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CME November Questions # 1-12

Research articles on amplicon-based next-generation sequencing panels for detection of germline *BRCA1* and *BRCA2* alterations, curating sequence variants of transcripts of hearing loss—associated genes, and diagnostics of hepatocellular carcinoma genomic screening were selected for the **November 2018 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.

Questions #1-4 are based on: Vendrell JA, Vilquin P, Larrieux M, Van Goethem C, Solassol J: Benchmarking of amplicon-based next-generation sequencing panels combined with bioinformatics solutions for germline *BRCA1* and *BRCA2* alteration detection. J Mol Diagn 2018, 20:754-764; https:// doi.org/10.1016/j.jmoldx.2018.06.003.

Questions #5-8 are based on: DiStefano MT, Hemphill SE, Cushman BJ, Bowser MJ, Hynes E, Grant AR, Siegert RK, Oza AM, Gonzalez MA, Amr SS, Rehm HL, Tayoun ANA: Curating clinically relevant transcripts for the interpretation of sequence variants. J Mol Diagn 2018, 20:789-801; https://doi.org/10.1016/j.jmoldx.2018.06.005.

Questions #9-12 are based on: Paradiso V, Garofoli A, Tosti N, Lanzafame M, Perrina V, Quagliata L, Matter MS, Wieland S, Heim MH, Piscuoglio S, Ng CKY, Terracciano LM: Diagnostic targeted sequencing panel for hepatocellular carcinoma genomic screening. J Mol Diagn 2018, 20:836-848; https://doi.org/10.1016/j.jmoldx.2018.07.003.

Upon completion of this month's journal-based CME activity, you will be able to:

- Describe the cumulative risk of breast cancer associated with germline mutations in *BRCA1* and *BRCA2*.
- Describe the cumulative risk of ovarian cancer associated with germline mutations in *BRCA1* and *BRCA2*.
- Define the types of *BRCA1* and *BRCA* aberrations, including single-nucleotide variations, short insertion/deletion variations (indels) located in the coding regions or near intron-exon boundaries, large genomic arrangements with the deletion or duplication of one or several exons (copy number variations).
- Describe the demographics of hearing loss in infants.
- Discuss hearing loss—associated genes.
- Understand subtypes of Waardenburg syndrome (WS).
- Understand the mutational profile of hepatocellular carcinoma (HCC).
- Discuss coverage of a newly described HCC screening panel.
- Discuss the parameters of tumor purity when screening for HCC.

1. *BRCA1* and *BRCA2* are reported to be the main penetrant genes causing a hereditary predisposition to breast and ovarian cancer syndrome. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:754-764.]

a. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of breast cancer at the age of 70 years of approximately 45% to 60% and 45% to 55%, respectively.
b. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of breast cancer at the age of 70 years of approximately 35% to 60% and 35% to 55%, respectively.
c. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of breast cancer at the age of 70 years of approximately 57% to 65% and 45% to 55%, respectively.
d. Germline mutations in *BRCA1* and *BRCA2* each confer a cumulative risk of breast cancer at the age of 70 years of approximately 45% to 65%.

2. Information about the germline alteration status of *BRCA1* and *BRCA2* will enable patients and health-care providers to make informed decisions about cancer prevention, screening, and treatment. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:754-764.]

a. Germline mutations in *BRCA1* and *BRCA2* each confer a cumulative risk of ovarian cancer at the age of 70 years of approximately 15% to 18%.
b. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of ovarian cancer at the age of 70 years of approximately 39% to 44% and 11% to 18%, respectively.
c. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of ovarian cancer at the age of 70 years of approximately 25% to 40% and 15% to 25%, respectively.
d. Germline mutations in *BRCA1* and *BRCA2* confer a cumulative risk of ovarian cancer at the age of 70 years of approximately 35% to 45% and 15% to 18%, respectively.

3. One of the main difficulties encountered by PCR enrichment methods is the specific and accurate detection of copy number variants (CNVs). Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:754-764.]

a. CNVs account for approximately 7% of all inherited BRCA alterations.
b. CNVs account for approximately 9% of all inherited BRCA alterations.
c. CNVs account for approximately 10% of all inherited BRCA alterations.
d. CNVs account for approximately 11% of all inherited BRCA alterations.

4. The emergence of next-generation sequencing (NGS) technologies has modified the genetic testing workflow in molecular diagnostic laboratories. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:754-764.]

a. The authors of the referenced article assessed four PCR-based kits and two bioinformatics software solutions on a set of 128 samples previously characterized for the detection of *BRCA1* and *BRCA2* alterations, followed by validation on an independent cohort of 135 samples.
b. The authors of the referenced article assessed four PCR-based kits and two bioinformatics software solutions on a set of 28 samples previously characterized for the detection of *BRCA1* and *BRCA2* alterations, followed by validation on an independent cohort of 152 samples.
c. The authors of the referenced article assessed four PCR-based kits and two bioinformatics software solutions on a set of 28 samples previously characterized for the detection of *BRCA1* and *BRCA2* alterations, followed by validation on an independent cohort of 135 samples.
d. The authors of the referenced article assessed four PCR-based kits and two bioinformatics software solutions on a set of 128 samples previously characterized for the detection of *BRCA1* and *BRCA2* alterations, followed by validation on an independent cohort of 152 samples.

