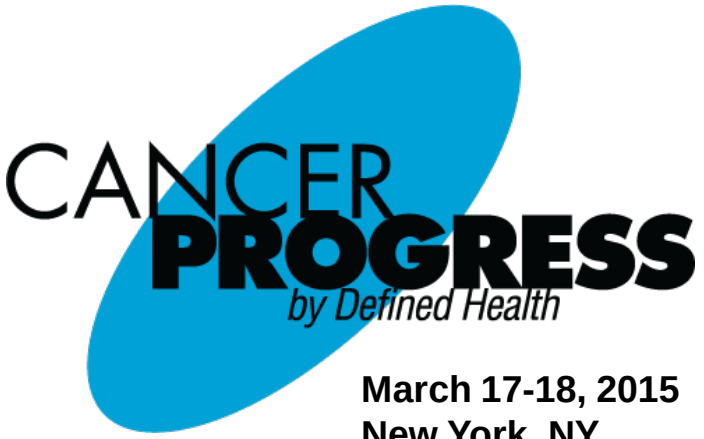
Moving Beyond Mutations to Key Drivers: From Sequence to Function to Decision



March 17-18, 2015
New York, NY

Moving Beyond Mutations to Key Drivers: From Sequence to Function to Decision

Moderator:

Jeremy P. Goldberg, President, JPG Healthcare LLC

Panelists:

- Robert Cohen, MD, Calico Life Sciences
- Christoph Lengauer, PhD, MBA, Chief Scientific Officer, Blueprint Medicines
- Ronnie Morris, MD, President, Champions Oncology
- Rob Ruijtenbeek, PhD, Chief Scientific Officer, PamGene BV
- Jeffrey Settleman, PhD, Senior Director, Discovery Oncology**,** Genentech

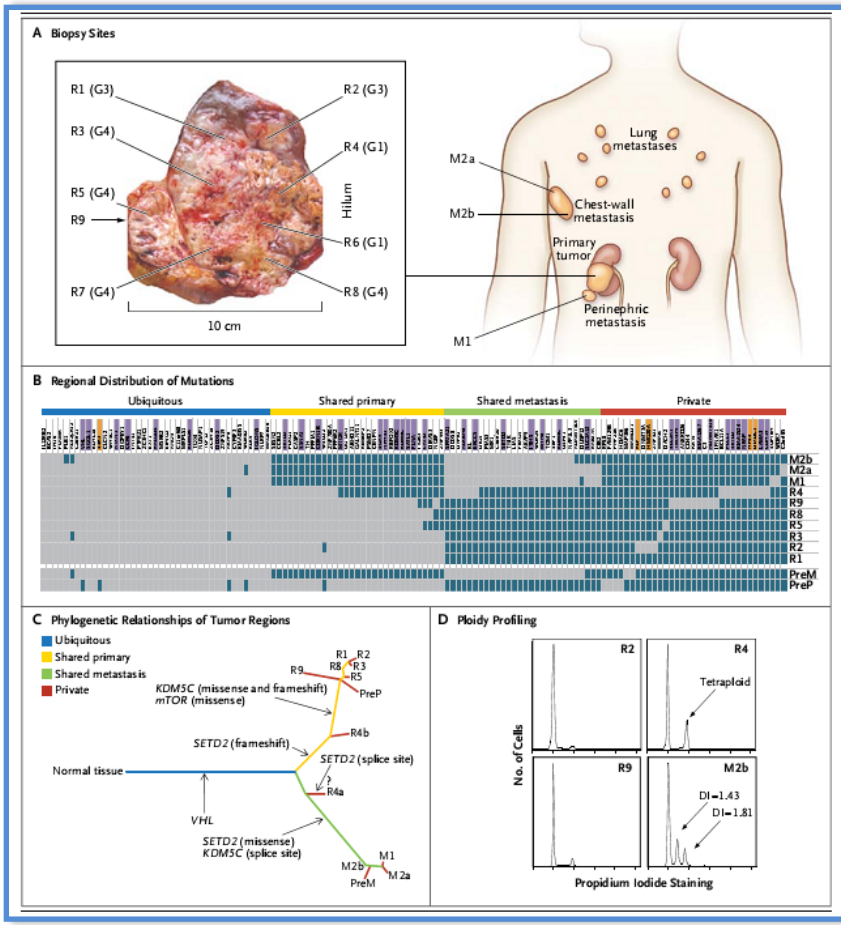
Challenges of Conventional Targeted Therapy: Inherent Heterogeneity and Diversity

