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THE CONSORTIUM FOR CLINICAL METAGENOMICS IN INFECTIOUS DISEASES

Public Comment for Federal Register Docket No. FDA-2026-N-8692 for “Microbiology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments-Pathogen-agnostic sequencing.”

Submitted on behalf of the undersigned members of the Consortium for Clinical Metagenomics in Infectious Diseases (CCMID)

November 3, 2026

To the Microbiology Panel of the Medical Devices Advisory Committee

The Consortium for Clinical Metagenomics in Infectious Diseases (CCMID) appreciates the opportunity to provide input in response to FDA’s request regarding the scientific, clinical, and public health dimensions of pathogen-agnostic sequencing and the opportunities and challenges associated with development, validation, and implementation of these tests—particularly the establishment of agile, effective, and validated bioinformatics systems that can account for frequent sequence changes and emerging threats

CCMID is a collaborative group of microbiologists, scientists, physicians, public health experts, and industry partners working to facilitate implementation of next-generation sequencing (NGS) approaches for infectious disease diagnostics. Active since 2022, CCMID convenes monthly to advance patient-centered, value-focused clinical metagenomics through education, research, and multi-stakeholder collaboration. CCMID includes national and international field leaders, and is well positioned to partner with FDA as it develops future guidance.

Executive Summary

CCMID recommends that FDA guidance:

- Adopt a risk-based, fit-for-purpose framework for pathogen-agnostic sequencing.
- Support validation approaches that include both DNA and RNA pathogens.
- Emphasize standardized performance assessment rather than technological standardization.
- Provide a lifecycle framework for bioinformatics updates and database changes.
- Establish expectations for detection and escalation of divergent and novel organisms.
- Facilitate development of benchmark datasets and reference materials.

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1. Overarching Opportunity: A Broad-Spectrum, Preparedness-Oriented Diagnostic Capability

Pathogen-agnostic sequencing—particularly metagenomic NGS (mNGS)—offers a unique capability for clinical diagnostics, as well as for emergency preparedness and response. Pathogen agnostic sequencing assays have the capacity to detect a wide array of pathogens (viral, bacterial, fungal, parasitic), with the potential to identify pathogens not anticipated by targeted tests. This agnostic approach is particularly relevant to:

- Unknown or unexpected pathogens
- Rapidly evolving organisms with new variants
- Unusual clinical presentations or syndromic clusters
- Situations where target panels may lag behind epidemiology

However, achieving this potential requires clear regulatory expectations that acknowledge the distinct tradeoffs and operational realities of pathogen-agnostic approaches. In addition to the comments below, please read the following manuscript which thoroughly addresses these considerations:

> Gauthier NPG, Kapoor V, Gaston DC, Prasad N, Nwaobia P, Kraft CS, Mittar D. When tests don't fit the rules: regulatory challenges for agnostic metagenomic next-generation sequencing in infectious diseases diagnostics. J Clin Microbiol. 2026 Sep 10:e0098726. doi: 10.1128/jcm.00987-26. PMID: 42720301.

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2. Core Development Challenges for Pathogen-Agnostic Sequencing Tests

A. Breadth of Detection vs. Analytic Sensitivity (Compared with Targeted PCR)

A central challenge is the inherent tradeoff between broad breadth of detection and analytic sensitivity:

- Targeted PCR assays typically achieve very low limits of detection because they concentrate amplification on a specific target.
- Pathogen-agnostic sequencing distributes sequencing reads across host background and diverse microbial content, and performance depends on factors including sample type, pathogen burden, host nucleic acid content, extraction efficiency, and sequencing depth.

Additionally, with broad detections comes challenges with clinical significance. FDA guidance should address expectations for clinical interpretation frameworks, including distinguishing clinically relevant pathogens from colonizing organisms, contaminants, and incidental findings

Recommendation: FDA guidance should recognize that fit-for-purpose performance for pathogen-agnostic tests may differ from that of dedicated PCR assays. Performance frameworks should explicitly address intended use in preparedness (e.g., early situational awareness, detection of unexpected pathogens, outbreak characterization) alongside clinical diagnostic use.

