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CME March Questions # 1-12

Articles on solid tumor genomic profiling of *ERBB2* amplification status, *TSC1*/*TSC2* gene analysis in patients with tuberous sclerosis complex, and clinical genomic profiling of oncology specimens were selected for the **March 2017 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 #1-5 are based on: Ross DS, Zehir A, Cheng DT, Benayed R, Nafa K, Hechtman JF, Janjigian YY, Weigelt B, Razavi P, Hyman DM, Baselga J, Berger MF, Ladanyi M, Arcila ME: Next-generation assessment of human growth factor receptor 2 (*ERBB2*) amplification status: Clinical validation in the context of a hybrid capture-based, comprehensive solid tumor genomic profiling assay. J Mol Diagn 2017, 19:244-254; http://dx.doi.org/10.1016/j.jmoldx.2016.09.010.

Questions #6-10 are based on: Ismail NFD, Rani AQ, Malik NMANA, Hock CB, Azlan SNM, Razak SA, Keng WT, Ngu LH, Silawati AR, Yahya NA, Yusoff NM, Sasongko TH, Zabidi-Hussin ZAMH: Combination of multiple ligation-dependent probe amplification and Illumina MiSeq amplifcon sequencing for *TSC1*/*TSC2* gene analyses in patients with tuberous sclerosis complex. J Mol Diagn 2017, 19:265-276; http://dx.doi.org/10.1016/j.jmoldx.2016.10.009.

Questions #11-12 are based on: Sireci AN, Aggarwal VS, Turk AT, Gindin T, Mansukhani MM, Hsiao SJ: Clinical genomic profiling of a diverse array of oncology specimens at a large academic cancer center: Identification of targetable variants and experience with reimbursement. J Mol Diagn 2017, 19:277-287; http://dx.doi.org/10.1016/j.jmoldx.2016.10.008.

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

- Define human epidermal growth factor receptor 2 (HER2 or ERBB2).
- Understand HER2-positive breast tumors.
- Explain the significance of HER2 status in patients with gastroesophageal adenocarcinoma.
- Describe HER2 evaluation methods.
- Understand hybrid capture-based next-generation sequencing (NGS) assays.
- Describe tuberous sclerosis complex (TSC).
- Understand the function of tuberous sclerosis complex 1 (*TSC1*) and tuberous sclerosis complex 2 (*TSC2*) genes.
- Explain *TSC1/TSC2* mutation analyses.
- Understand the characteristics of the *TSC1* and *TSC2* genes.
- Describe multiple ligation-dependent probe amplification and amplicon sequencing.
- Explain and understand the challenges associated with Current Procedural Terminology (CPT) code 81455.
- Understand the challenges and uncertainties of developing large cancer genomic test panels.

1. Establishing the *ERBB2* [human epidermal growth factor receptor 2 (HER2)] amplification status in breast and gastroesophageal carcinomas is essential to the patient's treatment plan. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:244-254.]

a. HER2 is a 93-kDa transmembrane tyrosine kinase receptor encoded by the *ERBB2* gene.
b. HER2 is a biomarker and therapeutic target in patients with breast and gastric/gastroesophageal (GE) cancers.
c. Approximately 10% to 15% of all breast and 30% to 40% of all gastric or GE cancers are classified as HER2-positive as a result of *ERBB2* gene amplification and the subsequent overexpression of the HER2 protein on the surface of tumor cells.
d. Therapies targeting HER2 are currently not approved for clinical use.

2. Therapies targeting HER2 include the HER2-directed humanized monoclonal antibodies and small molecule HER2 kinase inhibitors. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:244-254.]

a. HER2-positive status in breast cancer predicts response to HER2-targeted therapy.
b. Multiple prospective randomized trials of HER2-targeted therapy in breast cancer have failed to show significant improvement in time to tumor progression.
c. HER2-positive breast tumors have been associated with better prognosis compared to HER2-negative tumors.
d. Trastuzumab and lapatinib are HER2-directed humanized monoclonal antibodies.

3. The prognostic significance of HER2 status in patients with GE adenocarcinoma is under investigation. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:244-254.]

a. The prognostic significance of the HER2-positive status in patients with GE adenocarcinoma has been clearly demonstrated in multiple studies.
b. Results of a randomized phase 3 trial demonstrated poor response when pertuzumab was added to chemotherapy in patients with HER2-positive adenocarcinoma of the stomach and the esophagogastric junction.
c. *ERBB2* amplification is not a potential therapeutic target in lung cancer.
d. The role of HER2-targeted therapy in solid malignancies, including bladder, endometrium, colorectal cancers, among others, is an area of active study.

4. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) have recommended several methods for evaluation of HER2 in breast and gastric cancers. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:244-254.]

a. ASCO and CAP HER2 evaluation methods include immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH) and bright field *in situ* hybridization.
b. FISH detects the expression of the HER2 protein in a tumor.
c. IHC detects amplification of the *ERBB2* gene.
d. *ERRB2* assessment by next-generation sequencing (NGS) methods has been clinically validated and is becoming incorporated in molecular diagnostic laboratories.

