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**References:**
Growing Genetic Testing Fraud

Federal, State Officials Warn of

As awareness grows of direct-to-consumer genetic testing kits, local and national government agencies are warning about an uptick in fraud that capitalizes on consumers’ eagerness to take advantage of their genetic information.

Within the federal government, the Department of Health and Human Services Office of Inspector General (OIG) is alerting the public about a fraud scheme in which scammers offer Medicare beneficiaries cheek swabs for genetic testing in order to steal their personal information. Criminals can use the information for identity theft or fraudulent billing. In an announcement, OIG said fraudsters target people through health fairs, telephone calls, booths at public events, and even door-to-door visits. Some of the schemes involve sending a test kit to the victim even if the only goal is to steal personal information. In another approach to this crime, the kit is mailed to the victim before information is requested.

OIG’s warning includes the admonition that “a physician that you know and trust should approve any requests for genetic testing.”

States’ attorneys general also are warning the public about the growing fraud. In some states, scammers have targeted Medicaid beneficiaries by claiming to be working with a local Medicaid insurer. For example, in Louisville, scammers paid $20 to Medicaid recipients as an incentive for them to take a DNA test before requesting their Medicaid insurance information.

In Nebraska, authorities reported receiving multiple reports of groups going to senior living communities, assisted living facilities, and senior centers and offering cheek swabs for DNA testing purportedly to check for cancer. Some of the fraud involves larger and more sophisticated networks that produce the test kits, send mail, and ostensibly provide customer service through staff call centers. When a viewer alerted television station WTHR in Indianapolis about receiving phone calls and a sample collection kit for DNA testing, a reporter called the customer service line to ask which kind of genetic testing would be performed. “It’s nothing scary. No craziness. It’s just going to tell her if she has the cancer gene,” a representative told the reporter.

Congress Takes Steps to Increase Harmonization Funding

Building on a significant achievement last year that provided $2 million in new funding for laboratory test harmonization work at the Centers for Disease Control and Prevention (CDC), AACC’s continued advocacy on this issue was behind a House Appropriations Committee vote that could increase harmonization funding to $6 million for fiscal year 2020. Harmonization aims to achieve uniform test results across different laboratories and instruments and ensure the best treatment decisions possible for patients.

The $4 million increase is part of the 2020 Departments of Labor, Health and Human Services, Education, and related agencies spending bill that includes CDC’s budget. The next step is for the entire House of Representatives to vote on the bill. Then it’s up to the Senate to complete work on the measure before both chambers consider a final bill in advance of a September 31 deadline.

AACC for more than a decade had led advocacy for this issue on Capitol Hill, including congressional briefings, grassroots campaigns, meetings with legislators and their staff, and publishing a position statement. AACC will be seeking a new legislative partner since the association’s previous congressional advocate, Rep. Kevin Yoder (R-Kan.), did not win re-election.

So far, CDC has been using this special funding on projects that will enable harmonization of tests for free testosterone, thyroid stimulating hormone, and estrogen. The agency also is examining harmonization for parathyroid hormones, free thyroxine, and free testosterone.
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According to Quest and LabCorp, since AMCA was a billing vendor, only financial information, and not laboratory results, were affected by the breach. However, medical information other than that about testing could be vulnerable, according to a statement from Quest. “Certain medical information on AMCA’s affected system was provided by Quest to help patients understand what they were being charged for, and to allow patients to submit an insurance claim where appropriate,” the company said in the statement. AMCA is offering affected patients free credit monitoring and identity theft protection.

Hackers have hit both laboratory companies before. Most recently a ransomware attack targeted LabCorp in July 2018, but the hackers did not steal patient data.

### SENATORS QUESTION GENOMIC TESTING LINKED TO CHINA

As both China and the U.S. prepare for what could be a protracted battle over trade and technology, Senators Marco Rubio (R-Fla.) and Chuck Grassley (R-Iowa) are asking the Department of Health and Human Services Office of the Inspector General (OIG) to look into how the U.S. shares genomic data with China and whether the U.S. government pays for genomic testing provided by laboratories linked to Chinese companies.

The senators are particularly interested in whether the Centers for Medicare and Medicaid Services (CMS) has paid for genetic testing performed by domestic laboratories that partner with two Chinese firms, Shenzhen BGI Technology Company (BGI) and WuXi Nextcode Genomics (WuXi). The Federal Bureau of Investigation (FBI) has flagged these two companies as having links to the Chinese government, the senators noted in a letter to OIG.

The National Institutes of Health (NIH) has ramped up efforts in recent years to collect and study genomic data through numerous studies and data repositories, and the senators cite in their letter a February OIG report that recommended NIH bolster how it mitigates national security risks from Chinese companies.

Both companies have sought to expand U.S.-based operations. WuXi since 2016 has operated a CLIA-certified genetic sequencing laboratory. And BGI—an early participant in the Human Genome Project—has collaborations with Children’s Hospital of Philadelphia, University of Washington in Seattle, the Bill and Melinda Gates Foundation, and the Smithsonian Institution. All these factors make it “necessary for the OIG to determine whether CMS has the proper security protocols in place to protect Americans’ genetic information,” the senators wrote.

Part of the reason these Chinese firms have come under scrutiny may be their cloud computing ties to Huawei, a company that the Trump administration has effectively banned from U.S. networks.
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Millions of baby boomers are nearing their retirement years. Soon enough, employers will be faced with the challenge of not only finding, but more importantly, keeping the succeeding generations of employees involved and satisfied.

Employee engagement has been a popular management concept as organizations seek to motivate workers. Convincing evidence now shows that improving employee engagement significantly improves company performance across several key areas.

As managers, keeping our employees engaged is perhaps the greatest challenge we face. It’s also a huge opportunity to gain long-term commitment and discretionary effort from our teams to apply their full capabilities and perform at the highest levels. Energetic and dedicated employees can make a true difference for organizations that want to be maximally efficient and productive.

The clinical labs at Children’s Hospital of Philadelphia (CHOP) have undertaken several initiatives to better engage our employees and improve retention, particularly among our younger millennial and Generation Z team members, whom we need in our workforce for decades to come. While these have been long-standing concerns of ours, staff surveys in 2016 and 2018 found that we had some ground to cover, so we focused more specifically on employee engagement initiatives. Our efforts, rolled out across CHOP labs, cover six key engagement strategies.

**Encourage employees to speak up.** When staff don’t feel as if they can speak up, they might be holding back valuable ideas and solutions that could move our lab forward. We ask our team members to bring ideas during daily huddles or meetings and to implement them if appropriate. We use bottom-up decision-making and encourage the staff’s input. For example, we created staff focus groups involving process improvements and design of a lab. They came up with workflow and design recommendations that made significant improvements in our operations.

**Be flexible.** We hold employees accountable for their performance yet give them flexibility as long as it doesn’t impact negatively on our operations. For instance, if someone’s train schedule were to change, we would allow the individual to modify work hours a
little to better accommodate his or her needs while also ensuring that we had adequate coverage.

Help employees move forward in their careers and education. We have a comprehensive career ladder with multiple steps to accommodate staff development, which supervisors discuss during one-on-one check-ins with staff. Based on a team member’s interests, he or she will be assigned additional responsibilities, bench assignments, or projects to help progress toward those goals. If this includes pursuing further education, we will work with the team member to flex his or her working days/hours. We want to help employees reach their goals, even if that means they may someday leave CHOP.

Celebrate staff milestones. When employees feel like they’re getting the proper amount of attention, they typically have more of a pull to be as engaged as possible in their work. Each month, we have cake for staff members who have a birthday in that month. In our daily departmental huddles, every Thursday is recognition day when we acknowledge team members for their accomplishments and send to all 400 lab employees a communication about these kudos.

One-on-one check-ins. Our standard is that supervisors meet one-on-one with staff members multiple times a year rather than just once at annual evaluation time. We’ve found that this enables employees to open up, and it’s particularly helpful to those who are not comfortable making suggestions in public. It also cuts down on the work needed to fix any issues that come to light.

Bring employees into the hiring process. In our view, there’s no better way to make employees feel like they’re an important part of the organization than to bring them right into the hiring process. In our labs, when an applicant comes in for an interview, he or she after meeting with the hiring manager will spend 30 to 45 minutes talking with our bench staff in the absence of a supervisor. This exchange enables both parties to assess whether the job in question is a good fit for the candidate and vice versa. We value our staff’s feedback from these sessions.

We have more experience with some of these strategies than others and expect it will take some time to fully assess their overall effects. However, a very hopeful early sign that they’re having the intended results is that all the new graduates we hired in the last 1 to 2 years are still with us.

One thing for certain is that we’ll be monitoring our progress closely and evolving our strategies as needed to keep our valued staff with us and our operations moving forward.

Vipul Shah, MBA, MLS(ASCP), DLM(ASCP)/CM, is division manager of clinical labs in the department of pathology and laboratory medicine at Children’s Hospital of Philadelphia.

EMAIL: shahv@email.chop.edu
Big Data Used to Delineate 4 Sepsis Phenotypes

University of Pittsburgh (UPMC) researchers deployed computer algorithms that mined the electronic health records (EHRs) of 63,858 patients to derive four phenotypes of sepsis, marked by demographics, lab values, and outcomes (JAMA 2019;321:2003-17). While acknowledging that more research is needed about these sepsis types, the investigators also suggested that their findings might lead to better treatment for this life-threatening condition.

