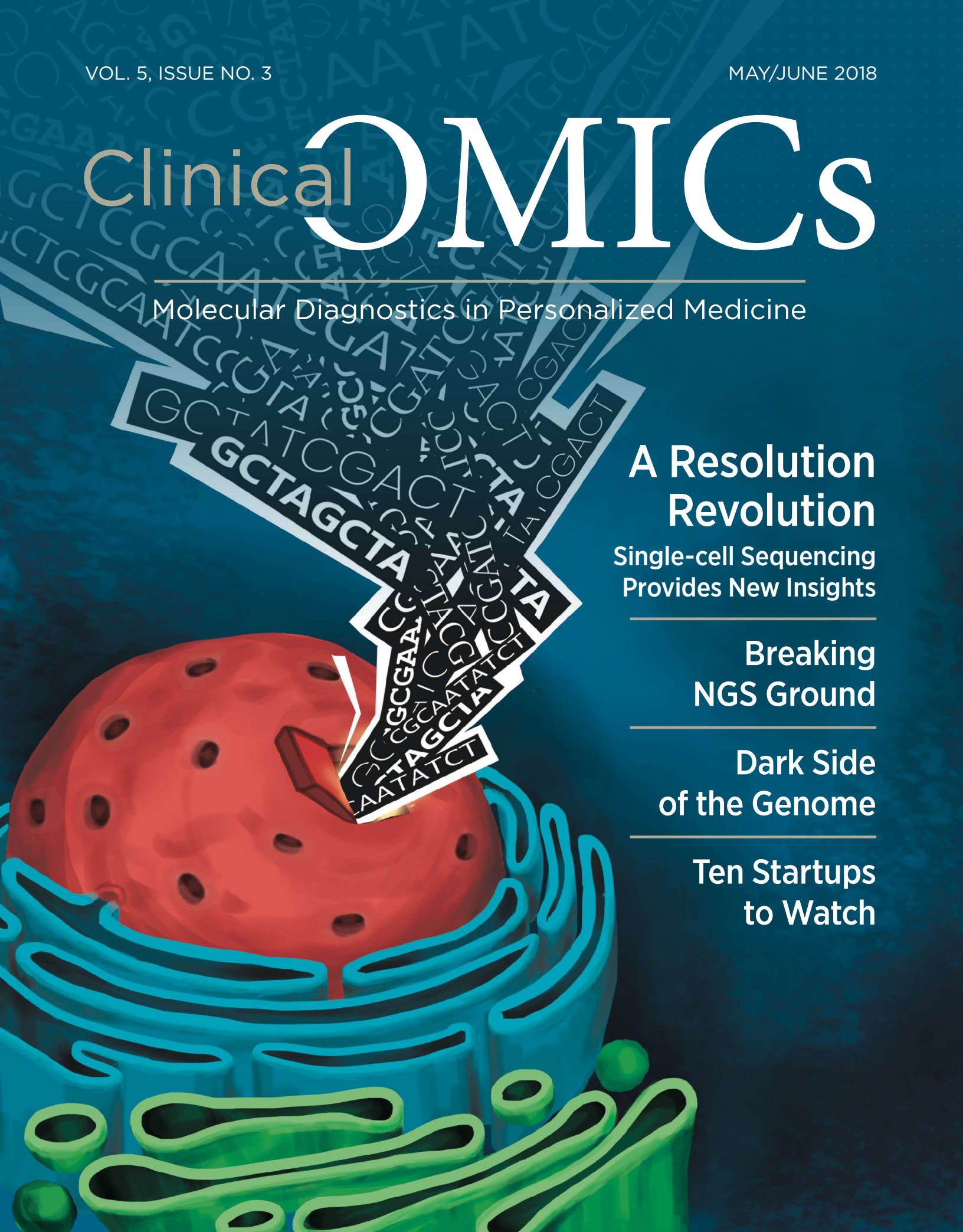
VOL. 5, ISSUE NO. 3 MAY/JUNE 2018

Clinical OMICs

Molecular Diagnostics in Personalized Medicine



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Breaking NGS Ground

Dark Side of the Genome

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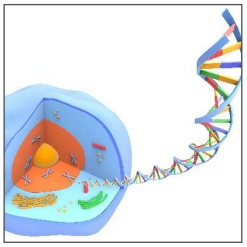

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Pollution and Genes Work Together to Increase Severity of Rheumatoid Arthritis

By Sophia Ktori

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Studies by researchers at the University of Michigan, Ann Arbor, have uncovered a mechanism by which a particular variant of the HLA-DRB1 allele and exposure to environmental pollutants such as cigarette smoke or vehicle exhaust work together to increase rheumatoid arthritis (RA) risk and the severity of bone damage in patients with the disease.

"We found a particular enzyme that acts as a channel, or pathway, in the cell for a conversation between the two culprits, so they work together to do greater damage," said research lead Joseph Holoshitz, M.D., professor of internal medicine and associate chief for research at the University of Michigan School of Medicine's Division of Rheumatology. "Individually they are bad, but together, they're worse."

Reporting on their *in vitro* and *in vivo* studies in the *Proceedings of the National Academy of Sciences*, the University of Michigan team and collaborators at the University of Tennessee Health Science Center suggest that their findings could lead to the development of drugs that block the gene-activated pathway and so reduce the incidence of RA and severity of bone damage.

About two-thirds of RA risk is attributed to genes, and the single most significant genetic risk factor for RA is the shared epitope (SE), a five-amino-acid sequence motif encoded by the RA-associated HLA-DRB1 alleles, the researchers explained. But RA isn't all down to genes. Environmental factors also influence RA susceptibility. The autoimmune disease is associated with exposure to environmental pollutants such as dioxin-like compounds and tobacco smoke, and RA is more prevalent in urban populations and among people who live near highways, irrespective of whether or not they smoke cigarettes.

Recent evidence also suggests that genes and environment may work together to further increase the risk of RA, such that the likelihood of developing the disease is "significantly amplified in genetically susceptible individuals who have been exposed to various environmental pollutants." Cigarette smoke, for example, "increases the disease risk of SE-positive individuals in a multiplicative, dose-dependent fashion," the researchers pointed out. What scien-

(continued on next page)

Thermo Fisher Launches International Childhood Oncology Network

chanut iamnoy / Getty Images

Thermo Fisher Scientific established the International Childhood Oncology Network (ICON) with the concurrent launch of its Oncomine Childhood Cancer Research Assay, a next-generation sequencing (NGS) targeted panel developed in collaboration with Children's Hospital Los Angeles to identify pediatric and young adult cancers. The goal of ICON is to help foster a global community of academic and clinical researchers focused on pediatric and young adult cancers via sharing of data, best practices, and experiment protocols. According to a press release from Thermo Fisher Scientific announcing the launch of ICON, research into these types of cancers has lagged behind research into adult cancer, perhaps due to their different causes. "While adult cancers are commonly carcinomas with mutations that accumulate over time, childhood cancers are most often embryonic or neuro-ectodermal in origin and are largely driven by gene fusions," the release noted. ■

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tists haven't yet uncovered, however, are the mechanisms that underpin the genetic and environmental risks for RA, "let alone the synergism between these two factors."

Existing RA therapies target the inflammation, but the University of Michigan studies point to a novel potential approach to targeting bone destruction. "Once we have better drugs that directly and specifically address bone destruction in this disease, we'll have better treatment," Holoshitz adds.

The team is already carrying out preclinical tests with potential drug molecules, he explains. "As a separate project, we have a couple of early-stage drug candidates that block the HLA gene-activated pathway and are effective in preventing bone damage. These drugs almost completely inhibit experimental rheumatoid arthritis and bone damage in mice. By understanding the mechanisms, we may be able to develop better inhibitors to prevent disease and identify therapeutic targets for new treatment strategies."

Curetis MDx Wins FDA Clearance for Lower Respiratory Tract Infection

Curetis will launch its Unyvero System and Lower Respiratory Tract Infection (LRT) Application Cartridge in the U.S. this quarter after the FDA granted the molecular diagnostic a *de novo* clearance. The FDA nod marks the first time the agency has granted clearance to market an automated molecular diagnostic test for the atypical microorganism *Legionella pneumoniae*, and other lower respiratory tract infections. According to Curetis, the test covers more than 90% of infection cases of hospitalized patients with pneumonia and provides clinicians with a comprehensive overview on genetic antibiotic resistance markers detected.

"The launch of our Unyvero System and LRT Application Cartridge in the United States will address a pressing unmet medical need as it delivers results much faster than current standard of care microbiology culture," Curetis co-founder and COO Johannes Bacher said. ■

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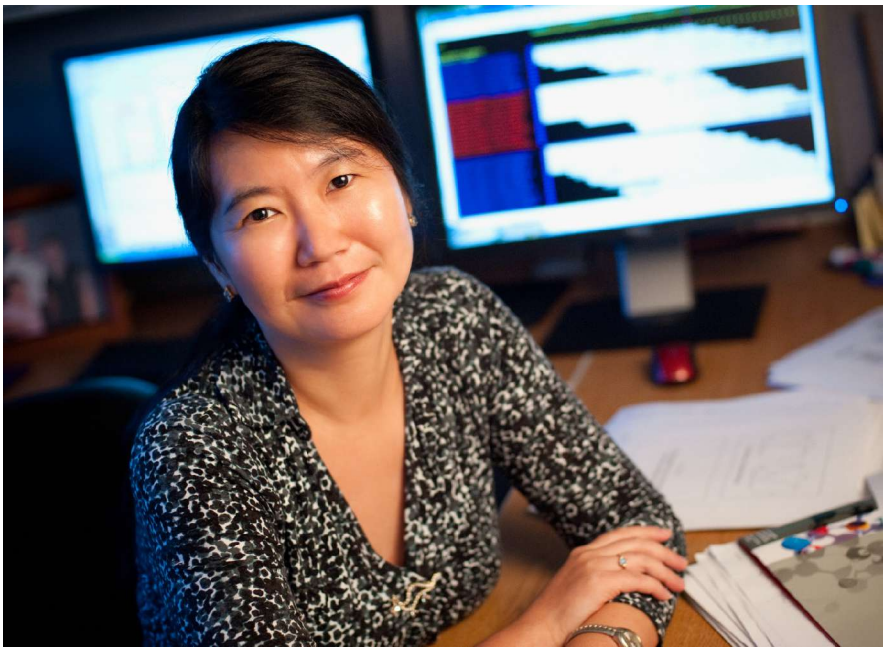
Free for All

St. Jude Cloud Makes its Pediatric Cancer Genomics Data Free for the Asking

By Diana Manos

St. Jude Children's Research Hospital, home of the largest public repository of pediatric cancer genomics data in the world, is now offering it free of charge to any researcher who wants to use it—along with tools it has designed to aid in cancer research. St. Jude Cloud launched April 16 aided by collaborators Microsoft's Azure cloud and platform provider DNAnexus.

The St. Jude Cloud will allow researchers to conduct their own novel research with their own data, or leveraging St. Jude's data, and will allows investigators to collaborate on the cloud, without having to incur the expense of building an infrastructure capable of handling the vast amount of complex data inherent in genomic research, according to Jinghui Zhang, Ph.D., chair of the Department of Computational Biology at St. Jude Children's Hospital. On the first day of the launch, more than 2,000 researchers worldwide signed up to use the service, from countries including Australia, China, France, Germany, and the U.S., she said.



Jinghui Zhang, Ph.D., chair of the Department of Computational Biology at St. Jude will also head St. Jude Cloud. Zhang said she hopes other organizations will follow the St. Jude lead and make other large genomic data sets freely available to any researchers that want to use them.

St. Jude Cloud should take pediatric cancer research—and even adult cancer research—to a whole new level, Zhang said. Leveraging cloud computing is important because it keeps all the data in one place, without different copies of the data being downloaded by researchers all over the world. In addition to saving infrastructure expenses for researchers, it also will save time. Without the use of the cloud, downloading all of St. Jude's data takes up to a month, she said.

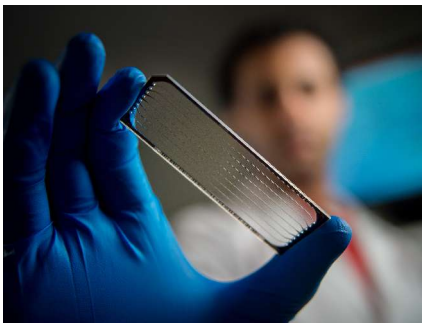
"What makes genomics data useful is to mix genomic and phenotypic data. This can only really be done on the cloud right now."
—Richard Daly, CEO, DNAnexus

Several scientists have told Zhang since the launch that they want to apply St. Jude's tools to analyze data in ways that St. Jude hasn't yet. "That's exactly what we want," she said. "We're thrilled to see it."

Zhang, a computational biologist who heads the St. Jude Cloud project, has spent her career conducting integrative analysis of large-scale, multi-dimensional genomic data to help understand and cure diseases like rare childhood cancer. She said St. Jude's dream for the project is that other organizations may follow suit and be willing to share their data freely, as well. Rare diseases, in particular, need more data to find cures. A by-product of the work will be that discoveries made regarding pediatric cancer usually lead to findings that have implications on treating adult cancer, she said. St. Jude wants its data and tools to attract a variety of experts, not just cancer researchers, but those outside of the field, such as computational analysts, who will approach the research from different perspectives.

On St. Jude Cloud, researchers will be able to access whole genome data from more than 700 paired tumor/germline samples for common and rare pediatric cancers, which was sequenced as part of the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. The interactive data-sharing platform allows scientists to explore more than 5,000 whole-genome, 5,000 whole-exome and 1,200 RNA-seq datasets from more than 5,000 pediatric cancer patients and survivors. St. Jude expects to make 10,000 whole-genome sequences available on St. Jude Cloud by next year.

According to St. Jude, the data on St. Jude Cloud is accessible by disease, publication, and curated dataset. A tool created by St. Jude, called PeCan data explorer, allows researchers to drill down into the samples. In addition, researchers will also have access



St. Jude Cloud will house the datasets of 10,000 WGS sequences by next year.

to a genomic visualization engine developed by St. Jude and a unique data browser that "allows frictionless navigation through the genome, including coding and non-coding regions."

The goal was to make the platform "truly useful to regular researchers," Zhang said. "Nothing like this is available in the world for regular researchers with no computational skills."

Zhang said both DNAnexus and Microsoft were selected for their unique skillsets and expertise—particularly in privacy and security. "Data security on the cloud is extremely important, and we did not have the expertise to deal with this ourselves," she said. "Privacy is our number one concern."

Researchers who apply to use St. Jude Cloud must consent to a series of federally mandated privacy protocols. "We believe that with the data being centralized on the cloud, it will provide a better way of monitoring it," Zhang added.

Microsoft has extensive experience in both the cloud and genomics. Microsoft's cloud, Azure was launched in 2010. "We understand the complexities of large-scale genomics data and are proud to say we've processed half a petabyte of data for St. Jude Cloud to date," said Geralyn Miller, director of Microsoft Genomics. "Microsoft has been involved in genomics for 12 years, with partners that include UC Santa Cruz Genomics Institute, Stanford Center for Genomics and Personalized Medicine, University of Medical Center Hamburg–Ependorf, and the University of Washington. Partners like DNAnexus, Curoverse, BC Platforms, and WuXi NextCODE have deployed platforms on Microsoft Azure to help manage, process and share genomic and biomedical data,."

"The sheer scale of genomics data requires technology that can help researchers harness data in a more secure way," Miller said. "Microsoft Azure is uniquely positioned to

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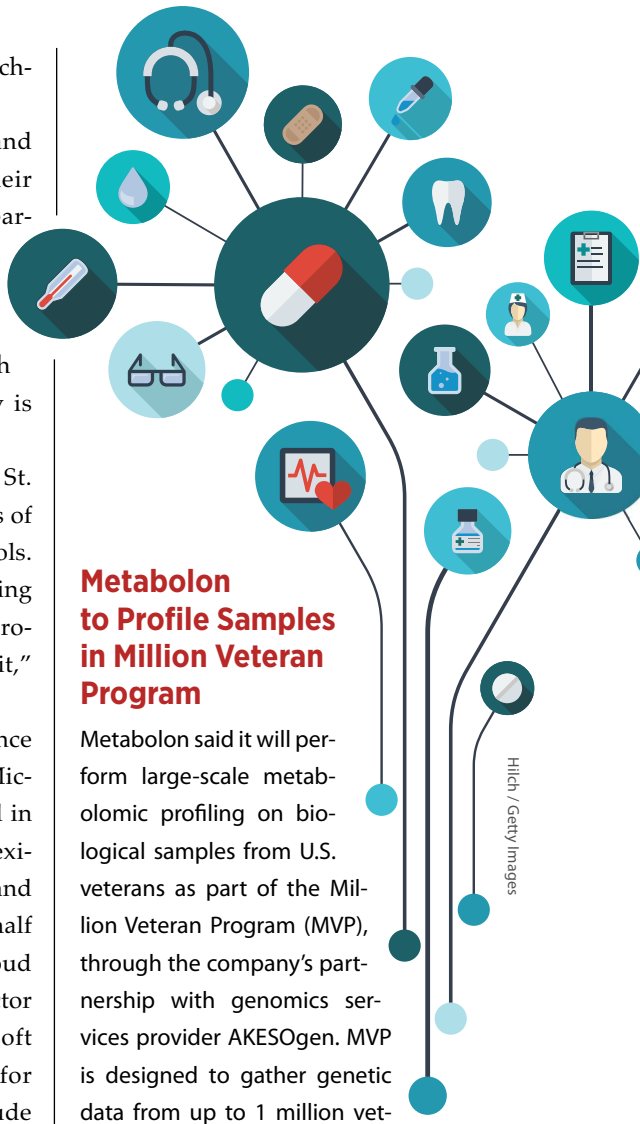

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Metabolon to Profile Samples in Million Veteran Program

Metabolon said it will perform large-scale metabolomic profiling on biological samples from U.S. veterans as part of the Million Veteran Program (MVP), through the company's partnership with genomics services provider AKESOgen. MVP is designed to gather genetic data from up to 1 million veterans into a single database, in a study to advance knowledge about the links between genes and health. To date, nearly 640,000 vets have enrolled in the project, which collects and stores genetic, health, lifestyle, and military-exposure data gathered from questionnaires, medical records, and omics analyses.

"By combining the genetics data already collected, the extensive clinical and lifestyle information that is unique to the VA healthcare system, and Metabolon's expertise in human metabolism, MVP aims to be one of the largest databases of its kind in the world," said Michael Gaziano, M.D., an MVP principal investigator. ■

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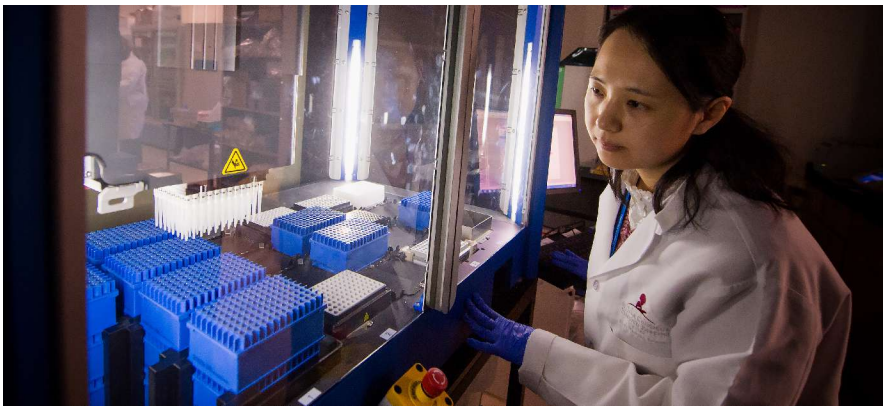
help with this as it offers scale, efficiency, and data-analysis capabilities researchers need to manage and analyze massive datasets. By augmenting researchers, it in turn helps institutes and organizations advance their work all while meeting stringent data use, security, and privacy requirements."

