DWIH Interview

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How would you differentiate between precision medicine, personalized medicine and individualized medicine?

The three terms more or less mean the same! Precision medicine, dubbed in 2015 by US President Barack Obama, describes medical decisions and treatments that are tailored to the individual patient (customized healthcare). It uses diagnostic tests such as the patient's genomic DNA information, other molecular tools, systems biology, machine learning algorithms and cellular analysis such as imaging, to determine particular changes on the molecular level, which can then be targeted with precise medical products to achieve optimal treatment. Due to this precise method, medical interventions can be concentrated on the patients who will benefit, sparing expenses and side effects for those who will not. The kind of precision medicine that addresses cancer is referred to as "precision oncology." Since in cancer several molecular aberrancies occur, medical products are often combined (combination therapy), making it a personalized treatment strategy. In this respect, the terms precision and personalized medicine are often used interchangeably. The term individualized medicine was created in Germany when personalized medicine was put in place as an action plan by the German Federal Ministry of Education and Research (BMBF) in 2010. It is used synonymously with precision and personalized Medicine.

What is the state of precision medicine today in Germany, and what are the differences compared to the US?

Because the Human Genome Project and most of the precision or personalized medicine (PM) studies have been performed in the US, awareness, acceptance and use of PM is expected to be much higher in the US than in Germany. However, based on a survey conducted in 2016 with public representatives and physicians in Pennsylvania (US) and Bavaria (Germany), there are only a few differences between the two countries (Kichko et al., J. Pers. Med. 6, 15:doi.10.3390/jpm6020015). In both countries there are strong concerns about privacy protection and there is no support for a central genetic database or data maintenance by the government. The costs of personalized medicine/drugs are expected to be covered

by health insurances and governmental funds. Most survey participants think that PM will become the medicine of the future, but most likely at higher costs which may not be affordable under basic health insurance. So far PM has not yet become a standard treatment for many conditions in either the US or Germany. However, it is widely used in oncology for the treatment of melanoma, metastatic lung, breast, or brain cancer, and leukemia. Moreover, patients can benefit from PM drugs in the areas of pneumology, endocrinology and rheumatology as well as cardiovascular and inflammatory bowel diseases.

It seems that the willingness to rapidly implement PM is higher in the US. US physicians think that personalized drugs are more effective, because fewer adverse side effects, and can save money in the long term. They also want to perform more PM training and have fewer concerns regarding genetic data storage in the Electronic Health Record (EHR) than their German colleagues. (The reluctance of German physicians to accept the EHR may be due to strong data security regulations in Germany and their modest willingness to provide patients access to their genetic data.) Both US physicians and the public wish to increase patient involvement in medical decisions. There is also a difference in the speed at which PM is implemented in the US, as three times more public representatives want personalized drugs and tests to be offered online. The most significant prerequisites for PM implementation are biomarker research, better pharmacogenetic tests, reimbursement systems, genetic privacy and legal protection. The discovery of more disease-related biomarkers will determine if PM stays a niche innovation or becomes a wide-spread, applicable method to treat and cure diseases.

The wish to standardize PM regulations seems to be much stronger in Germany than the US, and Germans want more physicians' involvement in genetic data evaluation. Most people view the exchange of biological samples and genetic data in their country as insecure, and they worry about genetic data misuse. In the US, a high percentage of citizens preferred genetic data to be managed by private companies, while in Germany, the majority were against giving private companies the right to manage the genetic data. Access to genetic data was seen as very critical in both countries. All public representatives and physicians polled were against giving employers or health insurers the opportunity to get the genetic data of their employees or clients, respectively. Thus, for wide implementation of PM, there will be a need to adjust the healthcare reimbursement system, as well as to adopt new laws which protect against genetic misuse and simultaneously enable voluntary data provision.

Decision-making regarding PM reimbursement and legal ramifications has challenges particular to the US and Germany; in the US, there are wide differences between the 50 states. In Germany, the need to achieve an agreement with other

European countries on at-times fragmented European regulations and approval authorities' present difficulties.

Since it is specifically geared to individual patients and customers, is precision medicine well suited to generate successful start-ups?

Start-ups in precision medicine are best suited to the area of basic research where new targets are identified and validated. The development of a precision drug against these new targets and its testing in animal models and patients (clinical trials) is then best performed by pharmaceutical companies, because it requires an immense infrastructure and investment that is difficult for start-ups to achieve. Another area where start-ups in precision medicine have been created is the management of genomic and biomedical datasets, which has become an increasing challenge given the worldwide generation of big data from molecular, genetic and imaging/cellular analysis. Moreover, systems biology approaches and artificial intelligence/machine learning algorithms have become crucial tools to help define better targets and improve drug design. Examples of start-ups in these areas are DNAnexus, which created a cloud-based platform for genomics and biomedical datasets, Genoox, a healthcare and technology company which provides users a cloud-based advanced framework to easily manage the entire genetic sequencing process, 2bPrecise, which offers a platform for delivering integrated, actionable genomic information along with existing patient data directly into the clinician's workflow in any Electronic Health Record (EHR), Taliaz, which uses in-house big data and machine learning algorithms to predict responses to medication, and Medial EarlySign, which developed machine-learning-based decision-support tools to enable personalized, outcome-based interpretation of medical data, yielding individualized predictions and treatment options for each patient, including early prediction of life-threatening conditions.

