G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

Issue 4-13/April 2013

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Study Shows Noninvasive Prenatal Testing Is Clinically Beneficial and Cost-Effective

Noninvasive prenatal testing (NIPT) improves detection of trisomy 21 (T21) with lower total health care expenditures compared to conventional screening methods. A study in the *Journal of Maternal-Fetal and Neonatal Medicine* highlights the cost-effectiveness of NIPT with cell-free DNA in high-risk women. NIPT test makers, including Ariosa Diagnostics (San Jose, Calif.), which funded the study, are hopeful that such data will enhance ongoing reimbursement discussions with payers.

The researchers used a decision-analytic model with a cohort of 4 million pregnant U.S. women and three screening strategies: first trimester combined screening, integrated screening, or NIPT (first-line testing in women 35 years or older or those with a personal or family history that elevates risk or as a second-line test in women with a positive conventional screening test).

NIPT was shown to have clinical benefit over conventional screening tests (detected 65 percent to 85 percent more T21 cases, reduced invasive procedures by over 95 percent, and reduced more than 99 percent of unnecessary fetal loss). At a price point of $795 per test, NIPT demonstrated cost savings to the health care system over both other strategies. For more information on how studies of clinical utility and cost-effectiveness impact coverage and reimbursement of next-generation sequencing-based tests, please see *Inside the Diagnostics Industry* on page 5.

Strategic Divestitures of Diagnostics Seen As Companies Refocus Resources on Core Business

Recent acquisitions in the diagnostics in the industry have been notable, not for being of blockbuster size, but rather because they represent a trend toward continued focus on strategic growth and, increasingly, divestiture of assets not core to the company's franchise.

"Broadly speaking diagnostics is an area of faster growth, relative to the rest of health care, and players are looking to seal up a leadership position in a certain space or get into a faster-growing piece of that space, which is molecular," says Nicholas Jansen, an associate health care analyst at the investment firm Raymond James and Associates. "But there is probably much more of a laserlike focus on what makes a good acquisition target than five years ago."

An examination of transactions in the first quarter of 2013 reflects strategic acquisitions likely to improve the leadership position of the acquirer in a

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▲ **Strategic Divestitures of Diagnostics Seen,** *from page 1*

specific market and an opportunity for the seller to consolidate its resources on its most promising channels.

For instance, Quest Diagnostics (Madison, N.J.) announced at the end of February that the company signed a definitive agreement to sell its HemoCue diagnostic products business to Radiometer Medical ApS (a Danaher company, Denmark) for approximately $300 million. HemoCue is focused on point-of-care hemoglobin and glucose testing systems and will complement Radiometer's portfolio of acute-care point-of-care products. Quest CEO Steve Rusckowski said at the time of the announcement that the divestiture, along with Quest's sale of its dental OralDNA unit in December 2012, was part of the company's strategic plan to refocus its efforts on diagnostic information services.

Similarly, HYCOR (Garden Grove, Calif.), a maker of diagnostic products for the allergy and autoimmune markets, sold its urinalysis business to private equity firms Laurel Crown Partners and StoneCreek Capital in mid-February. Financial terms of the deal were not disclosed, but the urinalysis business will be renamed Kova International, after its flagship Kova system of urinalysis products. In a statement, Dick Aderman, CEO of HYCOR, said the divestiture will better position HYCOR to grow its pipeline of allergy and autoimmune products, which share "important synergies" including common platform and the same target users, both in the clinic and in the laboratory.

Refocusing of Capital Critical With Fewer Investment Dollars

This strategic focus on core competencies is critical, particularly for privately held companies, given new data showing that venture capital investments are increasingly difficult to obtain.

The 2012 *MoneyTree Report* by Pricewaterhouse Coopers and the National Venture Capital Association, based on data from Thomson Reuters, found that both the biotechnology and the medical device segments experienced double-digit drops in investment dollars in 2012 (15 percent and 13 percent, respectively), compared to 2011. While the life sciences sector (biotech and medical device segments combined) accounted for 25 percent of all venture capital dollars invested in 2012 ($6.64 billion over 779 deals), decreased investments were seen across companies of all stages of development with investments into seed-stage life science companies experiencing a 31 percent decrease in investment dollars, reaching the lowest annual seed dollars since 2003.

