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Food and Drug Administration
Dockets Management Staff (HFA–305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

To Whom it May Concern:

On behalf of the Consortium for Clinical Metagenomics in Infectious Diseases (CCMID), we appreciate the opportunity to comment on FDA's proposed rule on laboratory developed tests (LDTs).

The CCMID is a collaborative group of microbiologists, scientists, physicians, and industry partners working to facilitate implementation of next-generation sequencing (NGS) approaches for infectious disease diagnostics. The CCMID engages stakeholders at multiple levels of care via patient-centered, value-focused projects, education, and research. We agree with the FDA that the safety of the public's health is paramount, and we support the need for accurate and safe diagnostic tests. However, we also assert that patient access to testing, including advanced diagnostic methods, is critical. We are deeply concerned that the proposed rule will negatively impact patient access to testing and our ability to provide comprehensive testing for diagnosing infectious diseases.

The CCMID focuses on advancing NGS-based infectious disease diagnostics. Assays using NGS technologies are significantly more complex than standard molecular-based testing, and development requires extensive expertise in molecular biology as well as in computational bioinformatics. Accordingly, clinical microbiology laboratories seeking to implement NGS-based assays will most likely do so as LDTs. At present, there is only a single FDA IVD certified assay using NGS for a specific infectious disease application (the Vela Sentosa assay for HIV genotyping). However, NGS-based assays are undergoing development and investigation for many uses in diagnostic infectious diseases, and we believe these assays will provide a major component of future microbiology testing. The proposed FDA rule will prevent further development and clinical implementation of these assays.

Laboratory developed tests fill gaps in clinical diagnostic testing for infectious diseases.

LDTs serve an important function bridging the gap between development of new diagnostic technology and IVD availability. Many academic laboratories and small companies use LDTs to bring innovative diagnostics into clinical use and establish their utility before larger companies are willing to make the investment to submit these assays for regulatory approval. Further, clinical practice guidelines recommend the use of LDTs, or sample types that are not approved on IVDs, for diagnosis and monitoring of infectious diseases (Baddour et al., 2015; Daley et al., 2020; Fowler et al., 2023; Freifeld et al., 2011; Kalil et al., 2016; Lewinsohn et al., 2017; Metlay et al., 2019; Tunkel et al., 2017). It is highly unlikely that all of these clinical use cases will have IVD-approved products within the aggressive 5 year time frame. LDTs fill gaps in clinical diagnostic needs for infectious diseases, and NGS-based assays are an excellent example of this process.

NGS-based laboratory developed tests for infectious diseases, including clinical metagenomics, provide unmet diagnostic needs.

Although there are numerous commercially available IVDs for nucleic acid amplification test (NAAT)-based detection of infectious diseases, many of which use polymerase chain reaction (PCR) based approaches, many infectious diseases remain undiagnosed. For example:

- Greater than 50% of cases of acute encephalitis remained undiagnosed after routine diagnostic testing (Granerod et al., 2010)
- The percentage of community acquired pneumonia cases with no pathogen detected after bacterial and viral testing is ~60% (Jain et al., 2015)
- Approximately 30% of cases of clinical sepsis had no pathogen identified (Novosad et al., 2016)

NGS-based LDTs provide a solution to unmet needs that are not currently met by standard IVD certified NAAT assays. This is particularly notable for the NGS-based diagnostic approach referred to as clinical metagenomics. Clinical metagenomics uses NGS technologies and bioinformatics to diagnose infectious diseases by identifying genetic sequences of pathogens directly from patient specimens. There are two pertinent examples of clinical metagenomic LDTs offered in the United States for patient testing that have clearly benefited patients with infectious diseases. The first is the LDT offered by the University of California San Francisco (UCSF) used to diagnose the cause of meningitis / encephalitis using cerebrospinal fluid as a specimen (Miller et al., 2019; Wilson et al., 2019). The second is the Karius test offered by the biotech company Karius. The Karius test detects microbial cell-free DNA from blood using a clinical metagenomic approach (Armstrong et al., 2019; Bergin et al., 2023; Blauwkamp et al., 2019; Hogan et al., 2021). These clinical metagenomic LDTs have benefited patients by providing diagnostic answers where standard testing has not been able to do so. Additionally, these clinical metagenomic LDTs serve as prescient examples, as academic medical centers are developing similar assays for patient use and investigating how to best implement these into routine clinical care (Flurin et al., 2022; Ivy et al., 2018; Kamau & Yang, 2023; Simner et al., 2018).

