FDA Executive Summary

General Issues Meeting on Use of Pathogen-Agnostic Sequencing for Emergency Preparedness and Response Efforts

Prepared for the Meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee

November 19, 2026

Office of Readiness and Response (ORR)
Office of Strategic Partnership and Technology Innovation (OST)
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration
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I. Introduction:

The FDA's Center for Devices and Radiological Health (CDRH) is organizing an Advisory Committee (Panel) meeting on November 19, 2026, to exchange knowledge with relevant stakeholders and discuss the development and use of pathogen-agnostic sequencing (PAS) for emergency preparedness and response. This session is consistent with the requirements under section 3302 of the Food and Drug Omnibus Reform Act of 2022, which was signed into law as part of the Consolidated Appropriations Act, 2023 (Pub. L. 117-328).

CDRH regulates medical devices, including *in vitro* diagnostic devices (IVDs) and is responsible for assessing the safety and effectiveness of devices that are used in response to an emerging infectious disease. Pathogen-agnostic sequencing (PAS) is one type of device that may be useful in such scenarios. The November 19, 2026, Panel provides an opportunity for stakeholders to discuss and share recommendations on the scientific, clinical, and public health dimensions of the development and use of pathogen-agnostic sequencing as it relates to emergency preparedness and response efforts. This includes development and implementation considerations, as well as potential priorities for future coordination. The preparedness use could cover local and national outbreaks, known pathogens, or unknown pathogens. The meeting will address topics including development, validation, and use of pathogen-agnostic sequencing in response to an emerging infectious disease.

II. Background:

Early detection of an emerging pathogen is a vital first step at the onset of any outbreak. Historically, initial outbreak investigations relied primarily on clinical and epidemiological methods to characterize illness patterns and identify likely sources of exposure. When patients present with illness of unknown etiology and tests designed to detect a specific known pathogen return negative results, identifying the causative agent becomes considerably more challenging. Traditional approaches in this setting have included culturing the sample to grow and isolate an organism for further characterization or using methods such as electron microscopy to visualize the morphology of an unknown agent [1]. While valuable, these approaches can be time- and resource-intensive and may not be feasible for all specimen types or settings. Advances in sequencing technology offer a potential alternative or complement to these traditional approaches, including in the context of emerging infectious disease.

Sequencing Technology:

Sequencing is a laboratory method used to analyze genetic material. Nucleic acids are found in the cells of all living organisms and viruses and contain unique genetic information

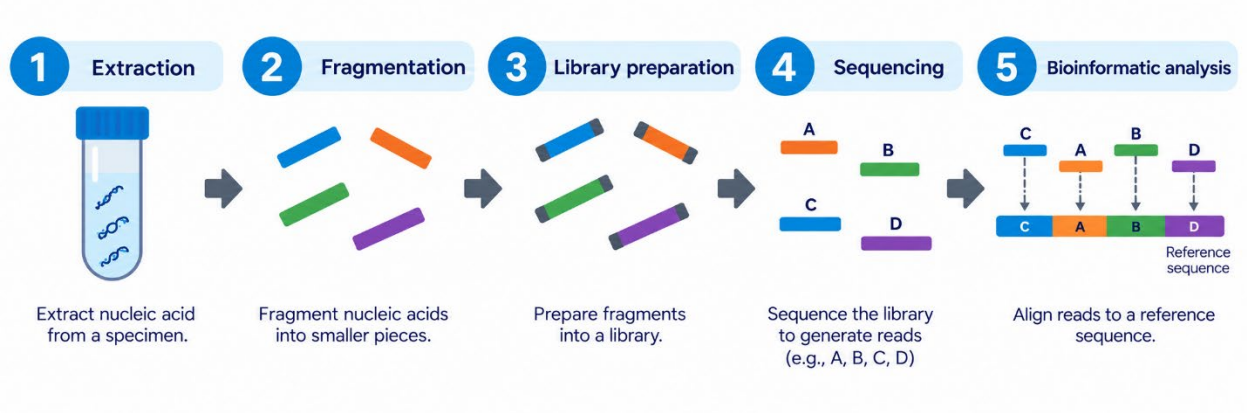
of the organism. The complete set of genetic information in an organism is called the genome. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are the two main forms of nucleic acids and are made up of nucleotide bases, often referred to as the building blocks of DNA and RNA. The nucleotide bases include adenine, thymine, cytosine, and guanine for DNA, and adenine, uracil, cytosine, and guanine for RNA [2]. These are represented in genetic sequences by the first letter of the nucleotide base name, A, T, C, and G for DNA, and A, U, C, and G for RNA. These are often referred to as genetic letters. The specific order of these genetic letters encodes biological information, and differences in the order of the genetic letters can distinguish one organism, variant, or individual from another. Modern sequencing platforms, commonly referred to as next-generation sequencing (NGS), have expanded the speed and scale at which sequencing can be performed, enabling broad applications in medicine and research.

