G2 INTELLIGENCE

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USAF Initiates Study to Link Genetic Data To EMR-Based Decisionmaking

While it will be several years before genetic information will be widely integrated into electronic medical records (EMRs) for clinical decisionmaking, several efforts are under way to evaluate best practices for incorporating the data. In late spring Coriell Institute for Medical Research (Camden, N.J.), announced an alliance with the U.S. Air Force Medical Service. The collaboration between the two organizations unites Coriell Personalized Medicine Collaborative (CPMC) Clinical Utility Study with the USAF Patient-Centered Precision Care Personalized Medicine (PC2-Z) program.

Recruitment has already begun to target 2,000 active duty Air Force Medical Service (AFMS) personnel for participation in the longitudinal study over the next six years. Participants will submit saliva specimens for DNA analysis and will complete online medical, family history, and lifestyle questionnaires. Participants will receive personalized risk results for actionable medical conditions and can opt to have their deidentified data used for studies linking genetic variants to diseases and medication response.

"PC2-Z will systematically review, evaluate, and summarize medical evidence regarding genomic associations that are clinically actionable for application in clinic settings and [will] develop and enhance existing AFMS information technology systems to capture and analyze genetic information for enhanced clinical decision making," said PC2-Z Program Director Major (Dr.) Cecili Sessions in a statement.

For more information on how increased EMR utilization will affect laboratory testing, please see *Inside the Diagnostics Industry* on page 5.

New Tests Aim to Reduce Unnecessary Thyroid Surgeries Through Improved Molecular Testing

Two companies, Quest (Madison, N.J.) and Veracyte (San Francisco), have recently launched molecular panels aimed at improving the accuracy of thyroid cancer diagnosis. The panels are intended to better assess the risk of malignancy in patients with indeterminate thyroid cytology results and improving clinical management of these patients by reducing the number of unnecessary thyroid removals in patients with benign cases.

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▲ **New Tests Aim to Reduce Unnecessary Thyroid Surgeries,** *from page 1*

These tests directly address the 2009 American Thyroid Association guidelines recommending molecular testing for markers associated with malignancy in patients with indeterminate fine-needle aspirate (FNA) cytology. Experts say that 15 percent to 30 percent of the estimated 350,000 FNA biopsy samples tested each year in the United States produce indeterminate results.

Veracyte, which nationally launched its Afirma gene expression test in April in partnership with Genzyme (a Sanofi company; Cambridge, Mass.), presented results of a large, prospective, multicenter study at the Endocrine Society's annual meeting (Houston; June 23-26). The company says the study, which was also published June 25 in the *New England Journal of Medicine*, demonstrates the ability of its test to reduce the number of unnecessary surgeries by more than half.

> ***"Approximately half of all patients with indeterminate thyroid nodule cytology will have a benign gene expression test. This means that tens of thousands of thyroid nodule patients in the United States each year can potentially be spared a thyroid surgery they do not need."***
>
> ***—Erik Alexander, M.D., Brigham and Women's Hospital***

The Afirma Gene Expression Classifier evaluates 142 genes to classify indeterminate FNA samples as benign or suspicious for cancer. The test also uses 25 supplemental genes to improve classification of rare cancer subtypes. In a study of 265 indeterminate thyroid FNA samples the genomic test had a negative predictive value of 93 percent, based on the study's cancer prevalence rate of 32 percent. The test had a sensitivity of 92 percent and a specificity of 52 percent.

"Approximately half of all patients with indeterminate thyroid nodule cytology will have a benign gene expression test. This means that tens of thousands of thyroid nodule patients in the United States each year can potentially be spared a thyroid surgery they do not need," says co-principal study investigator Erik Alexander, M.D., from Brigham and Women's Hospital in Boston. "The gene expression test, when benign, should now enable physicians to consider recommending against surgery and confidently monitor patients in a more conservative fashion."

An economic impact study, published in the *Journal of Clinical Endocrinology & Metabolism* in November 2011, concluded that routine use of the Afirma test would provide more than $600 million in direct medical savings over five years. The test, which lists for $4,200 and is covered by Medicare, costs significantly less than thyroid surgery, which can run from $10,000 to $15,000 per patient, says Bonnie Anderson, Veracyte's co-founder and CEO. To date, Anderson says, the company has processed more than 3,000 Afirma Gene Expression Classifier tests and the company's CLIA-licensed laboratory has the capacity to handle a fourfold volume increase with existing equipment.

Quest Diagnostics (Madison, N.J.) launched a comprehensive panel of four molecular markers—BRAF and RAS mutations, RET/PTC rearrangements, and PAX8-PPARγ translocations. A recent study by researchers from Quest's research and development center, the Nichols Institute (San Juan Capistrano, Calif.), presented at the annual

meeting of the American Society of Clinical Oncology (Chicago; June 1-5) shows that in addition to identifying cases most likely to be malignant, the high prevalence of mutations found using the test suggests its potential application in determining targeted therapeutic strategies.

Using a combination of polymerase chain reaction and pyrosequencing the test identified that more than 60 percent of the 149 thyroid FNA specimens tested had at least one of the four molecular markers, with the presence of a marker usually being mutually exclusive. The company says the mutually exclusive pattern of alterations suggests a hierarchical screening strategy makes sense for small samples. According to a Quest spokesperson the national Medicare limitation amount for the test is about $595.