B. Need for Approaches that Capture Both DNA and RNA Pathogens

Pathogen agnostic sequencing must address the reality that major outbreak threats include both DNA and RNA organisms

- DNA-only workflows will miss RNA viruses unless complementary methods are used.
- RNA workflows require additional controls and are more sensitive to degradation and pre-analytical variability.
- Laboratory validation must address reverse transcription performance, fragmentation bias, and differential abundance.

Recommendation: FDA should encourage assay designs and validation paradigms that explicitly include both DNA and RNA detection, whether through unified workflows (when feasible) or well-validated dual workflows, with clear reporting and limitations.

C. Standardized Performance Assessment Across Diverse Methods (Not Standardization of One Method)

The field contains multiple legitimate technical approaches, including:

- shotgun metagenomics vs. targeted enrichment
- different extraction chemistries and depletion methods
- different sequencing platforms and read lengths
- different reporting thresholds and taxonomic classifiers

Attempting to standardize a single “best” approach would impede innovation and reduce real-world applicability.

Recommendation: FDA guidance should prioritize standardized methods of assessing performance, not standardization of the underlying test approach. Guidance should also support modular validation approaches that allow validation of individual steps in a workflow, and also end-to-end workflows. Guidance should define what must be demonstrated (e.g., sensitivity across pathogen classes, contamination controls, reproducibility, reporting criteria, robustness to sequence variation) while permitting flexibility in how developers meet those requirements.

Key performance concepts that would benefit from harmonization include:
- Minimum evidence thresholds for organism detection and reporting
- Analytical validation frameworks using contrived and clinical specimens
- Reproducibility across operators, instruments, sites, and time
- Contamination detection and control expectations (including reagent contaminants and environmental background)
- Standard reference materials and benchmark datasets for bioinformatics evaluation

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D. Bioinformatics Must Detect Reads That Do Not Adequately Align to Curated Databases (Emerging Pathogens)

A unique requirement of pathogen agnostic sequencing is the ability to detect what is not yet well represented in curated databases.

Rigid dependence on curated reference databases can lead to missed detections when:
- a pathogen is novel or highly divergent
- there are gaps in reference coverage
- the outbreak involves rapid genetic drift or recombination
- the pathogen is endemic but under-sequenced globally

Therefore, bioinformatics pipelines must include mechanisms to identify:
- reads/contigs with low-confidence alignment
- sequences with partial similarity to known taxa
- novel genomic structures that warrant escalation

Recommendation: FDA guidance should explicitly address expectations for “unknown” or “divergent” detection features, such as:
- de novo assembly and contig-based analyses
- translated (protein-level) search strategies where appropriate
- anomaly detection workflows for “unassigned” reads
- tiered reporting concepts (e.g., “detected—known,” “detected—divergent/near neighbor,” “signal requiring further investigation”)
- defined processes for reflex confirmatory testing and public health escalation

Such capabilities are central to the mission of preparedness and should be considered in validation and post-market change management discussions.

E. Bioinformatics for Detection of Potentially Genetically Engineered Organisms (Biosecurity)
Pathogen agnostic sequencing must consider not only naturally emerging pathogens but also the possibility of genetically engineered or otherwise manipulated organisms. While clinical laboratories should not be expected to provide definitive attribution, bioinformatics systems can incorporate screening indicators that support biosecurity awareness, such as:

- unexpected combinations of genomic elements
- signatures suggestive of synthetic assembly
- unusual codon usage, vector remnants, or engineered junctions
- antimicrobial resistance or virulence configurations inconsistent with known lineages
- sequence features incongruent with expected phylogeny or epidemiology

Recommendation: FDA should consider how guidance can support development of biosecurity-aware bioinformatics, including:
- approaches that can flag concerning genetic signatures for expert evaluation
- defined escalation pathways for confirmatory evaluation with appropriate authorities
- expectations for transparency, auditing, and minimization of false alarms
- coordination between sentinel laboratories and public health authorities

This should be addressed carefully to balance clinical utility, public health actionability, and avoidance of misuse or over-interpretation.

