Luminex

White Paper

Time and Motion Study: Molecular Testing with VERIGENE® Enteric Pathogens (EP) Test Accelerates Results for GI Infection Samples

Detailed workflow comparison finds that overall time and hands-on processing time are both reduced with the VERIGENE® Enteric Pathogens (EP) Test

Gastrointestinal infections, which can be caused by bacteria, parasites, and enteric viruses, are a common reason for visits to primary care clinics and hospitals. Despite the perception of gastrointestinal infections as minor illnesses in developed countries, there is significant associated morbidity. These common infections—seen in tens of millions of patients each year in countries including the U.S.— are also very costly, contributing billions to healthcare costs annually.[1-2]

The common symptom across GI infections is diarrhea. Patients who meet certain criteria such as travel history, immune status, and length of hospitalization, may have their stool tested using a battery of methods, including traditional microbiological cultures, immunoassays, nucleic acid assays, and microscopic examination.

As signs and symptoms of infectious diarrhea have significant overlap across the spectrum of causative pathogens, it can be challenging to arrive at an etiologic diagnosis using clinical criteria alone. Currently, 80% of all causes of diarrhea go unidentified, which could potentially result in inadequate or inappropriate treatment.[3]

Laboratories traditionally perform enteric testing in a serial fashion; initial results may lead to additional testing, depending on growth of suspected pathogens in culture. Organism identification may be conducted using techniques such as mass spectrometry, antigen testing, automated or manual biochemistry, or a combination of these methods. Testing for enteric pathogens is typically performed in more than one laboratory or in multiple areas of a single laboratory, requiring designated locations for specimen processing, general microbiology, virology, and molecular microbiology. This fragmented approach can prolong turnaround times and increase labor and overhead costs.

Today, laboratories are looking for efficient, cost-effective alternatives to traditional tests for GI infections. Culture methods typically require three to four days to reach completion, and studies have shown that traditional methods often under-detect enteric pathogens.[4,5] The adoption of faster, more sensitive molecular assays has allowed many labs to reduce time to results for improved patient care. One team noted a 75% reduction in hands-on time and technician labor costs, as well as a 93% reduction in time to results after replacing conventional tools with a multiplex molecular test for gastrointestinal pathogens.[6] Several studies have also illustrated the potential impact molecular GI testing can have on time to diagnosis, and appropriate treatment, reducing overall health care costs (see Discussion below for details).[7-9]

Estimated Savings from Adoption of Molecular GI Diagnostics

- **Time to appropriate treatment:** Reduced by 50 hours (from ~72 to ~22 hours)[7]
- **Health care cost per patient:** Reduced by ~$294/patient[8]
- **Isolation days:** Decreased by 34% (an estimated $70,000 savings over 8 months)[9]

A recent time and motion study was performed at TriCore Reference Laboratories to quantify the differences between standard and molecular testing for enteric pathogens. Data collection and analysis was conducted by Nexus Global Solutions, Inc., an independent third party healthcare consulting firm. Nexus was funded by Luminex Corporation to conduct time and motion analyses in an objective and impartial manner.

