Impending Federal Actions on Laboratory Developed Tests (LDTs)

Co-Sponsored by ACMG and the Association of Molecular Pathology (AMP)

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American College of Medical Genetics and Genomics
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Major Concerns and Risks

CONCERN

- No specifics upon which one can even judge the impact of proposed FDA oversight of LDTs

RISKS

- Loss of patient access to tests
- Closure of small innovative laboratories

Introduction

- There is broad consensus that we have to improve oversight of LDTs
- However, the question remains as to whether this should be through:
  - FDA whose legislative mandate is to regulate medical devices, or
  - CMS whose legislative mandate via CLIA is to regulate clinical laboratory tests

Faith-based Oversight

- No economic assessment of the impact of this significant change in laboratory oversight is available
- No specifics on what constitutes high, moderate, or low risk LDTs
- No specifics on what it will cost clinical laboratories to comply
  - Presume that FDAs current approach to notification of laboratories offering LDTs and the registration of the LDTs they offer would occur under any role they took with regard to clinical validity of tests

Hence, no way to practically assess costs or impact on access to critical clinical tests.

Presentations

- **Compare and Contrast the Diagnostic Test Working Group proposal, the FDA Guidance, and the CLIA Enhancement Models** – Sylvia J. Trujillo, Senior Washington Counsel, American Medical Association
- **Implications of LDT Oversight for Laboratories and Patients** – James P. Evans, MD, PhD, University of North Carolina
- **The Legislative Backdrop** – David Liss, Vice President External Relations, BioReference Laboratories/GeneDx and Marc Grodman, MD, President and CEO, BioReference Laboratories / GeneDx
- **Enabling Laboratories to Voice Their Views to**

Logistics

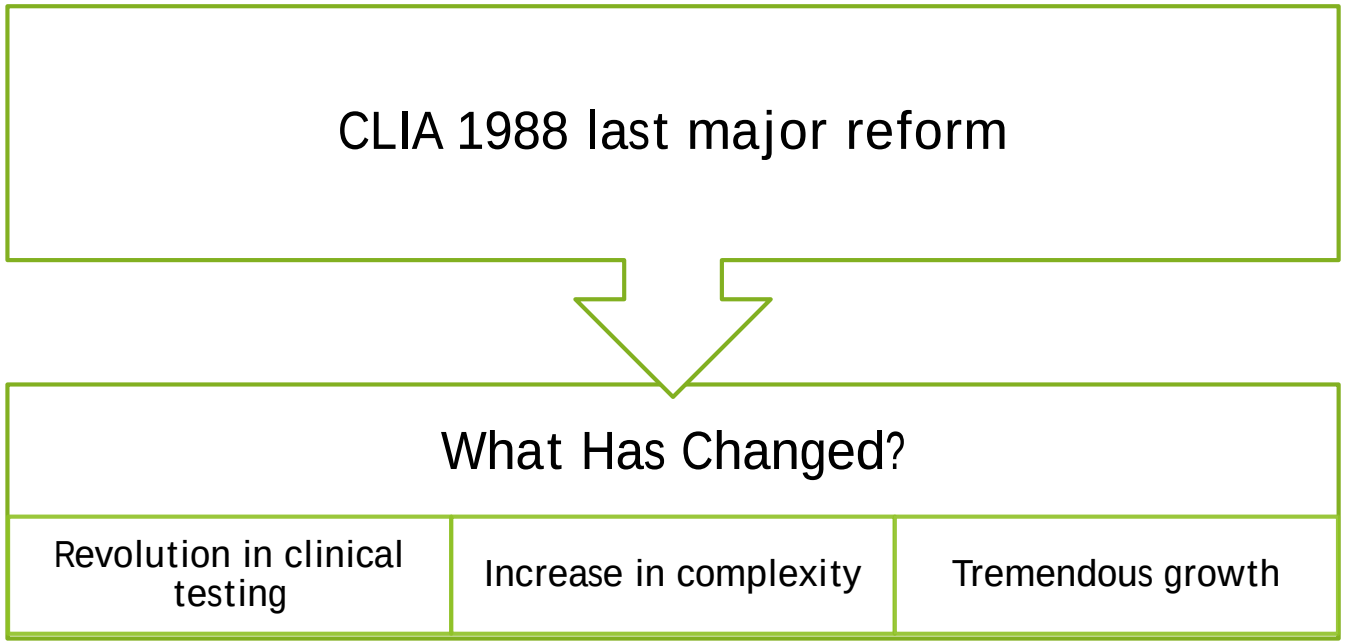
- Questions for speakers can be submitted at anytime during this webinar
- Type your questions into the questions and answers box in the right-hand corner.

