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MODERN PATHOLOGY

Clinical molecular subtyping for endometrial carcinoma

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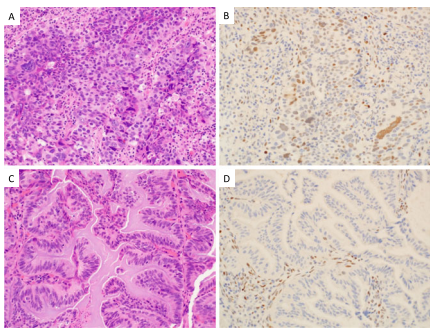

The identification of four distinct and prognostically significant subgroups of endometrial carcinoma (EC) will make molecular classification the next step in risk stratification for EC patients. Devereaux et al. performed immunohistochemistry for DNA mismatch repair genes as surrogate markers for molecular alterations (e.g., *MLH1*, *PMS2*, *MSH6*, *MSH2*) and *TP53*. They used a single-gene *POLE* SNaPshot assay for rapidly and sensitively detecting select POLE exonuclease domain mutations (EDMs). For rare POLE variants, pathogenicity is best determined in the context of a high TMB (100 mutations/megabase) and the genomic architecture or signatures. Across 310 ECs that were molecularly classified, the group showed that 5% were POLE mutant, 25% were mismatch repair–deficient, 44% had no specific molecular profile, and 26% were p53 abnormal. The authors have laid the groundwork for incorporating molecular classification of ECs in clinical diagnostic workflow.

Fusion transcript detection for sarcoma diagnostics

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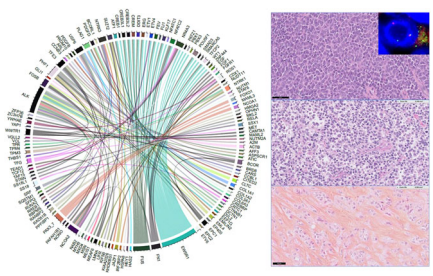

Lanic et al. developed a new molecular diagnostic assay for the detection of gene fusions of sarcomas that could be implemented in routine clinical settings. This targeted multiplexed next-generation sequencing–based method utilizes ligation-dependent RT-PCR to detect oncogenic fusion transcripts involving 137 genes, leading to 139 gene fusions known to be recurrently rearranged in soft-tissue and bone tumors. The authors tested 158 bone and soft-tissue tumors (formalin-fixed paraffin-embedded or frozen, specimens or core needle biopsies) encompassing 23 major translocation-related sarcomas. This RNA sequencing assay is rapid, robust, and highly sensitive. In-frame fusion transcripts were detected in 155/158 cases (98.1%). Similarly, gene fusion assay results correlated with orthogonal techniques (fluorescent in situ hybridization and RT-PCR) in 155/158 tumors (98.1%). The findings show that the new assay could become a first-line diagnostic test for unguided detection of fusion transcripts and classification of soft-tissue and bone tumors, with the potential to replace or complement more widely used molecular techniques. This assay can be easily customized to cover new fusions.

LABORATORY INVESTIGATION

Generating virtual FFPE images as quickly as frozen sections

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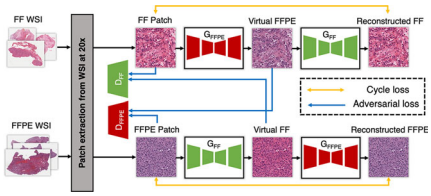

Falahkheirkhah established a protocol to achieve the efficacy of formalin-fixed paraffin embedded (FFPE) histology staining in the time frame of fresh-frozen (FF) processing while maintaining diagnostic accuracy. FFPE processing can take >24 hours compared with <0.5 hour for FF, but with FF there is morphologic deformation and more frequent artifacts. Using artificial intelligence, the group generated FFPE-like images from FF images using a generative adversarial network from 98 paired kidney samples from 40 patients. They conducted a blinded test with five board-certified pathologists to assess image quality and clinical accuracy. The virtual FFPE images showed higher interobserver agreement compared with FF images alone. The group proposes that in their protocol FF assessment is augmented with the benefits of FFPE information without adding to the cost, time, or effort

required. It thus increases the quality of histopathologic examinations using machine learning, with a positive impact on the timeliness of diagnostics.

