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.

Use of an RNA-based assay for evaluating HER2 status

March 2024—Human epidermal growth factor receptor 2 is a critical biomarker in breast cancer, gastrointestinal malignancies, and other cancers. HER2 protein expression can be evaluated using IHC, and the DNA copy number of its encoding gene, *ERBB2*, can be evaluated using FISH. In most clinical settings, IHC evaluation is categorized as positive (3+), equivocal (2+), or negative (0 to 1+), with equivocal cases being reflexed to FISH. Patients with HER2-positive tumors, defined as either 3+ or 2+/FISH positive, have been eligible to receive HER2-targeted therapy for many years. More recently, the FDA approved the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) to treat patients with HER2-low breast cancer, defined as tumors with IHC 1+ or 2+/FISH negative. This promising treatment has allowed many more patients to receive molecular-targeted therapy. Yet it can be difficult to distinguish IHC 0 from IHC 1+ cases because such categorization relies on subjective scoring by pathologists. While HER2 status is traditionally evaluated at the DNA level with FISH and at the protein level with IHC, one can also evaluate HER2 status at the mRNA expression level. RNAscope (Advanced Cell Diagnostics, Newark, Calif.) is an in situ hybridization assay that quantitatively assesses HER2 messenger RNA levels by whole slide imaging of a single formalin-fixed, paraffin-embedded tissue section. The authors compared RNAscope with IHC and demonstrated a strong correlation between RNA and protein levels, especially in clinical samples. They also evaluated the correlation between RNAscope results and patients' response to T-DXd treatment. The authors found that HER2 RNA levels were significantly higher in patients who responded to T-DXd treatment than in nonresponders. Furthermore, RNAscope scores better classified patients' T-DXd response rates than did IHC scores. While these findings are promising, additional validation with larger cohorts in prospective clinical trials will be necessary. Nonetheless, RNAscope is a promising alternative to IHC assays for evaluating HER2 expression in breast cancer.

Li X, Lee JH, Gao Y, et al. Correlation of HER2 protein level with mRNA level quantified by RNAscope in breast cancer. *Mod Pathol*. 2024. https://doi.org/10.1016/j.modpat.2023.100408

Correspondence: Dr. Xiaoxian Li at xli40@emory.edu

Study of the genetics of problematic alcohol use

Problematic alcohol use is one of the leading causes of death and morbidity worldwide, contributing to 2.2 percent of deaths among females and 6.8 percent among males. It is characterized by alcohol use that leads to numerous adverse medical, psychiatric, and social issues. Alcohol use disorder has a genetic and an environmental component. Some studies have demonstrated a heritability of approximately 50 percent, and genomewide association studies (GWAS) have identified specific loci associated with it. Despite these advances, knowledge gaps exist. The loci previously identified by GWAS account for only five to 10 percent of heritability. Furthermore, many of the previous studies were performed on people of European ancestry, limiting applicability to the global population. The authors conducted a series of ancestry-specific GWAS of problematic alcohol use followed by a cross-ancestry meta-analysis. They examined 1,079,947 people from five ancestral groups and included 165,952 cases of problematic alcohol use. In the European ancestry group, which was the largest study population (N=903,147), the ancestry-specific GWAS identified 85 variants at 75 loci that reached genomewide significance. Of these variants, 41 were in protein-coding genes, including five missense variants. Because of their smaller

population sizes, the non-European ancestry-specific GWAS had fewer loci that reached genomewide significance, but they identified some independent variants associated with problematic alcohol use. In addition, many of the variants identified in the European ancestry GWAS had analogous variants in the other ancestry-specific GWAS. Combining ancestry-specific GWAS of problematic alcohol use and a cross-ancestry meta-analysis of all data sets, the authors identified 110 variants significantly associated with risk of problematic alcohol use. They then performed analyses to identify likely causal variants. Because problematic alcohol use is a psychiatric condition, the authors focused on genes enriched in brain tissue and associated with brain function. Through these relationships, the genes affected could be prioritized for potential causal relationships and future pharmacological studies. Overall, this multi-ancestry study elucidates the genetic underpinnings of problematic alcohol use disorder, demonstrates a shared genetic architecture across multiple ancestry groups, and identifies promising potential therapeutic targets.

Zhou H, Kember RL, Deak JD, et al. Multi-ancestry study of the genetics of problematic alcohol use in over 1 million individuals. *Nat Med*. 2023;29:3184–3192.

Correspondence: Dr. Hang Zhou at hang.zhou@yale.edu or Dr. Joel Gelernter at joel.gelernter@yale.edu