“Hopefully, by seeing sepsis as several distinct conditions with varying clinical characteristics, we can discover and test therapies precisely tailored to the type of sepsis each patient has,” said first author Christopher Seymour, MD, MSc, an associate professor of medicine at UPMC.

Based on statistical machine learning and simulation tools, the algorithms analyzed 29 clinical variables in patient EHRs to identify the four phenotypes:

- **Alpha**: The most common type (33%), with the fewest abnormal lab values, least organ dysfunction, and lowest in-hospital death rate (2%);
- **Beta**: Patients in this type (27%) were typically older and had the most chronic illnesses and kidney dysfunction;
- **Gamma**: These patients (27%) had elevated measures of inflammation, mostly pulmonary dysfunction, and the second-highest in-hospital death rate (15%);
- **Delta**: These patients (13%) typically were the sickest, often with liver dysfunction and shock. 85% were admitted to intensive care, and 32% died in hospital.

The authors developed and validated the algorithm and their findings in three patient groups and assessed reproducibility, correlation with biological parameters, and clinical outcomes in one patient group and in other recently completed international clinical trials involving sepsis care. The patient groups included 20,000 UPMC patients recognized to have sepsis within 6 hours of hospital arrival from 2010-2012, 43,000 UPMC sepsis patients from 2013-2014, and 583 patients at 28 U.S. hospitals who developed sepsis due to pneumonia.

The researchers used simulation models to apply the four sepsis types to three randomized clinical trials—ACCESS, PROWESS, and ProCESS—and found that doing so would have changed the overall picture of the trials. For example, early goal-directed therapy—a hallmark of sepsis care—benefited Alpha type patients but worsened outcomes for Delta type patients.

In a literature review the investigators included 18 studies involving 1,170 ITP patients that met the criteria of having at least 20 ITP patients, using direct testing to measure autoantibodies against glycoprotein (GP) IIbIIa or GP IbIX of the IgG iso-type bound to the platelet surface or indirect testing detecting GP-specific platelet autoantibodies in plasma or serum, as long as the latter also reported direct assay results. The authors’ pooled estimates for...

**DIRECT PLATELET AUTOANTIBODY TESTING BESTS INDIRECT IN RULING-IN IMMUNE THROMBOCYTOPENIA**

A systematic review and meta-analysis of platelet autoantibody testing in immune thrombocytopenia (ITP) concluded that this testing has high sensitivity but low specificity in assessing patients for ITP but that using an optical density (OD) >3 standard deviations (SD) above normal improved sensitivity without compromising specificity (J Thromb Haemost 2019;17:787-94). Based on the latter finding, the authors suggest that OD >3 SD above normal should be established as a threshold to improve standardization of these assays across laboratories.

While guidelines state that autoantibody testing is not useful for diagnosing ITP, the authors also suggest, based on their findings, that it helps rule-in ITP.
sensitivity and specificity of direct testing and indirect testing were 53% and 93%, and 18% and 96%, respectively. In studies that used a cutoff of OD >3 SD as the threshold for a positive test, the pooled sensitivity and specificity for direct and indirect testing were 58% and 94%, and 21% and 96%, respectively.

In the subset of six studies that used both direct and indirect testing methods, the authors found that direct assays are more sensitive than indirect tests, consistent with a 2012 report that recommended direct assays over indirect ones on account of their improved sensitivity.

TRIAL DESIGN DESCRIBED FOR ASSESSING ANALYTICAL, CLINICAL PERFORMANCE OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

Researchers have described a trial design for assessing the analytical and clinical performance of high-sensitivity cardiac troponin (cTn) I assays in the U.S., including the Siemens Healthineers’ Atellica TnI H, ADVIA Centaur TNI H, Dimension EXL 200 TNI H, and Dimension Vista 1500 TNI H systems (Contemp Clin Trials Commun 2019;14:100337). They did so based on Food and Drug Administration requirements for patient enrollment and in accordance with at least five Clinical and Laboratory Standards Institute guidance documents on different aspects of assessing a test’s performance.

The investigators determined the assays’ 99th percentile upper reference limits in a healthy population by recruiting patients at least 22 years old from 12 sites across the U.S., excluding those with various lifestyle or health risks.

They assessed the assays’ clinical performance in emergency departments (EDs) by enrolling subjects at least 22 years old at 29 sites who presented as patients to EDs with symptoms of possible acute myocardial infarction (AMI) and who were enrolled within 1.5 hours of their first clinical blood draw. Study adjudicators classified subjects for AMI status based on the Third Universal Definition of Myocardial Infarction.

The researchers considered a battery of analytical performance factors for each assay, such as detection capability; limit of blank, detection, and quantitation; analytical measurement range; and high dose hook effect.

In assessing the assays’ clinical performance, the researchers tested the hypotheses that each assay had a sensitivity for AMI ≥90% or <90%. They also calculated four measures of diagnostic performance, including sensitivity, specificity, positive predictive value, and negative predictive value.

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When it comes to oncology diagnostics and care, immunotherapies and other personalized medicine approaches are among the leading treatment efforts. As the number of new cancer diagnoses continues to rise, clinicians need tools that can more quickly—and affordably—offer answers.

Within the next 5 years, the use of precision medicine in oncology is set to balloon, benefiting millions of patients globally. According to industry estimates, 5.1 billion precision cancer diagnostic tests will be performed between 2018 and 2023, with a market value rising to nearly $20 billion in 2023. Genetic and genomic testing account for a significant portion of those analyses, but the current predominant practice of analyzing patient samples for specific mutations takes longer and is less efficient in connecting patients with the best available treatments for their tumor profiles. This is where next-generation sequencing (NGS) comes in. Rather than examining single genes, NGS allows laboratorians to use molecular barcoding to test multiple genes simultaneously. Test results provide diagnostic and therapeutic answers more efficiently.

From Research to Practice
Tried and tested in clinical trial settings, NGS now is spreading its wings into oncology practice. According to Dhananjay Chitale, MD, vice chair of anatomical pathology at Henry Ford Hospital in Detroit, implementation has moved off the bench to academic medical institutions, large cancer centers, and beyond.

In fact, explained Razelle Kurzrock, MD, associate director of clinical science at the University of California San Diego School of Medicine, wider NGS utilization is a growing trend. Previously in her practice, only patients who sought medical care in academic environments benefited from NGS, but that is no longer the case. “If you go back three or four years, patients would almost never come in having already done next-generation sequencing, and now the majority come in with it already done,” she said.

Even with this new level of NGS adoption, the technology still has a way to go on its journey of dissemination, said Rondell Graham, MD, associate professor of laboratory medicine and pathology at the Mayo Clinic in

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“With a larger NGS panel, you have one large pipeline, one large workflow, that really simplifies things and makes more efficient use of your technology and time.”

– MARC LADANYI, MD

Rochester, Minnesota. Most NGS is still offered in large metropolitan areas, but as the volume of cancer care needs continues to rise, smaller, more suburban facilities could find themselves searching for avenues to bring this testing online. Indeed, some community hospitals are beginning to embrace NGS as a routine testing technology.

The Aha Moment
In many cases, a facility’s decision to take on in-house NGS will rest on patient need and volume, said Marc Ladanyi, MD, chief of the molecular diagnostics service and William J. Ruane chair in molecular oncology at Memorial Sloan Kettering Cancer Center in New York City. Before delving into NGS, interested groups should analyze how many of these tests they run monthly or annually to ensure they can generate enough revenue to overcome the setup costs. Outsourcing NGS testing is a viable option if creating a lab isn’t financially feasible, he added.

“The ‘aha’ moment happens when you find yourself running many individual assays, and you’re really struggling to keep up with the number of technologists it takes to run those screenings,” he explained. “You have to look at that and ask whether you could replace all those tests with a one-panel [NGS] assay to simplify your laboratory workflow while generating more information.”

Artur Rangel-Filho, MD, medical director of Memorial Regional Hospital South (MRHS) in Hollywood, Florida, agreed that patient volume is a major driving factor because it largely determines whether a lab will generate revenue through NGS. Outlining any cost savings can help get administrative stakeholders on board with a lab launch, he said.

Before offering NGS, MRHS spent roughly $1 million annually on outsourcing its NGS testing. After implementing NGS earlier this year, he explained, that expenditure has dropped by approximately 80%. The hospital not only has realized substantial cost savings but also now controls the data and can use it to improve overall patient outcomes long-term, Rangel-Filho stressed.

But being successful means more than doing the math to show a boost to the bottom line. Labs that perform

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NGS also need a clinical champion, Chitale emphasized, preferably an oncologist who can help determine how data generated from this powerful tool will be used, as well as PhD-level molecular genetics lab professionals on board to oversee processing and analyzing of these tests.

Additionally, Kurzrock said, facilities should have a molecular tumor board consisting of clinical laboratory professionals and oncologists that meets regularly to discuss findings and next steps for patient treatment.

Choosing Tests, Finding Techs
To date, NGS has been used to identify genetic mutations in solid tumors associated with several cancer groups, including colon, lung, and breast. Myriad large panel options, such as whole-genome or whole-exome sequencing, are available, but they also increase the number of variants undergoing analysis. Instead, many facilities opt for multi-gene panels. Often these are laboratory-developed tests, but the number of analysis options approved by the Food and Drug Administration (FDA) is growing.

For example, Ladanyi’s lab offers a 468-gene panel, called MSK Impact, that detects genetic mutations in solid tumors for both rare and common cancers. As of 2017, he said, more than 20,000 patients had been screened with this FDA-approved NGS test. Final approval is also expected soon on a new cell-free DNA liquid biopsy test called MSK-Access. These types of panels greatly facilitate screening efforts, he said.

