Mosaicism describes the presence of two or more populations of cells with different genotypes in one individual that have developed from a single fertilized egg. This article reviews the various clinical presentations of mosaicism associated with hereditary cancer syndromes and the challenges in providing patients and their families with appropriate genetic testing, as well as provides recommendations for cancer presentation and early detection. Management of mosaicism is based on personal and family history, along with genetic testing results.

**AT A GLANCE**
- Newer technologies and more widespread use of genetic testing have resulted in the detection of more cases of mosaicism.
- Recommendations for care are made following careful review of the patient’s personal and family history and discussion with the laboratory; additional testing may be needed to further clarify the meaning of the results.
- Oncology nurses should communicate with the genetics professional to obtain a clear understanding of the rationale behind the recommendations for care, as well as implications for testing in other family members, to ensure comprehensive care and psychosocial support for the patient and his or her family.

**KEYWORDS**
mosaicism; Li-Fraumeni syndrome; juvenile polyposis syndrome; genetic testing

**DIGITAL OBJECT IDENTIFIER**
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**Mosaicism**

**Implications for genetic counseling and medical management**

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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. However, if the TP53 is confined to a subset of blood cells, she would be at increased risk for a hematologic malignancy but not at risk for other LFS cancers. E.W.’s personal and family history did not meet diagnostic criteria for LFS (Daly et al., 2017). She had no history of cancer, and although her mother had breast cancer, no other family members had any of the core cancers associated with LFS.

"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.

**Note.** From “Mosaicism,” by Genomics Education Programme, 2014, licensed under CC BY 2.0 (https://creativecommons.org/licenses/by/2.0). Retrieved from https://www.flickr.com/photos/genomicseducation/1308075533.
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):

**FIGURE 2.**

**CASE STUDY 1: PEDIGREE FOR PROBAND WITH MOSAICISM FOR TP53 MUTATION**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of males or females</th>
</tr>
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<tbody>
<tr>
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<tr>
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<tr>
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<td>lung 67</td>
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</tr>
<tr>
<td>42</td>
<td>cervical 35</td>
</tr>
<tr>
<td>61</td>
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Note. Genetic testing was performed because of a family history of breast cancer. The 63-year-old proband did not have a diagnosis of cancer, but her mother had early onset breast cancer. A blood sample was sent for multigene panel testing, which used next-generation sequencing to analyze the following 32 genes: APC, ATM, AKT1, BARD1, BMPR1A, BRCA1, BRCA2, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLE, PTEN, RAD51, RAD51D, SCCS/GREM1, SMAD4, STK11, TP53, VHL, and XRCC2.
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.

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**REFERENCES**


Genetics & Genomics aims to educate oncology nurses about the emerging role of genetics and genomics in cancer care. If you are interested in writing for this department, contact Associate Editor Suzanne M. Mahon, DNSc, RN, AOCN®, AGN-BC, at mahonsm@slu.edu.