NGS can be performed in different ways depending on the clinical or research question. Targeted sequencing can focus on specific genomic regions, genes, or it can cover entire genomes selected in advance, making it well-suited for situations where the pathogen or genetic variant of interest is already known or suspected [3]. In the infectious disease context, targeted sequencing has been applied to characterization of SARS-CoV-2 sequence variants over time. In contrast, untargeted sequencing makes no assumptions about suspected sequences, instead aiming to identify all nucleic acids present in a sample [4].

To sequence a genome, a sample of the organism's genetic material is needed. A typical NGS workflow begins with extraction of the nucleic acid, the organism's genetic material, from a specimen collected from the patient. Because genomes can be very long, the nucleic acid may be broken into smaller pieces (called "fragments") and undergo processing so they can be more easily read by the sequencing instrument. This collection of processed fragments is called a "library." Finally, the sequencing instrument analyzes the millions of nucleic acid fragments in the library to determine the order of genetic letters in each fragment. The genetic sequences of each fragment are called "reads." The reads collectively provide information about the genetic material present in the specimen [5].

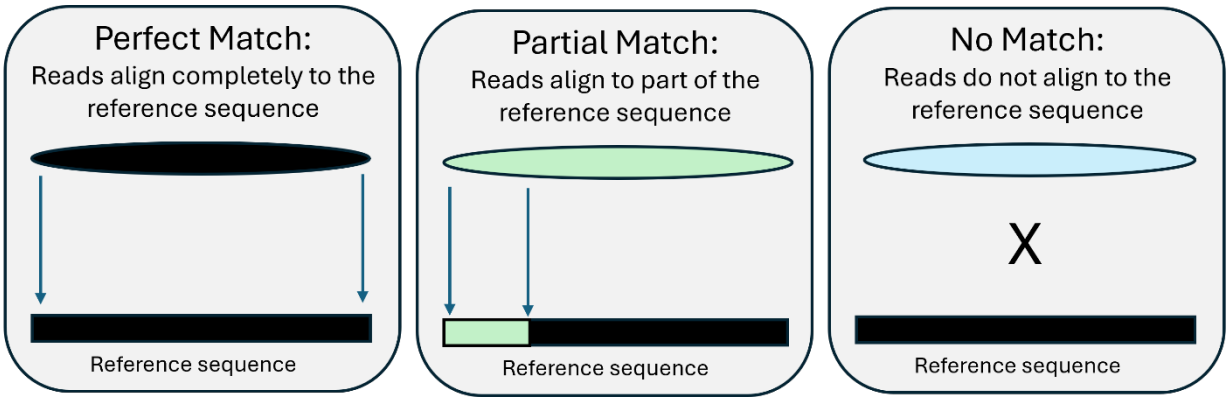
Once the reads have been generated, a computer analyzes them and attempts to match them against a previously determined genetic sequence from a known organism (a reference sequence). Reference sequences may be stored in databases that contain the genetic sequences of many different organisms and can be used to compare and identify the sequences found in a sample. Figure 1 depicts a very general NGS approach.

Figure 1: Next Generation Sequencing Steps



The process of using computers to compare reads against a reference sequence database is called bioinformatic analysis. Bioinformatic analysis is a necessary component of NGS that transforms raw sequencing reads into interpretable results [6]. The ability to identify and characterize a target sequence therefore depends not only on whether the reads match a reference sequence, but also on the number, distribution, and quality of those matches. Reads can match a reference sequence completely or partially, or not at all (Figure 2). "Sequence similarity" describes how closely the order of genetic letters in a sequencing read matches the order found in a reference sequence [7].

