Modern Pathology (2015) 28, 322–323

INSIDE THE USCAP JOURNALS

doi:10.1038/modpathol.2015.32

Modern Pathology

Measuring pathologists' workloads

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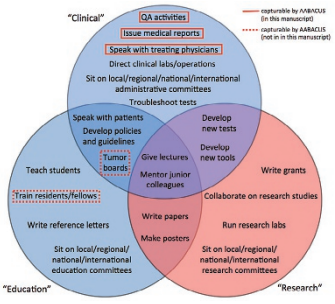

The value proposition of pathology is essentially to provide critical information for optimal patient management. This process has become more complex with the increase in evaluable biomarkers, including histologic, immunohistochemical, and molecular biomarkers. As a result, the traditional method of evaluating pathologists' workload based on number of cases modified by relative value units often underestimates the work required for complex cases and overvalues small, simple biopsies. Comparison of workloads is critical for determining the subspecialty workloads for pathologists who see only certain types of cases and for obtaining overall staffing resources to maintain an effective pathology group. Cheung *et al* propose a system called the Automatable Activity–Based Approach to Complexity Unit Scoring (AABACUS) that captures the clinical activity of pathologists from documented parameters within the laboratory information system. In their study, this system provided robust data—across multiple performance sites, institutions, and both subspecialty and generalist practices—that could be useful for supporting staffing models and resource allocation.

Heterogeneity of metaplastic breast carcinoma

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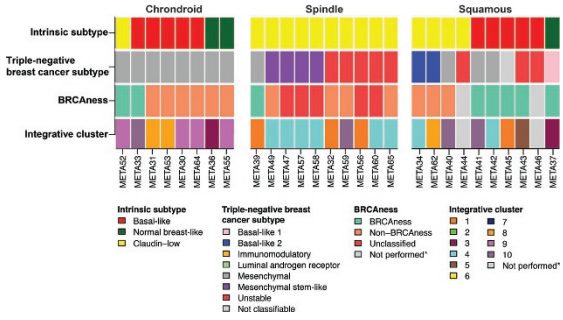
Few cancer types are monolithic in their genomic properties, and Weigelt *et al* now demonstrate remarkable heterogeneity in metaplastic breast carcinoma. To accomplish this, they studied 28 consecutive triple-negative metaplastic breast carcinomas using gene-expression profiling and copy-number analysis. Cases with spindle cell metaplasia were classified as claudin low subtype, whereas squamous or chondroid metaplasia preferentially clustered with the basal-like subtype. A triple-negative breast cancer subtyping program used in cases of chondroid metaplasia demonstrated a mesenchymal subtype, spindle cell metaplasia grouped with unstable or mesenchymal subtypes, and squamous metaplasia clustered into multiple subtypes. BRCA1-like properties were present in 31% of cases with no association with metaplasia type. Integrative clustering



revealed preferential grouping of chondroid and spindle cell metaplasia with clusters 4 and 9, whereas squamous metaplasia joined various clusters. Thus, genomic and transcriptomic analysis showed histology-linked clustering on multiple analyses, although squamous metaplasia was more divergent than the chondroid and spindle cell types.

Eosinophils and colorectal carcinoma recurrence

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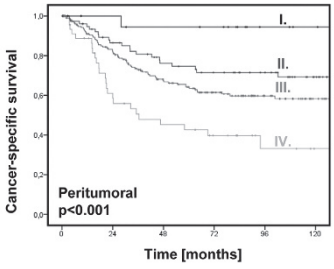

Tumor-associated lymphocytes have long been associated with outcome, and some properties of these lymphocytes may help determine sensitivity to immune checkpoint inhibitors. Harbaum *et al* expanded on these studies by further defining the role of eosinophils in colorectal carcinoma. Evaluating 381 primary colon cancers, they assessed peri- and intratumoral eosinophils across all American Joint Committee on Cancer/Union Internationale Contre le Cancer. At least 75% of the specimens had tumor-associated eosinophilic infiltrates. Peritumoral and intratumoral eosinophil counts were closely correlated with each other, and both were significantly correlated with the overall degree of tumor-associated inflammatory cell infiltrate. However, an increase only in peritumoral eosinophils, not in intratumoral eosinophils, was associated with more favorable progression-free and disease-specific survival, independent of other traditional prognostic variables. Eosinophil levels have been examined by others, who found that, in general, higher eosinophil counts are associated with better outcomes. Harbaum and colleagues' study confirms that higher eosinophil levels are a good prognostic sign, but it also indicates that their location is critical.