"Investors are paying more attention that capital is being employed in the most shareholder-friendly fashion," says Nicholas Jansen, an analyst at the investment firm Raymond James and Associates. "Investors expect acquisitions to drive existing franchises. They don't want ones that take a long time to build out. Scale is needed to survive."

J&J Looks to Divest Ortho Clinical

Notably Johnson & Johnson (New Brunswick, N.J.) said in late January that it is interested in divesting itself of its Ortho Clinical Diagnostics business, either through a sale or a spinoff of the company. The Raritan, N.J.-based unit had 2012 sales of $2.07 billion, a 4.4 percent drop compared to 2011, J&J reported. The Ortho Clinical Diagnostics business unit, which includes a portfolio of chemistry and immunodiagnostic systems for clinical laboratories as well as blood screening diagnostics, is No. 5 in the diagnostics market based on its sales, Reuters reports. J&J does not believe the diagnostics unit will contribute strongly to its overall future growth.

"When you look at diagnostics, we have good technology and a lot of good businesses, but they are not No. 1 or 2 in the market," J&J CEO Alex Gorsky told an investor conference when reporting the company's 2012 financial results.

Jansen says J&J is looking to "monetize the asset" and deploy the resources in an area where they are a market leader. While in totality these sales mark individual

company needs and not an exodus from the diagnostics space, Jansen does expect acquisitions to reflect this trend toward continued concentration on establishing scale and leadership within specific diagnostics markets.

Hologic's (Bedford, Mass.) announcement in early January that it entered into a definitive agreement to sell its transplantation diagnostics unit LIFECODES to Immucor (Norcross, Ga.) provides further evidence of this trend. LIFECODES, which specializes in pretransplant human leukocyte antigen typing, had previously been part of Gen-Probe, which Hologic acquired in August 2012. The $85 million cash acquisition (with an additional $10 million in milestone-related payments) solidifies Immucor's leadership position in the transfusion area by broadening its reach to organs and stem cells. At the same time the deal allows Hologic to concentrate on the portion of the Gen-Probe portfolio most interesting to it—the women's health segment as well as the Tigris and Panther systems.

AMA, McKesson to Offer New Product Mapping CPT, Z-Codes in 2014

The American Medical Association (AMA) and the consulting and revenue management firm McKesson have announced a licensing agreement that will allow the AMA to create a new reference product mapping McKesson's Z-Codes, identifiers for specific molecular diagnostic tests, to the AMA's Current Procedural Terminology (CPT) code set. The product, which is expected to become commercially available in 2014, is intended to improve identification and tracking of molecular diagnostic tests.

While the real-life implications of this agreement for the laboratory and diagnostics industries are not yet fully understood, experts don't believe the product is likely to impact reimbursement levels or affect the current process of assigning pricing to existing molecular pathology CPT codes.

"We believe this product will bring clarity and take some of the confusion out of the market [surrounding molecular diagnostic tests]. This is about specificity of use and we believe this is a good tool to improve the identification and tracking of tests," Robert Musacchio, Ph.D., AMA's senior vice president for business products and services, tells *DTTR*. "We believe this will improve communication among physicians, laboratories, and payers."

Musacchio says that improved description and quantification of molecular diagnostic tests has the potential to better assess the value of a test and can likely aid in more efficiently establishing effective pricing and coverage policies. In initial discussions with the AMA, he says, private payers have expressed interest in the product.

While financial terms of the AMA-McKesson arrangement were not disclosed, the organizations say that the new reference product mapping Z-Codes to CPT codes will be available for licensing from AMA in early 2014. Not all of McKesson's 2,000-plus Z-Codes are expected to immediately map to CPT codes, and some of the current CPT codes will be associated with multiple Z-Codes.

Despite the AMA's previous opposition to Z-Codes (in 2011 the AMA charged that use of Z-Codes in Palmetto's MolDx molecular diagnostic payment program violated the Health Insurance Portability and Accountability Act), this marks the second recent step the AMA has taken to improve transparency in the rapidly growing molecular diagnostics market. In late January the AMA agreed to integrate its CPT codes into the National Institutes of Health's Genetic Test Registry.

