

See end of this section for full program information and registration details.

## JMD CME Program in Molecular Diagnostics 2008

American Society for Investigative Pathology *and the*  
Association for Molecular Pathology

*The Journal of Molecular Diagnostics*, Volume 10, No. 1 (January 2008)

<http://jmd.amjpathol.org>

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### CME Questions # 1-8

**1. Fragile X syndrome is the most common inherited cause of mental retardation. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:2-12]\***

- The incidence of Fragile X syndrome is higher in males than in females.
- In contrast to affected males, females with Fragile X syndrome exhibit severe retardation and behavioral abnormalities, including autism spectrum disorder.
- Fragile X syndrome and *FMR1*-associated phenotypes are usually caused by expansion of a (CGG)<sub>n</sub> repeat sequence in the 5' untranslated region of the *FMR1* gene.
- Genetic testing for Fragile X mutations is important at all life stages, prenatal to adult.
- Some groups have suggested that *FMR1* testing should be offered to women diagnosed with premature ovarian failure and reproductive or fertility problems associated with elevated basal FSH levels as well as those with a low response to gonadotropin stimulation.

**2. Assays to analyze the triplet region of the *FMR1* gene are technically challenging. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:2-12]\***

- The National Institutes of Standards and Technologies (NIST) has produced standard reference materials for Fragile X syndrome testing that are highly characterized and are produced in sufficient quantities to be utilized by most clinical laboratories in North America as a daily-use reference or quality control material.
- The high GC content of the (CGG)<sub>n</sub> repeat complicates conventional polymerase chain reaction (PCR) by reducing amplification efficiency.
- Genomic DNAs with known allele lengths are the most critical reference materials for laboratory-developed assay validation because they most closely resemble patient specimens.
- Nine clinical laboratories measured the (CGG)<sub>n</sub> repeat size in DNA samples derived from 16 cell lines containing clinically relevant *FMR1* alleles in the normal and premutation range.
- Consensus was not achieved for all samples, including three DNA samples with the largest estimated allele sizes.

**3. Molecular classification of colorectal cancer is rapidly evolving. Based on the referenced Review article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:13-27]**

- In general, as a primary discriminator in classification of colorectal cancers, emphasis should be placed on molecular classification based on global cellular events such as chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).
- CIN is considered to promote carcinogenesis through loss of tumor suppressors and copy number gains of oncogenes.
- CIN is commonly assessed by DNA ploidy analysis or loss of heterozygosity (LOH) analysis of microsatellite markers.
- Markers in the 1p region have been shown to be more sensitive for LOH analysis of CIN than markers in other chromosomal regions such as 2p, 3p, 5q, 8p, 17p and 18q.
- Colorectal cancers that have multiple reciprocal translocations with little net changes in allele copy numbers or DNA content can be misclassified as CIN negative by copy number assays such as LOH or array-based comparative genomic hybridization.

**4. Transcriptional inactivation by cytosine methylation at promoter CpG islands of tumor suppressor genes is an important mechanism in human carcinogenesis. Based on the referenced Review article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:13-27]**

- a. CIMP is a unique epigenetic phenotype in colorectal cancer.
- b. CIMP-high colorectal tumors have a distinct clinical, pathologic, and molecular profile, including associations with distal tumor location, male sex, poor differentiation, MSI, and high *TP53* mutation rates.
- c. The method of assessment of CIMP involves different panels of CpG islands but is not yet standardized.
- d. The frequency of HNPCC/Lynch syndrome in the general population is estimated to be 1 to 3%.
- e. The absence of CIMP-high in MSI-H tumors increases the likelihood of HNPCC/Lynch syndrome, but it does not necessarily indicate HNPCC/Lynch syndrome.

**5. The use of appropriate extraction and amplification controls for acellular specimens such as cerebrospinal fluid, stool and serum is not standardized in the clinical laboratory community and can lead to the reporting of false results. Based on the referenced Technical Advance article, select the ONE statement regarding internal controls that is NOT true: [See J Mol Diagn 2008 10:28-32]\***

- a. Extraction controls and amplification inhibitor checks for cellular specimens are most often accomplished by amplification of an internal human genomic target.
- b. Ribosomal 16S or 18S RNA is a convenient control for reverse transcription-PCR.
- c. Packaging of plasmid-derived DNA in a bacteriophage can protect the DNA from nuclease degradation prior to extraction.
- d. An advantage of armored RNA is that inhibitors of reverse transcription and of PCR can be readily distinguished.
- e. Specifically engineered Lambda phage DNA fragments have been generated to co-amplify with viral assays to detect the presence of PCR inhibitors, but these fragments are not used as extraction controls, they are assay specific, and construction of each synthetic phage is time consuming.