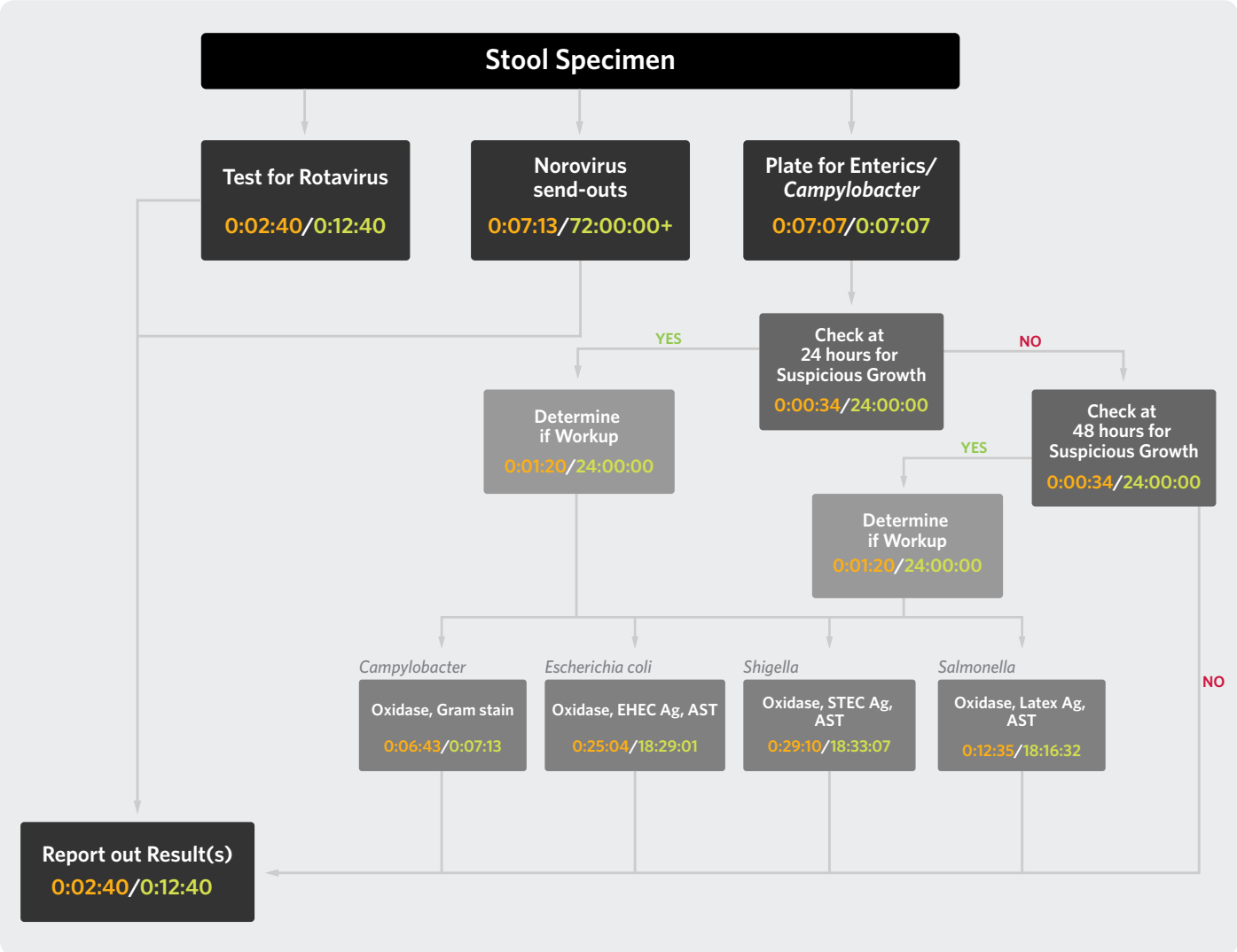
The VERIGENE® Enteric Pathogens Test (EP) is a rapid molecular panel that detects nine common bacteria, viruses, and toxins that frequently cause gastroenteritis. In this study, special attention was given to time, processes, and workflow, all of which must be carefully considered in a plan to introduce molecular testing for infectious gastroenteritis.

Standard Workflow

In a typical clinical microbiology laboratory, the standard workflow for processing stool samples associated with possible cases of gastroenteritis begins with the delivery of samples, which are then processed in batches by a medical technologist using traditional microbiology methods, outlined in Figure 1. Stool specimens are inoculated in media such as Hektoen enteric agar, *Campylobacter* isolation agar, MacConkey agar, and an enrichment broth. This process does not cover samples being tested for *Vibrio* or *Yersinia*, which are tested only on request and have a specialized workflow, or norovirus, which is a send-out test at this facility.

In cases where no colonies are identified (which is true for the majority of samples tested), turnaround time for the standard workflow takes up to two days, with about eight minutes of hands-on time. When a full workup is required based on colony growth, this time frame is substantially longer and may require inoculation into other media as well as susceptibility testing. *Campylobacter* takes 3 days for the full workup, while *E. coli*, *Salmonella*, and *Shigella* take more than 90 hours—close to 4 days, with as much as 38 minutes of hands-on time.

