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Session 9A Regulatory: Approval processes, reimbursement, diagnostics

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Investigator, Dana-Farber Cancer Institute

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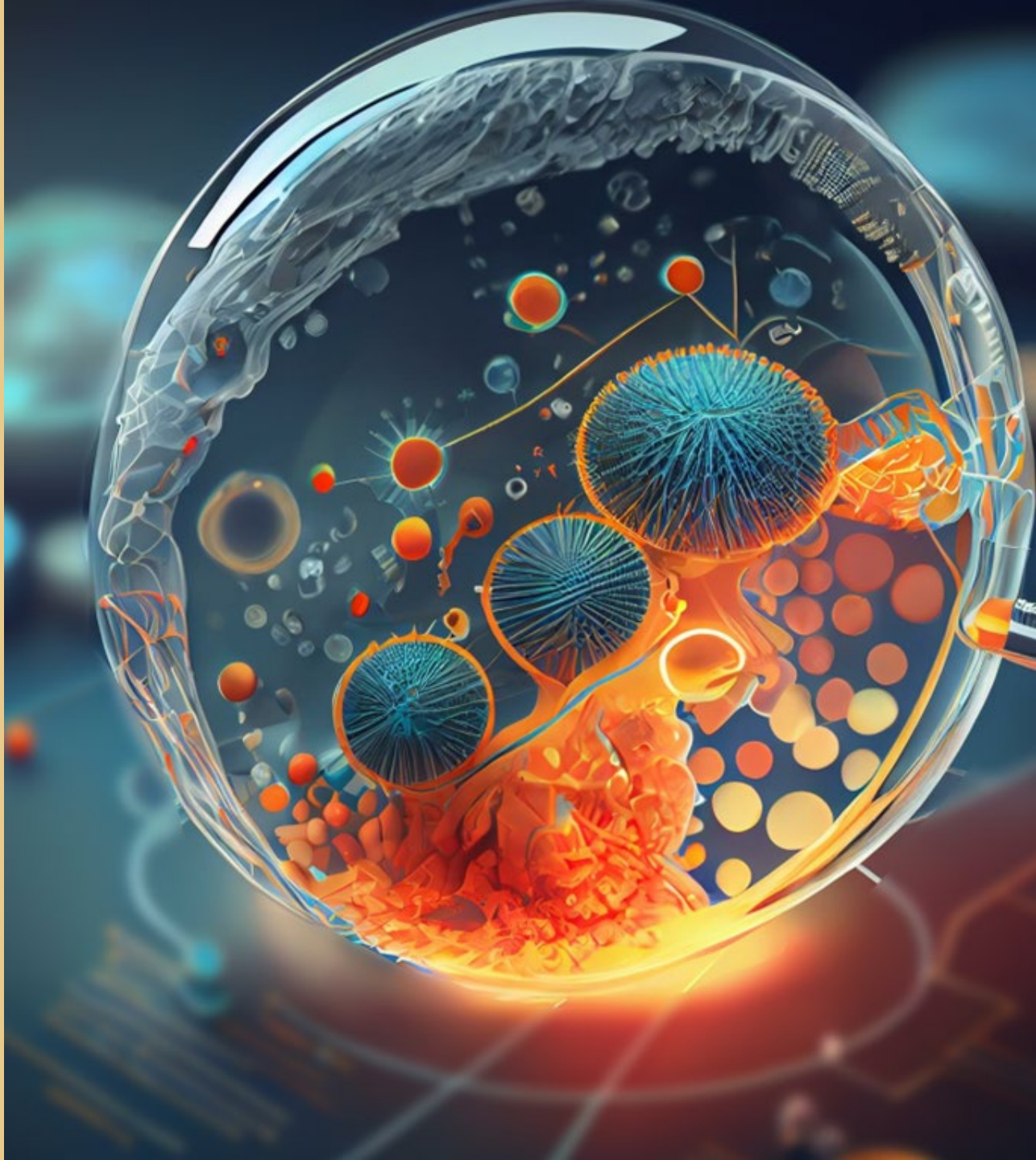
26 September 2024 Technologies Session



