The Beginner’s Guide to Establishing Molecular Diagnostic Testing

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Outline

1. Introduction to CLSI and Consensus Process
2. MM-19
3. Strategic Planning
4. Implementation
5. Unique considerations for subspecialties
   • Heritable diseases
   • Oncology/Malignant Hematology
   • Pharmacogenetics
   • Infectious Disease
CLSI and the Consensus Process

Clinical and Laboratory Standards Institute
An accredited developer of global voluntary consensus standards and guidelines

MM19-A is an approved CLSI guideline
Since January 2005
Why Have Standards?

• Ensure, at a minimum, compliance with rules and regulations

• They tell you WHAT to do; not HOW to do it

• Optimally, they are a tool for healthcare providers and the best way to ensure higher levels of health and safety for patients
Members and Volunteers

Diverse representation from:

**Industry**
- IVD Manufacturers
- LIS Vendors
- Startup Companies
- Suppliers
- Trade Organizations

**Government**
- Public Health Agencies
- Regulatory Bodies
- Accrediting Organizations
- Others

**Professions**
- Professional Societies
- Educational Institutions
- Healthcare Delivery Systems
- Hospitals & Laboratories
Establishing Molecular Testing in Clinical Laboratory Environments
Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline

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Molecular tests are moving from the solely esoteric to the more routine testing environment

- Availability of IVDs
- Relative technical ease of implementation by generalists
- Decreases send out testing, which will improve financial health of the laboratory
- Improves TAT
Disclaimer

• Time constraints allow us to only highlight some of the things we think are important

• We encourage laboratories to use FDA approved or cleared tests when available

• We discourage laboratories to perform fetal studies (prenatal diagnosis)
Think Ahead

• Clinical relevance of result cannot always be derived from the analytic result alone
  • Genotype/phenotype correlations
  • Method limitations
  • Incorporation of family/ethnic information (heritable diseases) and clinical information (oncology)
Think Ahead

- Personnel must oversee all phases of testing: consultants may be needed
  - Select appropriate clinical specimen
  - Order the appropriate test
  - Maintain robust assays
  - Generate clinically useful patient-specific reports
  - Provide supplemental consultation
- Medical Director must ensure test has clinical validity and utility
### Strategic Planning: SWOT Analysis

**S** - **Strengths**: internal strengths that can be leveraged

**W** - **Weaknesses**: internal weaknesses that could negatively impact ability to implement

**O** - **Opportunities**: weaknesses in the external environment (with current or potential competitors) that could be turned into opportunities

**T** - **Threats**: threats in the external environment that could negatively impact ability to implement

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strengths</td>
<td>Weaknesses</td>
<td>Opportunities</td>
<td>Threats</td>
</tr>
<tr>
<td>Internal</td>
<td>External</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Positive**

**Negative**

**Internal**

**External**
Involve Everyone

• The **laboratory director** and **clinicians** determine the clinical utility, clinical validity, and test performance requirements.

• The **laboratory manager**, who oversees the area in which the test will be implemented, ensures that the workflow, personnel, and physical requirements are part of the planning process.

• The **finance (or business) group** determines the pricing, cost, potential revenue, and, with the **marketing director**, plans for the assay.
Involve Everyone

- The *sendout person* provides current sendout volumes

- The *molecular professional* provides input on the unique aspects of molecular testing across all considerations of the decision.
Things to Consider for Go / No Go

- Indications for testing and potential reflex tests:
  - Reflex tests may require a higher level of expertise
  - Prenatal testing for heritable diseases *not* recommended for routine labs
- Regulatory requirements: IVDs are strongly recommended over LDTs
- Specimen processing/extraction and testing platform
- Laboratory workflow: closed vs. open test format
- Throughput and automation
- TAT requirements; batch vs. immediate testing
Things to Consider for Go / No Go

- Freedom to operate
- Finance / cost effectiveness: cost vs. U.S. reimbursement
- Space and facility design
- Personnel requirements and expertise
- Availability of reference material for quality assurance
- Proficiency testing
- Business continuity planning
# Go: Factor V Leiden