Expanded Molecular Bird Flu Kit Developed in Asia

Public health departments have a new tool in their arsenal to fight a potential pandemic outbreak of bird flu. A new, rapid bird flu test kit is capable of examining all known strains of the H5N1 viruses in a single test with high accuracy, within a few hours, potentially improving infection control intervention and patient management.

"Our technology has greatly simplified and accelerated the process of detection and identification of new H5N1 variants. Such information is especially critical when the virus mutates to become more dangerous, such as in drug resistance."
—Masafumi Inoue, Ph.D.

The H5N1 real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay is the only detection kit commercially available that can accurately detect all known strains of the H5N1 avian influenza A virus in a single test, says molecular diagnostics company AITbiotech (Singapore), which has the rights to market the kit in Southeast Asia.

"Our technology has greatly simplified and accelerated the process of detection and identification of new H5N1 variants," said co-developer of the test Masafumi Inoue, Ph.D., group leader of molecular diagnostics at the Experimental Therapeutics Centre (ETC; Singapore), in a statement. "Such information is especially critical when the virus mutates to become more dangerous, such as in drug resistance."

The H5N1 RT-PCR test was developed collaboratively with researchers from ETC and Tan Tock Seng Hospital, both in Singapore, and has been validated at several hospitals in Southeast Asia, the company said. The H5N1 test kit is designed to be compatible with the previously launched "4-plex" Influenza diagnostic kit.

Shirley Tan, the business director at AITbiotech, tells *DTTR* that the company is "very close" to receiving ISO 13485 certification and will then commence selling the kits in Europe. The list price for the 100 reaction kits, she says, is S$1,800 (approximately $1,422 U.S.), but the company has no short-term plans to pursue U.S. Food and Drug Administration approval as it is cost-prohibitive for the company. Without approval the kit can be imported into the United States for research use only, adds Tan.

Qiagen Unveils NGS Sequencing Initiative: Launch of Benchtop Sequencer Expected in 2013

Qiagen (Hilden, Germany) is entering the next-generation sequencing (NGS) market. At the end of June the company formally announced a new NGS initiative, which included the acquisition of instrument maker Intelligent Bio-Systems (Waltham, Mass.), a privately held company. The two companies have been developing a previously undisclosed next-generation benchtop sequencer that will be part of Qiagen's sample-to-result NGS solution, expected to launch next year.

"While next-generation sequencing is viewed today mainly as a research tool, our initiative is to expand beyond this and to offer applications designed to address the needs of customers in clinical research and molecular diagnostics," said Qiagen's CEO Peter Schatz in a statement.

Qiagen currently offers QIAquick and MinElute PCR purification kits that are commercially used in NGS protocols, but the company plans on broadening its product portfolio to provide an end-to-end solution. The cornerstone of the product line will be an NGS benchtop sequencer that uses proprietary sequencing by synthesis technology, exclusively licensed from Columbia University (New York City). The system will enter beta testing with customers in 2012, the company says, and was designed with clinical work-flow in mind. It can process multiple samples in parallel and allows for continuous loading of reagents and random samples, with up to 20 different assay types able to be processed simultaneously. The upcoming platform integrates the NGS module into the QIAsymphony platform or the QIAcube automated sample preparation system.

Rounding out the solution, Qiagen plans to add content through an initial launch of eight preconfigured gene panels for use in cancer, an expanded range of sample preparation products, and built-in bioinformatics capabilities in development through a collaboration with SAP (Walldorf, Germany). The collaboration aims to apply the SAP HANA platform to next-generation sequencing interpretation with the goal of reducing the time required for the analysis of sequencing.

G2 INTELLIGENCE
Inside the Diagnostics Industry

EMR Utilization and Its Effect on Laboratory Testing

While physician adoption of electronic medical records (EMRs) began slowly, new evidence shows uptake is quickening, driven largely by financial incentives defined under meaningful use provisions of the Health Information Technology Economic and Clinical Health (HITECH) Act.

According to the Office of the National Coordinator for Health Information Technology (ONC) in 2011 about 34 percent of non-hospital-based physicians had adopted a "basic" EMR, doubling the adoption rate of 2008. The trend is expected to continue based on results of a survey conducted by the U.S. Centers for Disease Control and Prevention, which found 52 percent of office-based physicians in the United States intend to take advantage of the financial enticements available through the Medicare and Medicaid EHR Incentive Programs. EMR incentive payments for eligible health care professionals can total as much as $44,000 under the Medicare program and $63,750 under the Medicaid program.

Stage 1 of meaningful use had limited impact on laboratories, but stage 2, which will begin attestation in 2014, calls for greater data exchange and includes several core laboratory-related proposed requirements including using computer physician order entry for laboratory testing, incorporating laboratory test results into EMRs as structured data, and compliance with Logical Observation Identifiers Names and Codes.

Changes in Test Utilization

With greater adoption of EMRs combined with payment reform efforts, like accountable care organizations aimed at improving care coordination, laboratories are looking for clues as to how these changes in clinical practice will manifest themselves in future laboratory test utilization. Early indications, though, point to a mixed bag with potential reductions in test volume driven by "intelligent ordering," but potential increases in volumes as ease of ordering becomes simplified with improved integrations between laboratory information systems (LISs) and EMRs.