Disclosures

Travera Inc.	founder, consultant, equity holder
BMS	consultant, research support
Servier	consultant
Blaze Bioscience	consultant
LEK	consultant
Integragen	consultant

The Panel

Moderator

Keith Ligon MD PhD (Dana-Farber/Brigham and Women's)
Pathology, clinical diagnostics and FPM

Discussants

Philipp Staber MD PhD (MedUni Wien)
European hematological tumor clinical trials and FPM

Shannon McWeeney PhD (Oregon Health and Science Univ)
Medical informatics, data and AI in medicine

Keith Flaherty MD (Mass General Hospital)
USA solid tumor clinical trials and genomics

Session Agenda

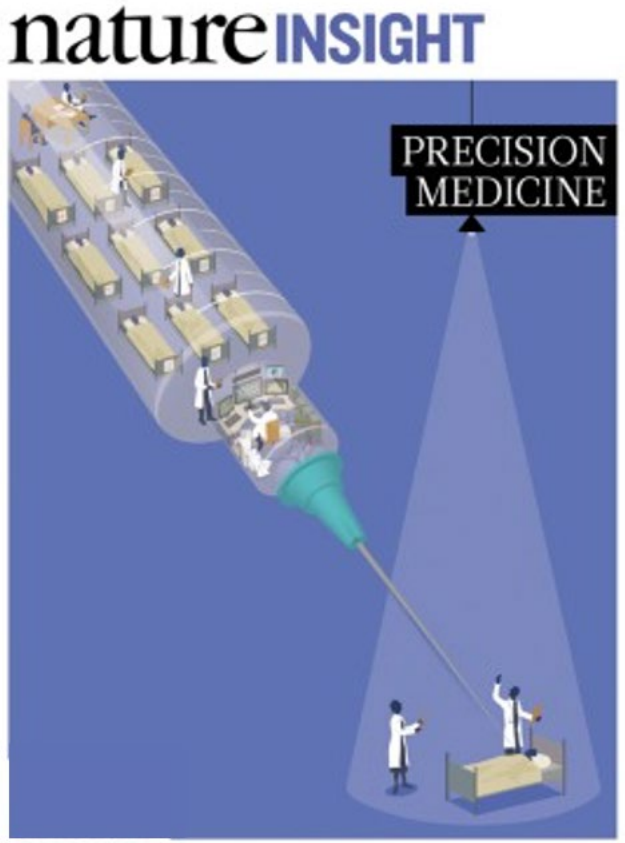
- Introduction to regulatory and reimbursement environment for precision medicine diagnostics *(15 mins)*

- Panel Discussion *(45 mins)*
  - Research and early diagnostics development and planning for incorporation into clinical trials (Leads: Staber, McWeeney)
  - Clinical trials and companion diagnostics and FDA/EMA considerations (Leads: Flaherty, Staber)
  - Data science, AI/ML development, and regulatory management of data in clinical trials and diagnostics (Leads: McWeeney, Staber)
  - Reimbursement pathways and experiences in public and private sectors for precision medicine (Leads: Ligon, Flaherty)

- Audience discussion with questions *(30 mins)*

Introduction

- Laboratory diagnostics and pathology is driving a positive transformation in health care through precision medicine
- Huge industry: 300,000 labs in the US, 14 billion tests, 8000 new tests/yr, $84 billion market
- ~70% of clinical decisions rely on in vitro diagnostics (IVD)
- **Precision medicine in oncology** is a premier example of power of technology innovation



Innovation in precision medicine….is just beginning

- Genomics
- Liquid Biopsy
- Digital Pathology
- Single cell- omics
- Spatial-omics
- Functional precision medicine
- Proteomics
- In vivo monitoring

