Integrating Genetics and Genomics Into Oncology Nursing

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Genetic and genomic research is creating new and more individualized approaches to better manage a person's disease or predisposition to disease, including cancer. This approach to healthcare is called personalized healthcare.[1] These discoveries have important implications for oncology nursing practice throughout the cancer care continuum. This continuum encompasses primary prevention, screening, diagnosis, treatment, survivorship, recurrence, and progression through the end of life.[2] In recognition of the expanding role of genetics and genomics in nursing practice, the Essentials of Genetic and Genomic Nursing was first published in 2006 by an independent consensus panel of nursing professionals. It is now in its second edition.[3] Using the Essentials of Genetic and Genomic Nursing as a basis, this article provides an overview of where and how oncology nurses will be or already are integrating genetics, genomics, and personalized healthcare into their daily practice.

Genetic/Genomic Research and Understanding Cancer

In 2003, an international research effort to sequence the entire genome of human beings, called the Human Genome Project (HGP), was completed. The completion of the HGP has opened doors for scientists to understand more about the role of genes in health and disease.[4] Genes, units of hereditary information located at specific positions in a chromosome, code for proteins that contribute to particular characteristics or functions. For example, genes play a role in 9 of the 10 leading causes of death in the United States, including cancer.[4] Genetics investigations have traditionally involved assessment of how single genes influence relatively rare, single-gene disorders. Studies of the human genome are leading to greater knowledge of the ways in which genes interact with each other and with the environment, helping to improve health and prevent disease.[5] This new focus of research, genomics, involves all genes in the human genome and their interactions with each other, the environment, and cultural and psychosocial factors.[6] Table 1 provides more information and resources on genetics and genomics, and their roles in health and disease.

One approach to learning about the genetics of common, complex disorders is known as a genome-wide association study (GWAS). A GWAS uses rapidly scanning markers across the genomes of many people to identify genetic variations that are associated with a specific disease. The GWAS allows scientists to find the common genetic changes that contribute to small increases in disease risk.[7] When the genetic associations are located, researchers can use the information to develop
better ways to prevent, diagnose, and treat disease. GWAS approaches have been very helpful in finding genetic variations that contribute to common, complex diseases such as diabetes, heart disease, mental illness, and cancer. The Cancer Genome Atlas (CGA) project is another area of research that is further illuminating the genetic basis of cancer. The CGA applies genome analysis technologies to systematically investigate the entire spectrum of genomic changes involved in human cancer. Cancer involves many gene changes, or mutations, that accumulate over a person's lifetime and have an impact on cell growth control mechanisms. As cell growth control mechanisms are altered, a normal cell can change to a cancerous one. With new gene-sequencing technologies and analytic tools, researchers are able to sequence many of the genes suspected to cause cancer. Researchers can also compare the entire genomes of cancerous tissue to those of healthy tissue, to identify the mutations that have occurred. Investigators are beginning to use this information to design new and improved diagnostics and treatments for many cancers.

**Personalized Healthcare**

The growing body of information in human genetics and genomics is leading towards a revolutionary new approach that is transforming healthcare—personalized healthcare. Discovering the influence of genetic and genomic factors in health and disease is creating opportunities for earlier diagnosis, more effective and individualized prevention and treatment of disease, better response to treatments, and improved health outcomes. In recognition of the importance and increasing use of a personalized approach to healthcare, the US Department of Health and Human Services has created a Personalized Healthcare Initiative. The overall goal of this Initiative is to improve the safety, quality, and effectiveness of healthcare in the US through a proactive approach. Using the identification of genes and their relationship to drug treatment, the Initiative supports and enables tailoring of medical treatment to each person's specific genetic profile and needs. This personalized approach is expected to give individuals the opportunity to become more involved in their health and wellness.

