Transitioning from Culture to Molecular

Implementation and Integration of BD MAX™ Enteric Bacterial Panel at Cincinnati Children's Hospital

By Mavis Bauman, Medical Freelance Writer

"We are on the cusp of the biggest change in microbiology since Louis Pasteur declared that life does not arise spontaneously," says Dr. Joel E. Mortensen, Ph.D., Director, Diagnostic Infectious Disease Testing Laboratory, Cincinnati Children's Hospital, Cincinnati, Ohio. "Molecular testing is a huge paradigm shift in microbiology; therefore, a carefully considered strategy is required to move your laboratory into the molecular world. We were interested in a single platform with multiple analytes and multiple assays. We chose the BD MAX™ Enteric Bacterial Panel on the BD MAX™ System because of its syndromic and operational advantages for regional stool pathogen detection."

Millions of cases of acute diarrhea occur around the world each year. As every laboratorian knows, diarrhea leads to stool cultures but, in most circumstances, the positivity rate for cultures is only ~2-6%. Although culture may yield good specificity, the sensitivity of this labor intensive effort can be variable. In addition, the time it takes to get culture results into the hands of the clinical staff ranges from 48 to 96 hours or more. Recent revolutions in the molecular detection of pathogens in stool can offer significantly better sensitivity, specificity, and time to results, and may double the positivity rate over conventional methods.

From left: Barb Deburger, Cindi Ventrola, Dr. Joel Mortensen, Sarah Hanna

Molecular Testing Considerations

Dr. Mortensen emphasizes the importance of examining the needs and opportunities related to testing stool for bacterial pathogens, and to connect those needs and opportunities to the implementation and integration into a specific laboratory setting. In a recent series of webinars, he discussed a number of important general points when one is considering a molecular-based answer to these diagnostic questions:

- What pathogens need to be tested for your specific patient population (syndromic or broad-based testing)?
- Are you sure that results will influence patient outcome?
- Are there specific clinical scenarios that require advanced or different molecular methods?

"With any new instrument or methodology, start by looking at new technologies and what is a feasible fit for your institution and targeted patient population," says Cindi Ventrola, Manager of the Diagnostic Disease Testing Laboratory. "For us, it's not just children who are affected. Most of our stool cultures come from children, so the family is affected, as well. If a child proves positive with an enteric pathogen in the stool, that child cannot go to school or daycare, which means a parent cannot go to work. Therefore, a negative culture within 24 hours vs. 3 days has great value."

Key Analytes to Test

Given the most common gastrointestinal pathogens in its particular patient population, Cincinnati Children's evaluated which analytes should be on its ideal test panel, following IDSA Clinical Testing Guidelines (see Figure 1).

When deciding on the best platform to use for molecular testing, peer reviewed, published studies are the place to start. At that time, the BD MAX™ Enteric Bacterial Panel (BD MAX™ EBP) was too new for that type of information to be available. So, Cincinnati Children's decided to participate in a multicenter trial, comparing the BD MAX™ EBP to conventional culture methods. The net result of the trial showed very high positive and negative percent agreement (between 97.3% and 100%) and, importantly, that the BD MAX™ EBP detected a significant number of additional pathogens not found by culture. (The full results of this trial have been published in the *Journal of Clinical Microbiology*, March 4, 2015.)

BD MAX™ Enteric Bacterial Panel

The BD MAX™ Enteric Bacterial Panel detects these bacteria, which cover 95% of the causes of bacterial gastroenteritis in the U.S.:

- *Salmonella* spp.
- *Campylobacter* spp. (*jejuni* / *coli*)
- *Shigella* spp.
- Enteroinvasive *E. coli*, as well as Shiga-toxin producing *E. coli*

The BD MAX™ System is a fully-automated, closed system. Its batch mode allows for simultaneous processing of up to 24 individual tests.

Operational Impact On the Laboratory

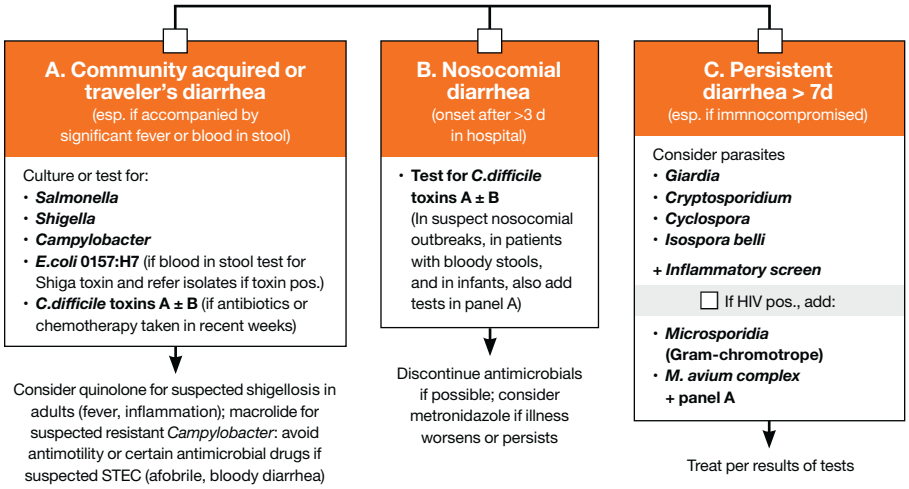
Workflow

To better understand the impact of this technology, Cincinnati Children's put together a team to do time motion studies and examine numerous measurable parameters within the laboratory.