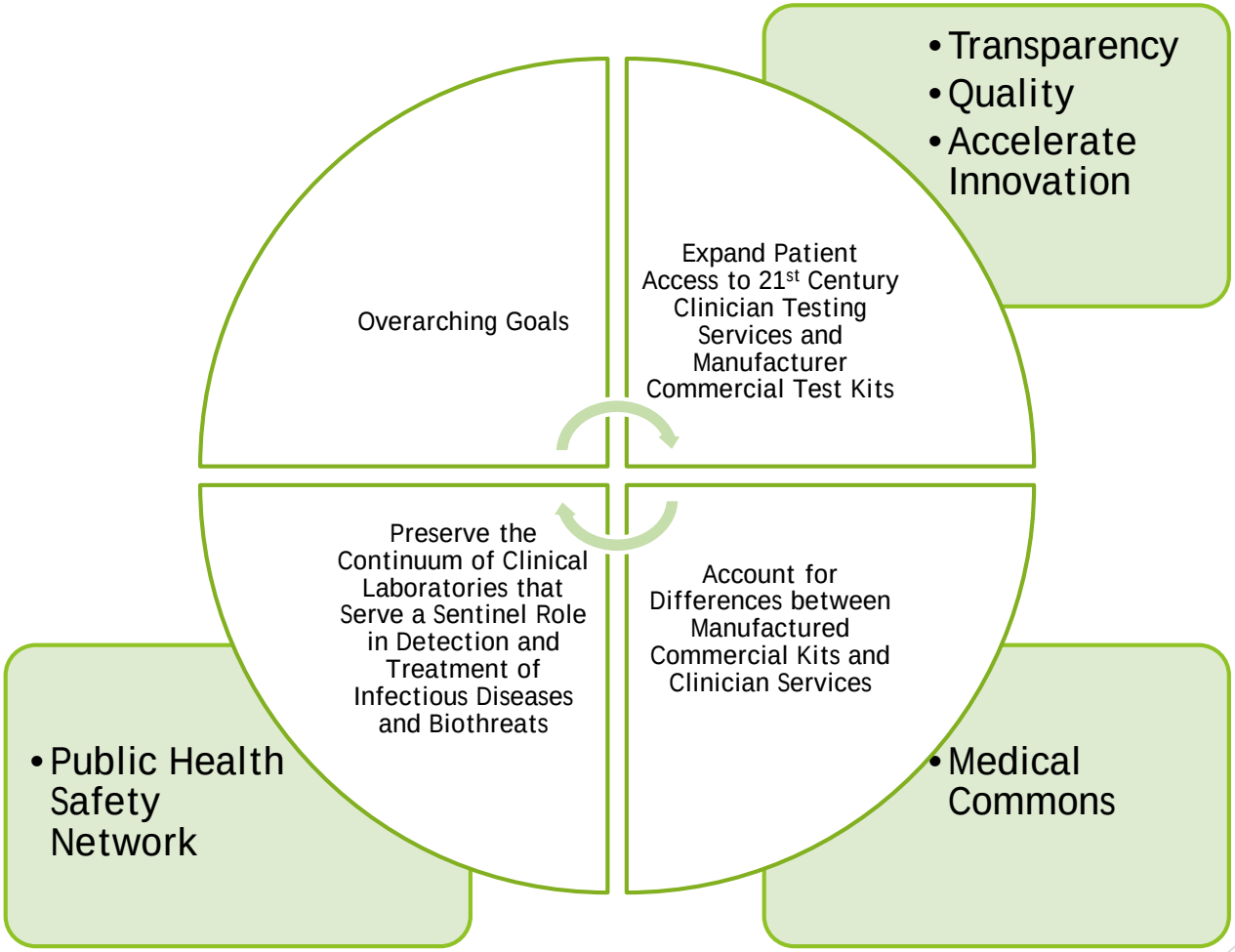
Reform Models & the Optimal Pathway

Innovation, Ensuring Patient Access, Protecting Public Health Network, & Enhancing Quality Testing Modernization of Clinical Testing Oversight

