G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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NGS Improves Bladder Cancer Assay Sensitivity

Diagnosis of bladder cancer has been notoriously hampered by the low sensitivity of urine cytology even among patients presenting with hematuria. Complicating management efforts is the high rate of recurrence that necessitates invasive and costly long-term surveillance.

Predictive Biosciences (Lexington, Mass.) believes that its CertNDx bladder cancer offerings can improve risk stratification of patients with hematuria and provide a better alternative for recurrence monitoring.

Previous studies analyzed urine samples for levels of the protein (MMP-2), two methylation markers (Twist1/Nid2), and mutations of FGFR3 using quantitative polymerase chain reaction. In an abstract presented at the American Urological Association annual meeting (May 7; San Diego) investigators used a similar multianalyte assay but incorporated next-generation sequencing-based mutation analysis of TP53 and FGFR3. The new marker combination increased the identification of the cancer-negative patients from 56.2 percent to 67.9 percent while increasing sensitivity from 87.9 percent to 92.5 percent (99 percent negative predictive value). The combination of FGFR3 and TP53 increased the sensitivity for identifying patients likely to have cancer from 34.5 percent to 50.9 percent while maintaining specificity (99.7 percent), a 93.1 percent positive predictive value.

The researchers say the results demonstrate that the assay can stratify patients with high confidence into those that do or do not have bladder cancer. For more information on diagnosis of bladder cancer please see *Inside the Diagnostics Industry* on page 5.

Diagnostics IPOs Slow as Companies Face Evolving Investor Expectations

So far this year there have been double the number of diagnostics companies with initial public offerings (IPOs) as there were in all of 2012, bringing the total in the past 12 months to a paltry three IPOs. Experts say that they don't expect to see any significant uptick in IPO activity in the industry both because of the broader financial market environment and because companies in the space must adapt to changing investor expectations.

"The broader perspective is that it is a tough time for any IPO, forget about for diagnostics companies," says Keith Batchelder, M.D., founder and CEO of the advisory firm Genomic Healthcare Strategies. "I am bullish on diagnostics; however, unless companies can present their case in the context of why there is clinical utility and economic utility it is going to be very tough times in the marketplace."

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▲ **Diagnostics IPOs Slow,** *from page 1*

The three diagnostics companies that have successfully entered the public markets over the past 12 months all did so with markedly scaled back offerings.

Cancer Genetics (Rutherford, N.J.) closed its initial public offering of 690,000 shares of common stock at a price to the public of $10 per share with gross proceeds of $6.9 million in the beginning of April. Since filing its initial IPO registration with the Securities and Exchange Commission (SEC) in May 2012, the firm three times scaled back its IPO plans from $41.9 million (4 million shares at about $12 per share). As of May 1 its stock price was being traded above its initial list price. The company will reportedly use $2 million of its proceeds toward its diagnostics joint venture with the Mayo Clinic and will use the rest to pay down debt and fund operations. Given the significant reduction in capital raised, the company is said to have scrapped plans to invest further in research and development.

In January, **LipoScience** (Raleigh, N.C.) raised $45 million (from 5 million shares at $9 per share plus 750,000 shares exercised by the underwriters). Earlier plans calculated $75 million in proceeds based on a share price of $13 to $15. The company said the capital raised will be used to ramp up sales and marketing efforts for its cholesterol tests. The company's U.S. Food and Drug Administration (FDA)-cleared automated clinical analyzer, the Vantera system, uses nuclear magnetic resonance to identify and quantify concentrations of multiple subclasses of lipoproteins and, potentially, small molecule metabolites. The company says it currently has 9 million orders for its tests but has large growth plans given that 75 million traditional cholesterol tests are performed annually. The company also plans to expand its personalized diagnostic test menu for metabolic and other diseases.

Withdrawn IPO Plans

The following diagnostics companies have withdrawn filings for IPO plans over the past year.

Autogenomics (Vista, Calif.) withdrew its $60 million IPO in mid-February. The firm originally filed for an IPO in 2008, hoping to raise as much as $86.3 million but withdrew that filing in 2011 without providing a reason.