> ***"There are counterinfluences that will change utilization a little bit."***
> ***—Pat Wolfram, Ignis Systems***

"There are counterinfluences that will change utilization a little bit," explains Pat Wolfram, vice president of marketing for middleware vendor Ingis Systems (Portland, Ore.). "Using paper, doctors don't do a good job of managing disease states. My mechanic and my vet are better able to tell me when to bring in my car or my dog. So this will be a positive influence on utilization when there is awareness that a test is needed. On the other hand, a little further down the road when EMRs are utilized well and there is confidence in the data, there will be a decrease in testing, as doctors see when test orders are redundant to those ordered by other care providers."

A 2011 study published in the *American Journal of Managed Care* confirms this mixed forecast. Physicians who use EMRs provided 7.1 percent fewer laboratory tests on average across all visits, but the study found that EMR users provided, on average, 8.7 percent more total diagnostic/screening services, particularly among

office visits by chronic disease sufferers. Surprisingly, though, EMR use had little to no association with utilization during visits for preventive care. "EMR use had a mixed association with utilization, and the relationships varied by type of service and by major reason for visit," concluded author Michael F. Furukawa, Ph.D., who is now serving as acting director of the Office of Economic Analysis, Evaluation, and Modeling within the ONC.

Lab-EMR Integration Challenges

Laboratory integration and electronic ordering, in particular, have not been a priority for EMR vendors. While they are expected to pay more attention to such integration efforts as stage 2 of meaningful use approaches, many laboratories and physicians have turned to middleware vendors to sync EMRs with LISs and improve the rates of clean, reimbursable electronic orders placed.

"A doctor might not realize that Margaret went to Dr. Jones down the street who ordered the same tests," explains Michelle Del Guercio, director of marketing at Atlas Development (Calabasas, Calif.). "The lab won't be reimbursed and once that patient is out of the office they are out of luck as it will be tough to get an advance beneficiary notice signed."

But middleware systems can aid in verifying medical necessity and even an individual laboratory's test requirements. While generally the interoperability of EMRs in the United States has been described as "piecemeal," experts point to the Veterans Affairs (VA) and U.S. Department of Defense (DOD) systems as a positive example of the potential for integrating laboratory data into clinical decisionmaking.

The DOD and VA departments announced a milestone in their effort to combine their health records in what will become the world's largest electronic system by 2017. In May, the Capt. James A. Lovell Federal Health Care Center (North Chicago, Ill.) became the nation's first fully integrated DOD-VA medical facility, and by 2014 sites in San Antonio and Hampton Roads, Va., will also be able to access an integrated electronic health record (iEHR) for any service member or veteran seen in any DOD or VA medical facility throughout their lifetime. The iEHR will unify the departments' now-separate legacy EMR systems. Beth McGrath, a DOD deputy chief management officer, says that "the clinical capabilities [being deployed] first are focused on laboratory and immunizations."

In an effort to spur the integration of laboratory capabilities into the iEHR, in mid-June the DOD solicited a request for information from vendors to advise on the deployment of commercial LISs that can integrate iEHRs and clinical laboratory and anatomic pathology business processes for DOD/VA. Currently, the statement said, the DOD and VA manage lab test orders, specimen collection, processing, and lab test results reporting using separate information technology systems, with separate data repositories and complex sharing processes that do not allow for access to a patient's full laboratory results record for clinical care. The goal is a system that will provide access to the patient's full EMR for clinical decision support to include receiving the specimen and/or test order, analyzing it, validating the results, and notifying providers.

Integration of private health system LIS-EMRs is occurring in a much more isolated fashion.

"People are trivializing lab integration because they have seen a simpler way to integrate medications and think labs should follow suit," says Wolfram. "We are waiting for when there is sharing of good, structured data that all can access. It will take time to get a lot of data into that repository and agreement on coding could take awhile, but we see it coming. It will be an incremental process with no 'aha' moment in the transition to a better state."

A Move to Decision Support

Integrating evidence generated from aggregated data sources to inform clinical decision support tools adds another layer of complexity to the integration equation. Some are already looking to the future where genetic test data will need to be stored in EMRs.

"Decision support is still embryonic as the knowledge base is changing so rapidly. . . . It becomes a chicken-and-egg problem."
—Joyce Mitchell, Ph.D.

"It is difficult from a technological point of view to get test data used in EMRs for decisionmaking," says Joyce Mitchell, Ph.D., a professor of biomedical informatics at University of Utah (Salt Lake City). "Most genetic testing is done outside of the lab. The test report might come back as a fax. Even if you scan it in or elect to enter it as a text note it is not in a fielded report format."

Mitchell says that in order for genetic test results to truly be integrated into clinical care, decision support is needed. But for that to happen, there must be a stronger evidence base.

"Decision support is still embryonic as the knowledge base is changing so rapidly," Mitchell says. "There are few cases, but that is not enough to be the standard of care, and they aren't doing it because of the lack of evidence. It becomes a chicken-and-egg problem."

In the short term there is a major movement toward cooperation, she says, citing the National Human Genome Research Institute's efforts to coordinate national clinical variant databases.

"In five years it will be a whole different situation with one place to access a definitive source. From there decision support in EMRs will develop rather quickly," says Mitchell. "We will have a better idea of the health significance and frequency of these variances. It will change a lot in people's comfort level of knowing what to do."

