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Cell-Free DNA Next-Generation Sequencing in Pancreatobiliary Carcinomas .................1040
Précis: Prospective analysis reveals the accuracy and sensitivity of cell-free DNA-based sequencing in detecting tumor-derived actionable mutations in patients with advanced pancreatobiliary cancer.

An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101 ..........1049
Précis: A highly selective TRK inhibitor induced rapid tumor regression in a patient with metastatic soft-tissue sarcoma harboring an oncogenic LMNA–NTRK1 gene fusion.

Detection of Enhancer-Associated Rearrangements Reveals Mechanisms of Oncogene Dysregulation in B-cell Lymphoma ..............1058
Précis: The PEAR-ChIP method identifies enhancer-associated genomic rearrangements and highlights mechanisms of enhancer regulation in lymphoma subtypes.
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Précis: The BRAFV600E-induced, TGFβ-dependent upregulation of p15 causes growth arrest of melanocytic nevi, which can be reversed by p15 loss to drive melanomagenesis both in vitro and in vivo.

Pancreatic Cancer Metastases Harbor Evidence of Polyclonality ........1086
R. Maddipati and B.Z. Stanger
Précis: Lineage tracing experiments in an autochthonous mouse model implicate polyclonal seeding and metastatic site–specific clonal outgrowth in PDAC progression.

Regulatory T-cell Response to Enterotoxigenic Bacteroides fragilis Colonization Triggers IL17-Dependent Colon Carcinogenesis ................. 1098
Précis: Regulatory T cells drive differentiation of procarcinogenic Th17 cells and promote the early stages of colon tumorigenesis in response to bacterial infection.

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Geis and colleagues found that depletion of regulatory T cells (Treg) unexpectedly impaired early microadenoma formation in multiple intestinal neoplasia mice colonized by the bacterium enterotoxigenic Bacteroides fragilis (ETBF). This reduction in neoplastic growth was accompanied by a decrease in Th17 cells and IL17 production and an increase in the IFNγ-producing Th1 cell population, suggesting that Tregs modulate the balance of Th1/Th17 cells. Treg consumption of IL2 resulted in an increase in Th17 polarization and a subsequent decrease in the Th1 population following ETBF colonization, consistent with a cell-extrinsic role for Tregs in promoting Th17 differentiation. These results demonstrate that Tregs drive Th17 polarization to establish pro-tumorigenic colitis and are necessary for the early stages of tumorigenesis in colitis-associated colorectal cancer. For details, please see the article by Geis and colleagues on page 1098.