DNAnexus, another genomics heavyweight, has created the global network for genomic and biomedical data, operating in North America, Europe, Asia-Pacific (including China), South America, and Africa. In 2015, DNAnexus was awarded a research and development contract by the FDA's Office of Health Informatics to build precisionFDA, an open source platform for community sharing of genomic information. DNAnexus also provided the platform for the Regeneron Genetics Center.

"The whole point of the [genomic] analytics is to take these monstrously huge files and make them into something useable," said Richard Daly, CEO of DNAnexus. "What makes genomics data useful is to mix genomic and phenotypic data. This can only really be done on the cloud right now." According to Daly, the ability to operate on the cloud with more and larger datasets helps to increase research insights and provide more opportunities for cures.



St. Jude Children's Research Hospital is making its pediatric cancer genomic data freely available via St. Jude Cloud with the hope of significantly accelerating pediatric cancer research.

"The amazing thing, the most notable thing" is the truly visionary work of St. Jude, which offers care to children for free, along with its "incredible research," Daly noted. "You can't visit St. Jude without getting recruited to their mission. We're really excited to be a part of this, not because it's an important technological advancement, but you have to love the mission. This is special." Daly is particularly impressed that St. Jude is making its data freely available to further cancer research. "This is unique," he said.

About 7,500 patients are seen at Nashville, Tenn.-based St. Jude annually, with most of them treated on a continuing outpatient basis, and they are part of ongoing research programs, according to the hospital. St. Jude has treated children from all 50 states and from around the world. Patients at St. Jude are referred by a physician, and nearly all have a disease currently under study and are eligible for a clinical trial.

Richard Williams Leaves GRAIL to Head Oncology Program at WuXi NextCODE

Genomic data company WuXi NextCODE has announced the appointment of Richard Williams, M.D., as managing director and head of oncology programs to lead continued development of the company's cancer business. Williams served most recently at Illumina spin-out GRAIL as program lead and lead medical director for the Circulating Cell-Free Genome Atlas (CCGA) program.

At WuXi NextCODE, Williams will oversee the company's cancer business, including working on the company's SeqPlus service that promises to significantly improve sequencing and data generation from FFPE samples, and creating massively scalable and instantly queriable databases of tumor and patient sequence and phenotypic data. His work will also incorporate AI and deep learning to gain novel insights into cancer initiation, development, and therapeutic sensitivity and resistance. ■

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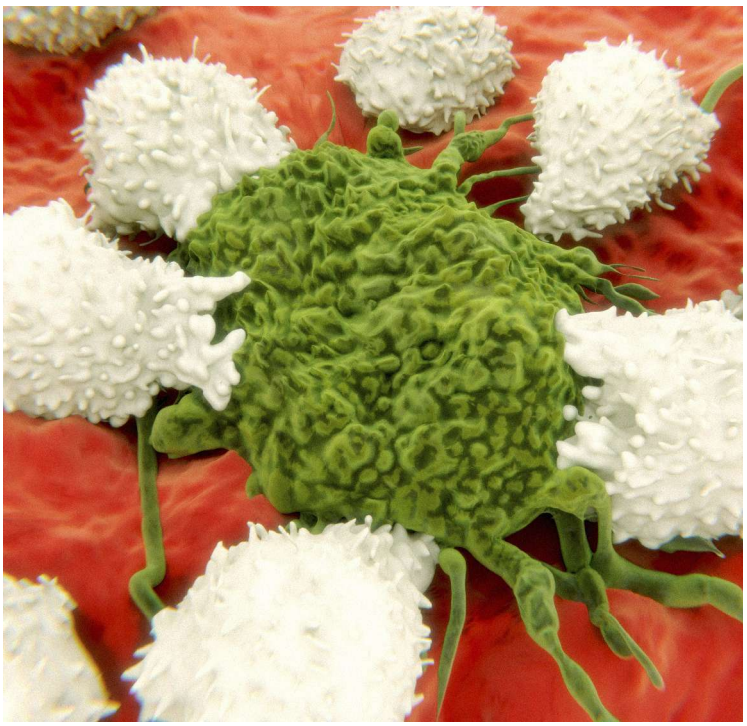
CellMax Life, IncellDx to Develop CTC-based Liquid Biopsy Diagnostics

Liquid biopsy diagnostic developer CellMax Life and single-cell diagnostics company IncellDx announced they will join efforts to develop and market circulating tumor cell (CTC) blood tests across multiple solid tumors and indications to provide personalized therapy selection and monitoring.

CellMax Life's CTC blood test, based on its CMxTM platform, which captures CTCs with a proprietary microfluidic chip with biomimetic coating and custom antibodies, will be combined with IncellDx's proprietary microfluidic reagents BioINK to analyze both protein and/or mRNA expression. BioINK enables highly sensitive and specific quantification of protein or mRNA expression at a single-cell resolution.

The first product created under this collaboration is a proprietary blood test to quantify the expression of PD-L1—a key protein involved in suppressing the immune system—used for immunotherapy selection and monitoring.



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There are close to 3,500 active biomarker-driven cancer clinical trials currently recruiting patients, and many of these trials rely solely on tissue-based biomarkers. Unfortunately, tissue tests may be inadequate, putting clinical trials at risk. This is true of tissue testing for PD-L1 expression for immunotherapy selection.

According to David Gandara, M.D., oncologist and director of the Thoracic Oncology Program at University of California, Davis, "PD-L1 can be unevenly distributed in tissue, leading to a false negative, and denying patients the opportunity to receive immunotherapy. A PD-L1 blood test can overcome these issues and would be an attractive alternative to tissue testing."

Several published studies have demonstrated the utility of CTC PD-L1 tests for immunotherapy monitoring, including a study showing that patients without PD-L1+ CTCs after six months of treatment showed a clinical benefit from nivolumab—an immunotherapy used to treat cancer—while patients with PD-L1+ CTCs experienced disease progression.

Performance data of the PD-L1 test in non-small cell lung cancer (NSCLC) were presented recently at the American Academy of Cancer Research (AACR) annual meeting. The test was able to capture CTCs for PD-L1 testing in blood in about 90% of patients across all stages of cancer. About 50% of the patients tested for CTCs were PD-L1 positive. This is consistent with previously reported PD-L1 positivity rates in clinical studies.

Bruce Patterson, M.D., CEO and founder of IncellDx said, "Cancer is driven at different levels: DNA, RNA, and protein. With CTC-based liquid biopsies, we can analyze all of these analytes simultaneously in intact cells, combining antibodies, quantitative RNA *in situ* hybridization, and DNA cell cycle. This is not possible with most current liquid biopsies that analyze only DNA from lysed cells. CellMax Life's CTC blood test has unprecedented sensitivity in isolating rare CTCs, which can be readily analyzed by the BioINK platform at the single-cell level. Our joint efforts will lead to reliable diagnostic solutions throughout the patient treatment continuum."

The tests will be processed at CellMax Life's CLIA-CAP accredited lab in Sunnyvale, CA and will be jointly marketed in the United States by the companies' sales forces.

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Is it Time to Sequence Everyone's Genome? Not yet.

Recent research published from the MedSeq Project, which is examining the effects on health costs and health outcomes, has shown encouraging results that suggests providing these tests to both healthy people and to cardiology patients may not increase downstream costs and healthcare utilization—at least in the six-month window data was available for these cohorts.

But let's not kid ourselves into thinking that the broad use of whole-genome, or whole-exome sequencing for all patients is right around the corner. There simply is no indication that healthcare systems, or individual doctors and other health providers are ready or equipped to make meaningful use of these data to guide health and wellness decisions.

FROM THE EDITOR

Chris Anderson
Editor in Chief

There are a number of hurdles standing in the way of this broad application of genomic medicine.

First is the issue of data integration with electronic medical records. It's no secret EMR vendors' systems are not good at data integration. HL7 efforts to encourage adoption of the FHIR data standard may help solve this problem to an extent, but then there is an additional problem: EMRs were primarily designed to help with insurance coding, not as a comprehensive picture of a patient's health. Both need significant work to accommodate genomic data.

Second, most health systems, hospitals and care providers are not up to speed on what might be actionable information in a patient's genome, or even whether a variant that indicates an elevated risk of a specific disease is worth addressing. The folks at the National Association of Genetic Counselors will say this is an appropriate role for their members, and they'd be right, but there just aren't enough genetic counselors in this country to handle such broad use of genomics in healthcare.

And finally, there is the question of who will pay for the testing. The MedSeq Project cited sequencing costs of $5,000 per genome. Granted, the cost of whole-genome sequencing has decreased since the time of the tests in this pilot study. But despite a broad belief this would be a one-time cost that could pay dividends for a lifetime, no payers in this country, public or private, are showing any willingness to take on this cost without more proof of value.

Which is exactly why projects like MedSeq, or the work at health systems like Sanford in North Dakota and Geisinger in Pennsylvania, or the 100,000 Genomes Project in the U.K.—which has a stated goal of applying genomics within the NHS—are so vital. MedSeq measured downstream costs for six months and have consented many in the study to be followed for five years. Now, BabySeq will begin tracking and measuring the value of providing sequencing from the very beginning of life. It's data from these sources that will help advance genomics as normal and routine in healthcare.

The time is coming. It's just not time yet.

Why Amazon, JPM, and Berkshire Hathaway Can Succeed with Healthcare

In late January, the healthcare and tech industries were rocked by an announcement that Amazon, JP Morgan Chase (JPM), and Berkshire Hathaway (BH) were joining forces to take on healthcare. They aren't the first to tackle healthcare, but their combined acumen and unique market positions make this alliance different. No plans detailing how they will accomplish this have been published, but this alliance has the potential to succeed where others have failed—if they focus on what they (and their companies) know how to do best.

OP-ED

Harry Glorikian
General Partner
New Ventures Funds

Regulation

One of the biggest barriers in the healthcare industry is the amount of regulation, making it difficult for new, non-healthcare–specific players to enter the industry. Yet, banking and insurance are tightly-regulated and have learned how to navigate complex rules, even when they differ significantly globally. Both industries have been utterly transformed by technology. Online banking and access to accounts through ATMs and smartphones is nearly ubiquitous and interoperability is standard. Insurers have similarly embraced technology.

Understanding how the banking and insurance industries navigated regulation while embracing transformative technology and data analytics will be invaluable for the new company. Security will be of paramount concern and the banking industry has taken the lead on using blockchain for this purpose. Lessons learned by JPM and BH's insurance subsidiaries can be leveraged for healthcare.

Consumer Experience

Amazon has utterly transformed the way consumers purchase everything from books to home goods, and developed an overall positive user experience along the way. The company has successfully developed a method for easy price and feature comparisons, driven down prices, and created an efficient logistics system. Their user experience is so good that recent surveys found consumers open to Amazon health insurance plans and an Amazon-like experience for health benefits enrollment. Amazon's background developing the optimal consumer experience will be essential for the new venture.

Business Acumen

Warren Buffett's business acumen and management of BH has been well-documented throughout the years and Buffett has demonstrated that he's not adverse to technology, investing in tech companies like Apple and IBM. Jeff Bezos' business skills have led some to call him "the smartest guy in business." Though some of Amazon's initiatives have fallen flat with consumers, the company's market value is ranked third globally. Buffett's steady, conservative approach will be valuable for the new company as it seeks to separate hype from capabilities in healthcare technology, while Bezos' daring, even at the cost of failing, can keep the new company on the cutting edge.

Technology

The three companies have seen technology transform their industries over the decades. As healthcare increasingly relies on Big Data and analytics, Amazon's tools, data, and expertise in cloud computing will come in handy to predict what and when consumers will buy products. This isn't that different from what health systems are looking to do for their patient populations: identify patients who will utilize specific resources and determine a more efficient and less costly mechanism for them to do that. While the three have been criticized for jumping into healthcare without any experience in the industry, their technological prowess could level the playing field.

Is the Industry Ready for a New Model?

The Amazon-JPM-BH initiative has been met with both optimism and skepticism that the trio could produce meaningful change within the industry. But a change is on the horizon. The might of the three companies alone set them apart from earlier approaches. So is the timing. As the future of healthcare will rely increasingly on digital tools and analytics, there is plenty of room for new ways to do nearly everything in healthcare. Consequently, there is substantial interest in seeing how the new company will use technology and data to its advantage in this landscape.

Harry Glorikian is a general partner with venture capital firm New Venture Funds.

Cost Conscious

MedSeq Project Provides Snapshot to Suggest Genomic Sequencing does not Increase Downstream Healthcare Costs

KEXINO / Getty Images

Chris Anderson
Editor in Chief

When it comes to the notion of providing whole-genome sequencing to healthy individuals, there are not one, but two elephants in the room: the cost of the sequencing and analysis itself; and whether people, newly armed with specific information about themselves and their own set of specific genetic variants, might increase downstream spending in the health system.

Mitigation of the first hurdle, the cost of sequencing, should take care of itself over time, as sequencing continues its precipitous, Moore's Law–shattering, drop in price. And now, new research published by the MedSeq Project suggest that worries about significant increases in downstream costs may not be warranted. The research, "Short-term costs of integrating whole-genome sequencing into primary care and cardiology settings: a pilot randomized trial," published in *Genetics in Medicine* earlier this year tracked the costs associated with healthcare utilization of two 100-patient cohorts. The first was of 100 cardiology patients with cardiomyopathy diagnoses and the second was 100 healthy primary care patients. Each was randomized to receive a family-history report alone or a whole-genome sequencing (WGS) report. Examining the initial six months of healthcare utilization data, the researchers found "the short-term costs were driven primarily by the costs of sequencing, interpretation, and disclosure, and we did not find evidence that WGS increased downstream healthcare costs."

"One of the things that was interesting is our physicians were also study participants."
—Kurt Christensen
MedSeq

Lead author of the study, Kurt Christensen, Ph.D., an instructor of medicine at Brigham and Women's Hospital in Boston, said MedSeq is the first randomized clinical trial that is seeking to provide data on the clinical utility and value provided by WGS in a general healthcare setting, as opposed to disease-specific applications such

as cancer or rare disease diagnoses.

"I think the more exciting applications [of WGS] are in these asymptomatic populations where you can really capitalize on the full capabilities of the genome," Christensen said. "So not just providing information to diagnose a specific disease, but providing information that may prevent disease altogether, and inform not only medical decision making, but personal decision making also."

Data from the study showed that cardiology patients who had WGS spent, on average, $8,109 during the six months researchers collected data, which was $1,561 less than the average of the group who had medical history only. That spending may have been skewed by the small number of study participants. "Hospitalizations are expensive, and you are talking about cardiology patients, so one hospitalized patient could make a big difference," Christensen said.

To account for this, the authors also provided total costs excluding hospitalizations which showed slightly higher costs for the WGS group compared with those with family history ($5,392 versus $4,692). Among healthy patients in the study, those who had genome sequencing had slightly higher medical costs of $3,670, on average, compared with $2,989 for the family medical history group.

Christensen is encouraged that the early MedSeq data may begin to address the fears of many that having patients and their doctors having WGS data would significantly drive up healthcare costs and utilization. "It is a pilot study, so we haven't drawn conclusive evidence, but it suggests those fears may not be panning out," he noted.

Next steps in the program are to follow the study participants longitudinally and many in the study have already consented to being followed for a total of five years to provide a longer term view on the overall value provided by WGS to these two patient populations.

Not Just a Pilot—a Model

MedSeq is a pilot project run under the umbrella of the Genomes 2 People (G2P) Research Program at Brigham and Women's that also includes collaborators Partners Healthcare and Harvard University. The mission of G2P is to provide research on the integration of genomic research into clinical practice. Other research projects include MilSeq, a program to provide whole-exome sequencing to active members of the U.S. Air Force, and BabySeq, a study to determine the benefits of providing whole-exome sequencing for newborn babies.

Principal investigator for the program is Robert Green, M.D., who sees the organization's pilot studies as having broader impact than merely the data they return. "Sometimes I describe our projects as a hybrid between clinical trial pilots and demonstration projects," Green said. That's because the project had to take into account not only the normal clinical trial activities of enrolling and consenting patients, but also how the project would interrogate the genome, the level of variant classification, and how to create a relatively simple report of results that could would be useful to both highly knowledgeable genomics researchers and non-expert clinicians.

"There are people spending [all their time] in each of these individual areas," Green said. "Stringing them together to create a coherent process is one of the things I'm most proud of in all of our pilot studies. Not that we necessarily got each one right, but we have absolutely made an

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The staff of Genomes 2 People at their Boston-area offices.

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attempt to make a rational choice to put these all together in ways that make sense."

In addition, as much as MedSeq is looking to develop patient data, it also provides a glimpse of the realities of providing genomic information that doctors can use in the clinical setting.

"One of the things that was interesting is our physicians were also study participants as they needed to complete in-person education sessions and online educational modules in preparation to disclose information to their patients," said Christensen. "It was a natural experiment to what would happen if we incorporated genomics into everyday patient care rather than instances where you were trying to achieve a specific molecular diagnosis."

The influence of MedSeq is far reaching. Not only have lessons learned from it been incorporated in the other pilots Green's group is running like MilSeq and BabySeq, but it has likely influenced other implementations over the past five years.

"I believe this led the way in helping both academics and industry imagine how this could be done in a streamlined fashion," Green said. "Then by doing it—even in a small sample size—and showing that it can be done safely and with reasonable results, we've opened the door to so many things and other projects."

The Value Proposition

The cost of sequencing the patients in the MedSeq study came in at just north of $5,000 per patient. Proponents of incorporating WGS as a fundamental component of patients' primary care note that, while steep, it is a cost that theoretically will pay dividends over time, as the sequencing data can be re-queried throughout patients' lives as their health changes.

For this reason, public and private healthcare payers are keeping a keen eye on studies such as MedSeq, as they are increasingly faced with making decisions on whether or not to cover new genomic analytic tools.

According to Joe Ferrara, president of healthcare consulting firm Boston Healthcare Associates, the data generated by MedSeq and other studies isn't simply about costs, but about the overall value sequencing might bring to the clinical setting.

Green shares this view. "Cost isn't the problem. Value is the problem," he said. "Is the genomic information valuable to an average individual over the length of their life? My hypothesis is it is. And as costs come down, it will be even more valuable."

