Modern Pathology (2020) 33, 1240–1241

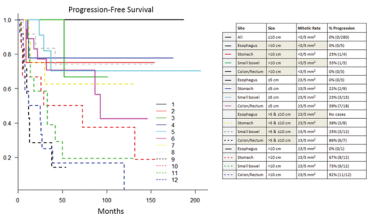

# INSIDE THE USCAP JOURNALS

https://doi.org/10.1038/s41379-020-0590-4

## MODERN PATHOLOGY

### Prognostic features of smooth muscle gastrointestinal tumors

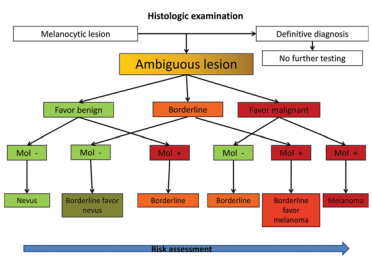
https://doi.org/10.1038/s41379-020-0492-5




Smooth muscle gastrointestinal tumor samples were collected from patients across 31 institutions—407 in total: 97 from the esophagus, 180 from the stomach, 74 from small bowel, and 56 from the colorectum. Data regarding disease progression following surgery were collected and confirmed in 56 patients. Patients with colorectal tumors were the most likely to progress, whereas none of the patients with esophageal tumors in this cohort progressed. Expert gastrointestinal and/or soft-tissue pathologists from each institution assessed pathologic features by immunohistochemistry and sought features strongly associated with progression, including moderate to severe atypia, high cellularity, abnormal differentiation, tumor necrosis, mucosal ulceration, lamina propria involvement, and serosal involvement. Neither age, sex, nor margin status correlated significantly with progression, but tumor site, size, and mitotic count did. Alpert et al. propose criteria for identifying potentially aggressive tumors requiring additional clinical follow-up: nonesophageal gastrointestinal smooth muscle tumors measuring >10 cm and/or showing at least three mitoses per 5 $mm^2$.

### DNA copy-number variations with clinical data

https://doi.org/10.1038/s41379-020-0499-y

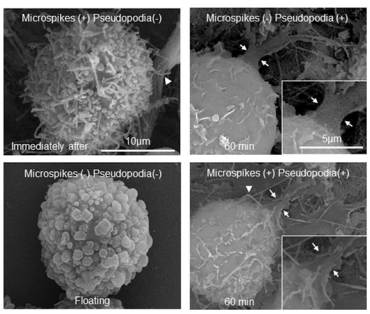



To further investigate how DNA copy-number variations (CNVs) correlate with clinical behavior in melanocytic neoplasms, Alomari et al. correlated data from a single-nucleotide polymorphism (SNP) array platform with clinical data. CNV data for 95 melanocytic tumors from 92 patients revealed that the average number of CNVs increased with the degree of histologic atypia from benign nevus to melanoma. When melanomas and ambiguous tumors were evaluated together, those with an adverse event had more CNVs than those without an adverse event, even after controlling for the Breslow depth. No neoplasm associated with an adverse event had fewer than four CNVs. While they acknowledge that future clinical validation, using a larger cohort of relevant tumors, will be necessary, the authors did provide evidence that SNP array testing for CNVs may be helpful in the classification and prognostication of ambiguous neoplasms.

## LABORATORY INVESTIGATION

### Isolating MSCS with microspikes to improve transplantation outcome

https://doi.org/10.1038/s41374-020-0421-8

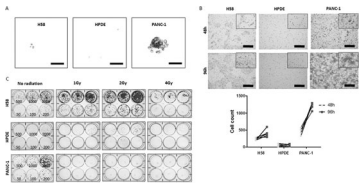



Suzuki et al. sought to quantify, observe, and ascertain the mechanism by which synovial mesenchymal stem cells (MSCs) adhere to porcine abraded meniscus. The group used scanning electron microscopy to examine the meniscus surface. Analysis of 50 cells randomly selected at 10 and 60 min and 6 and 24 h revealed that 28% of synovial MSCs immediately adhered to the meniscus. The group also saw microspikes in 36% of the floating synovial MSCs and 76% of the cells on the meniscus. They propose that these spikes, along with the development of pseudopodia, may play a role in the cells' adhesion to the meniscus. While acknowledging several limitations of their model and proposing future research, they nevertheless suggest that synovial MSCs with

microspikes should be isolated, and the meniscus should be abraded to achieve improved clinical outcomes due to increased adherence and entrapment of the MSCs.