**6. A method to detect the presence of inhibitors, while simultaneously providing a control for extraction in acellular specimens, is needed to meet quality assurance standards recommended by clinical laboratory accrediting agencies. Based on the referenced Technical Advance article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:28-32]\***

- a. The T4 bacteriophage has a capsid that is composed of only 50 subunits.
- b. Unaltered T4 bacteriophage is nonpathogenic, quantifiable, and inexpensive to produce.
- c. The T4 bacteriophage genome is roughly 169 kilobases long and contains approximately ten times more nucleotide base pairs than a typical plasmid DNA.
- d. The T4 bacteriophage capsid protects the encapsulated DNA from nucleases present in biological fluids.
- e. The T4 bacteriophage DNA detection assay was run simultaneously with the set of cycling parameters of in-house infectious disease tests, including those for cytomegalovirus, Epstein Barr virus, and herpes simplex virus, to test the implementation of T4 bacteriophage as a control to evaluate extraction efficiency and detect inhibitors of PCR in acellular specimens.

**7. Early detection of breast cancer improves survival rates and quality of life. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:93-101]**

- a. A platform for multiplex detection of DNA methylation at multiple genomic sites was tested using DNA from formalin-fixed, paraffin-embedded clinical specimens.
- b. Infiltrating ductal carcinoma (IDC) was defined as malignant mammary epithelial cells invading stroma.
- c. Atypical ductal hyperplasia (ADH) was defined as lesions between 2 mm and 4 mm in size and having all of the characteristics of low-grade ductal carcinoma *in situ* (DCIS) or lesions larger than 4 mm having only some characteristics of DCIS.
- d. Samples of ADH were from core biopsies, whereas other specimens were from gross sections of surgically removed tissues.
- e. Specific methylation signatures were identified for ADH, DCIS, and IDC.
- f.

**8. Denaturing high performance liquid chromatography (DHPLC) profiling has been suggested as a method to allow the correlation of a characteristic chromatographic profile with a specific sequence alteration. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:102-108]**

- a. The screening for mitochondrial tRNA<sup>Leu</sup>(UUR) A3243G mutation in the diabetic population using blood samples is problematic because blood may contain low levels of the A3243G mutation, which can be as low as 3% in some patients with maternally inherited diabetes mellitus and deafness.
- b. Published protocols were used to attempt to detect the mitochondrial tRNA<sup>Leu</sup>(UUR) A3243G mutation in blood DNA obtained from the mother of a patient affected with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).
- c. Site-directed mutagenesis was used to generate a panel of 5 mitochondrial mutations to explore whether mutations lying in the tRNA<sup>Leu</sup>(UUR) region of the mitochondrial genome can be identified by their chromatographic patterns.
- d. Heteroduplex levels in the purified heteroduplex fraction of the mutation standards fell short of the theoretically predicted level of 50%.
- e. The degree of heteroplasmy for some mitochondrial DNA mutations varies considerably among tissues with urine epithelial cells and muscle specimens reported to carry lower levels of mutation than peripheral blood lymphocytes.

**\*Disclosures:**

**J Mol Diagn 2008 10:2-12:** Most of the authors lead molecular genetics laboratories in academic institutions that offer clinical testing for fragile X on a fee-for-service basis. Two of the authors received support from Celera (Alameda, CA). Some of the authors are employed by Quest Diagnostics, Nichols Institute (Chantilly, VA), Myriad Genetic Laboratories, Inc. (Salt Lake City, UT), Amicus Therapeutics (Cranbury, NJ), and Sequenom, Inc. (San Diego, CA).

**J Mol Diagn 2008 10:28-32:** Attostar LLC (Medina, MN) provided free of charge reagents for initial evaluation. After an abstract related to this research study was accepted for presentation at a scientific meeting (by a Program Committee on which Attostar LLC played no role), Attostar LLC provided a travel grant to one author to attend the meeting. Attostar did not place any restrictions on the research activity or request pre-approval for submission of the abstract or the manuscript. No honoraria or consulting fees were provided, and none of the authors holds stock in the company.

**SEE EXAMINATION ANSWER SHEET – NEXT PAGE**

**REGISTRATION INFORMATION FOLLOWS FOR  
THE 2008 JMD CME PROGRAM IN MOLECULAR DIAGNOSTICS**

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**CME Questions # 1-8**

<b>Examination Answer Sheet #1, Questions #1-8</b>					
<b>Answer</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>
<b>Question #1</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #2</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #3</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #4</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #5</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #6</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #7</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #8</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Name</b>					
<b>Email Address</b>					
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**Instructions for Completing and Submitting the Examination:**

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.\*\*

\* Register online at [www.asip.org/CME/journalCME.htm](http://www.asip.org/CME/journalCME.htm) or you may submit your CME 2008 Registration Form with payment prior to, or along with, your first Examination Answer Sheet of the year. You may download the JMD CME Registration Form at [www.asip.org/CME/jmdCME.htm](http://www.asip.org/CME/jmdCME.htm) or [www.amp.org/CME/jmdCME.htm](http://www.amp.org/CME/jmdCME.htm).

\*\* 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.**

**Complete Journal CME 2008 Information, including the CME Conflict of Interest Disclosure Policy, is on the ASIP and AMP websites at: [www.asip.org/CME/jmdCME.htm](http://www.asip.org/CME/jmdCME.htm) and [www.amp.org/CME/jmdCME.htm](http://www.amp.org/CME/jmdCME.htm)**

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