While there is little hard evidence of the kind insurers normally look for when making coverage decisions, Ferrara's view is insurers now are more open to paying for it. "I think in the U.S. payers are taking a longer term view on that evidence," Ferrara said. "Historically you could argue that payers would say we are going to look at a very narrow time window for some sort of ROI on new technologies. But with payer utilization and with key chronic conditions, it may take longer to realize the benefits of intervention, and sustained intervention, so they will need a longer time horizon."

"[Payers] will still be looking, at some level, for what is the budget impact on the patient population for investment in these tests."

—Joe Ferrara, Boston Healthcare

In the case of cardiac patients, like those in the MedSeq study, however, there may be an opportunity to develop some of the evidence payers have traditionally sought. "With cardiac patients, being able to identify their risk appropriately, if it leads to near-term more appropriate intervention or more intensive intervention, we should see that play out," Ferrara added.

"It is not to say that payers aren't interested in paying more for better outcomes—they are. But they will still be looking, at some level, for what is the budget impact on the patient population for investment in these tests."

For many other conditions however, developing the appropriate evidence could take decades and may even requires a leap of faith.

"The problem is the value of genomics is amortized over an entire lifetime," said Green. "Pharmacogenomic variance only becomes valuable 10, 15, or 20 years from now when a patient needs that drug. If you are a newborn baby, carrier traits only become valuable when the baby is [old enough] to reproduce. Cancer predisposition variants can take five, 10, 15, or 30 years to come through, during which time you may be able to avert, or lower the risk of cancer through increased surveillance.

"But it is very hard to demonstrate. You can demand clinical utility evidence until you are blue in the face, but the research that is available to us is research that tends not to look at benefits and costs over decades. That is our goal—to find creative experimental ways to demonstrate that value," Green concluded.

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Wrangle Over DTC Results

Ambry Study Highlights 40% False Positives, 23andMe Defends Tests, and Experts Weigh In

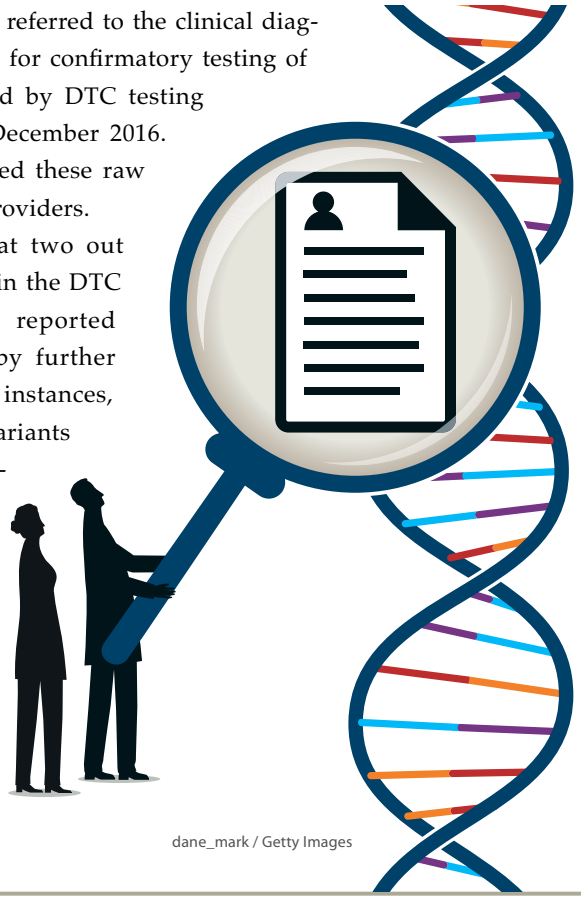
By Alex Philippidis

A study by Ambry Genetics researchers showed that as much as 40% of the variants in a variety of genes reported in the raw data of direct-to-consumer (DTC) tests were false positives. The researchers, and Ambry itself, said the study findings raise questions about the accuracy of DTC genetic testing—while the largest DTC test provider in turn has raised questions about the study and has defended its testing results.

A team of eight Ambry researchers analyzed the raw data of 49 patients who were referred to the clinical diagnostic lab of Ambry Genetics for confirmatory testing of variants previously identified by DTC testing between January 2014 and December 2016. The patients previously shared these raw test data with their medical providers.

The researchers found that two out of every five variants noted in the DTC raw data were incorrectly reported and could not be verified by further diagnostic lab tests. In eight instances, according to the study, the variants that were present were misunderstood by third-party interpretation services.

"While having access to raw genotyping data can be informative and empowering for patients, this type of information can also be inaccurate and misinterpreted," the researchers concluded in the study "False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care," published in *Genetics in Medcine*.



dane_mark / Getty Images

'Educational Piece'

While the study cast doubt on the accuracy of DTC testing broadly, the authors chose not to disclose the DTC companies whose results were examined.

"This was Ambry's choice," said Stephany Leigh Tandy-Connor, study leader and supervisor, genetic counseling–cancer at Ambry. "We did not want the specific DTCs and/or the third-party interpretation services involved to become the focus of the paper. Instead, we really wanted this to be an educational piece for not only the general public but also for medical providers who may not have a strong background in genetics."

According to Tandy-Connor, some discrepancies in the results may be explained by technical differences between the various testing methods used. The study's relatively small cohort also shows how few people who get DTC results don't seek confirmatory testing.

That patient cohort was nearly all-female (45 of 49; 92%), and mostly

A recent study led by Ambry Genetics found that rates of false positives among direct-to-consumer genetic tests was as high as 40%.

under age 50 (34 of 49; 69%) and white (25 of 49; 51%). For nearly all patients (43 of 49; 88%), the disease gene analyzed was cancer, followed by cystic fibrosis (four patients), connective-tissue disorder, and familial Mediterranean fever (one patient each).

Ambry says further efforts to gather data on a larger cohort are underway.

"We are planning on looking at the same issues (false positives and classification discrepancies) in a newly obtained cohort; however, this time we will include a much larger number of genes covering a wider range of diseases," Tandy-Connor said. "Depending on the dataset, we may or may not dive into other interesting topics that we see arise in the cohort."

A Matter of Interpretation

Arthur Caplan, Ph.D., the Drs. William F. and Virginia Connolly Mitty Professor and founding head of the Division of Medical Ethics at NYU School of Medicine, said the study's findings highlight why consumers need to follow up genetic testing with genetic counseling.

"Direct-to-consumer companies keep saying that the consumer can interpret the results. I don't believe that," Caplan said. "It's hard to interpret the results. How you explain risk gets confusing to people. People also have a false sense that if they turn up negative on a genetic test, they're not going to get a disease. A person might not turn up positive for breast cancer gene risk, but it doesn't mean they're not going to get breast cancer. It just means the particular marker for that particular hereditary form is not there."

Ambry acknowledged in its study that DTC testing can spark health-related discussions by consumers with their medical providers, whether they order such tests or not. Yet Ambry also cited a review of past research published last year that confirmed "low levels of objective and subjective genetic testing–related knowledge" among primary care physicians—as well as what it termed a shortage of genetic counselors and other trained genetic professionals, in raising concerns about how DTC test results are interpreted and used.

National Society of Genetic Counselors (NSGC) President Erica Ramos, told *Clinical OMICs* the number of certified genetic counselors currently stands at more than 4,600, and is expected to reach close to 5,000 by year's end.

"Our profession has doubled in size in the last 10 years. And we're expecting it to grow at least another 75% in the next 10 years after that. There are very, very few healthcare specialties that are

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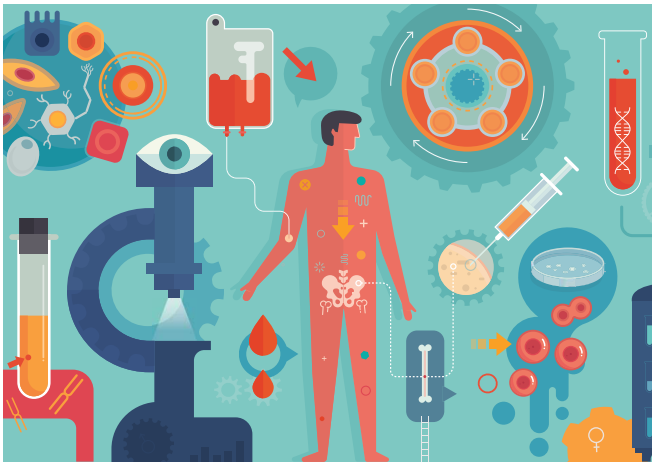
Almac Validates Illumina Cancer Mutation Panel for Prospective Testing in Clinical Trials



DrAfter123 / Getty Images

Almac Diagnostics announced it has analytically validated Illumina's TruSight Tumor 170 cancer mutation panel as an investigational use only assay for prospective testing in clinical trials. Almac Diagnostics was one of only a handful of labs globally to be granted beta test site status for the panel prior to its commercial release in 2016, which has allowed the labs at Almac to build significant experience with the cancer panel.

The Almac Illumina TruSight Tumor 170 Clinical Trial Assay is a next-generation sequencing (NGS) assay for use with FFPE tissue from solid tumours that targets DNA and RNA variants from the same sample. The Almac assay covers common cancer genes including key actionable mutations across multiple cancers. It targets single nucleotide variants, indels, and gene fusions. The clinical trial assay does not cover amplifications or splice variants, but these can be identified in the RUO version of the assay also offered by Almac Diagnostics.

"This Almac Diagnostics clinical trial assay will provide Pharmaceutical and Biotech companies with a new option in the marketplace to support their clinical trials and CDx development. The assay allows multiple biomarkers to be evaluated from one sample, thereby reducing the quantity of precious tissue sample necessary and offering a highly cost effective solution that will ultimately be kit-able further downstream," said Michael Sloan, global vice president of commercial development, Almac in a press release. ■

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growing at the rate of genetic counselors," Ramos said. "While I certainly recognize that there are sometimes big issues around access to genetic counselors, I think the idea of there being a shortage is really a little bit of a challenging piece of terminology."

Ramos said physicians and patients can find genetic counselors through NSGC's "Find a Genetic Counselor" online directory. "People should have a good understanding that DTC testing may be a starting point. But really, they should be engaging with experts like genetic counselors to really understand what their results mean, and how that might fit into their healthcare."

'Thousands of Samples'

The largest DTC testing company, 23andMe, said in a prepared response that the study was not specifically based on its data, "and has nothing to do with the information 23andMe interprets and reports to consumers.

"The study's small sample size of 49 is not enough data to support its conclusion. In contrast, 23andMe accuracy tests are performed on thousands of samples," the company noted.

23andMe also added that it is the only DTC company to gain FDA authorizations for its tests, showing them to be > 99.9% accurate. The FDA in March granted 23andMe the agency's first authorization for a DTC can-

National Society of Genetic Counselors President Erica Ramos advocates that individuals who receive results of genetic testing should consult with experts to interpret the results.

cer risk test, the company's third de novo authorization.

In 2015, the company was authorized to market the first direct-to-consumer genetic test for Bloom Syndrome, enabling the company to bring 40+ carrier status reports directly to customers. And in April 2017, 23andMe won FDA authorization to market the first direct-to-consumer genetic health risk reports.

But even DTC tests with 99.9% accuracy, Ramos said, leave open the possibility of errors in the reporting of variants. DTC companies typically report results on a fraction of genetic variants for which they may test. "The quality within each of those variants that are reported in the raw data can be extremely variable," Ramos said. "While it's true that these microarray chips generally have a very high degree of accuracy as a whole, when you're looking at a million different variants, even if it's 99.9% accurate, there are going to be errors in that sequencing."

Errors could arise, she said, if the original sequence data calls were incorrect, or if third-party data tools misinterpret the raw data.

Adds 23andMe: "We are extremely confident in the accuracy of the detailed results we provide to our customers. As we clearly state in our product, we do not recommend customers take 23andMe's raw, uninterpreted data to other third-party sites as we cannot account for the accuracy of those services."

Unlike 23ndMe, which allows individuals to order its tests online, Color Genomics requires that its tests be ordered by a patient's physician or one from its network of independent physicians. Color offers tests for BRCA, hereditary cancer, hereditary high cholesterol, and hereditary heart health. Those tests are marketed to consumers as well as physicians.

Color Genomics said the study was not reflective of its testing, which it equated to Ambry's since its test is diagnostic and uses NGS technology that analyzes the full gene in its CLIA-licensed and CAP-accredited laboratory.

"Our work has been to make it much easier and accessible to order clinical grade diagnostic testing along with complimentary genetic counseling with board-certified genetic counselors, that could provide people with knowledge of their risk for hereditary conditions such as cancer and heart disease," a Color Genomics spokesperson said.

Caplan said DTC genetic testing overemphasizes genes at the expense of environmental and behavioral factors contributing to disease. For instance, someone at risk of asthma may be exposed to too much pollution.

"I'm not convinced that even finding out you're at risk of something leads people to do anything," he said. "In some instances, there's nothing they can do. There's no lifestyle change that would reduce the risk. In other cases, they don't do anything because just knowing the risk doesn't necessarily lead to behavior change,"

Caplan also cited the approximately 40% of U.S. adults reported as obese during 2015–2016 by the National Center for Health Statistics: "There's a sophisticated technology that's called a bathroom scale. As you stand on the scale, it's giving you a prediction about risk. How are we doing in terms of changing behavior? Not too good."

Angle Enrolls First Patient in Trial of Parsortix CTC Liquid Biopsy

Liquid biopsy developer Angle said it has enrolled the first patient for its ANG-002 clinical study, designed to assess its Parsortix PC1 system in patients with metastatic breast cancer. The clinical study (NCT03427450) is intended to support FDA clearance of Parsortix PC1 as an *in vitro* diagnostic device. Angle says it is seeking to become the first company to receive FDA Class II clearance for a test designed to harvest intact circulating tumor cells (CTCs) from patient blood for subsequent analysis.

bluecinema / Getty Images

"This would be a key step in establishing the Parsortix system as the system of choice for CTC liquid biopsy, securing a leading position in the emerging multi-billion-dollar liquid biopsy market," Angle founder and CEO Andrew Newland said in a statement.

Parsortix uses a disposable microscope slide–sized cassette to capture and harvest CTCs from the blood samples of patients, based on the cells' size and compressibility. The platform uses a step-based reverse flow system that, according to Angle, allows the easy harvest of viable cells for analysis.

Researchers from The University of Texas MD Anderson Cancer Center are leading the clinical study, which involves recruitment of 200 metastatic breast cancer patients and 200 healthy volunteers enrolled at leading U.S. cancer centers. ■

Breaking NGS Ground

CMS Final Coverage Determination Promotes Sequencing-Based Testing for Advanced Cancer

Alex Philippidis
Contributing Editor

Developers of next-generation sequencing (NGS)-based diagnostics breathed a sigh of relief in March, after months of clashing with the Centers for Medicare & Medicaid Services (CMS) over NGS testing reimbursement for Medicare and Medicare Advantage patients with advanced cancer.

CMS rattled test developers in November with a draft National Coverage Determination (NCD) that limited Medicare coverage to FDA-approved NGS panels for the most advanced oncology patients. Diagnostic companies argued that numerous clinical applications of NGS within oncology are not directly related to therapy selection, and that NGS-based testing is used in numerous other areas outside of oncology.

"The concern among the broader industry was that this could actually nip in the bud all of the interesting developments in clinical diagnostics based on NGS before it's even really starting to flourish," Charles Mathews, principal with ClearView Healthcare Partners, a global strategy consulting firm serving the life sciences sector, told *Clinical OMICs*.

> "When you have events like FDA approval for Foundation Medicine and CMS ratifying payment, that's going to make the entire community more comfortable ordering these types of tests."
>
> **— David Spetzler, Ph.D.**
> **President and CSO, Caris Life Sciences**

However, when CMS issued its final NCD on March 16, test developers' fears turned mostly to cheers. The final coverage determination expanded eligibility for Medicare reimbursement by adding coverage for patients with Stage III metastatic, recurrent, relapsed, or refractory cancers, in addition to the Stage IV relapsed or refractory cancers included in the draft NCD. The final NCD also included repeat testing when a new primary cancer diagnosis is made by the treating physician and the patient meets other clinical criteria. As outlined in the draft NCD, it removed coverage with evidence development for tests not authorized by the FDA.

The action by CMS followed a concurrent FDA review of Foundation Medicine's FoundationOne CDx comprehensive genomic profiling assay through the agencies' Parallel Review Program. FoundationOne CDx is designed to detect substitutions, insertion and deletion alterations (indels), and copy number alterations in 324 genes and select gene rearrangements. The test also detects genomic signatures, including

Foundation Medicine

Caris Life Sciences

microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded tumor tissue specimens.

"As the FDA moves toward biomarker driven drug approvals that are tumor agnostic, like pembrolizumab [Merck & Co.'s cancer immunotherapy Keytruda] with MSI, having a test that is FDA approved, is mapped to a broad range of companion diagnostics, interrogates the entire cancer genome and provides TMB and MSI scores on every patient report, could have a dramatic impact on clinical care," said Gary Martucci, senior vice president, reimbursement and payer strategies at Foundation Medicine.

FoundationOne CDx became commercially available on March 30 at a list price of $5,800. For Medicare beneficiaries meeting NCD criteria, there is currently no anticipated co-pay or deductible amounts. CMS coverage also includes beneficiaries that are enrolled in Medicare Advantage plans. Depending on a member's plan, they may be subject to a co-pay or deductible. But for those patients, some may be eligible for Foundation Medicine's FoundationAccess program to assist with out-of-pocket expenses, Martuccis noted.

Automatic Approvals

FoundationOne CDx is among four NGS cancer tests that received FDA approval or clearance as an *in vitro* companion diagnostic, and thus automatically approved for coverage under the final NCD. The other three:

- Foundation Medicine's FoundationFocus CDxBRCA, designed to detect tumor BRCA1 and BRCA2 mutations, germline and somatic, in ovarian cancer. CDxBRCA has FDA approval as a companion diagnostic assay for Clovis Oncology's Rubraca (rucaparib), a poly ADP-ribose polymerase (PARP) inhibitor indicated for advanced ovarian cancer.
- Illumina's Praxis Extended RAS Panel, approved for use with the company's MiSeqDx System to help clinicians identify patients eligible for treatment of metastatic colorectal cancer with Amgen's Vectibix (panitumumab).
- Thermo Fisher Scientific's Oncomine Dx Target Test, designed to detect 368 variants in 23 cancer-associated genes clinically associated with non-small cell

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lung cancer (NSCLC)—three biomarkers validated for selection of relevant targeted therapies (EGFR, ROS1, or BRAF), and 20 additional genes relevant for NSCLC pathogenesis, analytically validated for variant detection from NSCLC tissue.

Joydeep Goswami, Ph.D., president of Clinical NGS and Oncology for Thermo Fisher, said the final NCD increased by 58% the number of U.S. lives covered for Oncomine Dx Target Test by adding CMS' 58.9 million lives. The balance of the 160 million lives covered for the test, Goswami said, is covered by commercial payers that include Cigna, Aetna, UnitedHealthcare, Independence Blue Cross, and Humana.

Laboratory workers prepare to run a diagnostic test on Thermo Fisher Scientific's Ion Torent NGS platform.

