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Results of a SDNA Test for Colorectal Cancer Screening Unaffected by Medications, Lifestyle Factors

The only clinical variable that influences test results of a multimarker stool DNA (SDNA) test for colorectal cancer (CRC) is age, according to a study presented at the American Association for Cancer Research annual meeting (Chicago; March 31 to April 4). The findings suggest patients do not have to adjust their diet, lifestyle, or medication regimens for this test, a potential boon for testing compliance as commercialization plans for the test are contemplated.

Obesity, tobacco and alcohol consumption, analgesic use, sex, race, and family or personal CRC or polyp history did not affect the levels of the four methylation markers studied. The only patient characteristic that significantly influenced all methylated marker levels was age, with the greatest effects on TFPI2 followed by vimentin, NDRG4, and BMP3 least affected by age.

These findings are important as Exact Sciences (Madison, Wis.) begins planning for the anticipated commercialization of the test in 2014. For more on this multimarker SDNA test and other advances in molecular stool testing, please see the Special Focus section on page 8. G2

Labs to Report Incidental Sequencing Findings

Simply ignoring secondary findings of medical importance found when using sequencing technology for either clinical or research purposes is not a viable ongoing strategy, experts say. The need to establish policies dealing with the return of results has grown with the proliferation of whole-genome sequencing and is highlighted in recommendations emerging from several organizations.

The looming practical and ethical questions for reporting of results centers on secondary findings. Secondary findings are incidental, but potentially meaningful, findings of genetic mutations, unrelated to the initial reason for undergoing sequencing in either the clinical diagnostic or research realm.

At the annual meeting of the American College of Medical Genetics and Genomics (ACMG) (Charlotte, N.C.; March 27-31) an ACMG work group released a draft of a new policy statement related to reporting secondary findings resulting from clinical whole-genome sequencing. The group is considering recommendations that encourage clinical laboratories to only analyze a limited number of high-penetrance mutations or gene variants from treatable conditions when conducting whole-genome or whole-exome sequencing. Examples of condi-

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▲ **Labs to Report Incidental Sequencing Findings,** *from page 1*

tions included in such a list would be inherited cancer syndromes, familial hypercholesteremia, and Fabry. Such a list, the working group proposes, would need annual updating. Even with limitations on sequencing to mutations of known clinical relevance, the group acknowledges many questions surrounding reporting remain, including the appropriate time to disclose a child's genetic information about disease predispositions that won't affect them until adulthood, the implications of results for other family members, and a patient's right to not know what is in their genes.

> ***Biobanks need to "shoulder significant responsibility" for addressing how to deal with incidental findings.***
>
> ***—Susan Wolf, et al.***

Consequently, the ACMG group charges that molecular laboratories conducting whole-genome or whole-exome sequencing have a responsibility to have clear, transparent, and stated policies in place regarding analysis and return of secondary findings.

At nearly the same time a working group funded by the National Institutes of Health released a consensus statement addressing the handling of secondary findings of whole-genome sequencing in a research setting, which was published online March 21 in *Genetics in Medicine*. The 26 researchers say that biobanks need to play a major role in setting up a system to handle secondary findings, whether the findings are discovered at the sample collecting site or elsewhere through sharing of research samples and data. If the biobank, a biorepository or database, is designed so that specimen donors are identifiable, the authors maintain, findings that are analytically valid and reveal an established risk of a serious but clinically actionable health condition should be communicated back to the participant. Currently though, less than half of U.S. biobanks return results to participants, according to a study done for the working group by Mao Thao, a doctoral student at the University of Minnesota.

The researchers, led by Susan Wolf, the McKnight Presidential Professor of Law, Medicine and Public Policy at the University of Minnesota, conclude that biobanks need to "shoulder significant responsibility" for addressing how to deal with incidental findings, including clarifying the criteria for evaluating findings and the roster of returnable findings. Additionally, the biobanks need to reidentify and recontact the original contributor regarding findings that are analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable.

Skeptics though say given that reanalysis will likely be conducted over time, possibly years after the original sample was collected, recontacting patients or research participants is a potential minefield that could prove costly and pose ethical and legal difficulties. Additionally, reporting secondary results poses a challenge for primary care doctors and patients who may have difficulty interpreting the results.

Computerized Access to Patient Test Results Reduces Lab Volumes

The sharing of patient information including lab test results between health care providers through health information exchanges (HIEs) reduces the volume of laboratory testing, according to a study published March 26 in the *Archives of Internal Medicine*. While more widespread adoption of HIEs is expected, the resulting anticipated decrease in testing volumes may not be bad news for laboratories' bottom line, experts say.

The reduction in laboratory test volumes for redundant tests may be as high as 50 percent, the findings suggest. The researchers conducted a retrospective study in which they analyzed the number of laboratory tests ordered at one hospital within a week of an outpatient encounter at the other participating hospital. The two tertiary care hospitals implemented an HIE in 2000. The researchers identified 346 cases in which recent off-site tests were available from the "other" hospital with 44 of these occurring in 1999 before the HIE implementation and the remaining cases occurring from 2001 to 2004. The study did not specifically identify the tests most likely to be reduced. Alexander Turchin, M.D., a co-author of the study, tells *DTTR* that he suspects the real reduction in test ordering may be higher in cases where a community hospital is referring patients to a referral hospital.

