What is personalized medicine?

There are widely varying definitions of personalized medicine. For some, it has to do with patient-doctor interactions, but, for the purpose of this discussion, the term will be used to refer to the use of genetic or molecular markers to better define a disease and guide treatment, often with a targeted therapy [1]. This approach to health care is also referred to as precision medicine or genomic medicine.

For decades it has been known that many diseases, including cancer, have underlying genetic causes, which may have been inherited, acquired during the course of a patient’s lifetime, or a combination of both. This deeper understanding of disease has inspired researchers to develop tests to pinpoint specific molecular or genetic alterations or variants that can predict an individual’s predisposition to a condition, accurately diagnose disease, determine disease aggressiveness and help direct treatment.

Personalized medicine has perhaps developed the most rapidly in understanding and treating cancer. The description of cancer has evolved from being largely defined by where it occurred in the body, such as breast cancer, toward the increasing practice that emphasizes specific molecular or genetic alterations, such as HER2/neu-positive, ER-negative breast cancer. The ability to identify the specific molecular or genetic signature of an individual’s tumor has resulted in the recognition that cancer is not a singular disease, but rather more than 200 unique diseases that each behave differently.

While a deeper understanding of the molecular alterations that cause a disease is useful by itself, ideally this knowledge will lead to the development of new and more effective therapies. Some of the earliest-developed cancer chemotherapies, for example, work by targeting any rapidly growing cell in the body, whether cancerous or not. Newer targeted therapies, on the other hand, often work through mechanisms that focus on cellular processes that are specifically altered only in cancerous tissue. Currently, however, targeted therapies are still the exception rather than the norm, and vary in terms of their impact on overall patient survival. While up to 50 percent of drugs currently in the clinical pipeline are estimated to involve the use of genetic or molecular markers [2], there are about 100 FDA-approved drugs being used in clinical practice that contain genetic information in their label [3].

While targeted drugs paired to specific genetic signatures are still lacking in many diseases, there are other important uses for molecular or genetic test results such as risk stratification. Certain genetic signatures in a person’s normal DNA can elevate the risk for developing a given disease, but they do not necessarily mean that a person will develop that disease. Individuals at higher risk can engage in preventive measures or enhanced surveillance. The BRCA1 and BRCA2 genes and their link to breast, ovarian and prostate cancers are well-known examples of this inherited risk. Testing for these genes was recently propelled into the public spotlight after actress Angelina Jolie found out she carried the mutated form of the BRCA genes and decided to undergo elective mastectomies in an effort to reduce her risk for developing breast cancer.

Another example for the use of genomic testing is to evaluate genomic signatures to inform treatment decisions. Genomic tests allow providers and patients to understand the biology of individual cancer tumors, providing information beyond traditional clinical measures about the aggressiveness of disease. For example, genomic tests can help determine whether or not to pursue chemotherapy after surgery for certain types of breast cancer. In some types of breast cancer, surgery followed by hormonal therapy is sufficient to arrest further cancer development, while for others recurrence is highly likely unless chemotherapy is pursued. The challenge for any woman in this situation is evaluating the risk-benefit balance of whether or not to undergo chemotherapy, given the side effects associated with treatment. The OncotypeDX® breast cancer test examines 21 gene signatures that has been found to accurately predict the likelihood of cancer recurrence and chemotherapy benefit in these women and can be used to inform their decision about whether or not additional treatment is likely to be beneficial.
One of the early targeted therapies for lung cancer, gefitinib (Iressa), became associated with its specific genetic signature due to an observation of different responses in certain subgroups of a clinical trial being conducted to support its approval. It was found that the drug worked better in lung cancer patients of East Asian descent than in other patients. Further research revealed that East Asian patients had a higher frequency of a specific genetic mutation that made gefitinib significantly more effective [4]. There are other examples of disease-risk genetic signatures that occur in higher frequencies for certain populations. BRCA1 and BRCA2 mutations occur at a five-fold higher rate in Ashkenazi Jews than in the general population. Triple negative breast cancer, which lacks receptor expression for estrogen, progesterone and HER2, results in poor outcomes due to a lack of effective therapies and is twice as prevalent in individuals of African descent as the general population. Sickle cell anemia is another disease that is genetic in origin and is more common among people from, or whose ancestors come from, Africa; Mediterranean countries such as Greece, Turkey, and Italy; the Arabian Peninsula; India; and parts of South and Central America [5].

The identification of genetic signatures that occur with higher than normal frequency in certain subpopulations presents both challenges and opportunities to affect existing health disparities. The development of effective therapies that target diseases in populations experiencing disparate health outcomes could help reduce disparities; however, targeted tests and therapies that either are not offered to underserved populations or are not relevant to some diseases could increase health outcomes disparities.

**Patient expectations of personalized medicine**

Patients often expect targeted therapies to have fewer and milder side effects, and while this has proven to be true in some cases, targeted therapies are not universally without side effects. From allergic reactions to nausea, targeted therapies still have the possibility of causing many of the same undesired side effects caused by non-targeted therapies. Many targeted therapies interrupt or attempt to correct specific cellular processes that have gone awry because of genetic reasons, but in the case of cancer, the processes might only be awry within a tumor. A therapy that is effective against cancerous tissue may cause detrimental changes to healthy tissue elsewhere in the body. The balance of these counteracting effects can affect the overall patient benefit. The corrective nature of some targeted therapies also means that a disease’s root cause may not be permanently eliminated by the one-time administration of a therapy, but rather in order to maintain a therapy’s benefits it must be continually administered throughout the life of a patient. While this approach has the potential to be highly effective, the ongoing use of a therapy has different implications for patients than receiving a time-limited treatment.

The underlying knowledge base and expectations of patients are important factors to be considered when developing approaches that promote personalized medicine. Personalized medicine has the potential to empower patients to make more informed decisions about their care. This empowerment, however, requires a certain level of awareness of the role, availability, and limitations of genetic and molecular tests and what this means for a patient’s prognosis or therapy options. Genetic testing has become much more commonplace, and in some cases can be ordered directly by individuals without the intervention of healthcare providers, leading to greater patient expectations of genetic testing as part of their medical care. Among the expectations are the assumptions that genetic and molecular tests used as part of a patient’s care are accurate, reproducible, and meaningful in improving patient outcomes. In some cases, however, the development of personalized medicine diagnostic tools has outpaced personalized therapeutic options, leaving patients with the ability to sequence their genome, but without treatment options based on specific gene sequencing or access to those treatments. In cases where targeted therapies have been developed, the associated outcomes have improved dramatically with some therapies, but have only marginally improved over traditional therapies in other cases.

**Conclusion**

Throughout the history of medicine, significant medical progress has been made with the introduction of new technologies and treatment paradigms, but the realization of disease-wide definitive breakthroughs has been elusive. The introduction of personalized medicine will surely lead to major improvements in the practice of medicine, but it
will be important to clearly identify obstacles and limitations to the successful implementation of personalized medicine. With these challenges in mind, policies can be developed to achieve the goal of maximally empowering patients with the most effective tools possible to improve their health outcomes.

References: