The Clinico-Genomics of Localized Prostate Cancer: Moving Beyond the Bench

Michael Fraser, Ph.D.

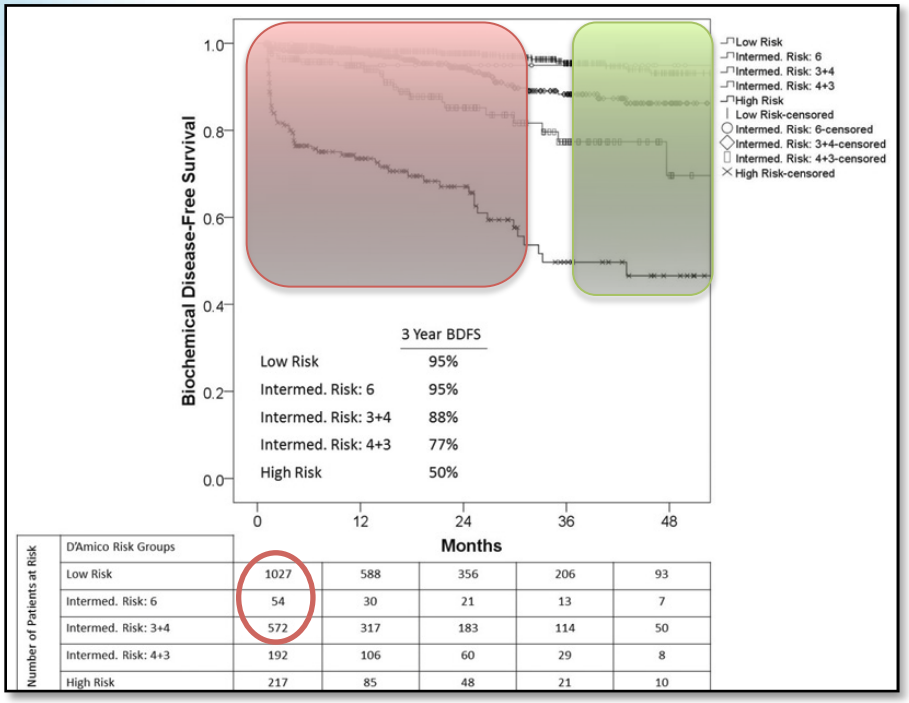
Director, Prostate Cancer Program

Ontario Institute for Cancer Research

Disclosures

- I have no relevant disclosures

The Problem of Heterogeneity



Pollard et al, 2017

Low/Fav. Intermediate Risk