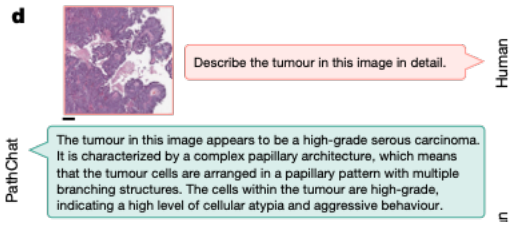
Pathology

Nature 2024

A multimodal generative AI copilot for human pathology

Ming Y. Lu[1,2,3,4,11], Bowen Chen[1,2,11], Drew F. K. Williamson[1,2,3,11], Richard J. Chen[1,2,3], Melissa Zhao[1,2], Aaron K. Chow[5], Kenji Ikemura[1,2], Ahrong Kim[1,6], Dimitra Pouli[1,2], Ankush Patel[7], Amr Soliman[5], Chengkuan Chen[1], Tong Ding[1,8], Judy J. Wang[1], Georg Gerber[1], Ivy Liang[1,9], Long Phi Le[2], Anil V. Parwani[5], Luca L. Weishaupt[1,9] & Faisal Mahmood[1,2,3,10]✉

https://doi.org/10.1038/s41586-024-07618-3



Genomics

Cell Reports Medicine

Review

The Liquid Biopsy Consortium: Challenges and opportunities for early cancer detection and monitoring

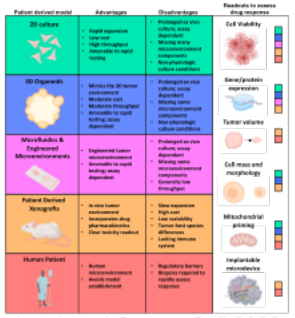
Batool SM et al Cell Reports Medicine *4*, 101198, October 17, 2023

Functional

NEWS FEATURE | 14 February 2024 | Correction 15 February 2024

The future of precision cancer therapy might be to try everything

Researchers are blasting patients' cancer cells with dozens of drugs in the hope of finding the right treatment.



Letai et al Cancer Cell 2022

Who regulates safety and efficacy of precision medicine testing and payment?

- CLIA/CAP or EU states regulate most labs
  - Regulates labs and provides certificates
  - Review lab tests and their ***analytical*** validity only

- FDA or EMA regulate tests (as devices)
  - Clearance or approval before test is used
  - Evaluate the ***analytical and clinical*** validity

- CMS and EU statues regulate reimbursement
  - Directly for Medicare and Medicaid
  - Indirectly by reference point for private sector

Forces of current concern to regulatory bodies in Dx space

- **Rapid escalation in sophistication**, automation, and complexity of testing in oncology
  - Most all testing in pathology labs now involves some degree of automation (a good thing!)

- **Laboratory developed tests (LDT) / EU exempt tests overuse** and beyond intent of single hospital practice without registration or tracking Safety and Efficacy (SE)

- **Increased risk potential and errors** with further technology advances[1,2]
  - Increased number and types of tests performed in cancer – particularly large companies
  - Cancer patient monitoring during treatment with decisions around complex tests

1. Reference 33: Memorandum to File: Examples of IVDs Offered as LDTs that Raise Public Health Concerns RE: Medical Devices; Laboratory Developed Tests https://www.regulations.gov/document/FDA-2023-N-2177-0076
2. PMID: 35944238 Offit K et al. Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities JCO 2023

What are FDA/EMA's goals and plans?

- Prevent future problems by **"Better assuring the safety and effectiveness of IVDs offered as LDTs"**[3]