"The potential for greater usage of Oncomine Dx Target Test is substantial given that the average age of NSCLC diagnosis in the United States is 70, with two-thirds of those diagnosed being of Medicare age," Goswami said. "Additionally, we expect this CMS decision to encourage the development of more NGS-based tests and greater adoption of these tests by labs to help patients. We are also hopeful that the FDA will continue to streamline requirements to help these tests to get to market faster and more cost-effectively."

The FDA on April 12 approved two final guidance documents designed to advance NGS test development. One allows developers to rely on clinical evidence from FDA-recognized public databases to support clinical claims for their tests. The other offers recommendations for designing, developing, and validating NGS-based tests, and explains what the FDA would seek in premarket submissions.

Looking Toward Expansion

Regulatory streamlining, Goswami added, should rapidly expand the pool of NGS-based FDA approved tests to include liquid biopsy and immuno-oncology-based tests. In January, Thermo Fisher launched the Oncomine Pan-Cancer Cell-Free Assay for liquid biopsy analysis, and the Oncomine Tumor Mutation Load Assay for immuno-oncology analysis. Last year, the company launched the Oncomine Immune Response Research Assay, Immune Repertoire Assay Plus, TCR beta, and Oncomine Myeloid Research Assay.

Oncomine Dx Target Test is designed for marketing overseas—it expects to launch the test in Europe and parts of Asia in the second half of 2018—and to eventually incorporate indications beyond NSCLC. Some of the 46 genes on the test's panel are being studied by pharmacetuical companies for drugs in their development pipelines.The company aims to develop companion diagnostics for Agios Pharmaceuticals' Phase III candidate ivosidenib (AG-120), aimed at identifying isocitrate dehydrogenase 1 (IDH1) mutations in patients with cholangiocarcinoma, and develop CDx for Blueprint Medicines' Phase I BLU-667, designed to identify RET fusions in NSCLC patients.

The FDA has also granted marketing authorization to Memorial Sloan Kettering Cancer Center (MSK) for another advanced cancer NGS test. MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) is a 468-gene panel designed to detect gene mutations and other critical genetic aberrations in rare and common cancers. In November, MSK-IMPACT became the first tumor-profiling laboratory-developed test (LDT) to win FDA approval. The single-site assay, performed at MSK,

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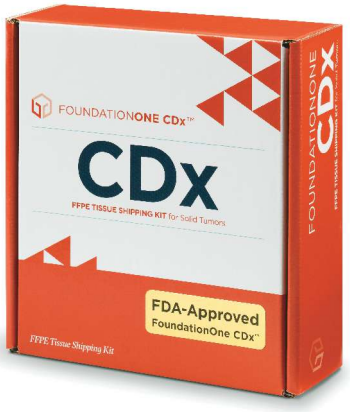
Foundation Medicine's FoundationOne CDx won FDA approval and a CMS NCD late last year via the agencies' parallel review program.



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carries no CDx indication.

As in the past, coverage determinations for NGS-based diagnostic LDTs performed in CLIA-certified laboratories for Medicare patients with advanced cancer will continue to be made by local Medicare Administrative Contractors or MACs.

Among companies with MAC-approved LDTs is Caris Life Sciences, which won coverage in 2016 for its flagship NGS offering, MI Tumor Seek; MI stands for "Molecular Intelligence." MI Tumor Seek is an *in vitro* diagnostic (IVD) NGS assay designed to provide physicians with clinically actionable information on 592 genes including, *MSI, TMB, EGFR, ERBB2, KRAS, NRAS, BRCA,* and *BRAF*. The $3,500 test has been ordered by more 10,000 oncologists in 81 countries, and about 40 biopharmas the company said.

Caris also offers 13 additional FDA approved/cleared assays, and an additional 23 FDA-registered IVDs through MI Profile, which uses a comprehensive genomic profiling-plus approach that assesses DNA, RNA, and proteins.

"The result of the [final NCD] decision is going to be a pretty significant expansion and acceptance by the provider community," said David Spetzler, Ph.D., Caris' president and CSO. "When you have events like FDA approval for Foundation Medicine and CMS ratifying payment, that's going to make the entire community more comfortable ordering these types of tests. I think we'll also naturally see a significant increase in the number of providers that start to perform this type of testing, to ensure that there is adequate access for every patient in our country."

A clinical lab scientist at Cancer Genetics, Inc. processes a non-small cell-lung cancer sample for testing using Thermo Fisher Scientific's Oncomine Dx Target Test.

'A Lot More' FDA Engagement

Spetzler said that he expected the final NCD "is going to promote a lot more engagement with the FDA" for diagnostic developers. Caris has a pre-submission with the FDA for MICDx, a combined DNA-RNA assay the company is developing, with the goal of improving detection of trans-

Commercial Payers Weigh CMS Determination

With the Centers for Medicare and Medicaid Services (CMS) approving a coverage framework for NGS tests for advanced cancer, a key question remains: How quickly will commercial payers do likewise?

"Private payers are evaluating the Medicare coverage decision, and making some determinations about whether or not they'll also cover these tests, and certainly what they'll pay for these tests if they cover them," Chandra Branham, Advanced Medical Technology Association (AdvaMed) vice president, payment and healthcare delivery policy, told *Clinical OMICs.*

A Thermo Fisher scientist hold an NGS sample vial.

Global healthcare strategy consulting firm ClearView Healthcare Partners recently surveyed 12 commercial payer medical directors, with many questioning whether the NGS tests have demonstrated clinical utility. The survey found that payers have yet to embrace NGS for broad tumor panel profiling: 45% do not cover the tests, while the remaining 55% only approved coverage on an exceptions-only basis.

Over the next one to two years, however, most payers (75%) expect their commercial coverage of NGS in oncology to fall in

locations that will inform decisions on therapy selection.

"We'll see a very significant increase in the number of applications to the FDA, whether it be clearance or approval, in order to ensure coverage for these types of tests," Spetzler noted. "Certainly, that's our intention and plan. We've engaged with the FDA already, and I believe that other providers will do the same thing."

Thermo Fisher made a splash with FDA approval last year with its Oncomine Dx Target Test. Now it plans to expand use of the test beyond NSCLC and to market the test overseas.

AdvaMedDx, a division of the Advanced Medical Technology Association representing diagnostics manufacturers, is "very hopeful and encouraged about the final NCD and its potential for expanding coverage for these types of tests to patients with advanced cancer," Executive Director Susan Van Meter said. "We're certainly seeing positive movement in the direction of ensuring patient access, but this is really the beginning."

CMS' focus on tying NGS test coverage to therapy selection means that diagnostics companies whose tests could show significant value, but are not companion diagnostics, will likely struggle with how their tests fit into coverage under Medicare. Mathews said ClearView Healthcare Partners is working with one such developer seeking to market a cancer–recurrence monitoring assay.

"The good news is, now it's not exclusively prohibited by the policy. But now we're back to, how can you convince the local MAC that there's value in that particular application of sequencing?" said Mathews, whose firm has offices in Newton, MA; New York; and San Francisco. "In general, having this pathway is better than not having this pathway, but it leaves open questions about how to bring forward assays that are not specifically focused on therapy selection or in oncology specifically."

Whatever ways those are resolved, Mathews added, "the final NCD has now established a recognizable and repeatable pathway for others that are interested in this space. That is really exciting for those of us that work in the space, because one issue people have had is the big overhang from investors all the way down through innovators, who have been saying, 'If we went and did this, and we built this big product, would anybody ever pay for it?' Now, there's a very clear pathway saying, 'If it fits the criteria of the policy, if we are able to get not an FDA approval but now clearance for it, then Medicare at least will pay for it.'"

line with the Medicare NCD.

"I think there is a chain of events in which it will be more widely used in Medicare patients, and that puts pressure on commercial payers, and people say, 'Wait! Because I'm 63 years old, I don't get this, but if I'm 65, I do? It doesn't make any sense,'" said Charles Mathews, principal with ClearView Healthcare Partners.

Near-term, roughly half of respondents indicated they would not change their commercial coverage from current policies.

"Payers have been of two minds. They do see potential value in NGS diagnostics but their whole world has been framed by clinical utility. 'Show me that this product is actually improving care, and then I will pay for it,'" Mathews said.

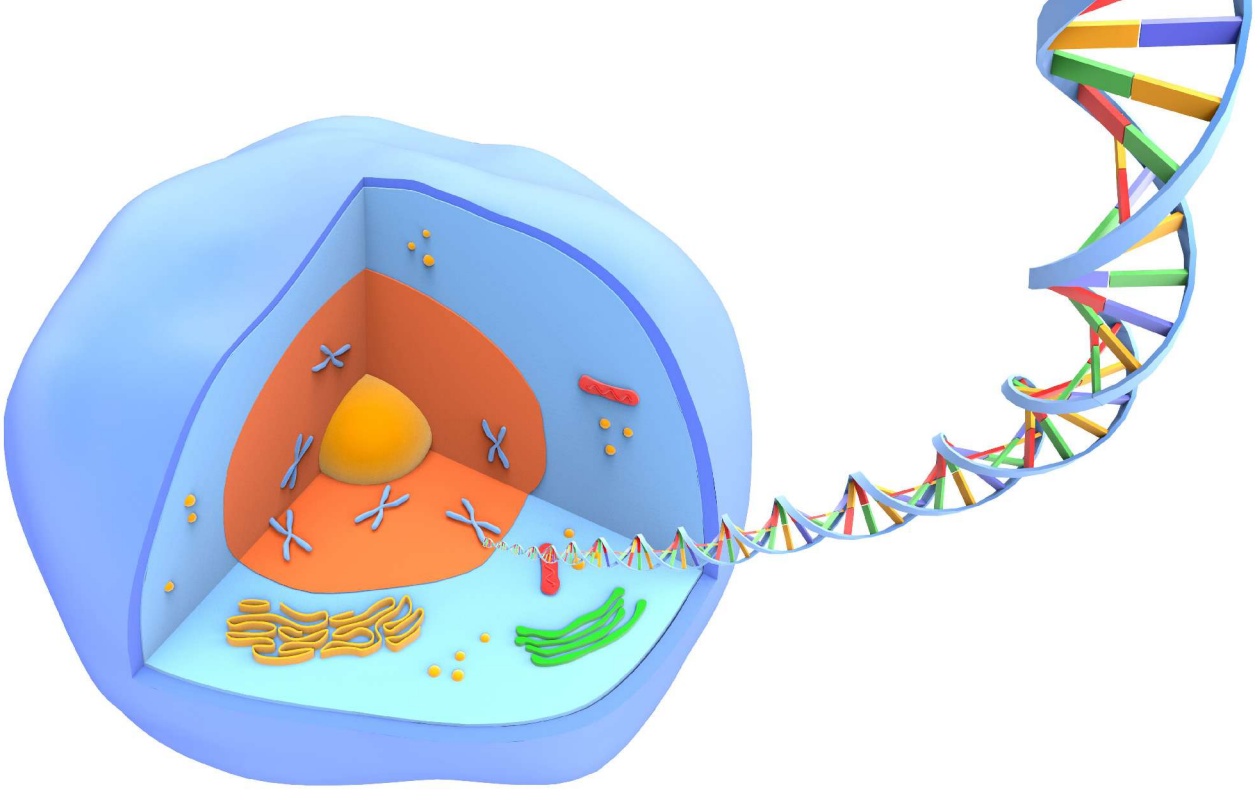
The final NCD, Mathews noted, combined policy considerations with the desire of CMS and FDA to be viewed as promoting innovation and being more adaptable to a changing landscape for technology and clinical care. That dynamic, he added, evoked CMS' 2014 coverage approval for Exact Sciences' Cologuard multitarget stool DNA test for colorectal cancer in asymptomatic, average risk beneficiaries ages 50–85.

He said payers also face unresolved implementation challenges of coding for the new tests, and paying for related tests. Will payers have to pay different rates for, say, FoundationOne CDx and the FoundationOne comprehensive genomic profile? Should CMS assign a single value to a suite of tests, and risk discouraging developers from bringing additional assays through the regulatory process?

David Spetzler, Ph.D., president and CSO of Caris Life Sciences predicts private payers will migrate in significant numbers toward panel codes.

Charles Mathews, principal, ClearView Healthcare Partners

"As the number of individual markers that have well defined and kind-of unassailable clinical utility increases, they will simplify their policy to include panels," Spetzler said. "It will probably take six months to a year for them to get there, but I think they will."



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A Resolution Revolution

Single-cell Sequencing Techniques are Providing Significant Advances Across a Broad Swath of Fields

Camille Mojica Rey
Contributing Editor

Until recently, scientists studying multicellular organisms at the cellular level had one big problem: their techniques did not allow them to account for cell-to-cell variation. That's because the technology required the use of bulk tissue samples and results could only be interpreted as an average of the cells in a sample. But today, due to advances in analytic methods developed over the past 10 years, scientists routinely conduct research of individual cells.

"Single-cell analysis is transforming how scientists study biological systems," said Alex Shalek, Ph.D., assistant professor of chemistry at MIT's Institute for Medical Engineering & Science. "The cell is the fundamental unit of biology and, thanks to recent advances, we can now comprehensively profile a cell's contents, its entire transcriptome," said Shalek, whose lab focuses on developing innovative technologies. Single-cell analysis is empowering discovery by removing the need to *a priori* select the most important variables, thus eliminating bias. "I wouldn't be surprised if single-cell approaches evolve to become the *de facto* standard for characterizing all biological specimens," he added.

The work conducted today for basic research using single-cell analysis techniques will very likely be used to improve clinical diagnosis, treatment and monitoring. Shalek's co-authored a paper in *Science Translational Medicine* last year stated that single-cell RNA sequencing (scRNA-seq), in particular, has the potential to "empower clinical implementation of personalized medicine."

Currently, single-cell DNA sequencing (scDNA-seq) is not as easy to perform as scRNA-seq. That's because a single cell can have hundreds of copies of a particular gene, while DNA only has two copies (one from each chromosome). Yet while scDNA-seq is in its infancy, scRNA-seq is in its adolescence, with multiple companies coming to market with technologies designed to create libraries for scRNA-seq (*see sidebar, page 29*). Employing these, researchers can now prepare sequencing libraries of thousands or tens of thousands of cells. Leveraging scRNA-seq, researchers are addressing previously intractable problems, including characterizing the evolution of cancer and the attributes of tumor cells that cause therapeutic resistance, revealing the complexity of the nervous system, and honing the genes that allow a parasite to cause disease.

"As the technologies become more stable, there will be a lot of opportunities for clinical applications."
—Nicholas Navin, Ph.D., MD Anderson Cancer Center

Characterizing Cancer

Despite its promise, a lack of spatial-temporal context is one of the challenges to making the most of single-cell analysis techniques. For example, information on the location of cells is particularly important when looking at how a common form of early-stage breast cancer, called ductal carcinoma *in situ* (DCIS) progresses to a more invasive form, called invasive ductal carcinoma (IDC). "Exactly how DCIS invasion occurs genomically remains poorly understood," said Nicholas Navin, Ph.D., associate professor of Genetics at the University of Texas MD Anderson Cancer Center. Navin is a pioneer in the field, developing one of the first methods for scDNA-seq.

Cellular spatial data is critical for knowing whether tumor cells are DCIS or IDC. So, Navin developed topographical single-cell sequencing (TSCS). Navin and a team of researchers published their findings in February 2018 in *Cell*. "What we found was that, within the ducts, mutations had already occurred and had generated multiple clones and those clones migrated into the invasive areas," Navin said.

Navin and his colleagues are also using single-cell techniques to study how triple-negative breast cancer, becomes resistant to the standard from of treatment for the disease, neo-adjuvant chemotherapy. In that work, published in an April 2018 online issue of *Cell*, using scDNA-seq and scRNAseq, Navin and his colleagues found responses to chemotherapy were pre-existing, thus adaptively selected. However, the expression of resistant genes was acquired by subsequent reprogramming as a result of chemotherapy. "Our data raise the possibility of therapeutic strategies to overcome chemoresistance by targeting pathways identified in this study," Navin said.

Revealing Complexity

The authors of research published in 2017 in *Genome Biology* also identified lineage tracing as one of the technologies that will "likely have wide-ranging applications in mapping developmental and disease-progression trajectories." In March researchers published an online study in *Nature* in which they combined single-cell analysis with a lineage tracing technique, called GESTALT (genome editing of synthetic target arrays for lineage tracing), to define cell type and location in the juvenile zebrafish brain.

The combined technique, called scGESTALT, uses CRISPR-Cas9 to perform the lineage tracing and single-cell RNA sequencing to extract the lineage records. Cas9-induced mutations accumulate in a CRISPR barcode incorporated into an animal's genome. These mutations are passed onto daughter cells and their progenies over several generations and can be read via sequencing. This information has

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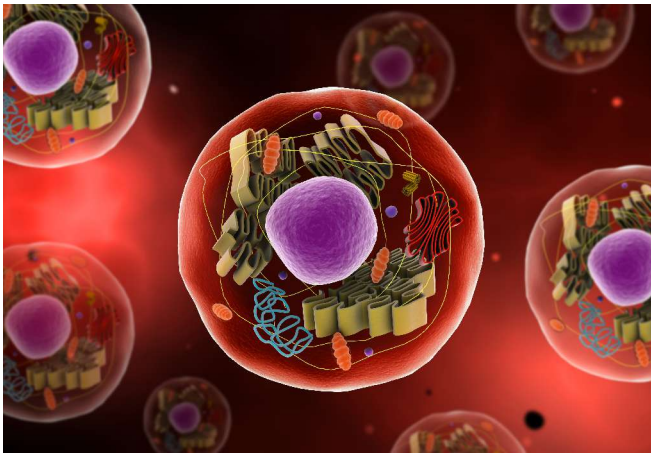

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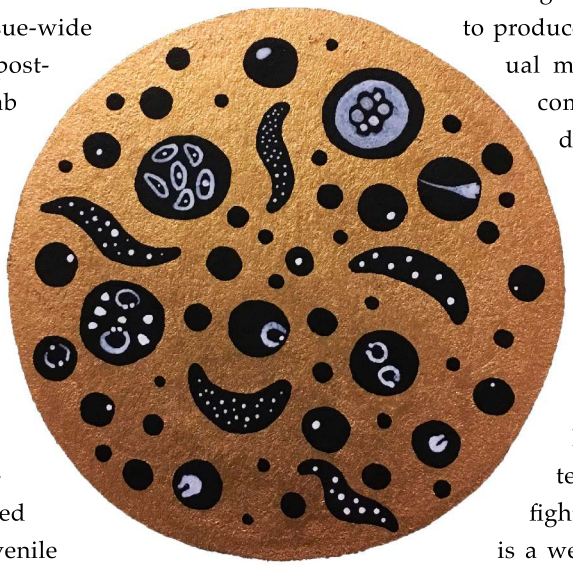
allowed researchers to build lineage trees. Using single-cell analysis, the team could then determine the diversity of cell types and their lineage relationships. Collectively, this work provided a snapshot of how cells and cell types diverge in lineages as the brain develops. "Single-cell analysis is providing us with a lot of information about small differences at cell type-specific levels, information that is missed when looking at the tissue-wide level," said Bushra Raj, Ph.D., a postdoctoral fellow in Alex Schier's lab at Harvard University and first author on the paper.

