36. Lung Cancer: Clinical Trials and Genomic-Based Therapy
1 unit, Charles Rudin, April 17, 2026

- There has been a remarkable increase in identification of clinically actionable driver mutations over the past 20 years
    - This increase has transformed the care of lung cancer patients and other diseases
    - Recent "tumor-agnostic" FDA-approvals underscore an oncogene-centric future for targeted therapies
- There has been increasing use of comprehensive sequencing approaches in cancer care
    - Multi-gene NGS picks up alterations missed by piecemeal approaches, is more efficient, and more cost-effective
    - "Liquid biopsies" are now complementing tumor sequencing, and offers quicker turnaround times
    - RNA-based sequencing can identify gene fusions missed by DNA-based NGS
    - NGS calls out microsatellite instability, a potent predictor of response to immunotherapy
- NGS has been an engine of discovery research in oncology
    - NGS has accelerated clinical trials identifying novel treatments for patients with rare oncogenic mutations
    - Sequencing of matched normal DNA from blood identifies clinically relevant clonal hematopoiesis
    - NGS has nominating new recurrent somatic mutations as putative oncogenes

Despite these several advances in both targeted and immunologic therapies, tumor heterogeneity, plasticity, and distinct interactions with tissue-specific microenvironments remain a major challenge. Lung cancers frequently metastasize to brain and to the leptomeningeal space, both of which are remarkably different in fundamental aspects of composition relative to lung. The paper by Peinado et al. attached describes a novel property of a subset of cells within a high-grade neuroendocrine lung cancer, small cell lung cancer. We will discuss this paper in detail. For consideration of the leptomeningeal environment, I am including an interesting paper from Chi et al. from 2020.

Discussion Paper:
Peinado et al., Intrinsic electrical activity drives small-cell lung cancer progression. Nature 2025. https://www.nature.com/articles/s41586-024-08575-7

Additional reading (optional):
Chi et al., Cancer cells deploy lipocalin-2 to collect limiting iron in leptomeningeal metastasis. Science 2020. https://www.science.org/doi/10.1126/science.aaz2193