Regulatory Challenges and Opportunities in Clinical Metagenomics

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In Vitro Diagnostic Products (IVDs) Are:

- Reagents, instruments, and systems used in diagnosis of disease or other conditions…
- In order to cure, mitigate, treat, or prevent disease…
- Intended for use in the collection, preparation, and examination of specimens taken from the human body.

[21 CFR 809.3]

US FDA Regulatory Review Process

Class	Class I	Class II		Class III
Risk	Low	Moderate		High
Clearance / Approval	Not required	510(k)	De Novo (New Tech)	PMA
Clinical Performance	Not required	Comparator Method	Clinical Truth or Comparator method	Clinical Truth
Controls	General	General and Special Controls		
Performance Studies	None Needed	Analytical and Clinical		

Pre-submission: Process to receive FDA feedback on analytical and clinical study design.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Intended Use Example

TECHNOLOGY

MEASUREMENT

"The FilmArray Gastrointestinal (GI) Panel is a qualitative multiplexed nucleic acid-based in vitro diagnostic test intended for use with FilmArray systems. The FilmArray GI Panel is capable of the simultaneous detection and identification of nucleic acids from multiple bacteria, viruses, and parasites directly from stool samples in Cary Blair transport media obtained from individuals with signs and/or symptoms of gastrointestinal infection….The FilmArray GI Panel is indicated as an aid in the diagnosis of specific agents of gastrointestinal illness and results are meant to be used in conjunction with other clinical, laboratory, and epidemiological data."

Specimen

ANALYTE

INDICATIONS FOR USE

INTENDED USE POPULATION

Review Totality of Submission to Assess Safety and Effectiveness

- **Clinical:** Multi-site clinical study including all claimed specimen types in the appropriate population
  - Goal is to establish clinical sensitivity and specificity for claimed analytes

- **Analytical:** Demonstration of analytical performance using simulated specimens in each claimed matrix (e.g., LoD, Inclusivity, Cross-Reactivity, Competitive Interference, Interfering Substances, Carryover/Cross-contamination, Specimen Stability, Fresh versus frozen)