In time, experts say, pooled data on genetic variants will be used to inform decisionmaking for prevention, prognosis, and treatment of individuals.

"The discipline of pharmacogenomics is identifying an increasing number of variants associated with drug responses, however, the very success of these efforts represents a barrier to implementation because no human can be expected to keep track of this increasing data set and its implications for drug prescribing," writes Dan Roden, M.D., a professor of medicine and pharmacology at Vanderbilt University (Nashville, Tenn.) in an April 25 article published in *Clinical Pharmacology & Therapeutics*. "The capability of advanced EMR systems to archive large amounts of individual data and deliver advice to providers at the point of care seems to offer an obvious solution to this problem."

More Complex Understanding of Tumors Requires Collaborative Paradigm

Emerging research suggests that hope surrounding the rapid implementation of personalized medicine may have oversimplified the complex relationships between identified genotypic variance and phenotypic exhibition, even in solid tumors.

At G2 Intelligence's MDx Next conference (Boston; April 17-19) Kenneth Buetow, Ph.D., director of computational sciences and informatics in the complex adaptive systems initiative at Arizona State University, explored the next frontier in personalized medicine, which he explained will require a collaborative paradigm to generate evidenced-based clinical support as researchers and clinicians try to unravel the complicated relationships between multidimensional molecular alterations and phenotypic disease.

The Root of Tumor Complexity

"What [researchers] are beginning to do in cancer is essentially transform the traditional histopathologic definitions of cancer into molecular definitions. They are no longer necessarily just simply describing cancer as what it looks like through a microscope but in fact are routinely now characterizing cancer at the molecular level," explains Buetow. "But even for an individual locus, we need to worry about the specific portfolio of mutations that may exist in that particular locus. . . . Just simply knowing the mutations is not sufficient for us to be able to do anything of real value in a clinical setting."

What's emerged from the last two decades of cancer research is the knowledge that cancer is a complex adaptive system, Buetow says.

"Now that we have the capacity to routinely do whole-genome characterization, we see tumors are the accumulation of literally hundreds of molecular alterations . . . and similar to the evolutionary process that creates new organisms, it actually creates a new organ within an individual."

The accumulation of alterations can take multiple forms and are not limited to simple DNA-based, nucleic acid base mutations, but can include modifications that change the expression of nucleic acids. Buetow says the alterations can also occur through additional processes such as microRNAs that are controlling mechanisms of how genes may actually work or through biochemical processes, not captured at the DNA base level.

"If we only look at any one of these particular dimensions, we actually recognize we get an incomplete picture of what is actually occurring in cancer," says Buetow. "And then in each individual tumor, in its evolutionary process, it has the ability to choose from this different portfolio of individual genes. . . . While you have this evolution of this new somatic mass to create a new organ, i.e., cancer, what one recognizes is the genetic environment in which this resides is also equally important . . . and can modulate a variety of external environmental factors such as chemicals or viruses or hormones or nutrition to determine how those individual influences determine your cancer portfolio."

The Evidence Base

There are ongoing efforts, including the Cancer Genome Atlas, to build an evidence base to translate new molecular insights into clinically actionable information.

Buetow cited Vanderbilt University Medical Center (Nashville, Tenn.) as "leading edge" both in its efforts to integrate molecular characterization of tumors into their next-generation electronic medical records, but also in that the center is "sharing out" this information in its My Cancer Genome portal.

"They can be part of a much larger community. You will see this is a theme that starts to emerge, and one of the reasons I highlight this is the recognition that in a certain sense for us to move into this molecular diagnostic universe, it takes a village," explains Buetow.

My Cancer Genome, Buetow says, can drill down all the way to specific references for a pinpointed mutation, reinforcing the importance of an evidence base in providing clinical decision support to translate molecular characterization into a clinical intervention. The challenge Buetow says, is that for the most part, the traditional organizational and business models currently used in health care delivery and research are insufficient to generate the necessary evidence base to support clinical adoption.

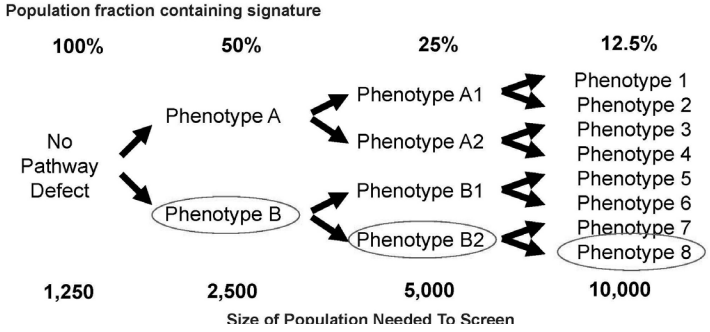
Buetow said that looking at HER2 status, "a poster child of molecular diagnostics and molecular stratification," provides evidence of why traditional clinical trial design, the generator of an evidence portfolio, is "ill equipped" to accommodate the increasing complexity associated with utilization of multiple molecular biomarkers.

"Traditional clinical design might have said that you need to look at 1,200 women in order to be able to have a statistically powerful answer," explains Buetow. "Suddenly the sample size looking at a single marker explodes and we have to now look at, because of the prevalence of the HER2 variant, at about 25 percent of the population. Instead of looking at 1,000 women, we have to look at 5,000 woman in order to be able to get the right portfolio of people to measure the therapeutic response."