Raj's collaborators included University of Washington's Jay Shendure, Ph.D., and Harvard Medical School's Allon Klein, Ph.D., pioneers in the field of single-cell analysis. The team sequenced 60,000 cells from the entire zebrafish brain across multiple animals. The researchers identified more than 100 cell types in the juvenile brain, including several neuronal types and subtypes in distinct regions, and dozens of marker genes. "What was unknown was the genetic markers for many of these cell types," Raj explained. "This work is a stepping stone," she added. "It's easy to see how we might one day compare normal gene–expression maps of the brain and other organs to help characterize changes that occur in congenital disease or cancer."



A gold leaf paint and ink depiction of the *Plasmodium falciparum* lifecycle by Alex Cagan.

"Single-cell analysis is providing us with a lot of information about small differences at cell type-specific levels, information that is missed when looking at the tissue-wide level."
—Bushra Raj, Ph.D., Harvard University

Raj credits single-cell analysis with accelerating the field of developmental biology.

"People have always wanted to work at the level of the cell, but the technology was lacking," she said. "Now that we have all of these sequenced genomes, and now that we have these tools that allow us to compartmentalize individual cells, this seems like the best time to challenge ourselves as researchers to understand the nitty-gritty details we weren't able to assay before."

Building an Atlas

Human disease-relevant scRNA-seq is not just for vertebrates. For example, a team of researchers at the Wellcome Sanger Institute are working on developing a Malaria Cell Atlas. Their goal is to use single-cell technology to produce gene activity profiles of individual malaria parasites throughout their complex lifecycle. "The sequencing data we get allows us to understand how the parasites are using their genomes," said Adam Reid, Ph.D., a senior staff scientist at the Sanger. In March 2018, the team published the first part of the atlas, detailing its results for the blood stage of the *Plasmodium* lifecycle in mammals. Reid contends these results will change the fight against malaria. "Malaria research is a well-funded and very active area of research. We've managed to get quite a bit of understanding of how the parasite works. What single-cell analysis is doing is allowing us to better understand the parasite in populations. We thought they were all doing the same thing. But, now we can see they are behaving differently."

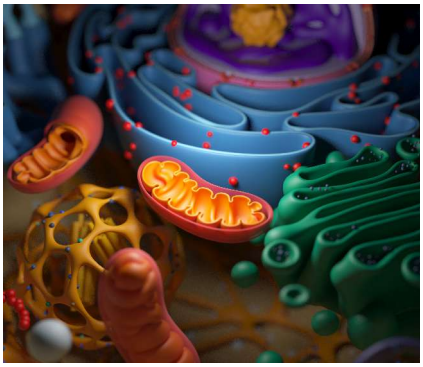
The ability to amplify very small amounts of RNA was the key innovation for malaria researchers. "When I started doing transcriptome analysis 10 years ago, we needed to use about 5 micrograms of RNA. Now, we can use 5 pico grams, 1 million times less," Reid said. That innovation allows scientists like Reid to achieve unprecedented levels of resolution in their work. For Reid, increased resolution means there is hope that science will be able to reveal how malaria evades the immune system in humans and how the parasites develop resistance to drugs. Reid predicted the Atlas will serve as the underpinning for work by those developing malaria drugs and vaccines. "They will know where in the life cycle genes are used and where they are being expressed," he said. Drug developers can then target those genes. The Atlas should be complete in the next two years, Reid added.

In the meantime, Reid and his colleagues are focused on moving their research from the lab to the field, particularly to Africa. "We want to look at these parasites in real peo-

ple, in real settings, in real diseases states," he explained. Having access to fresher samples is one reason to take the research into the field. "The closer we can get to the disease, the better chance we have of making an impact." Reid anticipates that RNA-seq technology is on the verge of being portable enough to go into the field (*See sidebar*). Everything from instrumentation to software is developing rapidly, he said. Reid also said that the methods used to understand the malaria parasite will likely be used to understand and create atlases for other disease vectors.

Path Ahead

It is clear to those using single-cell analysis in basic research that the path ahead includes using the techniques in the clinic. "As the technologies become more stable, there will be a lot of opportunities for clinical applications," Navin said. These include early detection by sampling for cancer markers in urine, prostate fluid, and the like. It also includes non-invasive monitoring of rare circulating tumor cells, as well as personalizing treatment decisions using specific markers. These methods will be particularly useful in the case of samples that today would be labeled QNS, or 'quantity not sufficient.' "Even with QNS samples, these methods allow you to get high-quality datasets to guide treatment decisions."



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Preparing scRNA-seq for the Clinic & the Field

In 2015, high-throughput single cell RNA-seq was described in two independent publications by Allon Klein (In-Drop) Evan Macosko (Drop-Seq). These methods allowed the simultaneous transcriptional profiling of thousands of individual cells at unprecedented resolution in one single experiment. At the time, *Molecular Cell* published an article by Jan Junker and Alexander van Oudenaarden which declared that single-cell transcriptomics had "entered the age of mass production."

Enter instrument manufacturers who have since been working to offer their sequencing customers high-throughput, scRNA-seq platforms that are easier to use and increasingly portable. They anticipate, based on the increasingly long list of potential applications, that single-cell analysis will one day be used in the clinic and in the field for precision diagnosis, monitoring, and treatment of a range of human diseases.

Today, scRNA-seq platforms are commercially available from Dolomite Bio, Bio-Rad, and 10X Genomics—to name a few. Dolomite Bio recently launched its latest Drop-Seq platform, the Nadia Instrument and the Nadia Innovate. The Nadia Instrument, in particular, is compact and designed to be easy to use. The Nadia Innovate allows for user-defined single-cell protocols. "The Nadia product family represents a huge leap forward in democratizing single-cell research and enabling potential clinical applications," said Heike Fiegler, Ph.D., vice president of biology at Dolomite Bio.

Christopher Love, Ph.D., was a co-senior author of the Seq-Well paper. He said Seq-Well's simplicity makes it possible for researchers to prepare samples in challenging environments, such as Biosafety Level-3 or -4 facilities. It will also help researchers wanting to collect and prepare samples in remote locations around the world. "Seq-Well removes the need to ship samples and potential artifacts or concerns from that process," said Love, who is a professor of chemical engineering at MIT. He also added that Seq-Well's low cost and ability to be analyzed using next-generation sequencing (NGS) make prospective banking and large-scale studies feasible.

The Nadia instrument from Dolomite Bio is one among many commercial tools developed in recent years to help spur single-cell research.

"Its sample efficiency makes it possible to process samples with a low concentration of cells, such as cerebrospinal fluid draws." These attributes will make Seq-Well, or something like it, useful for clinical applications because samples can be prepared in a small clinic or a foreign country and shipped to a laboratory for analysis.

Scientists at instrumentation giant Illumina see the single-cell market as maturing rapidly. "Although single-cell sequencing is still a relatively early stage market, adoption is quickly accelerating," said Gary Schroth, Ph.D., vice president, genomic applications, Illumina. The focus is shifting away from whole–transcriptome analysis using NGS, the company said. "Today, additional methods are being enabled to address a broader set of applications such as DNA somatic profiling, epigenomic characterization by measuring chromatin accessibility (ATAC-seq), and even protein expression (CITE-seq). As the market matures, we expect adoption of the tools and techniques by biotech and pharma customers conducting target and biomarker discovery, and diagnostic testing labs seeking higher resolution methodologies to better diagnosis and treat disease."—*Camille Mojica Rey*

Learning the Literature

Genomenon, Veritas Collaborate on Next-Gen Publication Prioritization Engine

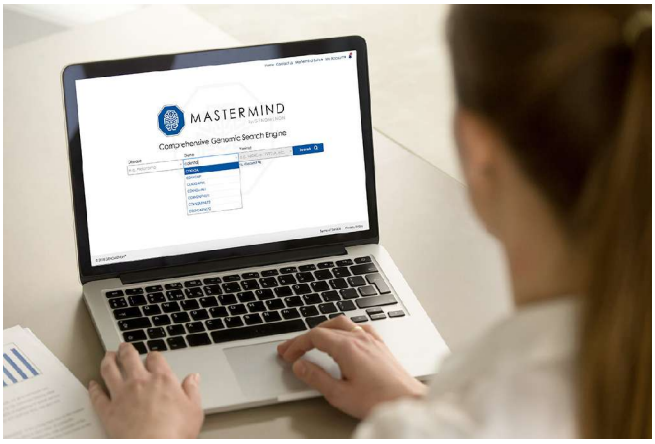
By Alex Philippidis

Genomenon has announced it will partner with Veritas Genetics to develop a next-generation literature prioritization engine the companies said will further scale the global adoption of whole-genome sequencing by reducing the time and cost of variant interpretation.

The engine will incorporate proprietary genomic language processing (GLP), machine learning (ML), and artificial intelligence (AI) tools—while following the American College of Medical Genetics (ACMG) and Association for Medical Pathology (AMP) variant classification frameworks, Genomenon said.

"As opposed to creating targeted panels for a specific disease, the interpretation challenge greatly increases when you're looking across the entire genome without a diagnosis," Genomenon CEO Mike Klein said. "The challenge gets even more daunting when you think about how to scale to meet the increasing demand, from hundreds of whole genomes per month to hundreds of thousands of whole genomes in the next three years.

The Genomenon-Veritas Collaboration will leverage machine learning and artificial intelligence to help create a literature prioritization engine with the promise of more accurate and cost-efficient variant interpretation.



"The ability to scale the clinical interpretation of whole genome sequencing by several orders of magnitude is what prompted us to partner with Veritas," Klein added. "Veritas is on the leading edge of sequencing whole genomes directly for individuals."

Veritas offers consumers whole-genome sequencing and interpretation services under the myGenome brand. The services are designed to yield insights on inherited disease risks, carrier status, drug sensitivities, traits, and ancestry for $999. They were the first such services to be offered for under $1,000 when launched in 2016, according to the company.

Veritas says myGenome delivers for customers clinically relevant findings on more than 1,200 conditions—including some cancers, cardiovascular diseases, immune disorders, endocrine/metabolic disorders, neurological disorders, organ health or multisystem disorders, and reproductive/carrier screening. Also included are findings on the 59 medically actionable genes recommended by ACMG for return in clinical genomic sequencing.

Under its collaboration with Genomenon, Veritas has agreed to integrate into its current workflow and interpretation tools Genomenon's Mastermind Genomic Search Engine. According to Genomenon, Mastermind is the world's first search engine to connect genomic data from patients with evidence retrieved from scientific literature.

Mastermind aims to comprehensively identify all clinically relevant and prioritized articles and is designed to link data on DNA mutations from patients with citations from scientific publications, with the goal of understanding the

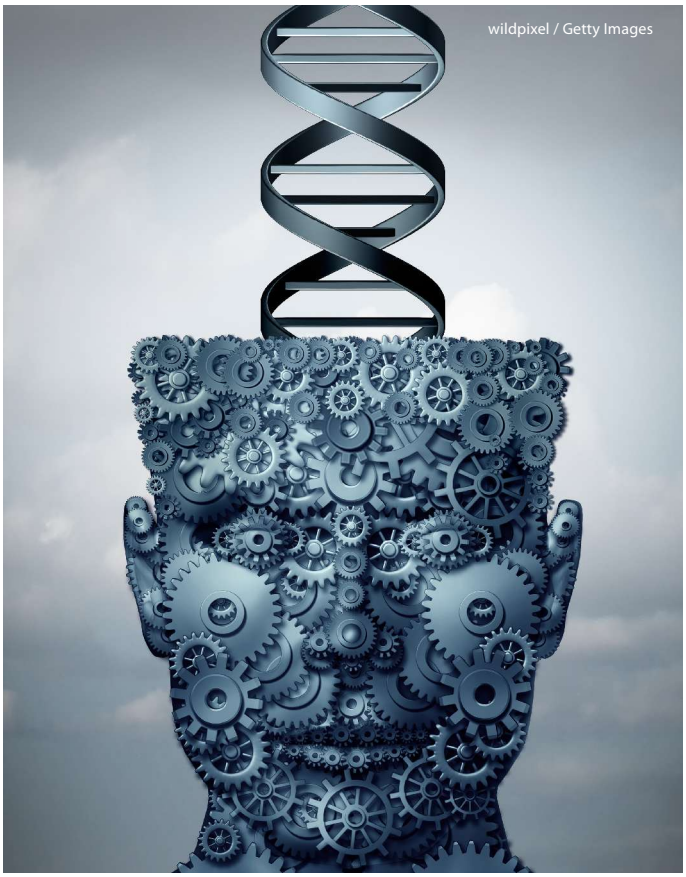
clinical impact of each mutation. To date, Mastermind has indexed nearly 6 million scientific articles covering every disease, gene and variant, out of the 30 million titles and abstracts in PubMed. The indexed articles contain data on more than 1.5 million variants, according to Genomenon.

"Our partnership is starting with enhancing the Mastermind Genomic Search Engine to determine the pathogenicity of variants by ACMG criteria," Klein said. "The latest release of Mastermind helps users to identify clinically relevant literature that is applicable to ACMG classification to accelerate variant interpretation. This is the first step in reducing the single biggest bottleneck in scaling the clinical use of whole genome sequencing."

At the American Association for Cancer Research (AACR) Annual Meeting 2018 in April, Genomenon and Veritas presented findings from a pilot study assessing Mastermind.

In "Evaluation of Genomenon Mastermind for Gene-Level Literature Curation," Ryan Schmidt, M.D., Ph.D., a Molecular Genetic Pathology Fellow at the Laboratory for Molecular Medicine at Harvard Medical School and a resident-physician-clinical pathology at Brigham & Women's Hospital, and colleagues, used three search strategies to examine 10 genes frequently included in diagnostic testing for hypertrophic cardiomyopathy with a range of known gene-disease association strengths (*MYH7*, *MYBPC3*, *TPM1*, *TNNI3*, *TNNT2*, *ACTN2*, *CSRP3*, *TNNC1*, *NEXN*, and *VCL*).

The researchers carried out a PubMed search; a PubMed search with medical subject headings (MeSH)-based disease terms, representing a curated vocabulary that is shared between PubMed and Mastermind; and a search via Mastermind. The searches yielded 1,910, 1,436, and 2,432 PubMed reference numbers, respectively. Mastermind increased the number of results by 69.4% over a matched PubMed/MeSH search, and 27.3% over a "real world" PubMed search.


wildpixel / Getty Images

The study also found that 22% of PubMed results were not found by Mastermind—but the percentage dropped to 3.9%, and number of articles rose to 4,892 following improvements made to Mastermind in response to these results.

"GM [Genomenon Mastermind] improves literature curation sensitivity due to its expanded search capabilities including examination of the full text and may improve on traditional literature search methods in certain situations," Schmidt and colleagues concluded. "Additional [development] to improve the specificity of GM search results is required to further eliminate 'off-target' results."

The companies have identified ensuring proper variant classification efficiently, at scale, by identifying and prioritizing relevant literature as one of two challenges that have held back the advancement of the genomics industry—and which their partnership is designed to address. The other challenge, the companies assert, is developing an efficient way to alert and update variant classifications as new knowledge arises.

In the partnership's second stage, Veritas and Genomenon plan to collaborate on using AI and machine learning to accelerate genomic interpretation. Genomenon has developed a proprietary GLP engine based on technology patented and licensed from the University of Michigan. The company's GLP engine is designed to recognize and index all synonyms that authors could use for diseases, genes, and variants

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into a single unified search database in a way that cannot be accomplished through natural language processing.

The GLP engine uses machine learning algorithms to continuously improve the quality of its genomic search results by intelligently eliminating false positive results from the indexing process, Genomenon said.

The partnership will go beyond Genomenon's past collaborations, which have involved sharing of data with partners that had their own variant curation/interpretation platforms:

- Saphetor agreed in February with Genomenon to share genomic variant data between their software platforms. The deal links Mastermind with Saphetor's VarSome.com knowledge base and aggregator for human genomic variants.
- Also in February, GenomeNext said it embedded results from Mastermind within its Olympus genomic-analysis platform, through a partnership aimed at simplifying and accelerating variant curation for genomic analysis.
- LifeOmic agreed in October 2017 to use Mastermind to automate prioritization of its genome sequencing data for clinical patients by annotating disease-causing variants with citations from relevant biomedical literature.

"Most of Genomenon's partnerships provide valuable guidance on how Mastermind needs to deliver high quality search results that can be used to speed genomic interpretation in a clinical setting and test data to hone the search engine to deliver the highest quality, clinically relevant search results for our partners," Klein said.

> Mastermind has indexed nearly 6 million scientific articles covering every disease, gene and variant, out of the 30 million titles & abstracts in PubMed.

As a development partner, he added, Veritas has provided direct input and guidance on the ACMG classification capabilities of Mastermind that will be helpful in accelerating their workflow. Veritas has also provided Genomenon with gold standard datasets to tune its data prioritization algorithms.

As part of the companies' collaboration, Veritas' clinical variant science team will advise Genomenon's product development team with ongoing requirements and product refinements.

"Genomenon and Veritas are collaborating on using AI to improve the speed of genomic interpretation," Klein said. "By applying this computational intelligence to Mastermind's indexed data, we can identify the evidence needed to suggest ACMG interpretation for variants with supporting clinical evidence, automating the biggest bottleneck in the clinical sequencing workflow."

Wave to Use Deep Genomics' AI Platform in Drug Discovery Collaboration

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Wave Life Sciences will use Deep Genomics' machine learning–driven biomedical platform to discover novel therapies for treating genetic neuromuscular disorders. The companies will test oligonucleotides against potential therapeutic targets within multiple genes implicated in neuromuscular disorders. Wave will develop the new therapies using its propriety chemistry platform to validate targets and elucidate the implications of target intervention across different phenotypes, the companies said.

The analysis of oligonucleotides will use Deep Genomics' machine learning platform to identify cause and effect relationships specific to neuromuscular-related targets that involve splicing regulation. Deep Genomics' platform is designed to discover drug candidates that target the genetic determinants of disease at the level of RNA or DNA. The platform produces on-target and genome-wide off-target effect data for every compound identified.

Deep Genomics is using the platform to evaluate more than 69 billion molecules against 1 million targets, *in silico*. The effort, dubbed "Project Saturn," is designed to generate a library of 1,000 compounds that are experimentally verified to manipulate cell biology as intended.

University Nebraska, GenomOncology Break Barrier with Genomics Data in EHRs

Since the human genome was first unraveled, it has played a role in significantly improving cancer treatment. But until now, cancer genomics data have mainly been shared by doctors via paper records, according to researchers at the Fred & Pamela Buffett Cancer Center at the University of Nebraska Medical Center (UNMC). Now, UNMC and GenomOncology, a genomic technology and services provider, hope to change that with their recent announcement that they developed a way to transfer genomics data directly to electronic health records (EHRs), and, in turn, making the data that much easier for researchers and doctors to use.

"Basically, this [breakthrough] allows us to take gene sequence data and treat it no differently than a blood test in EHRs," said Scott Campbell, Ph.D., assistant professor and director of informatics for the Public Health Laboratory and the Pathology Laboratory at the Buffett Cancer Center. Scott Campbell—who co-led the project at UNMC with James Campbell, M.D., professor of internal medicine for UNMC (no relation)—said the project had "been extensive," and had "involved significant involvement at the international level, the national trade association level and the local level."

