Next Generation Sequencing and Multi-Gene Panel Testing: Implications for the Oncology Nurse

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Objectives: *To review past, current, and future events in genetics and discuss how genetic testing information personalizes cancer screening, detection, and treatment. A case study is presented to illustrate key points.*

Data Sources: *National guidelines, evidence-based summaries, peer-reviewed studies, editorials, and web sites.*

Conclusion: *Multi-gene testing using next-generation sequencing has changed the landscape for hereditary cancer syndromes.*

Implications for Nursing Practice: *Nurses have key roles in personalizing health care including recognizing the complexities of genetic testing, assessing family history, understanding gene/environment factors, referring for genetics consultations, and promoting registry studies. In order to be effective, nurses must stay current with the rapidly-changing technology and guidelines for genetic evaluations and testing.*

Key Words: *genetic testing, next-generation sequencing, multi-gene panels, hereditary breast cancer, personalized health care, ATM gene.*

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"The best book that has ever been written is in us and nowadays we have opportunity to read it."

B. Utt Estonia

Genetics has undergone dramatic changes in the past two decades. We can now "read" changes in our "book of life" and identify how changes in our genetic makeup influence our risk for cancer.

This article is a snapshot of past, current, and future events in genetics, and of how genetics personalizes cancer screening, early detection, and treatment. Current approaches to genetic testing with multi-gene[a] panels and next-generation sequencing[b] (NGS) technology are introduced with the emphasis on hereditary breast and ovarian cancer (HBOC). A case report of a patient who tested positive for a mutation[c] in the *ATM* gene using NGS illustrates the complexities and challenges in interpreting and managing care when a gene mutation of moderate penetrance[d] is identified. Understanding the emerging field of multi-gene testing is challenging now and will continue to be challenging in the future. Nurses need to stay up-to-date in this rapidly changing specialty to remain effective in assessment, referral, research, and advocacy.

From Base Pairs to Bedside: The Past

The Double Helix

In 1953 American scientist James Watson and English physicist Frances Crick discovered the structure and function of DNA,[e] giving rise to a new field of molecular biology. They identified the double-stranded 3-dimensional DNA models that we now know as the double helix.[1] The double helix configuration incorporates the complementary pairing of the four bases, adenine (A) pairing with thymine, (T) and cytosine (C) pairing with guanine (G). This discovery provided insight into the genetic code and how the double-stranded DNA model replicates itself and carries the ATCG genetic code instructions via RNA for protein synthesis.[1]

Sanger Sequencing. The discovery of the double helix provided the groundwork for the technological advancement of Sanger sequencing.[f] In 1980, Fred Sanger developed the processes for separating the two strands of DNA, amplifying the genetic areas of interest using chemically altered bases, and then identifying the sequence of the four bases using a jigsaw-like approach.[2,3] Sanger sequencing techniques became more sophisticated over time with automated sequencing instruments, fluorescent labeling, and laser detection of nucleotides.[g,2,3]

[a]**Gene:** The basic unit of heredity that occupies a specific location on a chromosome. Each consists of nucleotides arranged in a linear manner. Most genes code for a specific protein or segment of protein leading to a particular characteristic or function. http://www.cancer.gov/publications/dictionaries/genetics-dictionary?expand=G.

[b]**Next-Generation Sequencing:** A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel. Also called massively parallel sequencing and NGS. http://www.cancer.gov/publications/dictionaries/genetics-dictionary?expand=N.

[c]**Mutation:** A mutation is a change in a DNA sequence. Mutations can result from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to chemicals called mutagens, or infection by viruses. Germ line mutations occur in the eggs and sperm and can be passed on to offspring, while somatic mutations occur in body cells and are not passed on. https://www.genome.gov/glossary/index.cfm?id=134.

[d]**Penetrance:** A characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present. http://www.cancer.gov/publications/dictionaries/genetics-dictionary?CdrID=339344.

[e]**DNA, (Deoxyribonucleic Acid)**: DNA is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases–adenine (A), cytosine (C), guanine (G), and thymine (T). The two strands are held together by bonds between the bases; adenine bonds with thymine, and cytosine bonds with guanine. The sequence of the bases along the backbones serves as instructions for assembling protein and RNA molecules. https://www.genome.gov/glossary/index.cfm?id=48.

[f]**Sanger sequencing:** A low-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique uses polymerase chain reaction (PCR) amplification of genetic regions of interest followed by sequencing of PCR products. http://www.cancer.gov/publications/dictionaries/genetics-dictionary?cdrid=763028.

[g]**Nucleotide:** A nucleotide is the basic building block of nucleic acids. RNA and DNA are polymers made of long chains of nucleotides. A nucleotide consists of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases used in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, the base uracil (U) takes the place of thymine. https://www.genome.gov/glossary/index.cfm?id=143.