**Laboratory Investigation (2021) 101,** 1306–1307


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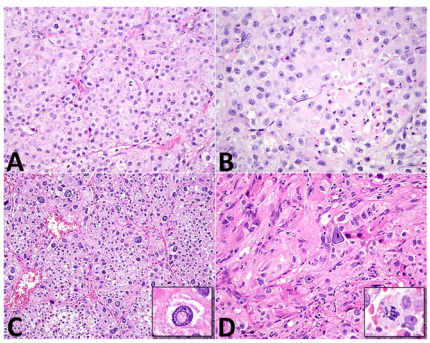
## MODERN PATHOLOGY

### Characterizing aggressive development of Leydig cell tumors

https://doi.org/10.1038/s41379-021-00845-3




Rizzo et al. explored the molecular distinctions between aggressive and nonaggressive testicular Leydig cell tumors (LCTs), a subset of sex-cord stromal tumors making up less than 3% of all testicular tumors. Approximately 90–95% of LCTs are indolent and easily cured; 5–10% have aggressive biology and metastatic potential. The group investigated the genetic landscape of each type, using next-generation DNA sequencing and immunohistochemistry with fumarate hydratase (FH) as a marker. *FH* inactivation was shown in 5 of 26 cases. *CTNNB1* mutations or biallelic *APC* inactivation (both resulting in *Wnt* pathway activation) were shown in 9 of 23 cases, and copy number changes without recurrent mutations in 6 of 23 cases. Integrating these findings, they identified three distinct subgroups of aggressive LCTs, characterized by *FH* inactivation, *Wnt* pathway activation, and copy number changes without recurrent mutations, with Wnt pathway activation as a possible driver and potential target for therapeutic intervention.

### Novel system assessing prognosis in melanoma

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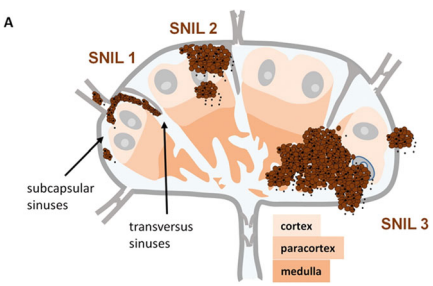


Aiming to develop a novel system for stratifying stage 3 melanoma, Kretschmer et al. utilized a cohort of 1250 consecutive patients undergoing sentinel lymph node (SN) biopsy. Their classification of the SNs with the highest tumor burden consisted of three categories they defined as the SN invasion levels (SNILs). SNIL 1 showed melanoma cells in subcapsular capsule or sinus distribution; SNIL 2 showed invasion of cortex; and SNIL 3 showed melanoma infiltrating through the medulla or capsule. In a comparison with the standard non-metric SNIL category, they correlated recurrence-free survival (RFS) and melanoma-specific survival (MSS). The MSS of patients with SNIL 1 was similar to that of SN-negative patients, whereas SNIL 2 and 3 were increasingly indicative of poor prognosis. This system can therefore provide a simple assessment to support subdivision of stage 3 melanoma and subsequent clinical management.

## LABORATORY INVESTIGATION

### AccuCor2; a new tool for metabolite labeling

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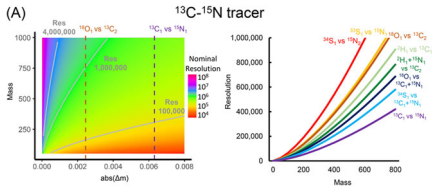
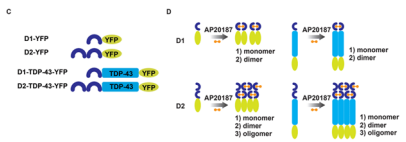



No tools currently exist for correcting isotope abundance in metabolomic and proteomic experiments using stable isotope labeling techniques. Wang et al. describe their development of AccuCor2, an R-based tool for correction of $^{13}$C-$^{15}$N or $^{13}$C-$^{2}$H labeling experiments. Their algorithm constructs correction matrices to link measured mass fractions and labeling patterns and then solves the labeling patterns using non-negative least squares. A common issue during dual-isotope experiments is that the mass resolution is often high, making it difficult to resolve other non-tracer elements such as oxygen and sulfur. AccuCor2 was designed to perform correction based on the actual mass resolution of the measurements. AccuCor2 is freely

available in open-source format and can assist in accurately calculating metabolite labeling patterns from mass spectrometry.