Buteau cautions the 5,000 needed to screen represents a study examining one marker.

"So, now let's just say that we have three markers. Now, instead of looking at 1,000 women, we have to look at over 10,000 women to get the subset of women that would actually have the right portfolio of markers to be able to test the hypothesis," says Buetow. "While the sample size may ultimately go down in molecularly specified medicine, what we can see is, as we ramp up the number of features that need to be characterized to define that subset. The global population that needs to be screened goes up geometrically."

Size of Population with 'Pathway' to Inhibit



Source: H. Kim Lyerly, M.D., Duke Comprehensive Cancer Center, and Kenneth Buetow, Ph.D.

It is not just clinical trials that will need to adapt to accommodate the emerging underlying molecular complexity.

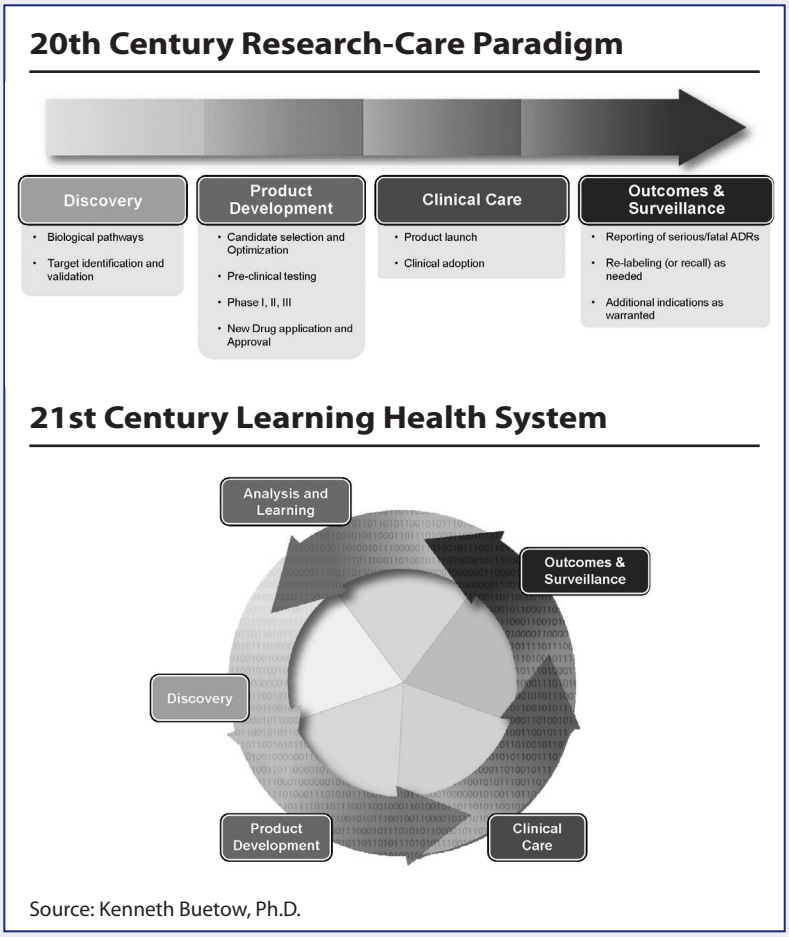
"At the risk of being a little hyperbolic, I might argue that our biomedicine is actually ill prepared right now to deal with this complexity," argues Buetow.

Buetow points to several challenges—that of the phar-

maceutical industry's business model (that they have declining research-and-development productivity coupled with astronomical increases in their development costs), the struggle to find a sustainable health care delivery business model, and a nascent understanding of the true underlying biologic portfolio of many of our common diseases—as evidence that there needs to be a paradigm shift in the health care universe in order to actually deliver on the next generation of molecular diagnostics and personalized medicine. Buetow says what is needed is for stakeholders to embrace biomedicine as a system.

"Rather than everybody working individually in fragmenting all the information, we need to actually be assembling this diverse collection of stakeholders into a multidimensional interacting ecosystem," says Buetow, although the question of how best to create efficient information flow between these individual agents remains unanswered. "Biology organizes its complexity through differentiated functions connected through well-defined interfaces and through layering. . . . How can we actually take these approaches to solve the problems of biomedicine and next generation molecular diagnostic development?"

In order for stakeholders to participate in an interactive ecosystem, Buetow says that some fundamental changes need to occur in evidence generation and in regulatory approval. Key to this is the recognition that not all molecular diagnostics are in the same category and there is no reason they should be treated equally, Buetow says. A layered approach that utilizes different approaches for risk biomarkers, diagnostic biomarkers, prognostic biomarkers, predictive biomarkers, or response biomarkers is in order.



Source: Kenneth Buetow, Ph.D.

"The process by which the FDA looks at biomarkers in molecular diagnostics is at best ad hoc, and it is not that they don't want to do this well, but there is not a well-established paradigm as to how one generates the evidence associated with the development of molecular diagnostics and biomarkers. Different biomarkers have different purposes and they can be qualified then at a regulatory level depending on what they need to be doing," says Buetow. "Similarly, in the context of validation, each one of these different types of validation experiments at a regulatory level requires a different design for each of these classes, so again we don't need to overburden. We don't have to do everything for every individual marker."

