CME May Questions #1-12

1. The phosphatidylinositol-3-kinases (PI3Ks) are heterodimeric lipid kinases. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:312-318.]

   a. PI3Ks are involved in regulation of cellular growth, transformation, adhesion, apoptosis, survival, and motility.
   b. PIK3CA encodes the PI3K p110-α catalytic subunit.
   c. PIK3CA is mutated frequently in invasive breast cancer as well as gastric, colon, lung, brain, endometrial, and other carcinomas.
   d. There are three mutational hotspots in PIK3CA: codons 542 and 547 of exon 9 (kinase domain) and codon 1005 of exon 20 (helical domain).
2. Studies have shown that PIK3CA mutations are associated with the activation of the downstream PI3K/Akt/mTOR signaling. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:312-318.]
   a. Point mutations in the three PIK3CA mutational hotspot codons account for more than 90% of PIK3CA mutations in human cancers.
   b. PIK3CA mutations are transforming in cell culture.
   c. PIK3CA mutations are tumorigenic when overexpressed in the mammary gland in mouse models.
   d. PIK3CA mutations have prognostic and therapeutic implications.

3. Several assays have been developed to identify PIK3CA mutations. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:312-318.]
   a. With the ongoing development of pharmacological agents targeting the PI3K pathway, detection of PIK3CA mutations will become increasingly important.
   b. High-resolution DNA melting analysis (HRM), pyrosequencing, and real-time PCR are among the assays that can identify PIK3CA mutations.
   c. Direct Sanger sequencing is one of the most commonly applied methods for the detection of PIK3CA mutations.
   d. Direct Sanger sequencing has a low mutation detection sensitivity of about 5% to 10%.

4. Locked nucleic acid (LNA)-PCR is an enrichment method that can enhance mutation detection. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:312-318.]
   a. LNA is a nucleic acid analog that contains a 2'-O,4'-C-methylene bridge in the ribose moiety.
   b. When incorporated into a DNA oligonucleotide, LNA raises its thermal stability with complementary DNA.
   c. The authors optimized the LNA-PCR assay to completely block wild-type DNA amplification.
   d. Decreasing the concentration of LNA oligonucleotide decreased the resultant mutant:wild-type peak height ratio.

5. Patients with cystic fibrosis (CF) manifest a multisystemic disease due to mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:331-340.]
   a. CF is the most frequent lethal inherited disorder among white people, with an incidence of 1:1000 newborns.
   b. The diagnosis of CF is based on symptoms, sweat chloride levels, and molecular analysis findings.
   c. CF patients manifest alterations of the chloride channel expressed by most epithelial cells.
   d. Causative mutations are identified in 90% to 95% of CF chromosomes using scanning procedures to analyze whole coding regions of CFTR and large gene rearrangements.

6. Despite extensive testing of coding regions of CFTR, a proportion of CF alleles remains unidentified. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:331-340.]
   a. CF exhibits a strong genotype-phenotype correlation.
   b. The molecular mechanisms underlying the transcriptional control of CFTR in different tissues and organs are poorly understood.
   c. Few regulatory elements of CFTR have been described in the literature.
   d. The 3.8 kb region upstream of exon 1 of the CFTR gene has high GC content (65%), no TATA box, multiple transcriptional start sites, and several potential Sp1 and AP-1 protein binding sites.

7. The region at the 5' of CFTR may have a relevant role in the regulation of CFTR expression. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:331-340.]
   a. The authors studied the 6000-bp region at the 5' of CFTR in a group of 118 unrelated Italian patients affected by CF or CFTR-related diseases (RDs) and identified 23 mutations.
   b. The c.-3966T>C allele had a relatively low frequency of 2.0% in patients with CFTR-RDs and 4.6% in patients with CF.
   c. The c.-5671C>T allele had a high frequency ranging from 24.2% in patients with CFTR-RDs to 75.9% in patients with CF.
   d. Unlike mutations of CFTR coding regions (whose effects involve CFTR activity in all cells), the mutations in the promoter region may have a different effect on different tissues, thus influencing the clinical expression of CF in the single patient.

8. Human papillomaviruses (HPVs) are the causative agents of both benign and malignant lesions of the uterine cervix. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:373-379.]
   a. HPVs are associated with a subset of other ano-genital cancers and head and neck squamous cell carcinoma.
   b. HPVs seem to be involved in the development of nonmelanoma skin cancer.
   c. A limited number of HPV genotypes have a role in the development of cervical cancer.
   d. HPV 16 is present in >90% of all cervical cancers worldwide.
9. The carcinogenic potential of the various HPV genotypes varies. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:373-379.]

   a. The risk of developing high-grade cervical lesions and cancer depends on the genotype(s) responsible for the infection.
   b. Accurate assessment of the spectrum of genotypes present in the uterine cervix is a major step toward reliable evaluation of cancer risk.
   c. A method based on amplification of a small fragment (65 bp) within the L1 region of the HPV genome is among the most valid for testing formalin-fixed, paraffin-embedded (FFPE) samples.
   d. HPV test results are the same whether xylene or high-heat treatment are used to remove paraffin in FFPE samples.

10. HPV genotype test results partially depend on the source and type of specimen. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 373-379.]

   a. In the described study, 10 biopsy samples tested positive for only one HPV genotype, whereas the corresponding cytologic scraping showed multiple infections.
   b. For the most part, cervical scrapings provide superficial cells of the uterine cervix, whereas biopsy specimens provide full-thickness tissue samples.
   c. Typically, both cervical scrapings and biopsy specimens are taken from several areas of the uterine cervix.
   d. Although it is plausible that only one HPV genotype is responsible for high-grade cervical intraepithelial neoplasia (CIN), it is also possible that multiple infections in FFPE samples are not easily detectable because preferential amplification of one HPV genotype, present at a higher viral load, may occur.

11. Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is the most frequent autosomal dominant colorectal cancer susceptibility syndrome. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:380-390.]

   a. Lynch syndrome is characterized by a high risk of early onset of colorectal cancer and several extracolonic malignant tumors, especially endometrial cancer in women.
   b. The phenotype of tumors from patients with Lynch syndrome is characterized by widespread microsatellite instability (MSI) and loss of protein expression from the affected enzyme.
   c. Most of the genetic defects in the human mismatch repair (MMR) genes responsible for HNPCC are a result of point mutations and small insertions and deletions that truncate and inactivate MMR genes.
   d. Mutations in PMS2 account for the majority of the patients with Lynch syndrome.

12. A major difficulty in diagnosis and management of Lynch syndrome is the existence of unclassified genetic variants (UVs) with unknown clinical significance. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:380-390.]

   a. UVs are nucleotide substitutions that are missense but generally not truncating.
   b. Missense-type mutations occur in 24% of all unique variants detected in MLH1.
   c. Missense-type mutations occur in 7% of all unique variants in MSH2.
   d. Rather than causing changes to a single amino acid, many variants are instead associated with defects in RNA splicing.