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3. Agile and Validated Bioinformatics

FDA's question regarding "an agile but effective and validated bioinformatics system that can account for frequent sequence changes" is pivotal. Bioinformatics components may change more frequently than wet-lab components due to:

- expanding reference databases
- improved classifiers and algorithm updates
- changes to filtering/host-subtraction methods
- new thresholds informed by real-world evidence
- rapid emergence of novel variants

Recommendation: FDA guidance should consider a lifecycle approach that supports agility while maintaining safety and effectiveness, including:

- Modular validation of pipeline components (e.g., preprocessing, classification, assembly, reporting logic), enabling targeted re-validation when modules change.
- Pre-specified change control plans describing what changes are anticipated, how they will be evaluated, and what performance metrics must be maintained.

- Use of standardized benchmark datasets (including simulated and real reads) to enable repeatable regression testing.
- Clear expectations for versioning, traceability, audit logs, and documentation of database versions and classifier versions used for each result.
- Post-update performance monitoring and quality management (e.g., ongoing proficiency challenges, negative control trending, and drift detection).

Importantly, guidance should recognize that “database updates” are not a trivial administrative step; they may meaningfully alter performance characteristics and should be handled within a structured and testable framework.

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4. How CCMID Can Partner with FDA

CCMID respectfully offers to partner with FDA to support robust and realistic guidance development in multiple ways:

A. Expert Convening and Consensus-Building
CCMID can convene multidisciplinary experts (clinical microbiology, bioinformatics, public health, industry, regulatory science) to generate consensus recommendations on:
- performance metrics and reporting thresholds
- clinical and public health use cases for preparedness
- approaches for “unknown/divergent” detection
- contamination control and interpretation frameworks
- modular validation strategies for analytic workflows in laboratories

B. Reference Datasets and Benchmarking Support
CCMID participants can assist in developing and/or evaluating:
- standardized benchmarking datasets (including divergent/near-neighbor organisms)
- mock community standards and contrived specimen panels
- approaches for evaluating both DNA and RNA workflows
- testing paradigms for pipeline updates

C. Bioinformatics Change-Management Frameworks
CCMID can provide technical input on:
- modular validation models
- change control planning that is feasible for clinical and public health labs
- performance monitoring strategies that reflect real-world practice

D. Public Health Integration and Escalation Pathways
CCMID includes stakeholders with public health expertise and can advise on:
- responsible reporting of novel/divergent signals
- coordination pathways between clinical labs, public health labs, and federal partners

- situational awareness workflows during outbreaks

E. Biosecurity-Aware Analytical Concepts
CCMID can facilitate careful, scientifically grounded discussion on:
- what is feasible and appropriate for clinical test developers to implement
- how to define and validate “screening flags” for potentially engineered features
- how to minimize harms from false positives or misinterpretation

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5. Conclusion

Pathogen-agnostic sequencing is poised to become an important capability for personal and public health, but its successful deployment requires guidance that acknowledges key realities: broad detection coupled with lower analytic sensitivity than targeted PCR, the necessity of supporting both DNA and RNA sequencing, the importance of standardized performance assessment across varied approaches, and bioinformatics expectations that include the capacity to detect divergent or novel organisms. FDA has a unique opportunity to establish a regulatory framework that encourages preparedness-focused innovation while maintaining rigorous analytical and clinical standards.

CCMID appreciates FDA’s leadership in convening the Microbiology Devices Panel to address these issues and stands ready to provide expert input, technical resources, and collaborative partnership to help develop guidance that is scientifically rigorous, operationally feasible, and aligned with public health needs.

With gratitude,

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The views expressed here are solely those of the signatories and do not represent their respective institutions, nor do they represent all CCMID participants.