80% of all cases

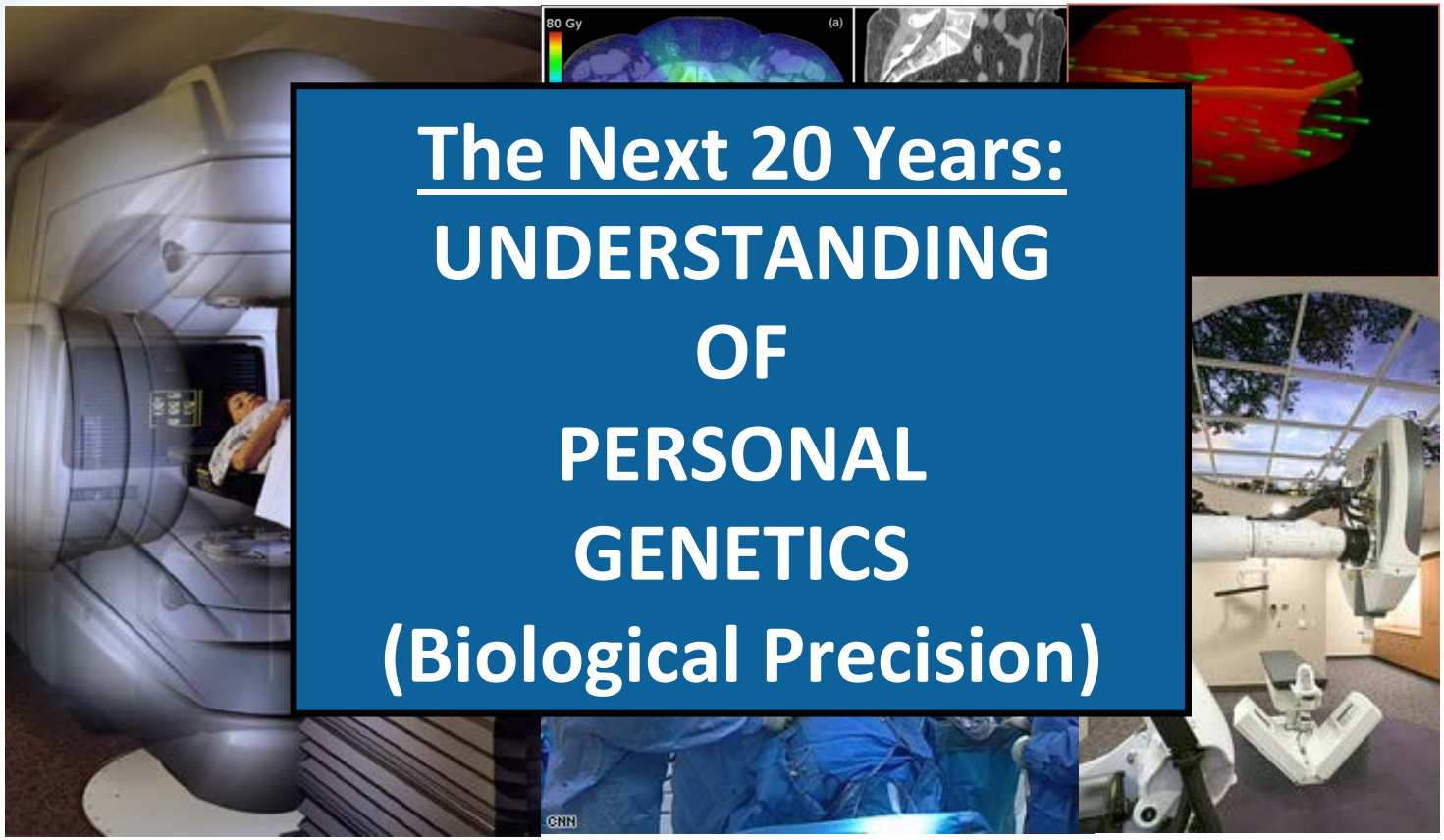
7% failing w/in 3 years

20,000 cases/year

1,400 rapid failures

PROGNOSTIC BIOMARKERS TO INFORM TREATMENT INTENSIFICATION/DEINTENSIFICATION

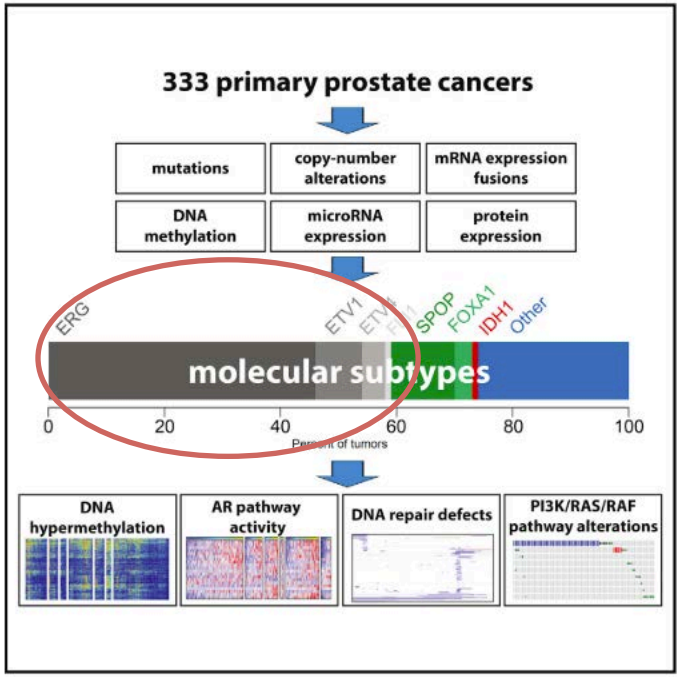
The Last 20 Years: Physical Precision



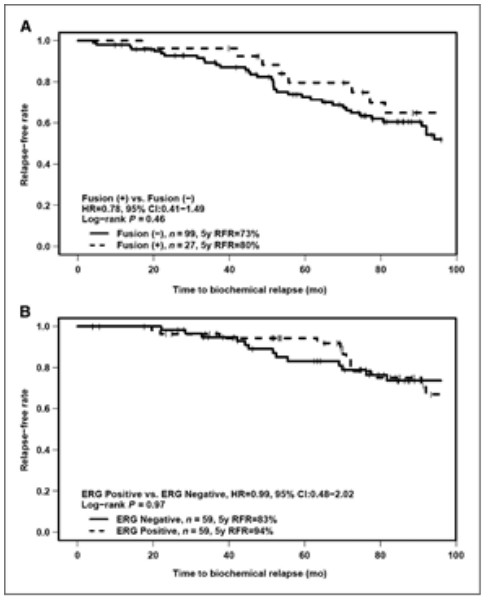
The Next 20 Years:

