The Harms of Regulating Laboratory Developed Testing Procedures as Medical Devices RIN: 0910-AI85

August 10, 2023

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Participants

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- **Mary Steele Williams, MNA, MT(ASCP)SM**
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- **Monika Franco, PhD**
  - Senior Policy Analyst, AMP
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  - Policy Analyst, AMP
- **Jennifer Leib, ScM, CGC**
  - Innovation Policy Solutions
- **Megan Anderson Brooks, PhD**
  - Innovation Policy Solutions
- **Lindsey Trischler, MPAP**
  - Innovation Policy Solutions

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AMP & Molecular Pathology

- 2,900 physicians, doctoral scientists, and medical technologists who perform or are involved with molecular laboratory testing.
- Molecular pathology is the heart of precision medicine, where experts apply knowledge to develop molecular and genetic testing approaches to diagnose, characterize, and monitor human disease, and help select therapies.

Infectious Diseases

Hematopathology

Solid Tumors

Inherited Disease

Informatics

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Molecular Pathologists are Healthcare Professionals

- Complete extensive post-graduate education and clinical training, taken board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education, or other recognized professional boards.
- Prefer the term ***"laboratory developed testing procedure"***
  - LDPs ≠ boxed and shipped test kits

AMP respectfully requests that prior to issuing a NPRM, that a request for information (RFI) is issued to collect data and better understand the impact of rulemaking on academic medical center laboratories and other clinical laboratories offering localized care.

Developing, Performing, Maintaining LDPs

- Laboratory must be accredited (42 CFR 493.61)
- Must establish performance specifications (42 CFR 493.1253)
- Subject to quality system requirements (42 CFR 493 Subpart K)
- Must be performed under supervision of a board-certified pathologist (42 CFR § 493.1443(b)(3))
- Subject to proficiency testing (42 CFR 493 Subpart I)
- Laboratory subject to inspections (42 CFR 493 Subpart Q)
- Must correct and report laboratory errors (42 CFR 493.2; 42 CFR 493.1233; 42 CFR 493.1291(k))
- ***CLIA requirements are the floor***

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The Impact of Additional & Duplicative Regulation

	**testing consolidation**
	**diminished localized testing**
	**longer turnaround times**
	**disruption to innovation**
	**greatly reduced patient access**
	**large economic impact**

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FDA Review is Costly, Burdensome, and Resource-Intensive

- 510(k): $24 million per test[1]
- PMA: $75 million per test[1]
- Medical devices were available to U.S. patients an average of two years later than patients in other countries[1]
- The majority of LDPs are IVDs used off-label to accommodate patient need and clinical circumstances

1. http://www.medtecheurope.org/wp-content/uploads/2015/09/01112010_FDA-impact-on-US-medical-technology-innovation_Backgrounder.pdf

FDA does not have the appropriate resources to handle the added workload

- 144 human genetic tests authorized to date[1]
- In 2018, 74,448 human genetic tests were actively being offered for clinical care[2]
- Beyond human genetic testing, Concert Genetics reported in 2021 that there were over 160,000 total genetic tests used in clinical care[3]
- 14 genetic tests are entering the market every day[2]

Result: FDA should anticipate more than 5,000 applications for molecular LDPs to review annually

1. https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests#human
2. http://www.concertgenetics.com/wp-content/uploads/2018/04/12_ConcertGenetics_CurrentLandscapeOfGeneticTesting2018.pdf
3. http://www.concertgenetics.com/wp-content/uploads/2021/06/Concert-Genetic-Testing-Unit-GTU-Unique-Test-Identifier-Whitepaper-June-2021.pdf