We in the CCMID advocate for advancement of this testing approach, as we believe it can well serve patients with infectious diseases. However, enactment of the proposed FDA rule will stifle further development and implementation of clinical metagenomics for infectious diseases.

NGS-based LDTs, including clinical metagenomics, defend against emerging infectious threats

A major benefit of the approaches that can be used in clinical metagenomics is the ability to perform agnostic sequencing. This is the discovery and characterization of the genetic sequences from unknown pathogens causing emerging diseases. Such discovery thereafter leads to development of targeted LDTs and IVD tests. A notable example of this process is the discovery of SARS-CoV-2 using clinical metagenomics at the beginning of the COVID-19 pandemic, with subsequent development of LDTs and now IVD assays during and after the emergency use authorization (EUA) (Mercer & Salit, 2021; Wu et al., 2020; Zhou et al., 2020). Enactment of the proposed rule will prevent the development of LDTs for emerging infectious threats, thus placing public health at unnecessary risk. This will have a heightened impact on minority and underserved populations as was seen throughout the COVID-19 pandemic (Liu, Dean, & Elder, 2023).

The proposed user fee model for LDTs will result in lack of access to much needed infectious disease testing, particularly for underserved populations.

The proposed user fees are untenable for the majority of diagnostic laboratories regardless of planned development of NGS-based LDTs. The end result will be the reliance on reference laboratories to obtain

FDA approval for LDTs, which may also be prohibitive. Currently, many LDTs are provided locally at institutions, including academic medical centers (AMCs), that do not have the financial resources nor infrastructure to submit assays for IVD approval. AMCs are major service providers for underserved populations, including Medicare beneficiaries and rural populations. Participants in the CCMID represent AMCs in the United States that are either actively developing or considering development of NGS-based LDTs for infectious diseases. If standard LDTs are no longer offered by these clinical laboratories, and development of NGS-based LDTs is stopped, patients in rural areas and marginalized populations will be adversely affected.

The proposed regulation does not provide any assessment of the impact on access and equity for healthcare delivery. Further, the cost impact estimates put forth by the FDA do not include any assessment of the lost ability to make patient diagnoses if LDTs are discontinued due to the proposed rule. This will likely have significant increases in healthcare expenditures and patient morbidity and mortality due to the inability to perform testing for conditions and situations where no IVD approved product exists.

CCMID's Proposed Path Forward: Collaborative Discourse

Given the impact of LDTs on patient diagnosis and public health, it is critical to fully understand how this proposed regulation will affect patient testing in the United States. It is also critical to reach alternative solutions that will effectively work toward the goals of ensuring the safety and effectiveness of LDTs without significantly restricting their availability, which is the most likely outcome if the current proposed rule is enacted.

The CCMID is confident that we can work with the FDA, other governmental bodies, regulatory agencies, and companion professional societies to collaboratively find beneficial solutions. For example, the FDA could enact a process of registering LDTs (without user fees or additional regulations) to monitor test development. Alternatively, the FDA could consider a process in which the regulation of LDTs only applies for assays where there is an available IVD that meets clinical needs. Many other solutions are possible, and collaborative discourse over time will benefit patients with infectious diseases in need of diagnoses made available only through the development and implementation of LDTs.

We request that the FDA does not enact the proposed rule regulating LDTs. Rather, we ask that the FDA please engage with the broader laboratory and clinical medicine communities to pursue a way forward that benefits patients in need of LDTs and the laboratories committed to developing high quality, safe, and effective tests.

Thank you for the opportunity to express our concerns, and thank you for your responses.

Authored and signed on behalf of the CCMID for the benefit of individual and public health,

David C. Gaston, MD PhD
Assistant Professor, Department of Pathology, Microbiology, and Immunology
Medical Director, Molecular Infectious Disease Laboratory
Vanderbilt University Medical Center, Nashville, TN
Co-founder, CCMID

Steve Miller, MD PhD
Chief Medical Officer
Delve Bio, San Francisco, CA
Co-founder, CCMID

Melissa Miller, PhD
Director, Clinical Microbiology and Molecular Microbiology Laboratories
UNC Medical Center, Chapel Hill, NC
Professor, Pathology and Laboratory Medicine, UNC School of Medicine

