SYMPOSIUM

Sequence Thyself: Personalized Medicine and Therapies for the Future

2012 Yale Healthcare Conference

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Now in its 8th year, the Yale Healthcare Conference has arguably come upon its most exciting and dramatic time within the U.S. health care system. Dynamic speakers from all over the country came together in April 2012 at Yale University to question, debate, creatively think, and examine challenges within health care organizations and institutions. One of the most prominent issues concerned the aftermath of sequencing the human genome and the explosion of information concerning gene polymorphisms and biomarkers in health and disease. Clinicians, scientists, and pharmaceuticals are looking to innovative individually tailored treatments for patients. During the conference breakout session, speakers Thomas Lynch, MD, director of the Yale Cancer Center and physician-in-chief of the Smilow Cancer Hospital, and Zen Chu, MBA, co-founder of Accelerated Medical Ventures and entrepreneur-in-residence at Massachusetts Institute of Technology, provided enriching discussion on the delivery of science and genetic care of the individual.

Genetic and genomic care is no longer the care of the future. Sequencing the first human genome began in 1988 and was completed in 2000. According to the National Human Genome Research Institute, the 12-year process cost about $2.7 billion [1]. Only 13 years after sequencing the first human genome, the scientific community has the power to determine the genetic sequence of cancer. The science of genome sequencing is routinely being performed on the West Campus of Yale University. Dozens of other universities have genome sequence centers, and several private companies are also working with this technology.

When analyzing the advancements with common solid tumors (such as breast, colon, prostate, and lung), outcomes of
these patients with advanced disease are not much different than in 1965. At the eighth annual Yale Healthcare Conference in April 2012 at Yale University, Dr. Thomas Lynch, director of the Yale Cancer Center and physician-in-chief of the Smilow Cancer Hospital, spoke to this issue.

“Though we have longer survival rates (20 to 30 percent), cure rates are not dissimilar to 45 years ago,” Lynch said.

What has provided a different approach to disease and illness is the ability to perform whole exome sequencing. Science and technological advancements have found that the majority of disease-causing mutations have been found in or around exons; therefore, the development of this technology to selectively sequence short coding regions of the genome has been in effect since 2009 and has been a paramount advancement. Exome sequencing (also known as targeted exome capture) is an approach that selectively sequences the coding regions of the genome (short sequences of DNA that represent regions in genes that translate into proteins) and is a cheaper alternate to whole genome sequencing [2]. The application of whole-exome sequencing spans from the “discovery of genes and alleles contributing to Mendelian and complex traits, to somatic mutations in cancers” [3]. The information that comes from these protein-coding regions is pertinent to the clinician, as it is estimated that 85 percent of disease-causing mutations stem from these protein-coding regions [3].

Research centers at Yale can do deep sequencing of cancer relevant genes within about 2 to 3 days of receiving a specimen and, when adding bioinformatics to the process, aspire to run and return data back to a clinician within 8 to 10 days. The science of sequencing has the potential to be clinically relevant in genetic diagnosis due to the current understanding of functional consequences in sequence variation [3]. In other words, by identifying underlying gene mutations, diagnostic and therapeutic methods can guide the projection of disease pathology and allow the identification of at-risk family members [2,4].

In a study by Choi et al. (2009), patients who underwent exome sequencing and were thought to have Bartter syndrome (a renal salt wasting disease) were found upon genetic analysis to instead possess congenital chloride-causing diarrhea, a mutation in SLC26A3. While evidence of salt wasting could easily have been mistaken for Bartter syndrome, this genetic discrimination was pertinent for clinical care as volume depletion was triggered by gastrointestinal losses from watery diarrhea and not renal losses [3].

Lynch purported that the advent of the $1,000 genome will soon be a reality and will allow for even greater use of these technologies. He said the potential for these technologies lies in providing clinicians with an idea of potential targets, yet challenges have surfaced in targeting these mutations and aberrations to pharmaceutical industries. This suggests that though the medical community might know the cause of a disease, industry and pharmaceutical companies are needed to develop tools and drugs in order to find a cure.

While these advancements are helpful to the medical and scientific community, there are still hurdles to overcome, such as the interpretation of these genetic advancements, specifically bioinformatics and computational analysis of data. With regard to whole exome sequencing, one of the challenges lies in the very number of variants found in individual exomes. It has been reported that each genome has 165 homozygous protein-truncating or stop loss variants in genes that represent an array of separate pathways [5]. This means that in order to use output data in a medical context, the very finding of a sequence variant cannot be taken as proof that a variant is causally related to a disease, but rather that the output must be put in a computational analysis that takes into account phenotypes, the prioritization of sequence variants, and makes use of information from multiple databases to interpret the significance and clinical implications [6]. Lynch gave an example of a 33-year-old patient who came in with lung cancer and had a whole exome sequence performed. Results showed all actionable genes were considered wild type normal, but the mutations that the patient possessed were all very hard to treat pharmacologically. The scientific and medical community, Lynch said, needs to come to...
gether to come up with tools to target these mutations and develop a more comprehensive treatment for cancer. “It is an exciting time to be thinking about cancer and how it can be treated,” Lynch said.