American College of Medical Genomics and Genetics Webinar
March 2016

Consensus: Modernization Necessary




Overarching Goals
Expand Patient Access to 21st Century Clinician Testing Services and Manufacturer Commercial Test Kits
Preserve the Continuum of Clinical Laboratories that Serve a Sentinel Role in Detection and Treatment of Infectious Diseases and Biothreats
Account for Differences between Manufactured Commercial Kits and Clinician Services
• Transparency
• Quality
• Accelerate Innovation
• Public Health Safety Network
• Medical Commons

Convergence: Two Part Modernization Needed
CLIA and FFDCA

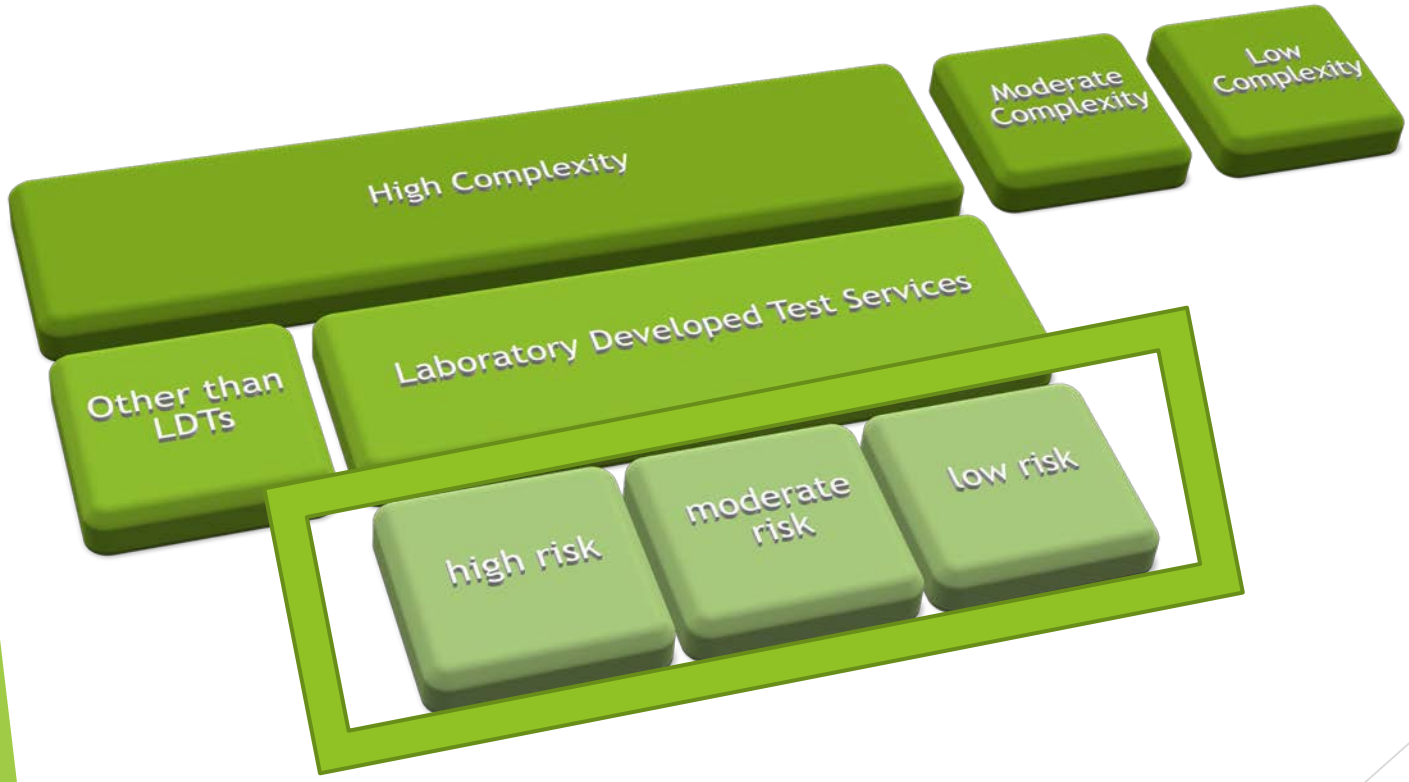
Modernize and Enhance CLIA Requirements for Laboratories

- Strengthen Role of 3rd Party Reviewers and Accreditors
- Increase Transparency of Test Validation (Clinical and Analytical) and Adverse Event Reporting
- Risk Stratification and Pre-Clearance for moderate-risk (CLIA) and high risk (FDA)