“With a larger NGS panel, you know you don’t have to maintain multiple separate assays for different cancers or for different targets,” Ladanyi added. “You have one large pipeline, one large workflow, that really simplifies things and makes more efficient use of your technology and time.”

Additionally, Kurzrock and her colleagues used multigene panel sequencing in the iPredict study and are looking to implement this approach in clinical practice. This research used NGS to determine the genetic profile of 149 individuals with stage IV cancers to identify personalized combination therapies that were more effective than monotherapies. Based on NGS data from the study, 88% of participants received individualized combination therapies that halted disease progression, she said (Nature 2019;25:744-50).

Establishing a lab outside of top-tier academic research institutions can be more complicated, however, said Rangel-Filho. “It’s not the same as in Boston or the Bay Area where
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you have several universities with a lot of postdoctoral fellows who are highly trained and are currently working with this technology,” he observed. “That wasn’t the case for us in Florida. We had to build our team from scratch.”

To overcome this challenge, MRHS hired medical technologists with research backgrounds and trained them in molecular biology techniques so they could accurately complete the NGS panels the system offers. Additionally, MRHS purchased commercially available software to handle its bioinformatics needs.

**Informatics: The Achilles’ Heel?**

Even though there are several benefits associated with performing NGS in-house, barriers to doing so effectively still exist. One of the most significant involves startup costs, Graham said. The initial cost of NGS machines can top more than $100,000, and getting sign off for that expenditure level can be difficult.

Securing reimbursement is also complicated. As of 2018, the Centers for Medicare and Medicaid Services limited payment to only FDA-approved NGS tests that analyze solid tumors. Reimbursement is currently unavailable for tests performed with in-house screening mechanisms or those conducted for research and investigation purposes.

Another major challenge, Ladanyi said, is the substantial need for bioinformatics support. The importance of having highly trained technologists with informatics credentials in place can’t be underestimated, he said, especially because there are still few individuals with a high comfort level with NGS. Chitale seconded that assertion. “Because this is new technology, you will need internal expertise to design your capabilities with assays,” he said. “Your bioinformatics team must be able to validate these assays, as well as interpret and report them.”

But, even with a qualified bioinformatics team in place, Graham cautioned, laboratory leaders and clinicians must remember that NGS is an extremely sensitive testing option. Consequently, it presents a greater opportunity for false positives. Laboratory technologists should also monitor the amount of noise in the assays to ensure each test provides the best quality information.

Having enough storage to accommodate the rich amounts of data collected from NGS also presents a problem, particularly for smaller institutions, Chitale said. Laboratory leaders should work closely with their information technology teams to ensure a system exists to keep patients’ test results secure. If on-site storage isn’t possible, cloud storage is an acceptable alternative, he said.

Ultimately, Chitale said, NGS is the next wave of oncology testing, and clinicians and their facilities need to be ready to take full advantage of it. “I think NGS is ready for prime time,” he said. “We know a lot about cancer genetics and other things, which are trickling down into the clinical arena. We must make use of that information in a precision medicine program.”

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The Evolution of Leadership in Point-of-Care Testing
As point-of-care testing (POCT) continues to grow in hospitals, physician offices, retail clinics, and other settings, professional roles are also evolving to keep pace with changes in this technology, the complexity of testing, and the need to engage with clinicians.

Once consisting of just a handful of assays, POC tests now number in the hundreds, ranging from blood glucose monitoring to rapid strep to prothrombin time/international normalized ratio (PT/INR). The market for POCT grew by an estimated 9.3% between 2013 and 2018, and worldwide, the POCT and rapid diagnostics market is projected to top $38 billion by 2022, according to industry experts.

With the growth of POCT comes challenges for laboratory directors, POC coordinators, and other professionals responsible for ensuring that...
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in areas where we haven’t traditionally seen POC use. For example, to facilitate cancer management, microfluidic methods are being developed to detect circulating tumor cells at the POC. We are already engaging clinical teams as we work to ensure the quality of our POC program, but as new tests are acquired and the number of personnel performing testing grows, we will need to engage them even more."

Being able to hire healthcare professionals who have advanced knowledge in POCT would be a huge advantage for Lurie Children’s Hospital, she added, noting that she hopes for the hospital’s POC coordinator to complete AACC’s new POCT professional certification program. This first-of-its-kind program, launched last year, certifies testing personnel who have demonstrated competency in all areas of POCT, including regulation and compliance, quality management, education and training, instrument selection, validation and verification, and connectivity and information technology.

-- BRENDA SUH-LAILAM, PHD, DABCC, FAACC

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“I think it’s great that we finally have a program that focuses on POC testing because it has different challenges from regular lab testing,” Suh-Lailam said. “POC testing is really exploding, and with this comes more personnel performing testing as additional hospital areas acquire POC tests.” The more staff there are performing POCT who have not been trained in the laboratory, the more pre-analytic, training, and competency-related challenges the POC coordinator will have to handle, she noted. “Going through a POC-specific training like this one will equip the POC coordinator to be able to take on the challenges that come with POC growth.”

“I wanted to be more invested in my role as a POC coordinator. I feel the more knowledge and education you have in a field, the more you can improve patient outcomes.”
– CATHY GUAGLIANONE, POC SUPERVISOR

A Path to Leadership Through Professional Certification
Debra Petracco, MT(ASCP), CPP, POC coordinator at Presence Saints Mary and Elizabeth Medical Center’s Alverno Laboratory in Chicago, and one of the first POC testing professionals to be certified through AACC’s professional certification program, said she feels the designation provides added value in her role as a POC coordinator and also gives her more job security. “I’ve been doing POCT for a long time, and I have always tried to keep up with the changes,” Petracco said. “Certification makes me feel more confident that I am doing things the right way. I feel like it gives me a boost in my position.”

To be eligible for POCT board certification, applicants must have a 4-year degree in a biological or physical science and 2-3 years’ documented experience in POCT. A healthcare expert who passes the certification exam is known as a Certified Point-of-Care Testing Professional (CPP). The POCT professional certification program is available to anyone with experience performing POCT, such as laboratory managers, nurses, and pharmacists.

“The exam is very thorough in testing your knowledge,” Petracco noted. “There’s a lot about chemistry, coagulation, validation processes, and instrumentation.”

Leh Chang, MT(ASCP), CPP, technical supervisor for POCT at Loma Linda University Medical Center in California, said she sees receiving the professional certification as a way to validate her knowledge about POCT. She believes the certification could one day become a requirement for someone overseeing POCT. “I also think there are more opportunities to involve POCT professionals, such as providing suggestions on device and testing development,” Chang said.

Cathy Guaglianone, MT(ASCP), CPP, POC supervisor for Kaiser Permanente in Fresno, California, said becoming a CPP has increased the confidence other clinicians have in her. “I wanted to be more invested in my role as a POC coordinator,” she said. “I feel the more knowledge and education you have in a field, the more you can improve patient outcomes.”

To prepare for the professional certification exam, Petracco, Chang, and Guaglianone reviewed published information on POCT, including the materials suggested on the POCT professional certification website. Petracco also completed AACC’s online POCT specialist certificate program, which consists of eight self-paced courses, before sitting for the professional certification exam.

POCT as a Separate Discipline
Not only are POCT professional roles evolving but so is the way POCT is treated in some health systems. Cleveland Clinic – Abu Dhabi (CCAD), for example, has established a separate POCT department. While POCT often is a subdiscipline of clinical chemistry, it also incorporates testing involving other departments,
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such as hematology, microbiology, and molecular biology, emphasized Jonathan Harris, senior manager of point-of-care testing and quality, who said hospital leaders were unanimous in their support of treating POCT as a discipline in its own right. The department includes a POCT medical director, POCT manager, and dedicated POCT technologists.

CCAD’s POCT program is accredited by the College of American Pathologists (CAP), which was especially challenging because none of the POCT department personnel were familiar with CAP requirements and associated language. The POCT department in 2017 also received ISO 22870 and 15189 accreditations with the United Kingdom Accreditation Service, which Harris called major milestones for any POCT program.

“Only a handful of hospitals have obtained this challenging requirement. Having dedicated resources gives us the ability to achieve this,” he said. “We have a constant focus on innovation and continual improvement. Typically, in POCT, you are putting out fires, but we are able to focus on doing things better.”

Harris added that the POCT department is working on establishing clinical metrics in collaboration with nursing and medical colleagues. This adds real value to the service they provide, he said. Examples include protocols and metrics dealing with the limitations of glucometers in critically ill patients, as well as glucometrics focusing on how patients are treated for hypoglycemia and the total number of hypoglycemic events by department. “The clinical teams now see us as valued partners in the delivery of patient care,” he said. “This focus on the clinical is leading to improved patient care and outcomes.”

**Education Is Key**

Both Suh-Lailam and Harris agree that there is a need for increased focus on POCT in the educational system. Many colleges and universities fail to properly teach POCT methods and protocols, they said. In fact, sometimes the subject is not covered at all.

“There’s a huge gap in knowledge,” said Harris, who would like to see POCT professional certification become mandatory for testing professionals. “Lab and nursing leadership need to be educated as to what us POCT personnel do. POCT seems deceptively simple but has a huge impact on patient care.”