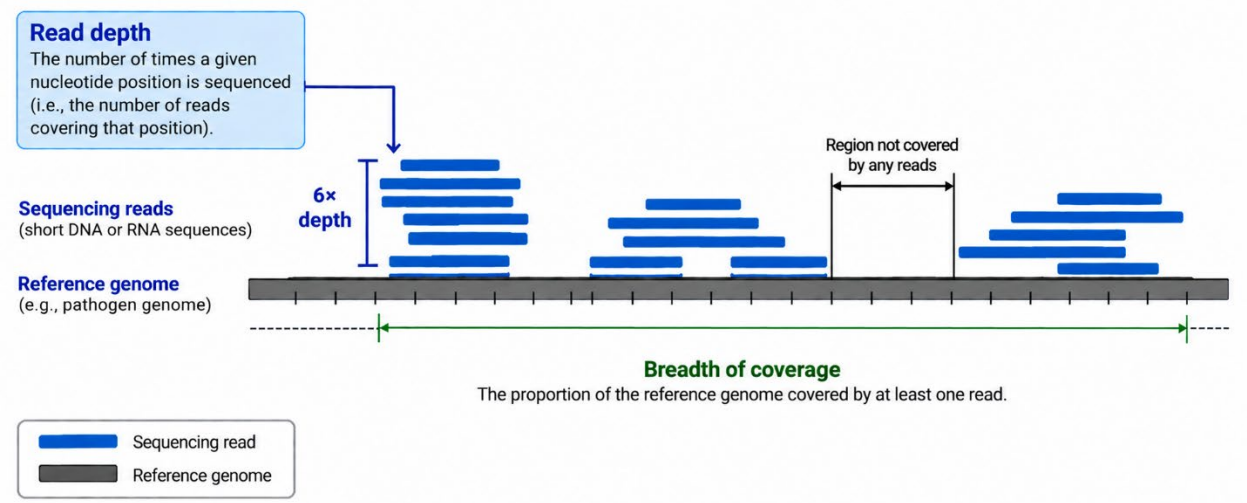
Figure 2: Matching Reads Against Reference Sequences



Two important aspects of sequencing results are read depth and breadth of coverage. Read depth refers to the number of times a given nucleotide position is sequenced, whereas breadth of coverage refers to the proportion of a reference sequence covered by at least one sequencing read (Figure 3) [8]. For example, multiple reads covering the same region increase the depth at that region, while reads distributed across different regions increase

the breadth of coverage. Together, these measures provide information about the completeness and confidence of sequence-based detection and characterization.

Figure 3: Read Depth and Breadth of Coverage



Regardless of approach, NGS workflows generally follow similar steps, as described above, including nucleic acid extraction, library preparation (the process of preparing nucleic acid fragments for sequencing), sequencing, and bioinformatic analysis. An untargeted approach forms the basis of pathogen-agnostic sequencing, which has particular relevance in infectious disease contexts where the causative organism has not yet been identified.

Pathogen-Agnostic Sequencing:

PAS is an untargeted sequencing approach that uses NGS to simultaneously sequence all the genetic material in a specimen, including host and microbial nucleic acid that might be present along with background nucleic acid contaminants from consumables, without selecting or suspecting a specific pathogen before testing [4]. This provides the ability to identify known, and potentially previously unknown, pathogens directly from patient specimens. This testing modality differs significantly from conventional microbiologic methods, including culture, antigen testing, and real-time polymerase chain reaction panels, each of which depend either on the growth of an organism or predetermined targets for suspected pathogens. PAS has the potential to reduce the time it takes to identify the likely source of an outbreak because a priori knowledge of the microorganism or nucleic acid sequence is not necessary [4].

PAS can also be used in other contexts beyond clinical diagnosis. In foodborne pathogen outbreak investigations, it can help trace the source of contamination and characterize the

causative agent [9]. In environmental monitoring, it can serve as a broad, population-level tool to detect circulating pathogens without testing individuals [10]. Experience from these applications may provide useful information while considering the benefits and risks of use in clinical outbreak identification and individual patient diagnosis.

