INSIDE THE USCAP JOURNALS
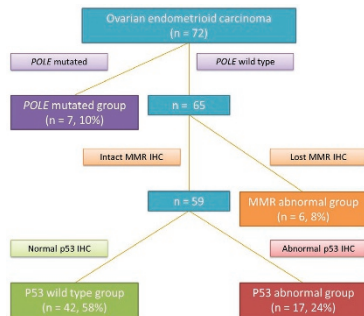
MODERN PATHOLOGY

### Ovarian endometrioid carcinoma molecular algorithm
See page 1748

Parra-Herran and colleagues sought to determine the role that markers commonly used to distinguish between subtypes of ovarian endometrioid carcinoma actually play in prognosis. The group assessed 72 cases with varying mutation profiles, which they found correlated with overall survival, approaching statistical significance. Polymerase ε (*POLE*)- and DNA mismatch repair (MMR)-mutated tumors were correlated with superior survival. The better survival of these heavily mutated tumors may be due to the effect of the immune system, which tends to be more active in this setting, perhaps owing to the accumulation of neoantigens. In contrast, TP53-disrupted tumors were associated with significantly higher rates of recurrence and death. On the basis of the correlations the group propose a molecular algorithm incorporating these mutation profiles to support the exploration and design of personalized treatment options for patients with ovarian endometrioid carcinoma.

### Clinical exomes in thrombotic microangiopathies
See page 1739
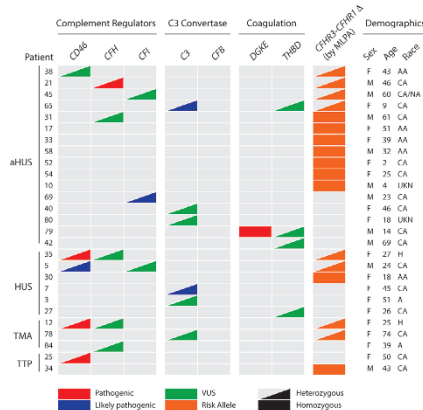
Next-generation sequencing is increasingly being used for clinical evaluation of thrombotic microangiopathies without a clear definition of its diagnostic yield. Gaut *et al* validated the thrombotic microangiopathy assay (sequencing relevant genes such as *C3*, *CD46*, *CFB*, *CFH*, *CFI*, *DGKE*, and *THBD*) using blinded blood samples from a range of patient backgrounds, using a standard method. After quality control assessment of the samples, the group analyzed the summarized genetic variants. Of the 73 patients, 27% had 24 variants of uncertain clinical significance. Current American College of Medical Genetics and Genomics/Association of Molecular Pathology guidelines suggest that markers of uncertain clinical significance not be considered in clinical decision making. Although the sample size was limited, this study describes the use of clinical exome-based next-generation sequencing testing with appropriately targeted bioinformatic analysis. The results show lower definitive diagnostic yield than previously reported and a high number of variants of uncertain clinical significance.

LABORATORY INVESTIGATION

### TcR recombinations in mouse tumor exome files
See page 1516
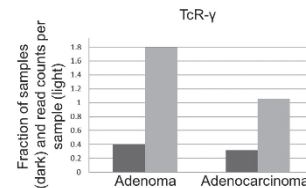
Recent investigations into tumor exomes and RNASeq data sets have revealed evidence of B- and T-cell-receptor (TcR) recombinations. Tu *et al* interpret these as being due to infiltration of lymphocytes. To explore the implications and uses of recovery of these reads, the group developed an algorithm to isolate the reads from a previously assessed mouse model of lung tumorigenesis. The mouse and human data for obtaining TcR recombination reads from tumor specimen exomes were consistent, and the authors conclude that more heavily mutated tumors are sites of elevated immune activity. With the development of immune checkpoint–based therapies, there is a need to develop correlative biomarkers to identify patients most likely to respond. This algorithm for recovering TcR recombinations allows reanalysis of existing data sets to mine for relationships between tumor genomic profiles and clones of associated T cells.