Figure 1. Standard Microbiology Work-up for Stool Specimens



KEY

Per sample time for labor (Hours:Minutes:Seconds)/Overall turnaround time (Hours:Minutes:Seconds)

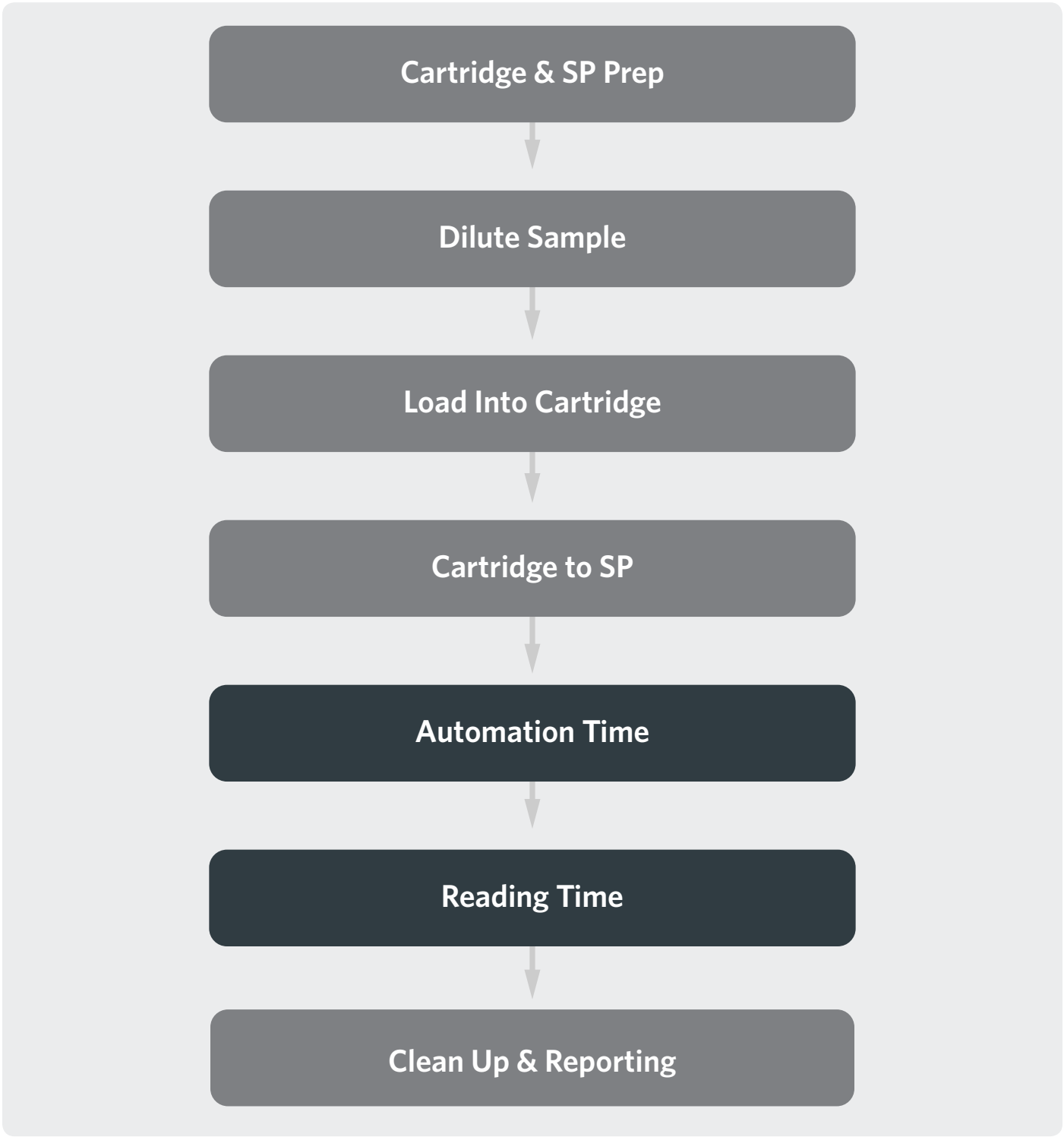
Doesn't include special orders or send-outs for positive results to the state health department for confirmation and/or serotyping.