Ridge Diagnostics Nears National Launch of Depression Test

Ridge Diagnostics (La Jolla, Calif.) is preparing a national commercial launch for its MDDScore test for the diagnosis of major depressive disorder. The multianalyte proteomic assay gives patients and physicians an objective measure for diagnosis, and developers believe it can lead to more successful treatment.

"The first thing is we need to get the right diagnosis," says Lonna Williams, Ridge's CEO. "Half of anti-depression prescriptions don't work. Contributing to that is that a patient might have depressionlike symptoms, but they may not actually have depression."

The enzyme-linked immunosorbent assay is based on nine biomarkers associated with four biochemical pathways: inflammatory (alpha1 antitrypsin, apolipoprotein CIII, myeloperoxidase, soluble tumor necrosis factor alpha-receptor type II), the hypothalamic-pituitary-adrenal axis (epidermal growth factor and Cortisol), neurotrophic (brain-derived neurotrophic factor), and metabolic (prolactin and resistin). Concentrations of the biomarkers are entered into an algorithm to calculate the MDDScore, which is presented as a value one through nine with an increasing value equating to an increasing likelihood of major depressive disorder—a score of eight represents an 80 percent likelihood.

"It helps for patients to see objective results," Williams tells *DTTR*. "When they see it is a disease it is more likely the stigma goes away. Their family understands it is a physical thing and psychiatrists have told us the patient is then more compliant with their treatment plan. It is a big positive for both patients and physicians."

The test is run out of Ridge Diagnostics' CLIA-certified laboratory in Research Park Triangle, N.C. The blood-based test is currently turned around in five days and lists for $745. The company's long-term reimbursement strategy is to contract directly with payers as the company believes there is an economic case for the test. Ridge Diagnostics has seen positive coverage decisions in its two pilot markets. A sales force has already begun selling directly to community-based psychiatrists in 15 major metropolitan areas.

In addition to the MDDScore, the company says its biomarker hypermapping affirms the heterogeneity of depressed populations and can aid in the subclassification of patients. Williams says the company is using this insight to pursue partnerships with pharmaceutical companies. The privately held company is also developing a separate test that will be used to monitor response to anti-depressants based upon changes in physiological markers. Preliminary data show that within one week response to treatment can be detected.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Next-Gen-Based Tests Face Significant Reimbursement Hurdles

During the first quarter of 2013 all eyes have been focused on early coverage and pricing decisions for molecular tests during the gap-filling transition to the new molecular pathology (MoPath) Current Procedural Terminology (CPT) codes. Like most molecular tests, tests utilizing next-generation sequencing (NGS) technology face challenges in establishing positive reimbursement decisions from payers and proving clinical utility. But NGS-based tests face an even greater battle for reimbursement since testing volumes remain low and the technology does not yet have dedicated CPT codes, making the desired test transparency virtually impossible.

The new MoPath codes are intended to bring greater transparency to laboratory coding for tests and allow payers to better track test utilization. But standardized evidence thresholds to prove clinical utility remain elusive, and test developers must pursue coverage and reimbursement conversations with each payer individually.

"The CPT system is just not structured to incorporate innovation as fast as it occurs."
—Jerry Conway, Foundation Medicine

"There is a great deal of uncertainty when it comes to reimbursement in part because of the deficit in education in molecular testing as a whole," says Jerry Conway, vice president of reimbursement and payer strategy for Foundation Medicine (Cambridge, Mass.). "As the system of payment evolves to accommodate other molecular technologies that have been on the market longer and drive higher volumes of testing, NGS tends to be back-burnered."

With the vast amounts of resources being dedicated to the transition to MoPath CPT codes in 2013, many fear that establishing reimbursement for NGS-based tests, may get pushed back even further in the queue.

"The CPT system is just not structured to incorporate innovation as fast as it occurs," Conway tells *DTTR*. "But in sharp contrast [to the reimbursement system] is the rapid migration of NGS to the clinic. Providers see the promise of being able to analyze enormous amounts of DNA data and to distill it down to actionable information."