Suh-Lailam agreed. “We definitely need more trained POCT professionals,” she said. “The more people who become certified in POCT, the more trained people there will be to develop quality POC programs that add value to patient care.”

**Kimberly Scott** is a freelance writer who lives in Lewes, Delaware.

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THE PROS AND CONS OF CENTRALIZING MICROBIOLOGY SERVICES

BY CORRIE C. SIMONS, MLT(ASCP)M, AND GERALD A. CAPRARO, PHD, D(ABMM)
The structure and location of diagnostic laboratory services have undergone a significant shift in recent years. As part of laboratory stewardship, laboratories continually review their scope of service in order to better utilize healthcare resources while still meeting the needs of patients and clinicians. In part due to this stewardship model, consolidation and centralization of laboratory services increasingly are becoming the norm. The goal of this article is to provide thoughtful discussion of the relevant issues surrounding centralization and consolidation of microbiology services for laboratories that might be considering such a model.

Why Consider Consolidation? Consolidation enables a laboratory to standardize pre-analytic, analytic, and post-analytic practices in microbiology and offers cost savings on instruments, reagents, and personnel. The many arguments for and against consolidation have been outlined in a number of excellent articles (1–5). Importantly, a centralized laboratory can provide a single set of orderable tests and the guidance to collect appropriate specimens for those tests through a concentrated, and highly integrated, center of expertise.

For example, testing for antibiotic-associated diarrhea caused by *Clostridioides difficile* requires a liquid stool specimen. Many laboratories use the so-called "stick test" to ensure that proper specimens are tested—specimens in which the stick falls over would be tested, but those in which the stick remains upright would be rejected as formed stool. This approach can be easily
standardized for one staff of microbiologists in a centralized laboratory.

Cost savings is a significant consideration as well. In a decentralized model with multiple low-volume sites, the number of instruments of each kind also multiplies, such as molecular platforms, antimicrobial susceptibility testing (AST) instrumentation, and pathogen identification systems. Quality control (QC) reagents also need to be available at each site. Even though laboratories should account for reagent volumes needed for their testing menus, with duplicate testing occurring at multiple sites there is bound to be waste in the form of extra reagents on hand.

Consolidating several microbiology laboratories into one centralized facility allows a healthcare system to allocate a single set of financial resources for its diagnostic microbiology services: one staff of microbiologists, one set of QC testing for each assay, and the appropriate amount of instrumentation to account for current and projected testing volume. Healthcare systems also can leverage bulk purchasing to secure lower reagent pricing, with minimal waste due to off-site testing.

In most cases, personnel costs account for the largest piece of a laboratory’s budget, and this is another area in which centralization eliminates duplicate effort and cost. For example, in many cases culture reading at a centralized laboratory can occur on three shifts whereas at off-site laboratories this task may only take place during the first shift. This system can allow for culture workup on a first-in first-out basis when the plates are ready to be reviewed, rather than batch reading when staff members are available.

Patient care takes a team of healthcare professionals, including physicians, nurses, pharmacists, and laboratorians. Consolidating microbiology services allows for subject matter expertise to be present in one location, with a trained microbiologist staff available to perform testing and report results according to a single, standardized operating procedure. An experienced microbiologist, with demonstrated skills in operational oversight and personnel management, also would be available to drive managerial success.

Importantly, in a consolidated services model, microbiology medical director(s) would be available in a centralized location with the rest of the microbiologist team. Hospital systems should have well-trained, professional scientists who are board-certified in medical microbiology available to provide vision for their centralized laboratory, guidance on standard-of-care-based improvements to the testing menu, and clinical consultation on microbiology testing to healthcare workers (6).

Other important ways a single, consolidated staff yields greater efficiencies include proficiency testing through the College of American Pathologists (CAP) or alternative proficiency testing services, employee training and annual competencies, continuing education opportunities, project work such as validating new tests, and preparing for inspections by accrediting agencies.

New Challenges With Consolidation
There are many advantages to consolidating clinical microbiology services; however,
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one must also consider trade-offs of such a model that create unique challenges. In a decentralized model, microbiology testing is physically located closer to the patients at all facilities, clinical care teams have direct contact with each laboratory, there is no need to transport microbiology specimens long distances, and staff members can respond faster to local questions and concerns.

The impact of consolidation on clinician practice also should not be overlooked. Infectious diseases (ID) practitioners, especially, are accustomed to visiting their institution’s microbiology laboratory prior to rounding on patients each day. This interaction provides the ID physicians with up-to-the-minute information on their patients and allows them the opportunity for special requests in real time.

Moreover, visualization of culture growth also reinforces important microbiology concepts like optimal growth requirements, normal flora of various anatomic sites, pathogen quantitation, and inherent antimicrobial resistance. Absence of this interaction is a missed opportunity not only for ID physicians but also for microbiologists: Centralized laboratory services can create a culture of disjointed patient care. Plate reading can become a rote, iterative activity, giving microbiologists the sense of no longer being connected to patients on the other side of petri dishes.

Another consideration is that even with a centralized microbiology laboratory, some microbiology testing must continue at off-site locations. Clinical impact should drive the decision to keep or send microbiology work to a centralized laboratory. For example, rapid antigen testing for pediatric pharyngitis caused by group A Streptococcus should be performed as a STAT test because immediate antimicrobial therapy lowers a patient’s infectivity while also reducing development of suppurative and nonsuppurative sequelae. Sending this testing to a centralized laboratory would slow down testing, delay the start of antibiotics, and put patients at increased risk.

Logistical issues also can be problematic within a healthcare system, especially when it comes to delays in specimen processing. The laboratory would slow down testing, and put laboratories at increased risk. Laboratory would slow down testing, and put laboratories at increased risk. Laboratory professionals should also be prepared to provide data to clinicians demonstrating the centralized laboratory’s successful performance.

Laborators will also need to educate clinical care staff about the risks of a centralized laboratory, such as specimen transport issues, and plan for how those risks will be mitigated.

Within the affected laboratories, staff must accept that organizational change will necessarily occur when transitioning to a centralized model. Shift start times, productivity expectations, workload, and the like all will probably differ post-centralization.

Critically, the healthcare system must decide what the standard of care will be for all patients in the organization, and the laboratory must be given the resources necessary to provide that standard.

A Centralization Checklist
Once a laboratory makes the decision to centralize microbiology services, leaders need to tackle several strategic hurdles. The following is a list that we have found helpful.

- **Get Constituent Buy-In**
  The stakes could not be higher when it comes to microbiology services. Hospital leaders, clinicians, and laboratory staff must all accept the centralized model. Leaders must understand the rationale for such a model and be willing to provide the necessary financial and personnel resources to succeed. Laboratory professionals should also be prepared to provide data to clinicians demonstrating the centralized laboratory’s performance.

- **Develop a Communication Plan**
  Questions and concerns from outside facilities—both generalist laboratorians and clinicians—will undoubtedly arise. These run the gamut from specimen collection requirements, to clarification of results, to requests for additional testing. The laboratory must decide between providing a single telephone number for calls directly to the microbiology team or calls to a client services division. Alternatively, email, secure text paging systems, or other electronic options may be considered.

- **Address Specimen Management**
  A curated electronic resource to guide appropriate specimen collection and submission should be available to clinical care teams. Additionally, a robust continuing education program on issues of specimen collection should be part of a laboratory’s competency program. Using these two tools together in a consolidated laboratory can minimize delays due to specimen collection.

  Upon receipt of an appropriate specimen, the question *to plate or not to plate?* becomes significant. To respond appropriately, laboratory staff need to know several things, including the distance traveled between a collection site and the centralized laboratory, the reliability of transport devices for maintaining organism viability, and whether offsite generalists have been trained to inoculate specimens into culture.

  If specimens are to be inoculated locally with plates sent to the centralized laboratory for workup, portable incubators will be required by the transport. The incubators also will require temperature monitoring, resulting in additional effort from the laboratory.

  The laboratory must also determine how it will handle performing and reporting Gram stains. In certain clinical situations a timely Gram stain can be the difference between life and death for a patient because it guides prompt and appropriate empiric antimicrobial therapy. Likewise, generalists at local sites need to maintain competency in performing and reporting Gram stains. There may be a role...
What lab products and services should be outsourced? Insourced?

Dr. Jackson is an associate professor of clinical pathology at the University of Utah School of Medicine and directs informatics efforts at ARUP. He also founded the podcast, LabMind. As more health systems merge, Jackson feels hospital leadership needs a deeper understanding of clinical and operational relationships. “You can end up with senior executives making decisions about functions they know little about, such as the lab.”

Q: How do businesses typically decide what to outsource versus keep in-house?
A: Some leaders label their organization’s most viable products or services as “core competencies” and try to outsource everything else. Others underestimate their organization’s internal potential, or believe that financial deal making is the best way to create value. Sometimes it just comes down to what’s trending. For example, in the 1990s, many IT and HR departments were outsourced largely because CEOs saw their peers doing the same thing.

A smarter approach is to base decisions on a strategic analysis of your organization and the outside marketplace. Outsourcing makes sense when the service or product is not a key differentiator and when it is okay for it to be just average. Outsourcing works best for plug-and-play products and services that do not require customization for your setting. The opposite of outsourcing is vertical integration, where functions remain in-house under the control of the organization. This approach makes sense when your organization’s success relies on tight integration of that product or service.

Q: What are some examples of vertical integration?
A: In the early 1990s, Apple’s vertically integrated manufacturing of Macintoshes made for a superior user experience. They successfully replicated the strategy years later with the iPod and later the iPhone. Microsoft, in contrast, treated printers and other devices as interchangeable commodities from early on, and users suffered the consequences.