Simultaneous H&E and immunostaining using invisible chromogens

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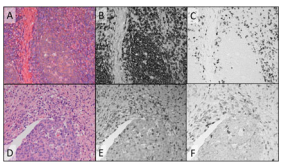

Hematoxylin plus eosin (H&E) staining and immunohistochemistry (IHC) are critical for pathologists to diagnose and characterize cancers. In solid tumors, H&E is performed first, with biomarker assessment by IHC often limited by the amount of specimen. Combining H&E and IHC on the same specimen slide would conserve specimen and enable IHC evaluation within the full morphological context. However, H&E absorbs light broadly across the visible spectrum, as do conventional chromogens, thereby obscuring one another. Morrison et al. addressed this problem by combining conventional staining with IHC using invisible chromogens so that the IHC is not visible when the H&E stain is evaluated and the H&E stain is suppressed when the IHC is viewed. The authors describe a dual-camera microscope system that permits simultaneous viewing of H&E (color) and IHC (monochrome) video as the specimen is manually scanned. The concept is demonstrated for several tissue types and several conventional stains, with single and duplex IHC.

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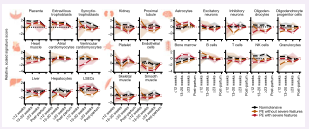
Cell-free RNA transcriptomic changes predict preeclampsia

Using liquid biopsy to analyze risk factors reduces the possible hazards of more invasive tissue collection. Moufarrej et al. used 404 blood samples from 199 pregnant mothers to identify and validate cell-free RNA (cfRNA) transcriptomic changes associated with preeclampsia. They demonstrated significant cfRNA transcriptomic changes associated with preeclampsia and also showed that these were distinct and stable early in gestation and preceded the onset of maternal symptoms. The genes involved show connections with neuromuscular, endometrial, and immune cell types, and the group proposes a correlation with progression and maternal organ health. Consequences such as proteinuria, impaired liver function, renal insufficiency, and epilepsy were seen in preeclamptic mothers. Increased astrocyte signal before 20 weeks of gestation along with decreased oligodendrocytes and excitatory neurons at 23 or more weeks of gestation were linked to preeclampsia relative to normotensive pregnancies. The authors validated a panel of 18 genes that, measured between 5 and 16 weeks of gestation, can be used to detect patients most at risk of preeclampsia long before clinical symptoms manifest themselves.



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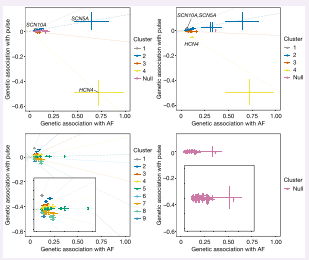
Combining biobanks to empower GWAS for disease detection and therapeutics

Genome-wide association studies (GWAS) provide provocative data but have limitations in identifying associations in the rare and low-frequency allelic spectrum due to lack of resolution. By combining whole-exome sequencing across two biobanks (UK Biobank and FinnGen), Sun et al. conducted association analysis and identified 975 associations, with more than one-third being previously unreported. The results illuminated population-level relevance for mutations, explained disease mechanisms, and related 117 biomarkers to their disease associations and clinical-stage drug targets. Mutations in *SCN10A* and *HCN4* were revealed as genetic components of atrial fibrillation, with one increasing and the other decreasing pulse rate. Deletion of *SLC34A1*—associated with kidney and urinary tract stones—was shown in 6.5% of the participants. The combination of the two biobanks (for a total of 653,219 individuals) lent power to validate findings on disease associations with replication and allowed the team to discover rare genetic variants. This trove of newly identified genotype–phenotype associations across many diseases will fuel many future studies.



Nature 2022;603:95–102; https://doi.org/10.1038/s41586-022-04394-w

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