VOL. 2, ISSUE No. 9 SEPTEMBER 2015

Clinical OMICs

Molecular Diagnostics in Personalized Medicine

Direct-to-Consumer Genetic Testing
Will it go away?

At the Heart of the Matter: The Genomics Underlying Cardiovascular Disease

CASE STUDY: Decision-Making Tools in Rheumatoid Arthritis

New Products & More

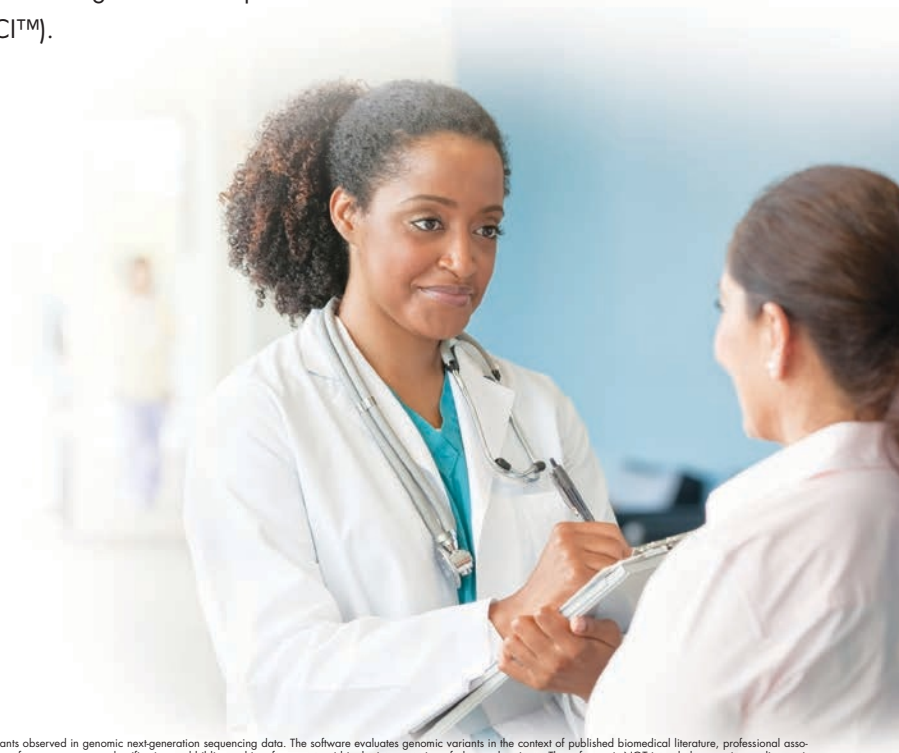
A digital publication of GEN, a Mary Ann Liebert, Inc. company

Enable precision medicine

Scalable clinical decision support

Cancer moves fast, but we can move faster. Next-generation sequencing (NGS) data analysis no longer needs to be the bottleneck. Speed-up your turn-around-time and increase your NGS test volume by streamlining your rate-limiting variant interpretation and reporting steps with QIAGEN® Clinical Insight (QCI™).

Scale your interpretation now with QCI™
qiagenbioinformatics.com/QCI-CO



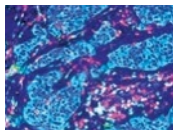
Clinical OMICs

Molecular Diagnostics in Personalized Medicine

At least direct-to-consumer pharmaceutical advertising keeps doctors in the loop. That's more than can be said of direct-to-consumer genetic testing.

DIRECT-TO-CONSUMER GENETIC TESTING: WILL IT GO AWAY? 8
DTCs, which are heavily marketed by the companies that create them, have created controversy among healthcare professionals.

AT THE HEART OF THE MATTER: THE GENOMICS UNDERLYING CARDIOVASCULAR DISEASE 12
In order to understand the impact of genetic testing on CVD diagnosis and treatment, it's important to examine the associated genetic complexities.



MOLECULAR PATHOLOGY'S CONTEXTUAL CUES 16
Disease doesn't have to play as tragedy—not if the cues directing the molecular players are understood in time, before the pathologic plot thickens.

Regular Features

CASE STUDY 21
Decision-Making Tools in Rheumatoid Arthritis
RA treatments pose challenges due to wide variation in patient response; therefore more complex individualized diagnostic decision-making tools are required.

NEWS 5

NEW PRODUCTS 15

MEETING ROUNDUP 26

Cover illustration: DepositPhotos/ Julia_Tim
(modified by Clinical OMICs)
Above (top): iStock/lovleah
Above (bottom): PerkinElmer

Clinical OMICs
Innovative Practices, Actionable Results

www.clinicalomics.com

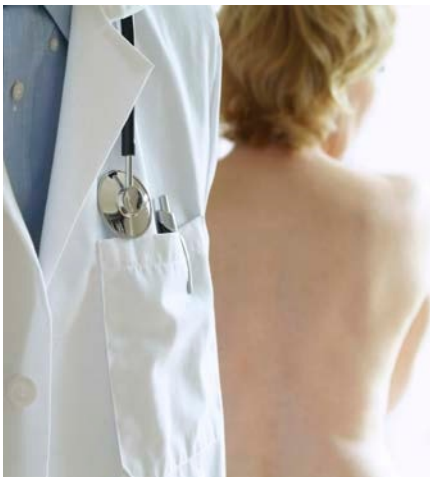
Clinical OMICs (ISSN-2334-1351) is published online monthly by Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801-5215.

For subscription information go to: www.clinicalomics.com

Precision Medicine Breast Cancer Registry Launched

Paradigm and TME Research launched the Paradigm Neoadjuvant Breast Registry. The system will use Paradigm's PCDx next-generation sequencing test and other advanced molecular capabilities to genomically characterize invasive breast cancer patients for targeted neoadjuvant therapies [presurgical treatment]. With more accurate accounts of individual gene variability driving disease, therapy selection will be refined for patient success, according to officials at Paradigm.

The initial six-month pilot for this project will enroll 100 patients across eight primary U.S. centers, potentially expanding to 1,000 patients across 50 U.S. centers. Patients enrolled into the Paradigm Registry will have neoadjuvant chemotherapy or hormone therapy. The patient's cancer will undergo tumor profiling with the Paradigm platform.



iStock/LilliDay

The primary goal of the Paradigm Registry is to accelerate tumor profiling based on disease biology.

Precision oncology is an emerging approach for cancer treatment utilized mainly in the metastatic setting but with great potential to direct initial therapy, said Robert J. Penny M.D., Ph.D., CEO of Paradigm. The primary goal of the Paradigm Registry is to accelerate tumor profiling based on disease biology so that relevant neoadjuvant clinical trials and/or refined treatment regimens can be identified particularly when competing options exist.

"Conventional thinking is that neoadjuvant therapy is offered to patients with large primary breast cancer to

(continued on page 24)

Decipher® Predicts Metastasis and Identifies Prostate Cancer Biomarkers in African American Men

GenomeDx Biosciences reported that its commercially available Decipher® testing platform identified, with statistical significance, a set of prostate cancer biomarkers predictive of aggressive disease in African American men after radical prostate surgery. This represents the first and only study describing a set of genomic markers that have the ability to predict tumor aggressiveness in a race-dependent manner, said Elai Davicioni, Ph.D., president and CSO at GenomeDx and an author on a study ("Novel Biomarker Signature That May Predict Aggressive Disease in African American Men With Prostate Cancer"), that was published online in the Journal of Clinical Oncology.

Additionally, the study demonstrated that the Medicare-covered Decipher test is an independent predictor of metastasis in African American men.

"African American men have historically experienced a higher incidence of mortality from prostate cancer than men of other races and eth-

iStock/gchutka

A genomic marker panel was recently described that has the ability to predict tumor aggressiveness in a race-dependent manner.

(continued on page 24)

Target Enrichment Technology Optimized for Analysis of SNPs, Mutations, and Copy Number Changes in 509 Cancer Gene Targets

GEN Webinars

Free Registration!

www.GENengnews.com/target

Speakers

Luke Sherlin, Ph.D.
Director, Technical Support
NuGEN Technologies

Stephanie Huelga, Ph.D.
Lead Bioinformatics Scientist
NuGEN Technologies

Moderator

John Sterling
Editor in Chief
GEN

Tuesday
Sept. 22, 2015
11:00 am ET
8:00 am PT

DURATION
60 minutes

COST
Complimentary

Targeted resequencing of DNA allows researchers to focus on genes of interest for cost-effective analysis of genetic variations. Typically, to analyze single nucleotide mutations and copy number changes in a single sample, researchers have had to employ completely different analysis platforms and sample-preparation methods.