Also speaking at the conference was Zen Chu, co-founder of Accelerated Medical Ventures and entrepreneur-in-residence at Massachusetts Institute of Technology. Chu comes from a different world altogether. As an investor and biomedical engineer, he highlighted the need to figure out solutions to data overload. This data information overload from whole genome sequencing is “untenable,” he said, and there are still limitations with tools that need to be addressed. The problem of data overload has been coupled with the problem of needing tools to aid scientists and clinicians in interpretation of genetic code. Chu spoke from his background funding a traditional company out of MIT that went public in 2011 and his work with George Church (Professor of Genetics at Harvard Medical School and serial entrepreneur) in creating focus teams to help drive the cost of sequencing down. He noted that these advancements in genomics have been five times that of Moore’s law (whereby the number of transistors on a chip roughly doubles every 2 years). The scientific community is moving to the mythical $1,000 genome, but the interpretation needed to make sense of this is necessary and technology can help medicine’s needs.

Both speakers focused on the need for software and hardware to understand the hundreds of targets of potential variants in order to figure out what disease could best be treated pharmacologically.

Chu suggested a collaborative and interactive team to attack this data overload problem. Software specifically needs to make sense of variants and techniques for output, and it has implications both for clinicians attempting to treat patients and patients in their decision making. Ways of displaying conceptual information include the ability to convey information and tell a genomic story to a health care provider, patient, or scientist in a concise and succinct manner. The goals are to solve the problems being faced right now in the industry and interpretation. Chu provided an example referring to the National Comprehensive Cancer Network’s guidelines that comprise pages upon pages of evidence-based cancer recommendations and treatments. He commented that these documents are un navigable and are a series of considerations upon considerations. Lynch said, “These decisions have gotten so complex, we need doctors to have tools to help them through this.” Chu and Lynch both spoke of the need to go out into the community and disseminate information and recommendations in a manageable manner to clinicians. They underscored the need for gatekeepers such as bioinformatics and genetic experts to provide clinicians with the authority to use a powerful tool in the ugliness of the data and go through the vast expanse of evidence-based data and variants, both pathogenic and actionable, and make sense of what this means for our patients, the goal being personalized and evidence-based guided treatment.

While there are challenges in genomic interpretive software, Massachusetts-based Foundation Medicine is changing the forefront of genomic medicine [7]. While it has been common for a patient with cancer to receive genetic testing for a panel of four genes that have been identified as strongly associated with a particular cancer, this methodology has not been overtly helpful for physicians. What Lynch and Foundation Medicine suggest is to immediately sequence a massive super panel of 300 genes that would be more informative and time effective in terms of risk and treatment. Foundation Medicine uses DNA from cancer biopsy tissue to sequence up to 300 cancer-related genes for all potential somatic alterations while providing evidence levels for targeted therapies and providing individual, actionable information to clinicians in a streamlined, easily accessible way. While many companies produce whole exome sequencing, Foundation Medicine has the ability to provide information in handling the results, and this is not yet available elsewhere. Companies such as Foundation Medicine hope to provide clinicians with tools
similar to those in an academic medical center to not only investigate the origin of cancer but to examine the origins of all mutations associated with a particular cancer by virtue of trials, preclinical work outcomes, and the creation of giant databases and supersets. Optimistically, these data storage houses will soon be collated into a giant biomarker database and partnered with pharmaceutical companies to provide the best and most innovative care for patients.

Gilead Sciences, Inc. (Nasdaq: GILD) and Yale School of Medicine announced in March 2011 that they would form a partnership to fund $40 million in research support and basic science infrastructure to search for the genetic origins and underlying mechanisms of cancer [8]. Scientists from both establishments are targeting new therapies to overcome drug resistance, identify novel molecular targets, and provide new advancements to the understanding of cancer genetics. With the recently announced Yale Cancer Biology Institute, led by Joseph Schlessinger, PhD, and the Yale Center for Genome Analysis, led by Richard Lifton, MD, PhD, Lynch and Gilead will have the infrastructure of the country’s experts in personalized medicine to target new therapies and approaches to the science of cancer genetics.

All of this should leave us with a newfound confidence in science, technology, industry, and genetics. The scientific and medical community have taken great strides in the last few decades, and the future is bright. While the primary challenge exists in the diagnostic interpretation of variants, the bioinformatics industry has a major part to play in bridging this gap. The goals of these advancements are to eventually have standard ontologies describing the human phenotype, reporting mechanisms, classification systems, and hopefully storage space for sequencing data for the communication and interoperability among scientists, researchers, and clinicians [6,9-11]. While these efforts are under way, a comprehensive database of mutations and phenotypes that would aid data interpretation efforts is not currently available. When this becomes a reality, the ability to connect groups of individuals across the globe, from patients to medical providers, will accelerate efforts, from improved diagnostics to new drug therapies to improved health trajectories [6]. As a multi-collaborative community pursuing a promising path to better science and patient care, we have come a long way from sequencing the first human genome to the abounding abilities of next generation sequencing taking place today. Only through the merging of industry and science will a greater understanding and interpretation of this data be a reality.

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