To be able to bring genomics data to an EHR, UNMC and GenomOncology took complex targeted gene sequences and paired them with very descriptive SNOMED questions, Campbell said. SNOMED describes itself as "the most comprehensive and precise clinical health terminology product in the world."

"We created specific and defined SNOMED questions that fit into HL7 (Health Level Seven International) and describe a gene sequence," Scott Campbell said. "We extended SNOMED and compressed Human Genome Variation Society protocol until it fit into an HL7 Version 2 message."

"HL7 is the most common communication method to move healthcare data between systems and is used by essentially every hospital in the U.S. and Canada to communicate laboratory test results between electronic health record (EHR) systems," according to HL7.

"This is the first time this has been done," Scott Campbell said. He has been traveling worldwide sharing the news at various meetings and conferences, and "it has been received well," he said.

Scott Campbell, Ph.D., director of informatics at the Buffett Cancer Center said the method developed to incorporate genomic data in an EHR is no different than bringing in data from a blood test.

The significance of having the genomics data available in an EHR is that it allows physicians to use decision-making software to determine the best course of treatment for specific gene signatures, he said. In the past, doctors had to "pour through written reports and disjointed computer files" to find patients that could be impacted by a new treatment. "This brings precision medicine into something really applicable," he added.

The project was funded by a National Institutes of Health big data research grant called, "Big Data to Knowledge," and UNMC is in the second year of the three-year grant. The work started with an effort to encode every aspect of the College of American Pathologists cancer reports so that researchers and doctors could have the records they need, "giving clinicians a leg up in the understanding of diseases," he said.

The information on how to share the genomics data is open-sourced and available on the UNMC website. "It's there to be used," Scott Campbell said. "It's available free of charge for non-commercial use if you have a license with the National Library of Medicine." — *Diana Manos*

Dark Side of the Genome

Study Links Noncoding Mutations in Regulatory Regions of the Cancer Genome to Altered Gene Expression

By Vicki Glaser

Researchers in the lab of Trey Ideker, Ph.D., at University of California, San Diego recently published results of a genome-wide analysis comparing paired normal and tumor tissues that led to the identification of mutations in noncoding regions linked to changes in target gene expression. Although previous whole-genome sequencing (WGS) studies of cancer tissue have uncovered recurrent somatic mutations at noncoding loci, there exists little evidence of functional associations between these mutations and regulatory control of particular genes. One clear exception are mutations that occur in the promoter of the telomerase reverse transcriptase (TERT) gene.

The current study was able to make important associations between noncoding mutations and gene expression because the method Ideker's team used to identify somatic mutations in noncoding regions was fundamentally different than the approach previously taken. As Wei Zhang, Ph.D., lead author of the article in *Nature Genetics* and a postdoc in Ideker's lab, explained, "they focused on mutations that are highly recurrent, beyond the background mutation rate." In contrast, "our analysis focused on mutations associated with changes in gene expression."

The new findings provide fascinating insights into the potential implications of functional somatic mutations in noncoding regions of the cancer genome. Using specific genes as examples, Zhang, *et al*. began to examine the link and possible causal relationship between a specific mutated noncoding locus, a change in target gene expression, and a cancer phenotype. As researchers begin to explore the significance of somatic mutations in noncoding regions of the cancer genome and learn if and at what point in the cancer life cycle they may exert an effect—from tumorigenesis to metastasis—then at least some of these recurrently mutated loci may one day have a role in advancing cancer diagnotics or therapeutics.

Researchers in the lab of Trey Ideker, Ph.D., at University of California, San Diego have identified 193 mutations in noncoding regions linked to changes in target gene expression in cancer.

Identifying Somatic eQTLs

The study by Zhang, *et al*. involved WGS analysis with matched mRNA expression profiles of 930 tumor-normal tissue pairs representing 22 cancer types. These samples were acquired from The Cancer Genome Atlas (TCGA). The researchers searched for single nucleotide variations (SNVs) in noncoding regions. "Instead of looking at the entire genome, we focused on regions that are known to have a regulatory impact and where there are recurrent mutations," said coauthor Jason Kreisberg, Ph.D. Recurrent SNVs that occurred within 50 bp of each other were grouped into clusters.

The researchers then tested each of the clusters for an association with increased or decreased mRNA levels of target genes. This led to the identification of 193 somatic expression quantitative trait loci (eQTLs). Somatic eQTLs are defined here as noncoding loci in which mutations affect target gene expression. The complete analysis yielded a "cancer transcriptional network of 206 regulatory interactions between 193 somatic eQTLs and 196 gene-expression-level changes," as described in the paper. In 820 of the 930 tumors analyzed, at least one locus in this network was somatically mutated, "suggesting that transcriptional dysregulation through noncoding mutations is a general property of most tumors."

"This study starts to show that there are probably cancer-relevant mutations in other parts of the genome that we need to start paying attention to."
—Jason Kreisberg, Ph.D., University of California, San Diego

The researchers reported that noncoding mutations in somatic eQTLs were linked to changes in expression levels of 13 known tumor suppressor genes or oncogenes. Overall, however, known cancer driver genes were not highly represented in the study findings. "We did not expect a lot of overlap," said Zhang, "because cancer driver genes are defined by the mutations in their coding regions." Kreisberg agreed: "Oncogenes are often characterized by mutations that lead to gain of function changes, and tumor suppressors are often characterized by somatic mutations that lead to loss of function. Therefore, we didn't expected to find a lot of noncoding mutations that would drive those genes up or down, because those genes carry out their cancer-causing functions due to mutations somewhere in the protein coding regions of the gene itself."

To validate the cancer transcriptional network, the researchers searched a second cancer database for the somatic eQTLs. They used the International Cancer Genome Consortium (ICGC) database, comparing their data against genome-wide somatic mutations for 3,382 patients. The majority of the somatic eQTLs found in the TCGA database were also recurrently mutated in the ICGC patient genomes. Interestingly, there are 12 somatic eQTLs from the initial TCGA study that were mutated almost exclusively in melanoma. Among these 12, 10 occurred almost only in melanoma in the ICGC data as well.

Linking Mutations to Gene Expression to Phenotype

The researchers selected three of the target genes in the study for more detailed investigation, and in particular *DAAM1*. According to Zhang, a key reason they chose *DAAM1* is that the somatic eQTL "makes a lot of sense for upregulation of the gene

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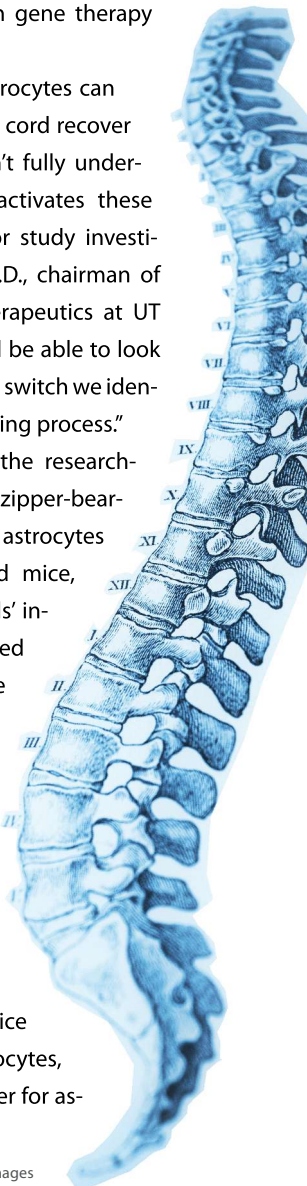
Gene Deletion May Aid Stroke, Spinal Injury Recovery

A researchers at the University of Texas Southwestern's O'Donnell Brain Institute have found a genetic trigger that may improve the brain's ability to heal from a range of debilitating conditions, from strokes to concussions and spinal cord injuries. Their research shows that turning on a gene inside astrocytes results in a smaller scar and, potentially, more effective recovery from injury. These results have implications for treating several brain conditions through gene therapy targeting astrocytes.

"We've known that astrocytes can help the brain and spinal cord recover from injury, but we didn't fully understand the trigger that activates these cells," explained co-senior study investigator Mark Goldberg, M.D., chairman of neurology and neurotherapeutics at UT Southwestern. "Now we'll be able to look at whether turning on the switch we identified can help in the healing process."

In the current study, the researchers deleted the leucine zipper-bearing kinase (*LZK*) gene in astrocytes of one group of injured mice, which decreased the cells' injury response and resulted in a larger wound on the spinal cord. Conversely, the scientists overexpressed the gene in other injured mice, which stimulated the cells' injury response and resulted in a smaller scar. Overexpressing the gene in uninjured mice also activated the astrocytes, confirming *LZK* as a trigger for astrogliosis. ■



jcrosemann / Getty Images

Congenital Heart Defects in Offspring Elevate Maternal Cardiac Disease Risk

MHJ / Getty Images

Investigators at McGill University and the University of Montreal Hospital Research Center have found that women who give birth to infants with congenital heart defects may have an increased risk of cardiovascular hospitalizations later in life. The new study published in the journal *Circulation*, which looked at the health data of more than one million women, is the first to show congenital heart defects in newborns may be a marker for an increased risk of their mothers developing heart problems, including heart attack and heart failure, years after pregnancy.

"Caring for infants with critical heart defects is associated with psychosocial and financial stress, which may increase the mothers' long-term risk for cardiovascular disease," explained lead study investigator Nathalie Auger, M.D., an epidemiologist at the University of Montreal Hospital Research Centre.

How heart defects in infants relate to post-pregnancy cardiovascular disease in their mothers is currently unclear, the study notes, and a genetic component cannot be excluded. Also, because 85% of infants with heart defects now survive past adolescence, the psychosocial impact of congenital heart disease on caregivers may have a cumulative effect over the long term. ■

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as it alters a well-known transcription factor binding site. From the literature, we found that the *DAAM1* gene is thought to be linked to cell migration. That's very intriguing because mutation of *DAAM1* only occurs in metastatic melanoma patients, and cell migration is related to metastasis. Thus, we were very interested in testing this gene, both for its ability to drive gene expression and because of the mutation's link to cell migration."

The somatic eQTL for *DAAM1* was situated 191 base pairs upstream of the gene. The DAAM1 protein is believed to have a role in a signaling pathway linked to the increased motility and invasiveness of cancer cells. Mutations at the somatic eQTL were associated with increased expression of *DAAM1*. By comparing the effects of wild-type versus mutated regulatory elements on expression of the reporter gene green fluorescent protein (GFP), the researchers were able to confirm a causative relationship between the eQTL and the upregulation of gene expression.

Experiments that probed the relationship between higher *DAAM1* expression and cell motility showed an association between *DAAM1* upregulation and a more invasive cell phenotype. Furthermore, cells that over-expressed the *DAAM1* gene "migrated with significantly greater persistence" and "invaded for longer distances" than did cell in which *DAAM1* was not over-expressed.

Subsequent studies focused on two additional somatic eQTLs. One was located in the promoter of the *MTG2* gene and was associated with down-regulation of *MTG2* expression. It was present in multiple types of cancer including lung adenocarcinoma and sarcoma. The other somatic eQTL was found situated in the enhancer region of the *HYI* gene. It led to increased *HYI* expression and was found in 21% of melanoma tumors studied.

All three genes—*DAAM1*, *MTG-2*, and *HYI*—were chosen for further experimentation because of their expression levels and available knowledge about their regulatory regions. Another factor contributing to the selection of these genes was the importance of doing the follow-on studies in tumor cell lines that could as closely as possible represent those of the patients in the cancer database and the ease of access to those cell lines.

Conclusions

Much of the interest these days in looking at patients with cancer and trying to characterize disease-related gene mutations is focused on somatic mutations in either oncogenes or tumor suppressor genes. "This study starts to show that there are probably cancer-relevant mutations in other parts of the genome that we need to start paying attention to," said Kreisberg. "The loci being mutated that we point out in the paper, which are ones that map to transcription factor binding sites, are experimentally the lowest hanging fruit. If we see a transcription factor binding site being created or destroyed, that seems like a good place to start doing experiments. But we've only looked at 3 of 193 somatic eQTLs. There's a lot more room to characterize more of these and more broadly understand their functional consequences. Understanding these better might reveal new vulnerabilities."

System Qualification, Inter-Sample, and Intra-Sample Quality Control

An Essential Approach for Translational Proteomics

We are in a new age of clinical research, where experimental design is moving from relying on cohort sizes of 2x2 and 10x10 for putative biomarker panel identification to hundreds or even thousands of samples. A new focus has been put into setting up the experimental design for translational studies and the resulting concepts that can then be transferred across labs and projects. The amount of time and cost associated with large-scale studies mandate high-quality data acquisition for every project.

Scientific Challenge

Translational and clinical research studies profile individuals against a cohort to mine for the presence of putative biomarkers. Study size has grown tremendously over the last five years to include hundreds and even thousands of samples. Increasing sample numbers for these studies create significant challenges when successfully assessing an original experimental hypothesis due to:

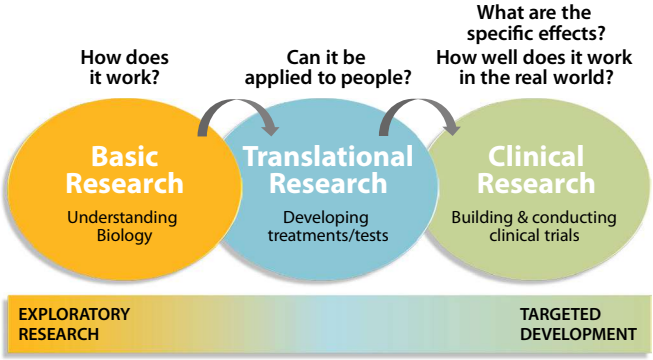
- Study duration, which can span potential interruption of data acquisition.
- Amount of data generated, which becomes challenging to process and interpret.
- Experiment set-up or method development, particularly within a consortium where transferability becomes critical for reproducibility.

Adding to these challenges, current analytical methods create a gap from bench studies to clinical application and from small to large-scale experiments. Quality control (QC) standards are not used correctly or tend to be tailored for specific applications and thus cannot be shared. With failure to assess reproducibility at each step of the analysis, methods cannot be verified by other labs. This issue directly causes the inability to bridge the translational gap and has resulted in circumstances where bench studies don't make it to the clinic.

Solution for Translational Proteomics

The use of an optimized, systematic, and standardized approach to proteomics experiments permits the direct comparison of results across experiments, projects, and laboratories.

Identifying and evaluating each step within a workflow allows the inclusion of QC steps along the way. Incorporating standardized QC into sample collection and storage, sample preparation, system suitability testing, and sample analyses ensures data integrity, and also reproducible analyses. Commercially available standards that are externally validated, support this uniformity across workflows.



Approach to proteomic biomarker studies

Once QC methods are in place, system suitability and performance can be measured within the study as well as post-study and determine systematic and experimental variance to facilitate more accurate quantification of biological variance. Successful QC methods can then be qualified and further implemented into subsequent translational studies on biological systems.

Future Plans

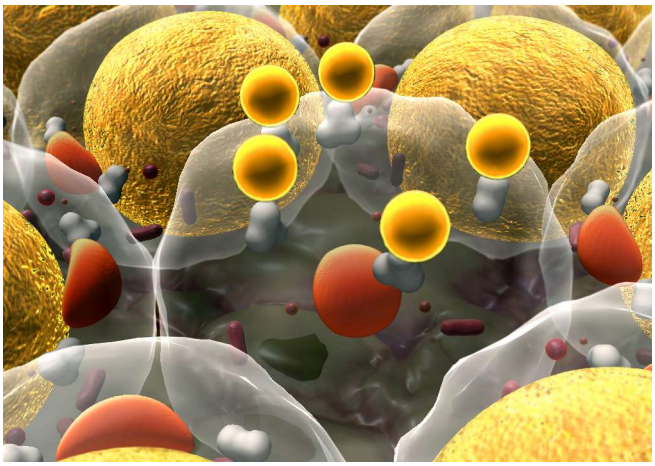
Harmonization of QC methods across studies has been observed with new studies in targeted metabolomics. Using systems such as Biocrates Absolute IDQ p180 that include calibration standards, QC Standards, integrated software, and clear QC metrics provide reliable QC tested commercial standards that can be applied to any analytical method related to metabolomics studies.

Steps toward reproducible quantitative analyses within and across labs implementing common QC samples, analytical standards such as SIL peptides, and biological QC standards such as reference pools of serum/plasma from NIST and Golden West, are improving experimental results and providing a solid foundation for further analysis, ensuring monies are not wasted reinventing the wheel. Further assistance from industry partners such as Thermo Fisher Scientific to help with workflow standardization and QC reporting make it easier for the individual lab to start discovery experiments with a high level of quality to ensure they are meaningful long-term.

ThermoFisher SCIENTIFIC

Exposure to Cold Spurs Epigenetic Changes in Fat Cells

New evidence from investigators at the University of Tokyo and Tohoku University in Japan has revealed a molecular mechanism that controls how lifestyle choices and the external environment affect gene expression. This mechanism includes potential targets for next-generation drug discovery efforts to treat metabolic diseases including diabetes and obesity.



Ugreen / Getty Images

The Japanese researchers tracked how the epigenome changes after long-term exposure to cold temperatures, and how those changes cause energy-storing white fat cells to become heat-producing brown-like, or "beige," fat cells. Findings from the new study were published in *Nature Communications* through an article entitled "Histone demethylase JMJD1A coordinates acute and chronic adaptation to cold stress via thermogenic phospho-switch."

"We believe that this is the first time that anyone has collected data to prove that there are two steps between the environmental stimuli and epigenetic changes," explained Juro Sakai, M.D., Ph.D., an expert in the epigenetics of metabolism and professor at the University of Tokyo and Tohoku University.

Shivering creates body heat short-term by warming up the muscles, but thermogenesis is the chemical process by which brown fat cells can use lipids (fat) to create heat to keep the body warm long-term. Brown fat is regarded as healthier and is not associated with the metabolic diseases linked to excess white fat. Scientists have long suspected that there may be a stepwise process inside the cell to manage environmental influences on the epigenome, but no specific molecular mechanisms had been identified previously.

"Understanding how the environment influences metabolism is scientifically, pharmacologically, and medically interesting," Sakai noted.

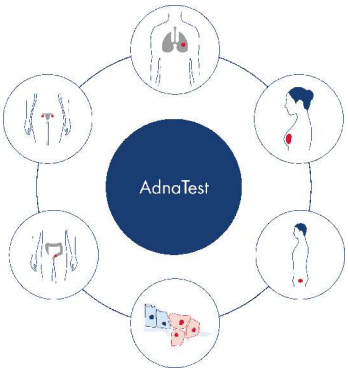
Researchers have shown previously that when organisms are cold for a long time, the sympathetic nervous system responds by releasing adrenaline. If cold temperatures persist, those adrenaline signals eventually reach white fat cells. In the current study, the research team set out to uncover the epigenetic control pathway that the cell initiates to make the necessary metabolic switch.