## Oligomerizable TDP-43: a model of ALS in vivo

https://doi.org/10.1038/s41374-021-00623-4

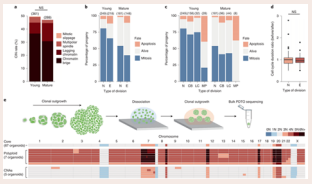



Mislocalized, cytosolic aggregation of TAR DNA-binding protein-43 (TDP-43) is characteristic of amyotrophic lateral sclerosis (ALS). To date, studies have been unable to clearly illustrate how the cytosolic aggregation of TDP-43 occurs, although liquid–liquid phase separation (LLPS) has been proposed following recent experiments using optogenetics. Yamanaka et al. created a chemically oligomerizable TDP-43 system using a compound called AP20187 that resulted in TDP-43 aggregation, cytosolic mislocalization, and cell toxicity. Further mimicking ALS pathology, the TDP-43 co-aggregated with other proteins. The model highlighted several other potential elements in ALS pathology, including N-terminal domain, RNA recognition motif, and nuclear export system. The group proposes that their model will allow more extensive study of the underlying mechanisms of ALS pathology in vivo, with a view to identifying possible treatment options.

# nature.com/pathology

## Punctuated evolution of malignant karyotypes early in carcinogenesis

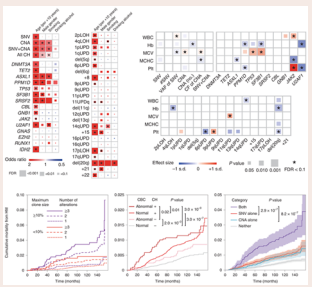
Understanding genetic diversity is key to tumor evolution. Exploration of de novo karyotype alterations within cells at a single-cell level is the next step in understanding the extent to which these changes influence the development of human tumors. Bollen et al. use 3D Live-Seq, integrating live-cell imaging of tumor organoid outgrowth with whole-genome sequencing of each imaged cell to reconstruct changes to tumor cell karyotypes over successive cell generations. Using a combination of fresh tumor biopsies and patient-derived tumor [colorectal cancer] organoids (PDTOs), their technique shows that karyotype alterations are prevalent and can occur within just a few cell generations. De novo CNAs emerge and propagate during PDTO outgrowth, and chromatin errors during mitosis are phenotypes. Gross karyotype alterations result from multipolar spindle defects and were seen following a single erroneous cell division, leading the group to suggest that aneuploid tumor genomes can evolve via punctuated evolution as opposed to graduation change over many generations of daughter cells. Cells with novel karyotypes frequently remain proliferative, show malignant fitness, were able to seed new PDTOs, and were ongoing in mature tumors. The group proposes that their data provide valuable parameters for understanding the historic trajectories and temporal dynamics of an evolving aneuploid genome.



*Nature Genetics* 2021;53:1187–1195; https://doi.org/10.1038/s41588-021-00891-2

## Detecting both SNVs/indels and CNAs in CH

To explore clonal hematopoiesis (CH)-related single-nucleotide variants and indels (SNVs/indels) and copy number alterations (CNAs)—a combination of factors previously not studied together—Saiki et al. performed target sequencing and array-based CNA detection of blood-derived DNA. Using a biobank of >10,000 individuals aged ≥60 years, the authors delineated a comprehensive registry of CH in a general population of elderly individuals in terms of both SNVs/indels and CNAs. The group put their data into context analyzing somatic alterations in combination with mortality from hematological malignancies (HMs) and cardiovascular disease. Blood-count abnormalities and mortality from HMs correlated with total number of CH-related lesions and clone size. Co-occurrence of SNVs/indels and CNAs affecting *DNMT3A*, *TET2*, *JAK2*, and *TP53* resulted in biallelic alterations and were associated with higher HM mortality as well as with modulated risk for cardiovascular mortality. Taking into account the demographics and medical history of the patients, the findings showed that SNVs/indels in *ASXL1*, *PPM1D*, splicing factors, and *TP53* were significantly associated with male gender and smoking as well as with CNAs. The group also showed co-occurrence of *TET2*-related SNVs/indels and deletions involving the *TCRA* locus that were suggestive of evolution of *TET2*-mutated T-cell clones. The number of all co-occurring alterations, SNVs/indels or CNAs, and VAF of SNVs/indels predicted significantly lower hemoglobin values, while mutant cell fractions of CNAs predicted higher mean corpuscular volume and lower mean corpuscular hemoglobin concentration values in blood cells. Their data support the importance of detecting both SNVs/indels and CNAs when exploring the development and clinical significance of CH.



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Reviews written by Emma Judson.

For a Chinese version of Inside the USCAP Journals, see the supplementary material.

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