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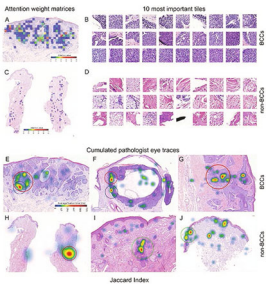
MODERN PATHOLOGY

Pathologist vs. artificial neural networks in BCC diagnosis

https://doi.org/10.1038/s41379-020-00712-7



Medical image analysis has been enhanced by the creation of algorithms aided by artificial intelligence. Using histological slides from basal cell carcinoma (BCC), Kimeswenger et al. performed a proof-of-concept study implementing an accurate and intuitively interpretable artificial neural network (ANN) for detection of BCC in histological whole-slide images (WSIs). An attention-ANN was trained with WSIs of BCCs, and diagnosis-relevant regions used by the ANN were compared with regions of interest for pathologists. The ANN was able to identify BCC through distinctly different patterns. Given that microscopically controlled surgery is considered standard for BCC, automated systems that prescreen WSIs for cancerous tissue could be timesaving for pathologists. The group proposes that neural networks and machine learning algorithms can potentially enhance diagnostic precision in digital pathology and result in unused classification patterns by revealing alternatives to the patterns used by pathologists in eye-tracking results.

Patterns of residual disease following neoadjuvant chemotherapy

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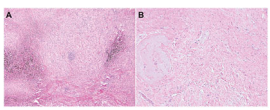

The lack of pre-treatment clinicopathologic features that predict variations in responses of breast cancer patients to neoadjuvant chemotherapy (NAC) was the basis for a study by Pastorello et al. The authors assessed histologic sections of post-treatment surgical specimens from 665 patients with stage I–III breast cancer treated with NAC followed by surgery. Of 389 patients with residual invasive cancer, 287 (73.8%) had a scattered pattern of residual disease and 102 (26.2%) had a circumscribed pattern. Broken down by subtype, 89.4% of HR+/HER2− tumors had a scattered pattern and only 10.6% had a circumscribed pattern, whereas among triple-negative breast cancer specimens 52.8% had a circumscribed pattern and 47.2% had a scattered pattern. Lower histological grade and larger tumors were other factors that skewed toward a scattered response pattern. Increasing our understanding of clinicopathologic features before treatment may improve decision-making for post-chemotherapy and surgical management of these patients.

LABORATORY INVESTIGATION

Improved assay could replace FISH in thoracic oncology

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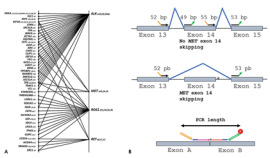

Piton et al. provide data on their upgraded ligation-dependent reverse-transcription polymerase chain reaction (LD-RT-PCR) assay for detection of theranostic translocations in lung adenocarcinomas. The assay's ability to detect *ALK*, *ROS1*, and *RET* rearrangements was tested across the Rouen molecular platform against immunohistochemistry (IHC), genotyping, and fluorescence in situ hybridization (FISH). The assay had global sensitivity of 91.43% with specificity of 100%; detecting 15 of 18 *ALK* and 4 of 4 *ROS1* translocated tumors and 6 of 6 tumors with *MET* exon 14 skipping, along with 7 alterations that were missed by routine processes. The assay is fast, inexpensive, sensitive, specific, and easily upgradable (to include additional translocations), but it still requires IHC in parallel for confirmation. The group suggests that LD-RT-PCR, in combination with IHC and genotyping, could replace FISH and other expensive RNA-sequencing assays for systematic testing in lung adenocarcinoma.

Tissue cytometry provides spatial maps to describe changes in kidney disease

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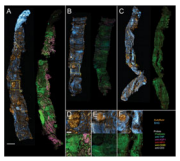

Tissue cytometry can be used to enumerate and characterize cells in a tissue in the context of intact tissue. The approach enables preservation of spatial information, making it distinct from methods such as flow cytometry that break down tissue into individual cells. Because it been out of the reach of most laboratories owing to requirements for specialized techniques, Ferkowicz et al. sought to develop an alternative method. They describe a system that includes methods for sample preparation, microscopy, and image and data analysis for large-scale three-dimensional tissue cytometry of human kidney tissues. The authors validated their process in millimeter-scale tissue samples obtained from human nephrectomies and renal biopsies. The system uses common laboratory techniques and equipment along with an image-review software plugin available for commonly used software. Preserving the three-dimensional relationship between cells in situ provides spatial maps of changes that occur in kidney disease.

