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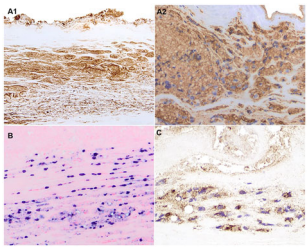
## MODERN PATHOLOGY

### Defining a novel breast implant–related neoplasm

https://doi.org/10.1038/s41379-021-00863-1




Medeiros et al. investigated eight cases of Epstein–Barr virus (EBV)-positive large-B-cell lymphoma associated with breast implants. This entity has morphologic overlap with breast implant anaplastic large-cell lymphoma (ALCL), a T-cell neoplasm that arises around textured breast implants and was recently acknowledged by the World Health Organization as a distinct diagnosis. In the authors' comparison of the seven EBV+ large-B-cell lymphoma cases with breast implant ALCL cases, the former showed a thicker capsule and were associated with calcification as well as lymphoid aggregates outside the capsule. Patients with EBV+ large-B-cell lymphoma more commonly presented with discomfort or pain at the site of implantation, whereas patients with breast implant ALCL distinctly presented with swelling/seroma. The authors suggest a pathogenetic role of breast implants, along with EBV, in the pathogenesis of EBV+ large-B-cell lymphoma. They further propose that breast-implant-associated EBV+ large-B-cell lymphoma be recognized as a unique and distinct entity.

### Superiority of tissue-NGS over plasma-NGS

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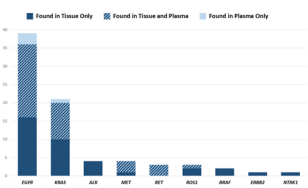


Molecular diagnostics for therapeutic targets usually relies on the presence of tumor tissue, which is not available for every case. Plasma-based liquid biopsies are easier to obtain and allow next-generation sequencing (NGS) assays to utilize circulating tumor DNA to identify relevant targets. Using a retrospective cohort of non-small-cell lung cancer patients in whom paired NGS testing had been performed on both solid tissue and plasma, Lin and colleagues compared the specificity, sensitivity, and accuracy of the two assays. The patients included both those at initial diagnosis and others at disease progression. Tissue-NGS identified clinically relevant mutations, including 52 therapeutic targets (95% sensitivity), whereas plasma-NGS identified 41 clinically relevant mutations (53% sensitivity). Tissue-NGS should remain the preferred method wherever tissue is available; however, plasma-NGS is a key tool with excellent positive predictive value but much more limited negative predictive value.

## LABORATORY INVESTIGATION

### Exosomal tau in Alzheimer's disease

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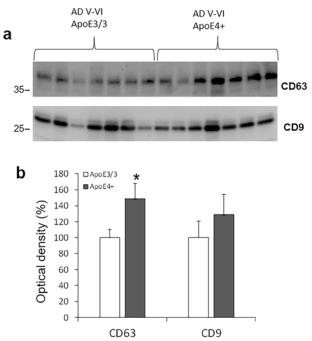


Miyoshi et al. explored the synaptic transfer of tau, which has been hypothesized to be a seeding mechanism from the human pathology pattern of Alzheimer's disease, although without the precise mechanism being known. They used a novel flow cytometry assay to quantify depolarization of synaptosomes where fluorescence reduction was associated with synaptic vesicle release. Several tau peptides were released, including tau oligomers; released tau was primarily unphosphorylated and C-terminal truncated, with seeding activity enhanced by Aβ release just above the background. Misfolded aggregated tau, accelerated by terminal amyloid levels, would subsequently be loaded to exosomes and exported from the synapse, resulting in an exosomal transfer of tau across synapses. Since the authors' model demonstrates that Aβ accelerates the aggregation of synaptic tau, this could lead to the development of aggregation inhibitors

and tau-targeted therapeutic approaches by reducing the secretion of tau-bearing exosomal subpopulations.

## Diagnostic tool quantifies CD8+ T cells

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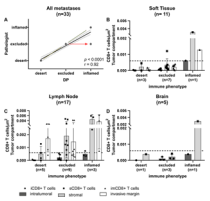

Tumor-infiltrating CD8+ T cells are an immune-oncology biomarker without a universal quantitative and reproducible method to establish their prevalence within tumors. To address this lack, Sobottka et al. employed a computational diagnostic algorithm to quantitatively measure spatial densities of tumor-infiltrating CD8+ T cells with digital pathology in three tumor compartments. They established the most relevant tumor locations for immune measurements (the central intratumoral area) and cut-off values for reproducible classification. This led to a robust algorithm that translates spatial densities of tumor-infiltrating CD8+ T cells into the clinically relevant immune diagnostic categories for clinical decision-making. The algorithm can assess metastatic lesions even when the invasive margin wasn't captured in the biopsy. Such a tool can provide standardization for assessing patients when immunotherapy is under consideration.

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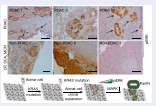
### TERT$^{high}$ acinar cells represent an early expansion step in PDAC

The mechanisms underlying cellular renewal and initiation of pancreatic ductal adenocarcinoma (PDAC) remain elusive. They seem distinct from those of many cancers in which stem cells sustain early mutations driving tumor development. Neuhöfer et al. used lineage tracing from the endogenous telomerase reverse transcriptase (*Tert)* locus and identified a rare TERT-positive subpopulation of pancreatic acinar cells throughout the exocrine compartment. While random acinar cells do not form clones, the TERT$^{high}$ acinar cells (also expressing mutant *Kras*) renew the pancreas by forming expanding clones. Human acinar progenitor cells sustain a *KRAS* mutation during replication, conferring growth advantage and supporting the formation of an acinar clone. The clonal expansion of abnormal cells then transdifferentiates by upregulating Ras-MAPK signaling and activation of downstream phospho-ERK to form a precursor lesion. Chronic organ damage can increase the proliferation of acinar progenitor cells and the likelihood of developing a *KRAS* mutation, while further enhancing the growth of *KRAS*-mutant clones and the risk of PDAC development. Knowing about this early expansion step in PDAC development supports the development of methods to intercept the development of pancreatic cancer.



*Nature Genetics* 2021;597:715–719; https://doi.org/10.1038/s41586-021-03916-2

### Machine-learning tool for evaluation of prostate cancer

To explore the molecular features that mediate clinically aggressive prostate cancer phenotypes, Elmarakeby et al. developed a pathway-aware multilayered hierarchical network (P-NET) to classify patients with prostate cancer by treatment-resistance state and evaluate molecular drivers of that resistance in a set of 1013 patients. The trained P-NET model correctly classified 73% of the primary tumors and 80% of the metastatic tumors, indicating that the model can generalize to unseen samples with an adequate predictive performance. P-NET, a biologically informed deep-learning model, was able to predict cancer state using molecular data and was even able to identify molecular candidates, such as *MDM4* and *FGFR1*, implicated in predicting advanced disease and validated in vitro. This in turn may inform the use of *MDM4*-selective inhibitors for genomically stratified (TP53-wild-type) patients with metastatic prostate cancer. Novel hypotheses for mechanisms of metastasis in prostate cancer were generated, and the group proposes that these may also be applicable to other cancer types.

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For a Chinese version of Inside the USCAP Journals, see the supplementary material.

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41374-021-00000-0.