- FDA "Final rule" ending LDT exemptions was enacted in April 2024

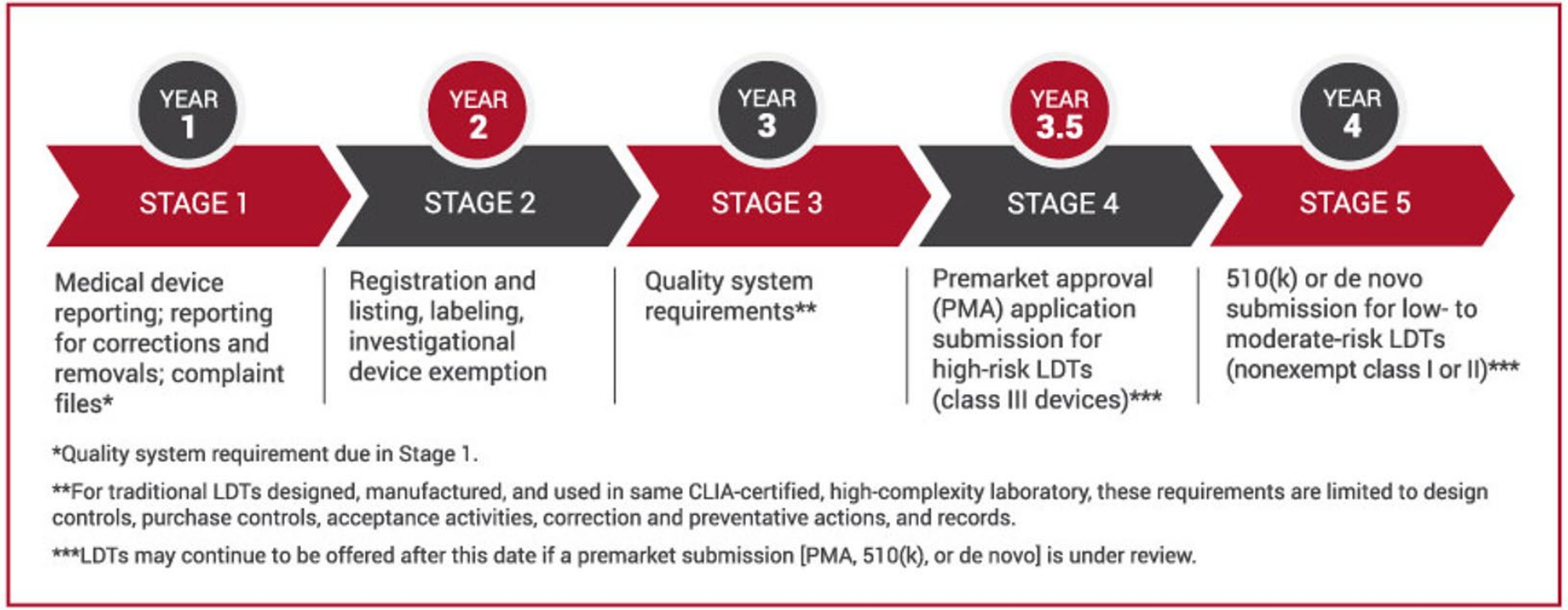
- EU Regulation 2017/746 (IVDR) in 2017 regulated similar tests with EU Article 5(5) exemption for "in house" IVDs being scrutinized

- Both seek to now review and regulate all IVDs at some level

3. ***21 CFR Part 809 [Docket No. FDA–2023–N–2177] RIN 0910–AI85 Medical Devices; Laboratory Developed Tests***
https://www.govinfo.gov/content/pkg/FR-2023-10-03/pdf/2023-21662.pdf

