

JMD CME Program in Molecular Diagnostics 2008

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CME Questions # 9-18

(See January Examination Sheet for Questions #1-8)

9. Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy that afflicts over 200,000 individuals worldwide every year. Based on the referenced Review Article of the molecular genetics of PDAC, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:111-122]

- PDAS is the fourth most common cause of cancer-related deaths in the United States.
- PDAC constitutes over 90% of pancreatic cancers in humans.
- The most common numerical changes observed in pancreatic cancer are losses on chromosomes 7 and 20, as well as gains on chromosomes 12 and 13.
- Frequent chromosomal breaks and rearrangements in PDAC occur in regions involving 1p, 1q, 3p, 6q, 7q, 11p, 17p, and 19q.
- Allelotyping studies have revealed allelic losses that commonly involve chromosomal regions 9p, 17p, and 18q.

10. A variety of genomic DNA abnormalities are found in PDAC, including chromosomal aberrations, copy number changes, and activating mutations of oncogenes. Based on the referenced Review Article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:111-122]

- Results from studies examining copy number aberrations should be interpreted with caution.
- Major drawbacks of conventional comparative genomic hybridization (CGH) on metaphase spreads include low resolution and frequent difficulties in precisely mapping the regions of genomic amplifications or losses.
- Allelotype analysis of microdissected pancreatic intraepithelial neoplasia (PanIN) samples revealed loss of heterozygosity in chromosomal regions also found in pancreatic cancer.
- In PDAC, the activating point mutation within the *KRAS* oncogene affects codon 14.
- Rare pancreatic cancers with wild-type *KRAS* usually harbor mutations of *BRAF*.

11. In addition to intragenic mutations and allelic loss, silencing of tumor suppressor genes through epigenetic mechanisms is a frequent finding in many cancers. Based on the referenced Review Article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:111-122]

- Aberrant DNA methylation is not found in PanIN lesions and appears to be specific for advanced disease.
- Epigenetic silencing in PDAC often affects genes that function as tumor suppressors or are involved in key homeostatic pathways.
- Promoter hypermethylation of human Hedgehog interacting protein was found in the majority of examined pancreatic cell lines and primary tumor samples, potentially contributing to increased Hedgehog signaling observed in pancreatic cancers.
- Hedgehog inhibition with cyclopamine has been found to increase cytotoxic effects of paclitaxel treatment and radiation on pancreatic cancer cells *in vitro* and to inhibit growth of pancreatic cancer xenografts and metastases *in vivo*.
- Promoter hypomethylation is also exploited by pancreatic cancer cells.

12. Laser capture microdissection (LCM) is widely used for genome and transcriptome profiling of tumor tissues. Based on the referenced Technical Advance article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:129-134]

- a. Formalin-fixed, paraffin-embedded (FFPE) tissues are not ideal starting materials for genome-wide molecular profiling.
- b. After incubation of LCM-captured cells for 30 minutes with the guanidium-based extraction buffer RLT Plus, less DNA was extracted as compared to the QIAamp DNA purification method.
- c. RNA integrity was not affected by extending the time of extraction with guanidium-based extraction buffer at room temperature.
- d. There was severe RNA degradation with the guanidium-based extraction buffer when the extraction temperature was raised to 42°C or 55°C.
- e. DNA was severely degraded when the guanidium-based extraction was conducted at temperatures of 42°C or 55°C.

13. Viruses of the genus *Flavivirus* are responsible for severe encephalitic, hemorrhagic, hepatic, and febrile illnesses in humans and other vertebrates. Based on the referenced article, select the ONE statement regarding internal controls that is NOT true: [See J Mol Diagn 2008 10:135-141]*

- a. Flaviviruses are single-stranded RNA viruses.
- b. It is estimated that over 100 million cases of dengue occur annually worldwide.
- c. A protective dengue virus vaccine is currently available.
- d. Typing of dengue virus is important in treatment because infection by a new serotype in a patient previously infected by one of the other serotypes is associated with an increased risk of developing dengue hemorrhagic fever and/or dengue shock syndrome.
- e. Typing of dengue virus is important for distinguishing endemic strains from new outbreak strains so that new outbreaks can be readily contained.

14. Development of rapid and specific molecular diagnostics for flaviviruses is an important global health challenge. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:135-141]*

- a. The current reference method for identifying and typing flaviviruses is isolation of the virus in cell culture followed by immunofluorescence typing.
- b. Tests such as hemagglutination inhibition, IgG-ELISA and MAC-ELISA are specific, are easy to use, can accommodate a large number of samples, and can easily distinguish dengue at the serotype level.
- c. The authors derived "almost-universal" primer pairs for flaviviruses in general and for all four serotypes of dengue from the literature.
- d. DEN2 and DEN3 can be readily resolved by base-specific cleavage masses derived from the NS5 region.
- e. RNase T₁ is an endoribonuclease that is highly specific for cleavage after G residues; however, incomplete digestion products yield final masses other than those predicted by complete sequence cleavage after every G.