On average, routine cultures at Cincinnati Children's required 141 decisions (i.e., the number of times the technologist needs to interact with the culture) for each and every stool culture. The BD MAX™ EBP required 25 decisions per sample – an 82% reduction of processing steps.

Figure 1: IDSA Clinical Testing Guidelines

Evaluate severity and duration | Obtain history and physical examination
Treat dehydration | Report suspected outbreaks | Check all that apply:



The BD MAX™ System also supports these additional FDA-approved assays:

- *S. aureus*
  - MRSA XT
  - StaphSR
- Group B Strep
- *C. difficile*

Further, the BD MAX™ Enteric Parasitic Panel (*E. histolytica*, *G. lamblia*, *Cryptosporidium hominis & parvum*) will soon have FDA approval. Also, in development are:

- Extended Enteric Bacterial Panel
- Enteric Viral Panel
- Vaginitis Panel
- CT/GC/TV

82%
reduction in decisions/steps

85%
average reduction in time to results

Further, the average time to results for cultures was 44 hours, 37 minutes. (Some of the cultures took up to 96 hours due to additional workup required.) Average time to results for the BD MAX™ EBP was 7 hours, 6 minutes – an 85% average reduction in time to results. Note that, in this initial study, Cincinnati Children's ran the BD MAX™ EBP in batch mode twice a day, once during first shift and once during second shift. Although the assay itself yields a rapid time to result, the cost savings occur when samples are batched. (The full results of this study have been accepted for publication in *BMC Clinical Pathology*.)

Another challenge to workflow that the BD MAX™ System answers is the number of additional assays available for this platform, with more on the way.

"We can't support a bunch of different platforms with one assay on each one of them," says Ms. Ventrola.

Costs

Understanding exactly how the cost of molecular testing compares with conventional cultures is crucial. Cincinnati Children's did a detailed, direct cost comparison, and a number of important factors were uncovered. For example, labor costs represent a significant variable because up to 20% of cultures require additional workup (see Table 1).

Table 1: Cost Comparison - Negative test

	Conventional Culture $ (min)	BD MAX™ System
Basic Test		
Labor (minutes)	$6.75 - 7.65 (15-17)	$0.67 (1.4 min)
Supplies	17.31	33.62**
Workup*		
Labor	15.75 - 18.00 (35-40)	N/A
Supplies	6.84 - 19.34	N/A
Total Cost in $	$26.00 - 64.00	$32.00 - 37.00**

*10-20% require significant work up of suspected pathogens **Cost dependent on contract pricing

Education

Early introduction and preparation is key when transitioning from conventional culture to molecular testing. Then, overlapping detailed training on how to use the technology allows for integration at a comfortable pace.

Dr. Mortensen and Ms. Ventrola began with general education of their staff about molecular testing of enteric bacteria. They discussed the concepts during their laboratory rounds and held more formal "Lunch & Learn" sessions for the staff.

"Our staff is very interested in new technology and new ways of doing things," says Ms. Ventrola. "The more educated our technologists are about the technology available, what our institution is considering and how it applies to what we do here, the more exciting it is for them, the easier it is for us to implement, and the better it is for our patients."

Dr. Mortensen and Ms. Ventrola continued education outside the laboratory for key user groups, such as infectious diseases and gastrointestinal physicians, some outpatient clinicians, nurses, and nurse practitioners. These individuals help support the integration process.

Training

Initially, core users were trained to serve as experts. Following that initial phase, a detailed training checklist was developed and the core users began to train additional technologists. In addition to internal facility training, BD provided several days of on-site support to train operators.

BD MAX™ System Training Checklist

- ☐ System overview
- ☐ Reagents and consumables
- ☐ Specimen collection and transport
- ☐ Software navigation
- ☐ System workflow
- ☐ Hands-on setup
- ☐ Results review
- ☐ Troubleshooting
- ☐ Quizzes to document understanding

Even laboratory staff that does not perform testing must understand the basic molecular testing methodology so they can answer questions.

A number of other tools have proved to be helpful in this transition:

- Technical service and other resources after training are also important.
- Online resources and training or paper manuals can supplement training.
- An instrument problem log can be valuable for sharing experience between technologists and to follow trends.

- Reaching out to colleagues through user groups and Listservs has become an important way to exchange information.

