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## MODERN PATHOLOGY

### Renal cell tumors and VHL

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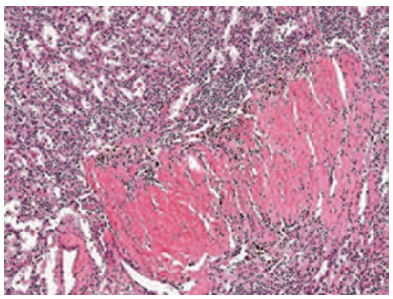

Favazza *et al* reviewed histological data for renal cell tumors that did not fit the accepted patterns of *VHL* loss of function or loss of chromosome 3p (93% of cases in the Cancer Genome Atlas). Of the remaining 27 cases, 9 (33%) were reclassified as distinct entities; clear-cell renal cell carcinoma (RCC), *TFE3* translocation–associated RCC, papillary RCC, and clear-cell papillary RCC. One feature observed was prominent fibromuscular stroma, shown by other investigators in tumors with *TCEB1* mutation. Five of 27 tumors exhibited this feature in the absence of *TCEB1* mutation while also exhibiting increased aggressive histological and higher-stage characteristics, whereas previous data on *TCEB1*-mutated RCC was linked with improved prognosis. Virtually all clear-cell RCCs show *VHL* mutation, copy-number loss, or methylation suppression, and some of the tumors lacking these properties may be reclassifiable as an alternative kidney tumor type.

### Esophageal epidermoid metaplasia: a precursor?

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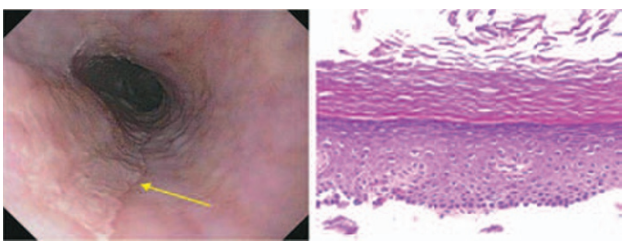

Esophageal epidermoid metaplasia (EEM) results in sharply demarcated histological features in the proximal to middle third of the esophagus. Histologically it is defined by epithelial hyperplasia, a prominent granular cell layer and superficial hyperorthokeratosis. To gain a better understanding of a hypothesized link between EEM and esophageal squamous neoplasia (ESN), Singhi *et al* performed next-generation sequencing. They found that 67% of EEM specimens harbored alterations in genes associated with esophageal squamous cell carcinoma: *TP53*, *PIK3CA*, *EGFR*, *MYCN*, *HRAS*, and *TERT* promoter. *TP53* inactivation is common in the early pathogenesis of esophageal squamous cell carcinoma. The group proposes that EEM is a precursor to *in situ* and invasive ESN and that *TP53* could serve as an early detection biomarker for high-grade dysplasia/esophageal squamous cell carcinoma.

## LABORATORY INVESTIGATION

### Flow cytometric sorting from archival paraffin samples

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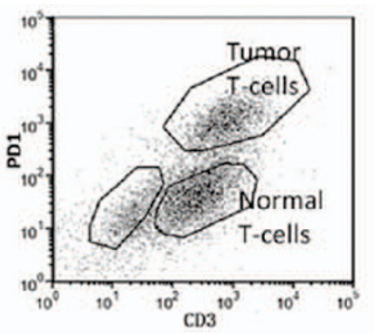


Jiang *et al* sought to develop a technique enabling analysis of lymphoma samples from archival formalin-fixed paraffin-embedded (FFPE) tissue. While immunohistochemistry on glass slides is a useful tool, sometimes it is necessary to isolate particular cells from a mixed population, and this can pose particular challenges. The group developed a method for extracting populations of single cells from FFPE blocks to perform flow cytometric sorting following antigen retrieval and labeling. They optimized the technique to sort cells in quantities sufficient to yield DNA from defined cellular populations for next-generation sequencing (NGS) as well as exon capture sequencing. This technique has the potential to unlock the vast archives of FFPE tissues for NGS sequencing and other genomic approaches, as well as single-cell assays and objective measurement of nonmalignant cells in the tumor microenvironment by flow cytometry.