While PAS offers the potential to support identification of the likely source of an outbreak and to fill diagnostic gaps that targeted tests may be unable to address, its complexity and turnaround time raise important questions about the design, validation, and deployment of these systems in emergency preparedness and response contexts. The following sections explore these considerations in greater depth.

III. Design Considerations

PAS approaches share certain design principles with pathogen-specific approaches but differ in fundamental ways that are important to consider during development and validation. Both approaches benefit from rigorous validation to demonstrate accuracy and reliability. However, because PAS is not designed to detect a single known target, traditional validation approaches, such as the use of characterized positive samples for a specific organism, may not be directly applicable. Instead, PAS design considerations include the ability to detect novel or unexpected pathogens, manage background signals from host or environmental nucleic acids, and produce results that are clinically or epidemiologically interpretable. These distinctions are relevant for discussions around how PAS approaches are designed, how controls are selected, and how performance is measured. Design considerations may include, but are not limited to, optimization of test parameters (i.e., reporting thresholds and organism cutoffs), background signal and longitudinal contamination monitoring, and bioinformatics infrastructure [11]. Understanding the most critical design considerations for PAS may help ensure they perform as needed at the onset of a potential emergency and remain reliable throughout the course of a response.

Informatics Considerations:

Unlike conventional microbiology assays, PAS sequence results are not easily interpreted. Instead, the sequencing instrument produces genetic results that are then processed using a range of computational analyses to distinguish human sequences from microbial, identify low quality reads and contaminants, and determine which organisms, if any, are present at a level and pattern consistent with clinically meaningful detection, while protecting privacy with respect to patient genomic sequence. Because emergency data sharing increases the

risk of unauthorized access or misuse, privacy and cybersecurity protections are also important considerations [12].

Reference databases are critical to the successful operation of PAS, and their quality, completeness, computational pipelines, contamination control, and curation directly determine what can and cannot be identified [13]. When sequencing reads match, or partially match, a known pathogen in a reference database, the degree and pattern of sequence similarity can provide important information beyond simple organism identification. For example, sequence data may help determine whether a detected agent represents a known variant or strain, a related but distinct organism, a recombinant strain, or a potentially novel organism. The distribution of reads across a genome, as well as the depth and breadth of coverage, can further strengthen identification and provide information about the completeness of the recovered sequence.

Reads that do not match entries in the reference database may also be informative. Although unmatched reads can result from sequencing artifacts, low-quality sequences, host or environmental nucleic acids, or organisms that are poorly represented in available databases, they may also indicate the presence of a previously uncharacterized or highly divergent pathogen. Consequently, the quality, accuracy, and comprehensiveness of reference databases are central to the utility of PAS. Gaps, outdated annotations, incomplete genomes, or biased representation of organisms within these databases can limit the ability to identify or accurately interpret detected sequences [13].

Genome assembly presents complementary complexities: accurate reconstruction can be limited by insufficient sequencing depth, uneven coverage, repetitive or highly conserved genomic regions, sequence variation within a sample, and the presence of closely related organisms. These factors can result in fragmented or chimeric assemblies, gaps in reconstructed genomes, or incorrect attribution of sequences to a particular organism [14]. Thus, interpretation of PAS results is impacted by consideration of sequencing depth and coverage, read quality, alignment or assembly performance, and database composition. The overall strength, distribution, and consistency of the sequence evidence are also important factors in reaching a reliable interpretation.

Given the potential to diagnose emerging pathogens and evolving genomes, planned updates to incorporate newly emerging pathogens, evolving genomes, improved understanding of how organisms are genetically related to one another, and findings of clinical and public health relevance can be helpful. Each bioinformatics update has the potential to alter performance, similarly to modifications to other aspects such as the reagents and instruments. A result generated before an update may not be reproducible after, and a change that improves detection of one organism may have a corresponding

impact on the ability to detect other organisms. Pre-defined protocols, appropriate verification and validation methods, version control, documentation, and pre-defined acceptance criteria can aid in evaluating the impact of updates on performance, streamlining the ability to rapidly deploy updates.