"There is a sort of linear approach to biomedicine, the discovery, the research-to-care paradigm, what I would like to refer to as the Purell shampoo model of biomedical research. The lather-rinse-repeat approach to doing evidence generation just doesn't scale if one has to do this for literally hundreds of biomarkers. There are just not enough study populations in the world to actually do this and actually have both test and validation samples."

Buetow proposes converting the current linear process into a cyclical, learning system.

"All of the observations that are occurring in a clinical setting can be leveraged to facilitate learning—an evidence generation in a new setting," explains Buetow. "In other words rather than completely separating our care environment from our research environment, what we need to do is systematically collect our care observations in a manner that feeds the research evidence-generation model and each research observation needs to then be immediately accessible and fed back into the care system."

Buetow cites Vanderbilt as an example of how this model is being put into action. "They immediately embed into their care setting the capacity to bring people into the research setting, so these are not two separate environments," emphasizes Buetow. "Given a particular mutation profile, [a patient] would qualify either for local trials or for national trials. . . . So as they are encountered in the clinic, the now 10,000 observations that you needed before are found in real time and then fed from the clinic. They are not de novo identified from some additional screening; they are screened as part of their clinical phenotyping."

In the village model, Buetow says focusing on research efforts at our own individual institutions is limiting. "If this individual information can't be used to generate evidence in my local setting, how can they be contributing to the much larger whole?"

Buetow also cites the I-SPY trial, a set of serial studies to predict therapeutic response using imaging and molecular analysis, as a "cutting-edge model" to explore the real-time generation of evidence and an adaptive model for doing clinical research, where a virtual cycle of care delivery and clinical research propels new evidence generation.

"For almost two decades the U.S. military has had a doctrine called network-centric warfare, . . . which recognizes to [be] truly competitive we need to have robust networking—well-informed, geographically, dispersed forces," says Buetow. "I might argue if you look at biomedicine we are just the opposite of that. Our biomedical processes are still very heavily tied to the publication cycle that maybe takes nine months to 12 months for any findings just to even get into the paper literature and then ultimately be translated and diffuse down into other settings."

The key to network-centric warfare, Buetow says, is that each individual unit still is largely autonomous operating under a broader operational framework but has access to incredible amounts of information and can in real time call up resources necessary to develop and to facilitate their specific mission.

Looking to the future, Buetow says, "In our networking-centric biomedicine, we are no longer operating alone or in our own individual institutional silo but in fact are part of a much border ecosystem connected through electronic interfaces that don't rob us of our information or our control of information but allow us to share with our colleagues so that we create this virtual community through a shared common infrastructure."

NGO Commits $30 Million to Expand Cepheid's TB Testing Program in Developing Nations

A new financial commitment from a global health nonprofit will expand access to Cepheid's (Sunnyvale, Calif.) diagnostic technology in developing nations with a high burden of tuberculosis (TB). Cepheid welcomed the $30 million commitment in mid-June by UNITAID (Switzerland), which will be administered by the Stop TB Partnership and the World Health Organization (WHO). WHO endorsed Cepheid's rapid Xpert MTB/RIF test in late 2010 to diagnose TB and multi-drug-resistant TB.

UNITAID is a global health initiative established in 2006 by the governments of Brazil, Norway, Chile, France, and the United Kingdom to increase access to HIV/AIDS, TB, and malaria diagnostics and preventive and therapeutic medicines and diagnostics in low- and middle-income countries.

While Cepheid says it is still in discussions regarding implementation details, the company said in a statement that the funds will be used to roll out Xpert-based programs in 20 of the 145 countries eligible for compassionate pricing. GeneXpert TB technology is already in use or in trials in 61 of these nations. A company spokesperson tells *DTTR* that Cepheid anticipates the funds will be used to purchase GeneXpert systems, fund MTB/RIF testing operations, and costs associated with administering the testing programs.

> ***"We believe that all parties are committed to working together to enable HBDC programs to access the test at around $10, which should accelerate adoption in the countries where it is most needed."***
>
> ***—John Bishop, Cepheid***

While unwilling to speculate how this financial commitment will impact its bottom line, as of March 31, 2012, Cepheid said it placed a cumulative total of 3,079 GeneXpert systems worldwide with 151 GeneXpert system placements as part of its High Burden Developing Country program during the first quarter. The company had earlier issued guidance that it expects MTB/RIF to contribute between $26 million to $30 million to total 2012 revenue. The company has additionally said that it expects clearance of the Xpert MTB/RIF in China this year and will submit MTB/RIF for U.S. regulatory approval by the end of the year.

Cepheid said previously that the GeneXpert systems cost $18,000 in developing nations and while the cartridges are currently sold using compassionate pricing of $16.86, discussions remain ongoing with UNITAID and other international aid organizations to further reduce cartridge costs to a target of $10.

"While discussions with UNITAID, USAID and the Bill and Melinda Gates Foundation are ongoing at this time and the final agreement is not yet completed, we believe that all parties are committed to working together to enable HBDC programs to access the test at around $10, which should accelerate adoption in the countries where it is most needed," said John Bishop, Cepheid's CEO in a statement. G2

One in Five Patients Unwilling to Share Cost of Genetic Cancer Tests

One in five patients who were referred for genetic cancer testing based on personal or family history say they would only follow through with testing if their insurance covers the cost. The rise in clinical use of genetic tests has been accompanied by a simultaneous rise in cost-sharing practices by payers. Researchers at the annual meeting of the American Society of Clinical Oncology (Chicago; June 1-5) say understanding how cost affects patients' decisions to undergo genetic testing is essential.

Researchers from Fox Chase Cancer Center (Philadelphia) analyzed data from the Gastrointestinal Tumor Risk Assessment Registry to identify patient-level factors associated with willingness to pay for genetic services. They found that 21.3 percent of the nearly 400 people surveyed were only willing to have genetic testing if insurance paid. Nearly 79 percent were willing to pay some level of the costs out of pocket, which varied from $25 to $2,000.

As may be expected people who were more worried about their risk of cancer and those that had more positive attitudes toward genetic testing were significantly more willing to pay higher costs. But surprisingly, women and those with more first-degree relatives who had cancer were less likely to agree to high copays for genetic testing. Higher expectation of a positive result was associated with testing paid for by insurance only.

"We need to discover more risk factors for genetic mutations, so we can spare those patients who really don't need to pay for genetic testing," says lead author Jennifer Madeline Matro, M.D., a medical oncology fellow. "The goal of genetic testing is to give patients the best opportunity to detect their cancers earlier, which can save costs in the long run." G2

Hepatitis B Screening Shown Effective Prior to Therapy Initiation

Two recently published studies call for universal hepatitis B (HepB) screening in patients getting ready to initiate treatment—both in lymphoma patients starting chemotherapy and in psoriasis patients initiating tumor necrosis factor-alpha (TNF-alpha) inhibitor therapy.

Screening all lymphoma patients prior to starting chemotherapy for HepB is a cost-effective strategy, according to a study published June 18 in the *Journal of Clinical Oncology*. Preemptive screening reduces the rate of potentially fatal HepB reactivation.

A decision model, created by lead author Urszula Zurawska, M.D., from the University of Toronto (Canada), and colleagues compared clinical outcomes, costs, and cost-effectiveness of three hepatitis B virus (HBV) screening strategies for patients with lymphoma. The options were to screen all patients for HepB surface antigen (HBsAg), screen patients identified as being at high risk for HBV infection, or to screen no one before the initiation of treatment. Factored into the analysis was the cost of administering anti-viral therapy upon a positive screening test result until six months post-chemotherapy and the cost of anti-viral therapy in those not screened, only if HepB infection occurred.

Although the projected absolute differences in cost were small, the researchers found that screening all prevailed as the most cost-effective strategy, costing $32,589, compared with $32,598 and $32,657 for screening high-risk patients only and screening no one, respectively. Screening all was also associated with the highest one-year survival rate.

The assumed prevalence of HBsAg positivity in the low-risk population affected the cost-effectiveness analysis, with screening high-risk patients becoming the least-cost strategy when the prevalence of HBsAg was less than 0.20 percent. The authors point out that due to the large foreign-born population in Canada, where the study was conducted, the HBsAg prevalence in the general population is 1.26 percent, higher than the 0.42 percent prevalence of HBsAg in the general U.S. population. Among U.S.-born noninstitutionalized persons, though, the prevalence is estimated to be as low as 0.1 percent.

"Thus, in some communities of low-risk individuals, screening only high-risk patients may be the least costly strategy, but screening all patients would still be cost effective," the authors write. They conclude that given "the expectation that universal testing is likely easier to implement than targeted testing, consideration should be given to routinely screening for HBsAg in all patients scheduled to receive R-CHOP chemotherapy for non-Hodgkin's lymphoma."

HepB Screening in Psoriasis Patients

A review of case studies, published online June 21 in the *Journal of the American Academy of Dermatology*, found that TNF-alpha inhibitor therapy may result in reactivated HepB in HBsAg-positive patients with psoriasis and less frequently in patients with an isolated positive HepB core antibody. Given that potentially fatal reactivations can be "greatly minimized or eliminated" by early or pre-emptive anti-viral therapy, the authors led by Amanda Abramson, M.D., from Baylor University Medical Center (Dallas) conclude that HepB screening (HBsAg and anti-HBc) all patients "is essential" prior to the initiation of TNF-alpha inhibitor therapy. The authors recommend against targeted screening based on ethnicity or high-risk behaviors. G2

Interest in Dengue Fever Testing Increasing

The U.S. Centers for Disease Control and Prevention (CDC) has received U.S. Food and Drug Administration (FDA) approval for a new diagnostic test for dengue fever, as incidence of viral cases is growing domestically among international travelers. Unlike previously approved tests, the CDC DENV-1-4 Real Time RT PCR Assay tests for the presence of the dengue virus, not immunoglobin class antibodies, allowing for earlier disease detection.

The CDC says the test can be performed using equipment and supplies many public health laboratories already use to diagnose influenza. The test was developed on the widely used Applied Biosystems (ABI) 7500 Fast Dx Real-Time PCR Instrument platform that public health departments frequently use for influenza testing. CDC is distributing the kits, which can run 200 samples, free of cost to state labs and some foreign national labs, says Jorge Munoz-Jordan, Ph.D., chief of molecular diagnostics and research at the CDC's Dengue Branch in Fort Collins, Colo.