15. Standard IUPAC base degeneracies are often used to develop degenerate forward and reverse primers for amplification. Based on the referenced article, select the ONE statement defining IUPAC nomenclature that is NOT true: [See J Mol Diagn 2008 10:135-141]*

- a. D = A or G.
- b. H = A, T, or C.
- c. Y = C or T.
- d. M = A or C.
- e. S = G or C.

16. Anti-epidermal growth factor receptor (EGFR) antibody therapy is currently available for the treatment of some cancers. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:160-168]

- a. The clinical experience with cetuximab in the treatment of colon carcinoma patients revealed that both EGFR-expressing tumors and tumors without detectable EGFR expression by standard immunohistochemistry had clinical responses.
- b. Gefitinib and erlotinib are small-molecule inhibitors of the tyrosine kinase domain of the EGFR that had severe side effects in colon cancer and lung cancer patients, resulting in premature termination of clinical trials.
- c. Characteristics associated with increased response of lung cancers to gefitinib and erlotinib include nonsmoking history, adenocarcinoma histology, Asian race, and female gender.
- d. Gefitinib-treated patients carrying *EGFR* amplification (detected by fluorescent *in situ* hybridization) to high polysomy had a statistically significant improvement in response, time to progression, and survival compared with patients with no or low genomic gain for *EGFR*.
- e. In the current study, some non-small cell lung cancer (NSCLC) patients with immunohistochemistry-negative but *EGFR*-mutant NSCLC tumors had complete responses to erlotinib treatment.

17. Imatinib is the recommended first line therapy for patients with chronic myeloid leukemia (CML). Based on the referenced Consultations in Molecular Diagnostics article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:177-180]

- a. More than 80% of CML patients treated with imatinib will achieve a complete cytogenetic response (CCR).
- b. After CCR is achieved, molecular response measured by reverse transcription-polymerase chain reaction quantification (RQ-PCR) is typically used to continue therapeutic monitoring and to detect loss of response at an early stage before overt relapse occurs.
- c. Most CCR patients on standard imatinib therapy will have residual disease detectable by RQ-PCR.
- d. The most common mechanism for a subsequent loss of response is acquired imatinib resistance due to the development of mutations in the BCR-ABL kinase domain that interfere with optimal drug-target interactions.
- e. Single nucleotide point mutations in the kinase domain are rarely reported in cases of imatinib resistance.

18. The spectrum of BCR-ABL kinase domain mutations discovered in CML patients with imatinib resistance is quite heterogeneous. Based on the referenced Consultations in Molecular Diagnostics article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:177-180]

- a. In three CML patients undergoing kinase inhibitor therapy, direct DNA sequencing of BCR-ABL RT-PCR products revealed that the same 35 nucleotides from ABL intron 8 had been inserted at the normal exon 8-9 splice junction.
- b. The insertion created a premature translational stop codon after 10 intron-encoded amino acids, resulting in truncation of 653 C-terminal amino acids, which included part of the kinase domain and the entire "last exon" region.
- c. Consensus splice donor and acceptor sequences were not detected flanking the 35-bp intronic sequence, excluding alternative splicing as the likely mutational mechanism.
- d. In the patient population studied, the estimated prevalence of the exon 8/9 insertion/truncation mutation was approximately 1.7% among patients with suspected drug resistance.
- e. The ages of the three patients with the unusual exon 8/9 insertion/truncation mutation varied between 15 and 60 years.

***Disclosures:**

J Mol Diagn 2008 10:135-141: Some of the authors are co-inventors on a pending U.S. Patent, "Microbial Identification Based on the Overall Composition of Characteristic Oligonucleotides," which has been exclusively licensed to BioTex, Inc (Houston, TX).

SEE EXAMINATION ANSWER SHEET – NEXT PAGE

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CME Questions # 9-18

Examination Answer Sheet #2, Questions #9-18					
Answer	a	b	c	d	e
Question #9	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #10	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #11	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #12	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #13	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #14	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #15	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #16	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #17	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Question #18	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Name					
Email Address					
CME ID# (For office use only)					

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1. You must be registered for the JMD CME Program prior to submission or you may register along with submission of your first Examination Answer Sheet of the year. *
2. Fill in the appropriate circle for each question to indicate your answer.
3. Enter your name and email address.
4. Mail or fax this completed Examination Answer Sheet (along with your payment and CME Registration Form if you have not already registered*) to the ASIP CME office.
5. Keep a copy of your Examination Answer Sheet for your records to compare with correct answers.
6. Your score and correct answers will be emailed to you within 1 month.**

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** You may mail or fax your completed Examination Answer Sheet from each issue of JMD in order to receive correct answers within 1 month, **OR** you may collect your completed Examination Answer Sheets throughout the year, and mail or fax to the ASIP CME office at the completion of the 2008 CME year.

Deadline for receipt of CME 2008 Registration Form, all Examination Answer Sheets, and CME Evaluation Form: January 15, 2009.

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