Molecular pathology selected abstracts

Editors: Donna E. Hansel, MD, PhD, division head of pathology and laboratory medicine, MD Anderson Cancer Center, Houston; James Solomon, MD, PhD, assistant professor, Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York; Erica Reinig, MD, assistant professor and medical director of molecular diagnostics, University of Wisconsin-Madison; Marcela Riveros Angel, MD, molecular genetic pathology fellow, Department of Pathology, OHSU; Maedeh Mohebnasab, MD, assistant professor of pathology, University of Pittsburgh; Alicia Dillard, MD, clinical pathology chief resident, New York-Presbyterian/Weill Cornell Medical Center; and Richard Wong, MD, PhD, assistant professor of pathology, University of California San Diego.

Genetic architecture of dilated cardiomyopathy in people of African and European ancestry

November 2023—Dilated cardiomyopathy is characterized by dilation and weakening of one or both ventricles combined with impaired contractility. Although several external etiologies are associated with dilated cardiomyopathy (DCM), a familial form (comprising about half the known cases of DCM) has symptoms that tend to arise in mid-adulthood. Despite the genetic nature of the familial form, little is known about the genetic profile of the disease. Black patients have an increased familial risk of DCM and often have a worse prognosis. The authors conducted a study in which they used genomic ancestry to compare the rare variant genetic architecture of DCM within a diverse patient population. The cross-sectional study comprised families from 25 advanced heart failure programs in the United States. It included 1,198 patients who represented three self-identified ancestry groups: African (505 patients), European (667 patients), and Native American (26 patients). There was a slightly increased ratio of male-to-female patients within each ancestry group, which likely could be attributed to the overall gender ratio of the disease. The median age at enrollment ranged from 47 to 55 years. The youngest age at enrollment directly correlated with an overall earlier age of onset in Native American patients (37 versus 43.0 to 45.3 years old). Exome sequencing was conducted on 36 DCM-associated genes, and manual review was performed to classify all variants as pathogenic, likely pathogenic, or variant of uncertain significance (VUS). Based on prior evidence of *TTN* loss-of-function alterations being associated with DCM, the study investigators separated variants into those with *TTN* predicted loss-of-function variants (pLOF) and non-*TTN* variants. The latter were subcategorized by the type of alteration (pLOF, missense, or other). As expected, *TTN* pLOF variants were seen in each ancestry group. However, patients of African ancestry had notably fewer *TTN* pLOF alterations than patients of European ancestry. The percentage of all pathogenic or likely pathogenic variants detected in the African ancestry group was significantly lower (8.7 percent of variants) than in other ancestry groups, particularly the European ancestry group (25.6 percent of variants). More variants of uncertain significance were identified in patients of African ancestry than European ancestry (48.9 versus 38.8 percent, respectively), with the vast majority consisting of missense alterations. Due to the small sample size of the Native American subgroup, the percentage of variants that were pathogenic, likely pathogenic, or VUS was relatively similar to that of the European ancestry group. Considering that prior investigations into the genetic architecture of DCM have relied heavily on gene-association studies of patients of European ancestry, this study provides a unique perspective into the genetic landscape of DCM patients of African ancestry. The authors concluded that this study underscores the differences in genetic profiles between ancestry groups and confirms the importance of establishing more diversity within genomic databases.

Jordan E, Kinnamon DD, Haas GJ, et al. Genetic architecture of dilated cardiomyopathy in individuals of African and European ancestry. *JAMA*. 2023;330(5):432–441.

Correspondence: Dr. Ray E. Hershberger at ray.hershberger@osumc.edu

Use of molecular classification to predict response to radiotherapy in two trials for endometrial cancer

Endometrial cancer is the most common uterine cancer, accounting for more than 90 percent of gynecological malignancies. An estimated 66,000 cases are diagnosed annually. The incidence of endometrial cancer has been

increasing due to the growing rate of obesity, which results in elevated estrogen exposure, a major contributing factor that can lead to endometrial hyperplasia, dysplasia, and malignancy. The current standard of care for treating endometrial cancer is surgical resection with the addition of postoperative or adjuvant therapy for patients with a higher risk of recurrence. Common forms of adjuvant radiotherapy are external beam radiotherapy (ERBT) and vaginal brachytherapy (VBT). The effect of adjuvant radiotherapy on recurrence rates was explored previously, primarily in the setting of high-risk endometrial cancer. The authors of this study compared the five-year locoregional recurrence (vaginal and pelvic) of intermediate-risk endometrial cancer using data from PORTEC-1 and PORTEC-2, two of the largest randomized radiotherapy trials in women with early-stage endometrial cancer. (The PORTEC-1 trial compared women who received ERBT with a control group of women who did not receive adjuvant therapy. The PORTEC-2 trial compared women treated using ERBT with women who received VBT.) The study included 880 molecularly classified tumors (484 from PORTEC-1 and 396 from PORTEC-2). It assessed the predictors of locoregional recurrence-free survival used in the PORTEC trials: *POLE* mutated, mismatch repair deficient (MMRd), p53 abnormality (p53abn), and no specific molecular profile (NSMP). The two most frequently identified molecular classes in this study were NSMP (56.5 percent) and MMRd (28.1 percent). The authors found the highest risk of recurrence in p53-mutated tumors. They determined that treatment with ERBT markedly improved recurrence-free survival in patients with p53-mutated endometrial cancer. The authors also found that *POLE*-mutated tumors, although rare, had a favorable prognosis independent of treatment and that adjuvant radiotherapy improved locoregional recurrence of tumors classified as NSMP. The authors' findings suggest a significant prognostic and predictive interaction between molecular classification and adjuvant radiotherapy, re-enforcing the importance of molecular assessment in endometrial cancer.

Horeweg N, Nout RA, Jürgenliemk-Schulz IM, et al; PORTEC Study Group. Molecular classification predicts response to radiotherapy in the randomized PORTEC-1 and PORTEC-2 trials for early-stage endometrioid endometrial cancer. *J Clin Oncol*. 2023. doi:10.1200/JCO.23.00062

Correspondence: Dr. Nanda Horeweg at n.horeweg@lumc.nl