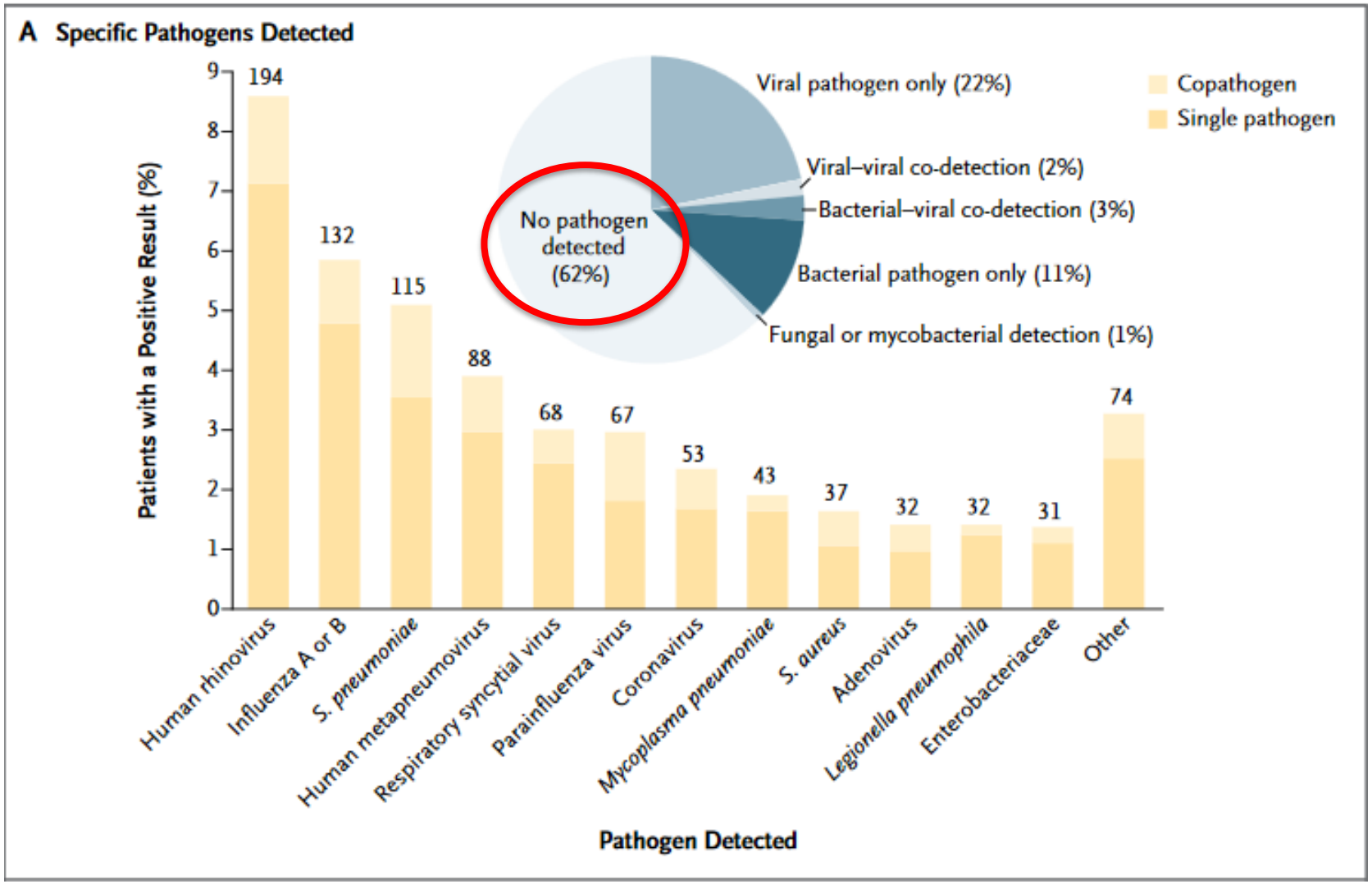
- **Software/Instrumentation**

- **Device labeling (package insert/instructions for use)**

Opportunities for Clinical Metagenomics

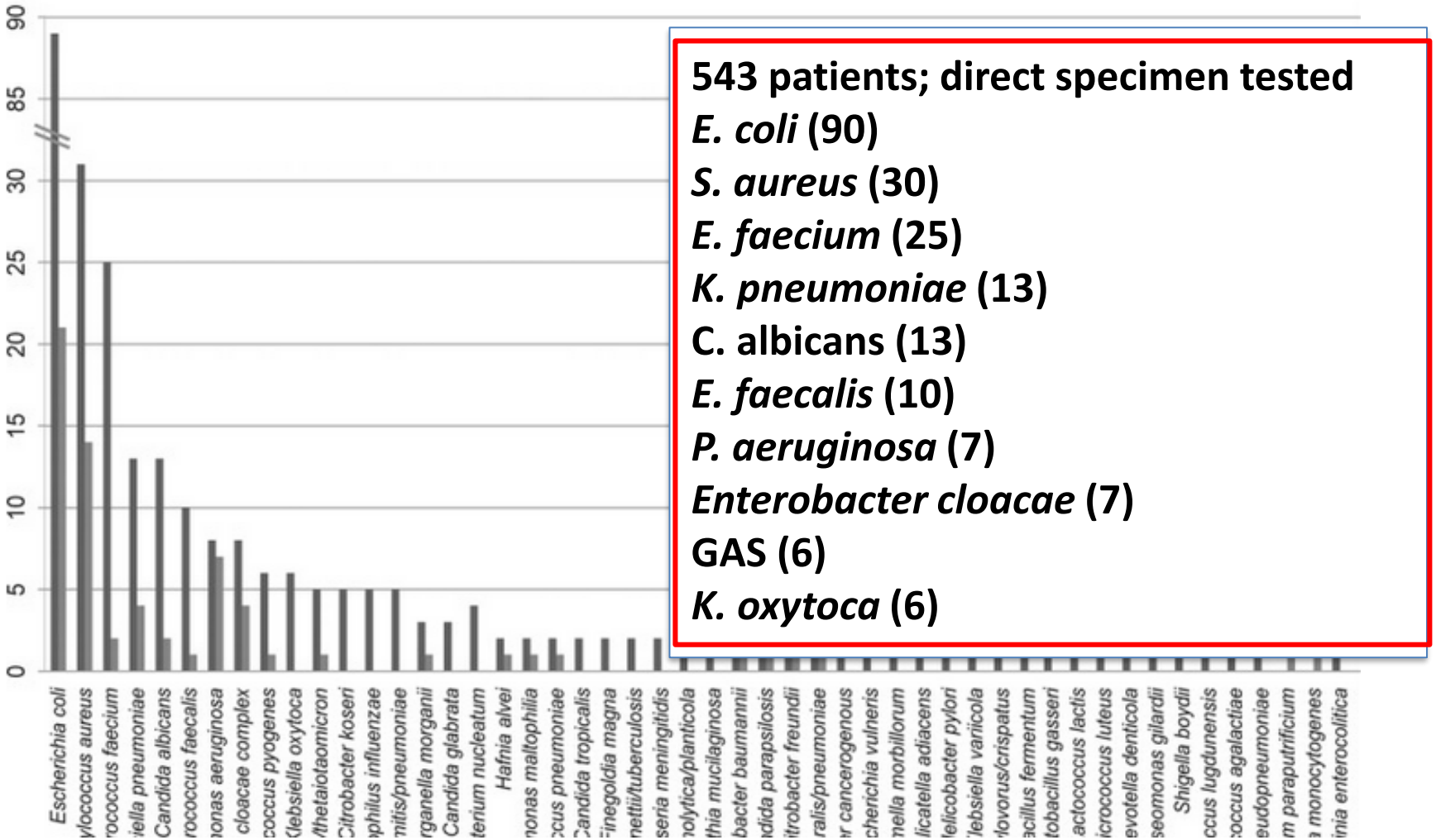
- **Slow growing** /Fastidious organisms (e.g. mycobacterial, fungal and viral infections)
- **Difficult to identify** organisms (e.g., mycobacterial, fungi, challenging bacteria, viruses)
- **Unexpected** presentation of common organisms or typical presentation of rare organisms (e.g., zebras)
- **Increase diagnostic yield** in challenging clinical syndromes (e.g. Sepsis/bacteremia, meningoencephalitis, pneumonia)

