A Special Article on the role of \textit{MGMT} testing in gliomas and research articles on a multiplex qPCR gene dosage assay for large-scale population screening for deletional \(\alpha\)-thalassemia, a real-time PCR assay for fusion genes in acute myeloid leukemia (AML), and miRNA profiling in bladder cancer diagnosis were selected for the \textit{September 2013 JMD CME Program in Molecular Diagnostics}. The authors of the referenced articles and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Questions #1-7 are based on: Cankovic M, Nikiforova MN, Snuderl M, Adesina AM, Lindeman N, Wen PY, Lee EQ: The role of \textit{MGMT} testing in clinical practice: A report of the Association for Molecular Pathology. J Mol Diagn 2013, 15:539-555; \url{http://dx.doi.org/10.1016/j.jmoldx.2013.05.011}.


Upon completion of this month’s journal-based CME activity you will be able to:
- Discuss the World Health Organization (WHO) classification of gliomas.
- Understand the stratification of low-risk and high-risk groups.
- Describe treatment options for gliomas.
- Understand the molecular mechanism of action of temozolomide for adjuvant therapy for glioma patients.
- Describe the structure of the \textit{MGMT} gene and its promoter.
- Discuss the use of bisulfite treatment of DNA in \textit{MGMT} testing.
- Describe the \(\alpha\)-globin gene cluster.
- Understand the spectrum of deletional \(\alpha\)-thalassemia.
- Describe recurrent fusion genes in acute myeloid leukemia (AML) and detection of AML molecular rearrangements.
- Describe nonmuscle-invasive and muscle-invasive bladder cancers.
- Understand miRNAs and their potential as biomarkers.
- Describe the expression profiles of miRNAs in bladder cancer.

1. Gliomas encompass a molecularly heterogeneous group of primary brain tumors arising from glial cells. Based on the referenced Special Article, select the ONE statement that is NOT true: \cite{Cankovic2013}.

a. Astrocytomas and oligodendroglialomas are common subtypes of gliomas.

b. World Health Organization (WHO) grade I gliomas are commonly seen in adults with a peak incidence at 50 years.

b. Approximately 2000 to 3000 low-grade gliomas (LGGs) are diagnosed in the United States annually.

d. The peak incidence of LGGs is between the ages of 35 and 44 years.
2. Although LGGs are slow growing, they are invasive and are associated with considerable morbidity and mortality. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. Headache is the most common presenting symptom of LGG.
   b. Magnetic resonance imaging is the imaging modality of choice for all glioma subtypes.
   c. One scoring system separates LGG into low-risk and high-risk groups according to five risk factors: age, tumor diameter, tumor crossing the midline, histology, and neurological deficits.
   d. Even though some LGG patients may enjoy relatively long survival times, almost all cases of LGG eventually progress to a higher grade.

3. High-grade gliomas are the most common malignant primary brain tumors in adults in the United States. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. High-grade gliomas are classified by WHO as grades III and IV.
   b. The incidence rate of glioblastoma (GBM) in the United States is 3.2 per 100,000 person-years.
   c. GBMs account for approximately 60% to 70% of high-grade gliomas.
   d. The median survival of patients with grade IV GBM is 3 years.

4. Treatments and outcomes for patients with gliomas vary according to grade. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. Treatment options for astrocytomas and oligodendrogliomas include surgery, radiation therapy, and/or chemotherapy.
   b. A multicenter, randomized, phase III clinical trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) established radiation therapy with concomitant and adjuvant temozolomide (TMZ) as standard therapy for newly diagnosed GBM.
   c. TMZ is an oral chemotherapeutic drug whose antitumor effect is primarily due to alkylation at the O6 and N7 positions of guanine, resulting in inhibition of DNA replication.
   d. For recurrent GBM, cetuximab received approval by the U.S. Federal Drug Administration (FDA) in 2007.

5. In recent years, O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation has been established as a biomarker in patients diagnosed with gliomas. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. The MGMT protein is encoded by a single gene located on chromosome band 10q26.
   b. The MGMT gene is a large gene of >150 kb.
   c. MGMT contains five coding exons.
   d. The MGMT gene has a TATA-less, CAT-less promoter containing a CpG island.

