Articles on a screening assay for myotonic dystrophy type 1 (DM1) and on miR-210 as a prognostic marker in clear cell renal cell carcinoma were selected for the March 2015 JMD CME Program in Molecular Diagnostics. The authors of the referenced articles, the planning committee members, and staff have no relevant financial relationships with commercial interests to disclose.


Upon completion of this month's journal-based CME activity, you will be able to:

• Understand the causes of myotonic dystrophy type 1 (DM1).
• Define the expansion of trinucleotide repeats in normal and premutation alleles of the dystrophia myotonica-protein kinase (DMPK) gene.
• Describe the available assays for the molecular detection of the DMPK CTG repeat expansion.
• Define renal cell carcinoma (RCC).
• Describe the 5-year survival rate of clear cell RCC (ccRCC).
• Understand the prognostic assessment of RCC.
• Describe miRNAs and their involvement in RCC pathogenesis.

1. Myotonic dystrophy type 1 (DM1) is an autosomal dominant neuromuscular disorder with a broad spectrum of clinical features. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 128-135.]

   a. DM1 is caused by abnormal expansion of a CTG repeat in the 3’ untranslated region of the dystrophia myotonica-protein kinase (DMPK) gene on chromosome 19q13.3.
   b. Myotonic dystrophy type 2 (DM2) is also caused by mutations in the DMPK gene.
   c. Among affected individuals, size of the expanded CTG repeat positively correlates with phenotypic severity and negatively correlates with age of disease onset.
   d. DM1 demonstrates a global prevalence of 1 in 8000.
2. DM1 is the most common adult-onset neuromuscular disorder. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 128-135.]

- Normal DMPK alleles are highly polymorphic in the general population, with repeat sizes ranging from 5 to 34 CTGs that are stably transmitted across generations.
- Individuals with DMPK premutation alleles of 35 to 49 repeats are asymptomatic but are at an increased risk of transmitting alleles of larger repeat sizes to their offspring.
- Among DM1 patients carrying mutant DMPK alleles, disease phenotypes are grouped into three categories based on CTG repeat size: mild DM1 (35 to 99 repeats), classic DM1 (100 to 1000 repeats), and congenital DM1 (>1000 repeats).
- CTG repeat size information is potentially useful in predicting disease severity and age at onset; however, there appears to be no significant correlation between size and age at onset beyond a threshold repeat size, in particular for classic DM1.

3. Molecular detection of the DMPK CTG repeat expansion is essential for definitive diagnosis of DM1. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 128-135.]

- Early molecular methods used repeat-spanning PCR, which detected and sized only normal-to-small expansion alleles.
- Southern blot analysis, although labor intensive, is the preferred method for detecting small to medium expansions.
- Triplet-primed PCR (TP-PCR) uses characteristic differences in amplicon pattern between normal and expanded alleles to differentiate between them.
- TP-PCR effectively detects all DMPK alleles.

4. The TP-PCR strategy is widely preferred for the molecular testing of DM1. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:128-135.]

- TP-PCR is recommended by the European Molecular Genetics Quality Network for samples showing apparent homozygosity for a normal allele after repeat-spanning PCR.
- The discovery of interruptions within the CTG repeat raised the possibility of TP-PCR failure due to inability of the triplet-primed primer to anneal.
- Bidirectional TP-PCR targeting both the 5’ and 3’ ends of the CTG repeat is used to prevent false-negative interpretations caused by interruptions in expanded alleles.
- For large-scale screening purposes, capillary electrophoresis is a cost-effective downstream analysis procedure after TP-PCR.

5. Epidemiologic data have shown a rapid rise in the incidence of renal cell carcinoma (RCC). Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 136-144.]

- RCC is the most common type of kidney cancer in adults.
- RCC encompasses a number of cancer subtypes that have distinct structural and cytogenetic characteristics, including clear cell (cc-RCC), papillary, and chromophobe subtypes.
- The most common RCC subtype is papillary, accounting for 50% of RCC cases.
- The morphologic classification is not always accurate and in the same subtype subgroups have shown distinct biological behavior.

6. The 5-year survival rate varies greatly in ccRCC. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 136-144.]

- The 5-year survival of ccRCC ranges from 80% to 85% for tumors <4 cm, to approximately 40% in locally aggressive tumors that extend through the renal capsule or to the renal sinus.
- The 5-year survival for metastatic tumors drops significantly to approximately 5% to 15%.
- An accurate assessment of prognosis is essential in guiding the treatment decision for both primary and metastatic kidney cancer.
- In addition to surgical removal, other options for early-stage cancer include watchful waiting and percutaneous ablative treatment of tumors.

7. Accurate assessment of prognosis of ccRCC is key in optimizing management plans to fit individual patient needs. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 136-144.]

- The prognostic assessment of RCC currently relies on clinical models.
- Studies have investigated the prognostic value of clinical parameters such as tumor size and staging of tumor, node, and metastasis (TNM), in ccRCC.
- The T1 stage of ccRCC is subdivided into three groups according to TNM.
- Small renal masses can be classified as either progressive or nonprogressive according to their biological behavior.
8. miRNAs are short noncoding RNA nucleotides that regulate target expression post-transcriptionally. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:136-144.]

a. miRNAs are dysregulated in RCC, pointing to their involvement in RCC pathogenesis.

b. miRNAs have the potential to be useful diagnostic and prognostic markers as well as therapeutic targets.

c. miRNAs are documented to be downstream effector molecules of the hypoxia inducible factor (HIF)-induced hypoxia response and may be involved in non-HIF-mediated pathways.

d. miR-160 has been implicated as a clinical marker because of its involvement with hypoxia in various cancers, including breast, colon, and pancreatic cancers.