Singulex (Alamdea, Calif.), which develops diagnostic testing for cardiovascular disease in nonacute settings, withdrew its $70 million IPO in late December 2012 citing poor market conditions.

Arrayit Diagnostics (Redmond, Ore.), a spinoff of Arrayit (Sunnyvale, Calif.), in December 2012 withdrew its IPO registration filed just the previous month in order to complete a private placement.

Anatomic pathology company **Aurora Diagnostics** (Palm Beach Gardens, Fla.) in June 2012 pulled its planned $150 million IPO, which was to fund the acquisition of smaller pathology practices. Speculation was that the company changed its plans as a result of weakening financial performance.

Breast cancer diagnostics company **Atossa** (Seattle) also completed a scaled down IPO of 800,000 shares at $5 per share, raising a total of $4 million, Nasdaq's qualifying minimum for the small-capitalization market tier, in November 2012. Initial SEC filings earlier in 2012 showed that the company anticipated selling 1 million shares in the range of $5 to $7. The company will use its proceeds to fund a national rollout of its two existing tests and bring new tests to market. The company's tests are based on its core FDA-approved MASCT technology (Mammary Aspirate Specimen Cytology Test System).

The prospects for near-term IPOs do not look very promising for early-stage diagnostics companies. This is due in part to evolving expectations on the part of investors. Given the increased focus on clinical utility and cost-effectiveness, diagnostics companies need a more compelling story than just that they have discovered a new panel of biomarkers or have a novel test technology to lure investors. They must provide compelling evidence of how their product provides value to the broader health care system.

"There needs to be a reset in how people think about diagnostics companies. No longer are there quick exits. You must have the money to be more patient for a liquidity event, and diagnostics companies have to be more cognizant of the complete story, the value proposition," explains Batchelder. "There has been overinvestment in diagnostics by venture capitalists and that has not yet cleared out. There is an appetite for diagnostics, but the winners will have good stories and there is still a glut of diagnostics companies based on technology without the full value proposition that, unfortunately, will go away."

Will Sequencing Technology Continue to Be an Acquisition Target Following Thermo Fisher's Buyout of Life Technologies?

On the heels of the March completion of Chinese giant BGI-Shenzhen's $117.6 million acquisition of sequencing service provider Complete Genomics (Mountain View, Calif.), Thermo Fisher Scientific (Waltham, Mass.) announced in mid-April it entered into a definitive agreement to buy Life Technologies (Carlsbad, Calif.), the maker of the Ion Torrent next-generation sequencing (NGS) instruments, for $13.6 billion in cash ($76 per share) plus the assumption of approximately $2.2 billion of debt. Taken together the acquisitions represent a strengthening of dominant positions in the emerging clinical sequencing space by two companies counting on adoption of NGS to drive long-term growth.

Onlookers can't help but wonder what these acquisitions mean for the remaining major U.S. players in the sequencing space—Illumina (San Diego) and Pacific Biosciences (Melo Park, Calif.)—as well as whether Roche (Switzerland) or other large diagnostics players will take notice and seek entry into the market.

"The strategic rationale for the acquisition is clear," says Charlie Miller, an analyst at Morningstar who follows Thermo Fisher. "Thermo can expand its already robust product portfolio and will be able to use its massive customer channels to drive revenue and cost synergies. As a better operator, we expect that Thermo will be able to reinvigorate Life's core consumables business. Further, Thermo will finally be able to fill its major product gap in NGS through Life's Ion Torrent business."

"I think there will continue to be a desire, in the near term, for the bigger companies to fill that [NGS] product gap by acquiring an instrumentation player."
—Charlie Miller, Morningstar

Thermo Fisher reportedly beat out a consortium of private equity firms, including the Blackstone Group and Kohlberg Kravis Roberts, and the biotechnology company Sigma-Aldrich, according to reports. Thermo Fisher believes the revenue Life Technologies brings ($3.8 billion in 2012) will add between 90 cents and $1 per share profit in the first full year. Analysts say that despite the expected $250 million in cost synergies, the acquisition price was higher than anticipated (14 times earnings before interest and taxes), possibly making returns on capital more challenging.

"From the competitive position perspective, Thermo Fisher is clearly a stronger company now, and we see qualitative merits for a wide moat going forward. However, returns on invested capital will take yet another hit because of the rich price paid," wrote Miller in a research note.

