

# JMD CME Program in Molecular Diagnostics 2008

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## CME Questions # 35-43

(See January-July 2008 Examination Sheets for Questions # 1-34)

**35. Immunoglobulin (IG) gene rearrangement analysis is one of the more commonly performed molecular hematopathology assays. Based on the referenced Review, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:396-410; the author of the referenced article did not disclose any potential conflicts of interest.]**

- Physiologic gene rearrangements refer to the normal intragenic shuffling of segments of antigen receptor genes, namely *IG* genes and T-cell receptor (*TCR*) genes in B and T cells, respectively.
- The *BCR-ABL1* fusion generated as a consequence of the t(9;22) in chronic myelogenous leukemia is an example of an intergenic translocation that causes disruption of genes, with the subsequent fusion of portions of the disrupted genes, resulting in the generation of a novel, pathologic chimeric gene and ultimately chimeric oncoprotein.
- Translocation involving the *LMO2* gene in T-cell acute lymphoblastic leukemia is an example of an intergenic translocation involving the removal of negative regulatory elements.
- There is a normal hierarchy of *IG* gene rearrangements, with light chains rearranging before *IGH@* in normal B-cell ontogeny.
- Finding an immunoglobulin light chain rearrangement is more likely to reflect the commitment to bona fide B-cell rather than T-cell lineage.

**36. Analysis of antigen receptor gene rearrangements (ARGRs) can be considered for initial diagnosis and for subsequent minimal residual disease (MRD) studies. Based on the referenced Review, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:396-410; the author of the referenced article did not disclose any potential conflicts of interest.]**

- The inability to assess lymphoid tissue architecture may compromise the ability to render a diagnosis.
- For initial diagnosis in specialized hematopathology centers, even when the tissue is optimal for microscopic and immunophenotypic analysis, the vast majority of ARGR cases require clonality testing.
- In the initial phase of chemotherapy, the ability to reduce the level of acute lymphoblastic leukemia (ALL) below a certain threshold is considered an extremely favorable prognostic variable.
- MRD testing can be applied to stem cell products that are to be used for autologous transplantation to ensure that the reinfused material is free of contaminating tumor.
- For MRD measurements to be clinically relevant, sensitivities need to be achieved on the order of 0.01%.

**37. In the early bone marrow phase of B-cell development prior to antigen exposure, the phenomenon of V(D)J recombination is the basis of clinical analysis of *IGH* gene rearrangements. Based on the referenced Review, select the ONE statement that is NOT true: [See *J Mol Diagn* 2008 10:396-410; the author of the referenced article did not disclose any potential conflicts of interest.]**

- a. Recombination signal sequences (RSSs) flank V, D, and J segments and provide binding sites for the primary enzyme complex that mediates the initial DNA cleavage and synapsis required for legitimate recombination.
- b. With regard to the *IGH* locus, DJ rearrangement occurs first and, only after this is completed, is V to DJ rearrangement able to occur.
- c. The enzyme terminal deoxynucleotidyl transferase (TdT) generates junctional diversity by mediating the random deletion and addition of nucleotides at the sites of V to D, as well as D to J, fusion.
- d. The recombinase activating genes *RAG1/RAG2* and the exonuclease activity of the DNA repair machinery contribute to junctional diversity by the inclusion of palindromic (P) nucleotides.
- e. The most distal (3') complementarity determining region (CDR) of the fully rearranged *IGH* gene (VNDNJ) is the most homogeneous of the three CDRs since it is encoded in the germline and is not affected by either recombination or the action of TdT.

**38. The immunoglobulin molecules generated by VDJ recombination in the bone marrow are of low affinity and must acquire higher affinity for pathogenic antigens to be functionally effective. Based on the referenced Review, select the ONE statement that is NOT true: [See *J Mol Diagn* 2008 10:396-410; the author of the referenced article did not disclose any potential conflicts of interest.]**

- a. Class switch recombination (CSR) typically occurs in the dark zone of the germinal center, which is characterized by smaller centrocytes.
- b. Activation-induced cytosine deaminase (AID) mediates both CSR and somatic hypermutation (SHM).
- c. Mutations in *IG* genes are predominantly point mutations, although insertions and deletions may also occur.
- d. Mutations in *IG* genes occur approximately six orders of magnitude more often than spontaneous mutations at other loci.
- e. Although SHM is somewhat influenced by the primary sequence of the DNA, it is essentially a random phenomenon.

**39. MicroRNAs (miRNAs) are emerging as potential markers in molecular diagnostics, particularly in the field of cancer diagnostics. Based on the referenced Commentary and related Technical Advance article, select the ONE statement that is NOT true: [See *J Mol Diagn* 2008 10:411-414 and *J Mol Diagn* 2008 10:415-423; five of the authors of the referenced Technical Advances article are employees of Asuragen, Inc., and one author has an affiliation with Luminex Corp; none of the authors disclosed any potential conflicts of interest with companies whose products were evaluated in this article.]\***

- a. MiRNAs are important gene regulators that have the capacity to down-regulate gene expression of target genes through translation inhibition and promotion of mRNA degradation.
- b. According to the most recent version of miRBase, over 600 different mature miRNA sequences have been identified in humans.
- c. Many miRNAs are highly specific in their expression in specific tissues and cell types; however, this specificity is rarely retained in the corresponding tumor tissues.
- d. An miRNA classifier consisting of 48 miRNAs was found to predict tissue origin with an overall accuracy of 89%.
- e. Cell-type-specific miRNA signatures correlate with mRNA expression patterns.