The Promise of Next-Gen

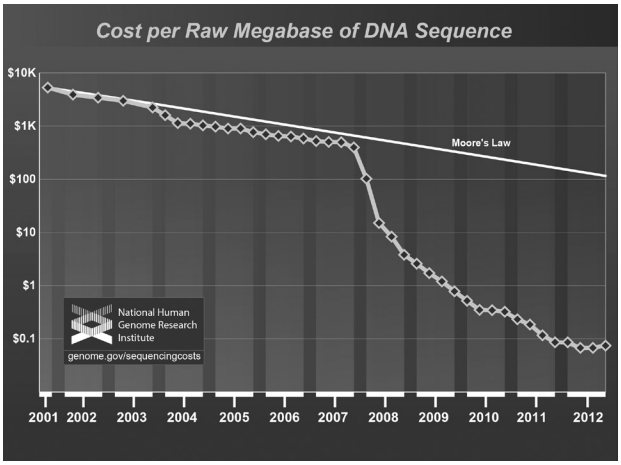
Technically NGS is capable of generating much more information than traditional molecular diagnostic assays at greater speed and volume. The research community is adopting NGS for complex genomic analyses, and NGS-based testing is emerging in clinical practice for applications such as pediatric inherited disorders and somatic mutation panels for treatment selection in oncology cases. As the number of known mutations of clinical significance increases, so too is the case that NGS is becoming the most cost-effective means for assessing all of these variants.

"We can anticipate for the foreseeable future that the current NGS paradigm will continue to evolve with improvements in performance, accuracy, and instrumentation options that will further facilitate clinical translation," writes the Whole Genome Analysis Working Group of the Association for Molecular Pathology (AMP) in a report published in the November 2012 issue of the *Journal of Molecular Diagnostics*. "The balance of time and effort required for NGS-based research or diagnostics is substantially shifted toward data analysis, as opposed to the technical component required to generate the data."

Most acknowledge, though, that sequencing technology has currently advanced beyond clinicians' ability to meaningfully apply all of the data generated.

"There is a disconnect. Technology vendors rolling out tests are ahead of physician adoption and professional societies," says Amanda Murphy, an analyst at William Blair & Co. "There are some personalized medicine cancer panels that are well established and it may be cheaper or the same price to look at 20 variants than one in Sanger, so it may be reasonable for sequencing technology to evolve, but whole-genome is way far away. NGS is really in the very early stages."

Production Cost of Sequencing



Source: *National Human Genome Reserach Institute*

There is much talk of the rapidly declining cost of genome sequencing. Falloff in production associated-costs are imperative for NGS-based tests to be priced in such a way to make clinical value possible and to generate the large amounts of quality DNA sequence data needed in public databases to find meaningful phenotypic associations. But costs associated with nonproduction activities, including the data analysis downstream of initial data processing, are not factored into the free-falling price models and need to be addressed to make whole-genome or whole-exome sequencing clinically feasible.

Lessons Learned From Noninvasive Prenatal Testing

Some clinicians have expressed interest in early NGS tests, but test adoption is too nascent to see trendlike behavior on the part of payers, with the exception of in noninvasive prenatal testing (NIPT), where a flurry of coverage activity is beginning to emerge from behind closed-door conversations. Most of the nations' top health insurance companies including United Healthcare, Aetna, and Wellpoint have announced positive coverage decisions for NIPT using circulating cell-free fetal DNA in maternal plasma. Blue Cross Blue Shield became the first carrier to announce positive coverage not just in high-risk women.

"We started to see positive coverage decisions really starting in December," says Brian Weinstein, an analyst at William Blair & Co. who covers Sequenom. "All that means is that they see the test as medically necessary and will cover it for their members. However, they did not state a price point, so now it is incumbent on the labs running these tests to negotiate plan by plan."

All of the players in the space are in negotiations for pricing and contracting and "some clarity" should emerge in the next couple months, Weinstein says.