Laboratory Investigation

Preanalytical variables for FFPE phosphoepitope detection

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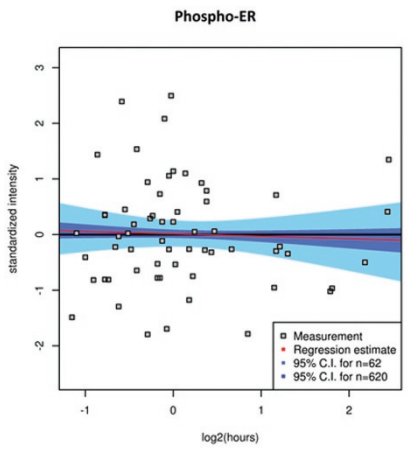

Biomarkers must be stable to be reproducibly detected. Vassilakopoulou *et al* examined preanalytical variables affecting the stability of phosphoepitopes in formalin-fixed, paraffin-embedded (FFPE) tissue. The phosphoproteins chosen were key signaling steps in cancer-signaling cascades. The authors focused on cold ischemic time (essentially, the period over which the tissue, having been removed from the patient, is at room temperature prior to formalin fixation) using a breast cancer tissue microarray with known cold ischemic times. For the great majority of the epitopes, the changes in expression levels detected varied according to the cold ischemic time. Changes were often very apparent within one to two hours. Some stress-related pathways showed increased phosphorylation levels, and other signaling phosphoproteins showed rapid loss of immunogenicity. Only a few of the tested epitopes, including phospho-Jak2 and phospho-ER, were stable across the varying cold ischemic times that are prevalent in routine clinical processing. Clearly, careful study of preanalytical variables is needed for biomarker implementation.

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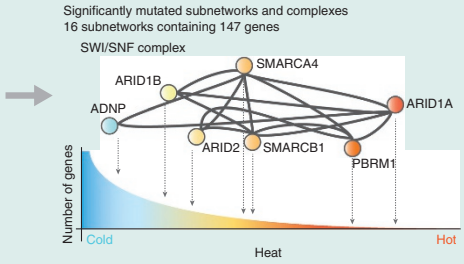
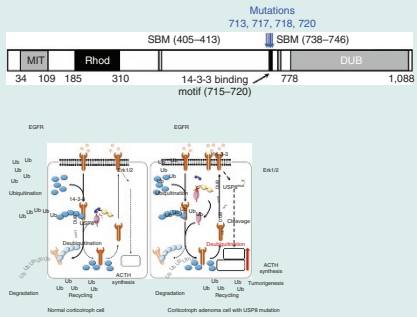
Pan-cancer analysis reveals networks of rare mutations



The mutational load and heterogeneity of cancer genomes provide long tails of very rarely mutated genes in most cancer types studied. Defining mutations as significant often amounts to identifying recurrent focused mutations in oncogenes and accumulated nonsense mutations in tumor suppressors. Such analyses are challenging for genes that are rarely mutated. In a study reported in *Nature Genetics*, Leiserson and colleagues applied a new algorithm, HotNet2, to 3,281 samples (12 cancer types) from The Cancer Genome Atlas. This algorithm assesses the significance of individual gene mutations along with the local topology where they act within protein complexes or functional pathways. The 16 significantly mutated subnetworks that were discovered include both well-known pathways in cancer and less characterized networks. The subnetworks are composed of dozens of genes and mutations across various cancer types. This approach could suggest new therapeutic opportunities using existing genomic data.

Nature Genetics 2015;47:106–114; doi:10.1038/ng.3168

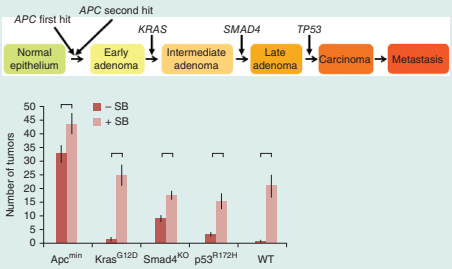
USP8 mutations cause Cushing disease



Cushing disease is caused by corticotroph adenomas of the pituitary that oversecrete adrenocorticotropin, leading to excessive adrenal glucocorticoid secretion. Reincke *et al* recently described in *Nature Genetics* an exome sequencing approach that they used to identify somatic mutations in the deubiquitinase gene *USP8* in 4 of 10 adenomas. There was clustering of these mutations in the 14-3-3 protein binding motif of USP8, resulting in enhanced proteolytic cleavage of the USP8 protein and augmented catalytic activity. The cleaved USP8 enzyme caused increased deubiquitination of the epidermal growth factor (EGF) receptor. The deubiquitination impaired the constitutive downregulation of the EGF receptor and thus sustained EGF signaling. This EGF stimulation could be an important driver of adenoma development, although other functions of the mutant USP8 activity and its lack of 14-3-3 binding remain to be discovered.

Nature Genetics 2015;47:31–38; doi:10.1038/ng.3166

Improved genetic understanding of colon cancer



To identify genes important for colorectal tumor progression, Takeda *et al*, as reported in *Nature Genetics*, used a *Sleeping Beauty* transposon mutagenesis screen to drive mutagenesis onto the background of mice with single *APC*, *KRAS*, *SMAD4* or *TP53* mutations in their intestines. Each of these genes acts at a different step in colorectal carcinogenesis. *Sleeping Beauty* mutagenesis accelerated tumor formation in all backgrounds. *APC* is known to play a gatekeeper role for subsequent development of both *KRAS* and *TP53* mutations in colorectal carcinogenesis. Interestingly, when *KRAS* or *TP53* was mutated first, the most common mutation induced by mutagenesis was *APC*, which indicates that it is still necessary as a gatekeeper. This was not true in *SMAD4*-initiated tumors. The newly described *RNF43* mutations in colon cancer (see last month's Inside the USCAP Journals) was confirmed as a tumor suppressor that results in increased activation of the Wnt pathway.

Nature Genetics 2015;47:142–150; doi:10.1038/ng.3175