What effect could precision medicine have on the existing German healthcare system and the cost of healthcare?

There is no doubt that treating people with precision medicine drugs will be a big advantage and improve their health. But this will come at a big cost and put a huge burden on the German healthcare system in the future, leading to increased premiums and a higher portion of patients who cannot afford these treatments. In addition, the increasingly large aging population who will be affected by various diseases, and their need for more precision drugs, will challenge the healthcare system.

Increased genetic and molecular screening of patients, as well as the production and testing of drugs that target individuals or a narrow group of patients, will get more and more expensive. Drug development involves hundreds of chemicals for a particular target which need to be tested in animal models and on patients in

laborious, expensive clinical trials. Since not all of the compounds succeed, pharmaceutical companies need to cover the costs of a failed product by selling the successful products at a higher price. Moreover, precision medicine drugs are often produced for a niche of patients and therefore will not be sold as often as classical medicines which are more widely used. As an example, the cystic fibrosis drug Kalydeco, made by Vertex Pharmaceuticals, approved for use in only 5% of the 30,000 cystic fibrosis patients in the US, costs $300,000 per year, per patient. Meanwhile, Gleevec, made by Novartis, has been approved for treating several other forms of cancer—and its price has tripled to more than $100,000 per year since it was introduced in 2001. Gleevec has proven successful for a higher proportion of patients than Kalydeco, and it has increased survival rates of chronic myeloid lymphoma (CML) patients five years after diagnosis from 30% to 89%.

The high-cost trend is worrying insurance companies who pay for the treatments, and it will become a growing concern for patients as they are increasingly forced to bear a bigger share of their medical expenses in the form of increased out-of-pocket charges. A 2013 paper in The HUGO Journal on personalized medicine argued that "the greatest challenges [facing the field] are economic, not scientific." (Jakka and Rossbach, The HUGO Journal 7:1, 2013) Many experts in the field, however, claim that higher prices of medicines may be worth it because, based on molecular and genetic screening, doctors can make sound decisions about who gets certain drugs or treatments (resulting in less failure), and because precision drugs are more effective than classical treatments. Thus, instead of giving an expensive drug to everybody (as was done in the past), the individualization of treatment should actually reduce costs. It will, however, take 10-15 years between the development of a personalized medicine and the collection of sufficient data to show significant, widespread improvements in health as a result. It seems unlikely that the German government, or any other government, will impose price controls on the costs of personalized medicine or any other prescription drugs in the near future, despite widespread public concern about drug costs. However, health-care leaders could try to help minimize an explosion of drug costs by evaluating the current patent protections that drug makers have and discussing how much companies should disclose about their development costs for drugs, for example.

Precision medicine requires a lot of information about the individual patient, like gene sequencing. What dangers and risks should a patient be aware of when it comes to protecting the knowledge about their state of health?

Today, doctors can analyze the genomic DNA of a cancer patient's tumor and then decide on a targeted, specific treatment that is tailored to the particular genetic footprint of this tumor, thereby increasing the effectiveness of the medicine at killing tumor cells, while sparing healthy surrounding cells. DNA can be taken from

tumor biopsies, small blood samples or swabs. This allows for the genetic characterization of an existing tumor, as well as the ability to determine the patient's predisposition to all sorts of human diseases. Doctors can then tell the patients what steps they should undertake to minimize the risk of developing the disease.

In addition to hospitals, private companies also now offer the service to sequence an individual's own genes. While in the past such an analysis used to cost several thousand dollars, the price for genetic sequencing has dropped to $1000. This seems low, but it is still not affordable for low-income earners. Moreover, the quality of the analysis may be suboptimal when it is done by labs that offer it at cut-rate prices.

The major problem is that although the knowledge of changes/mutations in a patient's genome can help find the right treatment option or determine the risk of a disease, it can also be dangerous because, without proper counseling, people do not exactly know what to think about the information and how they and other people may use it.

The first aspect is that aberrations in DNA/genes is not a guarantee that someone will develop a disease. Cells, organs and whole organisms are more complex, and whether a disease develops depends on the interaction of several macromolecules and cells in a multicellular organism.

Second, there is no perfect genome; there are genetic flaws in everyone's genome. It depends on how they manifest in the person's life--and this cannot be always foreseen or determined. Moreover, many changes or mutations fall into regions of the genome that do not code for any important functions.

Third, although people have a right to know about aberrancies in their genome, they also need to know what to do with this information and if there is a treatment option in case they fall ill. Even expert scientists, doctors and genetic counselors do not always know what the changes really mean for a patient's health.

Fourth, there is a worry that an individual's DNA could be sequenced secretly, or that insurance companies could use the information against some groups. This means that there is increasing ethical and moral concern about using genetic information. If insurance companies created "high risk" profiles and eventually deny medical coverage to these people, it would be an improper utilization of genetic information. On the other hand, if genetic screening helped people to adjust their behavior towards a healthier lifestyle, the technology would be morally praiseworthy.

In summary, as with every modern technology, whole genome sequencing can be both a blessing and a curse. We need to consider the ethical aspects in all that we do and formulate strict regulations on a global level that prevent misuse of genetic information.