Cancer genetic and genomic research is on the forefront of personalized healthcare. For example, the Tumor Sequencing Project (TSP) consortium has identified 26 genes frequently mutated in lung adenocarcinoma. This achievement more than doubles the number of genes known to be associated with lung adenocarcinoma. The TSP research team also was able to detail key pathways involved in the disease, and describe patterns of genetic mutations among different subgroups of lung cancer patients, including smokers and nonsmokers. This research is advancing understanding of the complexities of lung cancer, and supporting efforts to develop new strategies for prevention, diagnosis, and treatment of this disease.

**Screening for Cancer**

Human genome research is creating new opportunities for discovery of noninvasive methods to detect and reduce the risk of cancer. As an example, strategies for early detection of colorectal cancer include colonoscopy, sigmoidoscopy, and barium enemas. However, these are invasive procedures, and have been limited by patient compliance issues. Testing of stool samples for occult blood is a noninvasive method to screen for colorectal cancer; however, it has not been shown to be sensitive or specific enough for early detection. Furthermore, patients need to change their diet before testing is performed, or they must undergo multiple fecal occult blood tests to increase the sensitivity and specificity of the tests. Noninvasive methods to detect colorectal tumors are being researched, and have the potential to reduce the morbidity and mortality associated with colorectal cancer. Traverso et al. sought to determine the efficacy of detecting APC mutations (adenomatous polyposis coli gene) in DNA from stool samples using a newly developed method called digital protein truncation. Using this technique, researchers hypothesized that they would be able to identify many different mutations involved in colon carcinogenesis in a sensitive and specific way. Stool samples were collected and analyzed from 74 patients; some of these patients had nonmetastatic colorectal cancer and some did not have neoplastic disease. Results showed that 57% of the patients with neoplasia had identifiable APC mutations. No APC mutations were identified in the control group. The researchers concluded that APC mutations can be identified in DNA collected from a stool sample in patients with relatively early stage colorectal tumors. Their early feasibility study shows a new, noninvasive way to detect colorectal neoplasms, which has evolved to include more genes and is a clinically available test. Oncology nurses will be involved increasingly in this type of noninvasive cancer screening, and as noted in the Essentials of Genetic and Genomic Nursing, will be using new genetic- and genomic-based...
information and interventions to improve their patients’ health outcomes.[3]
In recognition of the importance of screening and prevention of common diseases, the Agency for Healthcare Research and Quality (AHRQ) created a Guide to Clinical Preventive Services. This includes the US Preventive Services Task Force (USPSTF) recommendations on screening; counseling; and preventive medication topics, with clinical considerations for each topic. The Guide provides healthcare practitioners including nurses and nurse practitioners with an authoritative source for making decisions about risk-management services.[13]

**Family History and Inherited Cancer Susceptibility**

Certain common, chronic disease predispositions are inherited in families. Individuals who have a family history of cancer in close relatives are more likely to develop the disease. The person’s risk increases when there are more affected relatives, and if the disease was diagnosed at an early age.[14]

All healthcare providers, including nurses, collect family history information. Family history is an important and powerful screening tool that can help identify at-risk individuals for whom specific clinical risk-management interventions would be beneficial. For example, certain specific family history patterns are associated with an increased likelihood for mutations in the *BRCA1* or *BRCA2* genes that predispose individuals to breast/ovarian and other cancers. For all hereditary cancers, collecting family history from both the mother’s and father’s side of the family is needed to assess risk, because inherited risk for any cancer can come from either side.[15]

People who are identified as being at increased risk can be advised to make specific lifestyle changes and initiate cancer screening at an earlier age, sometimes with greater frequency and using different modalities. Referrals of high-risk individuals and families can be made to a specialist for further assessment of genetic/genomic risk factors.[16]

In recognition of the importance of family history, the US Surgeon General developed My Family Health Portrait, a computerized tool to facilitate collection of data about family history. Using the Family Health Portrait, individuals can enter their own family health history information and create diagrams of their family health history (pedigree) to share with their family members and healthcare provider. Screening and risk-management guidelines based on family history are now available for many common diseases, including cancer.[17] Evidence regarding the effectiveness of these strategies for high-risk individuals is growing. Consistent with the *Essentials of Genetic and Genomic Nursing*, nurses at all levels of practice should be competent in constructing a pedigree from the collected family history information using standardized symbols and terminology.[3]

In addition to using family history to screen for hereditary diseases, genetic testing is used to identify and clarify levels of risk more precisely, to inform healthcare decisions. Genetic testing is available to individuals at risk for hereditary, early-onset diseases such as breast and colon cancer, as well as many other cancers. Furthermore, men and women who present with a family history of early-onset breast and ovarian cancer or with early-onset disease may be candidates for genetic testing for mutations in the *BRCA1* and *BRCA2* genes. Mutations in *BRCA1* or *BRCA2* are highest in families who have a number of family members affected with breast and/or ovarian cancer. Mutations in *BRCA1* and *BRCA2* also increase the risk for cancers of the pancreas, melanoma, and other malignancies.[16]

**Gene-Based Cancer Diagnostics**

Genetic testing was originally used to diagnose genetic disorders in infants and children born with birth defects suggesting a genetic condition, such as Down syndrome. As genetic and genomic research has expanded, genetic testing is now being used for diagnosis and prognosis of, as well as therapy decision-making for, common diseases like cancer. Both chromosome analysis and gene-based studies can contribute to the diagnosis and management of patients with cancer. Increasingly, genetic markers that are specific to particular tumor types are useful diagnostic tools.[18] Chromosomal rearrangements are often found in hematologic cancers and in some solid tumors. For example, a chromosomal rearrangement called a translocation in the MYC oncogene is associated with Burkitt’s lymphoma. A translocation involves the breakage and removal of a large segment of DNA from one chromosome, followed by attachment of the segment to a different chromosome.[19] In Burkitt’s lymphoma, the translocation occurs between chromosomes 8 and 14. The translocation causes MYC to be expressed at an inappropriately high level, thus contributing to Burkitt’s lymphoma.[20] Chromosomal rearrangements can also create novel chain fusion genes, resulting in fusion proteins that have abnormal biologic activity. This is the case with the BCR-ABL1 gene fusion that results from a translocation between chromosomes 9 and 22 in chronic myeloid leukemia.[18]

An alteration in an individual gene, called a point mutation, is another cause of activation of
proto-oncogenes through structural changes in their encoded proteins. These alterations can lead to the uncontrolled and continuous activity of the mutated protein. Point mutations, for example, identified in the family of proto-oncogenes (HRAS, KRAS, and NRAS) are present in a great variety of tumors and in the RET proto-oncogene in multiple endocrine neoplasia type 2A and 2B. These mutations can be detected and used to make the diagnosis.[18]

Approaches to screening for and diagnosis of cancer may be based in part on genetic changes. As a result of genome-wide association and other cancer research studies, new biomarkers are expected to be identified in the next decade.[21]

**Gene-Based Prognostics**

Research is ongoing to determine the genetic changes associated with cancer prognosis and disease progression. Waldman et al.[22] found that an intestinal tumor-suppressing receptor in the lymph nodes called guanylyl cyclase C (GUCY2C) may be a better means of determining the risk for metastatic colorectal cancer. At present, prognosis of colorectal cancer is determined through biopsy of the lymph nodes. Even when no cancerous cells are detected in the lymph nodes, however, patients have a one-in-four risk of recurrence. The risk of recurrence increases to one in two when four or more lymph nodes are involved with cancer.

Research of individuals who had no cancerous cells in their lymph nodes found that analysis of GUCY2C looked like an independent marker for prognosis and risk of recurrence. GUCY2C testing suggested malignancy in 87%, in comparison to 13% identified using the conventional molecular staging techniques. The researchers conclude that improving molecular staging using genetic technology has the potential to increase the detection of malignancy, and they call for studies with larger numbers of patients for further assessment of the accuracy and reliability of this approach.[22]

Tumor profiling is emerging in many malignancies and some tests are clinically available, such as MammaPrint and Oncotype DX. For example, Oncotype DX uses gene expression data to quantify recurrence risk in node-negative, ER-positive breast cancer.[23]

A new area of research in cancer prognosis involves the study of ribonucleic acid (RNA) gene products called microRNAs or miRNAs. MicroRNAs are small, non-protein-coding RNA gene products that contribute to regulation of gene expression. Researchers have investigated use of miRNAs as cancer-related biomarkers in hepatocellular carcinoma (HCC). HCC is an aggressive type of cancer that has a high incidence of metastasis and recurrence after surgery. The miRNA expression profiles of both cancerous and noncancerous specimens were examined in a group of patients who had HCC. Results indicate that miRNA expression profiles may help to identify HCC patients who are most likely to experience metastases and recurrence of their cancer. The researchers suggest that conducting a functional analysis of these microarrays may help scientists to better understand HCC metastasis.[24]

**Selection of Treatment**

Human genome research is leading towards a more individualized approach to the use of pharmaceuticals. Pharmacogenomics takes an individual's genetic makeup and uses this information to inform the selection of the drug and drug doses that will work best for that person. This area of research and treatment combines the science of pharmacology, or how drugs work, with the science of genomics.[25]

Treatment of cancer using the science of pharmacogenomics is advancing rapidly. For example, clinical research studies have shown that individuals with metastatic colorectal cancer who have specific mutations in the gene called KRAS benefit from anti-epidermal growth factor receptor (EGFR) antibody therapy with cetuximab (Erbitux). The American Society of Clinical Oncology now recommends that all patients with metastatic colorectal cancer who are candidates for anti-EGFR antibody therapy have their tumor tested for KRAS mutations. Patients found to have a KRAS mutation in certain areas of the gene called codon 12 or 13 do not benefit from cetuximab as a part of their treatment and therefore are not recommended to receive this agent.[26] The US Food and Drug Administration recently approved revisions to the US prescription information for cetuximab in the treatment of patients who have EGFR-expressing metastatic colorectal cancer. Labeling information for cetuximab now states that retrospective studies of metastatic or advanced colorectal cancers have shown no treatment benefit for use of cetuximab in patients whose tumors had KRAS mutations in codon 12 or 13, and therefore cetuximab is not recommended in those patients.[27] Another approach to personalized healthcare and cancer therapy involves targeted therapies. This therapeutic approach involves cancer drugs that specifically target genetic changes in certain malignancies. Treatment of breast cancer is an example of this approach. Trastuzumab (Herceptin) is a monoclonal antibody that binds to human epidermal growth factor receptor 2, called HER2.
Monoclonal antibodies are created in the laboratory and can locate and bind to substances in the body, including cancer cells.[28] This therapy has been found to work for women whose tumors have a specific genetic profile that causes overproduction of HER2, a protein found in some types of cancer cells, including breast and ovarian cancer. Standard practice now involves testing breast cancer tumors for ERBB2 gene expression. Those with HER2-positive breast cancer are candidates for therapy with trastuzumab.[18]

**Monitoring Cancer Treatment Effectiveness**

Genetic and genomic discoveries are also leading to new ways to monitor the effectiveness of cancer treatment. One example is the response to anticancer treatments of children who have acute lymphoblastic leukemia (ALL). Although the cure rates for ALL have increased greatly since the 1960s, individual variation in treatment response has been observed among affected children. Yang and colleagues[29] recently conducted a study to identify genetic factors that may affect treatment response in ALL. The research involved testing in two groups of affected children small genetic variations called single nucleotide polymorphisms (SNPs) for their association with minimal residual disease (MRD) after initial chemotherapy. Many SNPs were associated with MRD in both groups of patients, and some were associated with hematologic relapse. A significant number of the SNPs studied also were associated with early response to treatment and with relapse risk. The researchers concluded that inherited genetic variation of the individual patient affects the effectiveness of anticancer therapy.

**Case Study**

**Family History of Breast and Ovarian Cancer: Role of the Oncology Nurse in Family History Collection and Assessment**

**Patient Overview.** You are an oncology nurse practicing in a high-risk breast cancer outpatient clinic. The first patient of the day is a 41-year-old Caucasian woman who has been referred to your clinic because of her family history of breast and ovarian cancer.

**Risk Assessment.** In your role as an oncology nurse, you review and document her family history (See Figure 1). You learn that her sister, age 45, has a history of right invasive breast cancer diagnosed when she was 40; her mother was diagnosed with ovarian cancer at age 36 and died at age 40 from this disease; a maternal aunt was diagnosed with bilateral invasive breast cancer at age 42 and died at the age of 47 of metastatic disease; a maternal uncle, now age 65, has a history of prostate cancer diagnosed at age 50; the maternal grandmother died from cancer at age 55.
Your patient does not know the type of cancer her grandmother had or when she was diagnosed with the cancer. She has two sons, 15 and 18 years of age. When you inquire about her ethnic background, she tells you that her parents are both of Ashkenazi Jewish descent. The patient tells you that she is “really worried about my risk for breast and ovarian cancer,” and wants to know “What can I do about this?”

**Genetic Education, Counseling, and Nursing Management.** After completing her pedigree (Figure 1), you tell her you will share her family history with the oncology care team. Following a discussion with the oncology care team, you and the oncologist talk with the patient about her family history. You tell her that her family history suggests hereditary breast/ovarian cancer associated with mutations in the \textit{BRCA1} and \textit{BRCA2} genes, which are transmitted in an autosomal dominant pattern. You also let her know that individuals who are of Ashkenazi Jewish ancestry have a higher chance of having an inherited susceptibility to breast and ovarian cancer.\cite{30} You recommend a referral to a genetics specialist who can evaluate her personal and family history and talk with her in detail about genetic testing for mutations in \textit{BRCA1} or \textit{BRCA2}. The patient agrees to see the genetic specialist, and you make the referral that day.

You learn from the genetic specialist several weeks later that your patient and her family have agreed to pursue genetic testing. The genetic specialist explains to you that it is most informative to test an affected family member first for mutations in \textit{BRCA1} or \textit{BRCA2} to learn whether a gene mutation is associated with the cancer in the family. Your patient’s sister has agreed to genetic testing and the results are pending. You learn from your patient several weeks later that her sister was found to have a \textit{BRCA1} gene mutation, 185delAG, which is one of the three specific mutations that are found in a greater frequency in persons of Ashkenazi Jewish heritage. You explain that there are several gene mutations in \textit{BRCA1} and \textit{BRCA2} that are more common in individuals of Ashkenazi Jewish ancestry. These are called founder mutations.\cite{31} Founder mutations are gene mutations that are more frequent in specific populations derived from a small isolated ancestral group in which, generations ago, one or more people carried a gene mutation. The genetic
testing that you and the healthcare team recommend will include these founder mutations, including
the mutation 185delAG that has been identified in your patient's family. Your patient decides to
proceed with genetic testing to learn whether she carries a BRCA1 or BRCA2 mutation. You arrange
for a follow-up visit with your patient in a month.

At the follow-up visit, your patient tells you that she has been found to have the same BRCA1
mutation as her sister. She expresses deep concern and tells you “I want to do whatever I can to
keep from getting breast or ovarian cancer.” You explain to her that you and the oncology team will
talk with her about her options for screening to reduce her risk of breast and ovarian cancer. You and
the team meet with the patient to review her cancer risk management options, which are intensive
screening, chemoprevention, and/or risk-reducing surgery. Breast cancer screening involves a
combination of monthly breast self-exams, annual or semiannual clinical breast examination, annual
mammograms, and annual breast magnetic resonance imaging (MRI).

