Mosaicism

Implications for genetic counseling and medical management

Laura Waldman, MS, CGC, and Suzanne M. Mahon, DNSc, RN, AOCN®, AGN-BC

Although the idea that all cells in the body contain an identical genetic component (genotype) may be a tempting one, the reality is that cells often differ genetically. Mosaicism refers to the occurrence of two or more genetically distinct populations of cells having developed from a single fertilized ovum (Machiela & Chanock, 2013). When a mutation occurs in a single cell after conception (postzygotic mutation), this leads to an individual having a mixture of cells, some with the mutation and some without (see Figure 1). Mosaicism can affect any cell or tissue from the developing embryo through adulthood. A mutation may be confined to only a subset of cells or may be present in multiple tissues and/or organs (Nussbaum, McInnes, & Willard, 2016). Mosaicism has been studied extensively in oncology because tumor initiation, maintenance, and evolution are mediated by the sequential acquisition of genetic variants in single cells (Vijg, 2014).

Gonadal or germline mosaicism is the occurrence of two or more genetically distinct cell populations present in the egg or sperm (Fernández, Torres, & Real, 2016). This phenomenon can result in de novo mutations (an alteration in a gene present for the first time in one family member as a result of a mutation in a germ cell or the fertilized egg). When the mutation is present in egg or sperm cells (germline mosaicism), the mutation can be passed on to an individual’s offspring. Somatic mosaicism is the occurrence of two or more genetically distinct cell populations exclusively in somatic cells.

When mosaicism is detected only in cells from adult tissues, it is often impossible to determine when the genetic event leading to mosaicism occurred. An individual who is mosaic for a somatic mutation may or may not show the clinical signs (phenotype) of the disorder caused by that mutation (Vattathil & Scheet, 2016). Because of the exponential rate of growth during embryonic development, somatic mutations must occur early to have expression of phenotypic effects over large portions of the body (Freed, Stevens, & Pevsner, 2014).

Technological advances have resulted in the detection of genetic mosaicism (Biesecker & Green, 2014). When genetic testing reveals mosaicism for a specific mutation, determining what proportion of cells and tissues have this mutation, as well as the impact on cancer risk and whether this mutation could be transmitted to offspring, can be difficult (Cohen, Wilson, Trinh, & Ye, 2015). The following cases illustrate how mosaicism can lead to challenges in genetic counseling and medical management.

Case Study 1

E.W., a 61-year-old woman, was referred for genetic counseling because of a maternal history of breast cancer (see Figure 2) and underwent genetic testing. Results demonstrated that she was “apparently mosaic for a pathogenic variant in TP53: TP53c.916 C>T, p.Arg 306Ter (R306X),” meaning that some, but not all, of the cells had this TP53 mutation. Interpretation of results included the following: The TP53 mutation was a somatic, not inherited,
mutation, or the TP53 mutation was an inherited mutation but not detected in all cells for technical reasons (Gawad, Koh, & Quake, 2016). Individuals who have an inherited TP53 gene mutation have Li-Fraumeni syndrome (LFS). Classic LFS is characterized by certain core cancers, including sarcoma, brain cancer, breast cancer, leukemia, and adrenocortical carcinoma.

To clarify whether the TP53 mutation was attributable to mosaicism or inherited from a parent, a punch biopsy of the skin was performed to determine if the TP53 mutation was present in skin cells in addition to blood cells (Nussbaum et al., 2016). Results demonstrated that the TP53 mutation was not present in the skin cells; this indicated that it was a somatic mutation that occurred after conception, resulting in two cell lines: some with the TP53 mutation and some without the mutation.

Although this patient’s genetic testing results represent mosaicism for the TP53 mutation, the percentage of cells and tissues affected cannot be determined. The TP53 mutation may be present in multiple cells and tissues or confined to the blood cells. Mosaicism confined to a subset of blood cells (hematopoietic clonal mosaicism) is increasingly common with aging and is associated with a heightened risk of hematologic malignancy (Genovese et al., 2014; Jaiswal et al., 2014). Age-related somatic mosaicism for TP53 mutations appears to be common, with one study reporting that TP53 mutations were detected in 9 of 20 blood samples in healthy, cancer-free adults aged 68–89 years (Wong et al., 2015).

Because the level of mosaicism can vary within different tissues in an individual, providing exact cancer risks is not possible. If the TP53 mutation is present in multiple cells and tissues, E.W. would be at risk for LFS-related malignancies.

"Mosaicism can affect any cell or tissue from the developing embryo through adulthood."

