Next-Generation DNA Sequencing: Implications for Oncology Care

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Genetic testing for germline hereditary predisposition syndromes usually involves traditional Sanger DNA sequencing (see Figure 1). New advances in genomic technologies have led to reduced cost and turnaround time with the simultaneous testing of multiple genes. This, in turn, has led to the introduction of next-generation sequencing (NGS) panels that analyze less common high- and intermediate-penetrance cancer susceptibility genes. The ultimate goal of NGS is to reduce the cost of whole genome sequencing to about $1,000 and provide robust and comprehensive information about hereditary risk for developing a myriad of diseases (Rizzo & Buck, 2012).

NGS is quite different from direct-to-consumer (DTC) genetic testing. DTC genetic testing includes tests that are marketed directly to the individual and can be performed without the inclusion of a physician, genetics professional, pre- and post-test counseling, or an insurance company (Hudson, Javitt, Burke, Byers, & ASGH Social Issues Committee, 2007). Many of these tests reportedly can assess for future risk of multiple diseases. DTC typically involves analyzing hundreds to thousands of single nucleotide polymorphism (SNP) chips to simultaneously examine thousands of small changes found across the genome. Some of these SNPs are known to be associated with a disease, although the exact clinical implications, penetrance, and disease risk conferred by many of these SNPs are unclear.

Laboratories that perform clinical genetic testing must be certified by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. However, many of the laboratories offering DTC testing do not disclose their CLIA certification. NGS typically is carried out in CLIA-approved laboratories, involves genes that have known associations with disease susceptibility, and uses different laboratory techniques.

Laboratory Techniques

Sanger sequencing has evolved from the original sequencing technique that used the manual chain-termination sequencing method to automated sequencing instruments that detect fluorescently labeled nucleotide sequences, and it was the method used to sequence the first human genome (Ross & Cronin, 2011). It often is referred to as first-generation sequencing (Rizzo & Buck, 2012). Automation has been accompanied by decreased costs and turnaround time for results (see Figure 2). Despite these advances, the main limitation of Sanger sequencing is that only a limited amount of data can be read with each sequence reaction (Rizzo & Buck, 2012).

More recently, efforts have been underway to increase efficiency by sequencing massive numbers of different DNA sequences in a single reaction, which is called a parallel reaction. This is referred to as NGS or massive parallel DNA sequencing (Desmedt, Voet, Sotiriou, & Campbell, 2012; Rizzo & Buck, 2012).

In the future, whole exome and whole genome sequencing are anticipated to become the gold standard in genetic testing. Although 100% of the human genome has been sequenced, only about 10% has been characterized (i.e., all possible genomic alterations and mutations identified), so doing whole genome sequencing is currently of limited clinical utility (Rizzo & Buck, 2012). Therefore, only sequencing the exome, which comprises the 2% of the genome denoted by protein-coding regions known as exons and is associated with coding regions of about 3,000 known diseases, is more efficient (Rizzo & Buck, 2012).

Clinicians already are using targeted exome sequencing to make clinical diagnoses, including panels to identify cancer susceptibility genes (Biesecker, Burke, Kohane, Plon, & Zimmern, 2012; Ku, Cooper, Iacopetta, & Roukos, 2013). For example, Ambry Genetics Laboratories offers several next-generation cancer panels. CancerNext™ is an NGS panel that simultaneously analyzes 22 genes that contribute to increased risk for breast, colon, ovarian, uterine, and other cancers. Ambry Genetics Laboratories (n.d.) also offers similar tests specifically for breast, ovarian, and colon cancers.

The National Comprehensive Cancer Network ([NCCN], 2013) has just updated its recommendations to include NGS for hereditary breast, ovarian, and other cancers. However, because of the complexity and variety of results interpretation, NCCN states these panels should only be ordered in consultation with a genetics professional.

Implications for Clinical Care

The implications of NGS for clinical care should not be underestimated. The American College of Medical Genetics and Genomics (2012) issued a policy statement on the use of NGS that emphasized the importance of correctly identifying families likely to benefit from testing, comprehensive pretest counseling, post-test considerations, and the role of genetics professionals. Clearly, genetics professionals as well as other healthcare providers will require education about NGS, how to manage results, and the interpretation of large amounts of genetic data (Rizzo & Buck, 2012).