The premium that Thermo Fisher paid for Life Technologies (a 25 percent jump over Life Technologies' stock price on Jan. 18 when the company announced it had hired two investment banks to explore its strategic options) leads some to speculate that

Illumina was justified in demanding a higher buyout price than Roche was willing to pay in its failed takeover bid last year.

"I think there will continue to be a desire, in the near term, for the bigger companies to fill that product gap by acquiring an instrumentation player," Miller tells *DTTR*. "That said, I certainly believe smaller companies with just a sequencing test or two—particularly within oncology, prenatal testing, and inherited diseases—are valuable acquisition targets as NGS technology begins to move into the clinical and diagnostic arena."

While Industry Awaits Supreme Court's Decision in *Myriad*, Some Believe Implications of Ruling May Be Overstated

As the industry awaits the Supreme Court's decision regarding the patentability of genes, experts are reviewing the mid-April oral arguments for clues as to which way the court is leaning. Court watchers speculate based on oral arguments in the *Association for Molecular Pathology, et al. v. Myriad* case that the Supreme Court may try to find a middle ground in which it denies the patentability of isolated genomic DNA but accepts that synthesized cDNA is a human construct, and thereby patentable.

This halfway position, which was argued by the U.S. solicitor general in court (and seemingly well received by some of the justices) and in an amicus brief, marks a clear departure from the position previously taken by the U.S. Patent and Trademark Office. Aside from the product-of-nature argument, one theme that penetrated questioning was a seeming unease about the economic and scientific consequences of the court's decision, with concern for maintaining adequate incentives to propel innovation. This concern, while echoed by many in the life sciences industry, may be overstated, experts say, as there are not many successful companies built around existing single-gene patents.

"Beyond personalized medicine's potential interest in the Myriad outcome . . . the significance of the case is probably overrated," writes John Conley, Kenan Professor of Law at the University of North Carolina, Chapel Hill, and counsel with Robinson, Bradshaw & Hinson (Charlotte) in the *Genomic Law Review* blog. "Going forward, single-gene patents are going to be hard to get regardless of this decision because of a stricter obviousness standard. And . . . newer sequencing technologies may be able to avoid using patented single genes in isolation, which would avoid Myriad-style patents entirely. So the Supreme Court's decision will attract huge, if not hysterical, academic and public interest, but the market may already have moved beyond it."

Even Myriad Genetics (Salt Lake City), whose BRCA1 and BRCA2 genes are at the center of this case, is shying away from a reliance on patents in its strategic planning. Nonetheless, the case has put some pressure on Myriad's stock.

"We expect the stock will continue to be volatile around the court case and debate will remain around Myriad's ability to compete as technology moves to whole genome sequencing," writes Amanda Murphy, an analyst at William Blair & Co., in a research note. "Still, we ultimately believe that the company's proprietary variant database provides a meaningful competitive advantage beyond Myriad's intellectual property and that potentially competing platforms may take longer to pervade the clinic (providing the same level of accuracy and VUS rate at a meaningfully lower cost) than some expect."

G2 INTELLIGENCE
Inside the Diagnostics Industry

Urine-Based Assays Emerging as Valuable Means to Better Stratify Risk of Bladder Cancer

Despite efforts to identify highly sensitive urine-based markers that are able to better identify patients with a true risk of bladder cancer, primary evaluation still relies upon hematuria screening and urine cytology. Even in cases of abnormal cytology, assays to risk-stratify patients have yet to gain widespread clinical adoption or acceptance in professional guidelines. Workup and monitoring of patients requires unpleasant, sometimes unnecessary, invasive techniques leaving many in urology seeking better tests.

Standard Tests Have Low Sensitivity

Hematuria is relatively common in the general population (9 percent to 18 percent) while the prevalence of urinary tract cancers is low in the general population (0.01 percent to 3 percent), experts say, making screening for the disease difficult. Clinicians would like alternative measures that better identify patients who truly require further evaluation and those who can be spared unnecessary workup, including radiation exposure and invasive cystoscopy.