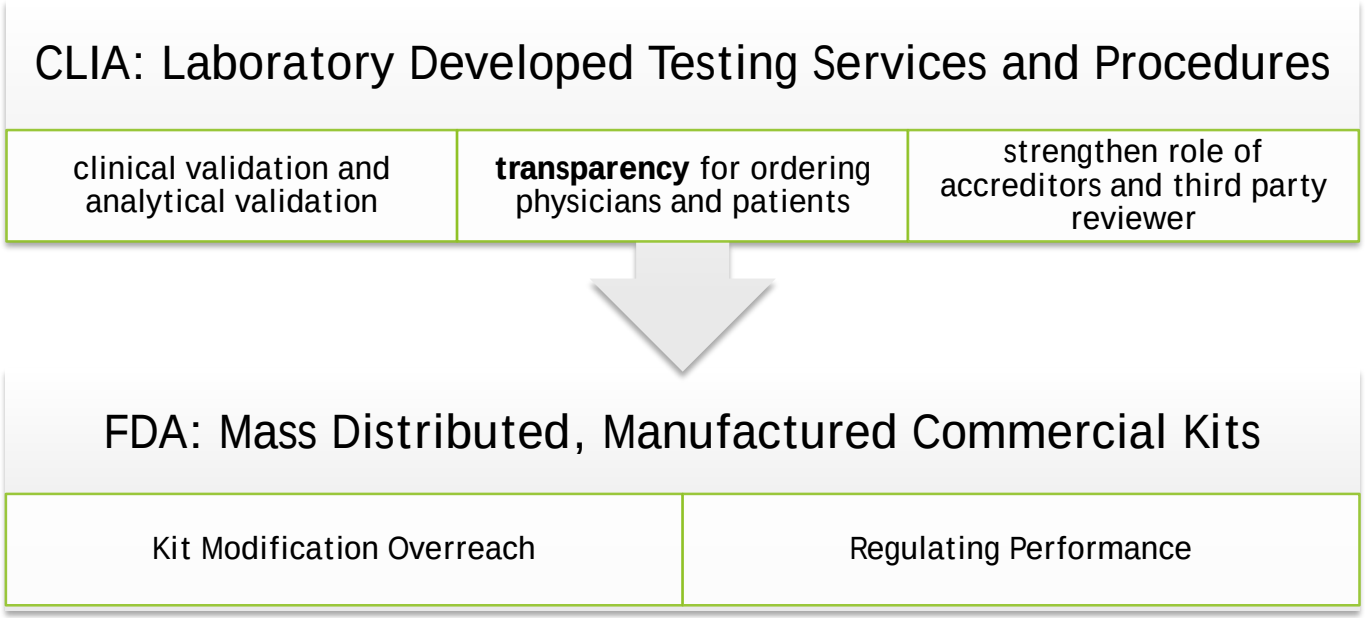
Reform and Streamline Federal Food, Drug & Cosmetic Act (FFDCA) Provisions Applicable to Manufacturer Distributed Commercial Kits

- 510K or PMA: Only Clinically Meaningful Performance Modifications Trigger submissions/supplemental for manufacturer kits
- FDA pre-clearance for high risk tests that reviewers and/or accreditors unable to use medical commons to validate
- Ensure manufacturers are not subject to duplicative or conflicting CLIA/FFDCA requirements