Q: Isn’t lab testing “plug-and-play”? Doesn’t it make sense to outsource it?
A: Actually, laboratories are some of the least plug-and-play departments within modern healthcare. Clinical departments such as EDs, surgical centers, primary care offices, and ICUs all have markedly different laboratory testing needs. An in-house laboratory can adapt and fine-tune services to meet these needs. Health system laboratories are not a commodity, and are not likely to become one any time soon.

On the other hand, within any given health system laboratory, there are likely to be specific components that could make sense to outsource. Take esoteric tests, for example: the volume doesn’t justify the resources to maintain them in-house, and turnaround time greater than a day is acceptable for clinical needs. It also makes sense to outsource services such as online test directories and courier services.

Q: When a laboratory loses profitability (e.g., due to reimbursement pressure) isn’t that a good time to outsource it?
A: Actually, that might be the worst time. For one thing, knowing that you’re under financial pressure will give a commercial lab tremendous negotiating leverage. More fundamentally, a lab’s direct costs and reimbursements give an extremely incomplete and biased perspective on the overall financial impact of testing services.

For example, suppose a lab sets up near-patient testing for an outpatient infusion center. Based on internal lab accounting, this arrangement will be much more expensive than sending those same tests to a core lab or a reference lab. However, rapid TAT in that setting means that patients do not have to come in the day before their chemotherapy just to get their labs drawn. This can positively impact patient satisfaction, leading to growth in a health system’s lucrative oncology business. The bottom line is, unless you’re a completely independent reference lab, profitability can only be properly assessed within a clinical service line or clinical enterprise, and not within the lab in isolation.
Healthcare systems must consider how they will manage regulatory issues under CLIA, JCAHO, COLA, and state agencies must also consider how compliance with this requirement is maintained once microbiology services are no longer being performed locally. Other regulations also apply, and the laboratory must develop appropriate testing and a plan for the scope of those tests, and the ability to respond in real time is critical.

**Make Decisions on Rapid Testing**
Clinical impact of the result should drive the decision to perform rapid testing locally or at the centralized laboratory. One rule of thumb is to perform locally any testing that requires a result in less than 3 hours. Examples of testing that meets this criterion include streptococcal antigen testing for suspected bacterial pharyngitis and cryptococcal antigen testing for suspected meningitis.

The laboratory also will need to tackle how to handle rapid molecular testing. Sample-to-answer molecular testing is available commercially as either moderate complexity or waived testing. Rapid identification of positive blood culture pathogens and suspected influenza are two clinically relevant examples. The expertise of the personnel performing these assays should guide the decision to provide such testing. Questions will undoubtedly arise from the results of these tests, and the ability to respond in real time is critical.

**Optimize Courier Schedules**
The healthcare system must decide between using an internal fleet of couriers or a third-party provider. Courier routes and schedules must keep the risk of specimen transport issues and delays as low as possible. A reliable electronic tracking program helps reduce the risk of lost specimens.

Labs also need to determine the acceptable length of time that a specimen can sit idle prior to being transported. The laboratory must perform validation studies to account for the loss of organism viability. These studies must be performed regardless of whether the system decides to ship specimens or inoculated plates to the centralized laboratory.

**Assign Responsibility for Result Review and Corrective Action**
If a healthcare system decides to centralize most microbiology testing and perform just a few tests locally, it will need to determine how to perform this testing, how to report the results, and how to perform corrective action when errors occur. The microbiology manager and director should be responsible for these decisions, regardless of the operational/managerial infrastructure present at local laboratories.

**Design With Regulatory Compliance in Mind**
Healthcare systems must consider how they will manage regulatory compliance, both on a continuous basis and when accrediting inspections occur. If a central lab performs all microbiology testing, the scope of a CAP inspection checklist rests entirely on that laboratory. However, if local labs perform minimal microbiology (e.g., inoculation of specimens, Gram stains, rapid testing), these off site laboratories are subject to a limited microbiology checklist that still requires following many regulations.

There is a specific CAP requirement for supervision of microbiology services that must be considered. Two years of microbiology experience are required to supervise microbiology services, even if the only task being performed is the Gram stain. The laboratory must consider how compliance with this requirement is maintained once microbiology services are no longer being performed locally. Other regulatory issues under CLIA, JCAHO, COLA, and state agencies must also be considered.

Infectious diseases (ID) practitioners, especially, are accustomed to visiting their institution’s microbiology laboratory prior to rounding on patients each day. This interaction provides the ID physicians with up-to-the-minute information on their patients and allows them the opportunity for special requests in real time.
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The Automation Question

Total laboratory automation (TLA) in microbiology is becoming commonplace for high-volume and lower-volume laboratories alike. With TLA, a laboratory receives specimens, inoculates them into appropriate culture media, and sends them via conveyor belt to an incubator that takes high-resolution images of the plates at regular intervals. Microbiologists read plates digitally and electronically order testing to be performed for identification and AST, which can be performed manually or automated, depending on the types of enhancements a laboratory purchases as part of its automation system.

The decision to implement TLA is beyond the scope of this article. However, implementing automation in microbiology can impact the decision to centralize microbiology services. A consolidated laboratory that uses TLA is likely to have better efficiency: Cultures showing no growth can be dismissed as negative with the click of a button, and microbiologists would only need to touch those cultures with significant pathogen growth.

Automation in microbiology laboratories is a relatively new concept, with the general model being that specimens are sent to the processor for inoculation and plates are read on-site. However, in the future microbiology automation may offer scaled-down versions of the processor and incubator maintained locally while enabling microbiologists at centralized laboratories to read plates. This would alleviate courier delays, non-viable organisms, transporting inoculated plates, and other problems. However, this possibility would require much thoughtful consideration prior to implementation.

Conclusion

Centralizing microbiology services can be achieved successfully with careful preparation. Chief among the many concerns we’ve raised is clinician buy-in: Clinical care staff must be able to rely on timely, accurate results from microbiology laboratories regardless of their location.

Before making such a consequential decision for a health system, laboratory leaders must reflect on many issues of logistics, resources, and regulation in order to determine if centralization is the right model for the healthcare system and, importantly, the patients being served by that system.

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CD Diagnostics Test for Joint Replacement Infection Gets FDA Nod

The Food and Drug Administration (FDA) has permitted marketing of CD Diagnostics’ Synovasure Lateral Flow test kit for the detection of joint replacement infection, making this the first FDA-authorized diagnostic that helps determine whether the inflammation around a prosthetic joint is due to an infection or another cause. Specifically, the test is designed to help healthcare providers evaluate patients for revision surgery, a procedure to replace or compensate for a failed joint implant. Physicians typically evaluate for potential infections using X-ray images or laboratory analysis of joint fluid, the latter of which can take days to produce results. The Synovasure Lateral Flow test kit, in contrast, provides results in approximately 10 minutes by detecting proteins in patients’ synovial fluid called human alpha defensins. These antimicrobial proteins are released by activated neutrophils in response to infection. The test is not intended, however, to identify a specific type of infection.

FDA reviewed the Synovasure Lateral Flow test kit through the de novo premarket review pathway. For this review, the agency looked at data from a clinical study that analyzed 305 prospective synovial fluid samples collected from individuals who had total knee or hip joint replacements and who were being evaluated for revision surgery. The study showed that, among subjects with an infection diagnosis based on standard of care criteria, the Synovasure Lateral Flow test kit identified 89.5% as positive for alpha defensins.
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software update to these analyzers may help reduce the risk of inaccurate results. FDA has not yet evaluated this software, though, and is working with the company to determine whether the software update alone will solve this problem.

WHO APPROVES ABBOTT’S POINT-OF-CARE HIV VIRAL LOAD TEST

Abbott has received World Health Organization (WHO) prequalification approval for the m-PIMA HIV-1/2 VL, a point-of-care test for HIV viral load. WHO recommends that all HIV patients receiving antiretroviral therapy (ART) undergo a viral load test—the gold standard for monitoring ART treatment failure—at 6 months and 12 months, and then annually thereafter if the individual is stable on ART. However, in certain resource-limited countries in sub-Saharan Africa, Asia, and Latin America, very few people have access to viral load testing. Abbott’s m-PIMA HIV-1/2 VL is designed to increase the availability of this testing in these areas. As a quantitative nucleic acid amplification test, it measures viral load for HIV type 1 groups M/N and O, and HIV type 2 in plasma samples. It is also designed to deliver results in under 70 minutes while the patient is still present. This quick turnaround time should be particularly valuable for monitoring the viral load of HIV-positive pregnant women, according to Abbott.

