Articles on next-generation sequencing to detect \textit{RB1} mutations and on the cytogenetic analysis of \textit{JAZF1}, \textit{PHF1}, and \textit{YWHAE} in endometrial stromal tumors were selected for the \textbf{July 2016 JMD CME Program in Molecular Diagnostics}. The authors of the referenced articles, the planning committee members, and staff have no relevant financial relationships with commercial interests to disclose.


Upon completion of this month’s journal-based CME activity, you will be able to:
- Define retinoblastoma.
- Describe the \textit{RB1} gene and the \textit{RB1} mutation.
- Explain the difference between bilateral and unilateral retinoblastomas.
- Define retinoblastoma with \textit{MYCN} gene amplification.
- Define and explain the difference between endometrial stromal tumors (ESTs), endometrial stromal nodules (ESNs), and low-grade endometrial stromal sarcomas (ESSs).
- Understand the fusion of \textit{JAZF1} to \textit{SUZ12} in ESTs.
- Describe the function of fusion genes involving \textit{JAZF1}, \textit{PHF1}, \textit{EPC1}, and \textit{YWHAE}.

1. Retinoblastoma is a childhood eye malignancy that can lead to the loss of vision, eye(s), and sometimes life. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:480-493.]
   a. Retinoblastoma is a malignant retinal tumor that occurs most often in the first three years of life.
   b. Retinoblastoma can occur as either a hereditary form or a nonhereditary form.
   c. The overall incidence of retinoblastoma is approximately one in 5,000 to 10,000 live births.
   d. Without proper management, retinoblastoma leads to metastatic disease and death, which occurs in 50% to 70% of affected children worldwide.

2. Retinoblastoma can present as bilateral or unilateral disease. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:480-493.]
   a. Approximately 50% of bilateral retinoblastomas are caused by a heritable germline mutation in the \textit{RB1} gene.
   b. A small percentage of retinoblastomas are caused by a mosaic \textit{RB1} mutation.
   c. Germline \textit{RB1} mutations can lead to nonocular malignancies in both childhood and adulthood.
   d. Nonocular tumors (notably osteosarcoma, the most common second malignancy) are generally more aggressive and less curable than retinoblastoma, highlighting the importance of identifying germline carriers.
3. Determining whether mutations are germline or somatic is essential for establishing prognosis, implementing cancer screening regimens, and guiding genetic counseling of retinoblastoma patients and their families. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:480-493.]

a. Most unilateral retinoblastomas are caused by RB1 somatic mutations during retinal development.
b. Five percent of unilateral retinoblastoma patients carry germline mutations.
c. Most unilateral retinoblastomas are nonhereditary.
d. Rapid molecular diagnosis can facilitate patient management and improve treatment outcomes by identifying patients and family members who are at risk for second malignancies.

4. Current procedures to identify disease-causing RB1 mutations can be lengthy, often requiring weeks or months to do thorough analyses. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:480-493.]

a. The RB1 gene contains approximately 103,000 bp with 18 exons.
b. In retinoblastoma, 11 recurrent premature termination codon mutations comprise approximately 22% of all RB1 mutations, with the remainder composed of various types of mutations scattered throughout the gene.
c. Clinical laboratories use a variety of methods to ensure comprehensive RB1 testing, including Sanger sequencing to identify point mutations and small insertions and deletions (indels) in exons and in exon-intron splicing junctions.
d. Large deletions and duplications in the RB1 gene can be detected by an alternate technology, such as multiplex ligation-dependent probe amplification (MLPA) or quantitative multiplex PCR.

5. Defining the molecular etiology of retinoblastoma when no RB1 mutations are detected is a diagnostic challenge. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:480-493.]

a. Approximately 2% to 3% of childhood retinal tumors do not have an RB1 mutation that can be identified using current approaches.
b. Approximately 70% of retinal tumors with no RB1 mutations had MYCN gene amplifications.
c. Retinoblastoma with MYCN amplification has an aggressive phenotype and etiologically resembles MYCN amplified neuroblastoma.
d. Because MYCN amplification in combination with wild-type RB1 has been observed only in nonhereditary retinoblastoma, in cases where no RB1 mutation can be found, MYCN amplification status can be tested to differentiate between RB1 mutation and MYCN amplification–driven retinoblastomas.

6. Diagnosis of endometrial stromal tumors (ESTs) can be challenging, particularly endometrial stromal sarcomas due to variable histologic appearance, long latency to recurrence, frequent metastases with unknown primary, and overlap with endometrial stromal nodules and undifferentiated uterine sarcomas. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:516-526.]

a. ESTs represent the second most prevalent group of uterine mesenchymal neoplasms and have variable malignant potential.
b. Endometrial stromal nodules (ESNs) are well-circumscribed, encapsulated tumors.
c. Low-grade endometrial stromal sarcomas (ESSs) are histologically similar to ESN but have a greater malignant potential due to infiltrative growth in a characteristic ‘finger-like’ pattern into the myometrium and/or vascular invasion.
d. Distinction between ESN and low-grade ESS is primarily based on evaluation of the tumor-myometrium interface.

7. ESTs are genetically heterogeneous. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:516-526.]

a. The fusion of JAZF1 to SUZ12, resulting from t(7;17)(p15;q11.2), occurs in both low-grade classic and variant histology tumors as well as in primary and extrauterine lesions.
b. Fusions of JAZF1/PHF1 and JAZF1/EPC1 are involved in low-grade cases.
c. PHF1 rearrangement partners in ESTs include EPC1 at 1p34 and MEAF6 at 10p11.
d. Disruption of JAZF1 or PHF1 can occur without any currently known partner.

8. The oncogenic mechanism of the genetic fusions in ESTs is speculative. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:516-526.]

a. The normal function of the zinc finger–containing JAZF1 gene is unclear.
b. PHF1 is known to affect processes, such as development and cell proliferation, through modulation of histone H3 methylation as part of the polycomb repressive complex 2 (PRC2).
c. The gene EPC1 also encodes a polycomb group protein that is involved in chromatin remodeling.
d. MEAF6 modulates phosphoserine-containing proteins and regulates multiple signaling pathways, including those affecting differentiation and survival.