## Initial Considerations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Strengths/Opportunities</th>
<th>Weaknesses/Threats</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Validity</td>
<td>S: Documented in literature</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Clinical Utility</td>
<td>S: Recommended by ACMG for specific patient populations</td>
<td>W: CER questions clinical utility</td>
<td>GO</td>
</tr>
<tr>
<td>Test Indication</td>
<td>S: Fits in with coag offerings; test will discriminate homozygotes from heterozygotes for APC resistance</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Test Volume</td>
<td>S: 20-50/month</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Regulatory</td>
<td>S: IVDs available</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Testing Platform</td>
<td>S: Extraction and detection commercially available, separate or integrate</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Technical Complexity</td>
<td>S: Both moderate and high complexity platforms are commercially available</td>
<td></td>
<td>GO</td>
</tr>
</tbody>
</table>
## Go: Factor V Leiden

### Initial Considerations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>S/O</th>
<th>W/T</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIS</td>
<td>S: Accessioning and patient reports generated from current LIS</td>
<td>W: Offline analytical process</td>
<td>GO</td>
</tr>
<tr>
<td>Freedom to Operate</td>
<td>No restrictions</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Lab Workflow</td>
<td>S: Testing completed in single shift or separated over 2 shifts or days</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>S: Closed system is available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throughput, Automation</td>
<td>S: Manual assay acceptable for expected sample volume</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Platforms amenable to scale up for larger volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAT</td>
<td>S: Samples can be batched to achieve clinically acceptable 5-7 TAT</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Equipment, Footprint</td>
<td></td>
<td>W: Additional space, power required</td>
<td>GO</td>
</tr>
<tr>
<td>Criteria</td>
<td>S/O</td>
<td>W/T</td>
<td>Decision</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td>Cost/Volume of Sendout</td>
<td>S: $75-100/sample; current volume is 25-50 tests/month</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Cost per In-house Test</td>
<td>S: ~~~$55/test, net cost savings</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Will decrease with increased volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reagents and Supplies</td>
<td>S: ~~~$12/test</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Will decrease with increased volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment and Facility</td>
<td>S: Amortized cost ~~~$7/sample</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Leverage for additional assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel Costs</td>
<td>S: ~~~$20/test</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Opportunity to cross-train existing staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Overhead costs</td>
<td>S: ~~~$16/test</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td></td>
<td>O: Will decrease with increased volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimbursement</td>
<td>S: Covered for indication population and sufficient to recover costs</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Liability</td>
<td>S: No additional, but test is performed once in a patient’s lifetime</td>
<td></td>
<td>GO</td>
</tr>
</tbody>
</table>
# Go: Factor V Leiden

## Resources

<table>
<thead>
<tr>
<th>Criteria</th>
<th>S/O</th>
<th>W/T</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel Requirement, Expertise</td>
<td>O: Cross-training existing staff</td>
<td>W: Local requirements vary; may require qualified staff</td>
<td>GO</td>
</tr>
<tr>
<td>Space</td>
<td>S: Small footprint O: Leverage unidirectional workflow for additional assays</td>
<td>W: Consider need to establish unidirectional workflow for PCR assays</td>
<td>GO</td>
</tr>
<tr>
<td>Reference Materials</td>
<td>S: Available from repositories <a href="https://cdc.gov/dls/genetics/rmmaterials">cdc.gov/dls/genetics/rmmaterials</a></td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Quality Controls and Standards</td>
<td>S: Available from repositories and in IVD kits</td>
<td></td>
<td>GO</td>
</tr>
<tr>
<td>Proficiency Testing</td>
<td>S: Commercially available</td>
<td>W: Consider cost</td>
<td>GO</td>
</tr>
<tr>
<td>Business Continuity</td>
<td>Many laboratories offer this test</td>
<td></td>
<td>GO</td>
</tr>
</tbody>
</table>
No Go: Fragile X

Test Complexity → Internal Expertise

Assessment and family history of developmental delay/mental retardation → potential high technical and interpretive bar

Two part assay:
1. PCR assay to determine size of $FMR1$ allele (CGG repeats)
2. Southern blot analysis to detect very large alleles, assess methylation and mosaicism

No IVDs; development and validation of LDT required

Interpretation of mosaicism can be complex

Carrier studies lead to prenatal diagnosis
No Go

Budget Impact Unfavorable

Peptide nucleic acid fluorescence *in situ* hybridization for yeast identification from blood culture

“Yeast” → ID of *Candida* fluconazole sensitive species

Fluorescent microscope with dual filter (~$1000, not standard)
Reagent direct costs ~$50, with limited shelf life
Low volume test → reagent scrap, further increasing costs
Things to Consider for Implementation

