Denise Myshko

The Genome: *The Next* 10 Years

Despite the promise of advancements in understanding the human genome, significant challenges remain for bringing products to market that take advantage of this evolving discipline.

In just one generation medicine will take a huge leap forward. That is, if researchers are right about how data from the human genome can be used to address disease. There has been a great deal of optimism about how sequencing the human genome might create new diagnostics and new medicines.

Ten years ago, when we had our first look at the human genome, it was thought that the era of personalized medicine was just around the corner. In reality, it has proven to be much more difficult to take the discoveries stemming from the unraveled genome in the lab and translate them to therapies.

Biology, it turns out, is far more complicated than first thought. Researchers have discovered there are plenty of disease-relevant targets available, but that doesn't automatically mean a therapy can be developed to address that target.

"Identification of genetic changes that are causing a disease doesn't always lead to development of drugs that can cure or slow down the disease progression," says Sridaran Natesan, Ph.D., scientific site head of R&D and head of external innovation and parftnering at Sanofi-Aventis. "The question remains: is the gene druggable? In other words, with the tools and technologies currently available, can we develop small molecules or biologics that can modulate the function of the gene attributed to the disease?"

Thomas Turi, Ph.D., VP, science and technology, discovery and translational services, and VP, biomarker center of excellence, at Covance, says genomics, as a discipline, needs to begin early in the development process.

"The goal of the human genome project (HGP) was to understand, sequence, and define the human genome," he says. "This goal was met, absolutely. The HGP delivered under budget and before the actual deadline. Genomics as a science is only about 15 years old, and the real fruits of those initial forays of applying genomics to developing medicines are just beginning to emerge."

Dr. Turi says in retrospect, there was probably a little too much hype around genomics initially; there was a lot of excitement and enthusiasm from the scientific community that genomics could and would change the way drug discovery and development would be done.

> "Eventually, a genomic test is going to be as routine as a blood test."
>
> **DR. CLIFFORD REID** / Complete Genomics

"When we first entered into genomics perhaps there were some misconceptions about how easy it would be to go from a set of DNA sequences to a validated target to a fully launched drug discovery and development program," he says. "We forgot that there was a little something called biology in the middle of the process."

Additionally, Shaf Yousaf, president, genomic analysis, at Life Technologies, says after the first genome was sequenced scientists didn't understand what it all meant, which led to some initial disappointment.

"The number of genes in the genome was 20,000 instead of the 100,000 that some expected," he says. "At the time, some thought this was called 'junk DNA' simply because the data weren't well understood."

To be fair, sequencing the human genome has led to tremendous advances in knowledge.

"The list of clinically useful genetic markers is growing, and the list of drugs that are best used with the aid of genetic information is also expanding," says Oren Cohen, M.D., chief medical and scientific officer at Quintiles. "Examples include HER-2 and KRAS testing to guide cancer treatment; cytochrome P450 testing to guide warfarin dosing and estimate the likelihood of response to clopidogrel; HLA typing to estimate the likelihood of developing abacavir hypersensitivity syndrome; and IL-28B testing to guide therapy for hepatitis C infection."

Dr. Cohen says sequencing technology continues to advance at an astonishing rate.

"With today's sequencing technology, it is possible to accurately sequence a human genome in about a 1.5 days at a cost of less than a tenth of a penny per thousand base pairs," he says. "This extraordinary pace of technological breakthroughs has enabled us to study genomics at a population and disease-specific level. Although still in its infancy, we're starting to be able to answer questions about genetic markers of disease, prognosis, response to therapy, and drug toxicity."

> "It was very simple at first: find genes. Later, the process became more challenging."
>
> **DR. THOMAS TURI** / Covance

New Technology

Now technology is allowing researchers to address this complicated science. New and better tools are being developed that can bring down the cost of gene sequencing, do the sequencing faster, and provide ways for managing and assessing the vast amount of generated data.

Some industry experts are still optimistic, despite the initial setbacks, that the knowledge and insights gained from sequencing the genome, as well as the technology advancements, will be truly transformative in the next 10 to 20 years, and that there will be a great deal of investment in this area.

Panna Sharma, CEO of Cancer Genetics, says the advances that will be made in applying genomic information to personalized medicine will be staggering.

"There is going to be a tidal wave in the next 10 years to 12 years," he says. "The last 10 years were about putting all of the technology, processes, and infrastructure together and ensuring that they worked consistently and reliably. The expectation that we would be pumping out dozens of new drugs by now was not realistic. This is just not feasible given the number of years it takes to get a new drug to market and given the number of years it takes to put a new, proven research and development infrastructure in place."

Mr. Yousaf agrees that this is a revolutionary period in the life sciences.

