Precision Medicine leverages most innovative tech advances

Dr. Andreas Scherer

ALMOST 2,500 years ago, Hippocrates captured one of the key principles underlying precision medicine. He stated, "It's far more important to know what person the disease has than what disease the person has."

In the 21st century we take the understanding of the individual characteristics of a person to a new level. By leveraging information about an individual's genome we are able to increase the effectiveness of medical treatments. The goal is to have more successful outcomes by providing targeted therapies. The cost of sequencing a genome has dramatically dropped since the first draft of the human genome sequence was published in 2001. This is a key enabler. Now, it is very much in reach for a wide range of patients to receive a gene panel analysis or even a whole exome/genome analysis. But there is more that is required. Through a collaborative effort between clinicians, pharma companies, scientists and regulatory agencies, we are working on a new framework for standard care on a global basis.

Tailoring diagnostic and therapeutic strategies

Clinicians have known for some time that diseases, as well as the way they are treated can affect individuals differently. Tailoring diagnostic and therapeutic strategies to a patient's individual characteristics is the field of precision medicine. Today, genomics has come to a forefront as a method to detect mutations and confidently diagnose patients.

For the implementation of precision medicine to be viable, there needs to be a biomarker associated with diagnosis, a test to detect the biomarker and a clinical decision in regards to treatment options such as lifestyle changes or selection and dosage of a drug.

DNA sequence-based testing is moving into the clinical realm as a successful means to detect disease causing mutations. However, because sequencing provides extremely large amounts of data, there are some obstacles with data management and analysis with which researchers and clinicians are faced. Knowing the mutation is a large focus, and in many cases there are viable treatment options, but in other rare, genomic diseases there may not be treatment options.

Cancer

Cancer affects everyone either directly or indirectly. There are a growing number of drugs used to treat cancer that can be prescribed and dosed based on the patients' genomic profiles. Not surprisingly, the National Cancer Institute is one of the key beneficiaries of Obama's initiative to further study this area. Some examples of targeted therapies include trastuzumab and crizotinib. Herceptin (trastuzumab) is used to treat breast cancer. The biomarker is the human epidermal growth factor receptor 2 (HER2) overexpression. The HER2 gene is expressed in certain cancer pathways, and the overexpression of HER2 in breast cancer causes a more aggressive form of cancer. Herceptin targets the HER2 gene and turns it off. However, if an individual does not have the HER2 biomarker but is given Herceptin, it is ineffective and may actually cause harm to the patient. More recently, the drug Perjeta has been developed and targets a different part of the HER2 gene. In individuals with the HER2 biomarker, Herceptin and Perjeta are given in combination to more effectively treat this aggressive form of breast cancer (FDA, 2013).

Xalkori (crizotinib) is used to treat some patients with non-small cell lung carcinoma lung cancer if they have an associated biomarker (Roberts, 2013). The biomarker is a mutated anaplastic lymphoma kinase gene (ALK). In patients where a fluorescence in situ hybridization test (FISH) shows a fusion of EML4-ALK genes, treatment with crizotinib is effective. This fusion is oncogenic, and treatment with crizotinib inhibits the oncogene's function (Sahu, 2013).

Predictive medicine and gene panel tests

Predictive medicine includes screening for inherited conditions, inherited cancers, carrier screening and noninvasive prenatal testing (NIPT). Gene panel tests are offered by several companies to determine risk of certain cancers or diagnose inherited and de novo genomic diseases. A commonly used gene panel test is the carrier screen for cystic fibrosis (CF) because CF has a high carrier frequency in individuals of European descent (ACOG Committee, 2011). This test is often offered during family planning or pregnancy. CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator gene (CFTR) (Rommens, 1989). A normal protein functions as a channel that transports chloride ions across cell membranes, which is required for normal mucous production necessary for normal organ functions. There are over 2000 mutations in the CF gene (CF Mutation Database, 2014), and gene panel tests are designed to evaluate a subset of the most common mutations seen in European Americans. Ambry Genetics offers the most robust carrier test, CF Amplified, which is a sequencing based test to determine which CFTR mutations if any exist in the patient (http://www.ambrygen.com/tests/cystic-fibrosis-testing).

Rare diseases diagnosed by whole exome/genome analysis

The use of whole genome and whole exome sequencing to diagnose Mendelian diseases has proven to be successful. One study (Need, 2012) demonstrated how NGS can successfully diagnose unexplained, but likely rare genomic disorders. This study involved the whole exome sequencing of 12 patients (and their parents) and concluded that 6 of the 12 probands had mutations in genes that are causal or related to known Mendelian disorders.