Opportunities: Pneumonia



CAP in hospitalized adults NEJM 373;5;2015

Opportunities: Blood Stream Infection



543 patients; direct specimen tested

E. coli (90)

S. aureus (30)

E. faecium (25)

K. pneumoniae (13)

C. albicans (13)

E. faecalis (10)

P. aeruginosa (7)

Enterobacter cloacae (7)

GAS (6)

K. oxytoca (6)

Crit Care Med. 2015 Nov; 43(11): 2283–2291.

Challenges in Metagenomics

- Improve patient care? Stewardship?
- Reduce unwanted outcomes such as inappropriate Abx usage, lengthened hospital stay?

User Challenges

- Is the result is reflective of the patient disease? This is driven in part by syndrome and specimen type.

Shared Challenges

- How to validate performance?
- How to report results?

Regulatory and Stakeholders Challenges

Reporting

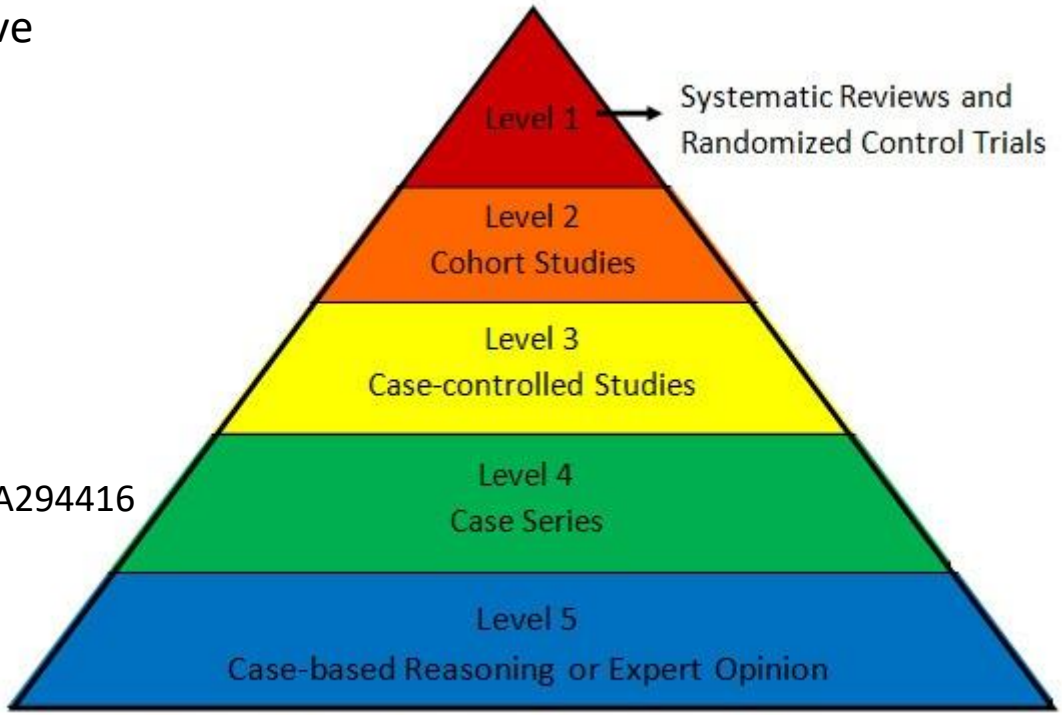
- How to safely report results?
- How to effectively report results?
- Is there an opportunity to report results along with the level of evidence?
  - Strength of evidence (statistical power)
  - Relevance of evidence (e.g. # of strain variants, database composition)