Detection Thresholds and Validation:

An important aspect of PAS is the determination of reporting thresholds, which are the minimum criteria for including detected organism in the clinical report [6].

A variety of parameters may be assessed to define reporting thresholds, including, but not limited to: minimum number of sequence reads, normalized metrics, statistical thresholds relative to negative controls processed in parallel, coverage of a minimum number of distinct genomic regions, a minimum breadth of genome coverage expressed as a percentage of the reference genome, and evidence that reads align to organism-specific regions rather than conserved sequences shared across related taxa [6].

Methodological consistency has direct implications for pandemic preparedness and response. During a public health emergency, it may be appropriate to compare, interpret collectively, or aggregate results generated by multiple laboratories to inform clinical and public health decisions. Differences in analytical thresholds or reporting criteria could result in inconsistent conclusions regarding the presence or absence of a novel pathogen, potentially affecting treatment decisions and other downstream response actions. Accordingly, the establishment of performance-based threshold criteria, supported by validation using known positive and negative specimens across clinically relevant pathogen categories and specimen types, may be an important consideration in the development of preparedness-ready PAS approaches.

However, while validation using known specimens remains important, this method of comprehensively validating performance across all potential targets presents unique challenges for PAS because of the scale and dimensionality of these approaches. In contrast, targeted diagnostic methods, including syndromic panels, may detect and report a defined set of microbial pathogens, sometimes exceeding 30 targets, for which analytical and clinical performance can be evaluated through direct validation of individual pathogens. PAS workflows, by comparison, may interrogate databases containing thousands of microbial sequences, making conventional validation methods for every potential target impractical or infeasible. Error modeling and other *in silico* approaches may provide useful methods for assessing analytical performance at this scale [15]; however, there is currently

no established consensus regarding appropriate methodologies, and the extent to which *in silico* performance assessments predict real-world clinical performance remains uncertain.

A representative-organism approach may provide another potential strategy for analytical and clinical validation by enabling wet testing across a relatively wide range of microorganisms. However, the extent to which performance demonstrated using representative organisms can be generalized to other microorganisms, including previously uncharacterized or divergent pathogens, remains unclear. More broadly, the ability of PAS systems to accurately and reproducibly identify and report the presence of a previously unknown pathogen in a clinical specimen presents additional challenges that may be particularly relevant to pandemic preparedness and response.

Background Signal and Longitudinal Contamination Monitoring:

A fundamental challenge associated with PAS involves background signal from low-level microbial nucleic acids originating from reagents, laboratory consumables, sequencing instruments, collection devices, or the laboratory environment itself [16]. Background signal may vary across sequencing runs due to differences in reagent lots, instrumentation, laboratory workflow, ambient environmental conditions, and specimen carryover. While background signal variation cannot be eliminated entirely, it can be characterized, monitored, and controlled to improve reliability [17].

Longitudinal contamination monitoring, which is the repeated, systematic assessment of negative controls over time, may potentially be an effective mitigation [18]. A sudden increase in background reads assigned to a particular organism, or the appearance of a new organism in negative controls may indicate contamination and could trigger investigation before clinical results are reported [18]. In the context of pandemic preparedness, standardized processes and protocols that aid in distinguishing true emerging pathogens from laboratory contamination may be an effective mitigation to ensure limited resources are allocated to the appropriate response.

IV. Use of PAS in Emergency Preparedness and Response: Benefit and Risk Considerations:

PAS could potentially be useful for emergency preparedness and response during the initial stages of an outbreak, when the causative pathogen is unknown or has not yet been fully characterized. Early pathogen identification is critical during an outbreak, as is the rapid development of diagnostic options. However, pathogen-specific tests necessary for an

emergency response typically cannot be developed until the pathogen causing the outbreak is identified. PAS has the potential to substantially reduce this lag by enabling broad-based pathogen detection and characterization before a specific etiologic agent has been identified, thereby accelerating the development of the downstream diagnostic infrastructure necessary for outbreak containment and response. For this reason, PAS may provide value during the earliest phase of an outbreak, when the clinical syndrome is recognized but the causative organism is not yet defined. Unlike historical approaches that depend heavily on epidemiological context to guide pathogen identification, PAS does not rely on prior knowledge of a patient's exposure history, travel history, immune status, or symptoms to generate actionable results. Beyond initial pathogen identification, PAS may also contribute to characterizing a novel pathogen once identified, monitoring for the emergence of variants over the course of an outbreak and informing the development of targeted diagnostic and therapeutic tools as the response matures. Additionally, PAS may offer value beyond the earliest phase of an outbreak, with potential for ongoing use in individual patient diagnosis as the emergency response evolves, for example, as a bridge before targeted diagnostic options become available.