Pharmacogenomics

An emerging field that is integral to personalized medicine is that of pharmacogenomics (PGx). PGx is the study of how an individual's DNA or RNA controls responses to certain drugs. One of the best characterized examples in pharmacogenomics is the Cytochrome P450 family of genes. This gene family includes 60 CYP genes, some of which are enzymes that are involved in drug metabolism. CYP2D6 is an enzyme that is primarily expressed in the liver and is involved in drug metabolism. In fact, approximately 20-25% of all drugs used in the clinical setting are metabolized by the enzyme CYP2D6 (Wang, 2009). Some drugs are substrates for this enzyme while other drugs may inhibit or induce the activity of CYP2D6 (Teh and Bertillson, 2012). Polymorphisms of the CYP2D6 protein cause a phenotypic outcome in individuals, depending on the variant that is in encoded in their own genome. Depending on their genotype, individuals may be poor metabolizers (two non-function alleles), intermediate metabolizers (two reduced-function alleles), extensive

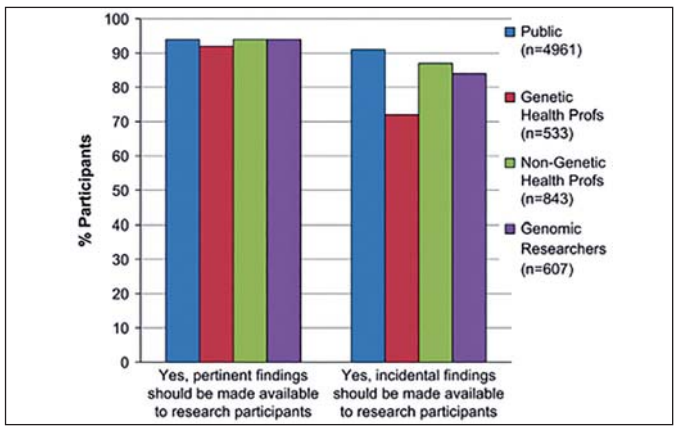

Figure 4.1. The Desire of Study Participants to Be Informed of their Genomic Profile (Middleton, 2015).

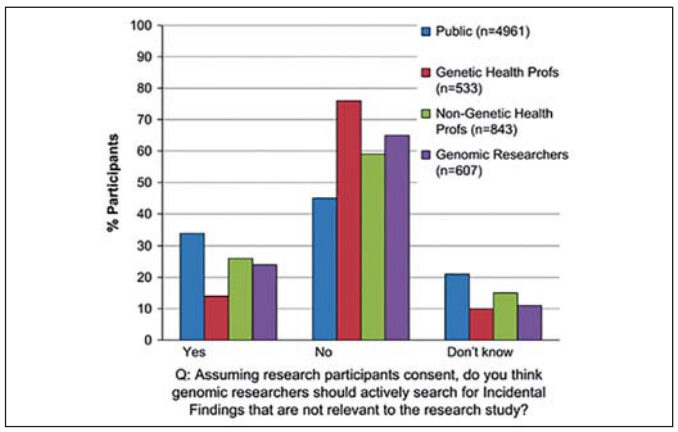

Figure 4.2. Study Participants' Opinions on Whether Incidental Findings Should be Actively Sought by Researchers (Middleton, 2015).

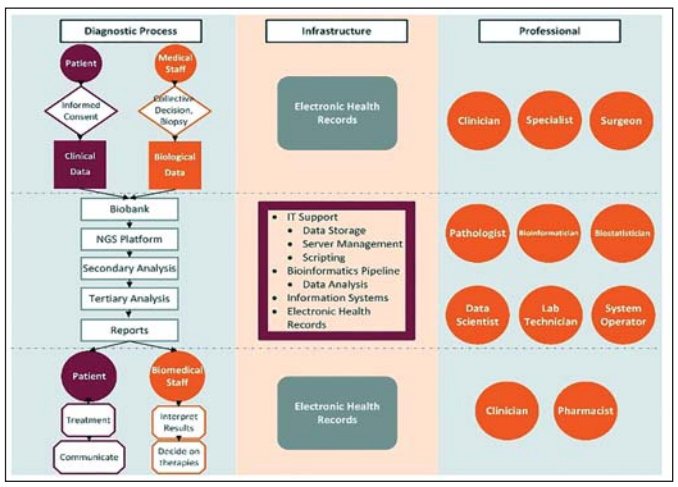

Figure 7.1. The Data Workflow and Downstream Clinical Action of Personalized Medicine.

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Traditional approach leaves lot of room for improvement

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metabolizers (normal allele function) or ultrarapid metabolizers (extra allele copies present in the genome which translate into more than normal amounts of CYP2D6 function). An individual's response to certain drug and dosing of drugs varies based on his/her CYP2D6 genotype (Ingelman-Sundberg, 2005). A patient with extra CYP2D6 alleles will require a higher dose, and individuals with no functioning CYP2D6 alleles will not benefit from drugs that use CYP2D6 as a substrate. A one-time genomic test to determine a patient's CYP2D6 genotype (biomarker) would inform clinicians about dosing and effectiveness for a multitude of drugs. This information would be invaluable to the patient throughout the patient's lifetime.