**Patient Samples**

- **Sources**: Direct patient tissues/fluids; processed pathology specimens; microbiology cultures
  - Product insert for IVD-cleared assay specifies specimen type
  - Testing of any other specimen type is OFF LABEL

- **Volume**: Know what you need; prioritize when more than one test ordered

- **Preferred specimen**: Each specialty has a particular type; ie, heritable disorders utilize whole blood, buccal swabs, saliva
Things to Consider for Implementation

Patient Samples

- Other considerations
  - Timing for sample collection (i.e., infectious disease)
  - Transport stability (e.g., RNA is less stable than DNA)

- **Note:** Excellent table (Table 5) in MM-19 re specimen type, collection device, ideal temperature, and unique considerations
Things to Consider for Implementation

**Extraction**

- Inhibitory substances
  - Sources: patient specimen, transport media collection devices, fixatives used in processing extraction process
- Preparation of nucleic acids – individual assay
- Nucleic acid extraction
  - Know your method – each method has caveats you need to know
- Characteristics of nucleic acids: RNA less stable than DNA
- Quality and quantity
  - The more you know about your analyte, the easier to troubleshoot
Things to Consider for Implementation

Facilities

- Each method has different requirements
- For example, target amplification (PCR) is very sensitive to backflow
- If not addressed → serious consequences
  - Incorrect patient diagnosis and patient management
  - Lack of confidence and test credibility
  - Negative impact on finances
  - Extensive laboratory clean up; laboratory closure; and retraining of personnel
Unidirectional Workflow

Backflow traffic – must be restricted to minimum!

Permitted workflow (unidirectional)

Restricted workflow

Reagent Preparation Room
- Reagent Storage
- Reagent Preparation
- Master Mix Preparation

Sample Preparation Room
- Specimen Preparation
- Nucleic Acid Isolation

Amplification Room
- Amplification
- Detection Analysis

Airflow Outward
Airflow Inward

POSITIVE PRESSURE
NEGATIVE PRESSURE
NEGATIVE PRESSURE
Facilities

- Control contamination
  - Dedicated micropipets in pre- and post- areas
  - Uracil-DNA glycosylase
  - Primers
  - Post-amplification control

- Detect contamination
  - Have a plan in place; it will happen
  - Contamination occurs around LoD
  - Perform regular swipe tests
Things to Consider for Implementation

Equipment Needs

• Unique equipment for molecular assays
  – Extraction equipment
  – Micropipettes, thermal cyclers, real-time PCR units, imaging systems, hybridization ovens, capillary electrophoresis systems, microarray instruments
  – Cold storage of reagents (manual defrost refrigerators)
• Separate storage for pre- and post-PCR
Things to Consider for Implementation

*LIS requirements*

- Capable of linking molecular test results to results from other test methods
  - Example: fragile X assay would also reflect the cytogenetic results (sex chromosome constitution of the parent)

- Anatomical pathology module has similar requirements and may be a good place to start

- Limited character fields; web based systems; flexible enough to handle new technology

- Ideally, laboratory would have access to patient’s record to assist clinician in selecting appropriate test
Things to Consider for Implementation

**Workflow**

- Accessioning: received in area isolated from testing area
- Samples should be processed promptly or stored appropriately
- Aliquoting specimens should be avoided to prevent contamination
- Avoiding repeated freeze/thaw of specimens to prevent nucleic acid degradation
- Sample transport, handling, preparation/nucleic acid protocols, sample storage
Things to Consider for Implementation

**SOPs**

- Sample receipt and accessioning
- Nucleic acid isolation method
- Nucleic acid quality and quantity assessment
- Control preparation and testing before use
- Reagent prequalification processes
- Analyte detection
- Analysis and release of results
- Equipment maintenance
Things to Consider for Implementation

Reference and Control Materials

- Reference standards can be used for many purposes
  - Test development and validation
  - Development of quality control material
  - Alternative proficiency testing
  - Calibration
- Not all QC materials are reference standards
- Internal vs external controls
Things to Consider for Implementation

Validation and Verification Requirements for the Assay

- Analytical performance and clinical validity
  - Analytical validation and performance must be determined before reporting patient test results
  - The complexity of the validation process and parameters are related to the assay type: FDA-cleared or approved assays and CE-IVD-labeled assays need to be verified.
  - All others must have verification and validation

- This process focuses on all aspects of the assay including reagent components, instrument, and software.