"Using blood in the urine as an indicator for possible cancer when it is that common of a finding is problematic, and that is the inherent problem with bladder cancer screening," says Ronald Loo, M.D., regional chief of urology at Southern California Permanente Medical Group in Los Angeles. "The holy grail would be a quick test with a marker indicating when it is most likely bladder cancer—a test that can distinguish the population reliably so you can safely avoid working up people at low risk."

While Loo says a "litany of urine markers" have been discovered, his group has taken a different approach by examining common risk parameters.

"Rather than looking for a magical test, what if you took common parameters without sophisticated testing and expense. It turns out the most important factor is whether the patient sees blood in the urine," Loo explains. "Published studies have historically alluded to this."

Loo's findings are based on a study of real-world outpatient referrals from primary care physicians for patients with asymptomatic microscopic hematuria. His group developed a Hematuria Risk Index to predict cancer risk. In the algorithm, history of gross hematuria and age of 50 years or older were given four points, whereas factors with lower odds ratios (history of smoking, male sex, and greater than 25 RBC/HPF on a recent urinalysis) were given one point. Among the 4,414 patients that were evaluated for hematuria, 32 percent of patients were identified as having a low risk of cancer, and only 0.2 percent had a cancer detected. Of the 14 percent of patients identified as high risk, 11.1 percent had a cancer detected. Overall, the three-year incidence of urinary tract cancer was only 0.43 percent.

"Most malignant tumors can be identified by a history of gross hematuria, a far more reliable indicator of the need for urologic evaluation and imaging," writes Loo in a study published in the February issue of *Mayo Clinical Proceedings*. "Patients with microscopic hematuria younger than 50 years and with no history of gross hematuria may not benefit from further evaluation and therefore could avoid unnecessary risk from radiation exposure and invasive endoscopy."

While Loo says that the index requires further validation before being adopted into evidence-based clinical decisionmaking tools, the findings do not diminish the need to identify sensitive urine-based markers.

"Let's say our model is validated; bladder cancer markers can still improve the diagnostic resolution or accuracy even further," Loo tells *DTTR*. "I suspect the lowest-risk patients are not a good place to do an expensive screening test and the highest-risk patients will still need to be worked up. What is left is the patients in the middle who may need further segregation to identify those at higher risk."

The Value of Bladder Cancer Testing

Researchers agree the ultimate goal would to develop a highly sensitive and specific urinary assay for bladder cancer. At this point, a number of candidate markers are both being investigated and are in commercial use. The ultimate measure of an assay for bladder cancer is not just its diagnostic accuracy, though, but its value: Would use of the test ultimately save the system resources through avoidance of unnecessary referrals and costly workups? Some studies are beginning to emerge in the literature demonstrating the potential for eliminating cystoscopies.

In a study published in the May issue of *European Urology*, investigators determined that when used as a reflex test on patients with atypical urine cytology, a negative ImmunoCyt/uCyt test (Scimedx, Denville, N.J.) may predict a negative cystoscopy in select patients, thus reducing urgency and further workup in those with no prior history or low-grade disease. uCyt is a triple immunofluorescent monoclonal antibody assay that detects cytoplasmic mucins and carcinoembryonic antigen.

Reflex uCyt was performed retrospectively on 506 atypical voided urine samples in patients who received a cystoscopy within 90 days. In those with a history of urothelial carcinoma (UC) the researchers found that reflex uCyt showed a sensitivity of 73 percent, a specificity of 49 percent, and an NPV of 80 percent. Without prior history of UC, reflex uCyt had a sensitivity of 85 percent, a specificity of 59 percent, and an NPV of 94 percent.

"When used as a reflex test to arbitrate atypical urine cytology, a negative ImmunoCyt result can be used to predict a negative cystoscopy in select patients," write the authors, led by Anoebel Odisho from the University of California, San Francisco. "The high NPV can be used to modify the urgency and nature of further urologic work-up, both in those without a history of UC and in those with a history of low-grade UC in which a routine follow-up schedule with fewer cystoscopies can be maintained despite a reading of atypical cytology."

The authors say prospective evaluation is necessary.

FDA-Approved Bladder Cancer Kits

UroVysion (Abbott Molecular)—This test looks for aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus that are alterations often seen in bladder cancer cells. It employs fluoresence in situ hybridization regents and is intended to monitor for recurrence in conjunction with cystoscopy.