Regulatory issues

Regulatory bodies such as the Federal Drug Administration (FDA) already have a full plate. In the US, FDA-regulated products account for 20% of each dollar spent by American consumers each year. It is likely that more targeted therapies in the area of precision medicine will become standard, which means more drugs that need to be approved and more therapies that need to be evaluated. One concern is that government agencies such as the FDA, which are already stretched thin, will quickly become overwhelmed. Fortunately, the primary order of business for regulatory bodies such as the FDA is to ensure that a medical product is safe and effective. It also makes sure that its intended use and benefits outweigh any associated risks. The traditional approach leaves a lot of room for improvement. According to Spear, Heath-Chiozzi and Huff (2001), the response rates per drug class for a general cross section of the population is: pain management, 80%; depression, 62%; asthma, 60%; cardiac arrhythmias, 60%; diabetes, 57%; migraine, 52%; arthritis, 50%; osteoporosis, 58%; Alzheimer's, 30%; and cancer, 25%.

By better understanding why some patients respond to new or already approved drugs, we will most certainly be able to tailor drug indication and dosage to certain populations. Companion diagnostics can substantially mitigate this problem and allow the correct patient population to receive the correct treatment and drug dosage. The use of companion diagnostics will essentially allow the FDA to approve drugs for more specific indications and patient populations. It will increase the FDA's ability to advise practitioners. It will reduce unnecessary exposure of patients to ineffective treatments.

Adoption by patients and health care professionals

Precision Medicine leverages the most innovative technology advances in the field of genetics. We know that the science will give us increasingly better treatment options, as discussed in Chapter 2, but precision medicine will only become a reality if both patients and the health care professionals treating them, act on the information at hand.

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Precision Medicine to change health care practice

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In this context, a recent study published in the European Journal of Human Genetics provides some helpful insights into this subject matter from researchers at the Wellcome Trust Sanger Institute. The study interviewed nearly 7,000 people including members from the general public, genomic researchers and genetic and non-genetic health professionals from more than 75 countries around the world about their preferences on receiving genomic information (Middleton, 2015).

As shown here in Figure 4.1 (taken from Middleton, 2015, Fig. 1), the clear majority of participants want to be informed or believe they should be informed about pertinent or incidental findings from genome studies.

Reimbursement and cost

The promise of Precision Medicine is to leverage highly targeted therapies for the benefit of the patient. By having a better understanding of what makes us unique and leveraging our genetic make-up, we hope to improve the outcome for the individual. This chapter focuses on one issue that we collectively have to overcome to make precision medicine a reality. And this issue is simply cost.

For some time, lung cancer has turned into the poster child for precision medicine. At this point, it is considered standard care for stage IV patients to identify targetable oncogenic drivers. As an example, the anaplastic lymphoma kinase (ALK) gene has emerged as an important oncogenic driver in a small population of patients with adenocarcinoma. The prescription drug crizotinib has received accelerated US Food and Drug Administration approval when used in conjunction with its companion diagnostic test to identify patients with the EML4-ALK gene rearrangement (FDA, 2011). From a medical perspective, there is no question that this treatment "moves the needle".

A recent phase III study compared crizotinib with standard chemotherapy in patients with locally advanced or metastatic ALK-positive lung cancer. Everything favored crizotinib: 1) median progression-free survival (PFS) was higher 7.7 versus 3.0 months, 2) response rate of the tumor was 65% versus 20% and 3) symptoms and quality of life were also substantially better during treatment. Overall survival was not improved. A cure has not yet been discovered. However, 64% of the group receiving chemotherapy crossed over to crizotinib, which is a powerful vote of confidence.

Two main questions remain unanswered. Can we afford to screen everyone with lung cancer, given that only 3% to 5% of the population will be ALK positive? And, can we afford to pay for crizotinib? These are the types of questions that the payers (insurance companies) need to answer. Currently, most insurance companies will not pay for genetic testing because they believe it is experimental. Lobbying for better coverage of biomarker screenings may change the outlook on the affordability of companion diagnostics.

Leveraging companion diagnostics as a standard method to screen for rare mutated genes is likely unsustainable. In the crizotinib example, we would test 100 people to find those 3 – 5 patients that are qualified based on their genetics to receive a highly specialized drug. This process takes too long, is too expensive and also creates workflow issues for the treating oncologist.