"From my perspective things are going quite well with reimbursement overall for NIPT. It is a stepwise process with positive coverage happening nearly universally with national payers and moving forwards with regional players," says Ken Song, M.D., CEO of Ariosa Diagnostics (San Jose, Calif.), which makes the Harmony Prenatal Test to detect trisomies 13, 18, and 21. "This is a tremendous

step forward, especially because the technology has really just introduced in the market for one year."

Song tells *DTTR* that adoption of NIPT tests has been rapid with an annualized rate of 250,000 tests expected to be run this year, across NIPT companies. Both Quest Diagnostics and LabCorp announced in February that they will be offering different companies' versions of NIPT tests.

Will Other NGS Tests Follow?

In addition to NIPT, payers are covering some multigene sequencing panels, more often performed with Sanger or microarray-based sequencing. As the technology transitions to NGS, for reasons of cost and complexity of data analysis, these targeted testing approaches are likely to lead both in adoption and in receiving reimbursement.

"There are some lessons learned from NIPT," explains Song. "First, the clinical value proposition is very clear. NIPT is improving upon something done today. With so many companies' genetic or sequencing tests they think have such great clinical value, but it is not part of the current standard of care or physician workflow. . . . Secondly we have [collectively] generated a tremendous amount of study data, with 6,000 patients alone in our lab. Having value, improving upon the existing market, and a ton of clinical data is a recipe for success."

But outside of NIPT, Murphy says NGS volumes are low, and given the existing coding structure, even when tests are being performed, they are still flying under the radar of payers.

"In cancer, as in other disease states, payers understand some of the issues that are surfacing as molecular testing is performed on a marker-by-marker basis and recognize the importance of transitioning to NGS testing over time," explains Conway. "It is therefore critical that NGS providers obtain sufficient funding in order to drive the development of adequate evidence through well-designed clinical trials, publications in peer-reviewed journals, and advocacy for inclusion in guidelines. . . . We have to generate the data to support the payers' decisionmaking process."

As for Foundation Medicines' comprehensive genomic analysis for cancer care, the company says that it is hard to determine what the impact of the MoPath CPT changes will be this year, but it is steadfast in its belief that the entire molecular diagnostics industry must continue to "take steps to build the case for a value-based approach to reimbursement."

NGS claims starting in January 2013 will need to use the new MoPath Tier 1, Tier 2, and/or miscellaneous (81479) codes. Conway emphasizes there could be 10 different ways to build a spreadsheet using a combination of Tier 1 and Tier 2 codes, and different payers may want claims delivered in unique ways.

The AMP says that "it is close" to finalizing a framework proposal for CPT coding for NGS assays that it will then submit to the American Medical Association in the hopes of obtaining NGS-specific CPT codes. To obtain a CPT code, test developers must have demonstrated clinical utility. Also complicating efforts to obtain NGS CPT codes is the issue of interpretation of test results, which some argue should be billed on the physician fee schedule with a component for professional services, which laboratory Ph.D. genetic experts are not eligible for.

High Serum Calcium May Indicate Ovarian Cancer

Higher serum calcium may be a biomarker of ovarian cancer, according to a study published Jan. 9 in *Gynecologic Oncology*. With further validation, serum calcium may aid in filling the present gap in biomarkers capable of detecting ovarian cancers earlier, at a more curable stage.

While acknowledging that only a small minority of ovarian cancers are actually characterized by hypercalcemia, the researchers theorized that since many ovarian cancers express parathyroid hormone-related protein, which acts to raise calcium levels in serum, higher serum calcium levels might predict ovarian cancer.

The Wake Forest University researchers used data from two independent, nationally representative population-based cohorts. In the primary analysis, using data from the third National Health and Nutrition Survey (NHANES III; 1988 to 1994), the researchers found that both higher ionized and total serum calcium were associated with ovarian cancer mortality. The risk for fatal ovarian cancer was 52 percent higher for each 0.1 mmol/L increase in total serum calcium and 144 percent higher for each 0.1 mmol/L increase in ionized serum calcium, the biologically active fraction of total serum calcium. These associations persisted after adjusting for nulliparity and the use of oral contraceptives.