UNDERSTANDING OF PERSONAL GENETICS (Biological Precision)

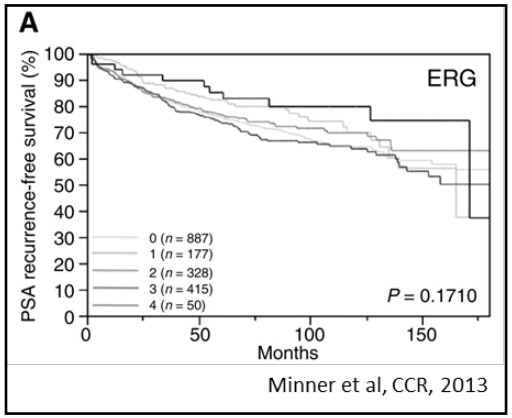
Molecular Subtypes…



TCGA, 2015

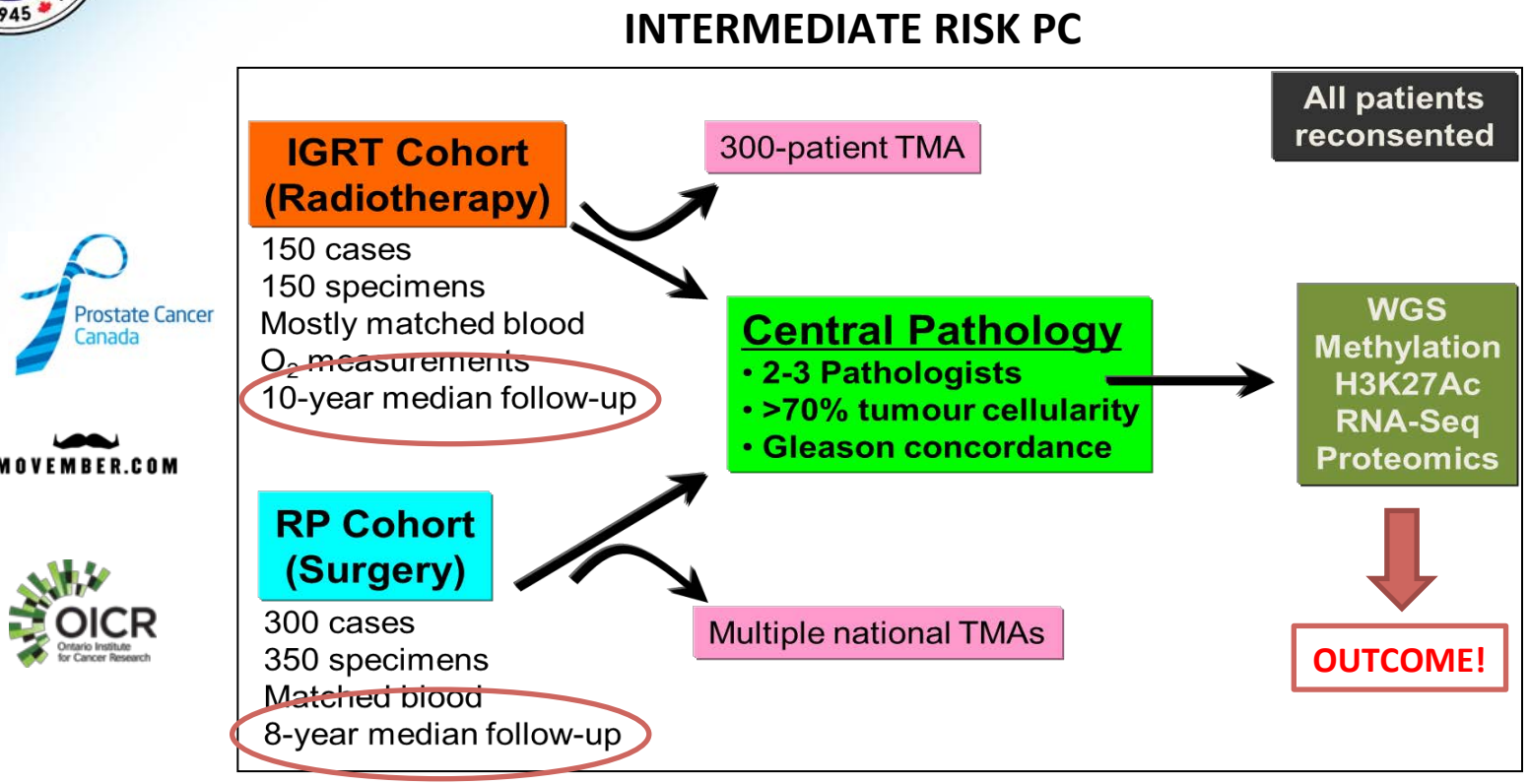