During this webinar we will describe and present data for an NGS target enrichment workflow, based on the novel Single Primer Enrichment Technology (SPET), for the simultaneous targeted analysis of multiple types of variations. This method can be employed for the analysis of SNPs, indels, and CNVs in a single assay, making conservation of precious patient samples and more efficient use of sequencing resources possible. We will feature data from target-enrichment studies with a 509 cancer gene panel using a simple protocol that generates sequence-ready libraries from good quality DNA as well as DNA derived from formalin-fixed paraffin-embedded (FFPE) tissues.

Who Should Attend

- R&D scientists using NGS as a tool for sequence analysis
- Researchers selectively targeting the genome to discover biomarkers for mutations, variant detection, and copy number variations
- Clinical research and development scientists developing NGS-based diagnostic and prognostic tests based on genomic biomarkers
- Clinicians using NGS-diagnostics to guide potential treatment
- Gene sequencing center scientists performing patient tumor genomic characterization

You Will Learn

- How the novel Single Primer Enrichment Technology (SPET) is superior to existing methods for analysis of copy number variation and loss of heterozygocity.
- How Single Primer Enrichment Technology (SPET) is employed with a panel of 509 cancer genes to enable a comprehensive view of the biology of a patient sample using a single assay.
- How the simple analysis method delivers CNV measurements with statistical significance and a broad dynamic range making it ideal for the analysis of low and high copy number changes which are common in cancer samples.

Produced with support from

NuGEN
imagine more from less

A Match Made in Cancer —Fickle Kinases, Promiscuous Drugs

The genetic basis of a patient's cancer is often unclear. A patient's cancer may be driven by just one out of many possible genetic causes, or it may be the culmination of multiple genetic causes. All of these possibilities exist in a kind of cloud, which is complemented by another sort of cloud, which consists of the various cancer-suppression activities that one drug, or a combination of drugs, may have. Some drugs are "promiscuous." For example, some cancer drugs inhibit multiple cancer-related kinases.

A patient's cancer-driver cloud might overlap with a particular drug's cancer-suppression cloud, but who could say? We're dealing with clouds, after all, not the crisply bound regions we see in Venn diagrams.

Since the overlapping region between a patient's cancers and an anticancer drug or drug combination is itself a sort of cloud, it can be hard to grasp—at least for us humans. Computers, however, are just the thing to deal with all the amorphous contingencies.

Computers have been used to match drugs to disease in the labora-

(continued on page 25)

Occupy Precision Medicine!

Inequality. The word had all but vanished from public discussion of economic policy. Then Occupy Wall Street happened, and suddenly "inequality" was on everyone's lips, as though people were waiting for an opportunity to recognize, however belatedly, an uncomfortable truth—individual virtue doesn't guarantee security, let alone prosperity. And, finally, people felt free to admit that there might be, after all, such a thing as society.

A comparable shift in discourse may be in store for precision medicine, if two public health scholars have anything to say about it. These scholars—Sandro Galea, M.D., Dr.P.H., and Ronald Bayer, Ph.D.—are adamant that differences in public health outcomes are less a matter of access to medical care than they are a matter of sheer socioeconomic differences. Moreover, they suggest that if access to medical care matters relatively little, the availability of precision medicine matters even less.

In other words, individual factors are not everything. Collective factors are important, too. This straightforward assertion, expressed in a Perspective article that appeared August 6 in the New England Journal of Medicine, directly challenges the individual focus that prevails in "personalized" medicine.

iStock/izusek

"There is now broad consensus that health differences between groups and within groups are not driven by clinical care, but by social-structural factors that shape our lives," wrote Dr. Galea, Dean of the Boston University School of Public Health, and Dr. Bayer, co-director of the Center for the History and Ethics of Public Health at Columbia University's Mailman School of Public Health. "Yet seemingly willfully blind to this evidence, the United States continues to spend its health dollars overwhelmingly on clinical care.

"It is therefore not surprising that even as we far outpace all other countries in spending on health, we have poorer health indicators than many countries, some of them far less wealthy than ours."

The authors hasten to add that precision medicine may eventually "open new vistas of science" and make contributions to "a narrow set of conditions that are primarily genetically

(continued on page 23)

Direct-to-Consumer Genetic Testing *Will It Go Away?*

Patricia Fitzpatrick Dimond, Ph.D.

The NIH defines direct-to-consumer genetic tests (DTCs) as those aimed at consumers via television, print advertisements, or the Internet. Also known as at-home genetic tests they provide access to a person's genetic information without necessarily involving a doctor or insurance company in the process.

Causing controversy among healthcare professionals and heavily marketed by the companies that provide them, the tests prompted concern among healthcare professionals, such as the American College of Medicine Genetics board of directors, which said in 2004 that due to complexities of genetic testing and counseling, the self-ordering of genetic tests by patients could potentially cause harm. Potential pitfalls, according to the organization, include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up, and other adverse consequences.

The widespread availability of these tests offered by multiple companies, including 23and Me, Decode Genetics, DNA Direct, and Genelux to name a few, had driven consumer demand and interest.

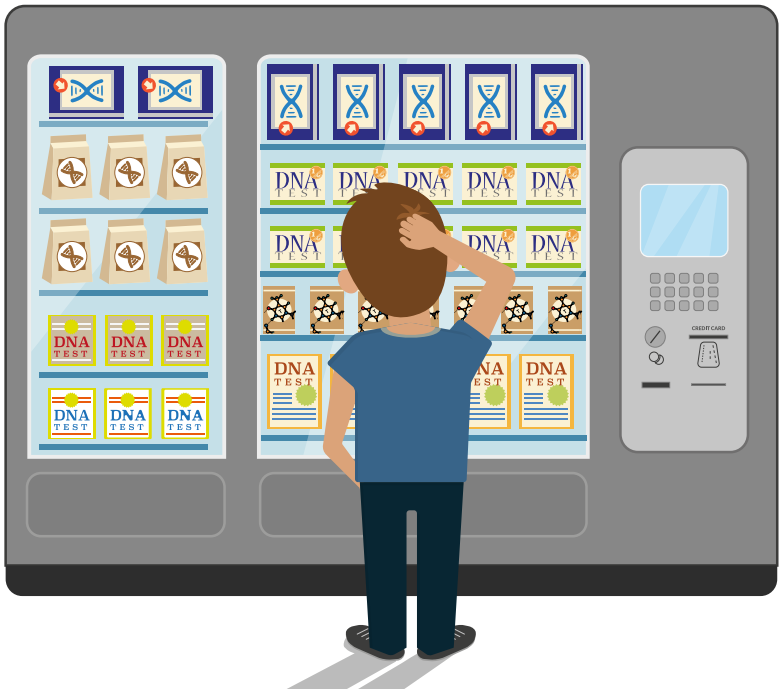
DTCs tests usually involve collecting a DNA sample at home, often by swabbing the inside of the cheek, and mailing the sample back to the laboratory. Consumers are notified of their results by mail or over the telephone, or the results are posted online. In some cases, a genetic counselor or a healthcare provider is available to explain the results and answer questions.

The price for this type of at-home genetic testing ranges from several hundred dollars to more than a thousand dollars. These companies offered consumers everything from identification of genetic predispositions to specific diseases to athletic capabilities assessments.

For example, GenePlanet offers personalized DNA analysis that enables individuals to utilize "targeted prevention,

PATRICIA FITZPATRICK DIMOND, Ph.D.

has been a long-time contributor to Clinical OMICs and currently serves as the publication's Technical Editor. She is also president of BioInsight Communications. During her career in the biotechnology industry, she was VP of strategic development and corporate communications at Coley Pharmaceutical Group (now Pfizer), where she developed and managed the company's investor relations and communications programs. (pdimond@liebertpub.com)



DepositPhotos/ Julia_Tim (modified by Clinical OMICs)

Healthcare professionals express concern that due to complexities of genetic testing and counseling, the self-ordering of genetic tests by patients could cause harm.

tailored nutrition and timely preventive check-ups in order to improve one's health, well-being, for disease prevention, early disease detection, reduction of adverse drug reactions and improve treatment, and the discovery and utilization of one's hidden potentials."

Whole-genome testing, offered directly to the public, is the latest development in personalized medicine. Companies typically offer to test for genetic traits that predict the risk of disease or estimate the effectiveness of drug therapies. In a typical test, up to a million single nucleotide polymorphisms (SNPs) may be analyzed. A customized report is generated, describing the SNPs and one's individual risk factors, usually based on population-level studies of what these SNPs mean.

Complexities and Concerns

But given the complexities that have merged in characterizing the human genome, and the storm of questions about the practice of providing consumers with DNA sequence information without the guidance of professional interpretation, companies have stopped offering the tests or nimbly turned to analytic services that go way beyond sequencing.