5. With further advancements in genomic medicine, new clinically relevant biomarkers are rapidly emerging and options for targeted therapy are increasing in patients with advanced diseases, driving the need for comprehensive molecular profiling. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:244-254.]

a. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay, a hybrid capture-based NGS assay interrogating the coding regions of 200 cancer-related genes, was performed on unstained sections from formalin-fixed, paraffin-embedded (FFPE) breast and gastroesophageal tumors submitted for clinical mutation profiling.
b. *ERBB2* status was assessed using a custom bioinformatics pipeline and NGS results were compared to PCR amplification.
c. NGS *ERBB2* amplification calls had an overall concordance of 86.3% with the combined IHC/FISH results in the MSK-IMPACT validation set.
d. Discrepancies between NGS *ERBB2* amplification calls and IHC/FISH results in the MSK-IMPACT validation set occurred in the context of low tumor content and HER2 heterogeneity.

6. Tuberous sclerosis complex (TSC) is a neurocutaneous disorder. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:265-276.]

a. TSC is characterized by tumor growth in multiple organs, including the breast, colon, stomach, pancreas, and liver.
b. TSC is characterized by a broad phenotypic spectrum, including loss of appetite, blood disorder, renal dysfunction, dermatological abnormalities, and tumors.
c. TSC is an autosomal dominant neurocutaneous disorder.
d. Most TSC patients experience short-term mild symptoms.

7. TSC is caused by mutation in either one of two disease-causing genes. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:265-276.]

a. TSC disease-causing genes include tuberous sclerosis complex 1 (*TSC1*) and tuberous sclerosis complex 2 (*TSC2*) encoding hamartin and tuberin, respectively.
b. Up to 20% to 40% of TSC patients showed no *TSC1/TSC2* mutation identified by conventional genetic testing.
c. There are four mutation hot spots in *TSC1* and *TSC2*.
d. Most TSC patients harbor mutations in exon 1 of *TSC1*.

8. The most recent criteria (2012) for diagnosis of TSC emphasized the significance of *TSC1/TSC2* mutation analyses in establishing the diagnosis. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:265-276.]

a. Up to 10% of *TSC1/TSC2* mutations are small mutations involving one to several nucleotides.
b. Approximately 90% of *TSC1/TSC2* mutations are gross changes in the *TSC1/TSC2* genes.
c. All types of mutations have been reported to be found in both TSC loci.
d. According to the Human Gene Mutation Database, more than 700 and 200 unique mutations have been reported in *TSC1* and *TSC2*, respectively.

9. The new diagnostic criterion of identifying *TSC1* and *TSC2* mutations to make a definitive diagnosis of TSC presents challenges in molecular methodology. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:265-276.]

a. *TSC1* and *TSC2* genes comprise a total of 60 kb.
b. *TSC1* and *TSC2* genes comprise a total of 62 coding exons.
c. *TSC1* and *TSC2* genes are transcribed into 9.2 kb of mRNA.
d. *TSC1* is located on the short arm of chromosome 12.

10. The authors of the referenced article used multiple ligation-dependent probe amplification and amplicon sequencing in an attempt to simplify the *TSC1/TSC2* mutation detection strategy and yet come up with a reasonably high detection rate. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:265-276.]

a. *TSC1* pathogenic or likely pathogenic mutations were found in 15 patients.
b. *TSC2* pathogenic or likely pathogenic mutations were found in 28 patients.
c. Ten patients showed no mutations.
d. One patient showed a *TSC2* missense variant with uncertain significance.

11. The availability and accessibility of NGS technologies combined with the identification of increasing numbers of driver mutations from large scale cancer sequencing projects have led to evolving needs in the practice of oncology and precision medicine. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:277-287.]

a. Multi-gene panels performed on tumor tissue covering >100 genes inclusive of copy number and translocations are coded using a single Current Procedural Terminology (CPT) code 81455.
b. CPT code 81455 was adopted in 2013 by the American Medical Association under Genomic Sequencing Procedures.
c. Past experience with introduction of new molecular CPT codes suggested that Medicare administrative contractors and other payers quickly adopt consistent payment decisions.
d. Adoption of the 81455 code introduced uncertainty with regard to reimbursement because, unlike the prior codes, the 81455 code had not yet been valued on the Clinical Laboratory Fee Schedule nor had any coverage determinations been rendered.

12. Large cancer panels are being increasingly utilized in the practice of precision medicine to generate genomic profiles of tumors with the goal of identifying targetable variants and guiding eligibility for clinical trials. Based on the referenced article, select the ONE best TRUE statement: [See J Mol Diagn 2017, 19:277-287.]

a. To facilitate identification of mutations in a broad range of solid and hematological malignancies, a 1027-gene oncology panel was developed in collaboration with pathologists and oncologists and is currently available and in use for clinical diagnostics.
b. Of 350 submitted specimens, which encompassed a diverse range of tumor types, 85% of specimens were successfully sequenced.
c. The CCCP assay led to the detection of a targetable variant in 48.7% of cases.
d. Reimbursement from government and third party payers using the 81455 CPT code was at 39.5% of billed costs; 70% of cases were rejected on first submission.