Dal Pra et al, CCR, 2013

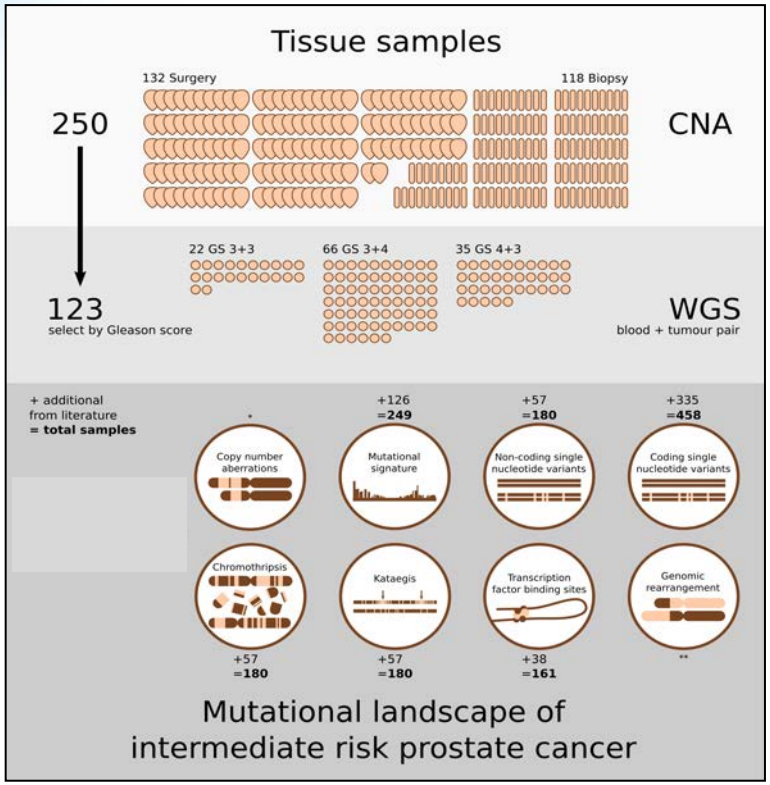


Minner et al, CCR, 2013

CPC-GENE: An Outcomes-Driven ICGC Program



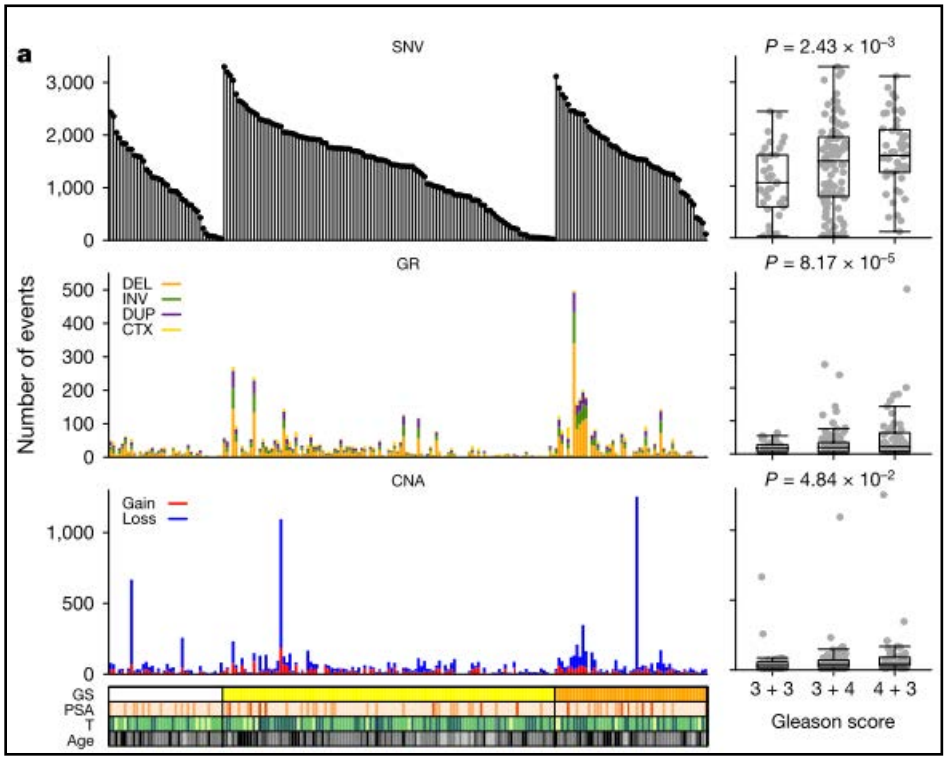
What Did We Find?