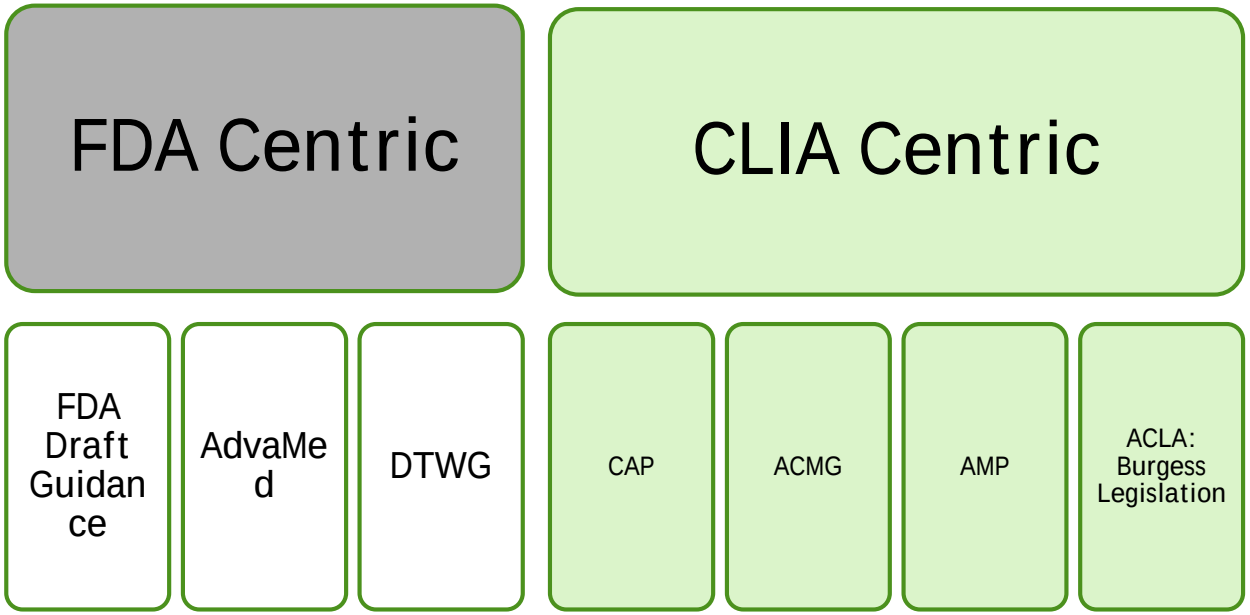
What are we talking about under CLIA?



Consensus: Modernization Needed



The Continuum



Fundamental Disagreement

Commercial Kits and LDTs Are Not the Same "Activity"

LDTs design, development, and validation inextricably tied to performance of test

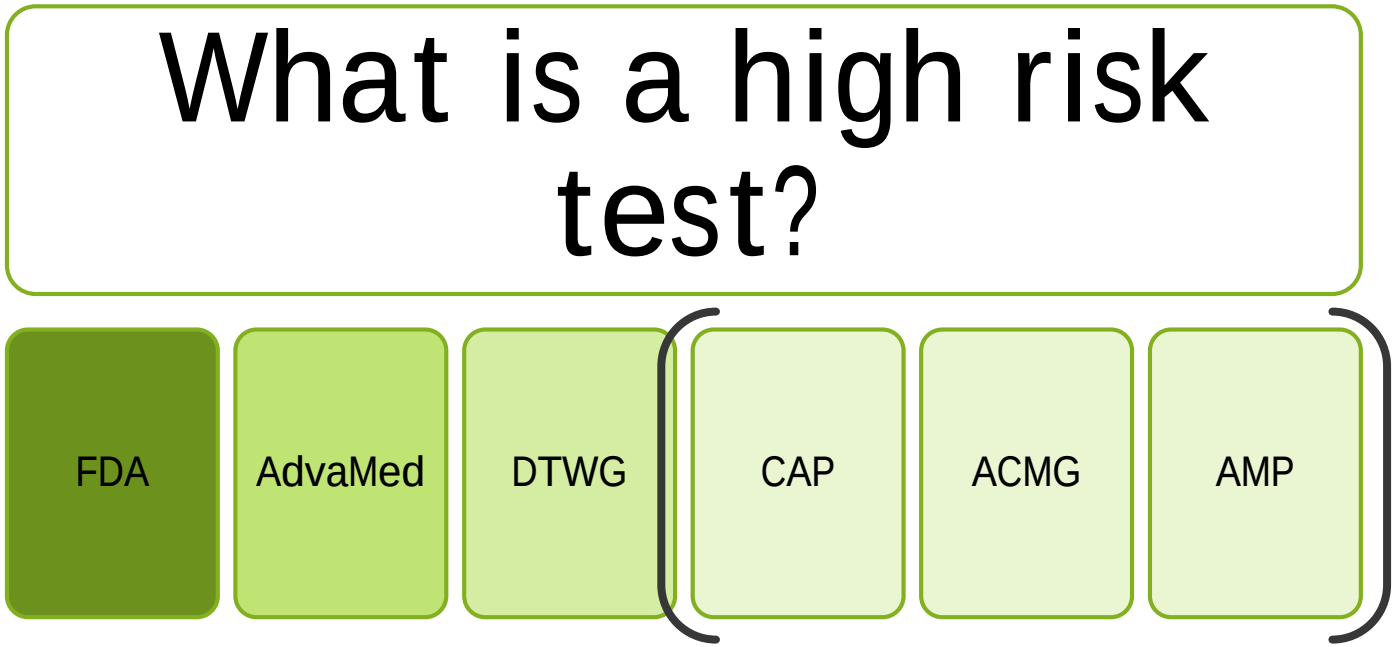
- interaction/established relationship with ordering physician with specifics of patient availabile
- interaction with individuals performing the test
- closed loop quality control
- limited number of locations/individuals involved in providing this service