The researchers say their findings demonstrate empirical evidence supporting the notion of the cost savings in the HIE model, particularly when patients receive care at multiple institutions. But reduction in volume of duplicate testing may not be all bad news for laboratories.

"As laboratories enter the era of bundled payments and there is a shift in reimbursements, this may be beneficial for a lab in an integrated health care delivery system," says Turchin, director of informatics research in the division of endocrinology at Brigham and Women's Hospital (Boston), one of the participating hospitals. "In reducing duplicate testing to improve overall reimbursement, everybody wins, but integration is critical for systemwide benefit."

Tumor Heterogeneity Complicates Personalized Medicine

A single tumor-biopsy specimen reveals only a minority of the genetic abnormalities that are present in an entire tumor, according to a study published online March 8 in the *New England Journal of Medicine*. Given the implications that tumor heterogeneity can have on therapeutic success or failure, experts say there must be a shift in sampling strategies away from single biopsy samples toward routine biopsies of both primary tumor and metastasis sites.

The researchers used whole-exome sequencing, single-nucleotide polymorphism array analysis, and mRNA expression profiling to study multiple spatially separated biopsy samples from both primary and metastatic tumor sites from four consecutive patients with advanced renal-cell carcinoma. Intratumor heterogeneity was found in every tumor, with spatially separated mutations significant enough to lead to phenotypic intratumor diversity. Mutations uncovered by a single biopsy did not represent the "mutational landscape" of the entire tumor mass. Roughly two-thirds of mutations were not detectable in every sequenced region. Any single biopsy from Patient 1 found on average only 55 percent of the mutations present in the whole tumor.

"We found that genetically defined subclones were spatially separated and not intermixed, indicating physical barriers in solid tumors. This is a major hurdle for the comprehensive genetic profiling of these cancers,"said lead author Marco Gerlinger, M.D., of the Cancer Research UK London Research Institute.

The researchers used intratumoral expression of 110 genes to create a prognostic signature. The researchers found both favorable and unfavorable prognosis profiles in different regions of the same tumor, concluding that gene-expression signatures may not correctly

predict outcomes if they are assessed from a single region of a heterogeneous tumor.

"We need to think about new sampling strategies to identify minority populations which carry mutations conferring drug resistance," Gerlinger tells *DTTR*. "Current personalized cancer medicine approaches often rely entirely on biopsies from primary tumors to predict drug sensitivity or prognosis. Routine biopsies of primary tumor and metastatic sites may be a reasonable first step to reveal a more representative genomic landscape of heterogeneous tumors."

While more research is needed to test the generalizability of these findings on other solid tumors, evidence shows that pancreatic cancers and triple-negative breast cancers are also heterogenous.

In an accompanying editorial Dan L. Longo, M.D., former scientific director for the National Institute on Aging's Intramural Research Program, says these findings should serve as a douse of cold water on the "overoptimism" in the field of personalized medicine.

"A serious flaw in the imagined future of oncology is its underestimation of tumor heterogeneity—not just heterogeneity between tumors, which is a central feature of the new image of personalized medicine, but heterogeneity within an individual tumor," writes Longo. "The simple view of directing therapy on the basis of genetic tumor markers is probably too simple." G2

IOM Lays Out Process to Improve Omics Translation

In an attempt to rectify some of the systematic weaknesses that contributed to the use of flawed gene expression tests in cancer trials at Duke University (Durham, N.C.) several years ago, the Institute of Medicine (IOM) has released guidelines titled *Evolution of Translational Omics: Lessons Learned and the Path Forward* with the aim of strengthening omics-based test development and evaluation to ensure scientific validity before they are used to guide patient treatment in clinical trial.

Citing a lack of independent verification at key steps along the development pathway as one of the problems that permitted "inappropriate" enrollment of patients in clinical trials, IOM's guidelines seek to establish a pathway to ensure safe translational research as well as encourage shared oversight responsibility by funding entities, academic institutions, and journal editors.

In the discovery phase, the IOM committee recommends that all information needed to verify the test should be disclosed through publication or patent application and that computational procedures must be "locked down" before confirmation studies begin. A new set of samples, not those used in the initial discovery, with blinded clinical information, should be used for confirmation.

In the validation phase test validation should be performed in a CLIA-certified laboratory with validation design and implementation of the test conducted under current clinical laboratory standards. The committee strongly urges investigator consultation with the U.S. Food and Drug Administration (FDA) prior to beginning a clinical trial, even if not legally mandated, as in the case of trials informing patient care decision. Additionally, the IOM committee urges the FDA to issue either guidance or a regulation that specifies when developers need to submit omics-based tests to the agency for review. G2

Everist Genomics Eyes Future Growth, International Expansion

Alex Charlton

Everist Genomics (Ann Arbor, Mich.) is a closely held, private diagnostic company founded in 2002 that has grown through the acquisition of assets, product portfolios, and intellectual property from Genetics Squared, Angiologix, and MedicalAlgorithmics. The company currently has two diagnostics portfolios—one focused on the noninvasive diagnosis of cardiovascular diseases through the integration of monitoring devices with smartphones and tablet computers and one focused on its newly launched molecular colorectal cancer (CRC) portfolio.

Alex Charlton, executive vice chairman of Everist Genomics, recently spoke with *DTTR* about the launch of its CRC portfolio and future growth opportunities for the company.

Can you tell us about the development of the newly launched portfolio of CRC tests and about your commercialization plans for the tests?