FDA Timeline for LDT Phase Out

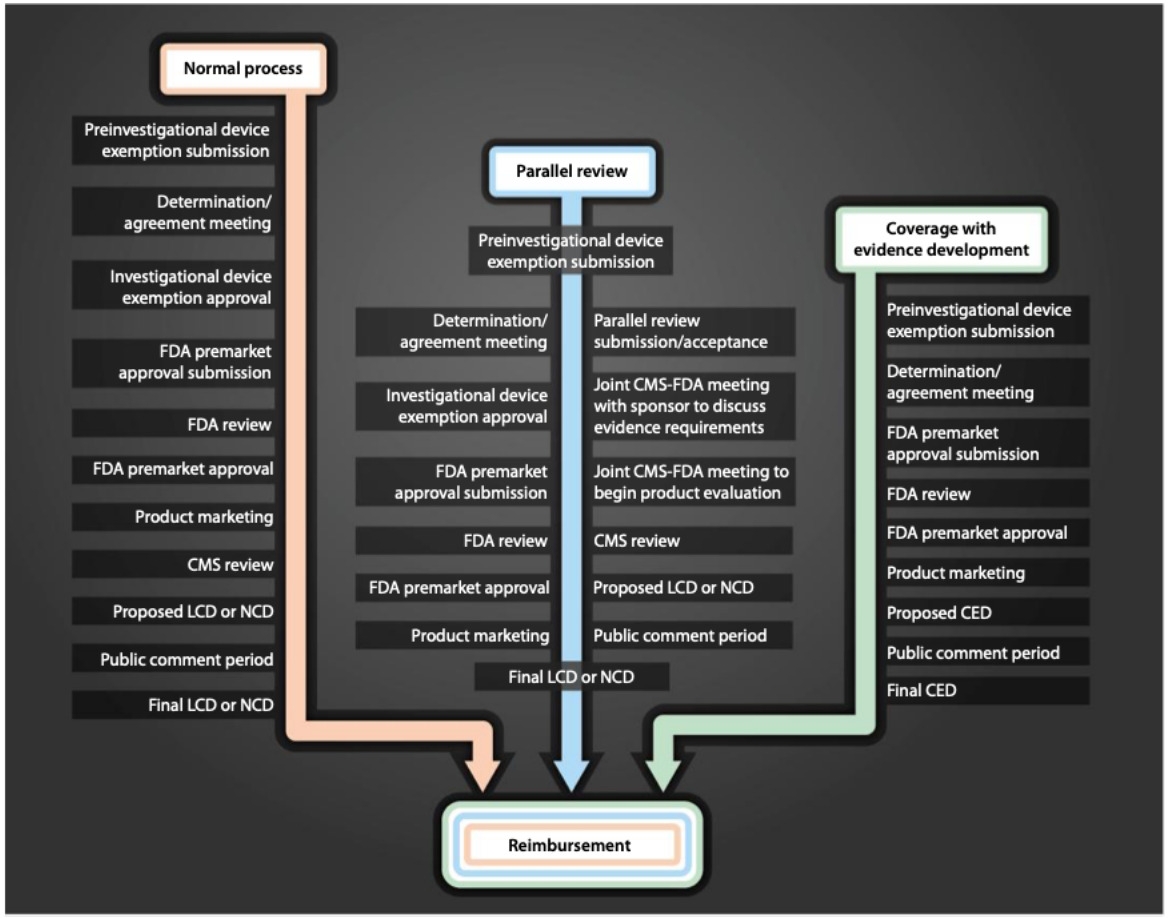
May 6, 2025	May 6, 2026	May 6, 2027	Nov 6, 2027	May 6, 2028