Fraser et al, Nature, 2017

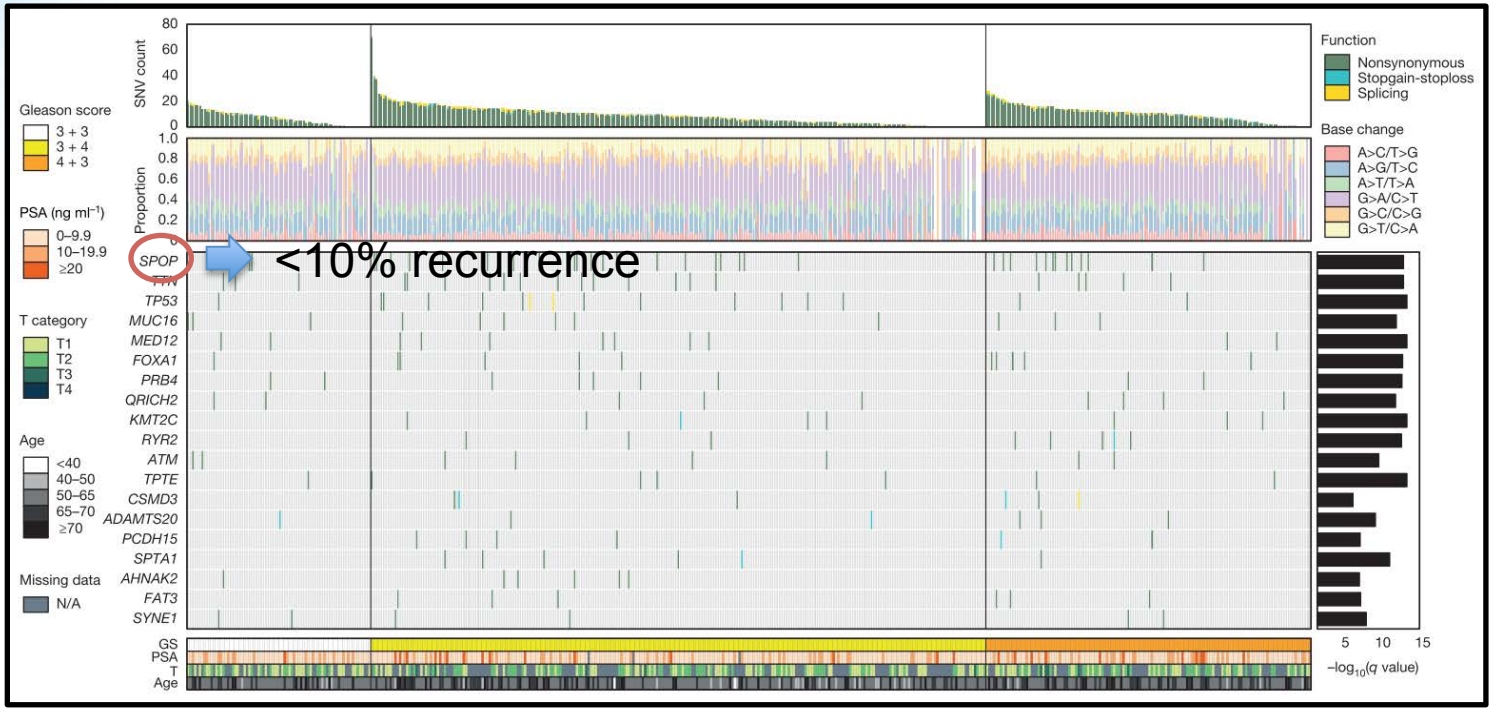
- 477 tumor whole-exomes (coding SNVs)
- 200 whole-genomes (coding/non-coding SNVs, SVs)
- 250 tumor SNP arrays (CNAs)
- 90 RNA microarrays
- 104 DNA methylation arrays

