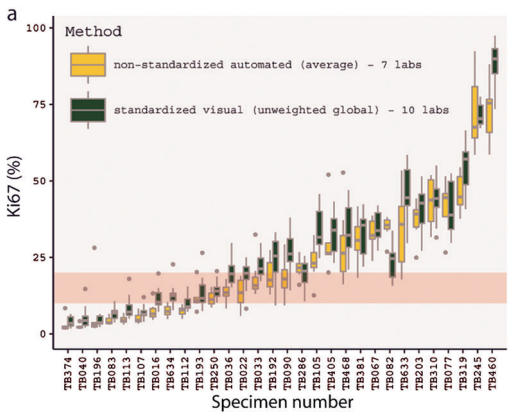
INSIDE THE USCAP JOURNALS

doi:10.1038/s41379-018-0190-8

MODERN PATHOLOGY

Automated assessment of nuclear Ki67 in breast cancer

doi:10.1038/s41379-018-0109-4

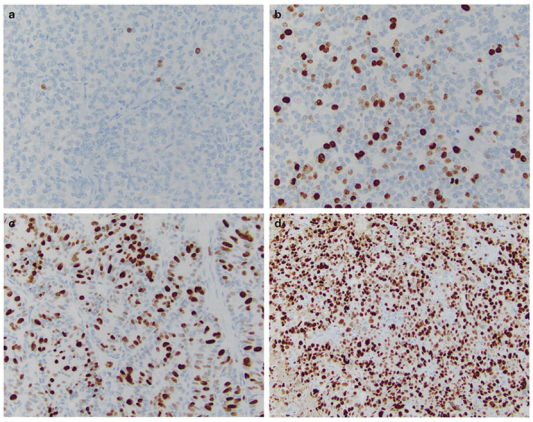


Immunohistochemistry for nuclear Ki67 in breast cancer is of interest for patient management, but interlaboratory variability has limited its clinical implementation and impact. Rimm et al. investigated whether automated assessment of Ki67 index utilizing machine learning approaches can achieve superior reproducibility. They used seven unique scanning devices and 10 different software packages. While their primary endpoint was concordance of results across all solutions, they also examined variability when same solutions were used. Measures of average and maximal scores were compared, and the former were more reproducible. The correlation coefficient for all solutions was 0.83; this improved to 0.89 for the solution deployed at multiple sites, which was similar to that obtained using the same slides in a pathologist-read study (0.87). These automated approaches are showing promise, and with some refinement and additional confirmation of clinical validity and utility could be deployed in clinical practice.

Common classification of NENs

doi:10.1038/s41379-018-0110-y

Neuroendocrine neoplasms (NENs) are a diverse group of tumors with disparate criteria for diagnosis and classification in different body sites. To address the need for a common classification framework, Rindi et al. consolidated information about these tumors, which arise not only in classical endocrine glands (pituitary, parathyroid, and thyroid) but also in sites where non-endocrine tumors are more common (e.g., lung, bowel, or pancreas). The authors recommend a single terminology for well-differentiated neuroendocrine tumors (NETs) and emphasize the importance of distinguishing NETs from the far more aggressive neuroendocrine carcinomas, which have

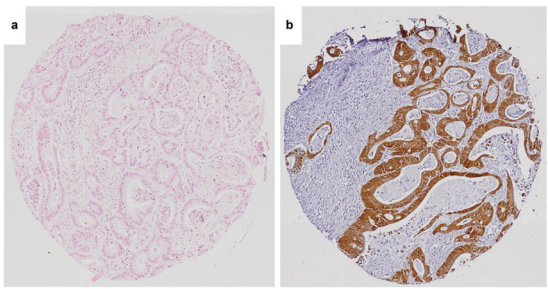


different behavior and underlying genetic abnormalities. While NETs have some similar genetic underpinnings in their various sites, and there is a common approach to treatment of these tumors, there is a need for more research to clarify prognostic biomarkers and to elucidate common and distinct genetic and epigenetic factors in the different metastatic capacities of the various types of NETs.

LABORATORY INVESTIGATION

Detection of *CTNNB1* mutations by immunohistochemistry

doi:10.1038/s41374-018-0121-9

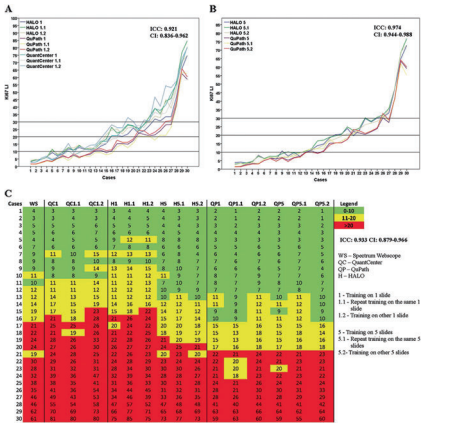


Using two antibodies against β-catenin, Akyol et al. distinguished between hypo-phosphorylated β-catenin and the total pool in the HCT116 colorectal carcinoma cell line, which has in-frame deletion of β-catenin serine 45. Some tumors showed an aberrant altered/mutant β-catenin staining pattern: strong cytoplasmic β-catenin staining with or without nuclear staining with the total β-catenin antibody but no staining with the antiactive antibody. Of 126 tumors in which *CTNNB1* mutations are known to be relatively common, 6 were colon adenomas, all of which had presumptively

pathogenic point mutations or deletions in *CTNNB1*. Several other factors were found not to exhibit a statistically significant association with β-catenin altered/mutant status. The altered staining pattern seemed to correlate with poorer survival, but not with statistical significance. These data may provide insights into β-catenin regulation and localization in both normal and cancer conditions, which will influence research into both.

