INSIDE THE USCAP JOURNALS

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MODERN PATHOLOGY

Pan-cancer analysis of multi-biomarker features in immunotherapy response

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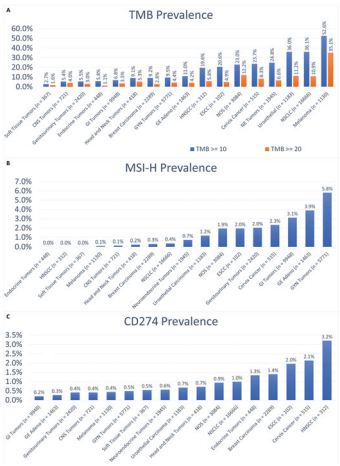

Programmed death ligand-1 (PD-L1) immunohistochemistry is a prevalent immunotherapy biomarker. Huang et al. examined the prevalence of PD-L1 expression across tumor types and in relation to microsatellite instability, tumor mutational burden (TMB), and *CD274* (PD-L1) gene amplification. They identified PD-L1 expression more frequently in immune cells rather than in tumor cells. There was a high correlation between PD-L1 expression and *CD274* gene amplification and the combination of PD-L1 and TMB with varying prevalence in different tumor types. To date, this study of 48,000 cases is the largest pan-cancer analysis of combined biomarkers associated with checkpoint inhibitors. It has guided the proposal for additional clinical trials to determine whether patients with double-positive PD-L1^{+}/TMB^{+} would have the best response to immunotherapy.

Validation of novel breast cancer staging protocol

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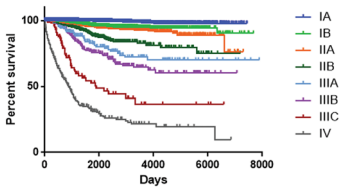

Anatomic stage groups (ASGs) have been the clinical standard for predicting breast cancer outcomes. The newly established prognostic stage groups (PSGs), which take into account prognostic influence of histologic grade and receptor status, have been revised to provide pathological and clinical prognostic stage (PPSG/CPSG) tables. PPSG cannot be assigned in a significant proportion of higher-staged breast cancers owing to increasing use of neoadjuvant therapy. Compared with ASG, the use of CPSG assigned 16.1% of cases to higher-stage and 27.2% of cases to lower-stage groups, with CPSG exhibiting greater overall discriminating power. The 8th AJCC CPSG was shown to be a superior overall staging system for predicting prognostic outcomes for patients receiving standard-of-care therapy. However, further evaluation and validation, with longer follow-up, are needed to refine the table.

LABORATORY INVESTIGATION

Kras mutation rate as a predictive marker of pancreatic cancer development

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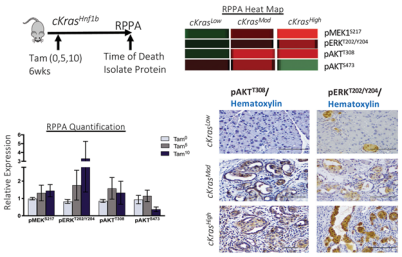

To better understand the development of pancreatic cancer in the context of *Kras* mutations, Singh et al. investigated the low frequency of pancreatic ductal adenocarcinoma (PDAC) in $Kras_{mut}$ mice. The group hypothesized a second genetic hit and explored ectopic expression and elevated levels of oncogenic mutant *Kras*. They found that ectopic expression of oncogenic mutant K-Ras in pancreatic ducts generates early and late PanIN (pancreatic intraepithelial neoplasia) as well as PDAC. This Ras rheostat model provides evidence that AKT signaling is an important early driver of invasive duct–derived PDAC

and will be a relevant model for studying how PDAC develops as well as for developing and calibrating novel therapeutic strategies.