Localized PC is Highly Heterogeneous



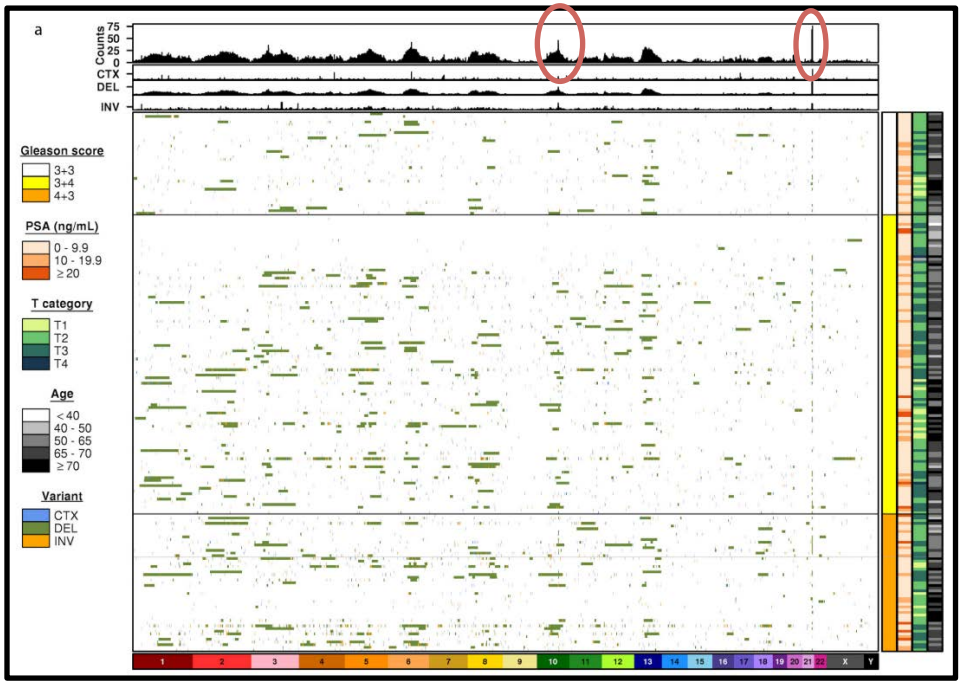
Fraser et al, Nature, 2017

Very Few Driver SNVs



Fraser et al, Nature, 2017

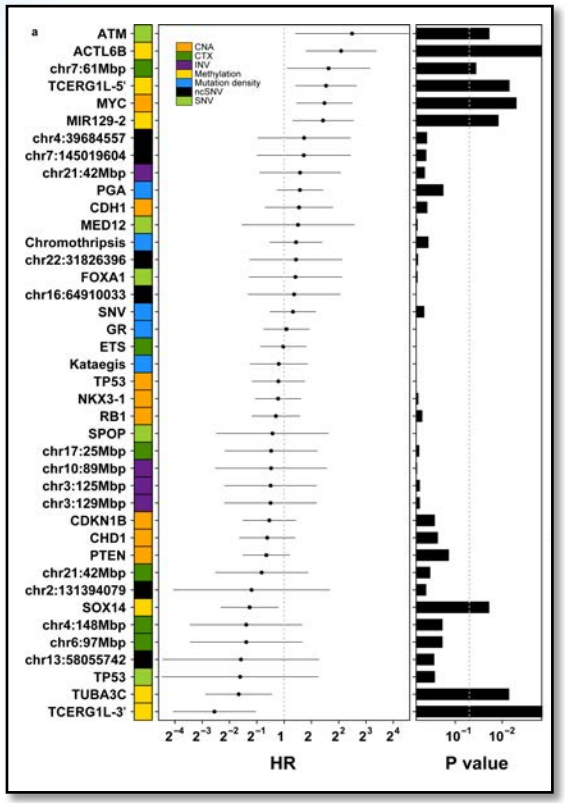
Novel Structural Variation



Fraser et al, Nature, 2017

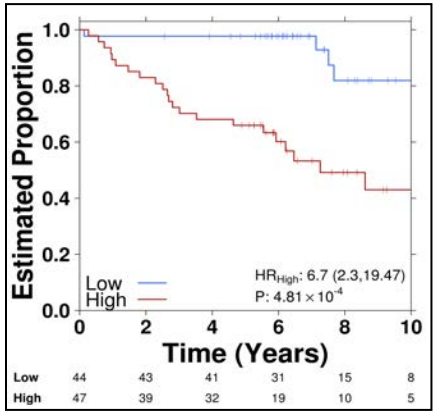
Does Any of This Matter?