5. Hearing loss is a relatively common condition. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:789-801.]

a. Hearing loss affects 1 in 250 infants.
b. Hearing loss affects 1 in 150 infants.
c. Hearing loss affects 1 in 350 infants.
d. Hearing loss affects 1 in 300 infants, half of whom have a genetic cause.

6. The auditory system is complex and highly heterogeneous, with >100 genes causative for nonsyndromic hearing loss alone. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:789-801.]

a. The authors curated a hearing loss panel of 105 genes consisting of 300 unique transcripts and 1446 unique exons across all genes.
b. The authors curated a hearing loss panel of 109 genes consisting of 240 unique transcripts and 2146 unique exons across all genes.
c. The authors curated a hearing loss panel of 105 genes consisting of 340 unique transcripts and 1446 unique exons across all genes.
d. The authors curated a hearing loss panel of 109 genes consisting of 340 unique transcripts and 2146 unique exons across all genes.

7. Curated hearing loss—associated genes were divided into three categories using National Center for Biotechnology Information (NCBI) reference sequence (RefSeq) transcripts (*https://www.ncbi.nlm.gov/ref/seq/rsg*). Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:789-801.]

a. Of the hearing loss—associated genes evaluated, 38 had a single RefSeq transcript and were classified as category 1 genes.
b. Of the hearing loss—associated genes evaluated, 43 had multiple RefSeq transcripts.
c. Of the hearing loss—associated genes evaluated, 33 had multiple RefSeq transcripts and were classified as category 2 genes.
d. Of the hearing loss—associated genes evaluated, 48 were classified as category 3 genes.

8. Waardenburg syndrome (WS) is a group of genetic conditions that can cause hearing loss and changes in pigmentation. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:789-801.]

a. *END3*, known to cause WS, type 1, was characterized as a category 2 gene.
b. *END3*, known to cause WS, type 4, was characterized as a category 3 gene.
c. *END3*, known to cause WS, type 4, was characterized as a category 2 gene.
d. *PAX3* is a common cause of WS, type 4.

9. Hepatocellular carcinoma (HCC) has a distinct mutational profile compared to common cancer types. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:836-848.]

a. *Genes such as APOB, ALB, TP53,* and *CTNNB1* are frequently mutated in HCC as well as cancers of the lung, breast, and colon.
b. Genes such as *TP53* and *CTNNB1* are frequently mutated in HCC and common cancer types (eg, lung, breast, and colon).
c. Most commercial sequencing panels target *TP53*, *CTNNB1*, *APOB*, and *ALB*.
d. Most commercial sequencing panels target *TP53*, *ALB*, and *HNF4A*.

10. The distinct mutational landscape of HCC is likely a result of the unique biology of hepatocyte differentiation and liver functions. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:836-848.]

a. Commercially available sequencing panels target noncoding regions such as *TERT* promoter mutation hotspot (c.-124C>T).
b. Long noncoding RNA (lncRNA) genes frequently mutated in HCC, such as *MALAT1* and *NEAT1*, have recently been added to commercially available sequencing panels.
c. Recent whole genome studies have uncovered an HCC mutational cluster in the promoter region of *HNF1A*.
d. Recent whole genome studies have uncovered an HCC mutational cluster in the promoter region of *HNF4A*.

11. The authors of the referenced study designed a custom HCC sequencing panel. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:836-848.]

a. Out of 39 cases profiled with the HCC panel, at least one somatic mutation was detected in 75% of the cases.
b. Approximately one-fourth of the mutations on the HCC panel were within the promoter and lncRNA regions.
c. The panel targeted exons of 23 protein-coding regions and promoter regions of three genes.
d. The panel targeted all exons of 33 protein-coding regions, two lncRNA genes, promoter regions of four genes, nine genes frequently affected by copy number alterations (CNAs), and mutation hotspots in seven common cancer genes.

12. In the clinical setting, the quality, type, and amount of input materials for genomic profiling are important considerations, particularly in light of the smaller tumors being detected. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2018, 20:836-848.]

a. The HCC panel could be used for genomic screening with high sensitivity and specificity with low-input DNA (20 ng) derived from formalin-fixed, paraffin-embedded (FFPE) samples.
b. At least 30 ng of input DNA from FFPE samples were required for high sensitivity and specificity.
c. Somatic genetic alterations could be detected from tumor samples with as low as 25% tumor content.
d. Somatic genetic alterations could be detected from tumor samples with as low as 40% tumor content.