Unlike genetic testing for mutations in known hereditary cancer susceptibility genes such as BRCA1/2, these genomic profiles examine DNA variants, which typically have a minimal risk impact, account for only a fraction of the heritable component of cancer, and do not consider family history or other known risk factors. Thus, the clinical validity and utility of personal genome scans for disease risk prediction remain for the most part unestablished, although some argue lack of evidence of harm and that there is the possibility of a positive impact on health behaviors or increased genetic awareness.

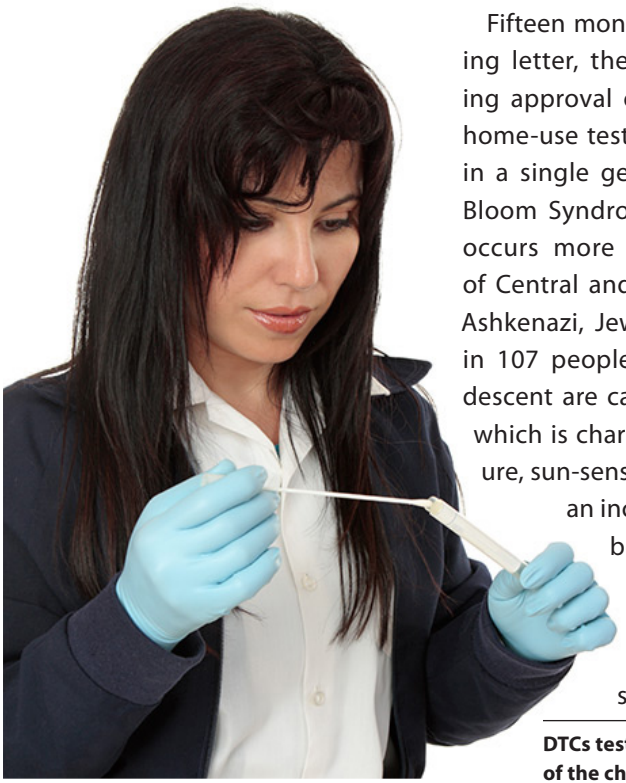
The FDA has to some extent clarified how it intends to regulate what some had referred to as the "wild west" of DTC genetic testing. In 2010, the agency the agency published letters it had sent to five genomics companies, 23andMe, Navigenics, deCODE, KNOME, and Illumina, informing the

(continued on next page)

(continued from previous page)

companies that they were violating medical device regulations by manufacturing and selling their testing products without appropriate review and approval.

In November 2013, the FDA changed the landscape for DTC testing, sending a warning letter to 23andMe, a provider of a so-called "spit kit," the company's saliva collection kit, and personal genome service. The letter enjoined the company from selling the kit, which the company said provides information on everything from the risk of breast cancer to a person's ancestry. The agency told the company it was marketing the kit without clearance or approval in violation of the Federal Food, Drug and Cosmetic Act.



iStock/lovleah

Regulators questioned both the reliability of the tests and the appropriateness of directly providing the consumer with potentially actionable medical information. The company had maintained that its DNA tests provided general information rather than a medical service. In 2012, however, the company reversed that stance, submitting paperwork for FDA clearance on its genetic tests.

The FDA's ruling against 23andMe may discourage companies from entering the direct-to-consumer genomics market.

Fifteen months after its 2013 warning letter, the FDA granted marketing approval of a specific 23andMe home-use test that detects a variant in a single gene, the BLM gene for Bloom Syndrome. The rare disorder occurs more commonly in people of Central and Eastern European, or Ashkenazi, Jewish background. One in 107 people of Ashkenazi Jewish descent are carriers for this disorder, which is characterized by short stature, sun-sensitive skin changes, and an increased risk of cancer. If both parents carry the autosomal recessive gene, there's a 25% chance of their offspring having a cancer-predisposing disease.

23andMe obtained the clearance through the agency's de novo regulatory pathway, reserved for low- to moderate-risk devices with no market precedent. The FDA has also classified autosomal recessive carrier screening tests as Class II, allowing the products to forgo premarket review and clearing the way for similar devices to enter the market, the agency said in a statement.

Thus, if FDA chooses to classify a specific lower-risk genetic test as Class I or Class II, full premarket approval would not be required for that test. Opinion remains divided as to whether the agency's ruling against 23andMe could further discourage companies from entering the already struggling direct-to-consumer genomics market.

In December 2013, 23andMe announced that it would comply with the FDA's directive to discontinue consumer access to its health-related genetic tests during the ongoing regulatory review process. The company has continued to provide consumers with both ancestry-related information and raw genetic data and to allow customers who bought kits before the warning letter was set to see their existing test results.

Now, new startups like Color Genomics that are focused on DTC tests offer spit kits only through physician's offices. Color Genomics offers a $249, 19-gene analysis, including BRCA1 and BRCA2, related to breast

DTCs tests often involve collecting a DNA sample at home by swabbing the inside of the cheek and mailing the sample to the lab.

and ovarian cancer, making it potentially accessible to most women. Following analysis at Color's CLIA-certified labs, results are returned to testers, who will be able to get in touch with board-certified genetic counselors at Color about the next steps based on results and a screening prevention plan.

The company's website clearly encourages every woman to get tested. "Every woman should have the choice and opportunity to get tested for her genetic risk of breast and ovarian cancer in an affordable, accessible, high-quality way, and that knowledge of a woman's genetic risk empowers her to work with her physician to develop a personalized plan based on that information" the site says.

The NIH says because harmful BRCA1 and BRCA2 gene mutations are relatively rare in the general population, most experts agree that mutation testing of individuals who do not have cancer should be performed only when the person's individual or family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2.

"People don't understand that results can be ambiguous," Debbie Saslow, Director of Cancer Control Intervention at the American Cancer Society, told Bloomberg News. "If you don't have any risk factors, nobody recommends genetic testing for the general population."

Changing the Game Plan

Having seen the writing on the wall, some companies that offered direct-to-consumer genome analyses have either gotten out of the business or changed their game plans. Knome now calls itself "The Human Genome Interpretation Company," with a disclaimer on its website stating that it does not offer personal genomic analysis.

In a 2012 article in Nature, Jonas Lee, Knome's Chief Marketing Officer said "We stopped working with the 'wealthy healthy' in 2010. The model changed as sequencing changed." The new emphasis, he says, is now on using Knome's technology and technical expertise for genome interpretation.

Rather than operate in an environment of uncertainty, companies have formed strategic alliances to further their interpretation enterprises. Genalice and Knome jointly announced on January 15, 2015 a strategic partnership to offer their products together as a turn-key solution for those using next-generation sequencing (NGS) data to interpret patients' genomes. Genalice Map will use its preprocessing solution for aligning and calling NGS data and seamlessly connects to Knome's informatics and genomics interpretation system, the knoSYS® platform.

Knome says its knoSYS platform provides an "end-to-end" solution for the operational needs of clinical labs that are developing tests based on NGS. Users can process raw data through all the remaining steps of analysis: sequence alignment, variant calling, quality control, annotation, filtering, and reporting.

Several new companies focused on post-sequencing analysis have emerged. Companies like Personalis says its goal is to enable accurate clinical grade insights into genomic data, not only sequencing DNA samples but also in alignment and variant calling, and variant analysis to find those that may cause disease.

In January 2015, Personalis announced it had raised $33 million in a Series C financing round, bringing the total amount of venture capital raised as of that date to $75 million. Personalis says it will use the funds to scale up its operations, having launched cancer genome analysis services (the ACE Exome for Cancer and the ACE Extended Cancer Panel) and updated its existing ACE Clinical Exome test for inherited diseases in Fall of 2014.

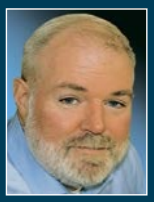
At the Heart of the Matter: The Genomics Underlying Cardiovascular Disease

Jeffrey S. Buguliskis, Ph.D.

Since cardiovascular disease (CVD) still represents the leading cause of death in the United States, researchers are, if anything, only more determined to identify the triggers of disease and those who may be at greatest risk. Science has made considerable progress over the years identifying and even treating many of the risk factors that contribute considerably to CVD progression (e.g., hypertension, type 2 diabetes, cigarettes, and physical inactivity), resulting in an overall decline in mortality rates.

However, in the genomic age, researchers feel they can push the diagnostic testing boundaries even further by testing for subclinical disease through specific genetic biomarkers. This spirit animates a recent report published online ahead of print in Nature and discussed in GEN. It describes how a scientific team led by researchers at Massachusetts General Hospital discovered the first gene linked to mitral valve prolapse (MVP).

