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MODERN PATHOLOGY

Guide for assay selection in *NTRK*-POSSIBLE PATIENTS

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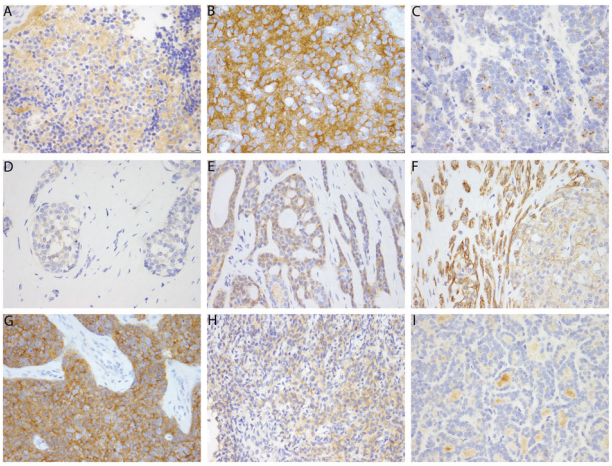

DNA-based sequencing showed sensitivity (81%) and specificity (~100%) for detection of *NTRK* fusions compared with RNA-based sequencing, while immunohistochemistry showed overall sensitivity and specificity of 88% and 81%, respectively, for *NKTRK* fusions (96% for *NTRK1*, 100% for *NTRK2*, and 79% for *NTRK3*). Specificity was 100% for colon, lung, thyroid, pancreas, and biliary tract samples; 83% for breast; and 52% for salivary gland. Both sensitivity and specificity were low for sarcoma. This diagnostic pitfall was demonstrated by positive pan-Trk staining in *NTRK* non-fusion neural derived tumors, as well as false negatives exhibited when fusions involved breakpoints not covered by DNA and RNA-sequencing assays. By comparing *NTRK* fusion detection sensitivity and selectivity across multiple assays and tumor types, Solomon et al. demonstrated that both the tumor type and the gene (*NKTRK1/2/3*) involved were considerations in determining the value of various approaches for screening and fusion detection.

Diagnostic accuracy over specificity of results

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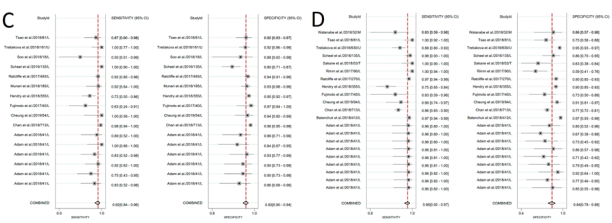

Torlakovic et al. performed a literature search of the MEDLINE database for publications referencing PD-L1 assays. Their goals were to ascertain how different clones, protocol conditions, instruments, and scoring and readout methods influence diagnostic accuracy. When compared with the original Food and Drug Administration (FDA)–approved PD-L1 assay, properly designed laboratory-developed tests performed in individual immunohistochemistry labs performed essentially equally. The authors found that tests designed solely to identify a positive/negative finding for PD-L1 expression did not perform as well as those that took clinical outcome into account, since the diagnostic goal of the test is to identify patients most likely to respond to targeted therapy. If an FDA-approved version of the test is not available, they suggest designing an assay to fit its intended clinical application rather than adopting a PD-L1 protocol designed for a different purpose.

LABORATORY INVESTIGATION

Automated cell counts for hematological disorders

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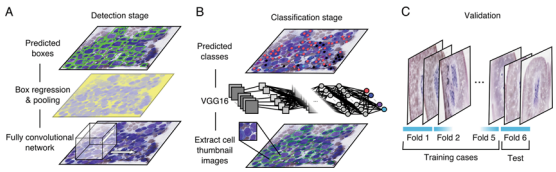

The application of machine-learning algorithms in diagnostic pathology could provide multiple benefits, including reductions in labor costs, time to results, and potential operator bias. However, the complexities and of the morphologic features involved present a significant barrier to development. Chandradevan et al. developed an algorithm for the analysis of differential cell counts in bone marrow aspirates in the classification of hematological disorders. Utilizing a web-based system developed for annotating and managing digital pathology images, the authors manually annotated over 10,000 cells from scanned whole-image slide images of bone marrow aspirate smears. Their applied algorithms achieved high overall accuracy in detection and classification using nonneoplastic samples, with similar results in a small set of acute myeloid leukemia and

multiple myeloma samples. This is an early step toward the goal of developing an objective, reliable method to automate differential cell counts to assist pathologists in disease diagnosis and prognosis in a clinical setting.