In a second confirmatory analysis using data from the NHANES Epidemiological Follow-up Study, there was an association between serum calcium and incident ovarian cancer. There was a 63 percent higher risk for ovarian cancer with each 0.1 mmol/L increase in total serum calcium (95 percent CI 1.14–2.34) after adjusting for other covariables. The association was strengthened to a 75 percent increased risk after adjusting for nulliparity and use of oral contraceptives. G2

Polygenic Causes of Hypercholesterolaemia Minimize Effectiveness of Cascade Testing

Familial hypercholesterolaemia can be caused by an accumulation of common small-effect alleles instead of a dominant monogenic mutation, which could compromise the efficiency of cascade testing, according to a study published online Feb. 22 in *Lancet*. The authors suggest such cascade testing should be restricted to patients positive for one of three known dominant autosomal mutations, rather than those with polygenic causes of hypercholesterolaemia.

Patients with familial hypercholesterolaemia typically have significantly escalated low-density lipoprotein cholesterol (LDL-C) and a five to eight times increased risk of early coronary heart disease. However, there is no single accepted criterion for the diagnosis of the condition. Clinical diagnosis misses significant numbers of patients, and genetic testing is complicated by the polygenetic nature of the condition. A strategy of cascade testing of first-degree relatives of an index patient with DNA-confirmed hypercholesterolaemia is employed in several European nations and New Zealand, but the effectiveness of this strategy may be compromised with these findings of polygenic causes of the condition.

"The inclusion of probands with polygenic rather than monogenic cause of hypercholesterolaemia would reduce the efficiency of any cascade screening program, since

much less than the expected 50 percent of first-degree relatives would be affected," write the authors, led by Philippa Talmud, D.Sc., from University College London (United Kingdom). "Therefore, identification and exclusion of individuals with polygenic hyperlipidaemia would enhance and enrich any cascade testing program."

Mutations in one of three genes are known to cause familial hypercholesterolaemia (LDLR, APOB, and PCSK9) but are onlydetected in 40 percent of patients suspected of the disorder, the authors say.

In the *Lancet* study data from a sample of 640 U.K. patients with familial hypercholesterolaemia (321 mutation-negative and 319 mutation-positive patients) were compared to a sample of 3,020 healthy controls. For validation analyses 451 mutation-negative and 273 mutation-positive Belgian patients were assessed. All participants were genotyped for 12 common LDL-C-raising alleles identified by the Global Lipid Genetics Consortium and a weighted LDL-C-raising gene score was constructed.

The researchers found the mean weighted LDL-C gene score of the controls was strongly associated with LDL-C concentration. Controls in decile 10 of the LDL-C score distribution had a much higher likelihood than those in decile 1 of having LDL-C concentrations above the diagnostic threshold of 4.9 mmol/L.

In primary analysis, mutation-negative patients with hypercholesterolaemia had a significantly higher mean weighted LDL-C score controls, as did the mutation-negative patients in validation analyses. Twenty percent of these patients had a score that fell within decile 10 of the controls' LDL-C score distribution, 52 percent had a score within deciles 7 to 10, and 11 percent had a score within deciles 1 to 3. This suggests, the authors say, that a substantial proportion of the mutation-negative familial hypercholesterolaemia group's raised LDL-C concentrations can be explained by coinheritance of common LDL-C-raising single nucleotide polymorphisms. Mutation-positive patients, both in primary and validation analyses, also had significantly higher LDL-C scores than controls, suggesting that even in patients with a detected causative mutation, their raised LDL-C concentrations have an additional polygenic component.

Universal Cancer Test May Be Possible From Circulating Tumor DNA

Sequencing cell-free tumor DNA from a patient's blood can identify chromosomal alterations that can aid in the diagnosis of cancer, as well as the selection of treatment and monitoring for cancer recurrence. This proof-of-principle may ultimately lead to a universal blood-based screening test for cancer and the ability to treat cancer without invasive biopsies, according to the authors of a study published in *Science Translational Medicine*.