Levels of Evidence

- Prospective clinical trial
  - Statistically significant number of positives
  - Comparator method data for each positive
- Retrospective specimens
  - Previously characterized as positive
- Contrived specimens
- In silico evidence

<u>Evaluation resources</u>

- FDA ARGOS
  - Bioproject 231221
- FDA/CDC AR isolate bank
  - Bioproject PRJNA316321 and PRJNA294416
- NIST quality control material

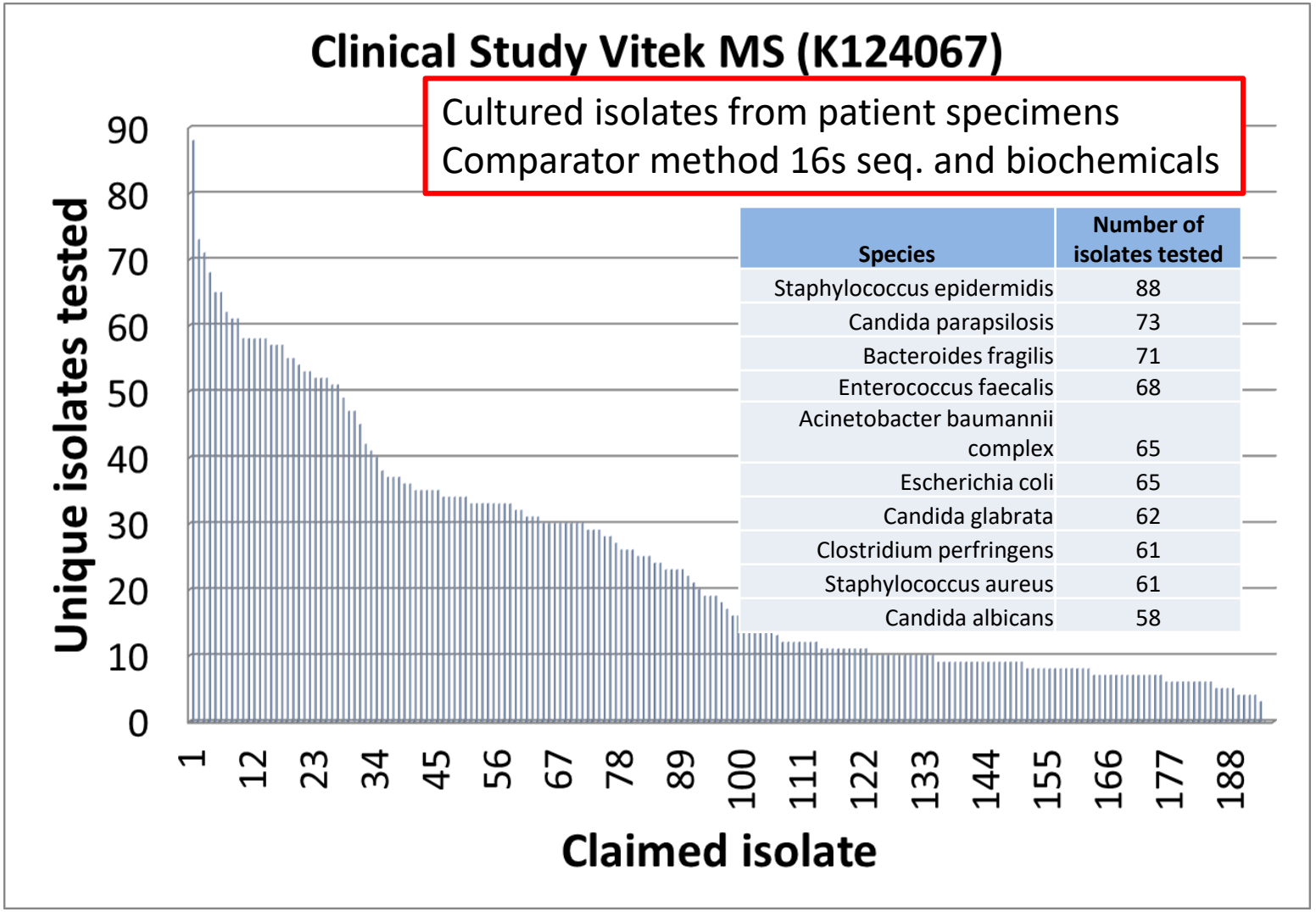


*based on the Oxford Centre for Evidence-based Medicine – Levels of Evidence

Case Study Mass Spectrometry (MS)