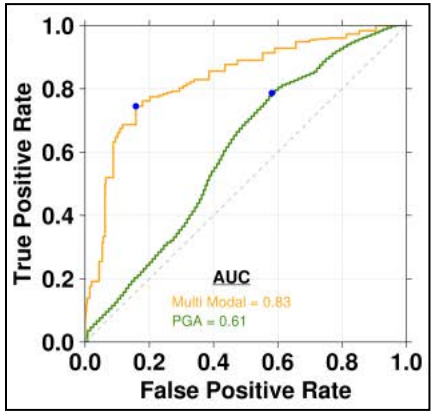
40 Driver Features



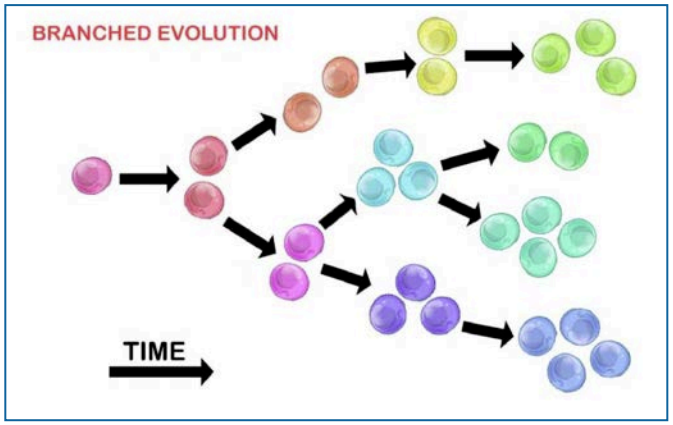
Fraser et al, Nature, 2017

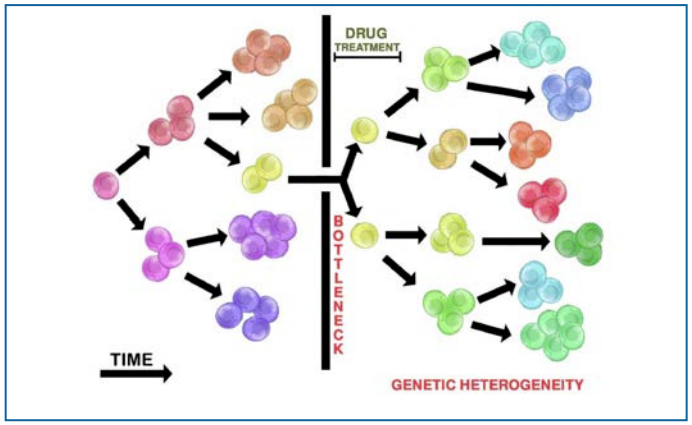
- Clinical T stage
- *ACTL6B* hyper-methylation
- *TCERG1L* hypo-methylation
- Chr7:61 Mbp translocation
- *ATM* SNV
- *MYC* amplification