Our cancer portfolio today consists of four products that all target CRC. We are focused on developing diagnostics, prognostics, and therapeutic selection products that span the entire continuum of care in CRC. The entire portfolio is enabled by what we like to refer to as our biological Google, a proprietary machine-learning algorithm called Evolver. Evolver allows us to enter a query to a complex question involving large quantities of biological data. One of the queries we posed to Evolver was which genes and protein expression levels are relevant and predictors of highly aggressive CRC tumors in early-stage patients. That is exactly what we did with Evolver in the development of OncoDefender-CRC.

OncoDefender-CRC is the world's first prognostic to identify patients that are at very high risk of having a recurrence of their tumor if treated with surgical removal alone, which is critical in determining which patients are good candidates to have adjuvant therapy. That is an enormous beneficial impact. By accurately pinpointing early-stage CRC patients that will likely benefit from adjuvant therapy, we have the opportunity to not only save lives, but to also lower costs to the healthcare system through effective treatment planning.

In the four key geographic markets that we are focused on, which is the United States, Europe, India and China, there are 750,000 early-stage CRC patients. That is the eligible market for OncoDefender-CRC.

OncoSelector is a companion diagnostic to OncoDefender-CRC. OncoSelector enables physicians to determine which chemotherapy CRC patients will best tolerate and respond to. So if you test positive for OncoDefender-CRC, the physician now knows this patient is likely to benefit from adjuvant therapy but they have to choose which therapy to administer—OncoSelector guides that decision. Also included in the portfolio is OncoDefender-MMR which is specifically focused on later-stage CRC patients. OncoDefender-MMR helps physicians develop a prognostic therapeutic strategy for stage III and IV CRC patients.

Finally we have [a test for Lynch Syndrome called] OncoDefender-Lynch Syndrome. Some people, because of the presence or absence of certain genes or protein

expression levels, are predisposed to contract CRC. If your test for OncoDefender-Lynch Syndrome is positive and you are a man you have an 85 percent lifetime risk of contracting CRC and a 65 percent chance if you are a woman. Because Lynch Syndrome is a hereditary condition, accurate identification of people with the condition also enables optimal surveillance of cancer development and preventative lifestyle modification in family members so that the lifetime risk for developing CRC is greatly improved and starts to approach the risk levels for a Lynch Syndrome-negative patient.

Physician preferenceand reimbursement are cited as the barriers to adoption of new diagnostics. How is Everist Genomics addressing these issues?
OncoDefender-Lynch Syndrome, OncoDefender-MMR, and OncoSelector are all reimbursed by private insurance and by Medicare. OncoDefender-CRC, which is the first product of its kind, is already reimbursed by several private insurance companies and we currently have the paperwork in process to secure Medicare reimbursement. I think it is an important point because one of the questions about molecular diagnostics is medical benefit and overall impact on total cost of care. Do these tests after you pay for them materially bring down the cost of care? The insurance companies and Medicare have answered that question for three of our tests and the initial indications for OncoDefender-CRC, which has already secured some private reimbursement, are favorable. It seems like we are passing that all-important economic test.

Everist Genomics 'By the Numbers'

Everist Genomics: Founded 2002; 53 employees

CRC Portfolio: Four tests

OncoDefender-CRC: Launched June 2011; Examines five genes and gene expression levels; 6,000 specimen collection kits distributed

The rate at which physicians are ordering specimen collection kits is also a good gauge to determine the potential for the tests. The requests for specimen collection kits for the OncoDefender-CRC test has just exceeded 6,000. That's a pretty useful indicator that physician acceptance is there.

In the last couple of years, other people have published work making the point that not all early-stage tumors within a specific cancer type behave the same way. You need a window into the genomic and metabolic profile at the individual level so that you can apply a treatment strategy that is best for the individual.

It may be premature to ask, but are there plans to expand the scope of the CRC tests? Also, what other molecular tests are in the Everist Genomics pipeline?
We currently have programs in development right now for bladder cancer and lung cancer. But the only limit to Evolver's ability to answer queries is a function of asking medically and cost outcome-relevant questions of Evolver. Where are the biggest unmet needs? What would be incredibly interesting to us is if a diagnostic manufacturer, a lab director, or a physician has a well-conceived view of a diagnostic, prognostic, or therapeutic selection product in any area of cancer, not in any way confined to CRC. Anybody with a view of what is needed, we would like to know about it.

How will the CRC market evolve in the coming years and what advantage does Everist Genomics have being early to market with its CRC portfolio?

In the past, physicians viewed patients in classes, focusing on whether patients had early- or late-stage disease, and making treatment decisions accordingly. Now what's known is that in terms of managing the patient and in trying to influence outcomes, those decisions have to be made at the individual level. To classify CRC as stage I or II, I think, within three to five years from now will be viewed almost as archaic, as a blunt instrument in terms of trying to develop a treatment strategy. What that will lead to is not a CRC market and a set of diagnostics or therapeutic selection products, but multiple niches across many different characterizations of tumors. It is going to make it possible to have multiple subsegmentations of CRC in which diagnostics, prognostics, therapeutics may vary quite substantially from one profile to another creating a real medical need and a tremendous financial advantage to have lots of different types of diagnostics, prognostics, and therapeutic selection products. The end game is a much larger number of products and therapeutics which in many instances are not necessarily competing with each other at all because they are fulfilling very different functions for very different tumors within CRC.

"To classify CRC as stage I or II, I think, within three to five years from now will be viewed almost as archaic, as a blunt instrument in terms of trying to develop a treatment strategy."
–Alex Charlton

What is the company's strategic plan over the next few years?

The company is closely held by a relatively small group of large family investment offices. The overall commercial strategy of Everist Genomics can be divided into two categories. First, we view a global market for our technology and products. However, we know the world is a big place so you have two options. You can go out and raise hundreds of millions to build your international infrastructure yourself or you can raise less money and partner and create joint venture companies, not necessarily just distribution agreements, but joint venture companies with extremely knowledgeable, well connected, and commercially proven companies within a particular region. We are choosing the latter.

We just completed our first international joint venture company for the India region. We formed a joint venture company called Everist Genomics India. Our partner is large multinational company headquartered in Bangalore called the Manipal Group, another family-owned business with revenues of $1 billion last year. They own and operate hospitals [and] medical device and diagnostic companies. They have tremendous market access and understand the diagnostics industry. They are bringing manufacturing, marketing, and sales expertise and customer access in India. We are bringing proprietary products and our pipeline. It is our design and intent to replicate that model to create jointly owned companies also in Japan and in China. In the United States we'll operate the business principally ourselves, although we are exploring distribution and copromotion partnerships in the United States. Our plan is to add at least three new tests per year in each of the next five years. So within five years we would have over 20 tests on the market. We are actively seeking to in-license technology from third parties, particularly to in-license or copromote products that would round out our portfolio.

Advances in Molecular Stool Testing: Evolution Expected in Colorectal Cancer, Infectious Disease Monitoring

Advances in the ability to extract DNA from stool samples and the mounting identification of disease-relevant markers present in stool has fostered incredible investment in research and trials in the hopes of capitalizing on the potential of this noninvasive testing modality. As stool DNA (SDNA) testing continues to expand into the commercial molecular diagnostics market, there is optimism that it will emerge as an increasingly important sampling method for not only gastrointestinal infectious disease and cancer diagnosis, but as a means for enhancing public health monitoring and environmental surveillance.

Colorectal Cancer Screening

Perhaps one of the most talked about applications of SDNA testing is for colorectal cancer (CRC) screening, where it is hoped that the test will increase notoriously low screening compliance and improve early diagnosis of the disease.

> ***"The core technology has advanced in the past five to six years and now the technology has caught up with the biological potential of the test."***
> ***–David Ahlquist, M.D., Mayo Clinic***

"SDNA really does represent a paradigm change. The promise of the test is that it is a patient-friendly, widely distributable, affordable test that could virtually eliminate colon cancer," says David Ahlquist, M.D., a professor of gastroenterology at the Mayo Clinic (Rochester, Minn.), whose SDNA research has been licensed by Exact Sciences (Madison, Wis.). "Fecal blood testing detects some cancer, but not polyps, the precursor. It does reduce mortality, but not the incidence of cancer. This test, if broadly applied, can decrease the incidence of colon cancer with the dream of eradicating colon cancer."

Many working on the development of SDNA tests say the screening paradigm for CRC parallels that of cervical cancer, which had been a significant cause of death for women before the introduction of the Pap smear.

"The sensitivity of the Pap is about 50 percent, but applied annually it virtually eliminates the risk of cervical cancer," explains Ahlquist. "This test already has sensitivity substantially higher than the Pap and with repeated tests, the sensitivity compares to colonoscopy. We hope colon cancer will go the road of cervical cancer."

There has been a previous attempt to bring SDNA testing for CRC to the market—the ColoSure test based on intellectual property that LabCorp (Burlington, N.C.) licensed from Exact Sciences. The test was pulled from the commercial market for unknown reasons. LabCorp could not be reached for comment.

"Fifteen years ago we had the idea of looking at exfoliated markers shed off of polyps and tumors versus bleeding that is non-cancer-specific. The problem was the assay was not sensitive enough," says Ahlquist. "We didn't have the right markers and we didn't have the right stabilization buffer for samples. The core technology has advanced in the past five to six years and now the technology has caught up with the biological potential of the test."

While currently there is no commercially available SDNA screening test for CRC, Exact Sciences has invested heavily to bring its high performance, multimarker

Cologuard test to the U.S. market in 2014. The test, built upon research both from Ahlquist and Sandy Markowitz, M.D., Ph.D., from Case Western Reserve University (Cleveland), uses 11 biomarkers comprising DNA methylation markers including vimentin, DNA mutation markers including KRAS, and a fecal hemoglobin marker ELISA. The company is currently conducting a $25 million U.S. Food and Drug Administration (FDA) pivotal clinical trial, called DeeP-C, which will enroll 10,000 patients in 60 sites across the country. Participants in the trial will be tested using Cologuard, Fecal Immunochemical Testing (FIT), and a colonoscopy.

"With colon cancer screenings every 10 years, a 1 centimeter polyp can become metastasized cancer," says Maneesh Arora, chief operating officer of Exact Sciences. "The power of screening is not that it can detect cancer, which it can, but in detecting precancerous polyps. In our validation studies we have better than 85 percent sensitivity for cancer, and importantly critical for this test, 59 percent sensitivity for precancerous polyps over 1 centimeter."