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FDA CLEARANCE, CE MARK GRANTED TO DIASORIN TESTS FOR VZV, HSV

DiaSorin Molecular has received Food and Drug Administration clearance for its Simplexa VZV Direct assay and has received CE marking for its Simplexa HSV 1/2 & VZV Universal Direct assay. Both of these tests are designed to run on DiaSorin’s Molecular Liaison MDx instrument. The Simplexa VZV Direct detects the polymerase gene of the varicella-zoster virus (VZV) and aids in the diagnosis of both meningitis and encephalitis caused by VZV. The test uses 50 μL of cerebrospinal fluid (CSF) and has a greater than 98% agreement with polymerase chain reaction/bidirectional sequencing for VZV in CSF samples. Meanwhile, the Simplexa HSV 1/2 & VZV Universal Direct assay detects and differentiates between herpes simplex virus (HSV)-1, HSV-2, and VZV DNA from cutaneous and mucocutaneous swab specimens. This test also demonstrated a greater than 98% agreement with another CE-marked nucleic acid amplification test.
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Overdiagnosis: An Unintended Side Effect of Diagnostic Testing
An interview with: H. Gilbert Welch, MD, MPH

Could you share an example of a poor patient outcome due to a lab-related overdiagnosis?
I’ll share an example that I include in Overdiagnosed. I was managing ulcerative colitis in a 74-year-old man. One day his routine lab tests showed that he had elevated blood glucose. It wasn’t that high, but it prompted more testing and ultimately the testing confirmed the diagnosis of diabetes. He had no symptoms, but this was during the period when we were getting much more aggressive about treating type 2 diabetes, and I started him on the sulfonylurea drug, Glyburide. Six months later he blacked out while driving on the interstate and his car went off the road. Paramedics on the scene measured his blood sugar and it was extremely low due to this medication. He had a long recovery from the accident. I took him off Glyburide, and he lived 2 more decades without any symptoms or complications from diabetes.

How did you first come to think about the issue of overdiagnosis?
There’s no single answer to this question. I could credit my mother; she was a hospital trustee at Boulder Community Hospital, and I remember her asking hard questions about the medical profession. Did our town really need another CT scanner? Did the orthopedic surgeons really need a laminar flow room? These kinds of questions about medical technology were common in our household.

I also could credit my internal medicine residency training at the University of Utah, where I saw well people become patients because of small abnormalities on scans that led to further testing and sometimes complications. Finally, I should credit William Black, MD, a radiologist who taught me the basic conundrum of early detection, that whenever we look harder for a disease, we find more, and the typical patient appears to do better.

You’ve mentioned that it is important to consider how well a screening test has been studied, and that we need to educate patients accordingly. Would you walk us through examples of these considerations?
Yes, it is important to carefully evaluate the available evidence for how a test performs and the benefit and harms of our likely response, i.e. the subsequent interventions based on the test. Given the evidence, you might decide it’s a slam dunk—something where everyone would look at the data and say, yeah, that’s a good thing to do. Or you might decide it’s a close call, which happens when different people look at the data and make different decisions depending on how they value things. Just to give you two examples, lowering really, really high blood pressure is a slam dunk, as is taking a statin post-heart attack. There are big benefits from these interventions and the harms are relatively small.

When I make the statement, in general, cancer screening is a close call, I know some people will think, this guy is extreme. Sometimes we have a lot of evidence, as is the case for screening mammography. More than half a million women have participated in randomized trials but the evidence of benefit for this test is mixed. A few probably benefit, but many more are harmed. The benefits and harms are different; they’re apples and oranges. The benefit—avoiding a breast cancer death—is extremely important but also extremely rare.

The harm of false alarms—false-positive results leading to a cascade of subsequent testing and anxiety—is less important but extremely common. The harm of overdiagnosis—being treated for a disease that was never destined to bother you—is less common but clearly more common than the benefit.

Different people can look at these data and come to different conclusions because it is all about how you value the various outcomes. One person might decide, I want to do everything I can to avoid a cancer death, and I accept the additional
Cancer screening involves value judgments. Are these types of discussions being had with patients?

basically just associations based on biomarkers looking at which combination best discriminates healthy individuals from diseased ones. It is important that these assays be re-validated with a different population of patients, independent from the company that developed the tests.

What are the key drivers of overdiagnosis? How would you rank these in terms of influence?

A test must have analytical validity, that it measures what it claims to measure (precision, accuracy, sensitivity). The second criteria is clinical utility: Is there good evidence for what should be done with a positive or negative result? Absent such proof, providers should be inherently skeptical and treat the patient, not the lab abnormality.

Tests that offer risk ratios or scores based on mathematical modeling are basically just associations based on biomarkers looking at which combination best discriminates healthy individuals from diseased ones. It is important that these assays be re-validated with a different population of patients, independent from the company that developed the tests.

What are the key drivers of overdiagnosis? How would you rank these in terms of influence?

There is a complex web at work, but the two most important forces are true belief and money. True believers think that early detection can only help, i.e. that it has no harms, and that too much screening is impossible. Then there’s the money—whether for pharma or device manufacturers, or increasingly, our hospitals. The easiest way to make money is to expand indications and recruit new patients. Screening and early detection are great ways to do this.

Many patients are true believers. They ask for more testing because we have trained them to believe the path to health is through testing. But we have to ask ourselves some hard questions: Is looking hard for things to be wrong good for a healthcare system? Or does it simply make the population more anxious (the “worried well”) and distract them from activities more important to their health, like eating healthy food, moving regularly, and finding purpose in life?

We also need to consider survivor stories. Patients who become really strong advocates and organize into advocacy groups are particularly misleading. I wish I could say that most survivors were actually helped by screening, but too many patients are actually helped by the screening.

What are a few specific ways that laboratorians can help reduce the overdiagnosis dilemma? Could you share an example of an intervention that was successful in reducing overdiagnosis related to lab testing?

I want to leave this last challenge to your readers. I will say that the first step is recognizing and then highlighting the problem. It is important to shine a light, and sometimes it really does make a difference. Be inherently skeptical when new tests come to market and think about the population on which the test is likely to be used. Don’t simply focus on the few who might be helped; think about what happens to everyone else.

Jane Dickerson, PhD, DABCC, is clinical associate professor at the University of Washington and co-director for clinical chemistry at Seattle Children’s Hospital in Seattle.

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As the direct-to-consumer (DTC) sector of the laboratory industry has exploded, advocates have asserted that these tests remove potential barriers in our traditional healthcare system and increase access to important health information while boosting both convenience and privacy. Consumers now have access to a wide range of tests without a physician’s order, including sexually transmitted infection and allergy screening, and assessments of cholesterol, vitamin D, and nutritional deficiencies.

DTC genetic testing has received the greatest share of attention in popular media and may be the most appealing to average consumers. Available testing ranges from identifying individuals’ ancestry and familial relationships to elucidating certain genetic traits along with wellness and genetic disease risk factors. Some genetic testing results may be benign—“likely to dislike cilantro.” However, many DTC tests report variants for which little evidence exists to support association with a trait or health condition, such as a DCDC2 gene polymorphism and reading ability. At the other end of the spectrum DTC testing for conditions with strong evidence to support phenotype-genotype relationship and evidence-based guidelines also raises concerns. In the case of BRCA1- and BRCA2-related cancers, these tests may change medical management and have resulted in de facto population-based screening.

Some DTC laboratories provide consumers with raw data files of genomic variant information that has not been validated or subjected to quality protocols. While the laboratories will often include a disclaimer that the data is for informational purposes only, consumers increasingly are sharing this raw data with third-party online interpretation tools. Some studies have found that around half of the results provided through these raw data interpretation services are inaccurate, in which a positive result is not confirmed through clinical testing. Similar problems may exist in other areas of DTC testing.

Guidance from regulatory bodies provides little clarity. For instance, the Food and Drug Administration (FDA)-approved 23andMe Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants) includes labelling that recommends “…prior to making any medical decisions, confirmatory clinical testing should be performed.” However, 23andMe operates a CLIA-certified laboratory, so it is not clear what differentiates clinical testing in this context, aside from being ordered by a physician.

Some have argued that at-home collection kits used by DTC companies do not adhere to chain-of-custody requirements that are upheld in clinical testing environments to ensure that results belong to the listed individual. However, many traditional clinical laboratories, particularly in the genetic testing realm, also provide at-home buccal or saliva collection kits which don’t require identity confirmation. Although CLIA certification, accreditation by the College of American Pathologists (CAP) or other entity, as well as FDA approval and ISO certification are important benchmarks, gaps remain in our current system that put quality and patient safety at risk.
Implications for Healthcare Providers

Clinicians face the challenge of navigating alongside their patients the shifting landscape of DTC testing, especially when DTC test reports yield unanticipated and sometimes anxiety-provoking findings. Indeed, healthcare providers may feel stuck sorting out a mess they had no part in creating.

Clinicians also need to determine when and how to incorporate test results into medical management decisions for their patients. Similarly, they need to decide when, if ever, a DTC test report should be included in a patient’s medical record if the DTC company does not have solid specimen collection and chain-of-custody procedures. Providers also discern when it is appropriate to repeat a test to clinically confirm or refute a DTC test result.

Clinicians without specialized training are left deciding which clinical laboratory to send follow-up testing to, sometimes relying on their experience in other areas of testing or the laboratory’s reputation. Given that CLIA certification and CAP accreditation are not always sufficient differentiators, they would benefit from trusted colleagues in clinical genetics or laboratory medicine to provide guidance under a laboratory stewardship program.

The Impact on the Healthcare System

Time will tell how DTC testing will shape healthcare policy. Societal and individual costs for healthcare are at an all-time high, and both policymakers and providers wish to move away from disease management toward preventive healthcare. This environment makes the availability of low-cost and easily accessible health information enticing. But for consumers who are anxious and confused about their reports, or whose results suggest a real medical problem, the path forward may be costly.

Clinicians presented with DTC results may feel compelled by ethical or medicolegal considerations to offer confirmatory studies and subsequent medical follow-up, but there are concerns about who should pay, particularly in asymptomatic patients without clear medical indications for such interventions. Many observers have celebrated recent announcements that some insurers may pay to have DTC testing confirmed through a clinical laboratory. However, it remains unclear and warrants investigation as to whether a DTC testing approach truly meets the goal of engaging patients in their own health and wellness, thereby improving health outcomes and decreasing the cost of healthcare across the population.

