An Update: Genetic Mutations and Childhood Cancers
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ABSTRACT
Cancer is a disease that arises from genetic mutations that are environmental, inherited, or random in nature. Improvements in technology with next-generation sequencing have made genetic testing and mutation profiling more accessible. It is possible to understand what drives cancerous cell growth and, in some cases, target therapy specifically to those mutations. This article reviews the pathways that can lead to cancer formation, the types of genes involved, options for genetic sequencing, and the role of the nurse practitioner in keeping patients and families informed.

Keywords: cancer, gene, mutation, pediatric

CLINICAL VIGNETTE
A 7-month-old infant was brought to her primary care provider with the chief complaint of refusal to eat, projectile vomiting, and weight loss. An abdominal mass was found on physical exam, leading the primary care provider to refer the family to a pediatric oncologist. Computed tomography scan of the abdomen revealed a retroperitoneal mass arising from the right kidney. Bilateral bone marrow biopsies were performed, excluding metastatic disease. The tumor was surgically resected and both ipsilateral lymph nodes were positive for disease. The patient was diagnosed with Stage 2B neuroblastoma. A biopsy of the tumor was sent out for genomic sequencing, and the tumor came back MYC amplified.

PATHWAYS TO CANCER
While cancers contain thousands of gene variations, approximately 200 are believed to be responsible for controlling tumorigenesis. These mutations are the “drivers” for common cancers; all other mutations believed to be “passengers” do not provide the cancerous cells with a growth advantage over the healthy cells. According to Vogelstein et al.,5 the driver genes can be classified into 12 signaling pathways that can be further organized into three cellular processes: cell fate, cell survival, and genomic maintenance. If these processes are interrupted the
cancerous cell receives a growth advantage, allowing it to proliferate beyond the capability of a healthy cell.

**Cell Fate**

Cell fate is determined when the stem cells differentiate into the specialized forms needed to populate various tissues. Stem cells are undifferentiated cells that have the ability to proliferate indefinitely, an important part of embryogenesis. Once differentiated, cells do not divide like stem cells, and they eventually die. Alterations in genes like APC (see Table 2 for clarification of genes and associated diagnoses) can overcome the processes that hold differentiated cells in check. This provides a selective growth advantage to those cells, allowing them to divide indefinitely (Tables 3 and 4).

**Cell Survival**

Some mutations allow for cancer cells to survive more easily. Mutations in RAS and PTEN genes confer the ability for cells to grow in environments that have limited nutrients. Genes such as CDKN2A and MYC regulate apoptosis, and mutations in these genes can prevent natural cell death. Tumors that have mutations in VHL secrete vascular endothelial growth factor, stimulating angiogenesis to the site of the cancerous cells. These genetic alterations allow mutated cells to survive in conditions where healthy cells cannot.

**Genomic Maintenance**

During cellular division DNA needs to be replicated. When mistakes occur during the replication process, there are checkpoints where corrections are made or steps are taken to prevent the cells from dividing again. Mutations in genes such as ATM and TP53 breakdown these protective measures. By preventing normal genomic maintenance, the cancer cells are able to continue dividing. Each replication includes the initial mutation and that initial genetic alteration predisposes the cells to additional...
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