"The power of screening is not that it can detect cancer, which it can, but in detecting precancerous polyps."
–Maneesh Arora, Exact Sciences

The company has given guidance that "top-line" results will be released this year and the FDA submission is expected to be completed in first quarter of 2013. Arora says the company's submission is among the first accepted for FDA and Centers for Medicare and Medicaid Services parallel review for concurrent device approval and Medicare reimbursement determination. The stakes are high in proving the performance of the test that could revolutionize the CRC testing market, which the company estimates is greater than a $1.2 billion U.S. market opportunity.

How Will Patients and Physicians Respond?

"We are in a unique position, a more positive one than many other diagnostics," says Arora. "This test is good for patients, costs less, and is good for the system. But to change the practice of medicine is really hard. We need to demonstrate through the prospective study that the performance is there."

More than 80 million Americans are eligible for CRC screening, a number expected to grow, both with the aging of the general population and with expected changes to the guidelines that will lower the recommended screening age from 50 years to 40 years. Patient adherence to CRC screening guidelines has been difficult with screening rates stubbornly hovering near 50 percent. New research is showing that physician insistence on colonoscopies may be backfiring and patient choice needs to be considered in selecting a screening modality.

Consideration of patient preference in selecting CRC screening strategies increases participation in CRC screening, according to a study published in the April 9 issue of the *Archives of Internal Medicine*. In a randomized study of nearly 1,000 patients, patients who were exclusively recommended colonoscopy completed screening at significantly lower rates (38 percent) compared to patients recommended fecal occult blood tests (67 percent) or those given a choice between the two methods (69 percent).

While trial participants have rated the acceptability of SDNA testing as "quite good" others say some patients may be wary of handling fecal matter.

"SDNA testing differs from FIT, which you smear stool on a card," says Gregory Cooper, M.D., a professor of medicine and gastroenterology at Case Western Re-

serve University. "This is an actual bucket screwed onto the toilet seat. A whole bowel movement goes into it."

"You would think patients would prefer the noninvasive test, but it doesn't always happen that way," says Grace Lin, M.D., an assistant professor of medicine at the Philip R. Lee Institute for Health Policy Studies at the University of California at San Francisco. "From the patient perspective there is a grossness factor in testing stool. They don't like the idea or don't want to do it every year. It's an interval issue. If I do the colonoscopy I can be done with it for a longer length of time."

But, Lin says, physician screening preferences are more complicated.

"There is a push by gastroenterologists for making colonoscopies the primary modality of screening," says Lin. "There is a feeling that if you do the colonoscopy you can remove a polyp too, so from a pathophysiology perspective it makes sense. Gastroenterologists obviously do have a financial incentive to do colonoscopies the way the reimbursement system is set up right now and that does play a role. But in other procedure-related specialties like cardiology, even salaried cardiologists prefer stenting to other approaches. Overall there is a bias in medicine that doing something is better."

But ultimately economics may make the case for SDNA testing. As cost-sharing places an increased portion of the price tag on consumers, lower-cost testing may be more appealing and as payers put greater incentives in place to contain the cost of care while diagnosing disease early, providers will likely look for the most cost-effective CRC screening strategy. Naturally some gastroenterologists may initially feel financially threatened by the SDNA test, but experts in the field see SDNA and colonoscopies as complimentary.

"I see stool testing as an adjunct to colonoscopy, a way to augment colonoscopy and maybe beneficial for patients during the years in between colonoscopies," says Cooper, who is the clinical primary investigator for trials using SDNA technology that exclusively looks for methylation of the vimentin gene and will compare that to the Exact Sciences multimarker panel, FIT testing, and a colonoscopy.

Infectious Disease

While the adoption of SDNA testing for CRC may be nearing clinical reality, the use of SDNA to combat infectious diseases can sound both routine and like something out of a futuristic germ-fighting thriller.

With E. coli and cholera outbreaks and a doubling of gastroenteritis-associated deaths in the United States over an eight-year period making headlines, the need for rapid diagnostics methods to identify infectious diseases is imminent.

At the International Conference on Emerging Infectious Diseases (Atlanta; March 14) U.S. Centers for Disease Control and Prevention (CDC) researchers presented data that gastroenteritis deaths more than doubled from 1999 to 2007. Clostridium difficile (C. difficile) and norovirus were the most common infectious causes of the gastroenteritis-associated deaths. Over the study period there was a fivefold increase in C. difficile deaths with 14,500 deaths reported in 2007 from the bacteria. Norovirus, the leading cause of gastroenteritis outbreaks in the United States, was a distant second with an average of 800 deaths annually.

Diagnostics manufacturers have responded to the need for rapid infectious disease diagnostics with the development of SDNA tests. Most recently, the FDA granted 510k clearance for Focus Diagnostics' (Cypress, Calif.; a business unit of Quest Diagnostics) Simplexa C. difficile Universal Direct Test on the 3M Integrated Cycler. The test relies on real-time polymerase chain reaction to qualitatively detect the bacteria in liquid or unformed stool samples and uses proprietary chemistry to eliminate the need for nucleic-acid extraction. Labs can complete the entire testing process in about an hour. A kit, which can run 100 tests, lists for $4,500, the company says. Focus Diagnostics is currently developing a Simplexa stool-based test kit for Norovirus.