Given the popularity and growth of consumer-driven medical testing, the time is now for the field of laboratory medicine to act on these ethical problems and regulatory gaps. We need to clarify the quality standards of DTC labs and to increase transparency so that consumers, healthcare providers, and insurers alike all will better understand these differences.

Continued line-blurring between DTC and clinical testing risks undermining the value and legitimacy of the entire field of laboratory medicine at a time when the promise of diagnostics to improve health is greater than ever.

References


Jacquelyn Riley, MS, LGC, is a genetic counselor in the molecular pathology lab at Cleveland Clinic in Ohio and participates in the organization’s laboratory stewardship committee to promote best practices for use of genetic testing.

Katie Stoll, MS, CGC, is a genetic counselor and executive director of Genetic Support Foundation in Olympia, Washington.

An Average Kid

By Katie Stoll, MS, CGC

Many medical organizations agree that patients and providers should exercise extra caution when considering genetic testing on children. In most cases, guidelines recommend that genetic testing only be performed when the results would affect current medical management and otherwise should be deferred to preserve a child’s autonomy and privacy.

I ordered a childhood direct-to-consumer (DTC) test to see firsthand as a trained genetic counselor what information the testing company included for caregivers who might be considering having their children’s DNA tested with the promise to “know your child even better” and receive information about their fitness and language abilities. The glossy DTC kit contained a swab and postcard requesting only a name, phone number, and email address. There was no further information about or consent for the test.

I decided to swab the cheek of our family dog, Ginger. As Ginger doesn’t have the best oral hygiene, the swab looked as though I had run it through a pile of dirt. To my surprise the CLIA-certified lab that processed the specimen did not flag Ginger’s sample as out of the ordinary. I received an email with a link to her test report a few weeks later. Ginger’s results suggested that she was an average kid.

I considered the possibility that a canine sample could have produced at least some of the polymorphisms the laboratory used in its panel. So, I sent in a blank specimen, only running the swab under the tap water of my kitchen sink. The tap water analysis varied slightly from Ginger’s result, but again the lab found nothing amiss. It was disheartening that the report was signed out by a laboratory director who is a geneticist with a doctorate. While both my dog and tap water might be average, it’s clear that this DTC lab offers below average performance.
Questioning Quality Assurance in Clinical Mass Spectrometry

Some laboratories struggle to implement best quality control practices
Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is not a panacea for inaccurate patient testing. While few laboratorians would disagree with this statement, many of us fall into the trap of thinking that LC-MS/MS results are inherently more reliable than those obtained by immunoassays. In reality, LC-MS/MS offers a range of sophisticated options for detecting and resolving potentially inaccurate results. This opportunity comes in large part from the wealth of analytical metadata—ion ratios, internal standard recoveries, and other quality assessment data—available for each patient result.

Are clinical laboratories using this metadata in their quality assurance (QA) programs? If so, which aspects of metadata do they utilize, and what alert mechanisms do they employ to warn of potentially erroneous results? These were the questions we sought to answer through a web-based survey that asked clinical laboratories worldwide what QA metrics they apply to 25-hydroxy vitamin D LC-MS/MS results.

A total of 50 respondents answered the survey, and the results yielded insight into how clinical laboratories are using LC-MS/MS metadata in their QA programs.

How Do Laboratories Define Acceptable Internal Standard Recovery?

Commonly used ionization strategies for LC-MS/MS assays are susceptible to ionization suppression and ionization enhancement, or matrix effect. This variability in ionization can lead to disproportional ion counts within individual samples compared with the average ion counts of the calibrators, resulting in quantification errors (1).

Including co-eluting internal standards helps to mitigate the inaccuracies introduced by these matrix effects. In addition, internal standards help normalize against differential losses that occur during the often multistep procedures used for sample preparation. Finally, monitoring the recovery of internal standards identifies signal variance caused by mis-injection of extracted sample by the LC-MS/MS instrumentation.

Perhaps not surprisingly then, most but not all laboratories (94%) reported monitoring recovery of internal standard peak areas. Respondents’ strategies and criteria for assessing internal standard recovery, though, varied substantially.

Labs calculate internal standard recoveries by dividing the internal standard peak area for each patient sample by some defined reference internal standard peak area. This defined reference internal standard peak area can be a static value determined during method validation, an approach 36% of laboratories reported taking. In contrast, 58% of laboratories reported calculating the defined reference internal standard peak area for each batch using the average of internal standard peak areas of calibrators and/or quality control and/or patient samples.

Defining acceptability criteria by batch is less stringent, allowing for typical batch-to-batch variations in internal standard recovery that may have no effect on quantitation. However, a simple batch-to-batch strategy would not identify systemic issues that develop over time and...
might negatively impact method performance.

Our survey found further differences among laboratories about what they considered acceptable variations in the internal standard recovery areas. Most laboratories set acceptable variation using a fixed percent recovery, which ranged from 10% to 200% of their defined reference. Others used standard deviations derived from the defined reference (22%). While internal standards effectively normalize results to compensate for matrix effects and process variance, laboratories must be careful, as excessively low recovery of the internal standard can lead to unreliable quantitation (2).

Furthermore, researchers have described differences between matrix effect for an analyte and its co-eluting internal standard (5). This phenomenon indicates that merely including an internal standard for each analyte is no substitute for robust method development and method validation.

How Many Ion Ratios Are Monitored and What Are the Acceptability Criteria?

While not necessary for quantitation, LC-MS/MS allows for the acquisition of multiple transitions for each analyte and calculation of ion ratios. To calculate an ion ratio, laboratorians divide the peak area of one transition by the peak area of a second transition.

By convention, the less intense transition, often called the qualifier, is typically the numerator while the more intense transition, the quantifier, is the denominator. If the ion ratio obtained from a patient sample differs substantially from the expected ratio, an interference may be present.

Use of ion ratios has been shown to reduce the likelihood of reporting inaccurate results due to interferences (3). However, 26% of laboratories in our survey reported that they do not monitor ion ratios. It should be noted that many respondents reported using a derivatization approach that precluded inclusion of a second transition in the method.

Within the majority of laboratories that did report monitoring ion ratios, there was substantial heterogeneity around both how they determined the expected ratio and how they defined acceptable deviation from this ratio. Among our respondents, 32% reported defining the expected ion ratios during method validation, while 34% said they do so for each batch of patient samples. Labs have several options for defining this ratio—analyzing calibrators, quality control samples, patient samples, or any combination of the preceding—and our respondents indicated that they use multiple combinations. Within this range of possibilities, the most popular in our survey was the combination of calibrators and quality control samples.

At a more granular level, what laboratories defined as an acceptable variation from the expected ratio ranged greatly. Most respondents cited

![Differences in How Clinical Laboratories Approach Quality Control](image)
20% but others reported variations as low as 10% to as high as 40%.

LC-MS/MS metadata tell us a great deal about the accuracy of patient results if this data is used as part of a well-defined QA program. Using metadata in this way requires both clear knowledge of which metrics should be monitored and how metric acceptability criteria should be defined. It also requires the tools to apply the metrics and acceptability criteria to each patient sample result during production.

The heterogeneity noted in this survey suggests that clinical laboratories need additional, more granular guidance on which metrics they should monitor and how they should define acceptability criteria. Furthermore, many laboratories noted challenges in knowing what corrective actions to take when certain metrics failed. For example, if the internal standard recoveries are consistently low even on re-injection of an extracted sample, what is the appropriate course of action? Certainly laboratories would welcome guidance based on clinical laboratory production experience that deals with these questions.

As for applying these metrics, respondents consistently identified limitations in vendor-provided software as a challenge to using metadata as a QA metric in routine practice. Consistent with this observation, almost half (46%) of respondents reported relying on manual application of QA metrics to patient samples. The vast quantity of metadata available, in addition to the high volumes of patient samples that laboratories are typically processing, requires sophisticated automation approaches for applying metrics and acceptability criteria. While this survey focused on 25-hydroxy vitamin D, more than half our respondents stated that the QA practices they described were similar for other methods implemented in their laboratories. This suggests that the lack of standardization observed here for applying metadata is endemic in clinical LC-MS/MS assays.

A previous CLN article observed a similar outcome using queries of a large database (4). Closing the gap with additional best practice guidance, better software applications, and more sophisticated regulation seems a worthwhile goal for clinical MS.

Joshua Hayden, PhD, DABCC, FAACC, is chief of chemistry at Norton Healthcare in Louisville, Kentucky.

Lorin Bachmann, PhD, DABCC, FAACC, is an associate professor of pathology, co-director of clinical chemistry, and co-director of point-of-care testing at Virginia Commonwealth University Health in Richmond, Va.

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The opioid epidemic is a serious global crisis affecting public health as well as social and economic welfare. Fentanyl abuse, misuse and diversion is a major contributor to this crisis.

Fentanyl is a potent synthetic opioid used in pain management, that can produce euphoric effects with rapid onset but short duration. While it is a useful prescription pain medication, it is also made illegally and used recreationally, often with heroin and cocaine.

Fentanyl is metabolized to norfentanyl and other metabolites. About 90% of the dose is excreted in urine as norfentanyl, while parent fentanyl accounts for less than 7%. Detection of both parent and this major metabolite is essential to determine fentanyl use and is an integral part of combating the opioid epidemic.