Screening of her ovaries will involve annual or semiannual transvaginal ultrasound examination, and annual serum CA-125; however, ovarian cancer screening has not been shown to consistently detect ovarian cancer early.[32] Therefore, when childbearing is complete, removal of the ovaries is considered. The patient tells you and the team that she and her husband do not plan to have any more children. She is also told that she has the option of chemoprevention using tamoxifen, which has been shown to reduce the risk for breast cancer by approximately 50%. However, the oncologist informs her that it is not yet clear whether women with a BRCA1 mutation derive the same risk-reduction benefit from tamoxifen.[33]

The oncologist also discusses the option of risk-reducing surgery, removal of her breasts and ovaries to reduce as much as possible her risk of those cancers. Also discussed is that women with a mutation who are premenopausal at the time of risk-reducing oophorectomy reduce their breast cancer risk by approximately 50% and that following oophorectomy, the use of tamoxifen does not add any additional reduction in breast cancer risk.[34–36] Therefore, if she opted for risk-reducing oophorectomy, chemoprevention would not be considered.

You and the team reinforce to the patient that these are difficult choices, none of which should be rushed into. You tell her that, at a minimum, intensive cancer screening should begin, and you arrange those appointments for the patient. You also discuss the fact that consultations with a breast surgeon and a gynecologic oncologist are important, to facilitate her decision-making and so that she can learn more about risk-reducing surgical options. The patient agrees to those consults, which you also arrange. Lastly, you provide her with summary of all the options reviewed during the appointment, your contact information, and instructions to call with any questions, and you schedule a follow-up appointment with the team in one month. You also mark your calendar with a reminder to call the patient in 2 to 3 days to check in and see whether she has any questions or concerns.

The patient returns with her husband for the 1 month follow-up appointment. She informs you and the oncologist that she has decided to undergo risk-reducing surgery for removal of her breasts and ovaries so she can do “whatever I can to prevent getting cancer.” You help your patient to get scheduled for her surgery and prepare for the sudden onset of menopause. Preoperatively you also schedule the patient for a baseline bone density scan and provide her with education about bone health, including the benefits of weight-bearing exercises and taking calcium and vitamin D. Your patient does well postoperatively but continues to struggle with hot flashes.

When you see your patient in follow-up after her surgery, she tells you that she is feeling well except for the hot flashes. However, she states that she is “still anxious about the cancer” and “worried about my two sons who are in their teenage years and their risk for cancer,” adding, “I wish that I had someone to talk with who has gone through this before.” To provide support to your patient, you give her information about a local support group for women at increased risk for cancer. You also refer her to the team social worker for additional support and assessment to be sure that she does not need to be referred to a behavioral health specialist.

In addition, you give her information about the Genetic and Rare Diseases Information Center (GARD). You explain that she can talk to a GARD information specialist about her questions and needs, and assure her that the GARD specialist will work to identify someone who can talk with her.[37] You also suggest that she can follow up with the genetic specialist to whom she spoke originally, to discuss both how to approach her sons with their risk information and at what time the sons should consider genetic education and counseling, to learn more about the BRCA gene
mutation that runs in their family and about genetic testing.

Conclusion
Genetic and genomic research discoveries are transforming healthcare through earlier diagnosis,
more effective risk management and treatment of disease, and avoidance of drug side effects. This new era of healthcare, personalized healthcare, is rapidly being realized in the field of oncology. Genetic and genomic testing and technologies are increasingly being used throughout the cancer care continuum—from prevention, to screening, diagnosis, treatment, and prognosis of many cancers. These discoveries have important implications for oncology nursing practice. The Essentials of Genetic and Genomic Nursing was created in recognition of the important role of genetics and genomics in nursing care. The Essentials provides a foundation for oncology and for all nurses as they integrate genetics and genomics into their daily practice.

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