Phthisis Diagnostics, a Charlottesville, Va.-based startup, is expanding stool-based molecular diagnostic methods to food- and water-borne diseases that are frequently symptomatic but rarely diagnosed. The more widespread use of molecular technology in general has allowed laboratories to rethink about stool samples, says Crystal Icenhour, Ph.D., president and chief science officer of Phthisis Diagnostics. "It is a very complex sample if you are relying on visual diagnostic measures. In the past, microscopy on stool samples was very difficult. It is very difficult to see, still, for parasites."

Icenhour's company's primary focus is on intestinal diseases and parasites, including development of a cryptosporidium and griardia kit that is entering FDA clinical trials followed by a microspiridia test, but she sees stool testing as evolving beyond gastrointestinal ailments.

However, molecular visionaries like Eric Schadt, Ph.D., chief science officer at Pacific Biosciences (Menlo Park, Calif.) see SDNA testing as taking on an expanded role beyond individual diagnosis of disease. He sees SDNA testing applied for broader community-based environmental surveillance of infectious diseases of public health concern. Schadt tells *DTTR* that about a year ago Pacific Biosciences began using its sequencing technology to conduct a real-time pathogen survey.

"We were assaying surfaces we encounter each day—desks, remote controls, toilets—and as we thought about it, we wanted to cast a broader net and turned to sewage," explains Schadt, who is also director of the Institute for Genomics and Multiscale Biology at the Mount Sinai School of Medicine. "The value is that everyone in a region contributes to it and does so each day."

Pacific Biosciences conducted a pilot study of approximately 100 viruses and used samples acquired from a sewage substation to see if pathogens of acute public health concern, like cold and flu, could be detected. The researchers could detect them as well as viruses specific to food like those found in commercial chicken and vegetables.

"Think in terms of molecular epidemiology," envisions Schadt. "Adoption would require industrialization of the process and education or social awareness. People react very differently. Some get the benefit. Others put privacy concerns front and center."

Schadt says agencies like the CDC, FDA, and the U.S. Department of Agriculture are very interested in using the technology to establish baselines for infectious diseases both in communities and on farms, before an outbreak occurs, and to track changes in the disease prevalence over time.

Testing May Play Future Role in Cerebral Palsy Diagnosis, Treatment

The application of sequencing technology is providing increasing evidence for the genetic basis of a heterogeneous group of neurological disorders present in cerebral palsy, according to a review study published in the March issue of *Lancet Neurology*. The continued discovery of gene mutations and disrupted molecular pathways could pave the way for expanded use of clinical diagnostic testing to more accurately diagnose and genomically guide treatment of cerebral palsy.

"There is a group of more than 50 genetic syndromes that we refer to as the cerebral palsy spectrum disorders," says study author Andres Moreno De Luca, M.D., a research scientist at Geisinger Health System (Danville, Pa.). "Some of these conditions can be treated pharmacologically. Therefore, making these genetic diagnoses can result in significant changes in medical management."

Comprehensive genetic testing is rarely currently offered as part of the diagnostic workup of individuals with suspected cerebral palsy, and in cases where genetic mutations were identified, the diagnosis of cerebral palsy is often changed, complicating the discovery of cerebral palsy-related genes. Currently, there are only six known mutations that cause mendelian forms of cerebral palsy—GAD1, KANK1, and a group of adaptor-related protein complex 4 genes (AP4M1, AP4E1, AP4B1, and AP4S1). Genetic association studies have not yielded replicable results likely because of the rare, and often private (mutations restricted to an individual or other afflicted family members), nature of the genetic mutations suspected in cerebral palsy. "Chromosomal microarray analysis is currently considered standard of care for individuals with unexplained developmental delay, intellectual disability, autism spectrum disorders, or multiple congenital anomalies, and all of these conditions are known comorbidities in cerebral palsy," says Moreno De Luca. "We still need to determine the diagnostic yield of microarrays in patients with cerebral palsy without the [those] comorbidities before recommending its use in this group."

Studies showing the diagnostic yield of microarray analysis and whole-genome sequencing are needed to demonstrate the need to change current cerebral palsy guidelines, Moreno De Luca, says.

"We estimate that the yield in cerebral palsy would be similar to that of other neurodevelopmental disorders such as autism and intellectual disabilities," Moreno De Luca tells *DTTR*. "Once the usefulness of genetic testing for cerebral palsy is proven, these technologies should be implemented in routine clinical practice."

HCV Screening for Jailed, Addicted Populations: An Opportunity to Partner

Jails and substance abuse treatment centers represent a largely missed opportunity for hepatitis C (HCV) screening. But the combination of new rapid-testing technologies and improved treatment options can together mark a turning point forHCV Screening for Jailed, Addicted Populations: An Opportunity to Partner.

Researchers estimate that persons released from the criminal justice system may account for at least one-third (29 percent to 43 percent) of the estimated 3.3 million persons infected with HCV in the United States and as many as 1 million people with undiagnosed HCV infection may come in contact with the correctional system each year, according to a view-

point piece published in the March 28 issue the *Journal of the American Medical Association*.

"Because treatment could not realistically be provided for short-term inmates, HCV screening has not been routinely conducted in jails," writes co-author Anne Spaulding, M.D., M.P.H., an assistant professor of epidemiology at Emory University's Rollins School of Public Health (Atlanta). "Jails are an ideal setting for routine infectious disease screening and with new treatments that are curing a substantially greater number of people infected with HCV, there is real potential to reduce the number of cases across the United States."