Commercial Kits are engineered for standard patient and standard laboratory

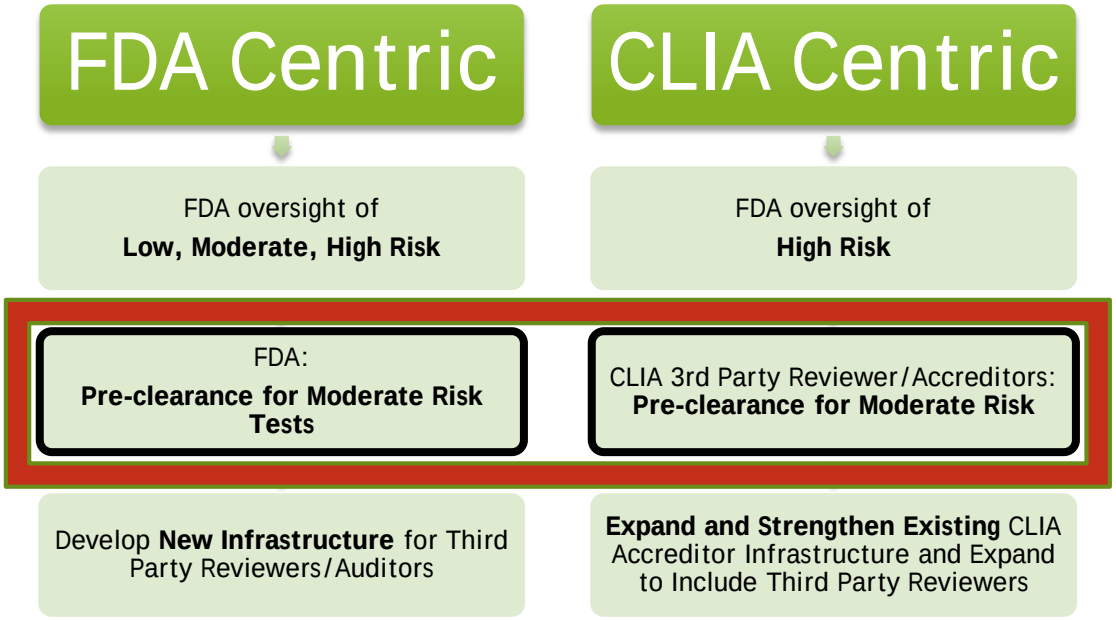
- engineers who designed and validated test are not in contact with laboratory staff performing test nor interacting with ordering physician
- modifications typically required to commercial kits
- adverse event reporting loop more attenuated and response substantially delayed

Critical distinctions exist between laboratory developed testing services and commercial diagnostic kits	
	Commercial diagnostic kits are an actual product that can be packaged, labeled, and shipped in interstate commerce to numerous laboratories, in contrast to the services and procedures offered by a physician in a single laboratory as part of his or her practice of medicine.
	Once the manufacturer distributes the commercial diagnostic kits, the manufacturer no longer retains control over how the test is conducted, what patient is tested, and how the information is shared with the treating physician, whereas physicians retain control and decision-making authority throughout the continuum from design to delivery of test results.
	Physicians who utilize a commercial diagnostic kit are not able to evaluate the underlying methods and components of the commercial kit, nor are the test results detailed; instead, they are limited to yes/no results. In contrast, when offering laboratory developed testing services physicians have a complete understanding of the results as well as the underlying methods, sample preparation, inputs, procedures, and validation of the test.
	A commercial diagnostic kit is a packaged product that is engineered to be performed anywhere for a “standard” patient, not a specific patient in contrast to laboratory developed testing services that physicians offer to a specific patient based on their clinical condition and in consultation with the patient's treating physician.

Key Difference?