Molecular Workflow

The VERIGENE® System includes two instruments—a sample processing unit (SP) and a reader—which are loaded with cartridges containing samples. Each processor works on one sample at a time, which is then analyzed by the reader when complete. A typical clinical laboratory would likely have three or four processing units and one reader. For the purposes of this study, time was assessed using one processor with one reader, as well as with multiple processors and a single reader.

Just like the standard testing workflow, the process for molecular testing begins when samples are received. Stool samples are placed into Cary-Blair medium and then processed according to the VERIGENE System workflow, shown in Figure 2.

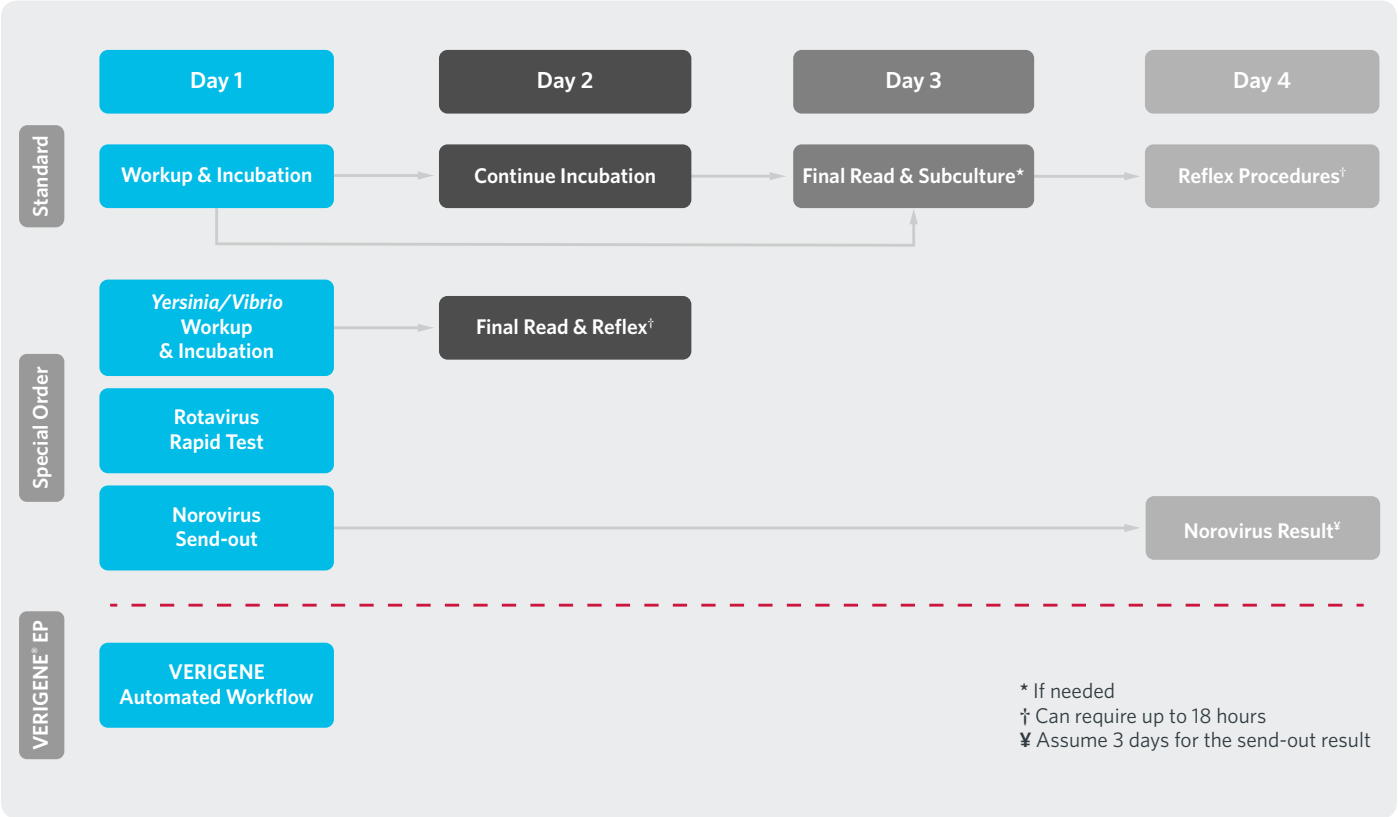
Figure 2. The VERIGENE® EP Workflow



Unlike the standard protocol, the VERIGENE System takes the same amount of time for negative and positive samples. For a single sample, the study found that clinical lab operators spent an average of 13 minutes working on the sample, while instrument run time took a little more than 2 hours. When multiple samples were handled simultaneously using the lab's four VERIGENE SP's, the average hands-on time per sample was reduced to seven minutes, while the instrument run time remained the same at just over two hours.