The authors used massively parallel whole-genome sequencing to compare circulating cell-free DNA from 10 late-stage colorectal cancer and breast cancer patients to 10 healthy subjects. The researchers were able to detect chromosomal aberrations (both copy number changes and rearrangements) in plasma from all of the patients. The detected alterations included amplification of cancer-driving genes ERBB2 and CDK6, both targetable with anti-cancer drug treatments. The copy number variations observed from DNA in blood samples matched samples from resected tumor in three of the colorectal cases, whose tumors were analyzed.

"Rearrangements and copy number changes are the hallmarks of cancer and we were able to find both in every case without knowing if the patient had cancer," says Victor Velculescu, M.D., Ph.D., co-director of the Cancer Biology Program at Johns Hopkins University (Baltimore) and co-author of the study. "We have developed a way to identify cancer from circulating tumor DNA without scans, without invasive biopsies."

Additionally, the authors quantified their ability to discriminate between cancer patients and healthy subjects by analyzing simulated mixtures of varying concentrations of tumor and control DNA. Tumor DNA could be detected at concentrations as low as 0.75 percent in the plasma of patients (sensitivity >90 percent and a specificity >99 percent). The authors acknowledge though, that in early-stage cancers, circulating concentrations may be lower and more difficult to detect without more extensive sequencing, as the sensitivity and specificity parameters were dependent on the amount of sequence data obtained.

Velculescu tells *DTTR* that perhaps in five years it would be possible to give 40-year-olds a blood-based screening test to identify if they have an early form of cancer. Such a test is still too expensive with current sequencing approaches, but the technology could begin to be implemented into clinical care for management of medium to late-stage cancers "in the next couple years."

Comprehensive Guidance Updated for Genetic Testing in Kids

Updating policies written over the past two decades, the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) have issued a comprehensive joint statement about genetic testing and screening of newborns and children. The new statement was issued in light of rapid proliferation of genetic testing and rise of new technologies since the initial sequencing of the human genome. The technical report was published Feb. 21 online in *Genetics in Medicine* to coincide with the online release of the policy statement in *Pediatrics* on Feb. 21.

Regardless of the testing circumstance, the groups emphasize two themes—the best interest of the child and that genetic testing should be offered with genetic counseling, which is acknowledged to be in short supply and will compel better genetics education among other health care providers. In the most straightforward situation, diagnostic genetic testing in symptomatic children is similar to any other medical diagnostic evaluation. However, the groups write "if the medical benefits of a test are uncertain, will not be realized until a later time, or do not clearly outweigh the medical risks, the justification for testing is less compelling."

The statement though, does not entirely rule out predictive genetic tests in asymptomatic children, although the groups do differentiate childhood-onset from adult-onset conditions. Parents are encouraged to pursue predictive genetic testing for asymptomatic children at risk of childhood-onset conditions, while predictive testing for adult-onset conditions is only advised if medical interventions during childhood are available to treat, prevent, or retard the later course of the disease. The AAP and ACMG also addressed genetic testing of children in other situations:

Newborn screening. The AAP and ACMG support the mandatory offering of newborn screening for all children but believe parents have a right to have informed refusal. If

carriers are identified during screening, carrier status should be disclosed.

Carrier screening. The groups do not support routine carrier testing or screening for recessive conditions if carrier status has no medical relevance during childhood.

Histocompatability testing. Tissue compatibility testing of minors of all ages for stem cell donation is permissible to benefit immediate family members, the groups say.

Disclosure of results. Ideally, health care providers and parents or guardians should address disclosure issues before genetic testing. A provider's legal duty to disclose results remains "unsettled."

Direct-to-consumer genetic testing. The AAP and the ACMG strongly discourage the use of DTC and home-kit genetic testing of children.

Biobank Diversity Presents Management Challenges

The diversity of biobanks presents challenges for management, conclude researchers, who urge that governing policies take into account the nuances of individual biobanks. While recognized for their increasingly significant role in biomedical research, biobanks as a whole remain generally uncharacterized. A new study, published Jan. 25 in *Genome Medicine*, begins to systematically study the entities.