Spaulding and her colleagues estimate that if 70 percent of the 1 million people with HCV who pass through correctional facilities are offered HCV testing, and if 70 percent accept testing, HCV screening in detainees may lead to the identification of half a million new cases of hepatitis C in the first year of the program. She stresses that early detection, even in short-term jail settings where treatment is not feasible, could ease the burden jails would face in treating felony, long-term prisoners later.

"Currently, many people first learn they are infected when they go to prison to serve felony sentences," says Spaulding in a statement. "If they had found out about their infection years earlier during a brief jail stay, which most of them have experienced, they could have sought care in the community."

Community health centers, Spaulding says, are better equipped financially to shoulder the responsibility of treatment than the state prison systems, which will face much higher disease prevalences.

But drug users also represent a substantial high-risk population and in *A Treatment Improvement Protocol: Addressing Viral Hepatitis in People With Substance Use Disorders,* the Substance Abuse and Mental Health Service Administration emphasizes the role that substance abuse treatment programs must play in both educating and screening clients for hepatitis and recommends treatment centers either implement or expand hepatitis services. On-site medical staff members at the treatment center can take a primary role and screen for hepatitis B and C at intake and periodically as indicated. In programs without on-site medical staff, establishing referral programs for testing is recommended.

Supreme Court Rulings' Impact on Diagnostics Industry Uncertain

The diagnostics industry is back in wait-and-see mode following two much watched U.S. Supreme Court decisions. In a 9-0 decision the U.S. Supreme Court reversed the U.S. Court of Appeals for the Federal Circuit and struck down methods patents held by Prometheus Laboratories (San Diego).

In its decision the Supreme Court found methods patents that "effectively claim the underlying laws of nature themselves" are invalid but did not give affirmative specific guidance about the extent additional steps need be to qualify for patentability. While the *Prometheus* case does offer the industry more clarity, experts don't believe the ruling will have much of an impact on the diagnostics industry.

"The Federal Circuit had said the core screen for patentability was not 101. Most patents would be caught by 102 (novelty), 103 (nonobviousness), and 112 (written description). The Federal Circuit had pretty much said 101 was dead and the Supreme Court said it is not," explains John Conley, Ph.D., Kenan Professor of Law at the University of North Carolina, Chapel Hill. One of the takeaway messages Conley says is, "You can't take mental process and append very simple real-world steps to it pre- or post-process."

So what does this decision mean for the diagnostics industry?

"To the extent you believed you could slip any diagnostic claim past 101 objection, that's no longer true," says Conley, who also contributes to Robinson, Bradshaw & Hinson's (Chapel Hill, N.C.) *Genomics Law Report* blog. "It may change the section patentability is decided under, but it won't change if a patent claim is failing. Marginally some monopolies may be cut back, but it doesn't change the landscape of the industry."

The lingering question is what does the *Prometheus* decision mean for the case against Myraid Genetics (Salt Lake City), which the Supreme Court remanded back to the Federal Circuit for reconsideration?

Conley says he expects the Federal Circuit will reconsider *Myriad* quickly, but regardless of the court's decision the Supreme Court would be unlikely to consider the methods portion of the *Myriad* case but may take on the gene patentability portion of the case.

"The question people are really asking is the product-of-nature question. *Prometheus* literally says nothing about it," says Conley. In looking for clues on how the Supreme Court may lean on gene patentability, Conley called it a "long and winding road" to derive direction from the Supreme Court's *Prometheus* decision. "I wouldn't know how to predict it. Liberal or conservative doesn't apply to this."

Genomic Health Funds New Clinical Sequencing Service Venture

Genomic Health (Redwood City, Calif.) has launched a new services-focused subsidiary, InVitae, which aims to accelerate the adoption of genomics into clinical practice. The March announcement came as a surprise to industry watchers but has been called a "logical" expansion of the company's resources.

Genomic Health will invest $20 million into the subsidiary that will be headed by Randy Scott, Ph.D., Geonomic Health's executive chairman. The company anticipates the subsidiary, which will focus on common and rare genetic conditions, will launch commercial services in 2013 and will contribute significantly to the company's long-term growth.

"We are at a unique turning point in medicine and believe the investment we have made over the past several years in the development of a robust next generation sequencing platform and the capabilities we have established in building a successful cancer genomic business make this the ideal time to expand into both common and rare genetic conditions and expect this new start-up to be a significant long-term contributor to the company's growth," Scott said in an announcement of the new venture.

"It was a surprising move, but not necessarily bad. It makes logical sense," says Dan Leonard, an analyst and director of life science tools and diagnostics at equity firm Leerink Swann (Boston). "They are trying to leverage their internal skillset into markets outside of oncology."

Leonard says he sees the three primary markets for sequencing technology as oncology, rare genetic diseases, and noninvasive prenatal testing, and with the creation InVitae, Genomic Health will be a player in two of them. "It will accelerate clinical adoption of sequencing technology because of the resources they are throwing behind it," Leonard says.

Genomic Health says InVitae will leverage both third-party and Genomic Health's research and development efforts.