## Study of an in vitro precancerous cell model

https://doi.org/10.1038/s41374-020-0372-0

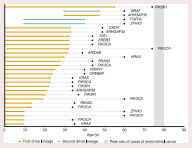


Modeling cancer in two-dimensional in vitro cell culture is a commonly used tool that can provide important insights, but these models are currently lacking for precancerous lesions. Felsenstein et al. sought to generate a three-dimensional organoid system for pancreatic cancer using a cell line (H58) that they generated from human pancreatic intraductal tubulopapillary neoplasm cells. The group went on to perform RNA sequencing and whole-genome sequencing that revealed somatic mutations in genes involved in DNA repair and Wnt signaling (*TP53*, *ERBB2*, *APC*, *BRCA2*, *CTNNB1*, *MRE11*, and *MUC4*), as well as structural rearrangements. They also examined colony formation, invasive tendency, plating efficiency, population doubling time, and aneuploidy to characterize the H58 cell line. The authors concluded that that the cell line falls somewhere between normal pancreatic ductal cells and cancer cells, making this line a crucial link for the study of precancerous lesions.

# nature.com/pathology

### The mutational landscape of normal human endometrial epithelium

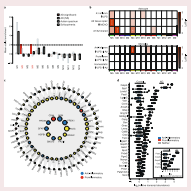
Normal somatic cells acquire mutations, but our understanding of the rate, cause and consequence of these mutations is limited. Moore et al. used whole-genome sequencing to show that normal human endometrial glands are clonal cell populations with total mutation burdens that increase at about 29 base substitutions per year, a rate many-fold lower than seen in endometrial cancers. The group was able to construct phylogenetic trees from specific individuals to assess mutational drivers and created a timeline of when driver mutations in these normal endometrial glands, statistically, show up. Their results suggest that endometrial cancers are initiated during childhood and slowly evolve to malignancy over a woman's lifetime. Further investigation of normal endometrial cells with drivers could generate targets for research into precursors of cancer development.



*Nature* 2020;580:640–646; https://doi.org/10.1038/s41586-020-2214-z

### Proteomic analysis of Alzheimer's disease

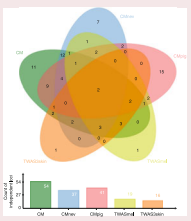
Johnson et al. employed quantitative mass spectrometry and coexpression analysis in the largest proteomic study thus far of Alzheimer's disease (AD) to better understand its pathophysiology. One protein network module (M4) linked to sugar metabolism was enriched in AD genetic risk factors, and proteins from this module were also elevated in cerebrospinal fluid in the early stages of the disease. M4 was enriched in microglia and astrocyte protein markers associated with an anti-inflammatory state, suggesting that its biological functions serve a protective role in AD. Comparing the data to those from existing studies revealed that 7 of the top 10 plaque-associated proteins that are most significantly decreased in rapidly progressive AD are found in the M4 module, including M4 hubs MSN and PLEC. This database, representing more than 2000 brains and nearly 400 cerebrospinal fluid samples, will provide a tool for identifying therapeutic targets and fluid biomarkers for the disease.



*Nature Medicine* 2020;26:769–780; https://doi.org/10.1038/s41591-020-0815-6

### The genetic architecture of cutaneous melanoma susceptibility

Because cutaneous melanoma does not yet have a defined genetic derivation, Landi et al. conducted a meta-analysis genome-wide association study (GWAS) of 36,760 cases of melanoma. The data enabled analysis of risk estimates across geographical regions and suggested that acral melanoma is unrelated to pigmentation. The discovery of new loci and genes (31 potential secondary loci, for a total of 85 cutaneous melanoma susceptibility loci) augments our understanding of cutaneous melanoma risk and provides many new insights into cutaneous melanoma's genetic architecture. The list included *MITF* and *NOTCH1/2*, along with *SOX10*, a key regulator of melanocyte development and differentiation, a direct regulator of melanocyte development and differentiation, and direct transcriptional activator of *MITF*. The authors' data suggest potential pathways new to melanoma susceptibility, but biological mechanisms underlying the findings remain to determined.



*Nature Genetics* 2020;52:494–504; https://doi.org/10.1038/s41588-020-0611-8

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Emma Judson contributed to these reviews.