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

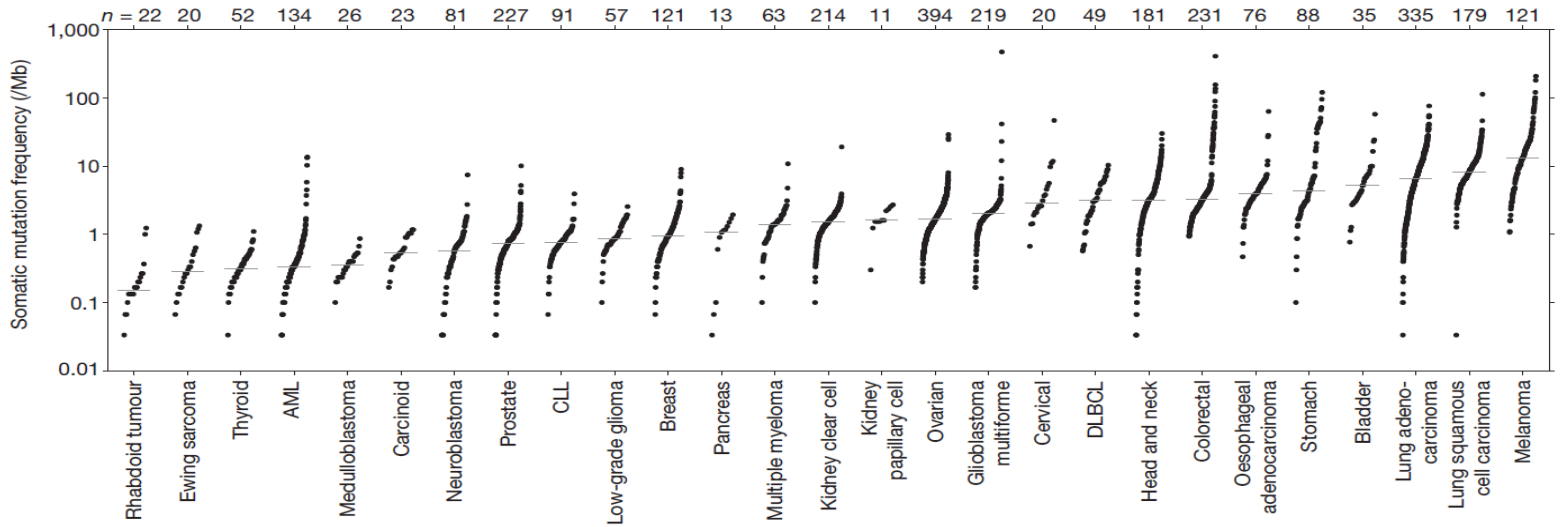
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.