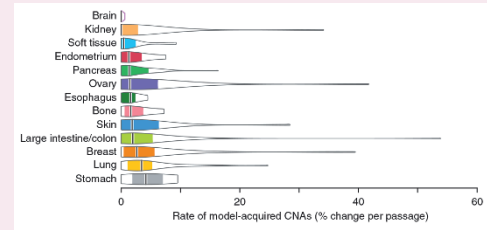# Whole tumor section quantitative image analysis

See page 1508
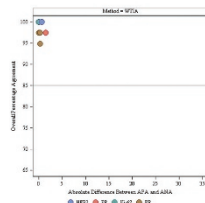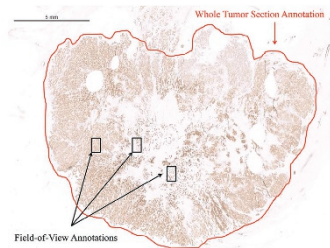
Barnes *et al* investigated the need for and the development of digital imaging–based quantification of immunohistochemistry for ER, PR, HER2, and Ki67 in breast adenocarcinoma to enhance between-pathologist reproducibility in clinical decision making. The group demonstrated that between-pathologist differences in interpretation of some biomarkers extend across multiple methodologies for assessing expression patterns. Field-of-view image analysis was not dramatically superior to manual read in between-pathologist reproducibility. However, whole tumor section image analysis was clearly better than the other methods and, with optimization, may be a robust approach in clinically based quantitative image analysis algorithms. Despite limitations of the study, including a small sample size and the limited selection of the pathologists involved in the test, this comprehensive study of immunohistochemical modalities across multiple biomarkers provides insight toward optimization of our diagnostic modalities and favors whole tumor section analysis.

nature.com/pathology

Copy number alteration in patient-derived xenografts

The chance to faithfully model the genetic features of a patient's primary tumor led to the development of patient-derived xenografts (PDXs). Ben-David and colleagues monitored the dynamics of copy number alterations (CNAs) in 1,110 PDX samples across 24 cancer types. One feature of PDX passaging was
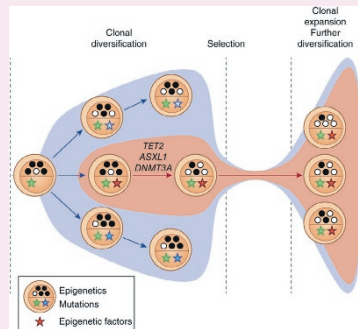

accumulation of CNAs, which correlated with tissue-specific aneuploidy as expected. Regardless of cancer type, the investigators found that CNAs often quickly became fixed in the population; a single *in vivo* passage made an undetected chromosomal aberration readily detectable at the population level. These strong clonal dynamics suggest that distinct selection pressures exist between patients and animal models and result in divergent tumor evolution. This makes the PDX a strong model only during engraftment and over the first few *in vivo* passages, with genomic instability comparable to that of cell lines and PDXs. These findings should be taken into account when utilizing PDX modeling in the arena of personalized medicine.

Nature Genetics, published online 9 October 2017; 10.1038/ng.3967

Clinical implications of clonal evolution in leukemia

Leukemias show diffuse infiltration of bone marrow by transformed hematopoietic progenitors. Clonal evolution of leukemia is an active process. In chronic lymphocytic leukemia, the dominant clone after relapse is present in pretreatment samples. In acute

lymphoblastic lymphoma, the relapse-driven clone is not directly derived from cells in the major clone at diagnosis but rather an ancestral tumor clone. In acute myelogenous leukemia, clonal evolution is linear with secondary acquisition of resistance-driving mutations. While the mechanisms are unclear, epigenetic factors are known to play roles in both tumor initiation and clonal evolution during disease progression in response to therapy. Therapy affects evolution of the disease, with cytotoxic chemotherapies and targeted therapies showing different mech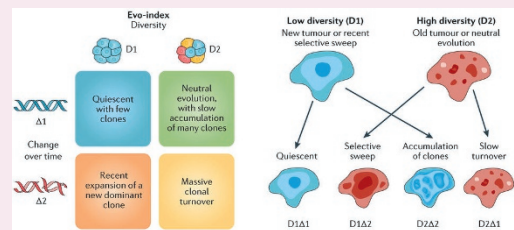anisms by which they override most other evolutionary selection factors. Furthering our understanding of these factors may be a step toward developing new clinical strategies.

Nature Medicine 2017;23:1135–1145; doi:10.1038/nm.4410

The ecology of neoplastic evolution

The evolution of neoplasms is a natural and necessary element of their genetic and epigenetic capacity. Maley *et al* noted the absence of a system for assessing the clinical significance of the changes as tumors evolve. They propose classifying tumors based on a four-tiered framework: the diversity

of neoplastic cells, changes in that diversity over time, hazards to the survival of neoplastic cells, and resources available to the cells. Having outlined their classification system, the authors explain how different cancer therapies affect different characteristics. For example, immunotherapy can increase a tumor's predation hazards whereas antiangiogenic therapy is designed to restrict a tumor's resources. The new framework suggests a consensus-shared lexicon for characterizing evolutionary differences across tumor types, with implications for clinical trials, personalized medicine, and basic cancer research.

Nature Reviews Cancer 2017;17: 605–619; doi:10.1038/nrc.2017.69

Emma Judson contributed to these reviews.