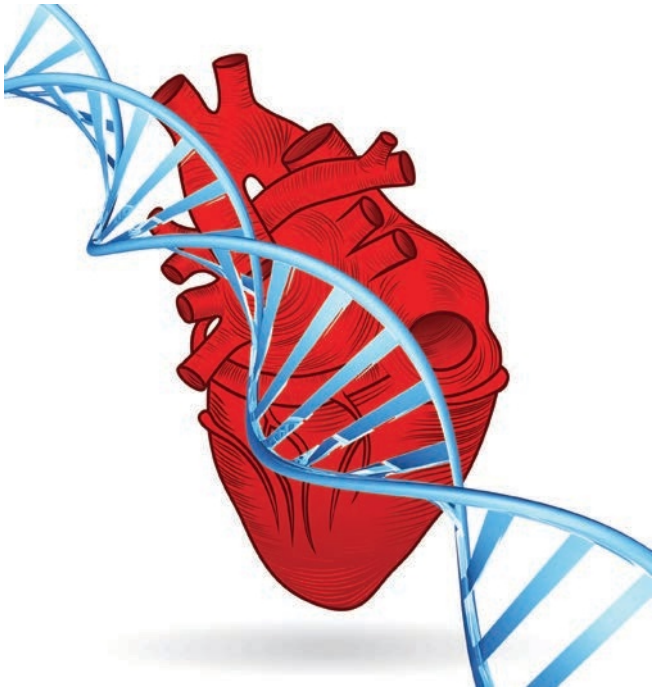
While it has been well documented that MVP is heritable and variably expressed in families, a specific genetic marker had not been previously identified. Although more work will need to be done with larger cohorts of MVP patients to determine the prevalence of the mutation in the DCHS1 gene, the identification of this genetic mechanism may hold potential for presurgical therapeutic intervention—an important discovery given that MVP affect nearly 1 in 40 people worldwide.



JEFFREY S. BUGULISKIS, Ph.D.,
is Technical Editor of GEN and Clinical OMICs.
(jbuguliskis@genengnews.com)

Mendel's Heart Was in the Right Place

To understand the impact that genetic testing has on the diagnosis and treatment of CVD, it's important to have an appreciation for the genetic complexities surrounding different diseases of the heart. Prior to the rapid rise in genomics over the last few years, several genes associated with Mendelian forms of CVD—those that follow classic inheritance



Heart illustration: iStock/SvetaP
DNA double helix: iStock/Kagenmi

NGS technology has enabled researchers to epidemiologically analyze DNA sequences by quickly deciphering mass quantities of genetic information in a short amount of time.

patterns—were identified. However, these diseases only represent a small percentage of CVD cases, albeit no less deleterious to those patients stricken with them. Some examples include aortic aneurysms, hypertrophic cardiomyopathy, long-QT syndrome, and premature myocardial infarction (occurring at or younger than 55 (men) or 65 (women). These diseases are often called simple, or monogenic, in that a single gene is sufficient to cause disease.

Additionally, there have been various recessive mutations identified that have been associated with familial forms of cardiovascular risk factors. Consequently, genetic studies led to the observation that mutations in the low-density lipoprotein receptor results in hypercholesterolemia and myocardial infarction—a Nobel winning discovery that eventually paved the way for the development of statin drugs.

The majority of CVDs, however, are not caused by a single gene mutation and are considered to be polygenic, having heritable and environmental contributions toward the disease phenotype. These multigenic defects have complicated diagnostic measures that are often employed to determine progression of the disease, as patient to patient variance makes it difficult to home in on the most important offending genes. Scientists realized a number of years ago that simple genetic analyses or even genetic linkage studies using several hundred DNA markers would not provide the requisite resolution to identify predisposing polygenic traits.

With the rise of next-generation sequencing technology, researchers have the power to analyze DNA sequences more epidemiologically, by rapidly deciphering mass quantities of genetic information from an array of patients in an extremely short period of time. These genome-wide association studies (GWAS) have allowed scientists to assemble catalogs of cardiovascular variants leading to the discovery of a large number of new genetic loci associated with CVD risk factors and subclinical indexes.

For instance, scientists from the China-Japan Friendship Hospital in Beijing recently reported in PLOS One on a GWAS using close to 5,000 type 2 diabetes patients, not currently taking lipid-lowering medications. The researchers found five single nucleotide polymorphisms (SNPs) that were significantly associated with increased triglyceride levels. Furthermore, the investigators found that one

(continued on next page)

(continued from previous page)

of the SNPs, TOMM40, was associated with increased LDL levels in study patients. These are important findings since it has been well documented previously that dyslipidemia is a strong risk factor for CVD.

Studies like this provide important insight into the molecular underpinnings that often initiate the progression toward CVD. Yet, GWAS are not the only tool accessible to genomic scientists. Many studies have looked at either specific mutations and/or SNPs, thought to have an association with various diseases of the heart, using NGS techniques such as whole-exome sequencing, which looks at only the coding regions of the genome. Alternatively, whole-genome sequencing, which deciphers the entire genome, can identify SNP's within the noncoding regions of DNA that often play a role in gene regulation.

"Whole-exome sequencing techniques, particularly in those with "panel-negative" cases, have provided additional yield in single center experiences, as it relates to identifying novel genetic determinants of inherited cardiovascular diseases, but current costs and lack of reimbursement remained limiting factors," explains W.H. Wilson Tang, M.D., Director of the Center for Clinical Genomics at the Cleveland Clinic. "Newer noncoding genetic and epigenetic markers (circulating or tissue-specific) are also emerging, but many are still in investigative stages. There is hope that whole-genome sequencing may someday unravel genetic regulation and complex interactions with noncoding regions (e.g. 9p21 polymorphism) that have long been linked to cardiovascular diseases, but via unknown mechanisms."

Cross My Heart and Hope to Thrive

As with all healthcare related research, the public and scientists alike tend to ask similar questions: how applicable is this to treating disease and when can we see it in use within a clinical setting? While NGS techniques have made some headway, converting from a pure laboratory method to a clinical diagnostic tool, obstacles still remain. Interestingly, the theme of reimbursement guidelines seems to be a common thread among the application of genomic methods in precision medicine—a "kink" that will need to be worked out sooner rather than later, if personalized medicine is to come to fruition.

"The lack of uniform reimbursement and guidance to treatment alterations in probands remain the single biggest limitation to widespread implementation of cardiac disease genetic testing. This is understandable at present because even with identified genetic mutations it may not be necessary to change treatment approaches, only to benefit from cascade testing for at-risk mutation carriers," states Dr. Tang. "Furthermore, there is a lack of basic genomic medicine education in cardiovascular disease training, and the paucity of clinically relevant or treatment-related translational research in cardiovascular genomics also poses some challenges."

Setting the bureaucratic complications aside, if the scientific strides made in CVD genomics and testing are any indication of its future, than we should be prepared for real meaningful cardiac therapies soon. Furthermore, the combination of fields like pharmacogenomics with cardiogenomics should help shape current drug regimens for CVD patients and aid in the rational design of new therapies.

"Specific therapeutic approaches targeting specific cardiovascular genetic diseases are in early-phase development, several of them provide opportunities to potentially prevent or delay onset of overt manifestations," notes Dr. Tang. "Some of them, including various rare systemic diseases such as transthyretin amyloidosis or Duchenne's muscular dystrophy, already have specific drug targets and have been in active clinical investigations."

Interestingly there may even be assistance to CVD testing coming from seemingly unrelated areas. As Dr. Tang points out, "there is increasing recognition of the contributory role of the gut microbiome in cardiometabolic disorders as well as cardiovascular disease pathogenesis—an area that is currently under active investigations."

Dr. Tang goes on to add that CVD genomics has already made an impact on patient's lives and that he is optimistic of a successful future. "The biggest yield so far in cardiovascular genetics has been the discovery of novel drug targets (like PCSK9) based on genomic analyses of rare variants that can identify disease mechanisms, and there is hope that more will come."

HPLC Instrument

Prelude LX-4 MD HPLC uses four parallel channels that deliver up to four separations in a single instrument, streamlining LC-MS workflows and reducing mass spectrometer idle time. The four channels can run identical or different LC-MS assays simultaneously, which provides flexibility for varying clinical separations and can maximize mass spectrometer utilization.

Thermo Fisher Scientific

MORE INFO

KRAS Mutation Detection

Target Selector™ assay is a new test that uses a patient's blood sample to detect KRAS, a predictive biomarker for solid tumor cancers. Testing for this predictive biomarker can help physicians identify patients who might benefit from targeted therapies currently available to treat solid tumor cancers. In addition, the high sensitivity of Target Selector allows the test to be used for monitoring patients for response to treatment and progression of disease during the course of therapy.