N Engl J Med Vol 366(10):883-892, March 8, 2012

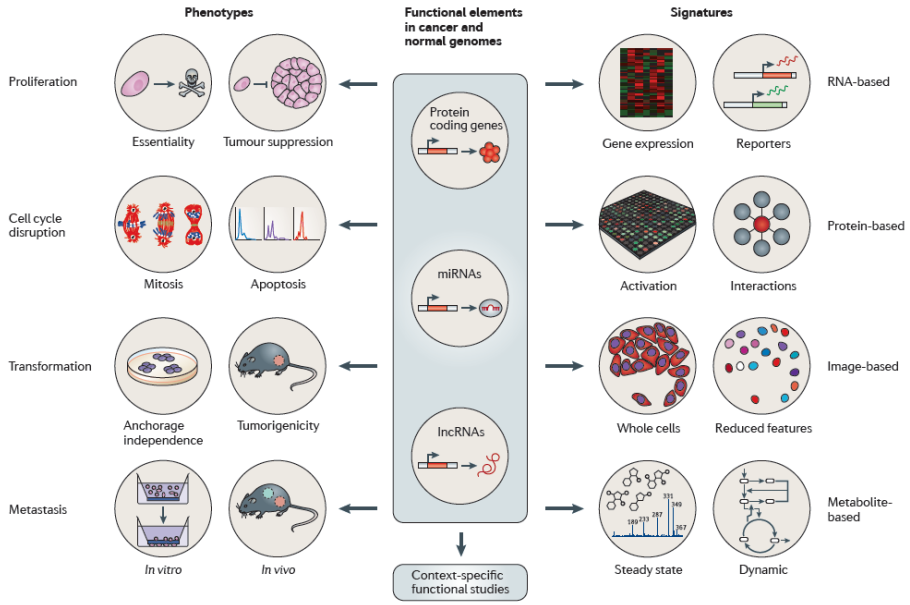
Cancer Cells Are Highly Mutated

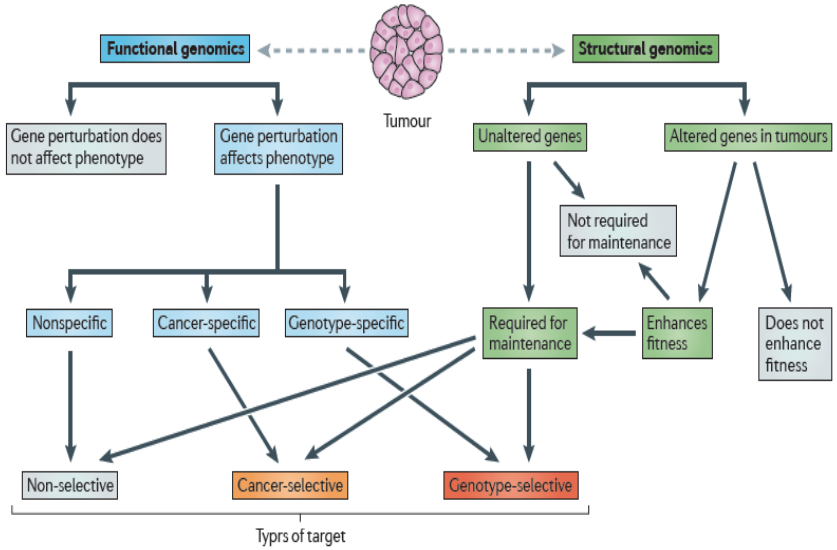
- While a number of drivers are well recognized (e.g., TP53, KRAS, and EGFR), due to their frequent mutation rate in tumors and biological characterization, they are not sufficient to explain the phenotypic diversity of cancer and many more drivers likely exist.



