Prescription *vs* Precision Medicine

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Why personalized medicine?

To date, medical treatment is usually designed to be beneficial for the average patient. However, since many diseases can be divided into multiple subtypes, each with a unique genetic profile, such a "one-size-fits-all" approach is not always effective. Physicians often employ a trial and error strategy until the most effective drug is found for a particular patient. Such an approach can be a high burden for patients, both physically and mentally.

Customized healthcare, or personalized medicine, with treatment tailored to the individual patient would allow earlier disease intervention, reduce the probability of negative side effects and enhance the probability of desired outcomes. Such a dedicated approach may eventually help prevent the onset of specific diseases and reduce healthcare costs.

For many diseases and disease sub-types, however, the genetic drivers are currently unknown. Genome sequencing and gene expression profiling of patients' cells will provide insight into the molecular mechanisms underlying disease pathogenesis. This knowledge is essential to develop targeted therapy for those diseases. Upon identifying disease drivers and developing targeted therapies, genome sequencing and gene expression profiling will allow doctors to diagnose specific disease subtypes, predict a patient's prognosis and select the most effective treatment strategy.

Targeted therapy in breast cancer and cystic fibrosis

Breast cancer is disease that can be divided into multiple subtypes. Identification of the genetic driver in a certain breast cancer subtype has led to the development of a dedicated, or personalized, treatment strategy. In 15-30% of patients suffering from breast cancer, the Receptor tyrosine-protein kinase erbB-2 gene is over-expressed or amplified. Over-expression of this gene, which encodes for the HER2/neu receptor, has been shown to play an important role in the development of breast cancer and is associated with increased disease recurrence and poor prognosis. Identification of *erbB-2* as the genetic driver in these patients has led to the development of a monoclonal antibody that interferes with the HER2/neu receptor. This blocking antibody reduces both the risk of death in early stages of cancer and relapse after surgery, and prolongs the average survival of patients with late-stage breast cancer. This antibody is only effective in cancers where HER2/neu is over-expressed.

Cystic Fibrosis (CF) is another example of a disease for which personalized treatment is already feasible. CF is a genetic disorder that primarily affects the lungs of patients. This disease is caused by the presence of mutations in the gene encoding for the protein Cystic Fibrosis Transmembrane conductance Regulator (CFTR). As many as 1,500 different mutations have been detected in *CFTR.* These mutations

have different effects, ranging from deregulation of the chloride channel and premature degradation of the receptor to disruption of the production of full length CTFR.

These mutations all result in imbalance of ions, cause mucus to become thick and sticky and block the respiratory tracts. Until recently there was no cure for CF. Patients were treated by alleviating the condition's symptoms. However, recently three different drugs have been developed that each target a specific mutation. Initial results from separate phase 3 clinical trials on patients with these specific mutations showed promising results, including a reduction in pulmonary exacerbations.

These studies are clear examples of the necessity and efficacy of targeted therapy. In addition to breast cancer and cystic fibrosis, patients with lung and colorectal cancers, melanomas and leukemias also routinely undergo molecular testing as part of personalized patient care. The first sequenced human genome cost nearly $3 billion, but as sequencing costs have dropped substantially, to approximately $1,000, physicians have recently begun sequencing patients' genome sequences to improve their care.

The 'precision medicine initiative'

Although personalized medicine is already reality for patients with specific types of breast cancer, CF and leukemia for the fast majority of the diseases such a treatment strategy is currently not feasible. President Barack Obama has therefore announced he will request $215 million from the Congress for the 'precision medicine initiative'. The main objective of this initiative is to match patients' genetic and physiological data in order to treat diseases more precisely.

The US National Institutes of Health (NIH) would receive $130 million to develop a national cohort of at least one million volunteers for a longitudinal study. The genomic, medical, physiological, environmental and life style data of these volunteers would be integrated into a single database. This database would be made available for researchers. The NIH's National Cancer Institute would receive $70 million to identify genomic drivers in cancer with the eventual aim to develop more targeted treatment strategies.

The US Food and Drug Administration (FDA) and the Office of the National Coordinator for Health Information Technology (ONC) would receive $10 million and $5 million, respectively, to develop databases needed to support regulatory aspects of the program and to develop new and better ways to ensure support systems for secure data sharing across systems.

Genome sequencing of a million volunteers will certainly provide insight into variations present in genes. However, translating this sequence information into a clinical treatment plan is highly complicated and requires experts of many different fields. In addition to the above described small molecule drugs and blocking antibodies, gene therapy, using, for example, CRISPR/Cas9 technology, may in the future also be considered as a method to specifically target or restore genetic drivers.