Biocept

MORE INFO

Detection of HTLV Infections

The Elecsys® HTLV-I/II immunoassay is a diagnostic test to help detect antibodies against human T-lymphotropic virus I or II infection in donated blood and routine diagnostic samples. It is designed for the needs of blood centers and clinical laboratories. The test is available as 100- and 200-test Rackpacs with clear separation of positive and negative results. It has a testing volume of 30 µL and provides results in 18 minutes.

Roche Diagnostics

MORE INFO

iStock/Dieter Meyrl

Immunoassay System

VIDAS® 3 is a low-throughput immunoassay platform that can perform tests on demand, individually, or in series. As a result, it is suited to centralized as well as satellite laboratories. The instrument uses the same reagents as the other instruments in the VIDAS range although VIDAS 3 features enhanced automation, in particular the pre-analytical section from the barcoded primary tube including dilution, improved traceability, and new software capabilities, as well as a quality control program in compliance with laboratory certification standards.

bioMérieux

MORE INFO

Molecular Pathology's *Contextual Cues*

DeeAnn Visk, Ph.D.

Molecular pathology attempts to describe and understand the origins and mechanisms of disease by evaluating the molecular content of patient samples. Increasingly, "molecular content" is being seen as an intricate, interconnected whole, a dynamic collection of interacting parts. In other words, context is all.

Context was a recurring theme at the Pathology Diagnostics Conference, a key piece of the Molecular Diagnostics Summit recently held in San Diego. At this event, several presenters emphasized the ways pathology results may become more meaningful if, for example, morphological and spatial information is preserved in molecular tests, or—more generally—imaging is integrated with data analysis.

Presenters also indicated that mining molecular pathology not only yields clinical paydirt, it also conserves scarce healthcare resources. For example, Bonnie Anderson, President and CEO of Veracyte, asked how molecular pathology could be used to impact the healthcare system and reduce costs: "Where can we impact the healthcare system to reduce cost? How can efficiency be increased by using genomic technology?" Patients, Anderson noted, often endure multiple procedures in expensive diagnostic odysseys.

DEEANN VISK, Ph.D., a freelance science writer, editor, and blogger, is also a consulting editor for Mary Ann Liebert, Inc., publishers. (editor@clinicalomics.com)

A Molecular Cytology Approach to Lung Cancer

Following in the footsteps of its Afirma® assay for thyroid diagnostics, Veracyte developed Percepta®, a test for clarifying diagnosis of lung nodules. Percepta was introduced to a select market last April.

Definiens, a provider of image analysis and data-mining solutions for tissue diagnostics, generated this image to represent the company's technological approach: providing detailed cell-by-cell readouts from target structures on tissue slides, and correlating this information with data derived from other sources. This approach is meant to generate new knowledge and support better decisions in research, diagnostics, and therapy.

In the past, lung cancer was usually found at stage 3 or 4. When lung cancer is found so late, it is too late to attempt a surgical cure. More timely results, however, may come from new procedures, such as a screen designed for asymptomatic patients who smoke or have smoked. High-risk patients undergo a low-dose CT. If nodules are discovered, the patient undergoes a nonsurgical procedure to biopsy the nodules.

According to Anderson, "About 250,000 bronchoscopy procedures for cancer are done in a year; 40% do not yield a clear answer. That is 100,000 inconclusive procedures a year." The next step in the diagnostic odyssey is traditionally a high-risk, high-cost surgery to reach the lung nodules directly.

To address this ambiguity in a conventional diagnostic procedure, Veracyte acquired Allegro Diagnostics, which had shown that gene expression of normal epithelial cells lining the lungs can aid in the diagnosis of lung cancer. From this information, Veracyte developed a test to determine the likelihood of cancer development based on a set of genes differentially expressed. This does not require a biopsy of the nodules, only brushing from the lining of the lungs.

According to a study published in the New England Journal of Medicine, the negative predictive value of Percepta is 94%. By offering a noninvasive diagnostic test for lung cancer, clinicians may help thousands of patients avoid unnecessary surgeries, decreasing costs and improving patient's lives.

A Sepsis Host Response Assay

Another malady being addressed by molecular diagnostics is sepsis. Again, the problem here is the ambiguity of diagnosis. The symptoms of bacterial-induced sepsis are very similar to those induced by other causes such as

(continued on next page)

(continued from previous page)

burns and trauma. Conventional tests for sepsis use blood plates to screen for bacteria in the bloodstream, with a 24 hour turnaround time. Such a lengthy delay is worrisome, particularly since time is of the essence when patients display symptoms of sepsis.

Blood culture tests have high false-negative as well as high false-positive rates. High costs of treatment are also associated with sepsis; for Medicare alone, $20 billion dollars a year is spent in treatment of sepsis.

Immunexpress approaches this problem not by hunting for pathogens, but instead identifying the body's response via gene expression in white blood cells. "We are basing the diagnosis on the host response to infection, not the infectious agent itself," states Roslyn Brandon, Ph.D., President and CEO of Immunexpress.

Liquid biopsies offer oncologists a simple, noninvasive way to monitor disease progress and response to therapy.

Through careful studies, a set of four differentially regulated genes was defined. A good indicator of a diagnostic test's accuracy (few false positives and few false negatives) is found in its ROC score; the numbers for SeptiCyte® range from 0.96 to 0.89.

From this information, Immunexpress developed a test that takes only four hours to perform. Having filed with the FDA in May, and pressing ahead with ongoing clinical studies, Immunexpress plans to launch SeptiCyte in the second quarter of 2016.

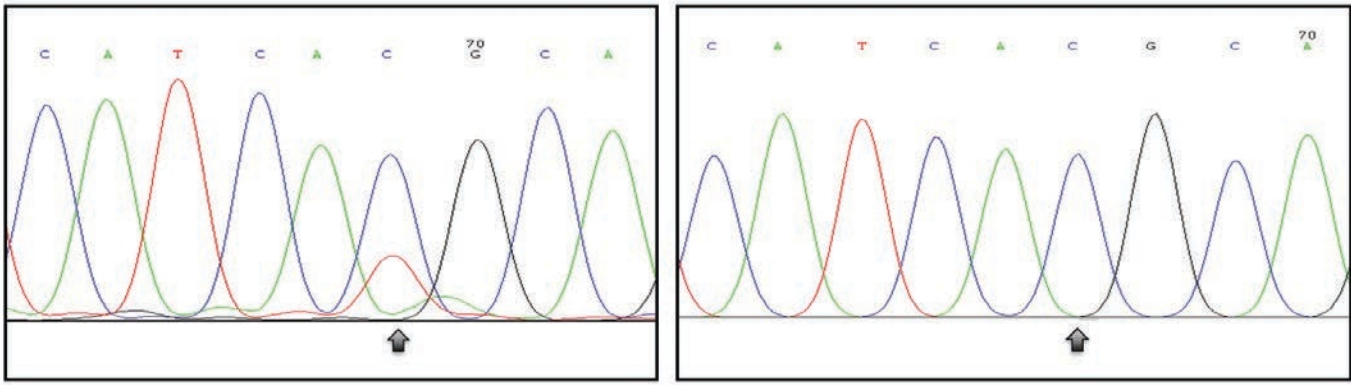
Dr. Brandon declares, "During clinical trials, diagnostic utility was compared to all clinical and laboratory diagnostic tools available to a clinician during the patient's hospital stay. SeptiCyte significantly differentiated infection-positive systemic inflammation from infection-negative systemic inflammation, [performing] better than other diagnostics, both individually and in combination."

