

FDA recognizes Sanger sequencing as the reference method in the absence of a predicate FDA-approved test. However, Sanger sequencing is poorly suited for cancer tissue (FFPE) mutation analyses.

1. Sanger sequencing followed a validated protocol conducted in replicate in an CLIA certified laboratory
2. True mutation status confirmed through discordant resolution using a 3rd method (Validated 454 RUO pyrosequencing)

Source: Anderson et al Arch Pathol Lab Med. 2012,136:1

Even Tests Using the Same Technology are Different

cobas® BRAF vs. Therascreen (Qiagen) BRAF RGQ

- 126 challenging samples selected for comparison (high necrosis, high pigmentation, low tumor content) - discrepant analysis by 454 deep sequencing

	cobas® BRAF	RGQ BRAF	Additional information
Invalid rate	5/126 (3.9%)	1/126 (0.8%)	• 2/4 RGQ valid results had correct mutation call (both WT) • 2/4 RGQ valid results had incorrect mutation call (one FP and one FN) • 1 sample could not be resolved by either method
False positive (FP)	0/121(0.0%)	4/121 (3.3%)	• 4 WT classified as V600E by RGQ
False negative (FN)	3/121(2.5%)	10/121 (8.3%)	• 3 V600E (<5% mutation) by cobas • 1 V600E and 9 V600K by RGQ

Longshore et al. Poster presentation at American Molecular Pathology Association meeting (October 2012) – submitted for publication

H. R. 3207 - "Modernizing Laboratory Test Standards for Patients Act of 2011"

How IVD Clinical Validity would be established; Clinical Utility not addressed

- STANDARD FOR ISSUANCE—The Secretary shall issue such an authorization letter if the notification provides reasonable assurance of the clinical validity of such claimed uses. One or more studies published in a peer-reviewed journal that is generally recognized to be of national scope and reputation or data from unpublished studies conducted by the submitter or for which the submitter has obtained a right of reference, shall be sufficient to constitute reasonable assurance of the clinical validity of the claimed uses.

AdvaMedDx Risk Based Approach

- Need for improvement in current regulatory scheme to address gaps (example: Class III Equivalence mechanism)
- Need for adoption of a modernized, risk based regulatory approach for all in vitro diagnostics
- FDA oversight of tests should focus on the risk of harm associated with how the test result is used to treat patients
- FDA oversight of safety and effectiveness of all diagnostic tests, regardless of where they are made because they have the same risk/benefit profile for patients.
- Improved transparency of FDA's decision processes
- Support public health and encourage innovation, including advances in genomic and molecular sciences

Diagnostic Payment Reform

- Payment reform is needed to recognize value of advanced medical diagnostic tests, their impact on health care and the resources needed to develop and clinically validate them
- Inadequate payment impacts innovation, as well as patient access to new tests
- The Palmetto GBA under the Medicare MolDx Program issues reimbursement coverage based on review of level of evidence (analytical and clinical), and may offer a model for a path forward

Comments Regarding Solutions Proposed

- Support the Coalition for 21st Century Medicine observations
- ACLA - Proposal that H.R. 3207 would strengthen demonstration of clinical validity and utility seen as inadequate
- CAP – Disagree that “companion analytes” should be defined; IVDs clearly vary in both analytical and clinical performance
- ASCO – Disagree that use of a single clinically validated CoDx prevents further Research aimed at understanding tumor biology and drug response

Concluding Thoughts

- When substantial clinical utility evidence results in an assay becoming standard of care (eg. NCCN, ASCO guidelines), CLIA Lab-developed in vitro diagnostics can address an unmet medical need when no FDA-approved CoDx exists
- FDA Enforcement Discretion of Lab-developed IVDs creates an un-level Playing Field when IVD Manufacturers are subject to FDA enforcement, sometimes moving targets of the analytical and clinical validation required, and must provide evidence supporting improved clinical outcomes and patient benefit (clinical utility)
- When an FDA approved or cleared companion IVD exists, use of CLIA lab-developed IVDs should be discontinued.
- FDA needs to develop a least burdensome approach to establish ***equivalence*** to an existing approved Class III CoDx IVD when clinical trials cannot ethically be repeated (regardless of whether lab developed or manufacturer distributed).