"Already there are pilot trials that are analyzing the sequence of a tumor, the sequence of the normal cells of the patient, and then researchers are looking at the metabolic vulnerability of the tumor as a way to design a new drug therapy," he says. "Within 10 years, this type of methodology should become routine in the treatment of cancer and genetic diseases."

TIPS

Implementing Genomic Strategies

- Begin by incorporating genomics or genomic-based approaches early in discovery and development programs. It takes time to understand the biology and variations within patients.
- In addition to identifying a gene's relevance to disease, identify the pathways affected by a gene. If the gene is not "druggable," it may be possible to develop a drug downstream or upstream from a particular target.
- Work internally and externally with partners who understand genomics and how to apply that in the drug discovery and development environment.

Source: PharmaVOICE

Mr. Sharma points out that the pieces are now in place to move the discipline forward.

"We have a better understanding of the genome's nuances, and a number of companies are making rapid strides in this area," he says. "Technology is now robust in a way that wasn't expected even five years ago. Costs are coming down rapidly. And the regulatory bodies, the major pharma and biotech companies, and government consortium are working aggressively on initiatives to put some parameters around how they can compare and synthesize genomic data and how this will impact clinical trials. All of the forces are coming together."

Dr. Cohen says sequencing technology has raced far ahead of our ability to synthesize and make sense of the massive amounts of information generated.

"This requires sophisticated information technology, a deep understanding of biology, and lots of creativity," he says. "While genomics has not yet fulfilled its promise, this is only because of our simplistic assumption that simply having DNA sequence information

> Knowledge about disease biology keeps changing, and our understanding of disease mechanisms keeps getting better.
>
> **DR. SRIDARAN NATESAN** / Sanofi-Aventis

> Pharma companies have been slow to fully adopt some genomic technologies and approaches simply because the small-molecule machine continues to work.
>
> **PANNA SHARMA** / Cancer Genetics

> The power of the new sequencing technologies is causing a revolution in genomics and its application to medicine.
>
> **SHAF YOUSAF** / Life Technologies

available would be sufficient to yield clinically meaningful insight, but the future is very bright indeed."

The Economics of Sequencing

Efforts to sequence the genome have been challenged by economic issues, says Clifford Reid, Ph.D., chairman, president, and CEO of Complete Genomics.

"When the first human genome was sequenced in 2000, there was a real ground swell of interest in understanding the genetic basis of disease based on a working hypothesis that a very small portion of the human genome was medically relevant to uncover the medical secrets and the rest was unimportant," he says. "This supposition turned out not to be true. There is a significantly large fraction of the genome that has medical relevance. But the measurement tools available at the time were too expensive. No researcher could go through these large portions of the genome to determine the genetic cause of disease and then conduct a study big enough based on the findings."

Several promising technologies in development now may make the "druggabilty" less of an issue in the future, and if these efforts are successful they will undoubtedly open the door for faster development of new classes of therapies for a variety of diseases.

"The latest estimate is that in five years the cost to sequence a complete genome could be just a few thousand dollars or less," Dr. Natesan says. "This is going to help the pharmaceutical industry significantly. There are a lot of diseases that we would like to understand in greater detail at the genomic level but the costs have been very prohibitive; it used to cost hundreds of thousands of dollars to sequence a human genome. Pharma companies will be able to put efforts into undertaking larger studies to understand disease mecha-

Personalized Medicines Are Shaping R&D

Personalized medicine development is leading companies to change their R&D paradigms, including how they make go/no-go decisions, according to a recently completed study by the Tufts Center for the Study of Drug Development.

The study found:

- The magnitude of resources required to create personalized medicines means developers must team with multiple external partners, presenting challenges for project stewardship and intellectual property rights.
- Biomarkers increasingly are used to better understand patient response, but companies still cannot use biomarker data to support approval until the regulators' capacity to evaluate the information catches up to the science.
- Oncology leads other therapeutic areas in the number of personalized medicines on the market as well as in the pipeline with the expectation that within the decade all oncology drugs will have a related diagnostic component.
- Other key therapeutic areas in which personalized medicine is making headway include: cardiovascular, central nervous system, and immunologic therapies. Personalized medicine development is just getting started for metabolic and respiratory therapies as well as virology.

Source: Tufts Center for the Study of Drug Development. For more information, visit csdd.tufts.edu.

> "Today, we are beyond what was thought possible based on what sequencing the genome has meant and the rate of next-generation technology advancements."
> **KEVIN HRUSOVSKY** / Caliper Life Sciences

Global Value of DNA Sequencing Products by End-Use Application (through 2015)

Application	2009	2010	2015	CAGR% (2010-2015)
Research, drug discovery/development	$822.3	$920.1	$1,694.2	13.0%
Commercial applications	239.1	241.6	615.1	20.6
Workflow solutions	108.2	139.4	497.2	29.0
Emerging applications	12.2	15.5	541.4	103.5
Total	1,181.8	1,316.6	3,347.9	20.5

Note: Dollars in millions
Source: BCC Research. For more information, visit bccresearch.com.

nisms if the whole genome sequencing cost gets cheaper."