Precise sequencing for genomic duplications

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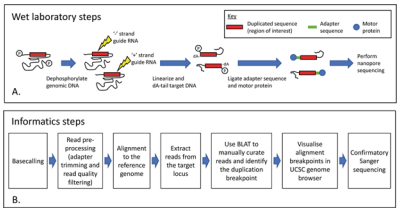
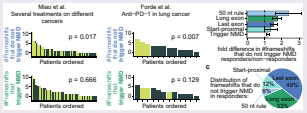


The ability to not only perform genome-wide diagnostic screening but also validate duplication variants at nucleotide resolution in order to gauge pathogenicity has presented challenges for clinical application of sequencing results. Watson et al. describe the development of a Cas9 enrichment strategy, in combination with long-read single-molecule nanopore sequencing, to address this need. Two case studies were used, and in both cases the long-read data yielded sufficient information to enable Sanger sequencing to define the rearrangement breakpoints as well as the creation of breakpoint-spanning PCR assays suitable for testing the relatives. They note that their assay can be easily adopted by laboratories for cost-effective and rapid characterization of challenging duplications-containing alleles, with wider scope in further diagnostic testing.

nature.com/pathology

Nonsense-mediated decay and immunotherapy

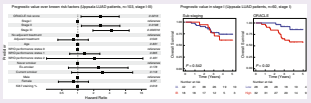
Distinct factors determine the effects of nonsense-medicated messenger RNA decay (NMD) on both disease progression and responses to immunotherapy. Downstream effects of NMD can thus alter diagnostic and prognostic decision-making. Lindeboom et al. developed a resource they call the NMDetective to explore the rules and downstream effects to better assess potential influence on clinical decision-making. NMD has been shown to both aggravate and alleviate the effects of premature termination codons (PTCs), and the resulting production of truncated proteins/degraded messenger RNAs. NMD is also a determinant of the efficacy of cancer immunotherapy. Frameshifted transcripts that escape NMD can improve response to immunotherapy. Thus, inhibition of NMD may enhance the efficacy of immunotherapy in some patients by preventing destruction of PTC-containing transcripts and enhancing expression of neo-antigens.



Nature Genetics 2019;51:1645–1651; https://doi.org/10.1038/s41588-019-0517-5

Identifying "ORACLE": a biomarker for lung cancer mortality

The search for biomarkers to support stratification of patients into disease subtypes predictive of outcome is a major goal of precision medicine. By analyzing multiregion whole-exome and RNA sequencing data for 156 tumor regions from 48 patients enrolled in the TRACERx study, Biswas et al. explored transcriptomic intratumor heterogeneity (RNA-ITH) in non-small-cell lung cancer. After identifying chromosomal instability as a major driver of RNA-ITH, they showed that existing prognostic gene expression signatures were vulnerable to tumor sampling bias. They selected genes expressed homogeneously within individual tumors, and these were often drivers of DNA copy-number gains selected early in tumor evolution. The authors' 23-gene prognostic signature—termed outcome risk–associated clonal lung expression (ORACLE)—was robust despite potential tumor sampling bias and associated with survival, independent of other risk factors. They propose that such signatures could refine the prediction of response to specific therapies, including immunotherapy.



Nature Medicine 2019;25:1540–1548; https://doi.org/10.1038/s41591-019-0595-z

150th anniversary of *Nature*

Since its inception in November 1869, *Nature* has published major advances across numerous fields. The papers published span wide-ranging topics and exhibit a spirit of collaboration that is, in itself, inspirational. From a generalist beginning, *Nature* has focused on core scientific disciplines such as biomedical, physical, chemical, and earth sciences for much of the twentieth century. The rapid turnaround time and weekly publication made *Nature* a favorite target for scientists, allowing them to publish results much more quickly than other existing learned-society journals existing in the nineteenth century. Advances in specific disciplines can be traced through publication histories in *Nature*, from discoveries about the origin of our own species to developments in plate tectonics and the existence of new particles in physics. While ever striving to improve, *Nature* and its growing family of both Nature-branded and society journals (including both USCAP journals) provide a worthy platform for disseminating scientific discovery, as well as a vision for our future.

Nature 2019;575:7–8, https://doi.org/10.1038/d41586-019-03304-x;
Nature 2019;575:22–23, https://doi.org/10.1038/d41586-019-03305-w; and
Nature 2019;575:32–34, https://doi.org/10.1038/d41586-019-03308-7

Emma Judson contributed to these reviews.