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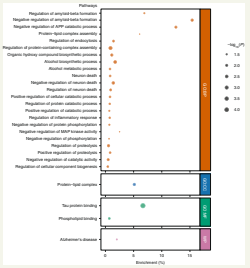
Genome sequencing in LBD provides potential therapeutic targets

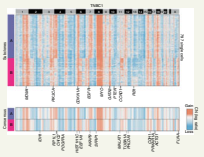
Lewy body dementia (LBD) is a clinically heterogeneous neurodegenerative disease with no effective disease-modifying treatments. Chia et al. performed whole-genome sequencing in large cohorts of LBD patients and neurologically healthy controls to study the genetic architecture and generate a resource for the scientific community. The analysis revealed five independent risk loci, whereas genome-wide gene-aggregation tests implicated mutations in the gene *GBA*. LBD was shown to share risk profiles with Alzheimer's and Parkinson's diseases. The findings provide a deeper molecular understanding of the condition, with implications for precision medicine and prioritization of targets for therapeutic development. The data, which reflect a large sequencing effort, have been made available to the wider research community.



Nature Genetics 2021;53:294–303; https://doi.org/10.1038/s41588-021-00785-3

Distinguishing within heterogeneity of tumor structure

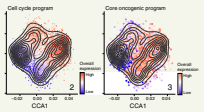
The tumor microenvironment is heterogeneous to the extent that it is challenging to distinguish normal cell types from malignant cells and resolve clonal substructure within the tumor when using single-cell transcriptomic analysis. Gao et al. developed an integrative Bayesian segmentation approach called copy number karyotyping of aneuploid tumors (CopyKAT) to estimate genomic copy number profiles. Acknowledging that not all tumors have aneuploid copy number events that can be used to distinguish normal from malignant in this manner, the group applied CopyKAT to 46,501 single cells from 21 tumors across multiple tumor types to accurately (98%) distinguish cancer cells from normal cell types. In three breast tumors, CopyKAT resolved clonal subpopulations with different expression of specific cancer genes such as *KRAS* and where epithelial-to-mesenchymal transition, DNA repair, apoptosis, and hypoxia signatures were also distinct. The authors conclude that CopyKAT can aid in scRNA-seqencing analysis in a variety of solid tumors.



Nature Biotechnology, published online 18 January 2021; https://doi.org/10.1038/s41587-020-00795-2

Blueprint for investigating heterogeneity in fusion-driven malignancy

SS18-SSX fusion drives the development of synovial sarcoma (SyS), an aggressive cancer characterized by low T-cell infiltration. Jerby-Arnon et al. took an integrative approach combining single-cell RNA sequencing (scRNA-seq), spatial profiling, and genetic and pharmacological perturbations. A malignant subpopulation of cells was identified by scRNA-seq that characterizes immune-deprived niches in situ and was shown to be predictive of poor clinical outcomes; functional analysis confirmed that it was driven by the SS18–SSX fusion. A combination of HDAC and CDK4/CDK6 inhibitors was shown to enhance malignant-cell immunogenicity in SyS models, leading to induced T-cell reactivity and T-cell-mediated killing—treatment responses that CTLA-4 and PD-1 inhibitors have so far not been shown to provide. The findings demonstrate an interplay between immune evasion and oncogenic processes that can be co-targeted in SyS and other malignancies. The authors propose their method as a blueprint for investigating heterogeneity in fusion-driven malignancies.



Nature Medicine 2021;27:289–300; https://doi.org/10.1038/s41591-020-01212-6

Emma Judson contributed to these reviews.

For a Chinese version of Inside the USCAP Journals, see the Supplementary Material.

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