An organoid biobank for pancreatic cancer evaluation

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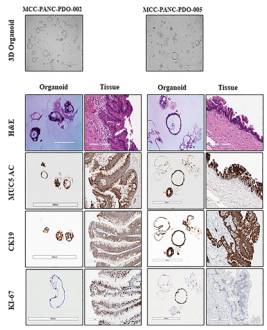

Pancreatic cancer (PaCa) is the third leading cause of cancer-related death in the United States. Beato et al. investigated strategies to detect PaCa early, when it is operable and before it has had a chance to progress. The group propose the use of organoids as a preclinical platform to mimic intraductal papillary mucinous neoplasms (IPMNs), cystic precursors of PaCa. They sought to develop a living biobank of patient-derived organoids from IPMNs. Samples of tumor and normal tissue were taken from 15 patients with IPMNs undergoing surgical resection. The success rate of organoid generation from tumor and adjacent normal tissue was 81% and 87%, respectively. The findings confirm that organoids derived from alternative tissues exhibit different morphologies and histologic features to match their origination tissue. The authors suggest that their preclinical model might improve patient outcomes and advance chemoprevention studies.

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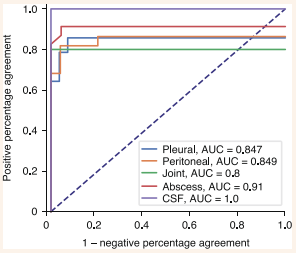
Early and specific identification of pathogens

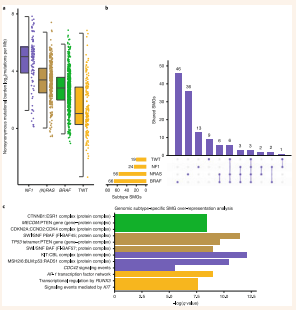
Gu et al. developed a metagenomic next-generation sequencing (mNGS) test using cell-free DNA from body fluids to identify pathogens. Taking 182 samples of body fluids from 160 patients with acute illness, the group evaluated two sequencing platforms and compared sensitivity and specificity for bacteria and fungi. In a sample of 12 patients for whom an infectious diagnosis was established despite negative culture/PCR body fluids, seven (58%) were mNGS-positive. Real-time computational analysis enabled a median 50-minute sequencing and 6-hour sample-to-answer time by nanopore sequencing. The group propose that their model is a promising tool for diagnosis of unknown infections from body fluids—where it has previously been used only as a test of last resort—and that it has the power to aid in faster diagnoses, reduction of false-negative and -positive results, and the identification of rare infections that might otherwise be missed.



Nature Medicine, published online 9 November 2020; https://doi.org/10.1038/s41591-020-1105-z

Exploration of integrated molecular drivers in melanoma

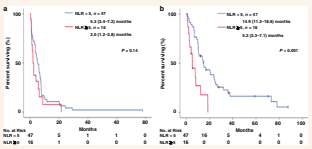
Subtypes of melanoma (*BRAF (N)RAS*, *NF1*, triple wild-type (TWT)) exhibit markedly different global genomic properties, down to the secondary driver genes and active mutational processes. Induction of transforming growth factor-β signaling in *BRAF* melanomas and inactivation of the SWI/SNF complex in *(N)RAS* melanomas were revealed as patterns of secondary driver genes specifically enriched to particular subtypes. This contrasted with TWT melanomas, which were shown to be associated with transcriptional downregulation of key DNA-repair genes. Observations of these alternative driver mutations were differentially linked with selective immune checkpoint blockade response, which the authors propose needs further evaluation. The opportunity to further distinguish melanoma subtypes by their enhanced secondary drivers could point to novel avenues for biological and therapeutic intervention.



Nature Genetics 2020;52:1373–1383; https://doi.org/10.1038/s41588-020-00739-1

A novel prognostic marker to explore the tumor microenvironment

Shirasawa et al. performed a retrospective study to examine the relationship between the pretreatment neutrophil-to-lymphocyte ratio (NLR) and clinical outcome in 63 patients with advanced large-cell neuroendocrine carcinoma (LCNEC). The group demonstrated that survival in patients with a low NLR (<5) was significantly longer than those with a high NLR (≥5). Connecting this with the impact of the immune-related tumor microenvironment (TME), they found that NLR was inversely correlated with tumoral and stromal $CD8^+$ tumor-infiltrating lymphocytes. Studies have confirmed this observation in non-small-cell lung cancer as well as small-cell lung cancer, but those findings were not corroborated in this study for lack of samples; further examination will be required. The group confirmed that the NLR of the recurrence blood test could be a predictor of the efficacy of PD-1 blockade in LCNEC patients, potentially identifying an alternative marker for assessing therapeutic options.



British Journal of Cancer, published online 30 November 202; https://doi.org/10.1038/s41416-020-01188-7

Emma Judson contributed to these reviews.