Case Study: COVID-19 PHE

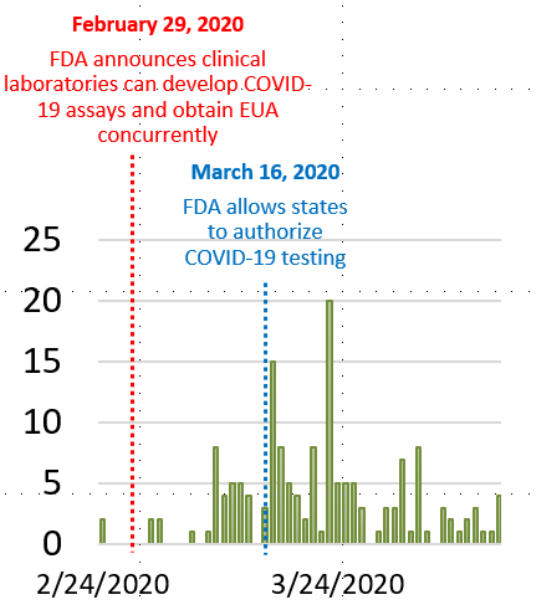
'It's Just Everywhere Already': How Delays in Testing Set Back the U.S. Coronavirus Response

A series of missed chances by the federal government to ensure more widespread testing came during the early days of the outbreak, when containment would have been easier.

By Sheri Fink and Mike Baker

Published March 10, 2020 Updated March 16, 2021

https://www.nytimes.com/2020/03/10/us/coronavirus-testing-delays.html



Number of tested introduced into clinical care per day

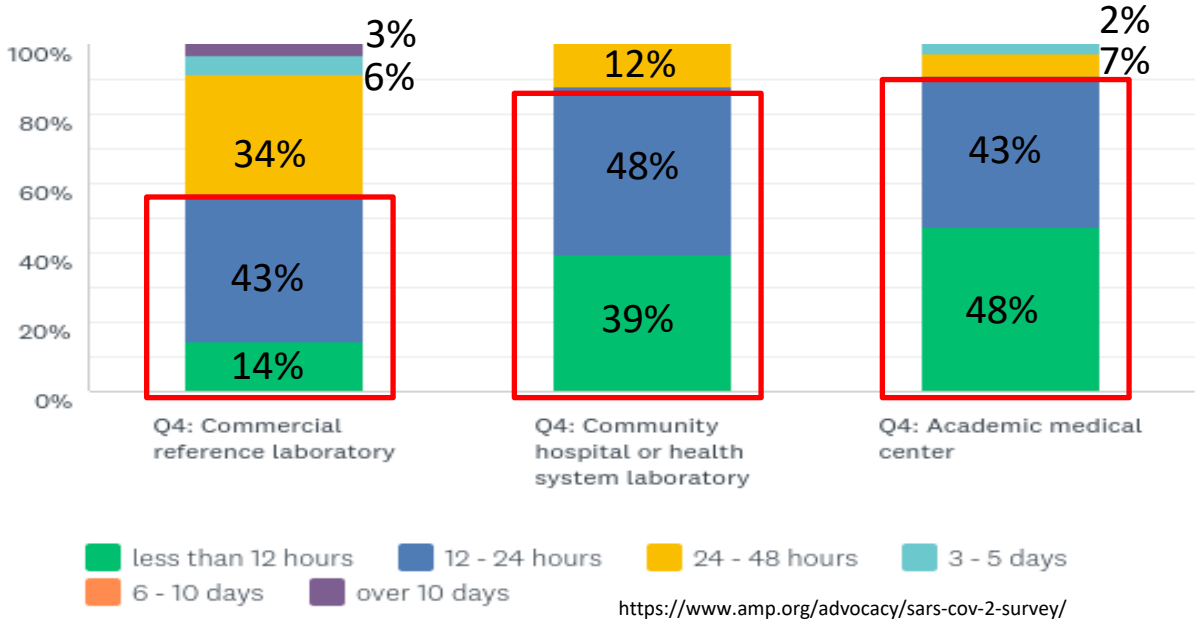
https://www.amp.org/advocacy/sars-cov-2-survey/

- According to an independent assessment, FDA received 3,672 COVID-19 IVD submissions to review between March 2020 and March 2021.[1]
- This comparatively lower number of submissions overwhelmed FDA and forced them to prioritize review and contributed to further delays.