BTAstat (C.R. Bard)—An immunoassay uses antigen-specific antibodies to detect bladder tumor-associated antigen (BTA) in the urine.

Immunocyt (Scimedx)—This is a qualitative immunocytoflourescence assay that looks at cells in the urine for the presence of mucin and carcinoembryonic antigen. It is intended to aid in management of bladder cancer in conjunction with urinary cytology and cystoscopy.

Accu-Dx (Organon)—This is an antibody-based immunoassay that detects fibrinogen degradation products.

NMP22 BladderChek (Alere)—This test looks for a protein called Nuclear Matrix Protein 22 (NMP22) in the urine.

"Because physicians are trained to find cancer, they like a high PPV," says Anthony Shuber, co-founder and chief technology officer of Predictive Biosciences (Lexington, Mass.), which offers the CertNDx line of bladder cancer tests for hematuria assessment, staging, and monitoring. "Personally I believe that if the performance of a noninvasive diagnostic is so good, physicians will move straight to the therapeutic rigid cystoscopy" thereby eliminating the need for invasive testing to rule out cancer's presence.

Predictive Biosciences' assay, which uses a combination of DNA and protein markers, can stratify patient populations into three groups: those without bladder cancer, those who might have bladder cancer, and those who should receive the standard care. While currently guidelines do not support the use of urine markers in this way, prospective studies may provide the evidence it is safe to forgo invasive diagnostics.

"Bladder biomarkers can obviate the need for cystoscopy and are a better indicator of urothelial cancers," says R. Jeffrey Karnes, M.D., associate professor of urology at the Mayo Clinic in Rochester and investigator for Predictive Biosciences. "If it is negative there is good certainty the patient doesn't have cancer. It obviates the need for a more thorough evaluation providing some reassurance. They might have something else, but it helps risk-stratify. If it is positive there is approaching 100 percent certainty they have bladder cancer, and you can fairly confidently take them to the operating room rather than have an office cystoscopy."

The Future of Bladder Cancer Testing

While experts in urology are hopeful that national recommendations will adopt urine biomarkers in the future as a means of stratifying patients, manufacturers of these kits face other challenges, including persuading physicians to adopt the tests in routine practice and reimbursement.

Given the uncertainty of future reimbursement coupled with the challenge of reaching physicians, some companies like Scimedx are finding the international market favorable to penetrate.

"We were interested in adding the test to the company's portfolio in large part because doesn't require significant capital expense of equipment typically needed with cytometry testing," says Thomas Britten, president of Scimedx, which manufactures the uCyt assay. "The test enables laboratories to get into bladder cancer test with an easy-to-read test, without significant investment, and with a test that runs one-third the cost per test of other kits. But adoption requires significant amounts of evangelizing."

And the sales cycle can be long.

"It takes a significant amount of capital to see revenue. It may take a year or two to get a reference lab to buy a couple kits. As a small manufacturer, you must weigh where to deploy resources." But despite the frustrations, Britten tells *DTTR* he sees a future for bladder cancer testing assays. "In the future, we can't have an assay out there for every antibody. Operationally it will run cleaner if they're with a high-quality multiplex assay. I am biased, but I see cytometry getting kicked. If you have an expensive test, few will get tested. Rapid tests, an early warning screening, would be nice, especially for at-risk groups. With a cheaper, easier alternative closer to the point of care with the doctor you can find cancer before there is a big problem."

As Next-Gen Sequencing Gains Traction, Challenges Remain

Few technologies have moved from the research laboratory to the clinical realm with greater speed than next-generation sequencing (NGS), a tool that promises more information and applications with less time and money. And while millions of patients have already benefited from clinical decisions made possible by NGS, a variety of questions remain about how to most effectively deploy in clinical settings what was originally a discovery tool.

The opportunities and challenges that NGS poses for the health care system were the topic of a conference held on March 26 in Baltimore by Palmetto GBA (Columbia, S.C.). The one-day summit brought together representatives from industry, research, and the clinical community to discuss the current status, challenges, and potential next steps.