- Different operators and multiple lots of reagents should be evaluated.
### Examples of Validation Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Applies to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Qualitative</td>
</tr>
<tr>
<td>Accuracy</td>
<td>X</td>
</tr>
<tr>
<td>Trueness</td>
<td>X</td>
</tr>
<tr>
<td>Precision</td>
<td></td>
</tr>
<tr>
<td>Reproducibility</td>
<td></td>
</tr>
<tr>
<td>Robustness</td>
<td>X</td>
</tr>
<tr>
<td>Linearity</td>
<td></td>
</tr>
<tr>
<td>Reportable range</td>
<td></td>
</tr>
<tr>
<td>Reference range</td>
<td></td>
</tr>
<tr>
<td>Interfering substances</td>
<td>X</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>X</td>
</tr>
<tr>
<td>Specificity</td>
<td>X</td>
</tr>
<tr>
<td>LoD</td>
<td>X</td>
</tr>
<tr>
<td>Limit of quantification</td>
<td></td>
</tr>
</tbody>
</table>
Things to Consider for Implementation

Reports

• Include indication for testing
• Have an interpretive category for the test result
• Specific methodology used
• Test limitations
• Sensitivity
• Relevant literature
• Recommendations for further testing, if needed
• ASR statement, if applicable
Things to Consider for Implementation

Interpretation

- Apparently negative results
- Clinical sensitivity
- Technical sensitivity
- Indeterminate results
- Nomenclature
  - Hereditary diseases and molecular oncology
  - Pharmacogenetics
  - Infectious diseases
Things to Consider for Implementation

Billing and Reimbursement—U.S.

- Infectious diseases have a measurand (analyte) specific current procedural terminology (CPT) code

- Molecular pathology and genetic tests have stacked methodology-based CPT codes (for now; analyte specific in 2013)

- All CPT codes are reimbursed at different rates by different payers, which also vary from state to state
The subspecialties may use similar molecular methods, but each presents unique clinical and technical challenges.

Interpretation of results in the appropriate clinical context may require expertise beyond what is readily available in the routine clinical lab.

Labs should not hesitate to seek expert consultation.
Unique Considerations for the Subspecialties

Subspecialties

1. Heritable diseases – Jean
2. Oncology/Malignant Hematology – Jean
3. Pharmacogenetics – Jean
4. Infectious Disease – Leslie
Heritable Diseases
Examination of Constitutional Human DNA Alterations

IN SCOPE indications for testing

• Diagnosis of genetic diseases in symptomatic patients
• Carrier screening of asymptomatic carriers of a recessive mutation to determine reproductive risk
• Presymptomatic/predisposition testing of asymptomatic adults for a disease that may develop in the future
• Analysis of bone marrow engraftment to follow engraftment of donor cells following bone marrow transplant (BMT)
OUT OF SCOPE indications for testing

- Newborn screening (eg, testing for affected neonates before onset of symptoms or irreversible damage)
- Prenatal diagnosis of a high-risk fetus
- Preimplantation genetic diagnosis to allow implantation of unaffected embryos
Heritable Diseases

Things to Consider

- Interpretive knowledge barrier
- Results may reveal undisclosed non-paternity and incest
- Liability
  - Genetic tests performed only once
  - Leave prenatal diagnosis to experts
  - Analytic errors can lead to both false positives and false negatives
- Minor children
  - Do not offer carrier testing unless pregnant
  - Do not offer diagnostic testing for a late-onset disorder
- Family members are often impacted by results
- 15 states address informed consent
Common Genetic Assays
Extensively Covered in MM19-A

- *F5* Leiden and *F2* (G20210A) mutation associated with DVT
- *CFTR* targeted mutation analysis associated with cystic fibrosis
  - Beware impact of allele frequency in different ethnic groups, impact of family history on prior and revised risks; test sensitivity varies
  - Negative result does not mean patient is not a carrier
- *HFE* mutations associated with hereditary hemochromatosis
  - LDT only
Common Genetic Assays