Co-signers (alphabetical by surname)

Esther Babady, PhD, D(ABMM), FIDSA, FAAM
Chief, Clinical Microbiology Service
Department of Pathology and Laboratory Medicine
Memorial Sloan Kettering Cancer Center

Benjamin Briggs, MD, PhD
Chief Medical Officer
CosmosID
Assistant Professor
Division of Pediatric Infectious Disease
Department of Pediatrics
University of Rochester Medical Center

Alexandra Bryson, Ph.D., D(ABMM)
Associate Director of Clinical Microbiology
Assistant Professor of Pathology
VCU Health

Charles Chiu, MD, PhD
Professor, Department of Laboratory Medicine and Medicine / Infectious Diseases
Director, UCSF Clinical Microbiology Laboratory
Chan-Zuckerberg Biohub Investigator
University of California, San Francisco

Jennifer Dien Bard, PhD, D(ABMM), FIDSA
Interim Chief of Laboratory Medicine; Director, Clinical Microbiology and Virology
Department of Pathology and Laboratory Medicine
Children's Hospital Los Angeles
Professor of Pathology (Clinical Scholar)
Keck School of Medicine, University of Southern California

Augusto Dulanto Chiang, MD
Assistant Professor
Transplant Infectious Diseases
Vanderbilt University Medical Center

Kenneth Gavina, PhD, D(ABMM), SM(ASCP)
Medical Director, Clinical Microbiology and Serology
Eskenazi Health
Assistant Professor of Clinical Pathology
Department of Pathology & Laboratory Medicine, Indiana University School of Medicine

Catherine Hogan, MD, MSc, DTM&H, FRCPC
Medical Microbiologist, British Columbia Centre for Disease Control Public Health Laboratory
Clinical Assistant Professor, Department of Pathology and Laboratory Medicine, University of British Columbia

Teny M. John, MD
Assistant Professor,
Infectious Disease, Infection Control and Employee Health
University of Texas MD Anderson Cancer Center

Ishminder Kaur, MD
Clinical Assistant Professor, David Geffen School of Medicine at UCLA
Medical Director, Pediatric Antimicrobial Stewardship Program, UCLA Health
Department of Pediatrics, UCLA Mattel Children's Hospital

Andrew P Norgan, MD, PhD
Assistant Professor of Laboratory Medicine and Pathology
Co-Director, Clinical Microbiology Molecular Laboratory
Department of Laboratory Medicine and Pathology
Mayo Clinic

Anne Piantadosi MD, PhD
Assistant Professor
Department of Pathology and Laboratory Medicine
Department of Medicine, Division of Infectious Diseases
Emory University School of Medicine

Kyle G. Rodino, PhD, D(ABMM)
Assistant Professor, Pathology and Laboratory Medicine
Perelman School of Medicine, University of Pennsylvania
Assistant Director, Clinical Microbiology Laboratory
Director, Rittenhouse Molecular Laboratory
Hospital of the University of Pennsylvania

Marie-Claire Rowlinson, PhD, D(ABMM)
Bureau Chief
Florida Bureau of Public Health Laboratories
Division of Disease Control and Health Prevention
Florida Department of Health, Jacksonville, FL

Rahul Sharma Ph.D., HCLD (ABB)
Chief Innovation Officer Advanta Genetics
Founder and CEO, RetroBioTech
Co-Founder and CSO, Scienetix
Tyler TX 75703

Patricia (Trish) J. Simner, PhD, D(ABMM)
Associate Professor of Pathology and Infectious Diseases
Director of Bacteriology, Division of Medical Microbiology
The Johns Hopkins University School of Medicine

Natasha Spottiswoode MD DPhil
Clinical Fellow
Division of Infectious Diseases
University of California San Francisco

Rita C. Stinnett, PhD, MHS
Senior Manager for Medical Affairs - Infectious Disease
Opinions my own

Michael Wilson, MD, MAS
Professor of Neurology
Director, UCSF Center for Encephalitis and Meningitis
University of California, San Francisco Weill Institute for Neurosciences

Shangxin (Shaun) Yang, PhD, D(ABMM), MLS(ASCP)
Director, Molecular Microbiology and Pathogen Genomics (MMPG) Laboratory
Associate Medical Director, Clinical Microbiology Laboratory
Associate Clinical Professor
UCLA Department of Pathology and Laboratory Medicine

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