Among the first speakers of the day, Paul Billings, M.D., Ph.D., chief medical officer of Life Technologies (Carlsbad, Calif.), began by highlighting the speed, coverage, and versatility of NGS. "Virtually every week in the *New England Journal*, you see the fruits of its applications," said Billings, pointing to uses in fields ranging from oncology and inherited disease to public health and transplantation. However, the practical considerations are vast. Among the top priorities, according to Billings and subsequent speakers, are more reliable bioinformatics tools to aid in parsing and interpreting NGS data, an appropriate evidence base for clinical data and outcomes, and better education and training of a new generation of "genomic physicians."

"We had a problem—smaller and smaller biopsies—and now we have a methodology that is scalable, at our discretion."
—John Pfeifer, M.D., Ph.D.

Offering a perspective from inside a clinical laboratory, Kenneth Bloom, M.D., chief medical officer of Clarient (Aliso Viejo, Calif.), offered a more sobering take on the buzzed-about tool. Questioning whether NGS is "a technology in search of a problem or a problem in search of a solution," he expressed his belief that "Today in the clinical world, we're not really at the point where this is practical." Among the limitations to the clinical use of NGS, according to Bloom, are the time and personnel required for downstream analysis and interpretation of the data, the need for a robust computational infrastructure, and questions of how to validate NGS: for example, how do you go about selecting the "correct" sample, in light of mutational heterogeneity, and what is the minimal mutant allele burden that is detectable?

The U.S. Food and Drug Administration (FDA) is actively monitoring ultra-high-throughput sequencing-based tests. "We're learning along with everyone else," said speaker Zivana Tezak, Ph.D., associate director for science and technology in the FDA's office of in vitro diagnostics and radiological health. She offered recommendations for evaluating test performance, discussed standardization initiatives, and highlighted the need for a unified resource of clinically relevant genetic variants. As NGS platforms move toward FDA-regulated systems, the agency is committed to a flexible approach to validation and endorses a collaborative approach among agencies, said Tezak.

And then there's the issue of payment for NGS-based tests. While not a primary topic of the meeting, several speakers touched on coverage and reimbursement issues. Billings emphasized that payment for NGS-based testing should reflect the potential benefit of the test as it relates to treatment planning and outcomes, and reimbursement levels should take into account all of the steps needed to conduct a test, from reagents and equipment

to information processing and professional interpretation. "Value, not cost, is the appropriate determinant of payment for diagnostics based on these technologies," he noted.

Among the most valuable and informative presentations of the day for clinical laboratory professionals in the audience was that of John Pfeifer, M.D., Ph.D., vice chair for clinical affairs in the department of pathology at Washington University School of Medicine (Seattle). He offered a case study detailing how Wash U, a tertiary care center, is using NGS to direct patient care. Noting his belief that NGS is "really only going to have niche applications" in light of the fraction of surgical pathology cases each year that will need to have more than one gene sequenced, Pfeifer positioned NGS as a solution to limitations of slide-based assays, which require larger sample volumes.

"We had a problem—smaller and smaller biopsies—and now we have a methodology that is scalable, at our discretion," said Pfeifer of how clinical NGS is being used at Wash U, for which costs and reimbursement were not an afterthought but an important factor in the decision to use the technology. He detailed two scenarios: using NGS to guide therapy selection for non-small-cell lung cancer and using NGS to identify therapeutic targets in poorly differentiated treatment or treatment-refractory tumors. Both cases highlighted the clinical utility of NGS as well as the cost savings relative to other methods. Added Pfeifer, "We focused on genes we knew insurance companies would pay us to sequence." G2

No Negative Long-Term Personal Effects Seen With DTC Genetic Testing

More than a third of individuals completing direct-to-consumer (DTC) genetic tests share their results with their own physician within a year, and this sharing is associated with higher screening test completion, according to a study published online April 4 in the *Journal of Medical Genetics*. Additionally, there doesn't seem to be any negative long-term psychological impact from DTC testing, whether or not results are shared. The researchers say that their findings suggest that potential test regulation mandating physician participation as a gatekeeper is unnecessary.