No single registry is kept of biobanks, which the researchers define as organizations that collect, store, and share human specimens for research purposes. The researchers identified 636 biobanks, of which 456 participated in an online survey. Among the key details discovered about the organizations are:

- **Age**. Two-thirds of biobanks were established in the last decade, but 17 percent have existed for more than 20 years.
- **Focus**. More than half (53 percent) were established to research a particular disease. Biobanks established after 2003 (the sequencing of the human genome) were significantly more likely to have been created to focus on research generally.
- **Size**. There is a great disparity in the size of biobanks with a few very large specimen collections in existence (range in number of specimens stored under 100 to 50 million; mean number 461,396; median number 8,000).
- **Specimens**. The majority (87 percent) store more than one type of specimen with serum/plasma (77 percent) the most common, followed by solid tissue (69 percent).
- **Specimen source**. Stored pediatric specimens (44 percent) and post-mortem specimens (36 percent) were common. Residual specimens from hospitals and other clinical settings were the source for 57 percent of stored samples.
- **Organization**. The majority (88 percent) are embedded in a larger organization.
- **Funding**. The federal government (36 percent) and the biobanks' parent organization (30 percent) are the largest sources of funding.

"Given different stakeholders and missions, it is unlikely that one-size policies will fit all biobanks, but attention to organizational diversity is critical for the promotion of appropriate and effective biobank governance," write the study authors.

G2 Insider

Zinc Protoporphyrin May Be Effective Screen for Iron Deficiency in Infants . . . Zinc protoporphyrin (ZPP) may be a simple screening test for iron deficiency (ID) and iron deficiency anemia in infants and toddlers, according to a study published online Feb. 18 in *JAMA Pediatrics*. Despite recommendations for universal screening for ID in all 1-year-olds, diagnosis remains a challenge for primary care clinicians because of the lack of an ideal screening test.

The authors say that using hemoglobin as a first screen misses large groups of infants with ID without anemia. The 2010 American Academy of Pediatrics recommendations call for screening for ID with ferritin and C-reactive protein or serum transferrin receptor-1 saturation and reticulocyte hemoglobin level, which are not routinely available to practitioners.

"The [ZPP] test is cheap and can be done on capillary blood at the point of service," writes Robert Baker, M.D., Ph.D., from Children's Hospital of Buffalo in N.Y., in an accompanying editorial. "However, there are a number of factors that affect ZPP levels including lead poisoning, myelodysplasia, chronic inflammation, and altered iron metabolism."

The *JAMA Pediatrics* study retrospectively reviewed longitudinal electronic medical records data collected at a primary care center (2002 to 2010) among 2,612 kids (between the ages of 8 months and 18 months) seen for routine care, all with baseline and follow-up screening results for complete blood cell count, lead, and ZPP. ZPP had been previously analyzed to screen for lead toxicity. ZPP was measured using hematofluorometry with abnormal levels defined as greater than or equal to 35 µg/dL.

At baseline 48 percent of children had an abnormal ZPP level, with 84 percent of these children not testing as anemic. Abnormal ZPP was not significantly associated with race or ethnicity. Among those with abnormal ZPP, 18 percent were prescribed iron. At follow-up, iron prescription was significantly associated with a reduction in abnormal ZPP results among those who were anemic and was tied to a substantial, but not statistically significant, trend to improvement in those prescribed iron with low-normal hemoglobin.

Company References

American Academy of Pediatrics 847-434-4000

American College of Medical Genetics and Genomics 301-718-9603

American Medical Association 800-621-8335

Association for Molecular Pathology 301-634-7939

Ariosa Diagnostics 855-927-4672

Foundation Medicine 617-225-0739

Hologic 781-999-7300

HYCOR 714-933-3000

Immucor 678-969-9435

Johnson & Johnson 732-524-0400

McKesson 415-983-8300

Quest Diagnostics 800-222-0446

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Ridge Diagnostics 800-578-7818

April 2013

Diagnostic Testing & Technology Report (ISSN 1531-3786) is published by G2 Intelligence, 17 Church Street, Suite 100, Keene, NH 03431-3885. Tel: 800-531-1026 or +1 603-357-8101. Fax: +1 603-357-8111. Web site: www.G2Intelligence.com.

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