https://www.aruplab.com/fda-ldt-final-rule/faq

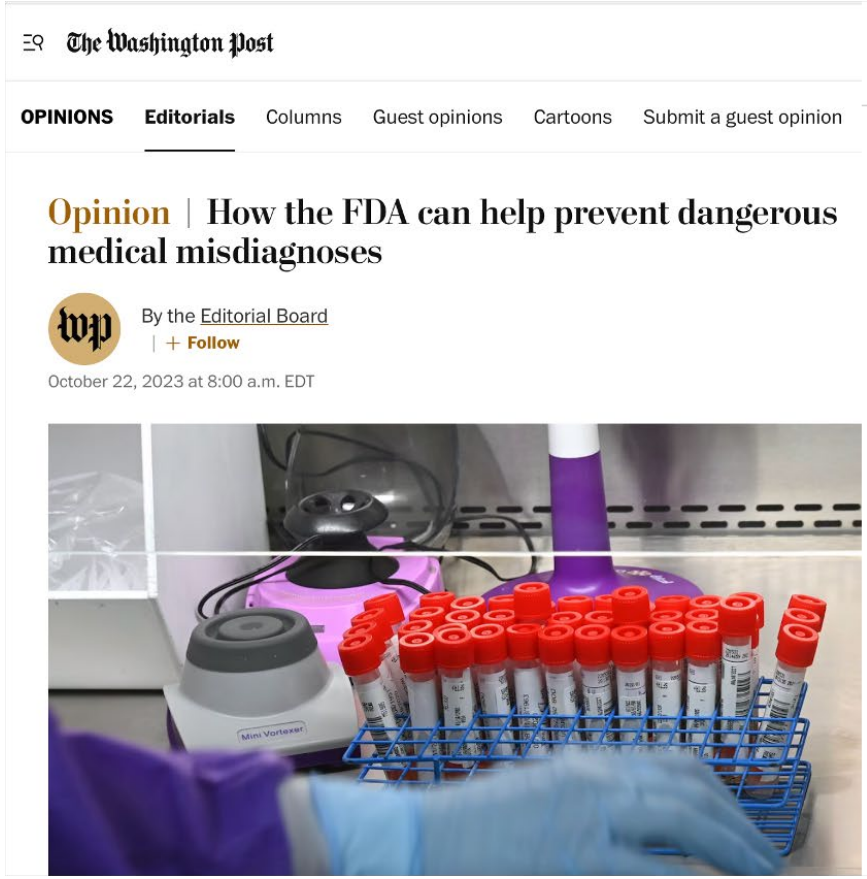
Pathways of formal EMA/FDA IVD review is a long one……no matter the road taken

- Test review for safety and efficacy (FDA)
- Test review for reimbursement (CMS)
- Local and national considerations
- FDA estimates
  - 12+ mos
  - 21K-483K USD fee/test
  - 5K/yr USD maintenance/test



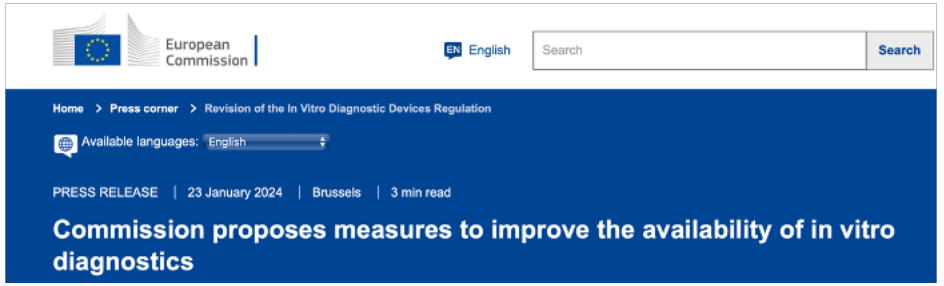
Lindor RA Sci Trans Med 2013

Lots of debate on “who” but most agree some additional regulations are needed



Regulation Increase Will Generate Risks to Patients and Innovation So Must be Balanced with Gains

- Testing costs will increase
- Test development less feasible
- Reduced patient access (= harm)
- Tests removed from market
- Hospital testing moved to industry
- Innovation risk
  - Functional precision medicine clinical assays are ***all*** LDT or exempt testing currently in US and EU



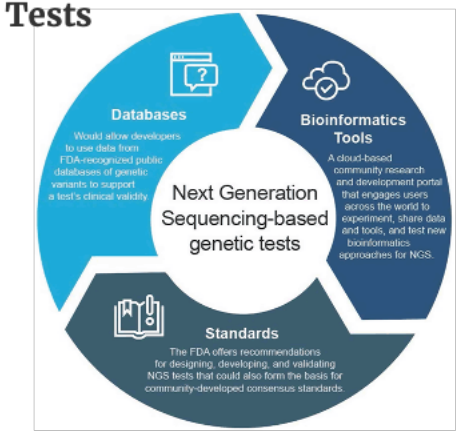
However, the available data shows that today a considerable number of *in vitro* diagnostics currently on the market do not yet comply with the new rules nor have been replaced by new devices. The situation is especially critical for high-risk IVDs, which are devices used, for example, to test for infections in blood and organ donations….