1. https://www.fda.gov/media/152992/download

The Importance of LDPs During the Pandemic

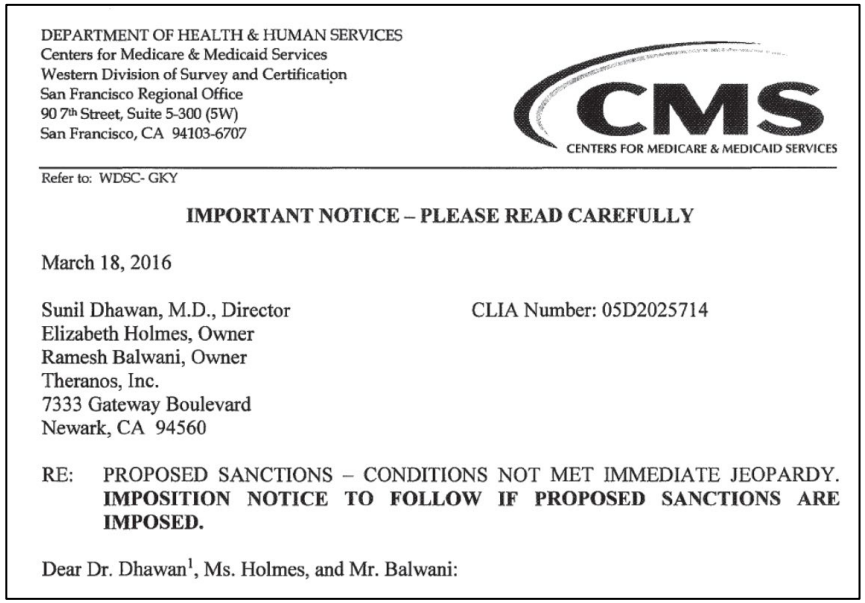
- 38% of respondents were using LDPs as at least one option
- Laboratories deployed multiple testing methodologies due to supply shortages and uncertainties
  - Commercial: 20% had 3 or more
  - AMCs/community hospital/health system labs: 57% had 3 or more
- Laboratories located close to patient care reported a rapid turnaround time for SARS-CoV-2 test results



https://www.amp.org/advocacy/sars-cov-2-survey/

NOT INCLUDING TRANSPORT TIME

Lack of evidence demonstrating widespread problem that FDA regulation will solve



DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
Western Division of Survey and Certification
San Francisco Regional Office
90 7th Street, Suite 5-300 (5W)
San Francisco, CA 94103-6707

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Refer to: WDSC- GKY

IMPORTANT NOTICE – PLEASE READ CAREFULLY

March 18, 2016

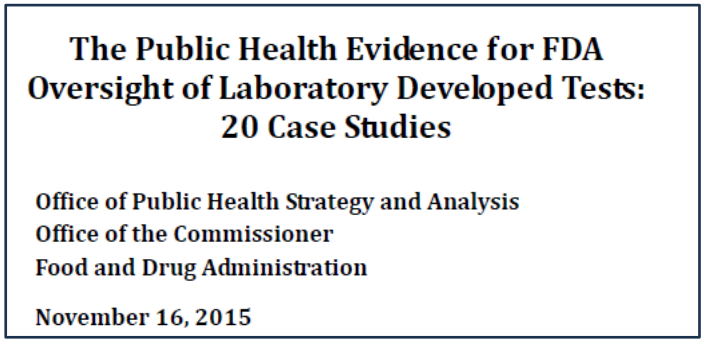
Sunil Dhawan, M.D., Director
Elizabeth Holmes, Owner
Ramesh Balwani, Owner
Theranos, Inc.
7333 Gateway Boulevard
Newark, CA 94560

CLIA Number: 05D2025714

RE: PROPOSED SANCTIONS – CONDITIONS NOT MET IMMEDIATE JEOPARDY. **IMPOSITION NOTICE TO FOLLOW IF PROPOSED SANCTIONS ARE IMPOSED.**