A chronological comparison of the standard and VERIGENE workflows is shown in Figure 3.

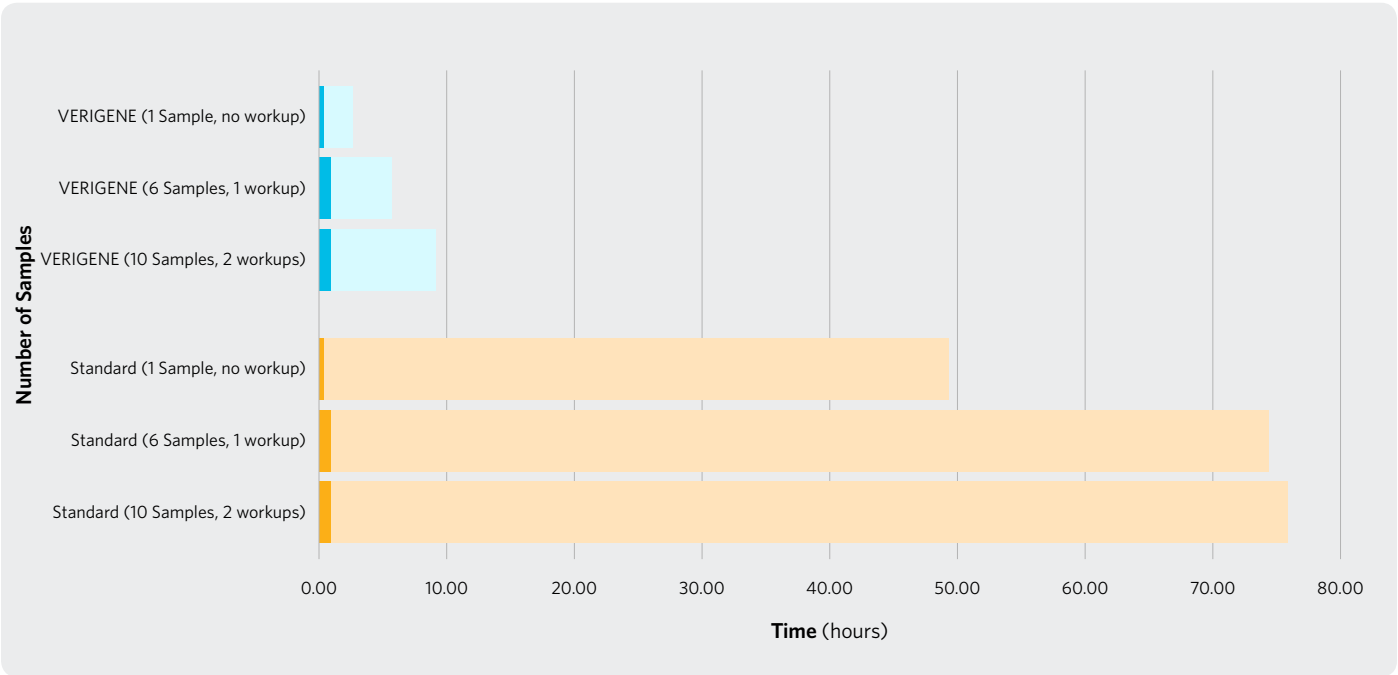
Figure 3. Chronological Comparison of Standard and VERIGENE® Workflows



Study Results

The final part of the study involved comparing results for a number of likely testing scenarios representing a range of facility throughput and testing demand (Figure 4). First, the study selected a low-volume scenario: three samples, none requiring workups. In this case, total turnaround time for the standard method was 48 hours (including 18 minutes of hands-on time). For the VERIGENE System, total turnaround time was 2.5 hours (including 22 minutes of hands-on time). Next, the study considered a mid-volume scenario: six samples, with one requiring a full workup. This situation would take 73 hours (including 67 minutes of hands-on time) for the standard workflow and 5 hours (including 46 minutes of hands-on time) for the VERIGENE System. Finally, the study analyzed a high-volume scenario featuring 10 samples with two full workups and 1 special-order test. The resulting turnaround time was 73.5 hours for the standard protocol (including 101 minutes of hands-on time) compared to 8 hours for the VERIGENE System (including 73 minutes of hands-on time).