This is very important, also taking into account the fact that many manufacturers producing IVDs are small and medium size enterprises.

What ways are emerging to manage new regulations?

- FDA/EMA streamlining
- FDA Third party review
- Hire consultants
- Education
- Advocacy

Streamlining FDA's Regulatory Oversight of NGS Tests



https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine

Current List of FDA-Recognized 510(k) Third Party Review Organizations (8/2024)

AABB
BeanStock Consulting
CENTER FOR MEASUREMENT STANDARDS OF INDUSTRIAL
COLA, Inc.
Global Quality and Regulatory Services
REGULATORY TECHNOLOGY SERVICES, LLC
THIRD PARTY REVIEW GROUP, LLC

AACR Annual Meeting 2024
Workshop on Regulatory Processes and Precision Med

Sheila Wolcoff JD
CEO Goldbug Strategies LLC

goldbug strategies

Advocacy through legal means

- Law not clearly supporting FDA involvement in hospital labs (“overreach”)
- Argue CAP – CLIA takes role
- Major question to EU and USA is line between professional practice and “production products”

Today’s Clinical Lab June 28, 2024

Future of FDA’s LDT Rule Uncertain with Latest Supreme Court Decision

In overturning the Chevron case, justices diminish the power of federal agencies like the FDA

STAT+ | HEALTH TECH Aug 19, 2024

Another suit filed against FDA over lab-developed test rule

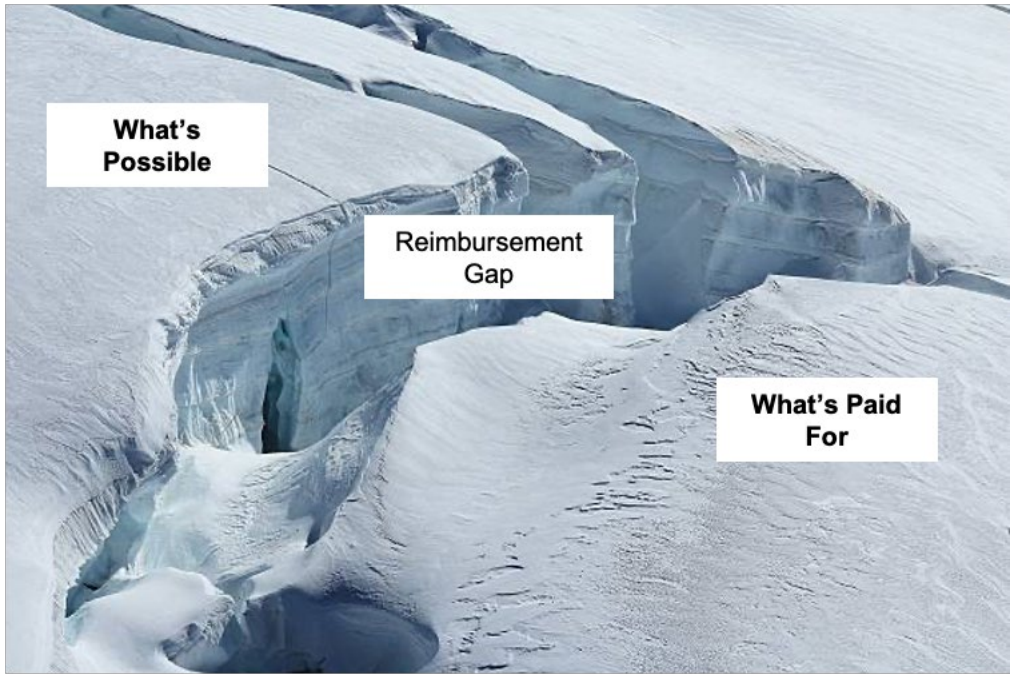
Trade group says the agency is overstepping its regulatory authority