The investigators showed the switch "occurs through a two-step process that requires both β-adrenergic-dependent phosphorylation of S265 and demethylation of H3K9me2 by JMJD1A. The histone demethylation-independent acute Ucp1 induction in BAT and demethylation-dependent chronic Ucp1 expression in beige scWAT provides complementary molecular mechanisms to ensure an ordered transition between acute and chronic adaptation to cold stress. JMJD1A mediates two major signaling pathways, namely, β-adrenergic receptor and peroxisome proliferator-activated receptor-γ (PPARγ) activation, via PRDM16-PPARγ-P-JMJD1A complex for beige adipogenesis."

In short, the epigenetic changes transform white fat cells into beige fat cells, which perform thermogenesis like brown fat cells. More beige fat cells and fewer white fat cells could reduce the symptoms or negative health outcomes of metabolic diseases like diabetes, obesity. Although transforming white fat cells into beige fat cells and increasing thermogenesis is naturally a stress response to chronic cold exposure involving adrenaline, researchers report that the same white-to-beige fat cell transition can be caused without adrenaline or cold stress.

"Our next experiments will look more closely at epigenetic modifications within the thermogenesis signaling pathway so that we may manipulate it," said Sakai.

Liquid Biopsy Kits for Prostate and Lung Cancer



Qiagen has launched two novel liquid biopsy panels to evaluate circulating tumor cells (CTCs) in the growing field of research into molecular mechanisms in prostate and lung cancers. The AdnaTest ProstateCancerPanel AR-V7 Kit provides insights into tumor biology by detecting the androgen receptor splice variant 7 in CTCs of prostate tumor origin isolated from blood samples to investigate potential resistance to drugs for advanced prostate cancer. The test is licensed from Johns Hopkins University for nucleic acid detection of the AR-V7 biomarker. The AdnaTest LungCancer Kit delivers unique insights into the molecular mechanisms of lung cancer through highly specific selection of CTCs, including stem cell–like cells implicated in cancer growth and epithelial–mesenchymal transition (EMT), an important marker of resistance to cancer therapy. A proprietary set of antibodies provides sensitive detection of lung cancer-associated targets through reverse-transcriptase PCR.

Qiagen *www.qiagen.com/us*

Research Kits to Identify Breath-Based Biomarkers

Owlstone Medical has introduced Breath Biopsy Kits, based on the company's proprietary Breath Biopsy platform. The kits allow academic, clinical, and pharmaceutical researchers to discover and validate breath-based biomarkers in early detection and precision medicine research. Breath Biopsy Collection Kits enable researchers to collect reliable breath samples that can then be analyzed in their own laboratory using instrumentation such as the Lonestar VOC Analyzer. Breath Biopsy Discovery VOC Kits include the consumables required for breath collection, as well as a comprehensive global breath VOC analysis performed in Owlstone Medical's Breath Biopsy Services Laboratory. The kits contain consumables for use with the ReCIVA Breath Sampler including a Breath Biopsy Cartridge to collect, stabilize and enrich VOCs in breath, enhancing the sensitivity for detection of VOCs, and a disposable Breath Biopsy Mask.

Owlstone Medical *www.owlstonemedical.com*

Integrated Metabolic Analysis and Imaging Platform

Agilent Technologies and BioTek Instruments have created an integrated solution that combines cellular metabolic analysis and imaging technologies. The solution integrates the Agilent Seahorse XFe96/XFe24 Analyzers with the BioTek Cytation 1 Cell Imaging Multi-Mode Reader to create a standardized approach for comparing XF datasets. It improves assay workflow, embeds images into WAVE software, and applies normalization values to Seahorse XF measurements. With the Agilent Seahorse XF WAVE software researchers can toggle between XF data, brightfield images, and fluorescence images in a unified software experience. The Agilent Seahorse XFe Analyzers simultaneously measure the two-major cellular energy-producing pathways—mitochondrial respiration and glycolysis—in live cells, in real time. The BioTek Cytation 1 Cell Imaging Multi-Mode Reader is configurable for fluorescence and high contrast brightfield cellular imaging with up to 60x magnification.

Agilent Technologies and BioTek Instruments

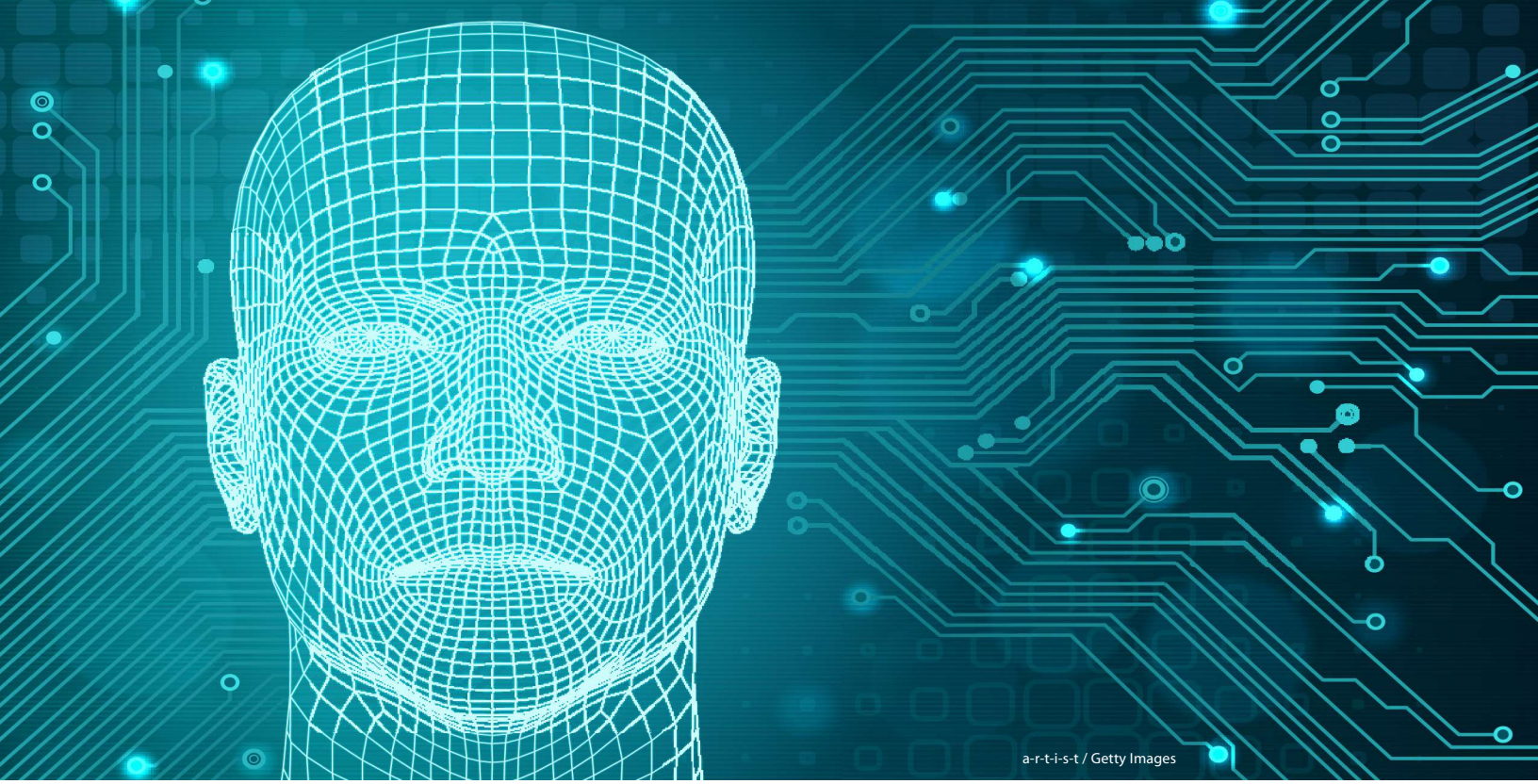
www.agilent.com

www.biotek.com

Massively Parallel Profiling of Single-Cell Genomes

The Chromium Single Cell CNV Solution is a scalable and easy-to-use technology for rapid and massively parallel profiling of single-cell genomes. This solution is the first to be built on the company's new technology advancement for generating Cell Beads and Gel Beads (CBGBs). Chromium Single Cell CNV Solution profiles the genomes of individual cells to reveal tumor heterogeneity, characterize somatic mosaicism of neurons, and authenticate cell line identity and clonal purity. The solution also includes a comprehensive software suite from 10x Genomics to rapidly analyze and visualize large single-cell CNV experiments. The Cell Ranger DNA analysis pipeline provides a turnkey solution for single-cell CNV calling and clustering. The Loupe scDNA Browser provides an easy-to-use tool for inspecting and interrogating genomic regions and cell clusters.

10x Genomics *www.10xgenomics.com*



10 U.S. Startups to Watch

From blockchain technology, artificial intelligence, and deep learning to new sequencing technologies and telehealth, these fledgeling U.S.-based companies are poised to make significant impacts in the precision medicine and multi-omics world of the future.

AI

doc.ai

Headquarters: Palo Alto, California. **Year Founded:** 2016. **Company Founders**: Walter De Brouwer, Ph.D., Sam De Brouwer, Alan Greenem, M.D., Cheryl Greene, Anthea Chung. **Employees:** 15. **Major Investors:** Comet Labs, Pantera Capital.

doc.ai is a blockchain-based AI platform that enables deep learning computations on quantified biology for personal health insights. The platform connects people, data scientists and research sponsors to develop predictive models. "I cannot think of a bigger mission for healthcare than to unlock people's medical data through the establishment of a cryptoasset economy using the most advanced market weapons at our disposal: machine learning, precision medicine (OMICs), distributed ledger technology, applied cryptography, and edge computing. It is the only strategy whereby a seller's market will eventually become a buyer's market," said Walter De Brouwer, Ph.D., company CEO. "Anything not exposed to the free market is mispriced. So are the millions of biomarkers in people's bodies. They have a market price, but it is waiting for a medium of exchange to become a store of value. Medical data will become a financial asset."

Headquarters: San Francisco. **Year Founded:** June 2016. **Company Founders:** Lisa Alderson, CEO; Randy Scott, Ph.D., chairman of the board; Robert C. Green, M.D., chairman of the Scientific Advisory Board. **Employees:** 16. **Major Investors:** Canaan Partners, GE Ventures, Illumina Ventures, Kaiser Permanente Ventures, Flywheel Ventures, and Health-Invest Equity Partners.

Genome Medical is a digital health company with a mission to integrate genomics into everyday health care. It is the first nationwide medical practice focused on genetics and genomics, and its clinical genetics experts provide virtual consultations over a tele-genomics platform (video or phone). The company helps patients, physicians, health systems, payers and employers navigate the rapidly evolving field of genomics to improve health, diagnose and prevent disease, and lower the cost of care. Services include pre- and post-test counseling, test requisition, development of clinical action plans based on test results, and peer-to-peer consultations.

"We are seeing unparalleled advancements in genetics and genomics, and yet most people do not have access to the benefits of genomic medicine. Genome Medical was created to change that, as the first independent, nationwide medical practice focused on genetic and genomics. The fast, direct access we provide to genetic experts (genetic counselors and medical geneticists) through virtual consultations helps patients and clinicians make informed genetic health decisions about testing and how to best integrate test results into healthcare planning," said Genome Medical CEO Lisa Alderson.

AI

Headquarters: San Diego. **Year Founded:** 2014. **Company Founders:** Ahmed Ghouri, M.D., CEO; Raghu Sugavanam, president; Gary Rayner, chairman of the board. **Employees**: Undisclosed. **Major Investors:** Centene Corp.

Interpreta is an analytics company that intelligently synchronizes healthcare. A real-time clinical and genomic interpreter and care-navigation platform that leverage AI, Interpreta helps physicians and insurers to deliver patient prioritization and actionable insights prospectively to enable quality care, population genomics, and precision medicine. "Interpreta continuously aggregates and interprets EMR, insurer, pharmacy, laboratory, EMR, and genome sequence data against always-current knowledge bases in real time to optimize patient treatment," said Ahmed Ghouri, M.D., CEO. Interpreta's analytics engine updates, interprets, and synchronizes clinical and genomics data, creating a personalized roadmap that is syndicated to multiple application workflows using a real-time API. "Like a GPS system for patient care, it continuously gathers and calculates multiple sources of data to deliver precision care guidance and real-time course correction as soon as new data arrives, without interpretation latency. This enables ACOs, health plans, pharmacists, care managers, and patients to quickly navigate next steps in priority order," Ghouri added.

AI

Headquarters: San Diego. **Year Founded:** 2014. **Company Founders:** Paul Mola, president and CEO; Barry Merriman, Ph.D., CSO. **Employees:** 14. **Major Investors:** Private Investors.

Roswell is taking a bold step to develop a transformative technology platform based on Molecular Electronics—ENDSeq Electronic Nano Detection Sequencing—to realize the $100, 1-hour genome. Low cost desktop systems, with simple single molecule workflows, will drive ubiquitous deployment of clinical-grade sequencing for equitable access to precision medicine for all. Roswell's ability to deliver ultra-long reads for phased genomes, with high accuracy, and direct reading of epigenetic status could transform the practice of medicine. "Roswell's ENDSeq System is an endgame technology that will defy the current status of reading DNA, to unlock the power of the genome to usher in the era of Precision Medicine. Roswell's technology will shift the paradigm from sequencing individuals to sequencing single cells for maximum power to unlock new insights in biology for the betterment of mankind," said Paul Mola, president and CEO.

Nebula Genomics

Headquarters: San Francisco. **Year Founded:** 2017. **Company Founders:** George Church, Ph.D.; Dennis Grishin Ph.D.; Kamal Obbad. **Employees:** 5. **Major Investors:** Undisclosed.

Nebula Genomics is a decentralized platform that leverages blockchain technology for the sharing of genomic and other healthcare-related data. "The Nebula platform leverages blockchain technology to eliminate personal genomics companies as middlemen between data owners and data buyers. Instead, data owners can acquire their personal genomic data from Nebula sequencing facilities or other sources, join the Nebula blockchain-based, peer-to-peer network and directly connect with and receive payment from data buyers," said co-founder Demmis Grishin, Ph.D. "This model reduces effective sequencing costs and enhances protection of personal genomic data. It also satisfies the needs of data buyers in regards to data availability, data acquisition logistics, and resources needed for genomic big data,"and how to best integrate test results into health care planning.

AI

TEMPUS

Headquarters: Chicago. **Year Founded:** 2015. **Company Founder:** Eric Lefkofsky, CEO. **Employees:** Approximately 400. **Major Investors:** New Enterprise Associates, Revolution Growth, and T. Rowe Price Associates.

Tempus is a technology company that is building what the company believes will be the world's largest library of molecular and clinical data and an operating system to make that data accessible and useful. The company enables physicians to deliver personalized cancer care for patients through an interactive analytical and machine learning platform. It provides genomic sequencing services and analyzes molecular and therapeutic data to empower physicians to make real-time, data-driven decisions. The goal of the company is for each patient to benefit from the treatment of others who came before by providing physicians with tools that learn as more data is gathered. "Tempus was born out of frustration with a healthcare system that too often let powerful data and real world evidence go to waste," said Eric Lefkofsky, CEO. "It is impossible to scale personalized medicine efforts without centralizing vast amounts of phenotypic, therapeutic, and molecular data. Tempus addressed this by building an ecosystem to collect, cleanse, analyze, and apply data solutions to oncology through products that are driving real-time, clinical decision support and cutting-edge research. Given the breadth and scale of our current data set, we're in a unique position to help usher in an era of precision medicine to support patients battling disease."

AI

SEQSTER™

Headquarters: San Diego. **Year Founded:** 2016. **Company Founders**: Ardy Arianpour, CEO; Xiang Li Ph.D., CTO; Dana Hosseini, CIO. **Employees**: 15. **Major Investors:** Executives in Genomics, Healthcare, Diagnostics and Clinical Trials.

Seqster contends it has created the Mint.com of health data, as the world's first company to aggregate and combine matched longitudinal electronic health records (EHRs), genomic and fitness data from any source to generate new insights using machine learning. It puts consumers in charge of all of their health data to disrupt EHR, genomic, and fitness data silos. "The greatest challenge we face in healthcare is our ability to bring all of the data together in a common form while simultaneously addressing data ownership, data security, and interoperability. This is because your information is siloed and stored in different EHRs, genomic labs, and wearable devices that don't talk to each other," said company CEO Ardy Arianpour. "With Seqster, you now have your own health data platform where you can unlock and generate value by engaging with your data and sharing it on your terms for the good of all." The platform allows consumers and their families to have all of their health data live in one place, in a common form. In addition to enabling data sharing for research, the platform allows users to designate access to caregivers and family members through HealthTrust—a legal framework for preserving and passing on health data. Seqster's platform currently connects to more than 1,000 healthcare providers comprising more than 2,000 hospitals and clinics nationwide."

RPRD DIAGNOSTICS
— Right Patient | Right Drug —

Headquarters: Milwaukee, WI. **Year Founded:** 2016. **Company Founders:** Ulrich Broeckel, M.D., CEO; Carter Cliff, director. **Employees:** 10. **Major Investors:** Children's Hospital of Minnesota.

RPRD (Right Patient Right Drug) Diagnostics is a precision medicine company offering clinical pharmacogenomics (PGx) testing, analysis and implementation services. RPRD's PGx tests inform drug selection and dosing to support clinical decision-making, thereby improving patient outcomes through increased drug therapy effectiveness and decreased adverse reactions, with an additional benefit of reducing overall costs. The company specializes in both comprehensive PGx and tailored panels, such as the CNT Panel for identification of leukemia patients at risk for toxicity from thiopurine drugs. "While clinical pharmacogenomics (PGx) testing has been around for more than a decade, institutions have struggled with the challenges of implementing these services, not the least of which includes clinical decision and electronic medical record decision support. With practicing clinicians ourselves, RPRD understands these difficulties and has a comprehensive view of the PGx services and support required to benefit healthcare," said CEO Ulrich Broeckel, M.D. "Our staff has over 60 years of combined clinical expertise and implementation experience. RPRD is committed to science-driven research and development as well as state-of-the-art testing platforms focused on highest impact yet cost-effective solutions for our customers and their patients." RPRD also serves the pharmaceutical and clinical trials industries as a pharmacogenetics testing and data-analysis resource.

AI

ROOT

Headquarters: Boston. **Year Founded:** 2016. **Company Founder:** Nathan Pearson, Ph.D. **Employees:** 4. **Major Investors:** pre-seed.

As a B-to-B-to-freemium-consumer play, Root helps institutions engage the world's largest living cohort of engaged, contactable, well genotyped people, by giving more than 29 million tissue-donor volunteers their own prismatically informative HLA data—securely and well interpreted—to use in life and for science. "As a genomicist who lost my mom young, to a blood cancer with no marrow donor, I know first-hand how our most diverse and prismatically informative genes, HLA, bond humanity together," said Founder Nathan Pearson, Ph.D. "But with no one offering good personal insight from HLA, I saw that doing so—clearly, brightly, wisely, and free—could help millions learn and thrive from the genes that say more, for each person and for science, than any other DNA."