ARK Diagnostics, Inc. now offers an FDA 510(k) cleared, CE-marked immunoassay that detects fentanyl in urine.

- Exceptional analytical sensitivity at a 1ng/mL cutoff level
- Detection of both the parent and major metabolite to identify more true positives
- Crossreactivity to norfentanyl extends the window of detection
- Liquid, ready-to-use convenience improves lab efficiency
- Three suitable kit sizes for low, moderate and high volume laboratories
- Application protocols for most general chemistry analyzers

If your fentanyl assay is not detecting norfentanyl...

True positive samples could be slipping through your fingers.

If your fentanyl assay does not detect the major compounds that are present in urine, your facility may already be losing the fight against fentanyl abuse.
Clinical Laboratory Markets in U.S., Canada to Surpass the $100 Billion Mark by 2022

The $78.34 billion U.S. clinical laboratory market is expected to grow to $91.31 billion by 2022, according to a new report by the research and consulting firm Frost & Sullivan. A number of factors are driving this growth, one of which is strong merger and acquisition activity and related service integrations. Another contributor is the trend of laboratories expanding their revenue streams, in response to the Protecting Access to Medicare Act’s reimbursement cuts, by collaborating with retail clinics and e-commerce channels to gain access to new customers. The report, titled “Growth Opportunities in the North American Clinical Laboratory Services Market, Forecast to 2022,” also predicts that the Canadian clinical laboratory market will grow to $13.30 billion by 2022, bolstered by funding from the Canadian Ministry of Health. Frost & Sullivan based these projections on an analysis of hospital-based laboratories, independent laboratories, physician office labs, and other labs throughout the U.S. and Canada.

As clinical laboratories navigate the changing diagnostic marketplace, the report also recommends that they take advantage of growth opportunities presented by the following trends: consumer preference for higher deductible plans, which could particularly benefit small laboratories where patients purchase services themselves; the increasing demand for integrated diagnostic services combining imaging and genomic data; and alternate business models such as direct-to-consumer testing.

TAKE2 LICENSES TECH FOR EARLY DETECTION OF NASOPHARYNGEAL CANCER FROM GRAIL

Take2 Health, a healthcare technology company based in Hong Kong, has received exclusive worldwide rights from Grail to a circulating DNA-based method for the early detection of nasopharyngeal cancer (NPC). Take2 was co-founded by Dennis Lo, MD, PhD, Rossa Chiu, MBBS, PhD, and Allen Chan, PhD, who are professors at the Chinese University of Hong Kong. Lo and his team developed the NPC early detection technology that this agreement covers, but they had licensed the technology to Grail prior to launching Take2. Overall, Take2 aims to make disruptive healthcare inventions widely accessible to the public in China and Asia. The company will initially focus on developing and commercializing technologies for screening early asymptomatic NPC due to the condition’s high prevalence in China and Southeast Asia, as well as the fact that the majority of NPC cases are currently diagnosed at late stages.

INSTITUT CURIE, PREDI LIFE COLLABORATE TO OFFER BREAST CANCER RISK TEST

The Paris-based company PrediLife has partnered with the Institut Curie to launch the breast cancer risk test MammoRisk. MammoRisk is designed to complement mammograms and predicts the risk of breast cancer by taking into account five factors: a patient’s age, breast density, family history, breast biopsy history, and a polygenic score. The score is calculated by analyzing hundreds of thousands of genetic polymorphisms, certain combinations of which have a major impact on the risk of breast cancer. Under the terms of this collaboration, the Institut Curie will perform the genetic analyses incorporated in the MammoRisk score. The institute and PrediLife will also study approximately 100 polymorphisms associated with a higher risk of breast cancer and will eventually pursue research projects that leverage the breast cancer expertise of the Institut Curie as well as PrediLife’s experience developing and marketing tests.

MERIDIAN BIOSCIENCES TO BUY MOLECULAR DIAGNOSTICS COMPANY GENEPOC

Meridian Biosciences has signed an agreement to acquire GenePOC, a Canadian molecular diagnostics provider, by the end of 2019. With this acquisition, Meridian will get GenePOC’s revogene molecular diagnostics platform, which currently features three Food and Drug Administration-cleared assays for *Clostridium difficile*, group A *Streptococcus*, and group B *Streptococcus*. Assays for these infectious diseases comprise the majority of Meridian’s current total molecular diagnostics sales, and this acquisition will enable Meridian to immediately offer the revogene platform to existing customers who are seeking better
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Automation doesn’t have to be BIG to be effective

INDIVUMED, GNOSIS DATA ANALYSIS PARTNER ON MULTIOMICS CANCER LIBRARY

Indivumed has joined forces with Gnosis Data Analysis to advance personalized cancer healthcare. Specifically, the partners plan to use Gnosis’ machine learning technologies to enhance IndiviType, Indivumed’s multiomics cancer library, with the ultimate goal of generating insights that would not be possible with a single-omics approach to cancer research. IndiviType is a knowledge and discovery platform that contains genomics, transcriptomics, proteomics, phosphor-proteomics, and immune-phenotyping imaging information together with clinical and outcome data. Over the course of 15 years, Indivumed worked with leading healthcare institutions around the world to collect and curate high-quality cancer biospecimens in order to create this database. When IndiviType is coupled with Gnosis’ data analytics capabilities, the partners believe the platform will provide deep insights into the underlying mechanisms of cancer that can then be translated into innovative drugs and molecular diagnostics.

EUROFINS TO PROVIDE TESTING FOR CLINICAL TRIAL OF ALCOHOL USE DISORDER TREATMENT

Eurofins Scientific has teamed with Adial Pharmaceuticals to provide genetic testing during Adial’s phase three clinical trial for AD04, a genetically targeted therapeutic agent designed to treat alcohol use disorder without the requirement of abstinence. Under the terms of the agreement, Eurofins will first validate a companion diagnostic that it developed for AD04 that uses quantitative polymerase chain reaction. Eurofins will then use this diagnostic to test potential subjects prior to their enrollment in the clinical trial for a genetic marker indicating whether they are expected to respond to AD04 treatment. Only patients who are positive for this marker will go on to be enrolled in the trial. “[Genetically prescreening patients prior to enrollment] is expected to dramatically enhance the efficacy rates of AD04 in the trial and reduce the time and cost needed to conduct the trial,” said William Stilley, president and CEO of Adial Pharmaceuticals.
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Following up on Positive Newborn Screening Results

What disorders do newborn screening programs typically include?

A: While there are no universal criteria for selecting disorders for newborn screening programs, there is consensus that included disorders should have a relatively high frequency in the general population, a well-defined natural history, and high mortality and morbidity rates when left untreated. Importantly, effective treatments and tests for these disorders should also be available.

The number of disorders screened varies from state to state and also between countries. Newborn screening programs in the U.S. tend to screen for the 61 conditions that are currently on the Recommended Uniform Screening Panel developed by the Health Resources and Services Administration. Out of these 61 conditions, 49 are metabolic disorders, and 12 are other types of disorders, including two (critical congenital heart disease and hearing loss) that are not screened for with clinical laboratory tests. Most of the metabolic disorders are classed as organic acidurias, amino acid disorders, and fatty acid oxidation defects.

What does the process of newborn screening and follow-up entail?

Newborn screening is usually a state-mandated program that various federal and professional bodies guide. It is not just a laboratory test but a complete process that begins with sample collection, transportation, and laboratory testing, and then proceeds to results notification, patient treatment and education, and finally, the evaluation of the patient’s long-term outcome.

To start, healthcare providers collect a heel-prick blood sample on filter paper from an infant and send it to a screening laboratory for testing—which for metabolic disorders is primarily done with tandem mass spectrometry. After testing, the lab then categorizes results as either low or high risk. For low-risk cases, the newborn screening laboratory generally contacts the primary care provider to collect an additional sample for repeat testing. For high-risk cases, in addition to contacting the primary care provider, the lab also notifies a specified genetic center with specialized care providers for immediate follow-up. Either the primary care provider or genetic center then contacts the patient for clinical evaluation and additional laboratory testing for confirmation of screen-positive results. This needs to be done in a timely manner, as most metabolic disorders require immediate patient management and treatment. Lastly, to close the circuit, the newborn screening laboratory is notified, usually by the genetic center, of confirmation results for quality control and assurance.

What are the challenges of following up on newborn screen positive results?

Coordinating a patient’s clinical evaluation and follow-up testing for result confirmation can be challenging due to the limited availability of specialized healthcare providers and laboratories, particularly for patients living in remote areas. This may delay the initial management and treatment of an infant with a serious disorder. Some confirmation tests also require a large volume of either blood or another sample type such as urine, cerebrospinal fluid, or fibroblasts, all of which are difficult to collect in newborns. Additionally, almost all of the methods used in the confirmation of metabolic disorders are laboratory-developed tests. This leads to significant variation in results from different labs.

As newborn screening programs continue to advance, these challenges should be kept in mind and addressed so that all newborns benefit from prompt and proper follow-up of screen-positive results.

Dr. Garg will delve further into this topic during two roundtable talks (session numbers 42112 and 52212) at the 71st AACC Annual Scientific Meeting on Monday, August 5 at the Anaheim Convention Center in California.

Utta Garg, PhD, DABCC, FAACC, is director of the division of laboratory medicine and professor of pediatric pathology at Children’s Mercy Hospital and University of Missouri School of Medicine in Kansas City. +EMAIL: ugarg@cmh.edu
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