While PAS offers potential benefits in early outbreak pathogen detection, an understanding of the potential benefits and limitations of this technology when deployed in the emergency response context is important. In non-emergency scenarios, a false-positive or false-negative pathogen-related diagnostic test result would likely affect only an individual patient and may be recognized and corrected through confirmatory testing and clinical judgment. However, in an emergent public health scenario such as a potential outbreak of an emerging or existing pathogen, the same error could have broader public health implications, including unnecessary quarantine measures, misdirected resource allocation, public alarm, or delayed recognition of the true causative pathogen, with consequences extending far beyond the individual patient.

Additional features of PAS may present challenges that are consequential in an outbreak setting. Turnaround time, which can be longer for PAS than for targeted diagnostic tests, may affect the timeliness of clinical management decisions and public health interventions. Result interpretation also presents a distinct challenge: PAS may detect multiple organisms in a single specimen, which is a scenario where expert review to distinguish the causative pathogen from incidental findings, commensal organisms, or background signal may be utilized. This interpretive burden is compounded in an outbreak scenario where rapid decisions about quarantine, contact tracing, and resource allocation depend on clear, actionable results. Additionally, PAS may not provide sufficient taxonomic resolution, meaning the level of specificity at which an organism can be identified, to guide these decisions. For example, identification to the genus level alone may be inadequate when species- or strain-level information is relevant to characterize transmissibility, virulence, or treatment options.

The risk of pathogen misidentification is greatest at the earliest stage of an outbreak, precisely when the pressure to act on preliminary sequencing results is high and when novel pathogen sequences are least likely to be well represented in reference databases. Additionally, the prevalence of false results may be affected by variation in analytical performance characteristics specific to PAS, including those associated with specimen type, laboratory workflow, pathogen challenges, bioinformatic methods, sequencing platform, and reference database quality [19]. Some of these challenges are unique to PAS, while others are present for other diagnostics as well. Many can be addressed through careful design, validation, and result interpretation. Thoughtful deployment of PAS, with appropriate safeguards, has the potential to meaningfully strengthen emergency preparedness infrastructure and improve outcomes at the population level.

V. Considerations for Preparedness Applications and Operational Implementation:

Deployment of PAS in emergency preparedness and response contexts raises practical considerations, including where in the clinical workflow PAS would be used, the laboratory infrastructure to support it, and how results would be reported and acted upon. These considerations are particularly important during a public health emergency, as they can directly impact emergency response operations.

Laboratory Infrastructure:

PAS is most likely to be deployed in reference laboratories, academic medical centers, specialized commercial laboratories, and select public health or federal laboratories, given that this technology typically uses specialized sequencing instrumentation, contamination-control capacity, computational infrastructure, and appropriately trained personnel. Many community hospitals, rural health systems, and smaller public health laboratories would need the expertise and infrastructure to appropriately identify which specimens to send to laboratories that are equipped to run PAS.

Understanding where PAS fits within the broader clinical and public health laboratory workflow is an important preparedness consideration. PAS may be used when no targeted diagnostic options are yet available, or as a follow-on approach when initial targeted testing is unrevealing. Each of these use cases carries different implications for turnaround time, result interpretation, and integration with existing clinical decision-making approaches.