AI

twoporeguys

Headquarters: Santa Cruz, CA. **Year Founded:** 2011. **Company Founders:** William Dunbar, Ph.D., acting CEO and CTO; Trevor Morin, Ph.D., CSO; Dan Heller, strategic advisor and board member. **Employees:** Undisclosed. **Major Investors:** Khosla Ventures.

Two Pore Guys is developing a portable device based on solid-state nanopore technology that detects and quantifies DNA/RNA and analyte targets in an inexpensive form factor. The 2PG sample-to-answer device in development can be used for a number of applications, including liquid biopsies, detecting and monitoring pathogens, and for agricultural applications. "At the heart of our technology platform is a solid-state nanopore that electrically detects single molecules and discriminates targets of interest from background using our patented biochemical methods," said William Dunbar, Ph.D., acting CEO, and CTO. "Among the advantages of this approach is that the solution is much faster and cheaper than traditional qPCR, with accuracy matching that of ddPCR. We believe the simplicity and cost-effectiveness of this approach, combined with a portable form factor, will disrupt markets as a multi-omcis platform."

Ready for Prime Time?

AI Influencing Precision Medicine but May Not Match the Hype

By Chris Anderson

Machine learning and artificial intelligence (AI) are prominent buzzwords when the topic of precision medicine comes up, but like many emerging technologies with the potential to make a significant impact, it can be difficult sometimes to separate the hype from the real-world impact.

AI entered that breathless, overhyped territory last year, and luckily there have been some in the life sciences and healthcare who have cautioned against over-promising on the potential. "There is so much hype and noise about the predictive power of the AI," said Ahmed Ghoury, CEO of clinical and genomic data interpretation company Interpreta. "This saturation of AI claims can make people sour on the field as a whole, so it is good to vet the accuracy of claims and ask organizations if they have any data that can validate their claims."

In addition, AI still suffers from the fear of the "black box"—the algorithms that are grinding the data fed into them to generate answers or diagnoses, or advice on how to treat patients. "If [AI] is drawing conclusions and you don't know what the underlying datasets are, that is what physicians will most react to. If they can't understand how it arrived at that answer, they can't trust it," noted Chris Cournoyer, CEO of molecular decision support company N-of-One. "And trust is a big thing with AI right now."

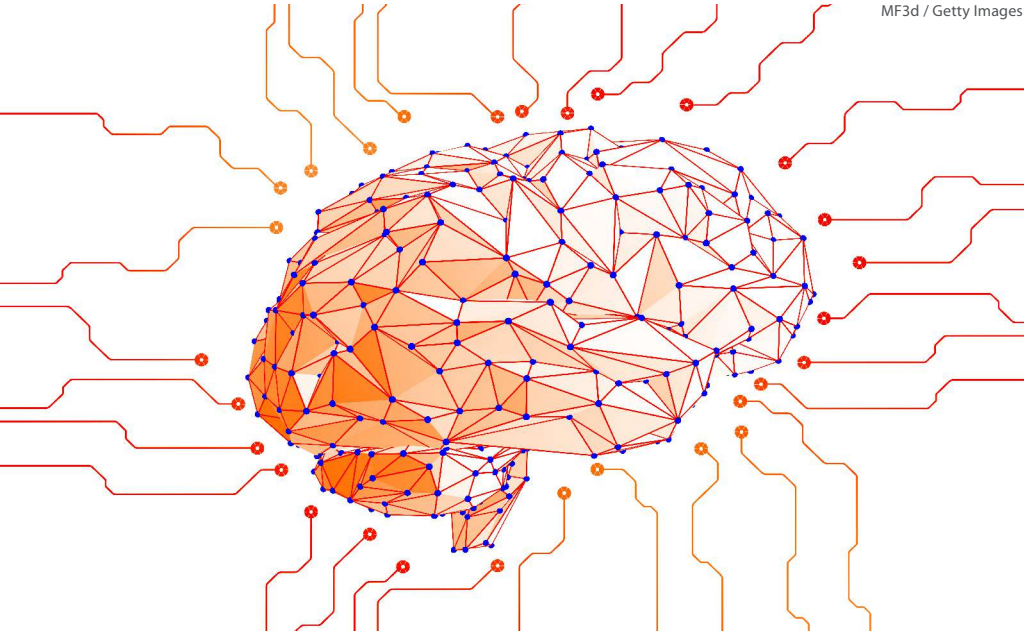
Pharmacogenomics

While care organizations that are looking to technology to help provide precision care are right to cast a critical eye toward AI, that doesn't mean it is not making contributions today in the clinical setting—and is poised for even greater influence in the future.

Pharmacogenomics is one area where AI-enabled technologies are making a noticeable impact today. Companies like Interpreta are leveraging data from the FDA's Adverse Event Reporting System and combining it with clinical data and insurance data to help doctors make more precise prescription choices and head off adverse drug events (ADEs).

"Right now most of the drug labeling for genomics tends to be focused on one-dimensional drug-to-gene interactions," said Ghoury. But the reality of drug prescribing is much more complex than one drug to one specific genetic variant. "If you look at patient's renal function, or if they have a heart murmur, the risk of an ADE goes way up. So we are using the FDA [data] as a baseline, but then we are

Interpreta Founder and President Raghu Sugavanam and CEO Ahmed Choury



MF3d / Getty Images

using AI to say a person with a certain condition has a 97% chance of having an ADE versus a 42% chance in the absence of the co-existing condition."

Other data leveraged in this process—in real time—include those from the electronic medical records, insurance claims, pharmacy data, genomic data, and information from the National Committee for Quality Assurance (NCQA).

Rare Disease Diagnosis

Whole-genome sequencing has made significant inroads to help doctors sniff out and treat Mendelian diseases quickly in neo-natal care. While the high-mortality rate cases will get the press, AI is also making inroads in the diagnosis of rare diseases that may not be a matter of life and death, and can significantly shorten the diagnostic odyssey that awaits so many patients and families.

Facial analysis company FDNA is leveraging AI for facial patterns, essentially automating the task that geneticists have used for years of looking for specific facial traits as clues to the basis of rare genetic diseases. What FDNA does via its facial recognition engine is to effectively broaden the base of available facial images used to reach a diagnosis.

"Geneticists would look at tell-tale signs in patients' faces and would take pictures of them, to help them reach a differential, or suspected diagnosis," said Dekel Gelbman, CEO of FDNA. "We are able to use de-identified photos of patients, classify them into syndromes based on the common patterns in the face—much the way a geneticist would. But we are bringing a much broader set of data and different patterns that they might not have seen in their professional experience."

The technology, when combined with the genomic data from patients, can also help tie variants of unknown significance (VUSes) to specific rare diseases, essentially linking the phenotype with the genotype. "As we look into the future AI will change the role of the geneticist and instead of being a diagnostician, they will become a treating physician, more involved in therapeutics and clinical development, and I think that is what geneticists want too," Gelbman added.

New Diagnostics

At AI-powered genomic diagnostic company Freenome, company CEO Gabriel Otte sees the potential of AI to upend how diseases are diagnosed. He points out that most clinical diagnostics that have been on the market for years experience significant declines in accuracy, a function of the stripped-down approach often taken by companies developing these low-margin tests.

Freenome, which is developing blood-based diagnostics and is currently working to attain premarket approval for its colorectal cancer test, has taken an approach to identify as many biomarkers as possible in the blood and then apply these signatures using AI to the diagnosis of disease.

"We have affected artificial intelligence on the software side to hone in on the signals that are relevant for a specific test," Otte said. "We do this in the software as opposed to in the laboratory. What this enables is, as we pick up on novel signatures that others haven't, it allows us to change the test. It is about picking up all the signals in first place to make this a software problem and not a lab problem."

Hurdles for AI

While AI is beginning to make an impact in clinical diagnosis and care, there still exist roadblocks to adoption. The biggest of these involve availability and accuracy of the data used to help train these systems.

"There is inherently a small data problem in AI applied to genom-

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ics especially, because we are never going to have billions of genomes sequenced," said Otte. "Most of the AI engines out there that are being built assume large datasets. That is just never going to be the case for healthcare. So anyone using existing AI technologies for this purpose is likely not going to have much success."

At N-of-One the view is a bit different, but it revolves both around the amount of data required and also the accuracy of the data, which is why the company employees its host of Ph.D.s and research scientists to annotate the data it leverages for clinical decision support.

Christine M. Cournoyer, CEO, N-of-One

In terms of using AI for highly precise cancer care, Cournoyer isn't convinced it is ready for prime time.

"We went from AI winning at Jeopardy, to suddenly wanting it to provide information for highly targeted cancer care," she said. "That's too far, too fast."

"I never want to come off as not supporting AI, because I do think there is a way here. We are going to have massive datasets eventually. We just need the right datasets and I don't think we have the right datasets yet," Cournoyer concluded.

Sanford Health to Power Genomic Cancer Care at Ireland's Hermitage Medical

Cancer patients at Hermitage Medical Clinic in Ireland will soon have access to the clinical methods of Sanford Health that will leverage the North Dakota health system's expertise in genomic profiling to inform more precise cancer treatment.

"As part of its strategic intent in the development of research and innovation, the Hermitage Medical Clinic has signed an agreement on Genomic Cancer Testing with Sanford Health, one of the largest health systems in the world. Through this collaboration we are now able to bring patients, in Ireland, a world-class Genomic Cancer Testing service," said its Chief Executive, Eamonn Fitzgerald, in a prepared statement.

Under the agreement, Hermitage Medical physicians will launch a clinical program to discover how genomic profiling patient tumors might lead to more targeted and precise cancer treatment for patients. The program is modeled after Sanford Health's Genetic Exploration of the Molecular Basis of Malignancy in Adults (GEMMA) and Community Oncology Use of Molecular Profiling to Personalize the Approach to Specialized Cancer Treatment at Sanford (COMPASS) programs, which are studying the use of molecular testing to personalize cancer treatment and measuring associated patient outcomes.

"This is just another way we are trying to make a difference around the world," said Jonathon Bleeker, M.D., an oncologist with Sanford Health. "Our ability to collaborate with the providers who treat patients at this clinic will help advance treatment options in Ireland."

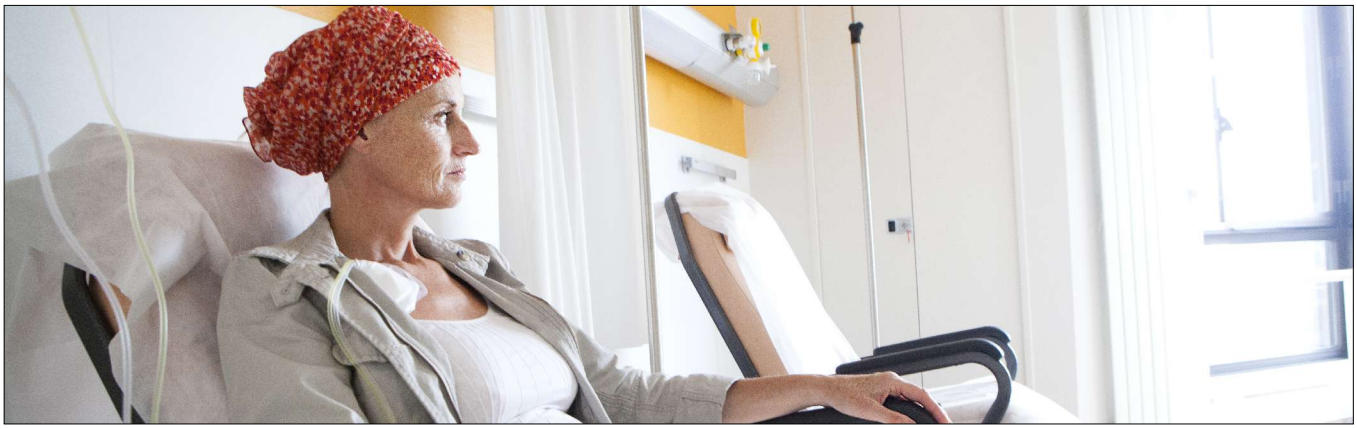
The Sanford program also makes a genetic tumor board from Sanford available to the care team at Hermitage via video conference. The board will work in concert with Hermitage physicians to help create personalized care plans the leverage the information of each patient's genomic test.

"We know from experience that our tumor board and our use of genomic medicine in cancer makes a difference in developing treatment plans for patients," said Dan Blue, M.D., executive vice president of Sanford World Clinic, in a press release.

The collaboration is a part of a planned expansion of Sanford World Clinic, Sanford Health's international health care arm, which is now deployed in nine countries with more than 30 locations. Sanford World Clinic also announced new initiatives in New Zealand, Vietnam, Costa Rica and South Africa. It already has working clinics in Ghana and China, and also owns a minority stake in a clinic in Germany.

Paper Boat Creative / Getty Images

UCSF Researchers Release Gene–Drug Interaction Map for Chemotherapy



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Researchers at the University of California, San Francisco (UCSF) have generated a detailed, quantitative gene–drug interaction map as an open resource that could help clinicians prescribe the most effective type of chemotherapy for each cancer patient, based on their tumor's genetic profile.

The UCSF scientists say that as well as allowing researchers to predict how genetically defined human cancer cell lines respond to different chemotherapy agents, the map has uncovered new genetic factors that appear to determine how breast and ovarian tumors respond to common chemotherapy drug classes. As proof of principle, they used the gene–drug interaction map to identify two gene mutations that appeared to contribute to ovarian cancer resistance to poly (ADP-ribose) polymerase (PARP) inhibitors, and confirmed their finding in patients participating in a clinical trial.

"We know very little about how gene mutations in tumor cells can change how a tumor might respond or not to certain chemotherapy drugs," said Bandy Opadhyay, a member of the UCSF Helen Diller Family Comprehensive Cancer Center and the Quantitative Biosciences Institute. "We're trying to take a systems view of chemotherapy resistance. With rarer mutations in particular, there aren't enough patients for large clinical trials to be able to identify biomarkers of resistance, but by considering all the different potential genetic factors that have been identified together in one study, we can robustly predict from experiments in laboratory dishes how cancers with different genetic mutations will respond to different treatments."

The vast majority of cancer patients receive chemotherapy, but the decision on which of the more than 100 chemotherapy agents to use is often based on historical average response rates, rather than on an understanding of genetic factors that may impact treatment efficacy or tumor resistance. "Choosing from multiple possible chemotherapy options can complicate clinical decision making," the researchers wrote. "Therefore, optimizing the use of chemotherapies is a significant and pressing challenge in precision oncology."

The team is making their chemical–genetic interaction map publicly available, with the hope that it will provide valuable new insights into the biological basis for chemotherapy success and failure, and potentially help researchers identify effective new chemotherapy combinations against tumors with specific genetic signatures.

"This work highlights the utility of a systematic chemical–genetic interaction map as a resource for the identification of clinically relevant biomarkers of drug susceptibility, as well as a foundation for integration with other cancer datasets to enhance drug and biomarker development," the authors noted. "This quantitative map is predictive of interactions maintained in other cell lines, identifies DNA-repair factors, predicts cancer cell line responses to therapy, and prioritizes synergistic drug combinations. In contrast to most standard genetic screens, this approach provides a quantitative readout that approximates genetic interaction strength and allows for the comparison of responses across many drugs."

Biomarkers and Immuno-Oncology World Congress

June 11–13, Boston

Now in its 14th year, the Biomarkers and Immuno-Oncology World Congress is the annual meeting of choice for those dedicated to biomarkers, diagnostics, and immuno-oncology research and implementation. The congress brings together a mix of large and medium pharmaceutical, biotech, and diagnostics companies, leading universities and clinical research institutions, government and national labs, CROs, emerging companies, and tool providers. Join more than 400 attendees to browse the exhibits and for an agenda that includes sessions covering: clinical and translational biomarkers, immuno-oncology biomarkers, combination immunotherapy, biomarkers for patient selection, intrinsic and acquired resistance to immunotherapy, and digital biomarkers encompassing wearables, biosensors and mHealth.

Molecular Diagnostics

July 9–10, London

The SMi group will convene the 5th Molecular Diagnostics Conference amid significant growth in molecular diagnostics market that is forecast to reach more than $10 billion in the next three years. The conference features presentations to help attendees say up to date with emerging diagnostics technologies and their applications, as well as how to manage within the challenging to evolving regulatory landscape. Other themes at this year's event include: personalized medicine and pharmacogenomics, point-of-care diagnostic methods, and molecular diagnostics for infectious diseases and cancer. Sessions of note include "Cancer Research UK's strategy in early detection research—precision diagnostics to precision intervention" by CRUK's, head of early detection research David Crosby; and "System's Approach to Immune monitoring—A path towards establishing genetic and microbial determinants of human immune variability" by Matthew Albert, principal scientist, cancer immunology, Genetech.

AACC Annual Scientific Meeting & Clinical Lab Expo

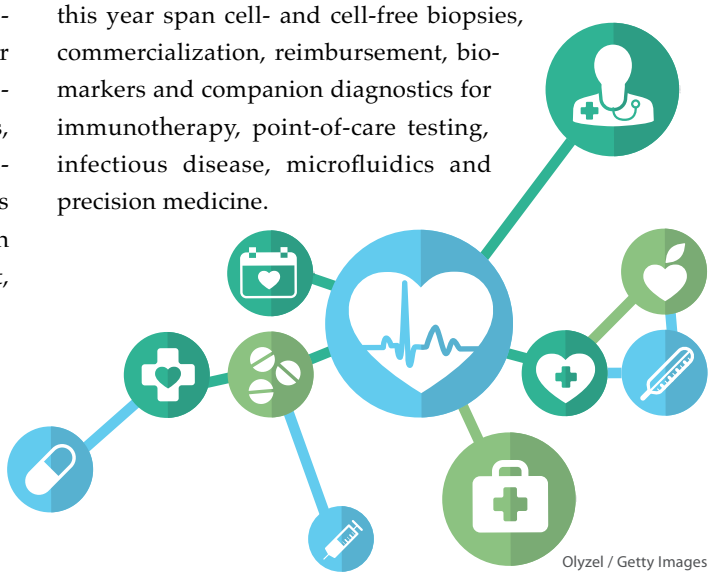
San Diego, July 29–August 2

Join more than 20,000 healthcare leaders at the 70th AACC Annual Scientific Meeting & Clinical Lab Expo to see the newest technologies and learn techniques for medical testing to allow patients to receive the highest quality of care. Network with attendees and presenters representing the disciplines of clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of emerging science in laboratory medicine. This year's meeting features more than 200 educational opportunities in the form of lectures, plenary sessions, symposia, short courses, and roundtable sessions, and the exposition hall will show products and services from more than 750 participating companies.

Next Generation Diagnostics Summit

August 14–16, Washington, DC

Now in its tenth year, the Next Generation Dx Summit attracts more than 1,000 international diagnostic professionals providing insight to this growing field. As the market demands faster and more precise diagnostics, and regulatory and reimbursement conditions continue to evolve, the conference provides opportunities for diagnostic professionals to build partnerships, gain industry knowledge, and network with and learn from their peers. The summit provides a venue to advance the science of diagnostics and improve the practice of medicine. Sessions this year span cell- and cell-free biopsies, commercialization, reimbursement, biomarkers and companion diagnostics for immunotherapy, point-of-care testing, infectious disease, microfluidics and precision medicine.



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