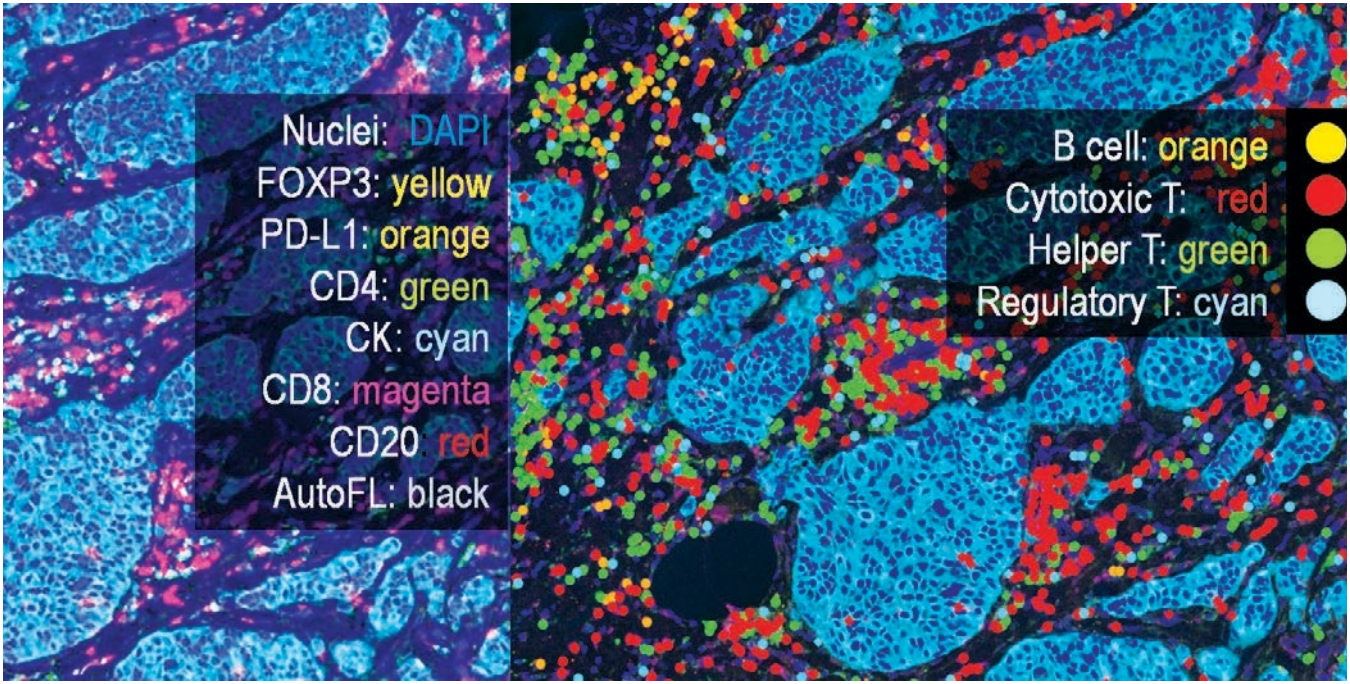
In cancer biology, conceptual exercises have encouraged researchers to think of tumors as organs in and of themselves. Researchers interested in following this line of thought not only want to know which cells in the tumor express different markers, they also want to keep the in situ context intact. Several technical hurdles stand in the way of this ideal: antibodies developed in the same species, autofluorescence of FFPE sections, and the tedium of hand-curating multiple slides.

In Situ Analysis of Solid Tumors

Other approaches to understanding cancer are being developed in the field of tumor immunobiology. "Obtaining phenotypic information about the various immune cells that play roles in and around the tumor has been a challenge," states James Mansfield, Director of Quantitative Pathology Applications at Perkin-

EKF Molecular Diagnostics is investigating the ability of its PointMan® kits to enrich mutant DNA from blood-based samples without the need for further biopsy. These chromatograms show PointMan-amplified cell-free DNA from patient blood (left) and nonamplified DNA (right) looking at the T790M mutation in EGFR. Arrow: position on the mutation.





The breast cancer section shown in these images was subjected to 6-plex analysis by means of PHENOptics™, a methodology developed by PerkinElmer. Stained for FOXP3, PD-L1, CD4, CD8, CD20, cytokeratin, and DAPI, the section was imaged multispectrally on the same slice. Left: unmixed composite image with autofluorescence removed and cross-talk corrected. Right: various phenotypes of immune cells are superimposed.

Elmer. "Existing methods, such as fluorescence-activated cell sorting (FACS) or polymerase chain reaction assays, offer phenotypic information on homogenous samples, or single biomarkers with morphological information intact with standard immunohistochemistry.

"Blood cancers have the benefit of being amenable to FACS analysis," continues Mansfield. "Our PHENOptics™ methodology, which includes reagents, imaging, and image analysis, enables researchers to analyze solid cancer tumors in a similar fashion while overcoming several technical hurdles."

One component of the methodology is PerkinElmer's Vectra® instrument, which can be programmed to remove FFPE tissue autofluorescence, correct cross-talk between fluorescent channels, quantify the per-cell marker expression, determine the cellular phenotype, and count cells. Of course, a high-resolution image of the slide is also available.

"What is truly interesting to people is not so much the staining, or even imaging and analysis, but what it does for them. It enables them to do the same kind of phenotyping and quantitation that they are currently doing in flow cytometry," asserts Mansfield. "When cells are analyzed in situ from FFPE or frozen sections, tissue architecture is maintained, enabling spatial distance calculations between the various cell types. The capacity to acquire this information for solid cancer tumors is now finally available."

The ability to look at multiple biomarkers in solid tumors while retaining cell location data is a recent development. As researchers determine which biomarkers are important in diagnosing and treating cancers, this instrument will be developed into a diagnostic platform. At present, it is for research purposes only.

Liquid Biopsies, Multimarker Panels

Historical diagnosis of cancer mutations requires a tissue sample and is based on immunohistochemical staining. Advances in technologies such as quantitative PCR (qPCR) and next-generation sequencing allow

(continued on next page)

(continued from previous page)

liquid biopsies from blood, urine, or other bodily fluids. The ease of this testing, with no requirement for solid tissue, offers oncologists a simple, noninvasive way to monitor disease progress and response to therapy.

"The ability to identify a particular mutation is essential in oncology, where treatment of cancer can be based on the specific mutation found in that cancer," explains Andrew Webb, CEO of EKF Molecular Diagnostics. "Tissue samples for some tumors are difficult to obtain. Using blood as a source for tumor DNA is simple—no need for further surgical biopsies."

EKF Molecular Diagnostics offers a system for liquid biopsy of various cancer mutations from blood samples. The source of tumor DNA is found in cell-free DNA circulating in the blood. To get enough of the mutant DNA, PointMan® PCR Primers selectively amplify the gene of interest, allowing detection of mutant DNA's down to 0.01% or 1:10,000 copies of the mutation compared to wild type.

Wild-type DNA is not amplified in this enrichment step. The mutation in the tumor DNA that is enhanced is not specific for a particular base pair change, but will pick up any substitution at a specific local.

At present, kits are for research purposes only. Two mutations can be tested: K-ras and EGFR (other mutations are in the pipeline). Only 10 ng of total DNA is needed. Once the amplification step is complete, multimutational testing can be run by means of qPCR, pyrosequencing, or Sanger sequencing.

Data-Enriched Image Analysis

Another quest in cancer diagnostics is the integration of large quantities of visual information. Ralf Huss, M.D., Chief Medical Officer of Definiens, states, "Pathologists use memories of images to determine what they are looking at, to diagnose." Contextual cues aid greatly in the determination of the diagnosis.

Definiens utilizes intelligent software to analyze tissue specimens. The software processes not just imaging data, but other kinds of information, such as cancer stage, patient data (age, sex, etc.), and point in treatment—the more data the better.

The goal of this software is to combine all relevant clinical data to determine how to best treat a cancer. Ultimately, the goal is to have a product available that can be used by anyone. This algorithm will allow the determination of which drugs to use, or conversely, not to use.

"Making pathology more quantitative is foundational in converting the pathologist's art of visually determining histomorphological spatial patterns into a mathematically solid science, by means of automated image and data analysis," explains Dr. Huss. "This approach opens the door for a new generation of prognostic and predictive diagnostic tests for the benefit of the patient."

This approach does for diagnostics what Google Maps does for finding directions. In Google Maps, various kinds of information—traffic information, satellite images, street views, and store information—are layered. Imagine a software tool doing the same, but for a specific tumor, based on information that had been gathered from numerous other patients. Such a tool could rely on its internal algorithms to generate "directions" to the best treatment for a specific tumor.

This approach employs mining multiparametric image analysis results for statistically significant morphological and spatial patterns. Data is then correlated with disease progression and other patient information.

The scope and complexity of this venture may seem overwhelming. But so did Google Maps just a few years ago. Someday there will be self-driving cars and cancers treated by algorithms.

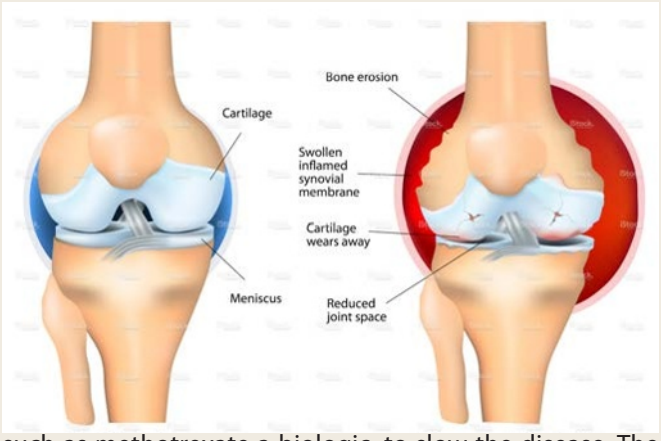
Decision-Making Tools in Rheumatoid Arthritis

Renee Deehan Kenney

With the emergence of a wide array of new therapies for the management of rheumatoid arthritis, not only has treatment improved markedly over the past two decades, it has also grown increasingly complex. With 10 approved biologic therapies in the United States comes a growing need for tools that can turn complex biological data into actionable insights for physicians and patients to make informed and personalized treatment decisions.