Key Difference



Where is their convergence because FDA draft guidance continues to raise questions shared by all?

Public Health:

- safeguarding the public health laboratories and their sentinel activities
- preserving the network of clinical laboratories provide front line detection and rapid test development

Evidentiary Requirements for Moderate and High Risk

Modifications:

- commercial kit manufacturers historically complained about burden
- if scope not modified, lead to volume

Volume:

- estimates highly variable – Agency testified no additional resources needed, DTWG reports volume will remain the same for moderate risk tests
- economic impact analysis

Capacity of Regulator(s)/ Capacity of Regulated

- The LDT Draft Guidance, if finalized in materially the same form, will further slow the regulatory clearance/approval pathway for manufacturers of commercial test kits due to the added LDT volume and will not address long-standing manufacturer concerns with existing regulatory burdens resulting from the FDA's application of the Device Amendments to regulate diagnostics.
- Depending on the level of specificity to differentiate tests there are tens of thousands to hundreds of thousands of clinical tests that would be considered and regulated as LDTs under the LDT Draft Guidance.
- The FDA does not have the infrastructure or resources to oversee a regulatory program of this scope. (As a point of reference, FDA databases show that the Agency has approved 187 PMAs (including supplements) and cleared 230 510(k)s for IVDs so far in 2015.)

Regulation of Laboratory Developed Tests

Practice of Medicine, Costs of Compliance & the Meaning of Risk

Jim Evans MD, Ph.D

University of North Carolina at Chapel Hill

My Perspective

- My interest in this topic derives from my daily activities as a clinician, both in the realm of Medical Genetics and as a General Internist.
- My only interest is in ensuring general availability of a nimble and diverse testing capacity that can respond to legitimate provider and patient needs
- Providers currently have access to a wide array of very useful tests that arose in an open and interactive environment between clinicians and laboratorians

Costs of Compliance

University of North Carolina

- UNC's "Core" Laboratory (chemistry, hematology, coagulation, cytogenetics, molecular pathology, molecular microbiology)
  - 258 LDTs
  - 103 modified tests
- Minimal costs for complying with FDA oversight will entail registration of LDTs
- Including modifications of approved kits
  - e.g. to test other fluids beyond serum or urine or any "unintended" use such as HCG for anything other than pregnancy testing

*Figures courtesy of Catherine Hammett-Stabler, Director of UNC's Core Laboratories

Costs of Compliance

- At a simple cost of $2,000/test for notification UNC's core lab will face $1-3 million/per registration period
  - Recurring fees exist for manufacturers
    - 510K compliance would incur an order of magnitude more cost per test
    - Full PMA would cost well over $100,000/test
- Bottom line is that even with only registration/notification required, the test menu offered by academic and most other labs will plummet
- Even ignoring the fact that test costs will inevitably increase if proposed regulation is enacted, reimbursement will not keep pace, leading to higher costs for patients and our Medical system
- High fees for regulatory compliance will drive the field towards monopolies/oligopolies
  - Undermining the ability of the vast majority of labs to offer tests in direct response to clinician and patient needs
  - We've been down this road before (e.g. BRCA1/2 testing)

The Proposed FDA regulation represents an existential threat to most laboratories and a threat to patient care

Clinical Validity and Medical Practice

- The use and full interpretation of laboratory tests are not under the exclusive purview of the clinical laboratory
- Rather, proper use and clinical validity result from interaction between the lab, clinicians and the medical literature
  - Unrealistic to think that the FDA can adjudicate clinical validity as it is well outside their scope of expertise
  - Requiring RCTs to demonstrate clinical validity of every test would be unworkable
- Clinical validity can be assessed to a large extent (and quantified) via systematic survey of the medical literature
  - Something being done by ClinGen currently
  - CLIA (or the 3rd party entities such as NYDOH, CAP, ACMG, etc.) could play a role in such a process

The FDA's Current Concept of High Risk is Incorrect and Unworkable

- Virtually any laboratory test can be high risk in a given clinical context
  - Not a good parameter by which to calibrate regulation
- To prevent problems from lab tests with no clinical validity regulatory agents should focus on claims
  - Dramatic claims (i.e. tumor detection through blood analysis) demand dramatic evidence
  - Proprietary and "opaque" tests are the riskiest - and should be the primary targets of regulatory scrutiny
  - Claims that are not consistent with a body of medical literature
  - Aggressive marketing of tests puts the cart before the horse
- Indeed, the vast majority of the 20 case studies cited by the FDA as showing problems with testing would have been addressed had regulation simply focused upon marketing and claims as signals of possible problems

