Genetic alterations play a role in the growth of all types of cancer, and researchers also have found that individual cancer tumors each have a unique genetic profile. The term “precision medicine” is used to describe how genetic information about a specific patient’s tumor can be used to more accurately diagnose and tailor effective individual treatment strategies.

Advances in the analysis of cancer tumors and the technology used for DNA sequencing now allow researchers to create detailed genetic profiles of individual tumors. New drugs have been developed that effectively target genetic differences in chronic myelogenous leukemia, lung cancer, and colon cancers. While only a few tumor types are currently known to respond to these new treatments, as we learn more about the “genetic Achilles’ heels” of specific cancer tumors, physicians will be turning to these targeted therapies to improve patient care.

**What are genetic codes?**

Deoxyribonucleic acid or DNA (the molecules inside cells that carry genetic information and pass it from one generation to the next) is often called the blueprint for all living things. DNA is made up of combinations of four chemical structures (known as bases): Adenine, Thymine, Guanine, and Cytosine. They are arranged on two strands in a complementary linear sequence. The DNA structure is like a ladder, with the bases as the rungs of the ladder holding the two strands together. The sequence or arrangement of the bases determines code units (referred to as genes) that have specific functions—most genes contain information for making a specific protein.

Our genes differentiate us from other species, and from each other, by coding for different proteins that create living organisms. With the exception of identical twins, the DNA of two individuals is different, and most of these differences are benign variations known as polymorphisms. But some DNA variations are mutations that alter protein function and can cause disease. These variations can consist of a change in a single base or alterations in larger DNA fragments.

**The first DNA sequencing**

Today there are many laboratory methods to detect differences in individual DNA. One of the most common methods is known as DNA sequencing, a process used to determine the exact order of the four bases that make up DNA.

Frederick Sanger was one of the first to describe a technique to report the sequential order of bases in DNA (for which he and his colleagues were awarded a Nobel Prize). They found that a chemical modification to naturally occurring base structures allowed them to determine the sequence of bases in a DNA fragment. This Sanger (or dideoxy) sequencing strategy was used by the Human Genome Project to map the human genome, a project that took ten years, many research-hours, and over a billion dollars to complete.

The Human Genome Project made the technology of DNA sequencing faster and less expensive. Using DNA sequencing to compare a patient’s DNA sequence to that of a “normal”
Broader clinical applications for genetic sequencing

While the first applications of NGS have focused on sequencing the 50 genes known to be related to cancer, other clinical applications include testing for traditional genetic diseases and for common chronic conditions such as atherosclerosis and diabetes.

For these applications, developing panels of genes specific to each condition may not be accurate or efficient. While the human genome (with 3 billion bases) contains approximately 20,000 genes, only parts of the genome code for proteins that cells use to function.

The clinical exome is made up of the protein-coding regions of the 4,500 genes responsible for most human disease. NGS is able to sequence a clinical exome of this size and, using this extensive panel, can provide clinicians with detailed information useful to managing patient care for most clinical scenarios, regardless of disease type. In this case, one diagnostic test may fit all.

The challenges of NGS: “incidental findings” and “difference of unknown significance”

While NGS can routinely sequence the clinical exome, the benefit of having this information remains unsubstantiated. Many genetic variants, all known as “incidental findings,” may be unrelated to symptoms or cell functions. For example, if NGS is performed on a patient with a suspected genetic disease, sequencing the clinical exome may identify variations associated with conditions not under diagnostic study at this time. Should these findings be shared with the physician? If an inherited condition is uncovered, should it be reported to the patient and/or family? Would the patient or relatives want to know information they were not seeking?

A second and even more likely possibility is finding “variations of unknown significance (VUS).” As more individuals are screened with NGS technologies, genetic variants not previously described will be identified. Some variants may be pathogenic, but most will be benign, without any known (or even likely) clinical significance. Diagnostic centers, such as Dartmouth-Hitchcock, have established ethics committees and molecular tumor boards to address these issues and develop the working policies needed to accompany this new diagnostic science.

Opportunities and unknown impact

In summary, we have entered a new and exciting era in which low-cost sequencing approaches can be applied to tumor samples and normal DNA from individuals. NGS sequencing has already identified mutations that respond to targeted therapies, and as more mutations are identified we expect that more tumors will respond. Tumors with mutations for which there are available targeted therapies often respond dramatically to those therapies, but the vast majority of the differences between individual and common genetic sequences do not affect an individual’s risk of developing a disease. While NGS provides the opportunity to revolutionize our management of cancer patients, its appropriate full impact remains to be defined and is an active area of research.