The new test can diagnose all four types of the dengue within the first seven days after symptoms of the illness appear, quicker than antibody-based tests, which frequently cannot detect the antibodies for four to seven days after illness appears.

The FDA approval is only for testing in symptomatic patients and is not intended for the screening of blood or plasma donors. But SeraCare Life Sciences (Milford, Mass.), in mid-June, launched what the company says is the first commercially available Anti-Dengue Mixed Titer Performance Panel. The panel is intended to help blood donor collection facilities, diagnostics manufacturers, and clinical laboratories evaluate and troubleshoot their dengue virus assays. It is derived from undiluted, unpreserved human plasma specimens representing all four virus varieties, with a wide range of reactivity for anti-dengue IgM and IgG antibodies, from negative to strongly positive.

Vitamin D Test Performance Questioned

A new study questions the analytical performance characteristics of two U.S. Food and Drug Administration-approved automated vitamin D immunoassays. The study, presented at Endocrine Society's annual meeting (Houston; June 23-26), concluded that Abbott Laboratories' (Abbott Park, Ill.) Architect 25-OH assay (ARC) and Siemens Healthcare Diagnostics' (Tarrytown, N.Y.) Centaur-2 assays (CT2) had "high degrees of random variability" and failed "to meet even a minimum quality standard for analytical bias" with both assays exceeding the allowable limits for error in at least 40 percent of cases.

Utilization of vitamin D tests has been increasing paralleling a rise in the body of research indicating an association between vitamin D deficiencies and a broadening range of conditions including type 2 diabetes, depression, bone health, and possibly cardiovascular disease and cancer. Given the increased reliance on vitamin D test results for clinical patient management, inaccurate results can lead to unnecessary and costly care.

Comparing the assays to the standard of liquid chromatography/mass spectrometry (LC/MS), both assays far exceeded the maximum allowable error for test results of ±25 percent, with results from the two tests ranging from -60 percent to +80 percent, the researchers found. Earle Holmes, Ph.D., from Loyola University Medical Center (Maywood, Ill.), and the study's lead author, found that the tests had error rates of 40 percent (ARC) and 48 percent (CT2). The errors tended to overestimate the frequency of vitamin D deficiency.

Using levels of less than 20 ng/mL to define vitamin D deficiency, 33 of the subjects' test results had vitamin D deficiency using LC/MS, but the two assays categorized 45 and 71 of the 163 randomly selected clinical specimens used in the study as having vitamin D deficiency measured by ARC and CT2, respectively.

"The inaccuracy of these immunoassays at 25OHD levels in the lower part of the analytical measuring range would have led to a marked overestimation of the prevalence of vitamin D deficiency in our study sample," concluded the authors. "The widespread use of new analytical methods with poor analytical quality may confound efforts to establish reference values for 25OHD in health and efforts to evaluate the role of vitamin D insufficiency as a risk factor in disease."

G2 Insider

NBS Overestimates Sensitivity of Congenital Adrenal Hyperplasia Testing … Over a 12-year period, a study of the Minnesota newborn screening program (NBS) shows that 22 percent of cases of congenital adrenal hyperplasia (CAH) are missed by initial screening resulting in delays in diagnosis well into early childhood, according to a research letter published June 13 in the *Journal of the American Medical Association*. Early identification of CAH due to 21α-hydroxylase deficiency can prevent life-threatening adrenal or salt-wasting crises, but the study results highlight that test sensitivity is lower than the generally reported 100 percent.

Lead author Kyriakie Sarafoglou, M.D., from the University of Minnesota in Minneapolis, and colleagues analyzed data from more than 838,000 newborns born and screened in Minnesota from January 1999 through December 2010. As is standard in NBS programs, 17α-hydroxyprogesterone level was measured with a time-resolved fluoroimmunoassay from a blood spot sample collected 24 hours to 48 hours after birth. Fifteen cases of CAH were missed by NBS—a false-negative rate of 22.4 percent—and were identified through review of the NBS registry and medical records of the three largest pediatric endocrinology centers in the state. Of the missed cases there were six males and nine females, most of whom had ambiguous genitalia. CAH was confirmed in the 52 cases identified and the 15 missed by NBS using clinical and biochemical presentation in combination with molecular testing of the CYP21A2 gene through either a mutation panel or sequencing.

Given the delayed diagnosis in the cases of false-negatives that the researchers found, they say that the true false-negative rate is likely even higher due to due to a number of factors including patients with CAH not yet diagnosed, patients who moved out of the state, or infants who passed away with unidentified CAH. The authors note that "the false-negative results were not due to procedural changes because one to two false-negative results were found every year from 1999 through 2010 except 2002, which had none."

Company References

AITbiotech (65) 6778 6822
Atlas Development 818-340-7080
Cepheid 408-541-4191
Coriell Institute for Medical Research 856-966-7377
Ignis Systems 888-806-0309
Qiagen +49 2103 29 0
Quest Diagnostics 973-520-2700
SeraCare Life Sciences 508-244-6400
Veracyte 650-243-6300
UNITAID +41 22 791 55 03
U.S. Centers for Disease Control and Prevention 404-639-3311
U.S. Department of Defense 877-874-2273

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Kimberly Scott, Managing Editor, kscott@G2Intelligence.com; Lori Solomon, Editor; Heather Lancey, Designer; Beth Butler, Marketing Director; Dan Houder, COO and Publisher

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