While debate still lingers over the clinical utility and clinical validity of commercial genomic risk testing for common disease, the researchers sought empirical data to assess the psychological, behavioral, and clinical impact that testing had on participants in the year following receipt of results. The researchers studied a longitudinal cohort study of adults who purchased the Navigenics Health Compass with surveys at baseline (2008 to 2009), short (three months), and long term (one year following receipt of test results). Long-term follow-up was completed by 1,325 participants.

There were no significant detrimental psychological effects from receiving test results nor were there significant improvements in lifestyle behavioral factors. Specifically, at long-term follow-up there were no significant differences from baseline in anxiety, fat intake, or exercise. Nearly 97 percent of participants had no test-related distress.

Although there were no significant differences in the total number of screening tests completed or intended to be completed between short- and long-term follow-up, a consistent 42.4 percent of the sample reported at long-term follow-up that there was at least one or more screening tests they intended to complete with greater frequency

post-genomic testing. Screening test completion was significantly associated with sharing genomic test results with a physician and perceived utility of the test (61.5 percent perceived high utility). Just over 14 percent of participants reported discussing their results with a Navigenics genetic counselor, and 39.5 percent reported sharing their results with their own physician or health care provider.

Composite measures of genetic risk were not significantly associated with long-term follow-up anxiety, test-related distress, fat intake, exercise behavior scores, or total number of screening tests completed. However, there was a significant association between composite measures of risk and total number of screening tests participants intended to complete with greater frequency.

"It is noteworthy that a very large fraction of our long term follow-up sample also reported perceiving that they generally understood their test results and that the test had high personal utility. . . . This, coupled with the lack of adverse psychological outcomes observed, is consistent with ongoing direct access by patients to genomic testing, assuming appropriate regulatory oversight is in place," write the authors, led by Cinnamon Bloss, Ph.D., from Scripps Translational Science Institute in La Jolla, Calif.

Breath Test May Enable Rapid, Drug Toxicology Screening

A commercially available breath sampling device (SensAbues AB, Sweden) can effectively detect 12 illicit drugs in exhaled breath, according to a study published April 26 in the *Journal of Breath Research*. With an increasing focus on alternative specimens for noninvasive drug testing, the researchers say their findings may bring roadside drug testing closer to a reality.

"Since exhaled breath may be as easy to collect as in alcohol breath testing it may present a new more accessible matrix than blood at the roadside and elsewhere when the sampling procedure is an obstacle," write the authors, led by Olof Beck, an adjunct professor of analytical toxicology and pharmacology at the Karolinska Institutet in Sweden. In the future, Beck says, the test could be combined with alcohol breath tests.

Breath, plasma, and urine samples were collected from 47 patients (38 males) undergoing recovery from acute intoxication in an emergency department. Collections occurred approximately 24 hours after last intake of drugs. The commercial breath device contained a mouthpiece and filter that traps larger particles and allows only microparticles to pass through. A chromatographic method was developed that allowed for the measurement of all analytes in the same run. Urine was screened using immunochemical reagents and positive findings confirmed with liquid chromatography-mass spectrometry methods. The 12 analytes investigated were all self-reported to have been used as was one self-reported substance, ketobemidone, that was not investigated.

The researchers found that in 40 of 46 cases (87 percent) breath analysis identified one of the investigated substances. Seventy-nine of the self-reported recent intakes were supported by analytical findings in plasma or urine. Additional substances, other than those self-reported, were detected in 11 of 47 (23 percent) of cases.

Aside from demonstrating "good agreement" between data collected from breath, plasma, urine, and self-report, this study provides an expanded evidence base of analytes detected in exhaled breath. Breath analysis was for the first time able to detect alprazolam and benzoylecgonine, whereas for methadone, amphetamine, methamphetamine, cocaine, morphine, 6-AM, tetrahydrocannabinol, buprenorphine, diazepam, and oxazepam, the results confirm previous observations. The detection rate for most investigated substances appears to be high, and higher than previously reported, with the exception of benzodiazepines. To achieve an acceptable detection rate, benzodiazepines may require increased analytical sensitivity, the researchers say, especially with oxazepam. But given the 24-hour lag between drug intake and sampling, the researchers characterize the overall detection rates as rather high and suspect breath detection rates will be even higher if sampling is done closer to intake.