6. Expression of the MGMT gene is regulated by methylation-dependent epigenetic silencing. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. CpG islands are long (typically >3000 bp) stretches of CG-rich DNA, found primarily in promoter regions.
   b. Methylation of cytosines in CpG dinucleotides is a covalent modification catalyzed by DNA methyltransferases.
   c. Methylation of a promoter acts to silence transcription of the associated gene by binding to specific methylated DNA-binding proteins that form multiprotein complexes, causing condensation of chromatin and inability to bind RNA polymerase and transcriptional machinery.
   d. Most CpG islands are associated with constitutively active genes and are normally unmethylated.

7. Most of the MGMT molecular assays in clinical use are designed to interrogate the first exon and enhancer. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 539-555.]
   a. It is technically difficult to evaluate multiple CpGs.
   b. Commonly used methods for detection of MGMT methylation include methylation-specific PCR, quantitative real-time PCR, and methylation-specific sequencing.
   c. All molecular assays for MGMT in clinical settings require bisulfite conversion of DNA before analysis.
   d. The MGMT promoter contains a 777-bp CpG island with 97 CpG sites.

8. The predominant determinants of α-thalassemia are deletions in the human α-globin gene cluster. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:642-651.]
   a. α-Thalassemia is characterized by the decrease or absence of α-globin polypeptide chains.
   b. In southern China, the prevalence of α-thalassemia carriers is as high as 4% in the Guangxi area and 12% in the Guangdong area.
   c. More than 95% of α-thalassemia genetic defects are deletions of variable size that remove one or both α-globin genes or even the entire gene cluster.
   d. In addition to deletion defects, point mutations have been described.
9. The clinical severity of α-thalassemia is directly proportional to the number of α-globin genes affected. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15: 642-651.]

a. Deletions of a single gene (−α/α) mainly produce silent carriers.

b. Deletions of two genes (−/−α or α/−α) result in hemoglobin H disease.

c. Deletions of four α-globin genes (−/−−) result in hemoglobin Bart’s hydrops fetalis.

d. The copy number variation mode of the α-globin genes can be used for designing a quantitative PCR assay that is suitable for mass screening of the carrier frequency in the population and for molecular epidemiology studies.

10. Detection of molecular changes contributes to a refined diagnosis and prognostic assessment in acute myeloid leukemia (AML) and enables monitoring of minimal residual disease. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:678-686.]

a. The WHO classification of AML includes several entities characterized by recurrent genetic abnormalities.

b. The molecular rearrangements inv(16)(p13.1q22) or t(16;16)(p13.1;q22) involve CBFB and MYH11.

c. The acute promyelocytic leukemia (APL) variant carrying t(11;17)(q23;q21) is responsive to all-trans retinoic acid.

d. The use of single RT-PCR to detect molecular rearrangements in AML is labor-intensive, costly, and time-consuming.

11. Urinary bladder cancer is a common cancer in the Western world. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:695-705.]

a. Nonmuscle-invasive bladder cancer (NMIBC) accounts for nearly 50% of urinary bladder cases at initial presentation.

b. NMIBCs include stage Ta and carcinoma in situ (cancer is confined to the mucosa) and stage T1 (cancer is confined to the submucosa).

c. The standard for the initial diagnosis and prognostic assessment of bladder cancer is cytoscopy and histopathological analysis of biopsy specimens.

d. Current prognosticators such as tumor grade, stage, size, and multifocality do not accurately reflect clinical outcome.

12. miRNAs may be useful as new biomarkers to improve the diagnosis and prognosis of different bladder cancer entities. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2013, 15:695-705.]

a. miRNAs are small nonprotein coding RNAs of 19 to 24 nucleotides.

b. miRNAs are known to regulate gene expression post-transcriptionally by degrading mRNAs or impairing their translation.

c. Members of the mir-8 family determine the epithelial phenotype of cancer cells.

d. miR-130a and miR-130b are part of the same mir family and their expression is correlated in normal and tumor samples, suggesting that conclusions on common expression behaviors can be drawn based solely on mir family affiliation.