Mr. Yousaf points out that the first genome sequence took about seven years to complete and cost about $300 million.

"We can now sequence a complete human genome within about two weeks at a cost of about $6,000," he says. "Now, many more human genomes have been sequenced, and the role of DNA in disease is much better understood."

Kevin Hrusovsky, president and CEO of Caliper Life Sciences, believes the cost of sequencing will continued to decline.

"In the next few years, the cost will be $100 to $1,000," he says. "There is already an evolution afoot. Next-generation sequencing technology is being developed. Current technologies require a lot of PCR, which is an artificial way to chemically amplify the DNA that creates biases and false positives. Newer technologies are attempting to reduce the amount of sample that is needed, perhaps even to a single molecule that is much longer. There is a fourth generation of sequencing technology being developed by IBM, called a DNA transistor, which might possibly reduce the cost to $10 to $100 per genome, but this technology is probably 10 years away."

According to BCC Research, the worldwide market for sequencing products will grow from an estimated $1.3 billion in 2010 to more than $3.3 billion by 2015.

Life-sciences research and drug discovery and development applications represent the two largest markets for DNA sequencing revenue, accounting for about $920.1 million in 2010. Analysts predict that these markets are forecast to grow at a compound annual growth rate of 13% to reach almost $1.7 billion in 2015.

Translational Efforts

Dr. Reid sequencing the genome provides a whole new set of addressable targets for the pharmaceutical industry to pursue.

"For the first time, researchers can tap hundreds of people with a disease using very high-accuracy sequencing tools and narrow down the potential causes for the disease to either a single gene or a handful of genes that are acting in concert," he says. "In the case of cancer, for example, there is a need to sequence not just one person but hundreds of people with the same cancer. We also need to sequence patients multiple times as the cancer evolves to see the patterns of mutation and use that information to change the course of drug therapy throughout the development of the tumor. This is how cancer will be treated in the future."

But Mr. Yousaf points out that at the moment translational genomics is very much an art.

"The challenge is that there isn't enough basic or even applied research available yet that relates DNA variation to disease," he says. "We need two or three more years of basic research to try and work out some of the disease mechanisms."

Jerry Coamey, senior VP, practice leader, personalized healthcare, at CAHG, says two of the most critical challenges are the approval gap and the knowledge gap.

"The combining of a diagnostic with a therapeutic is one of the greatest opportunities in genomics-based medicine, but the current drug approval process is not set up for that…yet," he says. "The FDA has a great opportunity to identify, clarify, and simplify the process for parallel approval of a companion diagnostic/therapeutic. To their credit, the agency has begun work in this area. The second challenge and opportunity is for industry to educate one of its most critical customers: the physician end-user of these new genomics-based tests and targeted therapies. As our landmark physician study reveals, they acknowledge a critical need for education and information about all aspects of genomics-based medicine, but also acknowledge being open to receiving that knowledge from pharmaceutical and molecular diagnostic companies, as well as their sales representatives."

One company making great strides in this area is Sanofi-Aventis. The company had significant efforts in the use of high throughput genomic technologies such as gene expression profiling to find targets for pharmacological manipulation.

"We identified several novel targets for different therapeutic indications and are currently in the process of validating them," Dr. Natesan says.

Dr. Natesan says going forward the therapeutic departments in the company will do any large scale genomic studies instead of dedicated genomic centers.

"We still have significant internal capabilities to do high throughput genomic studies when there is a need," he says.

Mr. Hrusovsky cautions that companies need to also think beyond the genome.

"Companies may think genomics is the only piece of puzzle," he says. "In fact, the genome itself is only half the equation. There are other factors that affect health. For the first time in U.S. history, a child born today has a shorter life expectancy than his or her parent. And the reason is obesity. There are so many factors in play that go beyond purely the genome. That's why we think the genome is

just one of the three themes impacting healthcare. We believe that biomarkers and imaging will also play an extraordinary role."

In a review of the trends in the diagnostic area, Mr. Hrusovsky has outlined several factors that will be critical for healthcare going forward.

"Eventually, when people are born they will have their genome sequenced and this will provide information about what their particular mutations are that make them unique," he says. "Additionally, biomarkers will play an important role in discovering the various mutations that a patient has, which will allow drugs to be tailored to the individual. About 40% of drugs coming to market have some type of genome marker or protein marker related to them. It is extraordinary to think that we are that far along and have companion diagnostics with drugs."

The third factor, Mr. Hrusovsky says, involves diagnostic imaging.