G2 Index Mixed, Ends Down 1%

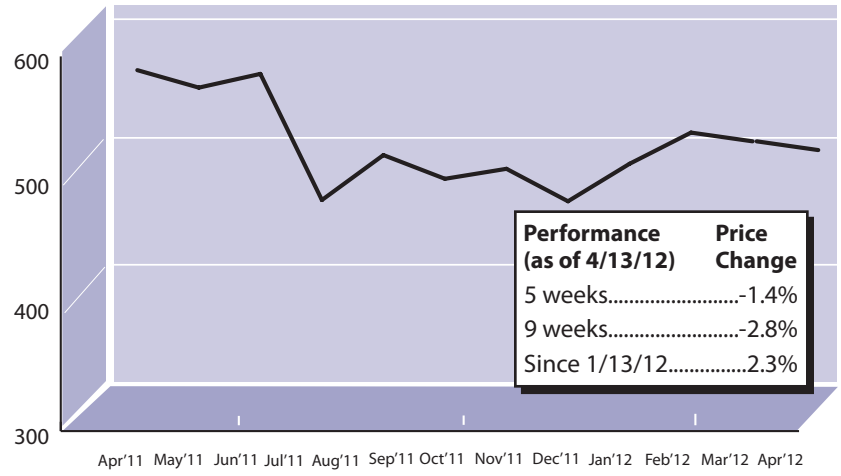
The G2 Diagnostic Stock Index was mixed for the period but closed the five weeks ending April 13 down 1 percent. Seven stocks gained for the period and 10 stocks declined. There was little movement in the Nasdaq and the S&P over the same period, with the Nasdaq gaining 1 percent and the S&P unchanged.

Among the stocks gaining ground was **Quidel** (San Diego), up 13 percent this period. The company received regulatory approval for several molecular diagnostics in Europe. The tests demonstrate the rapid expansion of the company's molecular diagnostics product line, which offers polymerase chain reaction reagent kits molecular laboratories can use with their existing thermocylers. Among the tests receiving CE markings were the Direct C. difficile assay and the RSV + hMPV assay for respiratory infections. These assays are among Quidel's five molecular product offerings to receive European regulatory approval in the last seven months.

Illumina (San Diego), which continues to fight off Roche's (Basal, Switzerland) takeover attempts, now must fight off a lawsuit, this one filed in the U.S. District Court, District of Delaware, by the trustees of Columbia University (New York) for patent infringement. The suit alleges that Illumina's instruments, next-generation sequencing (NGS) kits and reagents, and sequencing services infringe on five NGS patents assigned to Columbia University from 2009 and 2012 resulting from the work of chemical engineering professor Jingyue Ju, Ph.D., and others. Illumina has said the claims are without merit and it will vigorously defend against them. Illumina's stock declined 6 percent over the period.

Despite some positive company developments, **Becton, Dickinson and Co.'s** (Baltimore) stock fell 3 percent this period. At the end of March the company announced Food and Drug Administration clearance of its Group B streptococcus assay and Clinical Laboratory Improvement Amendments moderate-complexity test categorization on the company's second-generation BD MAX automated, bench-top molecular system. The company plans to expand its moderate-complexity assays in the coming months including for MRSA and C. difficile.

G2 Diagnostic Stock Index



Source: The G2 Diagnostic Stock Index is tabulated weekly by *DTTR* from the average percentage change in the stock price of 17 IVD companies.

Up	Price	% Chg
Abbott Labs	59.59	3%
Bio-Rad	106.80	3
IRIS	12.81	9
Luminex	23.86	3
Meridian	18.36	2
OraSure	10.41	10
Quidel	18.24	13
Down		
Affymetrix	4.05	-4%
Abaxis	26.46	-3
Alere	22.80	-12
Becton Dickinson	74.79	-3
Cepheid	38.00	-11
Gen-Probe	65.35	-2
Illumina	47.17	-6
Johnson & Johnson	63.54	-2
Qiagen	15.00	-1
Sequenom	3.99	-5

G2 Insider

Chlamydia Screening Rates of Sexually Active Women Alarmingly Low. . . Two recently released studies by the U.S. Centers for Disease Control and Prevention (CDC) illustrate the alarmingly low rate of chlamydia testing among young, sexually active women. Current guidelines advise annual chlamydia screening for sexually active women under 25 years old and high-risk women over 25 years, but the CDC says less than 40 percent of recommended women are screened.

The first study, presented at the National STD Prevention Conference (Minneapolis; March 12-15), shows that using self-reported data from young women, only 38 percent of sexually active women were screened for chlamydia in the previous year. From these data, CDC estimates that more than 9 million young women nationwide were not screened as recommended. Testing rates were higher for women in at-risk populations including blacks (55 percent) and those with multiple sex partners (47 percent).

According to the second study, published in the April issue of the *American Journal of Preventive Medicine*, CDC researchers found that among insured women, young women are undertested and older women are overtested for chlamydia. Of the 3.2 million women aged 15 years to 44 years who received reproductive health services in 2008, only 22.3 percent received chlamydia testing while 65 percent of those tested were aged 26 years to 44 years, causing the researchers to conclude that interventions to increase chlamydia screening for young, sexually active women are "urgently needed."

Two other chlamydia testing trends also emerged from the dual studies. First is the need to improve retesting rates for positive patients, both men and women, which might be as low as 11 percent and 21 percent, respectively. Finally, given the low nationwide prevalence of gonorrhea, the researchers say the commercial push for dual testing that is reinforced by generous reimbursement rates is misallocating STD resources. "The practice of dual screening for chlamydia and gonorrhea should be re-evaluated, especially the level of reimbursement, so that limited healthcare resources can be used more effectively," write the authors. G2

Company References

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Institute of Medicine 202-334-2352

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Pacific Biosciences 650-521-8000

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