Extensively Covered in MM19-A

- Sizing of \textit{FMR1} alleles associated with fragile X syndrome – LDT only
  - Newborn screening possible in the future
- Chimerism studies to monitor bone marrow engraftment – LDT only
<table>
<thead>
<tr>
<th>Indication for Testing</th>
<th>Molecular Pathology Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>BCR-ABL1 gene translocation</td>
</tr>
<tr>
<td>Lymphoma and leukemia</td>
<td>T- and B-cell gene rearrangement</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Microsatellite instability and KRAS mutations</td>
</tr>
<tr>
<td>Cytogenetically normal AML</td>
<td>FLT3 internal tandem duplication analysis and tyrosine kinase domain analysis</td>
</tr>
<tr>
<td>Cytogenetically normal CML</td>
<td>NPM1 duplication analysis</td>
</tr>
<tr>
<td>APL</td>
<td>PML-RARA translocation analysis</td>
</tr>
<tr>
<td>NSCLC</td>
<td>EGFR mutation analysis</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>KIT mutation analysis</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>EWSR1 translocations</td>
</tr>
</tbody>
</table>
## Pharmacogenetics

*Improve Efficacy and Avoid Adverse Reactions*

<table>
<thead>
<tr>
<th>Drug or Indication</th>
<th>PGX Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen and antipsychotic drugs</td>
<td>Cytochrome P450, <em>CYP2D6</em>, and <em>CYP2C19</em></td>
</tr>
<tr>
<td>Warfarin</td>
<td><em>CYP2C9</em> and <em>VKORC1</em></td>
</tr>
<tr>
<td>Irinotecan</td>
<td><em>UGT1A1</em></td>
</tr>
<tr>
<td>Clopidogrel, protein pump inhibitors</td>
<td>Cytochrome P450, <em>CYP2C19</em></td>
</tr>
<tr>
<td>Statins</td>
<td><em>KIF6</em></td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin</td>
<td>HLA-B*1502</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B*5801</td>
</tr>
</tbody>
</table>
What is unique about infectious disease molecular testing?

Many targets

- Viral
- Transplant-associated viral infections
- Viral respiratory agents
- Bacterial

- Hospital acquired infections
  - Blood stream
  - Vancomycin resistant Enterococci
  - *Clostridium difficile*
  - Methicillin resistant and susceptible *S aureus*

- Respiratory agents
- Yeast and filamentous fungi
Examples  
*Mycobacterium tuberculosis*

- Clinical validity: approximately 1/3 of the 40 million people living with HIV/AIDS worldwide are co-infected with TB.

- Conventional testing (skin testing, serology, bacterial smear and culture) have various disadvantages—specificity and sensitivity

- TAT and infectious nature of the organism
What You Need to Know
*Mycobacterium tuberculosis*

- Specimens should be processed in a BSL-2 laboratory with PPE
- Personnel need to be skin tested
- Specimens are digested, concentrated, and exposed to sodium hydroxide so the pH of the concentrate should be considered when used for nucleic acid extraction
- Specimens should be heat-inactivated before extraction
What You Need to Know

*Mycobacterium tuberculosis*

- When using automated extraction systems, **validate** the method to inactive infectious *M tuberculosis*

- When reporting, disclaimers should be included, eg, cultures should be performed on all specimens so the organism can be tested for drug susceptibility

- Not all platforms are approved for smear-negative specimens, so would require full validation before patient reporting
What You Need to Know

*Mycobacterium tuberculosis*

- Because of the importance of a negative test for patient respiratory isolation, inhibition testing must be done on negative molecular tests.

- Nonviable DNA may be present in the specimen if a patient is being treated, and that will make the molecular test positive when the patient no longer has active disease.
Example
HAI–C difficile

• Clinical validity: *C difficile* infection is a significant cause of diarrhea in hospitalized patients, especially the elderly.

• BI/HAP1/027 strains produce more toxins and are resistant to fluoroquinolones, causing 3-fold increase in hospital stays and 4.5-fold increase in mortality.

• Conventional testing, which includes culture, toxin production, cellular antigen detection, and detection of toxin specific genes, has disadvantages, most importantly long turnaround time and manual culture and toxin detection.
**Example**

**HAI–C difficile**

- Detection of the toxin B (found only in toxigenic *C difficile*) has good correlation with disease.

- A direct qualitative, real-time PCR that targets toxin B is commercially available and is performed on diarrheal stool.

- Rarely, *C difficile* organisms have mutations yielding false-negative results.

- A positive result can be from nonviable organisms due to treatment.
What You Need to Know
HAI–C difficile

• Non diarrheal stools can give false correlation to active disease and should not be tested

• The rapid TAT of the molecular assay will have impact on patient care

• Once the disease has been detected, patients may be placed in isolation to reduce transmission of the organism to other patients
Current Resources


• Web sites: FDA and AMP
Volunteer for CLSI
You Will Make Friends and Your Dogs Will Make Friends

Suki Hall

Penny Wilson, CGC