"Our theory is that over the course of time, it's not just about the DNA and what is going on in the body, but the environmental factors a person is exposed to," he says. "Many times environmental factors create conditions that an image will help understand. Sometimes we can see things with an image that we never would have been able to detect with a genome." PV

> "We are starting to be able to answer questions about genetic markers of disease and response to therapy."
>
> **DR. OREN COHEN** / Quintiles

USE YOUR SMART PHONE'S QR CODE READER TO ACCESS MORE ON THIS TOPIC.

> "The FDA has a great opportunity to clarify and simplify the process for approval of companion diagnostics/therapeutic."
>
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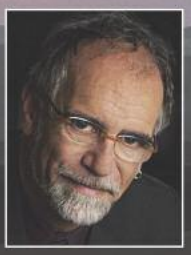

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Denise Myshko

The *Complex* Task of Managing Data

Managing data is one of the bigger technical problems associated with genome sequencing. The answer might just be the cloud.

FACT

THE GLOBAL BIOINFORMATICS MARKET IS EXPECTED TO REACH $8.3 BILLION BY 2014, A CAGR OF 24.8% FROM 2009 TO 2014.

Source: MARKETSandMarkets

> **"Current Internet connections in most institutions are relatively small. Moving vast amounts of data through these is like sucking the ocean through a straw."**
>
> **DR. PAUL ALDRIDGE** / Genomic Health

The amount of data being generated via genomic research and gene sequencing is huge, so vast that the industry has been unable to keep up.

The challenge of managing genetic information caught the industry by surprise, says Clifford Reid, Ph.D., chairman, president, and CEO of Complete Genomics.

"The old generation of tools produced very little data, and these data were well managed by a spreadsheet," he says. "But as the cost of generating data went down, the amount of data generated went up. In the last few years, we completely blew out the spreadsheet model of data management."

The discipline of genomics and informatics is very resource intensive, says Sridaran Natesan, Ph.D., scientific site head of R&D and head of external innovation and partnering at Sanofi-Aventis.

"It is difficult for pharmaceutical companies validate the hundreds of targets that come out of 'omincs' research, and they have had to rely on academia or biotech partners to validate most of these targets," he says.

Shaf Yousaf, president of genomic analysis at Life Technologies suggests that new disciplines within medicine will be needed to determine how genomic data are analyzed, stored, and tied to patient clinical data before the information can be used by doctors for new therapies.

Dr. Natesan says in addition to the large amount of data being generated — which cannot be easily interpreted — the reliability of the information is also an issue.

"There have to be better analysis tools developed to make the data reliable," he says.

Under the Cloud

Currently, while there is no computing power in place that can harness the vast amount of information being generated, Kevin Hrusovsky, president and CEO of Caliper Life Sciences, says there are advances being made in the computer industry, such as cloud computing.

"The cloud could significantly increase the power needed, by as much as a hundred times the current level," he says.

> **"People think they can press the easy button and the cloud works magnificently, but the cloud still has complexity to it. In reality, the cloud is probably an 'easier' button."**
>
> **DAVE POWERS** / Cycle Computing

FACT

WORKFLOW SOLUTIONS, WHICH INCLUDE SEQUENCE CAPTURE AND BIOINFORMATICS, ACCOUNT FOR $139.4 MILLION IN THE 2010 DNA SEQUENCING MARKET AND ARE FORECAST TO REACH $497.2 MILLION BY 2015.

Source: BCC Research

Cloud computing has the potential to address the data management/data storage needs of genomics, says Dave Powers, business development at Cycle Computing.

"Cloud computing is a disruptive technology, especially in large enterprises on two different levels," he says. "First, it reduces the time needed from weeks to minutes. Second, there is transparency of cost. Companies know exactly how much it's going to cost to launch those machines or use this much storage."

Mr. Powers predicts that in five years a significant percentage of a corporation's infrastructure will exist in the cloud, whether that consists of servers or storage.

Complete Genomics is addressing some of the issues; through an outsourced service the company can process raw data and provide a small set of finished, medically actionable data.

Paul Aldridge, Ph.D., chief information officer, Genomic Health, says his company uses the cloud for those times when the computation burden is greater than its internal computing and storage capabilities.

"Rather than build a data center and buy servers and populate them, which can cost tens of millions of dollars, we partner with a technology company to extend our capabilities," he says. "By using the cloud on demand, we only have to pay for the hours or days we use. And when we are done, we can pull the data back inside and work on the result.

"We're a small company and we want to be in the diagnostics business not in the data center business," he adds. "The math and computations that are required for some of the analysis we want to do are enormous. We want to be able to scale up that capability in the cloud on demand."

Dr. Aldridge says the one drawback is that standards and technologies are still emerging.

"We are still experimenting," he says. "We've done some experiments that have been successful. The longer term issue is determining how we can seamlessly create a hybrid model with internal and external capabilities." PV

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