FIGURE 1.
PRESENTATION OF MOSAICISM CAUSED BY POSTZYGOTIC MUTATION

Note. The egg and sperm join to form the zygote. After cell division, a genetic mutation occurs. The genetic change is present in some but not all of the cell lines. The earlier it occurs, the more cell lines that are affected and the more likely the genetic change is to be expressed.

the LFS core cancers. Based on E.W.’s skin biopsy results, her age, and her provided personal and family history, recommendations included the following: annual physical examination, including neurologic and skin examination; colonoscopy every five years; yearly breast magnetic resonance imaging; yearly mammograms; and annual screening (complete blood count) for hematologic malignancies. Because the TP53 mutation was likely somatic (not inherited), E.W.’s parents and siblings would not be expected to be at risk to carry the TP53 mutation. However, although E.W. did not inherit the TP53 mutation from a parent, this does not ensure that the mutation is not present in her ovum. E.W. was advised to have her son tested for the mutation.

Case Study 2
J.M., a 38-year-old woman, was referred for genetic counseling and also had testing (see Figure 3). She was offered testing based on having more than 20 polyps (both hamartomas and adenomas) and the extremely early age of first polyp (age 22 years). The polyps were initially detected after an episode of unexplained gastrointestinal bleeding. Her report showed “mosaic likely pathogenic mutation in BMPR1A c.176T>A (p.Leu59Ter).” Clinically, J.M. appears to have juvenile polyposis syndrome (JPS), based on the hamartomas (a benign growth or type of polyp) and early age of diagnosis. BMPR1A mutations are associated with JPS and characterized by multiple hamartomatous polyps in the colon, rectum, and stomach. JPS is usually diagnosed in the teenage years, following an episode of gastrointestinal bleeding. Screening is initiated in patients aged about 15 years because, on average, polyps begin undergoing adenomatous changes in patients aged about 18 years (National Comprehensive Cancer Network [NCCN], 2017). Because the mutation is mosaic, the number of cell lines affected is unclear. However, clinically speaking, J.M. has JPS. Recommendations for screening include annual colonoscopy with upper endoscopy (NCCN, 2017). Cancer risks for BMPR1A mutation carriers are estimated to be 50% for colon cancer and 21% for gastric cancer (NCCN, 2017). Genetic testing was offered to J.M.’s parents. When J.M.’s children are aged about 15 years, they will be offered genetic testing because the mutation could be present in J.M.’s ovum. Children are typically not offered testing except with syndromes in which screening recommendations would be affected (such as a BMPR1A gene mutation) (Ross, Saal, David, & Anderson, 2013).

Implications for Nursing
The finding of mosaicism for a cancer risk gene mutation can lead to several questions, including the following (Machiela & Chanock, 2013):
What percentage of cells, tissues, and organs have the mutation?

What is the estimated cancer risk?

What cancer screening is indicated?

Are the patient’s children and/or other family members at risk for having the mutation?

A thorough genetic evaluation that features assessment of the patient and his or her family history, communication with the laboratory that performed the testing, and review of the relevant literature are required to address these questions. Additional testing, such as analysis of cells from a punch biopsy of the skin, may also be indicated.

In the first case study, the patient’s results most likely represent somatic mosaicism from a postzygotic mutation that occurred later in development. Conversely, the second case study represents somatic mosaicism from a postzygotic mutation that occurred earlier in development. However, for both case studies, determining what percentage of cells and tissues have the mutation and whether the mutation could be passed to offspring is not possible.

The rapid evolution of genomic technologies has resulted in the ability to assess genetic variation between and within individuals. These technologic advances have led to increasing evidence that genetic mosaicism is common (Fernández et al., 2016). In both case studies, the genetics professional had extensive consultation with the laboratory to make the best possible recommendations for care. The clinical challenges presented by the finding of mosaicism require a strong genetics knowledge base to interpret these results and effectively communicate the findings to a patient. The case studies presented illustrate the importance of referral to and communication with a credentialed genetics professional when genetic testing reveals mosaicism. Oncology nurses should anticipate close collaboration with genetics professionals to ensure that families receive proper recommendations for testing, screening, and prevention, as well as the necessary psychosocial support.

**Conclusion**

Oncology nurses can anticipate that, with the ever-increasing use of genetic testing for hereditary cancer syndromes, they will encounter patients with mosaicism. Because this is typically an unexpected and confusing finding in genetic testing, these families will need support and education. Collaboration with credentialed genetics professionals and the subspecialists who provide the recommended screening will result in the best possible outcomes for these patients and their families.

Laura Waldman, MS, CGC, is a genetic counselor in the School of Medicine, and Suzanne M. Mahon, DNSSc, RN, AOCN®, AGN-BC, is a professor in the Department of Internal Medicine, Division of Hematology/Oncology and the School of Nursing, both at Saint Louis University in Missouri. Waldman can be reached at waldmanl@slu.edu, with copy to CJONEditor@ons.org.

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**REFERENCES**


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