- Five clearances –two manufacturers (2013-17): **~300 unique bacteria**; **~20 unique Nocardia spp.**; **~25 unique yeast**; **~50 unique molds**
- Identification of **cultured isolates**
- Mass spectra are generated from known organisms using a standard SOP
- Using device specific algorithm, unknown mass spectra are matched to database organisms
- Multiple databases can be queried however databases are technology specific

VITEK MS Clinical Study



Species	Number of isolates tested
Staphylococcus epidermidis	88
Candida parapsilosis	73
Bacteroides fragilis	71
Enterococcus faecalis	68
Acinetobacter baumannii complex	65
Escherichia coli	65
Candida glabrata	62
Clostridium perfringens	61
Staphylococcus aureus	61
Candida albicans	58

Performance Analysis

Multiple scores are possible along with and multiple levels of confidence in the comparator method

Bacteria		Correct: Genus Correct: Species				Correct: Genus Incorrect: Species				Genus: Incorrect			
		MBT≥2		1.7≥MBT<2.0		MBT≥2		1.7≥MBT<2.0		MBT≥2		1.7≥MBT<2.0	
		Reference Algorithm Score											
		High	Low	High	Low	High	Low	High	Low	High	Low	High	Low
Klebsiella pneumonia	Number of specimens	86	4	0	0	1	0	0	0	0	0	0	0
	% of total	95%	4%			1%	0%						
	Number of specimens	90		0		1		0		0		0	
	% of total	99%				1%							

https://www.accessdata.fda.gov/cdrh_docs/reviews/K163536.pdf

Device Result Interpretation

Users can evaluate the quality of the match and decide on next steps.

Score Range	Interpretation	Color
2.00 - 3.00	High confidence identification; Report Identification	Green
1.70 - 1.99	Low confidence identification 1) Repeat analysis with secondary extraction procedure 2) If extracted organism score is in this range interpretation is "Low Confidence Identification"	Yellow
	Grayed Out - Non-clinically validated Organism ID is not reported to physician or patient Reported to user as "hint"; requires further organism characterization	Grayed out
< 1.70	No organism identification is possible 1) Repeat analysis with secondary extraction procedure 2) If extracted organism score is in this range interpretation is "No Identification"	Red

Next Steps
Expanding the Intended Use Claims

- Totality of scientific evidence informs a risk based approach and future risk mitigation strategies
  - After initial clearance, we may discuss possible least burdensome paths to add additional organisms
  - Prevalence affects the benefit/risk equation
  - Updating taxonomy needs to occur to stay relevant

Similar and Differences

Cleared Mass Spectrometry Platforms	Metagenomic Sequencing
Similarities	
Capability to identify hundreds of organisms High quality databases are needed New reporting strategies are needed based on new technology Device performance affected by changes in matching algorithm Need for a regulatory path to support evolving capabilities	
Differences	
Testing from isolated organisms Low likelihood of multiple organisms Clinical relevance known Technology specific database	Direct from specimen testing Multiple organisms will be detected Clinical relevance unknown Technology agnostic database

Efforts to Support Diagnostic Sequencing

- Continue to build high quality organism sequence databases
  - FDA is Funding dedicated microbial sequencing projects at FDA-ARGOS and CDC (FDA/CDC AR Bank)
  - Develop quality metrics for existing sequences
  - Working with standards organizations (NIST) to develop high quality control material
  - Finalizing FDA Guidance

Resources

- **FDA Webpages for more information on databases in development**
  - **FDA-ARGOS**
    https://www.fda.gov/MedicalDevices/ScienceandResearch/DatabaseforReferenceGradeMicrobialSequences/default.htm
  - **FDA/CDC AR Bank**
    https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm454677.htm

- **Draft Guidance**

Infectious Disease Next Generation Sequencing Based Diagnostic Devices
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM500441.pdf

- **Decision Summaries posted in 510(k)/*de novo* database**
  - Search under product code PEX for MS devices

  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

- **Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff:**
  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Thank you!
FDA/CDRH/OIR/ Division of Microbiology

- FDA ARGOS – Heike Sichtig, Yi Yan
- FDA/CDC AR Bank – Ribhi Shawar, Faiza Benahmed, Patricia Conville
- NIST reference material – Heike Sichtig
- FDA Guidance – Heike Sichtig, Tamara Feldblyum

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