**40. The application of miRNAs for molecular diagnostic purposes is dependent on the development of methods for their accurate and high-throughput quantification. Based on the referenced Commentary and related Technical Advance article, select the ONE statement that is NOT true: [See *J Mol Diagn* 2008 10:411-414 and *J Mol Diagn* 2008 10:415-423; five of the authors of the referenced Technical Advances article are employees of Asuragen, Inc., and one author has an affiliation with Luminex Corp; none of the authors disclosed any potential conflicts of interest with companies whose products were evaluated in this article.]\***

- a. The real-time RT-PCR for quantitative measurement of miRNAs is similar to the standard real-time RT-PCR for the detection of mRNA, except that the former makes use of a stem-loop reverse transcription primer for the initiation of cDNA templates.
- b. The Invader assay directly detects specific RNA molecules using an isothermal amplification process with a fluorescent read-out.
- c. The method of choice for the simultaneous analysis of hundreds of different miRNAs is global expression profiling, which is most often performed on glass slide microarrays.
- d. Global expression profiling of miRNAs can be performed using bead-based flow cytometry.
- e. The use of locked nucleic acid (LNA)-modified probes in miRNA microarrays has not been successful due to decreased specificity.

**41. Large-scale analysis of miRNA microarray expression signatures can be accomplished by accessing archived formalin-fixed, paraffin-embedded (FFPE) human specimens. Based on the referenced Commentary and related Technical Advance article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:411-414 and J Mol Diagn 2008 10:415-423; five of the authors of the referenced Technical Advances article are employees of Asuragen, Inc., and one author has an affiliation with Luminex Corp; none of the authors disclosed any potential conflicts of interest with companies whose products were evaluated in this article.]\***

- a. MiRNA has been shown by RT-PCR to be a superior analyte compared to mRNA when FFPE materials are used since miRNAs are small and therefore less subject to RNA degradation.
- b. Independent of the tissue type, miRNA expression profiles in tissues fixed in formalin for 6 hours are nearly identical to those fixed for 24 hours.
- c. Irrespective of their level of expression, 100% of the miRNAs expressed in frozen tissues are detected in FFPE samples.
- d. Failure to capture a larger percentage of miRNAs in FFPE samples may be a consequence of a lower miRNA fraction recovery or excessive RNA modification during FFPE tissue storage.
- e. A gradual increase in the probe signal intensity of miR-494 and -513 was detected in aging myometrium tissue blocks, peaking at 460- and 161-fold in the 11-year-old samples compared to frozen tissue.

**42. The fragile X syndrome is the most common inherited disorder associated with mental retardation. Based on the referenced Consultations in Molecular Diagnostics article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:469-474; no authors of the referenced article disclosed any potential conflicts of interest.]**

- a. The fragile X syndrome in males is characterized by large ears, speech delay, autistic behavior, macroorchidism, and mental retardation.
- b. The estimated prevalence of fragile X syndrome in females is 1 in 8,000.
- c. Fragile X female patients uniformly exhibit severe learning and behavioral defects.
- d. Over 99% of fragile X cases have been associated with an expansion of a segment of CGG repeats in the 5' untranslated region of the *FMR1* gene.
- e. Full mutations with a large CGG expansion in the 5' untranslated region of *FMR1* are associated with inhibition of transcription of *FMR1*, causing deficiency or absence of the fragile X mental retardation protein.

**43. Diagnostic testing for the fragile X syndrome is designed to detect the most common mutation. Based on the referenced Consultations in Molecular Diagnostics article, select the ONE statement that is NOT true: [See J Mol Diagn 2008 10:469-474; no authors of the referenced article disclosed any potential conflicts of interest.]**

- a. In normal females, the 5.2-kb band on a Southern blot assay for fragile X syndrome represents the active, unmethylated X chromosome.
- b. Methylated full mutations are not detectable by polymerase chain reaction (PCR) and are often shown as bands larger than 5.8 kb on a Southern blot.
- c. High resolution chromosome analysis of the 7-year-old patient showed a normal female karyotype, and molecular cytogenetic analysis using an LSI Prader-Willi/Angelman region probe showed no deletion or duplication in metaphase and interphase cells.
- d. A 10.9-kb band was detected on the standard Southern blot of the proband but not her parents, while a Southern blot using only PstI digestion showed the predicted, normal-sized bands in the patient and her parents.
- e. The proband inherited a mutation in the EcoRI recognition site of *FMR1* at the 11114 position from her father.

**\*Disclosures: J Mol Diagn 2008:10:415-423: Five of the authors of the referenced Technical Advance article are employees of Asuragen, Inc., and one author has an affiliation with Luminex Corp; none of the authors disclosed any potential conflicts of interest with companies whose products were evaluated in this article.**

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**CME Questions # 35-43**

<b>Examination Answer Sheet #5, Questions #35-43</b>					
<b>Answer</b>	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>
<b>Question #35</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #36</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #37</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #38</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #39</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #40</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #41</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #42</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Question #43</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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