Standardized Ki67 analysis

doi:10.1038/s41374-018-0123-7



In the absence of standardization, immunohistochemistry staining has not seen widespread adoption despite the prognostic value of markers such as Ki67. Acs et al. aimed to optimize a standardized protocol for Ki67 analysis across 30 cases of estrogen receptor–positive breast cancer. They built a microarray from representative tissue blocks, with a median follow-up of 120 months, and used the Mib-1 antibody for Ki67 detection. The use of digital image analysis to eliminate operator discrepancy could be the key to increasing the interinstitution utility of this prognostic and predictive marker. The three tested platforms performed with high reproducibility (~93%). The results within each platform were also outstanding, with each platform essentially indistinguishable with respect to prediction of breast cancer patient outcome. The study showed that Ki67 scoring can be independent of platform, operator, or vendor, and a multi-institutional study currently under way might prove its utility in the clinic.

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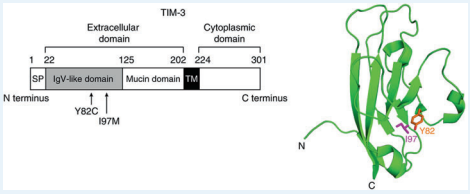
Effects of germline *HAVCR2* mutations

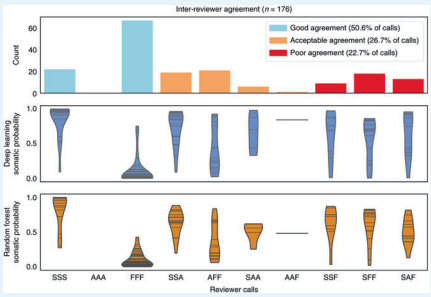
TIM-3 is a modulator of immune response. Gayden et al. found that 60% of subcutaneous panniculitis-like T cell lymphomas (SPTCLs) had mutations of the *HAVCR2* gene, which encodes TIM-3. SPTCL can be associated with hemophagocytic lymphohistiocytosis (HLH). Two *HAVCR2* mutations were identified that could be traced to very specific founder mutations of patients from specific ancestry: pTyr82Cys Tim-3 in patients from East Asia and Polynesia and p.Ile97Met Tim-3 in patients with European ancestry. Both variants induce protein misfolding and downstream alterations in pathway dynamics, such as secretion of inflammatory cytokines and activation of NLRP3 inflammasome, promoting both HLH and SPTCL. The clinical implication is that patients may receive benefit from immunotherapy. However, care will be needed in administering TIM-3 checkpoint inhibitors as this may have adverse effects, a possibility not shown previously. Interleukin-1 and interferon-γ could be safer and more effective therapeutics to treat HLH-SPTCL.



Nature Genetics, published online 29 October 2018; doi:10.1038/s41588-018-0251-4

Deep-learning model to refine cancer sequencing data analysis

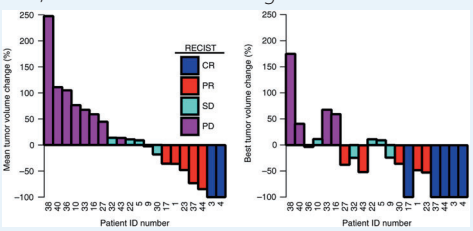
Ainscough et al. sought to develop an automated process using machine learning to refine the final step in somatic variant calling in cancer genomic analysis. The lack of reproducibility and the costs involved make the current manual review process error-prone and inefficient. The authors' model was able to accurately mimic manual refinement labels for 13,579 variants. As a computer model, it reduces the inevitable human bias in interreviewer assessment of data and, theoretically, will improve the reliability and reproducibility of data moving forward. Of 21,000 variants, 16,722 were identified as somatic by both the deep-learning model and manual review. Further analysis indicated that the results achieved with the deep-learning approach might represent an 8.9% increase in detection of clinically relevant variants, which would reduce expense and labor while possibly improving clinical outcomes.



Nature Genetics, published online 5 November 2018; doi:10.1038/s41588-018-0257-y

Radiotherapy augments CTLA-4 blockade

Radiotherapy, along with CTLA-4 blockade, induces systemic antitumor T cells in chemorefractory metastatic non–small cell lung cancer (NSCLC). Formenti et al. reported objective responses in 18% of enrolled patients, with 31% demonstrating stable disease. When the investigators looked for predictive markers of these responses, increased serum interferon-β after radiation along with early changes to T-cell clones were the strongest markers and were compatible with mechanistic preclinical data. These data indicated that radiation was inducing abscopal responses in patients by directly exposing immunogenic mutations to the immune system. One NSCLC patient who received radiation and ipilimumab showed expansion of neoantigen-reactive CD8 T cells; further evaluation showed this clone to be KPNA2, also known to be upregulated in colorectal cancer cell lines that have been exposed to radiation. Combination therapies have increasingly been shown to add efficacy and increase life expectancy, but most of the underlying mechanisms have yet to be determined.



Nature Medicine, published online 5 November 2018; doi:10.1038/s41591-018-0232-2