Results Reporting - Clinical Report Considerations:

The structure, content, and interpretive framing of a PAS clinical report are important features that inform subsequent steps in patient management. PAS reports may include the

organisms detected along with quantitative metrics supporting each detection and classification, including read counts, normalized abundance, breadth of genome coverage, and whether reads map to organism-specific genomic regions or regions shared with other related or unrelated organisms. Approaches to reporting unknown or potentially novel findings may incorporate predefined criteria addressing the quantity and quality of sequence evidence, the presence of a consistent microbial signal, potential contamination or other technical artifacts, and the potential clinical relevance of the finding. When an unusual or potentially novel organism is identified, additional evaluation may include expert review, orthogonal testing, or assessment by public health laboratories. These considerations reflect the broader complexities of interpreting unexpected sequence findings while distinguishing potentially meaningful signals from findings for which the available evidence is insufficient to support clinical interpretation.

Reports may also include comments on the clinical plausibility of each detected organism, its known association with the patient's clinical syndrome, and whether it is a recognized commensal, colonizer, or common environmental contaminant given the specimen type. Additionally, to support more informed clinical interpretation, it may be beneficial to include potential limitations, which may address the sequencing method, reference database, specimen type, sequencing depth and breadth, and any other potential detection caveats.

Accurate clinical interpretation may integrate the sequencing result with the patient's clinical presentation, specimen type, immune status, prior antimicrobial exposure, and the quantitative metrics for each detected organism. When multiple organisms are detected, determining which, if any, is the causative pathogen warrants careful expert review and clinical correlation. Terminology for pathogens, probable pathogens, colonization, and contaminants may not be consistent across developers and laboratories; however, these are relevant considerations in the context of how best to support reliable clinical decision-making and public health monitoring in an emergency response context.

Results Reporting - Escalation to Public Health Authorities:

A result suggesting a novel, unusual, or potentially transmissible pathogen may need to be escalated beyond the ordering clinician to infection prevention personnel, epidemiologists, and public health authorities [20]. This is especially important because PAS may identify organisms or genomic findings that do not fit neatly into existing reportable disease categories. Preparedness planning typically considers escalation pathways in advance, including thresholds for notification, designated points of contact at the laboratory, clinical, institutional, and public health levels, and communication protocols as contingencies that can be activated rapidly when an unusual finding is identified. Therefore, workflows for escalation and public health reporting are important considerations for the effective implementation of PAS in emergency preparedness and response.

VI. Conclusion:

PAS is a promising technology with the potential to meaningfully strengthen diagnostic capacity during public health emergencies, particularly in the earliest stages of an outbreak when targeted diagnostic options are not yet available. Careful consideration of the complexities associated with PAS development, validation, and deployment are important aspects in maximizing the potential of PAS technology. This document provides context for discussion of the questions FDA is posing to the Panel, focused on the potential use cases for PAS in the context of emergency preparedness and response, the benefits, risks, and limitations of implementation at different stages of an emergency, and design and validation considerations. The Agency intends to consider the Panel's perspectives to inform its thinking on how best to support the development and evaluation of PAS as a tool for national preparedness and response.

VII. Questions for Panel Discussion:

CDRH is seeking input from the Microbiology Devices Panel of the Medical Devices Advisory Committee on pathogen-agnostic sequencing used in emergency preparedness and response to future pandemics. Specifically, CDRH is seeking input on the following discussion points:

Use Cases for National Preparedness

1. What are the main benefits and risks of using pathogen-agnostic sequencing for emergency response, and how can the risks be mitigated?
2. How can the use of pathogen-agnostic sequencing be incorporated into the clinical workflow in the early stages of an outbreak? Later stages?
    a. What are the practical barriers to implementing these technologies in clinical and public health laboratory settings?
    b. How could the results be used to enhance the emergency response?
    c. What are the most critical factors for inclusion in the PAS results report in an emergency response context?
    d. Under what circumstances would reporting results to public health authorities be helpful for an emergency response?

Pathogen-Agnostic Sequencing Design

3. What are the critical design features for pathogen-agnostic sequencing to function safely and effectively in emergency preparedness/response scenarios?
    a. What are the considerations for establishing cut-offs for organism reporting?
    b. How generalizable is performance for one microbial species to another?
    c. What are the risks and potential mitigations in validating performance using a representative organism approach?
    d. What are the considerations for establishing and monitoring background signals (i.e., low level background contamination) over time?
4. How can bioinformatics systems and databases be designed and validated to remain agile even as pathogen sequences evolve?

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