Regulatory Challenges and Opportunities in Clinical Metagenomics

Kristian Roth, PhD
Branch Chief Bacterial Multiplex and Medical Counter Measures
Division of Microbiology Devices
Center for Devices and Radiological Health
US FDA
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

<table>
<thead>
<tr>
<th>Class</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Clearance / Approval</td>
<td>Not required</td>
<td>510(k)</td>
<td>PMA</td>
</tr>
<tr>
<td>Clinical Performance</td>
<td>Not required</td>
<td>Comparator Method</td>
<td>Clinical Truth</td>
</tr>
<tr>
<td>Controls</td>
<td>General</td>
<td>General and Special Controls</td>
<td></td>
</tr>
<tr>
<td>Performance Studies</td>
<td>None Needed</td>
<td>Analytical and Clinical</td>
<td></td>
</tr>
</tbody>
</table>

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

“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.”
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, meningocencephalitis, pneumonia)
Opportunities: Pneumonia

A Specific Pathogens Detected

No pathogen detected (62%)

Pathogen Detected

Patients with a Positive Result (%)

0 1 2 3 4 5 6 7 8 9

Human rhinovirus
Influenza A or B
S. pneumoniae
Human metapneumovirus
Respiratory syncytial virus
Parainfluenza virus
Coronavirus
Mycoplasma pneumoniae
S. aureus
Adenovirus
Legionella pneumophilia
Enterobacteriaceae
Other

Viral pathogen only (22%)
Viral–viral co-detection (2%)
Bacterial–viral co-detection (3%)
Bacterial pathogen only (11%)
Fungal or mycobacterial detection (1%)

CAP in hospitalized adults NEJM 373;5;2015
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)

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

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

Cultured isolates from patient specimens
Comparator method 16s seq. and biochemicals

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of isolates tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis</td>
<td>88</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>73</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>71</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>68</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>65</td>
</tr>
<tr>
<td>complex</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>65</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>62</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>61</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>61</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>58</td>
</tr>
</tbody>
</table>
Performance Analysis

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

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Correct: Genus</th>
<th>Correct: Species</th>
<th>Correct: Genus</th>
<th>Incorrect: Species</th>
<th>Genus: Incorrect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBT&gt;2</td>
<td>1.7&gt;MBT&lt;2.0</td>
<td>MBT&gt;2</td>
<td>1.7&gt;MBT&lt;2.0</td>
<td>MBT&gt;2</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Number of specimens</td>
<td>86</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>% of total</td>
<td>95%</td>
<td>4%</td>
<td>1%</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Number of specimens</td>
<td>90</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% of total</td>
<td>99%</td>
<td></td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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

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

• 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:
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

Kristian.Roth@fda.hhs.gov