Implementing the BD MAX™ EBP

Ordering and Resulting

Cincinnati Children's is inserting the BD MAX™ EBP results into its traditional reporting format, as if it is a biochemical test. Moving into the era of molecular testing for stool pathogens has involved a phase-in process. For now, clinicians follow the same syndromic-based ordering procedures that have been in place for decades. The new results look and feel much the same, except that results of tests using the BD MAX™ EBP are clearly noted.

When an extended bacterial panel becomes available on the BD MAX™ System, one order will cover all tests that were previously done using culture. As Cincinnati Children's moves into the next phase, when all testing will be molecular, stool screen orders will be syndromic for bacteria, viruses, or parasites.

"Make sure clinicians understand how fast results are returned and what is included," says Dr. Mortensen. "Communicate with outside clinics and offices through newsletters and other mechanisms to ensure they have reasonable expectations."

Information Technology Interfaces

A Laboratory Information System (LIS) interface is ideal in order to limit the likelihood of errors. In this and many other settings, a bi-directional interface between the LIS and the analyzer is best. BD supplies one side of the LIS interface for the BD MAX™ System, and various vendors can supply the other.

New BD MAX™ System users like Cincinnati Children's can begin with no interface and add as they progress. As Cincinnati Children's validates the BD MAX™ System and uncovers its interfacing needs, the laboratory will examine the costs of upgrading.

Verification

An necessary step in implementing the BD MAX™ System is the verification studies. Verification is a one-time process that is completed before an assay or a system is used for patient testing in the laboratory. Verification studies should be performed by the technologists who will run the patient tests and, whenever possible, should be done on samples from your institution to make sure all possible variables at your institution are taken into account (see Table 2).

Cincinnati Children's conducts its verification studies based on ASM Cumitech 31A. Cincinnati Children's recommends starting with a challenge set of 20 known positives and 40 known negatives for each analyte from a variety of sources. ATCC strains can be used, and additional challenge samples may be obtained from the vendor or other institutions. Also, Cincinnati Children's recommends including known negatives outside of your targets, such as *E. coli, P. mirabilis,* and *Citrobacter spp.*, to rule out cross-reactions.

Table 2: Assay Verification Checklist

Task
1. Create plan for verification with dept. leadership team
a. Design study with approval of director and manager
b. Write up study design
c. Study design reviewed and approved by director and manager
2. Electrical check & KN# issued for new equipment/ instrument by CE
3. Create verification claim sheet
4. Perform verification testing including repeat on discrepant samples
5. Write up QA of verification including statistical analysis of data:
a. Precision
b. Accuracy
c. Reportable range
d. Sensitivity & Interferences
6. Submit QA of verification for review by manager and director
7. Write procedures
a. Testing
b. Preventive Maintenence (PM)
8. Create following logs
a. QC sheet
b. Calibration log, if applicable
c. PM log
d. Inventory Sheet
e. Training checklist
f. Verified Results Review sheet, if applicable
9. Clinical Lab Index; submit medication on Issue Tracking
10. LIS: Interface with Instrumentation, if applicable
11. Order CAP proficiency or establish alternative if not applicable
12. Complete Chemical Inventory Product Form for new or deleted products
13. Communicate changes to clinicians, if applicable
14. Communicate changes to other lab departments, if applicable
15. Complete cost analysis with manager
16. Submit billing information (CPT code and cost) for compendium
17. Submit information to LIS vendor

Validation

Once an instrument or system has been verified, validation demonstrates that it repeatedly gives the expected results over time and meets the manufacturer's claims. A number of tools already in the laboratory can be used for this ongoing process.

- Quality Control tracking over time
- Proficiency testing results
- Maintenance and calibration records
- Correlation with clinical findings
- Reproducibility testing

For reproducibility testing, Cincinnati Children's recommends testing 20 replicates and multiple users on multiple days, in order to account for day-to-day variances and variabilities in technologists.

CPT and Billing

During its transition, Cincinnati Children's is using the codes listed below.

Test	CPT Code
Phase 1 stool (combined with culture)	
Campylobacter, *Salmonella*, *Shigella*, Shiga Toxin (BD MAX™)	87505 x 1 (3-5 targets by a molecular method
Aeromonas, *Plesiomonas*, *Vibrio*, *Yersinia* (culture)	87046 x 2 (BAP & MAC)
Phase 2 stool (all molecular)	
Includes all of the above, when FDA approves remaining enteric bacterial pathogens	87506 x 1 (6-11 targets)
C. difficile toxin testing	87150
Staph/MRSA screen (Molecular MRSA & MSSA assay)	87640 and 87641

In the BD MAX™ EBP, Cincinnati Children's has found a cost effective way to meet the testing needs of its clinicians with syndromic-focused molecular solutions on a single platform.

Cincinnati Children's Hospital Diagnostic Infectious Diseases Testing Laboratory is closely monitoring the impact of molecular testing on patient care, as it continues to adapt and integrate this new technology into its microbiology laboratory. ■

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