Nature. 2013 Jul 11;499(7457):214-8

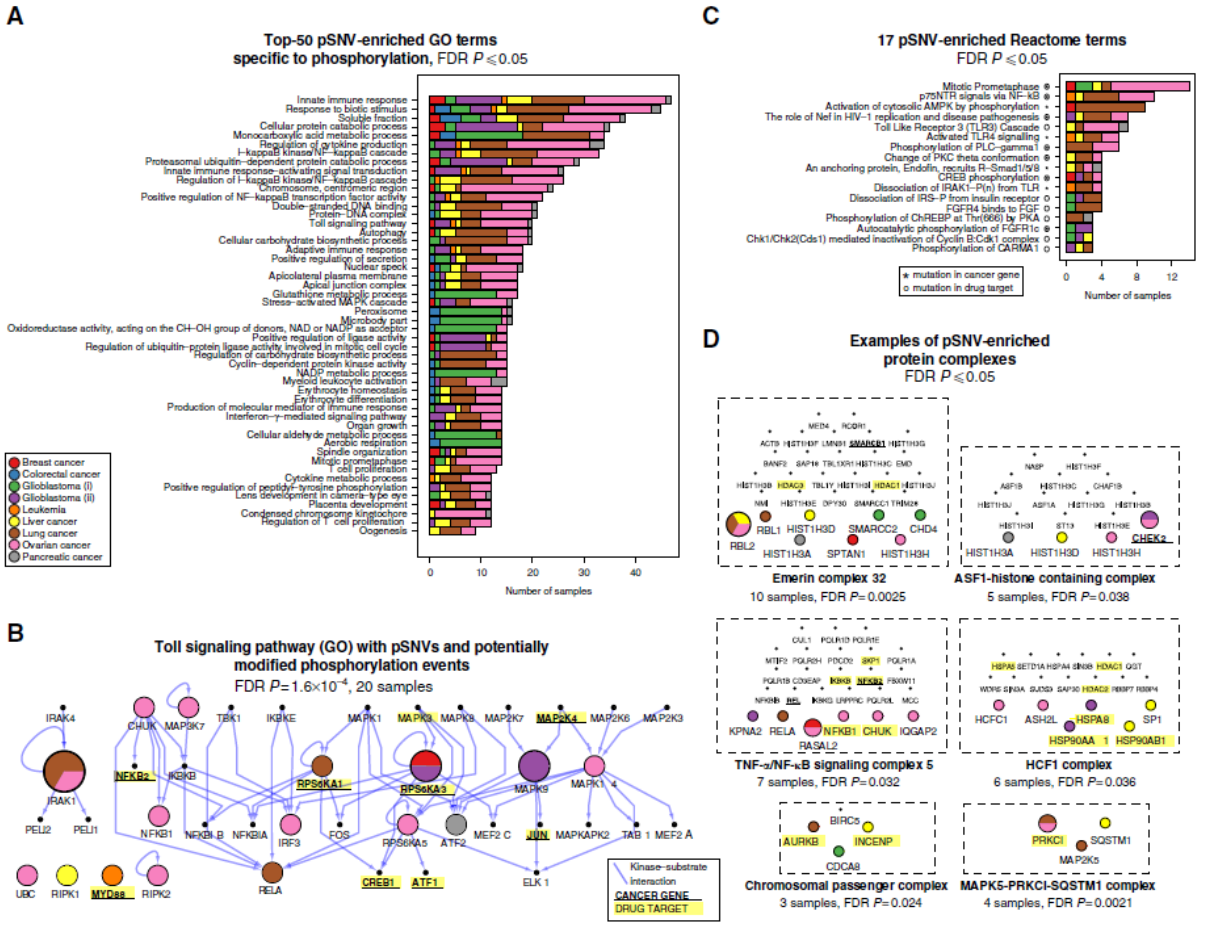
Moving Towards Functionally Characterizing Cancer Genomes





Nat Rev Genet. 2011 Jun 17;12(7):487-9

Example: Systematic Analysis of Somatic Mutations in Phosphorylation Signaling Predicts Novel Cancer Drivers



Key Questions to Address

- Need to find better way to get information that will enable more informed decisions to treat patients.
- 100s-1000s of mutations & DNA mutations are not sufficient -- DNA, RNA, methylation status not enough – need for more insight to get to a higher/deeper level of understanding.
- Multimodal approach, predictive models, New platforms may facilitate like PDX models both for drug development and informing patient treatment decisions, hypothesis testing.
- We have made poor choices as driver mutation may not equate with best targets – how to address ?
- Issues for predictive biomarkers :
  - non-representative models,
  - need for additional analyses,
  - lack of appropriate recognition of heterogeneity when defining a Cancer as having mutations x, y and z.

Moving Beyond Mutations to Key Drivers: From Sequence to Function to Decision

Moderator:

Jeremy P. Goldberg, President, JPG Healthcare LLC

Panelists:

- Robert Cohen, MD, Calico Life Sciences
- Christoph Lengauer, PhD, MBA, Chief Scientific Officer, Blueprint Medicines
- Ronnie Morris, MD, President, Champions Oncology
- Rob Ruijtenbeek, PhD, Chief Scientific Officer, PamGene BV
- Jeffrey Settleman, PhD, Senior Director, Discovery Oncology**,** Genentech