Beck tells *DTTR* that breath testing costs are comparable to oral fluid testing and are currently being offered routinely in select laboratories. He says that U.S. labs should "easily be able to pick this up." G2

Fasting Plasma Glucose Minimizes Need for Oral Glucose Tolerance Tests in Pregnant Women in Low-Resource Areas

A simple screening test for gestational diabetes mellitus (GDM) based on fasting plasma glucose (FPG) at 24 to 28 weeks' gestation can identify women in resource-constrained areas who might need a 75 gram oral glucose tolerance test (OGTT), according to a study published online ahead of print March 27 in *Diabetes Care*. Using a FPG value of 4.4 mmol/L as the cutoff point could eliminate the need for approximately one-half of the OGTTs required in China, the authors say.

The medical records of 24,854 pregnant women who underwent a 75 gram two-hour OGTT between 24 and 28 weeks of gestation (May 2011 through February 2012) at multiple hospitals throughout China were analyzed. Venous plasma glucose values were measured at zero (fasting), one, and two hours after the 75 gram glucose load.

The researchers found that the GDM diagnosis rate increased with rising FPG values. At values greater than 5.1 mmol/L, all 3,149 women with GDM (12.1 percent) were identified. An FPG cutoff value of 4.4 mmol/L ruled out GDM in 15,369 women (38.2 percent) and diagnosed 87.8 percent of women with GDM (specificity of 0.458). Using the cutoffs of 4.4 mmol/L and 5.1 mmol/L to determine who should have the 75 gram OGTT, there is the probability that 12.2 percent of patients with GDM may be missed.

"Women with FPG values between 4.4 and 5.1 mmol/L require a 75-g 2-h OGTT to confirm or rule out GDM," write the authors, led by Wei-Wei Zhu, M.D., from Peking University First Hospital in China. "This strategy will reduce the number of OGTTs by about half (50.3 percent)."

The authors caution that these conclusions are based on data entirely from the Chinese population but say United Arab Emirates studies also suggest the same cutoff points. G2

G2 Insider

Value of Urine Cytology Questioned for Hematuria Investigation . . . Urine cytology is of little clinical value in detecting urothelial cancers and should not be used routinely for first-line investigations of hematuria, according to a study published in the April issue of the *Journal of Urology*. The authors call for removal of urine cytology from current clinical hematuria guidelines.

The U.K. researchers analyzed data from 2,778 consecutive patients investigated for hematuria at a teaching hospital (January 1999 to September 2007). Patients underwent standard hematuria investigations including upper tract imaging (ultrasound and subsequent excretory urogram [IVP] or computerized tomography urogram, if necessary) and cystoscopy. Cytology findings were classified as negative (76.4 percent), malignant cells identified (4.5 percent; 124 patients), atypical/suspicious cells identified (9.4 percent; 260 patients), or unsatisfactory specimen (2.3 percent). In the analysis, suspicious and atypical cytology were combined with malignant samples.

In this study, the sensitivity for diagnosing urothelial carcinoma was 45.4 percent and the specificity was 89.5 percent with a false-positive rate of 10.5 percent, a false-negative rate of 54.6 percent, a positive predictive value of 40.9 percent, and a negative predictive value of 89.5 percent. Of the 2,778 patients, only two had a negative cystoscopy, ultrasound, and IVP with a positive cytology that was eventually diagnosed as urothelial carcinoma, meaning only two patients benefited from urine cytology.

"However, in the era of cost conscious medicine these rare and anecdotal cases cannot justify the routine use of a test with such a limited net contribution," writes Badar M. Mian, from the Stratton VA Medical Center in Albany N.Y., in an accompanying editorial.

The authors argue that urine cytology is not cost-effective in a low-risk population both for the cost of the test itself as well as the additional costs associated with false positives. Based on European estimates, the cost of urine cytology is approximately $61 per test. The further invasive endoscopic assessment, repeat cytology, and radiological upper tract imaging costs resulting from false positives total an estimated $18,400 per patient.

Company References

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Aurora Diagnostics 561-626-5512
Autogenomics 760-477-2251
Cancer Genetics 201-528-9200
Genomic Healthcare Strategies 617-715-3508
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