Thank you

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Regulation of Laboratory Developed Tests

Congress, the Administration, What's Coming and Why You Should Share Your Views of Views of Potential Impact

Marc Grodman, MD CEO BioReference Laboratories/GeneDx
David Liss, VP External Relations, BioReference Laboratories/GeneDx

Timeline on the Hill
House of Representatives

- Energy & Commerce is Committee of jurisdiction
- The draft legislative language related to LDTs were not included in the 21st CURES Act Bill, which passed the full House 7-10-15 (because there was no consensus among impacted stakeholders)
- Unclear if there is consensus in Committee
  - Health Subcommittee has 18 Rs, 13 Ds
  - Both appear to support a bigger role for the FDA (as opposed to CMS-CLIA), though
    - some Rs concerned about FDA expansion
    - some Ds concerned about interfering with the guidance.
  - 16 votes needed to promote an appropriate CLIA-centric modernization model
- In January, E&C staff convened a subgroup of the stakeholders who favored the Discussion Draft put forth by E&C.
- We are concerned that a new version will not reflect the input of the full array of laboratory and physician communities as many organizations were not included

Timeline on the Hill

House of Representatives

- The House goes out of session on July 15
- Legislation must pass out of sub by mid-April and out of full committee by mid-May
- Must pass full House before July 4 recess
- Must be reconciled with Senate
- This is an unlikely scenario-other legislative scenarios to be discussed after Senate review

Job #1: Urge Committee to support a CLIA-based solution

Timeline on the Hill

Senate

- Health, Education, Labor & Pensions (HELP) is Committee of jurisdiction
- Initially sought bipartisan approach to enhanced regulation
- Reportedly, Rs and Ds have been unable to reach consensus on the balance between FDA and CLIA oversight models

Job #2: Share with Committee expected impact of Draft Guidance and Urge Support of efforts to advance a CLIA-centric approach

Timeline on the Hill

- Are there “must pass” bills to which E&C could attach its LDT language?
  - Cures/Innovation reconciliation
    - 21st C. Cures passed in full House in July (344-7)
    - Senate is holding hearing now on related legislation-next is March 9, then April 6
  - Prescription Drug User Fee & Medical Device User Fee Amendments both expire 9/2017
    - MDUFA in particular can not only authorize FDA’s action but provide funding mechanism
    - FDA has already begun the process leading to reauthorization and Congress will hold hearings next session

Job #3: Urge inclusion of CLIA-Centric Reform in Germane Legislation and Explain Negative Impact of FDA-Centric language on your practice/laboratory

FDA Timeline

- Congress notified of impending guidance July 2014
- Draft guidance issued October 2014
- Comment period closed February 2015
- FDA will not release another draft. Agency stated that the next guidance will be the final one.
- Timing is unclear on final guidance. FDA has indicated end of 1st Q, early 2nd Q

Job #4: Itemize and quantify expected impact of Draft Guidance as such information will be needed if lawsuit needed based on final guidance

- Dr. Grodman will explain the need to act

Concerns to be Addressed

- We are truly entering into an era of uncertainty, what we do will change now and for generations.
- No evaluation or conception of cost or economic burden.
- Given the prevalence of LDP's, a massive investment in infrastructure
- There remains an essential lack of understanding and expertise of what we actually do
- Regulation cannot be used to promote economic or competitive advantage for a few in the name of patient safety.
- We need to define who we are

Engaging Your Legislators[1]

- Key messages
  - The medical genetics community has too little information (which tests at what cost) available to it to know that proposed oversight won't cause more harm to access to genetic testing in the US than good.
  - A CLIA-centric approach appears most viable ensure patient safety and access
  - Those developing and finalizing oversight plans should include individuals with expertise and training in medical genetics and genomics
  - There are concerns that giving explicit authority to FDA to regulate LDTs is worse than maintaining the status quo which would remain open to challenge.

Engaging Your Legislators[2]

- A draft letter has been developed that can be adapted for use by those wishing to communicate with their representatives. All particpants in the webinar will receive an email tomorrow with links to the draft letter, information on the names and addresses of their representatives, and copies of the slides from these presentations.

Please communicate with your representatives

Offer your expertise towards finding a workable path towards patient safety and access

Thank you