However, even if we accept that gene panels or a similar paradigm are better suited than companion diagnostic kits, our industry is facing this issue as a litmus test. The advent of NGS in the clinical realm has changed the concept and feasibility of only being able to test for one gene, but instead survey an entire genome. Many solution provides offering testing solutions create a dilemma for testing labs as they decided to adopt a business model that is based on per sample charges. Very often this is combined with a baseline fee. Now, as these types of therapies become part of standard care, this approach will create an unnecessary barrier for adoption. In addition, it creates grey zones. For example, what happens if a lab technician decides to rerun a sample as a quality control measure? Is the testing lab charged again for this rerun?

The second issue of course has to do with the drug cost itself. In our example, the treatment of a patient with crizotinib can increase the incremental cost-effectiveness ratio (ICER) to $148,000 per additional life year (Kelly, 2014). These are staggering numbers. Our collective goal is to find ways to reduce the monthly costs for targeted therapies to more reasonable levels. For the United States, the cost issue can only be solved by bringing representatives from the US Food and Drug Administration and other government organizations, researchers, clinicians, Medicare, pharmaceutical companies, patient groups and the insurance industry together. Obama's Precision Medicine initiative might be the right start for this dialog to occur.

The educational challenge

Precision Medicine will fundamentally change how health care is practiced. For most practitioners today, their knowledge of the human genome was established many years ago. However, new therapies and diagnostic methods are pouring in on a daily basis. So, how do we make sure that the current and future health care workforce understands the complexities and intricate details of this field?

A starting point is a better understanding of how to use an individual's genomic information to determine targeted treatment options, tailored to the individual patient. This requires baseline knowledge of genomics, an understanding of the clinical applications of genomic medicine, the capability to evaluate the clinical validity of new tests and a comprehension of the ethical and social issues associated with this type of approach. In more detail, practitioners need to understand at the very minimum.

- The structure of the human genome and different types of genetic variations
- Genetic screening and diagnosis including various screening and filtering methods for Mendelian diseases
- The use of next-generation sequencing for diagnostic purposes
- Methods used in patient populations to uncover associations between genome variation and common, rare and complex diseases
- Pharmacogenomics: testing for drug selection, dosing and predicting adverse effects of drugs
- Tumor profiling for targeting cancer treatment and the use of blood-based gene expression profiles in cancer prognosis

Currently, only an elite few have the requisite knowledge to utilize precision medicine in their practices. According to the CDC, over 18 million people work in the US health care system. The Bureau of Labor Statics determined in its 2014 report (http://dpeaflcio.org/professionals/professionals-in-the-workplace/healthcare-professionals-and-technicians/) that this workforce splits up in the following groups:

- Physicians & Surgeons - 8%
- Pharmacists - 4%
- Physician assistants - 1%
- Registered nurses and advanced practice nurses - 37%
- Technicians and technologies - 25%
- Other - 25%

Conservatively, if only physicians, surgeons and pharmacists are being retrained, we are essentially talking about a group of 2.1 million people that need to be caught up. This is in addition to

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Genetics industry undergoing fundamental shift

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the approximately 20,000 medical students and 15,000 pharmacy students who start their education each year.

Bioinformatics pipelines and systems infrastructure

The genetics industry is undergoing a fundamental shift from a clinical science focus to a bioinformatics focus. Genetic services require a greater level of data analytics sophistication than is required for other laboratory testing. Currently, data generated by new tests overwhelms current information technology systems and human interpretation capabilities. This is one of the reasons that we at Golden Helix strive to simplify the process of analyzing and interpreting the data so that it is possible for a wider group of users to conduct work in this space.

Ultimately, the output of the NGS pipeline needs to be integrated into the electronic health record and to be aggregated across a patient population. Robust informatics systems and trained bioinformaticians are critical new additions to the clinical team. Servant et al. (2014) covered this issue in detail. The good news is that precision medicine requires a strong interdisciplinary collaboration between several stakeholders covering a large continuum of expertise ranging from medical, clinical, biological, translational, technical and biotechnological know-hows. The chart below illustrates the different practitioners involved in the complex process, describes the data workflow starting from and coming back to the patient in order to tailor the therapy and shows the informatics and bioinformatics infrastructure supporting the workflow. To build the therapeutic decision, the most exhaustive data ranging from clinical to biological, environmental and family information (e.g., description of the tumor histology, list of previous treatments, family history, etc.) need to be collected along a complex healthcare pathway. During the process, physicians (such as surgeons, pathologists, radiation and medical oncologists, etc.), biologists, pharmacists, bioinformaticians, computational biologists, biostatisticians, biobank managers, biotechnological platform managers, clinical research associates and the technical staff will offer their expertise for the benefit of the patient.

Summary

This generation experiences a paradigm shift in medicine. Clinicians, empowered by state of the art bioinformatics pipelines, can make better informed and more targeted decisions. Patients benefit from individualized treatment plans and better clinical outcomes. There is still a lot to do. ◆

(The author is President and CEO of Golden Helix, Inc)