AMP Association for Molecular Pathology

ACLA American Clinical Laboratory Association

Reimbursement in precision medicine

- CMS/EMA review for reimbursement sets the rules
- Private coverage separate from CMS decisions is increasing (e.g. Kaiser)
- Overall cost focus is on drugs and systems not prepared for increased costs of highly effective diagnostics
- Need to ***<u>manage</u>*** the gap (can't eliminate it)



Example of Managing FPM Barriers and Patient Access

- ***SfPM formed a Workgroup on Reimbursement and Regulatory policies in Dec 2022 and identified areas of need to barriers to the field and patient access (Bruce Yeager, Keith Ligon Co-Chairs)***

- ***Reimbursement focus: Retirement of NCD190.7***

Bruce Yeager

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NCD 190.7 - Human Tumor Stem Cell Drug Sensitivity Assays

National Coverage Determination NCD 190.7 issued by CMS effective July 1, 1996

- NCD applied to “stem cells” but language could be read more broadly
- States that “[h]uman tumor **drug sensitivity assays are considered experimental**, and therefore, not covered under Medicare at this time”
- The company (Analytical Biosystems Corporation) that developed the Fluorescent Cytoprint Assay is **no longer in business** and to our knowledge, the Fluorescent Cytoprint Assay **is not currently available**.
- NCD reviewed again in 1999-2000, but no revised NCD was issued as the reconsideration request was withdrawn
  - Tests reviewed for NCD 190.7 utilized “2D cell culture” technology paradigm

- **Unecessary inhibition on innovation, investment, and access to FPM testing**

Proposal from SfPM: CMS consider use of Medicare Program Revised Process for Making National Coverage Determinations[1]

SFPM position: NCD 190.7 is **obsolete and should be retired**. Companies can submit their clinical data for review to the local MAC for coverage determination. An obsolete non-coverage NCD does not represent the interests of Medicare beneficiaries and healthcare providers

Actions Taken:

1. **Submitted 2023 Comment letter for reconsideration/removal under physician fee schedule**
2. **Submitted 2024 formal proposal for reconsideration with assistance of law firm Arnold and Porter**
3. **Meetings with CMS and education of policy experts on effects from reimbursement**

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Panel discussion

Talking points

- ***Research and early diagnostics development and planning for incorporation into clinical trials (Leads: Staber, McWeeney)***
- What is most important consideration when labs start to consider developing tests?
- What are the biggest mistakes you see that labs make in the early test development process?
- Most precision medicine testing generates large data – how best to manage this early?
- Should I make my own CLIA lab or add the test to existing labs?
- How do I know whether my test would be of value to the community?
- Should I launch a startup or stay in the academic hospital setting?

Talking points

- ***Clinical trials and companion diagnostics and FDA/EMA considerations (Leads: Flaherty, Staber)***
- What is the most “hot” diagnostic area now and in the future for clinical trials
- With new FDA regulations how best to perform stand-alone trial for diagnostics development
- Have recent LDT or other changes from FDA/EMA affected clinical trials
- What can we do to prevent clinical trials and diagnostic trials disruption

Talking points

- ***Data science, AI/ML development, and regulatory management of data in clinical trials and diagnostics (Leads: McWeeney, Staber)***
- What challenges have you had with data handling and management in diagnostics development
- Regulatory agencies are very focused on AI/ML in diagnostics: do you feel they are on right track
- What are future barriers you believe will emerge for diagnostics in the area of data
- How should labs engage with data specialists to enter diagnostics field

Talking points

- ***Reimbursement pathways and experiences in public and private sectors for precision medicine (Leads: Ligon, Flaherty)***
- Complexity costs money – how do you see precision diagnostics being paid for in future
- Should precision diagnostics cost more than they do now
- How can labs plan to seek reimbursement for tests
- Is there a place for academic lab tests in the future or will it all be private sector due to high costs and low reimbursement
- What is area of improvement in the reimbursement review that you would most like to see

Audience discussion with questions