A progressive and debilitating autoimmune disease, rheumatoid arthritis (RA) causes pain and stiffness and over time leads to joint damage and disability. It occurs when a person's immune system goes awry, causing inflammation in healthy joints. About 2.4 million people in the United States have RA; of those, more than 1 million have moderate to severe disease.

There is no cure. Treatments focus on controlling the inflammation or dampening the immune attack to prevent joint damage and slow the progression of the disease. Upon diagnosis, patients are typically treated with a combination of standard anti-inflammatories, including aspirin. Patients with moderate-to-severe disease are put on disease-modifying antirheumatic drugs, or DMARDs, such as methotrexate a biologic, to slow the disease. The biologics block key inflammatory pathways—including TNF, IL6, JAK, CD20, CTLA4, and IL1—to shut down the immune response in a targeted fashion.



iStock/ttsz

From a disease-management perspective, these treatments pose challenges due to wide variation in patient response. Response rates for biologics to treat RA range from 30 to 70%, and it typically takes more than three months to ascertain if a patient is responding to a particular therapy. This lack of clarity contributes to poor outcomes, with only 40% of patients achieving remission in one year from the flare-ups that are the hallmark of RA, and results in approximately $5 billion in spending on treatments that don't provide benefit.

(continued on next page)

RENEE DEEHAN KENNEY is Senior Vice President of Research and Development at Selventa. (rkenney@selventa.com)

(continued from previous page)

In light of these issues, the molecular diagnostic specialists at Selventa have been focused on addressing the central question of how they can both monitor disease activity, and also provide physicians and patients with clinically relevant information to make optimal treatment decisions.

Overcoming Disease Complexity

In contrast to targeted therapeutic approaches that focus on the identification of a single genetic mutation like HER2 in breast cancer or the Philadelphia chromosome in chronic myelogenous leukemia, diagnostic tools for RA treatment require an approach that can synthesize a multi-factorial web of biological information.

RA is mediated by complex, systemic and local biology that differs from patient to patient. While a few inflammatory-related proteins are measured as part of the diagnostic and disease-monitoring process, there is no single protein, DNA, or RNA factor that can diagnose, monitor, or effectively provide information about a patient's disease to a physician making treatment decisions. With the large number of different biologics available to the treating physician, currently there is no way to discern which one would be best for a patient at a given time.

The solution in RA, therefore, requires more complex individualized diagnostic decision-making tools—based on advances in "omics" technologies that allow the seamless integration of thousands of molecular data points and the exploration of complicated disease biology from patient to patient. An omics approach harnesses a comprehensive range of complex, biological information (genomic, epigenomic, transcriptomic, proteomic, metabolomic, electronic medical records), thereby enabling a clinically relevant dashboard of relevant patient-specific data that physicians, patients, and researchers can use to make optimal treatment decisions.

The clinical contributions made by an effective omics tool would be many. Such a tool could, for example, help identify in advance which therapy is most likely to be beneficial (a particularly important contribution, given how many biologic options are available); monitor whether the therapy is working; and indicate when the therapy can be safely stopped.

ClarifyRA Progress

The Selventa vision is to exploit omics technology and provide RA patients with a holistic RA management system to deliver information to the physician to aid in treatment decision. To realize this vision, Selventa is developing ClarifyRA, a blood-based, predictive decision tool for rheumatologists.

The company's first clinical validation study was heralded in a paper that appeared June 2015 in the journal BMC Medical Genomics. This paper—"Blood-based identification of non-responders to anti-TNF therapy in rheumatoid arthritis"—described the creation of a gene-expression classifier to predict, before treatment, which RA patients would be unlikely to respond to the commonly administered first-line biologic, the anti-TNF therapy infliximab.

Using data from a meta-study of patients treated with infliximab, Selventa investigators examined whole blood samples and detected the activity of 18 signaling pathways, applying an algorithm together with prior knowledge to characterize the activity of TNF in the blood.

This method made it possible to identify 30% of non-responders in advance, with high accuracy.

With these clinical validation results in hand, the company is pursuing multiple avenues to further enhance the clinical utility of ClarifyRA, while also exploring the development of other classifiers in other disease areas. In RA, Selventa intends to establish a molecular correlate to disease activity, which can also be monitored with a simple blood test—providing new insights into disease activity in response to treatment to further inform disease management strategies.

Selventa also plans to expand the test to include information about the biologic targets outside of infliximab/TNF, and to validate the findings through a large clinical study. With wider use of complex biologics, increasing attention being paid to improved disease management, and an emphasis on tighter cost control, the company believes the omics revolution in clinical decision making in autoimmune diseases has just begun.

Occupy! *(continued from page 7)*

determined." Nonetheless, the authors insist that the burgeoning precision medicine agenda is largely silent on a more immediate issue: the "steep social gradient that characterizes who becomes sick and who dies."

Arguing that clinical intervention will not remedy pressing health problems that arise from environmental conditions and inequities in income and resources, the authors cited a 2013 report by the National Research Council and the Institute of Medicine that found Americans fared worse in terms of heart disease, birth outcomes, life expectancy, and other indicators than their counterparts in other high-income countries. The report concluded that "decades of research have documented that health is determined by far more than healthcare.

"Without minimizing the possible gains to clinical care from greater realization of precision medicine's promise, we worry that an unstinting focus on precision medicine by trusted spokespeople for health is a mistake—and a distraction from the goal of producing a healthier population," the authors continued.

To substantiate this concern, the authors noted that according to the NIH Reporter, the proportion of NIH-funded projects with the words "public" or "population" in their titles had dropped by 90% over the past 10 years. The authors also pointed out that our investment in public health infrastructure, including local health departments, lags substantially behind that of other high-income countries, and the CDC's annual budget is dwarfed (by a factor of about five) by investment in the NIH, even as the latter pursues an approach increasingly focused on science and treatments that aim to promote individual health.

Both Dr. Galea and Dr. Bayer warned that specialized medicine could push larger public health initiatives aside. "We need a careful recalibration of our public health priorities to ensure that personalized medicine is not seen as the panacea for population health," said Dr. Galea. "We would love to see the same enthusiasm directed to research initiatives that would affect the health of millions of people, such as treatments of chronic diseases, and policy changes to address poverty, substance use and access to education."

"We face increasing challenges to improve health at the population level which entail addressing certain persistent social realities and have little to do with the frontiers of science," added Dr. Bayer. "We must not let the current focus on individualized medicine sidetrack us in advancing a broad agenda that reduces health inequities both domestically and across the globe."

Congratulations to the Winner

of the Clinical OMICs Word Scramble Challenge

Leesito Flores and his staff at UCLA Pathology & Laboratory

Thank you to all who participated in the first-ever Clinical OMICs Word Scramble Challenge that took place at AACC this year. The entire Clinical OMICs team would like to congratulate Leesito Flores, Clinical Laboratory Manager at UCLA Pathology & Laboratory, winner of this year's challenge and recipient of the Apple Watch. Flores manages the UCLA Outpatient Clinical Laboratory and several outpatient draw stations in the laboratory's outreach areas.

Breast Cancer Registry *(continued from page 5)*

increase the likelihood of breast conservation therapy," noted Pat Whitworth, M.D., a surgeon in Nashville and a co-principal investigator. "However, more breast oncologists are utilizing it as a way to determine if standard chemotherapy is effective. Genomic analysis of breast cancers will help refine treatment based on the patient's individual cancer and not just population based therapies."

"While these new molecular tests are more commonly used to inform treatment selection when treating aggressive, rare or refractory disease, they are also becoming increasingly valuable in earlier breast cancer treatment selection and management," added Peter Beitsch, M.D., a surgeon in Dallas and also a co-principal investigator.

Dr. Penny expects that patients enrolled in the breast registry project will not only benefit from tailored therapeutics but that the program itself will accelerate the pace of discovery in cancer genomics to move beyond the one-size-fits-all approach to cancer treatment.

"Determining if next-generation sequencing and other technologies assist in the selection of clinical trials and targeted treatments for patients being treated in the neoadjuvant setting with improved key clinical endpoints will be a first," he said.

Paradigm was established to bring cutting-edge diagnostics to cancer patients and industry by providing information about the genomic makeup of the patient's cancer and potential therapies based on the specific characterization of the patient's tumor that can impact the patient's course of treatment. TME is a network of clinicians, researchers, educators, and companies whose core mission is to improve the quality and access to targeted breast cancer care by fostering high quality and comprehensive educational programs and resources.