Figure 4. Comparison of Hands-on Time and Automation (or Incubation) Time for Standard and VERIGENE® Workflows



Hands-on time is shown in the dark shaded bars. Automation (incubation) time is shown in the light shaded bars.

In an effort to understand the impact of these differences on a long-term basis, the study extrapolated results for the mid-volume scenario for a full year of testing. For 1 year, the study assumed an average of about 5 samples per weekday, with 13% requiring full workups. Overall, the VERIGENE molecular workflow would reduce hands-on time for sample processing by nearly 46 hours over the course of the year.

Conclusion

Culture-based testing has long been the gold standard for determining the underlying cause of symptomatic gastrointestinal infection. However, since modern molecular testing generates results with equivalent or better sensitivity and specificity in a much shorter time frame, there is growing interest in shifting to molecular workflows.

This time and motion study shows that the VERIGENE EP test returns both positive and negative results within a single shift, even for high-volume laboratories. For low-volume labs, labor time is about the same for traditional and molecular testing; as volume rises, though, the higher throughput of the sample to answer molecular assay offers a significant reduction in hands-on time. This would allow laboratories to utilize their expert resources for other testing needs, potentially expanding the available test menu or performing other valuable tasks.

With the VERIGENE System, ordering physicians can get definitive answers for GI infection cases in less than 24 hours. This offers guidance for treatment selection in a clinically actionable time frame and has major implications for improved diagnoses, reducing the duration of hospital stays, return visits, and time spent on inappropriate therapies.

While molecular tests for gastroenteritis are fairly new to the market, their clinical utility has been underscored by some early studies. For example, a retrospective analysis of almost 1,000 clinical specimens from a study performed by the National Institute for Health Research found that 21% of the infection control team's time was spent on managing infectious diarrhea.[10] The same study concluded that improved diagnostics would be important for improving patient care.

A study by Beal *et al.* demonstrated that comprehensive molecular testing for gastrointestinal pathogens versus utilizing standard testing methods reduced the number of days on empiric antibiotic therapy, as well as the number of additional diagnostic tests, such as abdominal or pelvic imaging studies, per patient.[7] In this study, it was estimated that the overall health care cost could decrease by $293.61 per patient, primarily due to a decrease in the length of hospital stay.

A separate study from the University of Washington focused on a multiplex molecular GI test, with researchers performing a prospective, multi-center investigation.[8] They analyzed more than 1,800 fecal samples with a molecular assay and with traditional stool culture and found that the median time from collection to the start of antimicrobial therapy was 2 full days shorter with the molecular test—22 hours versus 72 hours for culture tests. In addition, molecular diagnosis led to more patients being treated with targeted antimicrobial therapy when indicated, instead of empiric therapy. Also, positive results for Shiga-like toxin-producing *E. coli* were reported 47 hours faster, facilitating discontinuation of empiric antibiotics.

Finally, an eight-month study from King's College in the UK comparing conventional testing to a multiplex molecular GI test found improved rates of diagnosis for the molecular test, particularly in the early stages of disease.[9] Researchers determined that multiplexed molecular testing would save 154 isolation days for patients included in the study—a 34% reduction to a 2-day average time in isolation. The savings to the hospital over the eight months of the study were estimated to be £66,765 ($105,000) in isolation costs, for a £44,482 ($70,000) return on investment. "Multiplex molecular testing using a panel of targets allowed enhanced detection and a consolidated laboratory workflow," the authors concluded. "This is likely to be of greater benefit to cases that present within the first four days of hospital admission."

While more studies are needed, the implications are clear: multiplex molecular testing for gastroenteritis reduces time to therapy, is more likely to lead to effective therapy and avoid inappropriate treatment, shortens hospital stays, and improves overall patient outcomes.

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