Dear Dr. Dhawan[1], Ms. Holmes, and Mr. Balwani:

http://www.wsj.com/public/resources/documents/hhslettertheranos.pdf

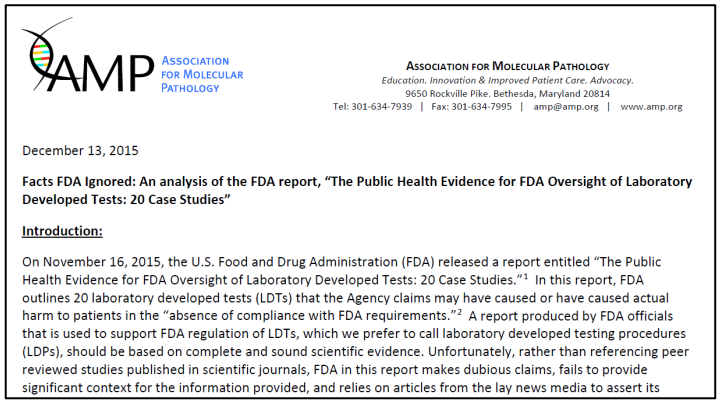


The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

Office of Public Health Strategy and Analysis
Office of the Commissioner
Food and Drug Administration

November 16, 2015

http://wayback.archive-it.org/7993/20171114205911/https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm472773.htm



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Association for Molecular Pathology
Education. Innovation & Improved Patient Care. Advocacy.
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December 13, 2015

Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies"

Introduction:

On November 16, 2015, the U.S. Food and Drug Administration (FDA) released a report entitled "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies."[1] In this report, FDA outlines 20 laboratory developed tests (LDTs) that the Agency claims may have caused or have caused actual harm to patients in the "absence of compliance with FDA requirements."[2] A report produced by FDA officials that is used to support FDA regulation of LDTs, which we prefer to call laboratory developed testing procedures (LDPs), should be based on complete and sound scientific evidence. Unfortunately, rather than referencing peer reviewed studies published in scientific journals, FDA in this report makes dubious claims, fails to provide significant context for the information provided, and relies on articles from the lay news media to assert its

https://www.amp.org/AMP/assets/File/position-statements/2015/AMPResponseFDACaseReportFinal.pdf

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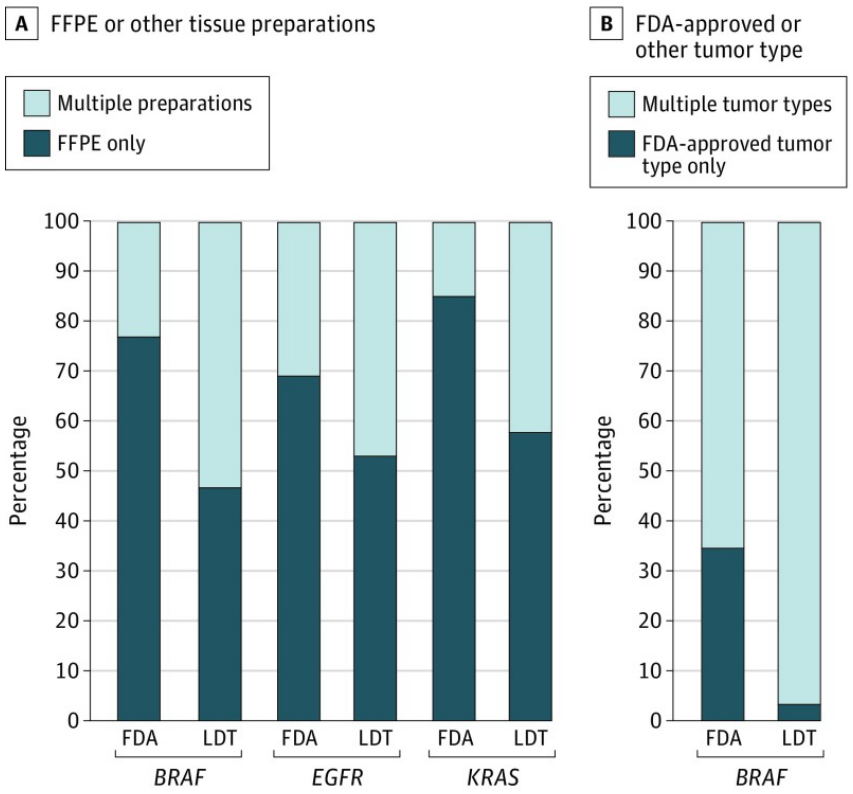
LDPs often perform better than FDA authorized tests