Prostate Cancer Biomarkers *(continued from page 5)*

nicities, and clinicians have long sought a better understanding of what drives this more aggressive disease," said Kosj Yamoah, M.D., Ph.D., Assistant Professor in radiation oncology, genitourinary program, Moffitt Cancer Center & Research Institute. "The ability to identify a subset of African American men who harbor aggressive disease will enable clinicians to more accurately identify appropriate treatments to enhance disease control and ultimately help to improve outcomes in this patient population."

The study, which included 154 African American and 243 European American patient samples pulled from the Decipher Genomics Resource Information Database (GRID), evaluated 20 validated biomarkers reported to be associated with prostate cancer initiation and progression. Of 20 biomarkers examined, six showed statistically significant differential expression in African American men compared with European American men. The results suggest that prostate cancer may arise from distinct molecular pathways in European men compared to African American men.

The uniqueness in the biology and evolution of prostate cancer in African American men may have clinical implications for applications in both diagnostics and therapeutics.

"These biomarkers provide a source of relevant knowledge in developing a signature that may be unique to African American men with aggressive prostate cancer," noted Dr. Davicioni. "[They] also provide new insights about the relationship between tumor biology and the racial disparity in prostate cancer outcomes.

"This study evaluated a number of biomarkers that were shown to predict risk of high-stage disease in a race-dependent manner, but also validated that Decipher can accurately and independently predict metastasis within five years after prostatectomy in African American men (AUC = 0.78)."

tory of Aik Choon Tan, Ph.D., a researcher at the University of Colorado. Dr. Tan's laboratory develops computational and statistical learning methods for the analysis and integration of high-throughput cancer "omics" data in understanding and overcoming treatment resistance mechanisms in cancer. "My lab," says Dr. Tan, "acts as a 'connector' to provide seamless integration of computational and statistical methods in experimental and clinical research."

The Tan laboratory's most recent work appeared July 23 in the journal Bioinformatics, in an article entitled, "Identifying kinase dependency in cancer cells by integrating high-throughput drug screening and kinase inhibition data." This article describes the Kinase Addiction Ranker (KAR), a tool to predict what genetics are truly driving the cancer in any population of cells. KAR also chooses the kinase inhibitor or kinase inhibitor combination that is most likely to silence dangerous cancer drivers.

In this context, the word "addiction" may need to be clarified. Cancer cells are often "addicted" to the mutated oncogenes, which are typically kinase-encoding oncogenes. Such cancer cells, then, are vulnerable to targeted therapies that can exploit "oncogene addiction." In targeted therapies, small molecules are deployed that can inhibit oncogenic kinases.

"A lot of these kinase inhibitors inhibit a lot more than what they're supposed to inhibit," explains Dr. Tan. "Maybe drug A was designed to inhibit kinase B, but it also inhibits kinase C and D as well. Our approach centers on exploiting the promiscuity of these drugs, the [so called] drug spillover."

Dr. Tan and colleagues combine kinase inhibition signatures with the results of high-throughput screening—a method for testing hundreds of drugs against a panel of cancer cells. Specifically, Dr. Tan used the publicly available Genomics of Drug Sensitivity in Cancer database to discover which compounds have been shown to be active against which cancer cell lines.

"KAR integrates drug sensitivity, comprehensive kinase inhibition data, and gene expression profiles to identify kinases dependency in cancer cells," wrote Dr. Tan and colleagues in Bioinformatics. "We applied KAR to published drug screen data from lung cancer cell lines and leukemia patient samples. Clustering analysis revealed lung cancer cell lines with similarities in kinase dependence."

On the basis of samples from 151 leukemia patients, KAR was able to correctly predict the outcomes of patients treated with certain drugs. The same was true in 21 lung cancer cell lines—KAR predicted the degree of sensitivity of these cells to certain drugs, matching the results of experiments that show these sensitivities.

In addition, KAR was asked to rank the kinases most important to the proliferation of the lung cancer cell line H1581, and to recommend a combination of targeted treatments to attack these cells. KAR suggested the combination of ponatinib with experimental anticancer agent AZD8055. This combination actually proved highly effective at controlling these cells, creating what the researchers called a "synergistic reduction in proliferation."

The investigators warned that given resource limitations when working with patient samples, it may not be possible to screen patient biopsies with large numbers of compounds. Therefore, future studies could benefit greatly from prior optimization of the set of drugs used for profiling.

Dr. Tan and colleagues concluded by emphasizing that their work is relevant to both researchers and clinicians: "We believe that the research reported in this study provides a new research strategy to delineate kinase dependency in cancer cells. This approach can be applied to other cancer cell lines and patient tumor samples to discover effective kinase targets for personalized medicine."

September 28–30

Point-of-Care Diagnostics & Global Health World Congress

to be held in San Diego

MORE INFO

This conference will provide an overview of the point-of-care (POC) testing landscape, from new technologies to regulatory approval. Experts in these fields will share their views on point-of-care in the clinical setting. The aim of this meeting is to bring together life science researchers that work at the nexus of biology and chemistry and technology development to discuss problems, highlight solutions, and facilitate collaborations. This conference covers POC detection, diagnostics, and POC-based treatment options.

October 7–8

Biomarkers in Diagnostics

to be held in Berlin

MORE INFO

A wide variety of topics will be covered at this conference including novel diagnostic technologies, new diagnostic biomarkers, the clinical utility of next-generation sequencing, the regulatory landscape for diagnostics, the health economics value of biomarkers, and the reimbursement environment. Attendees will hear from keynote speaker Miro Venturi, global head of diagnostics biomarkers at Roche, on how biomarkers are at the core of diagnostics and innovative drug development. Additional talks will explore microRNA biomarkers for noninvasive diagnosis, the role of biomarkers in ovarian cancer screening, and early diagnosis of pancreatic cancer.

November 16–17

Cancer Diagnostics

to be held in San Francisco

MORE INFO

This meeting offers delegates the opportunity to network with colleagues from industry and academia to discuss new research in cancer diagnostics including next-generation sequencing, the use of clinical utility of cell-free DNA liquid biopsy, patient selection for cancer drug development, and correlative predictive markers. Distinguished speakers include Robert Anders, assistant professor, co-director, center for noninvasive diagnostics at Johns Hopkins University, and Trevor W. Brown, vice president, precision medicine at SeraCare Life Sciences.

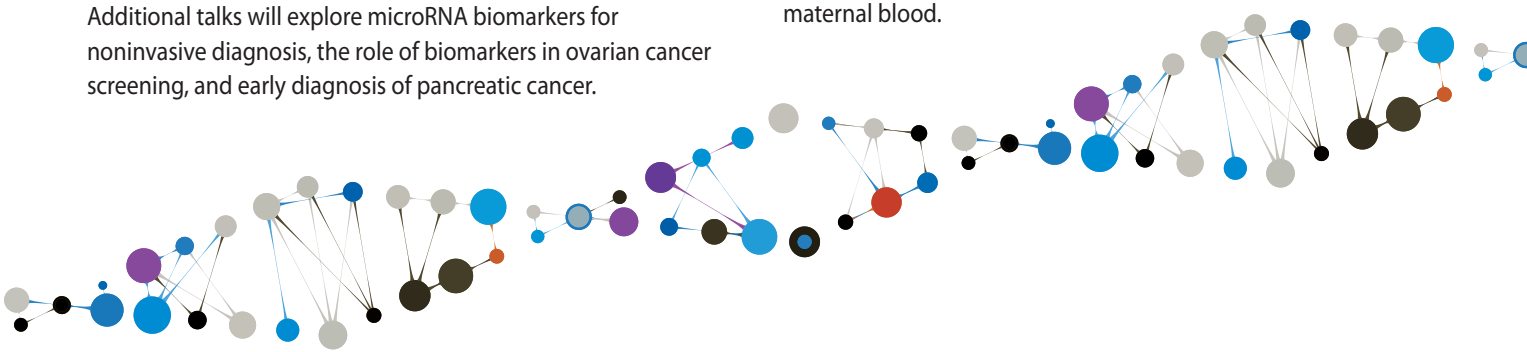
November 16–18

Advances in Prenatal Molecular Diagnostics

to be held in Boston

MORE INFO

This meeting will cover the trends and implications of noninvasive prenatal testing (NIPT). One result has been the steady decline in the number of women choosing invasive testing, with growing replacement of karyotyping by arrays or sequencing for analysis of these samples. Other NIPT trends—expanding NIPT applications beyond higher-risk pregnancies, and developing more comprehensive panels—will also be topics of discussion. Another focus will be the challenges associated with commercializing tests based on isolation of fetal cells from maternal blood.



iStockphotos/Ivcandy