## Polymorphisms and glucocorticoid signaling

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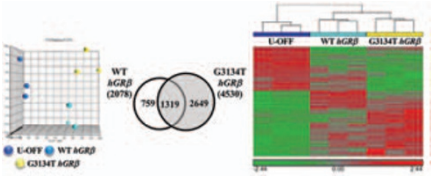
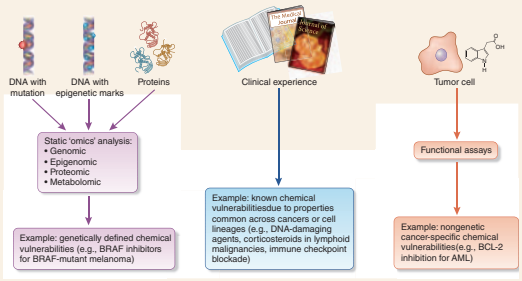



Whirledge *et al* characterized the *hGRβ* G3134T polymorphism, analysis that has heretofore been limited to a relatively small population. Seeking to identify the prevalence of the polymorphism in the wider population and correlate it with physiological outcome, the team performed a prospective cohort study. A genetically diverse pool of participants ($n$ = 3,730) were genotyped for *hGRβ* G3134T, and a subset was evaluated for clinical and biochemical features. In the racially diverse population the minor allele frequency was 74%, split between heterozygous and homozygous carriers, with higher prevalence in Caucasian non-Hispanic participants. Patients with the polymorphism were found to be more likely to have allergies (as self-reported), have higher serum cortisol levels, and exhibit lower levels of cortisol suppression in response to low-dose dexamethasone. The group conclude that the identification of this polymorphism and its association with a subset of inflammation-related transcripts suggests a regulatory mechanism that may be important to glucocorticoid therapy and the pathogenesis of glucocorticoid resistance.



## nature.com/pathology

### Precision cancer medicine: is pure genomics enough?

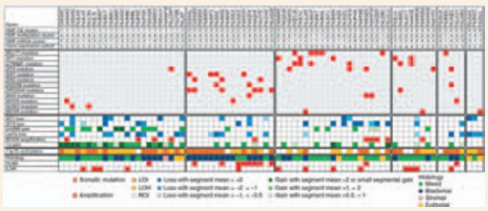



Anthony Letai provides an assessment of the highly prized paradigm of 'precision medicine'. He presents data from the National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) study (May 2016) showing that only 9% of all tested patients harbored a relevant mutation and ultimately only 16 of 645 (2.5%) cancer patients entered a treatment arm. While acknowledging that the unavailability of potent, tolerable, targeted agents in the clinic is problematic, he argues that relying solely on genetics to identify targets might also be contributory. Letai concludes his analysis of various assays at the disposal of scientists considering precision medicine options by suggesting that the reigning paradigm of cancer research (identifying the underlying mechanisms to develop therapeutics) is at odds with functional precision medicine (identifying therapeutic opportunities without examining the underlying mechanisms). He explains that the two approaches are not mutually exclusive but that precision cancer medicine must evolve beyond pure genomics to avoid continuing to 'fight cancer with one hand tied behind our backs'.

*Nature Medicine* 2017; 23:1028–1035; doi:10.1038/nm.4389

### The genomic landscape of Wilms tumor

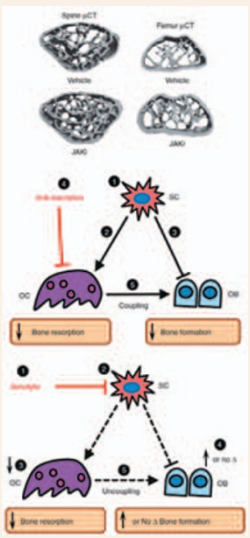
Gadd *et al* determined the genetic landscape of Wilms tumors, the most common malignant renal tumor in children. Using full genomic characterization of 117 tumors, followed by targeted sequencing of 651 tumors, they identified, along with the genes previously implicated in Wilms tumors, several genes not previously recognized. The group observed that few, if any, of the cases of Wilms tumor that they assayed were the result of only one genetic alteration, finding that multiple pathways were affected simultaneously. The authors discuss alterations in *SIX1* and *SIX2* in Wilms tumors—both genes are associated with preservation of nephron progenitors—as well as downstream upregulation of cell-cycle genes. Also seeming to perpetuate progenitor states were alterations in microRNA-processing genes, resulting in global reduction of mature microRNAs, including *MIRLET7A*, a potent mediator of differentiation during early development. This improved understanding of the driver mutations in Wilms tumors may facilitate future targeting of these pathways.



*Nature Genetics* 2017; 49:1487–1494; doi:10.1038/ng.3940

### Reduced bone loss when preventing cellular senescence

Seeking to explore the role of senescent cells in age-related bone loss, Farr *et al* looked at both genetic and pharmacological means to eliminate senescent cells in mice. The group demonstrated that activation of the *INK-ATTAC* caspase 9 in senescent cells of 20- to 22-month-old mice, or treatment with senolytics or a JAK inhibitor for 2–4 months, led to greater bone mass and strength compared with vehicle-treated mice. Senescent cell–conditioned medium impaired osteoblast mineralization and enhanced osteoclast-progenitor survival. The development of functional senolytics could replace existing therapies that target osteoclasts to decrease bone resorption. The authors propose that identifying a method for targeted elimination or prevention of senescent cells would provide a fundamental mechanism to prevent or delay the onset of age-related comorbidities, including osteoporosis.



*Nature Medicine* 2017; 23:1072–1079; doi:10.1038/nm.4385

Emma Judson contributed to these reviews.