Gene	FDA Companion Diagnositcs, No. (%)	Laboratory-Developed Tests, No. (%)	χ^2 Test	*P* Value
BRAF				
All	300 (93.0)	2224 (96.6)[a]	9.1800	.002[b]
Wild type	88 (100)	616 (99.0)	ND	.99
p.V600E	153 (99.4)	1300 (97.5)	ND	.25
p.V600K	59 (66.1)	308 (88.0)[a]	18.0775	<.001[b]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145687/



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CLIA Should Be Modernized

MEMORANDUM

TO: Stephen Hahn, M.D., Commissioner of Food and Drugs

CC: Eric D. Hargan, Deputy Secretary
Brian Harrison, Chief of Staff
Stacy Amin, Deputy General Counsel & Chief Counsel
Anand Shah, M.D., Deputy Commissioner of Food and Drugs
Keagan Lenihan, Chief of Staff FDA
Danielle Steele, Counselor to the Secretary

FROM: Robert Charrow, General Counsel

SUBJECT: Federal Authority to Regulate Laboratory Developed Tests

DATE: June 22, 2020

We believe that the Medical Device Amendments of 1976 ("MDA"), Pub. L. No. 94-295, may be broad enough, in certain settings, to accommodate FDA's view that LDTs, as opposed to the procedures used to run those tests, are "devices," within the meaning of section 201(h) of the FDCA.[2] However, the Agency's jurisdiction to regulate these devices is not uniform and not as plenary as it is for a traditional device; this lack of jurisdictional uniformity is dictated by the FDCA itself. FDA relies on FDCA section 301(k) and the premarket review regime in sections

determine which agency should exercise that authority. Policymakers may wish to consider whether CMS, which regulates through the Spending Clause and already regulates the actual use of tests in the laboratory, is better suited legally and logistically to regulate LDTs than is FDA, which is tethered by the Commerce Clause and by statutory commerce clause requirements.

https://www.thefdalawblog.com/wp-content/uploads/2021/11/HHS-Legal-Memo-on-LDTs-by-Charrow-00864663.pdf

CLIA Modernization of LDPs

Enhances Transparency • Ensures Quality • Preserves Innovation

A working group of the Professional Relations Committee developed a proposal to modernize the CLIA regulations and maintain oversight of Laboratory Developed Testing Procedures (LDPs) under those regulations. AMP released the proposal on August 4, 2015. The working group is to be commended for wrestling with the issues and drafting a viable proposal that will provide reassurance that clinical validity is being assessed and information about LDPs is easily accessed by ordering physicians and the public, without elements that would curtail the ability of medical professionals to offer vital clinical services. The proposal consists of a tiered, risk-based structure that avoids duplication of activities within and between federal agencies.

https://www.amp.org/advocacy/advocacy-resources/laboratory-developed-testing-procedures-ldps/clia-modernization/

42 USC 263a
(f) Standards
(1) In General
The Secretary shall issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations and other procedures. Such standards shall require each laboratory issued a certificate under this section shall…

(E)to meet such other requirements as the Secretary determines necessary to assure consistent performance by such laboratories of accurate and reliable laboratory examinations and procedures.

Impact on Academic Medical Centers and Community Hospital Laboratories

J Mol Diagn. 2009 Sep; 11(5): 369–370.
doi: 10.2353/jmoldx.2009.090132

PMCID: PMC2729833
PMID: 19710396

The Role of Community Molecular Diagnostics Laboratories in the H1N1 Pandemic

Jan A. Nowak* and Karen L. Kaul

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729833/

HEARING
OF THE
COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS
UNITED STATES SENATE
ONE HUNDRED FOURTEENTH CONGRESS
SECOND SESSION
ON
EXAMINING LABORATORY TESTING IN THE ERA OF PRECISION MEDICINE

The CHAIRMAN. What would happen if you had to submit each of the 350 laboratory-developed tests that you have to the current FDA approval practice?

Dr. KLIMSTRA. We would close the lab. There's no way that the institution could afford the cost associated with formal FDA review

https://www.govinfo.gov/content/pkg/CHRG-114shrg21906/pdf/CHRG-114shrg21906.pdf

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Questions?