A Special Article on microcosting analysis of genomic sequencing procedures, and an article and associated Commentary on an amyloid-seeding assay for detection of transmissible spongiform encephalopathy were selected for the May 2016 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.


Questions #6-8 are based on: Wille H: The detection of infectious prions: In vitro conversion assays change the (folding) landscape. J Mol Diagn 2016, 18:329-330; http://dx.doi.org/10.1016/j.jmoldx.2016.03.001

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

- Understand the role of Medicare Administrative Contractors in determining national pay rates for genomic sequencing procedures (GSP).
- Describe the CPT codes 81430, 81470, 81445, 81455, and 81415.
- Describe the role of the GJB2/GJB6-directed test for syndromic sensorineural hearing loss.
- Discuss the effect of selective exome sequencing in the diagnostic plan for pediatric neurodevelopmental disorders.
- Define transmissible spongiform encephalopathy (TSE) and prion-related protein (PrP).
- Describe TSE rapid tests and how they are used.
- Discuss the timed amyloid seeding assay (tASA).

1. The increasing use of advanced genomic sequencing procedures (GSPs) to diagnose and care for patients has made understanding the costs associated with GSP an important issue to be considered along with their value to patients, providers, and payers. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:319-328.]

  b. The Center for Medicare and Medicaid Services (CMS) announced that the gap-fill process will be used to determine payment rates on the Clinical Laboratory Fee Schedule.
  c. Effective 2016, payment rates assigned to new CPT codes by Individual Medicare Administrative Contractors (MACs) will vary depending on regional payment data.
  d. The Association for Molecular Pathology (AMP) has developed transparent cost data for representative procedures by collecting and analyzing the technical, analytical, post-analytical, and interpretation costs.
2. The AMP Economic Affairs Committee selected five CPT codes as representative applications of GSPs that reflect the spectrum of technology and data analysis. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:319-328.]

a. CPT code 81455 refers to a targeted genomic sequence analysis of hematolymphoid neoplasms in a panel of more than 30 genes.
b. CPT code 81445 refers to targeted sequence analysis of solid organ neoplasms in a panel of 5 to 50 genes.
c. CPT code 81470 refers to X-linked intellectual disability analysis of a panel of at least 60 genes.
d. CPT code 81415 refers to exome sequence analysis.

3. Patients with advanced non–small-cell lung cancer (NSCLC) in need of treatment optimization were one of the populations studied to analyze GSP cost impact. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:319-328.]

a. The model of GSP testing in patients with NSCLC focused on first-line treatment for advanced or metastatic (Stage IIIb/IV) NSCLC patients with a time horizon of 18 months from diagnosis.
b. The cost-impact model identified four treatment pathways; targeted therapy, nontargeted therapy, clinical trial, and hospice care.
c. Patients who tested negative for EGFR and ALK mutations were directed to traditional chemotherapy regimens or enrolled in clinical trials or hospice care.
d. Recent National Comprehensive Cancer Network (NCCN) guidelines have endorsed the examination of eight different genetic alterations to help assess next steps with individual patients.

4. A model of syndromic sensorineural hearing loss of unknown etiology was analyzed. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:319-328.]

a. The GSP-guided care pathway in the sensorineural hearing loss model begins with a GJB2/GJB6-directed test.
b. The GJB2/GJB6-directed test has a high diagnostic yield; however, it has a high cost.
c. A comprehensive sensorineural hearing loss–specific multigene GSP panel is utilized in patients that are GJB2/GJB6-negative.
d. The model assumed that patients who do not end up with a genetic diagnosis via GSP will be directed to tests that are utilized in the traditional care pathway such as radiology, electrocardiography, laboratory tests, physical examinations and consults, among others.

5. A model of exome sequencing in pediatric neurodevelopmental disorders of unknown etiology was analyzed. Based on the referenced Special Article, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:319-328.]

a. Two GSP-guided care pathways were analyzed depending on relative placement of chromosomal microarray, Fragile X, and exome sequencing.
b. In a plan size of 1 million members, there was a cost savings of $1.33 million and an increase in diagnostic yield to 40% in the care pathway of chromosomal microarray and Fragile X testing as first-line followed by exome sequencing as second-line.
c. When exome sequencing was first-line, followed by chromosomal microarray and Fragile X testing as second-line, there was a cost savings of nearly $1 million for a plan size of 600,000 members and an increase in diagnostic yield to 40%.
d. The analysis suggests that the selective use of exome sequencing results can demonstrate considerable cost savings.

6. Transmissible spongiform encephalopathies (TSEs) are invariably fatal neurodegenerative diseases, involving infectious proteinacious particles known as prions. Based on the referenced article and Commentary, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18:454-467 and 329-330.]

a. Prion-related protein (PrP) is host-encoded within the PRNP gene and is the principal component of prions.
b. PrP is understood to exist in either the cellular isoform (PrPC), which is regarded as normal/nonpathogenic, or as the prion/disease-associated isoform, PrPSc.
c. PrPSc is conformationally different from PrPC, has amyloidogenic properties, and is associated with TSE pathogenicity.
d. PrPSc has a mainly β-fold conformational structure.
7. Many countries have enacted TSE surveillance programs, aiming to eradicate livestock-related TSEs. Based on the referenced article and Commentary, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18: 454-467 and 329-330.]

a. A focal point of eradication strategies has been the development of highly sensitive TSE diagnostic methods, capable of detecting infections in their earliest stages.
b. In chronic wasting disease and Scrapie, the prion agent is shed into the environment during preclinical phases of disease.
c. TSE surveillance programs use streamlined biochemical screening tests known as TSE rapid tests.
d. TSE rapid tests use PrP-specific antibodies to capture and/or probe for PrP\textsuperscript{\textnormal{Sc}} by radioimmunoassay.

8. A new timed amyloid seeding assay (tASA) surpasses the sensitivity of TSE rapid tests. Based on the referenced article and Commentary, select the ONE statement that is NOT true: [See J Mol Diagn 2016, 18: 454-467 and 329-330.]

a. The tASA diagnostic protocol achieves its sensitivity by using an in vitro conversion approach in which recombinant PrP is seeded with brain homogenate containing infectious prions.
b. False-positive results (type I errors) arising from the spontaneous conversion of recombinant PrP were avoided in the tASA by introducing an 18-hour cutoff.
c. TSE infectivity can be titrated by timing in vitro PrP-conversion.
d. Recombinant PrP\textsuperscript{\textnormal{Sc}} is used as a conversion substrate in tASA as well as in real-time quaking induced conversion (QuIC) assays.