Tumours Are Not Static…





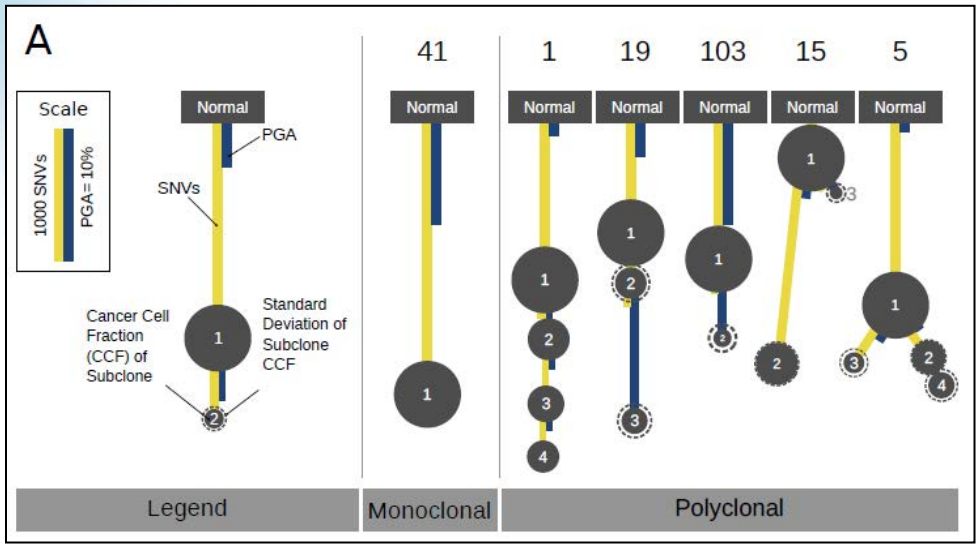
Creative Commons, 2014

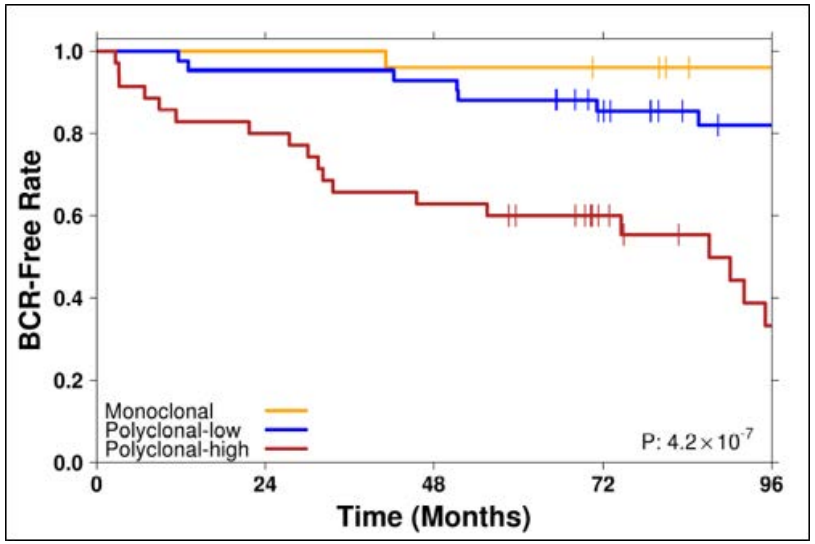
Spatial genomic heterogeneity within localized, multifocal

ALSO CONSIDER TEMPORAL EVOLUTION

Colin Cooper[10–12], Rosalind Eeles[10,13], David Neal[14,15], Bernard Tetu[16], Cenk Sahinalp[6], Lincoln D Stein[1], Neil Fleshner[17], Sohrab P Shah[18–20], Colin C Collins[21,22], Thomas J Hudson[1], John D McPherson[1], Theodorus van der Kwast[5] & Robert G Bristow[2,4,8]

Tumour Evolution and Clinical Outcome

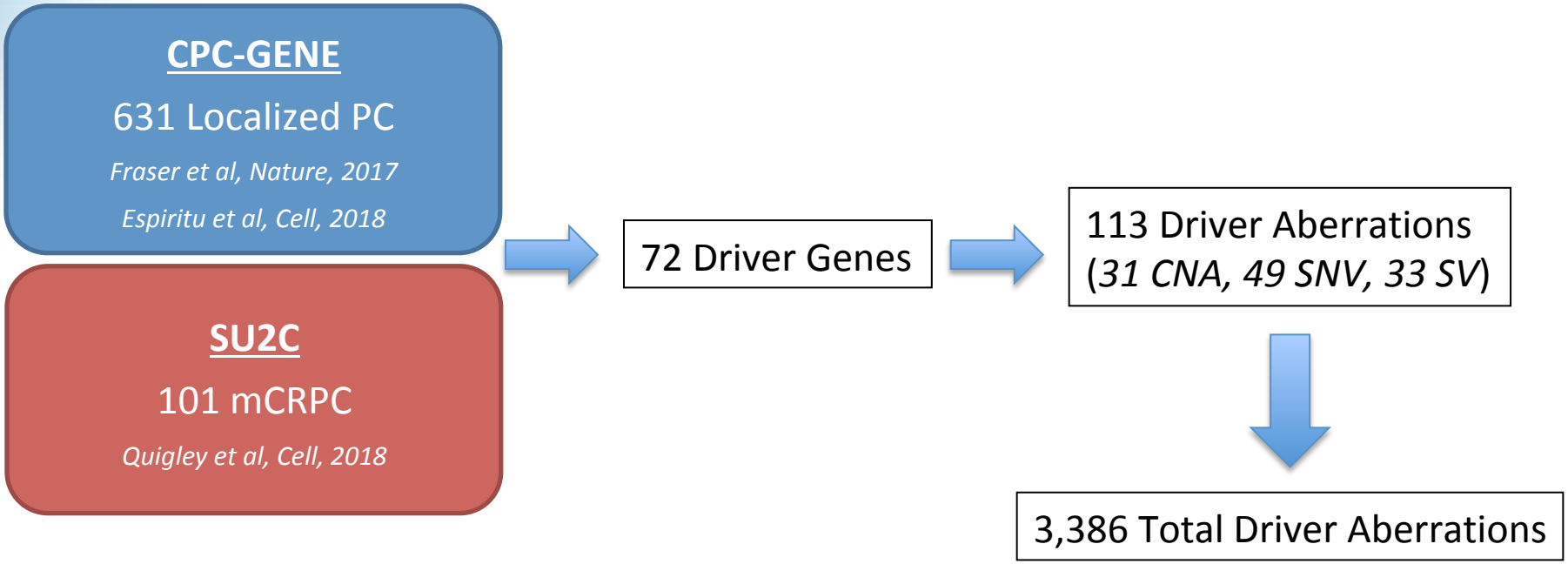




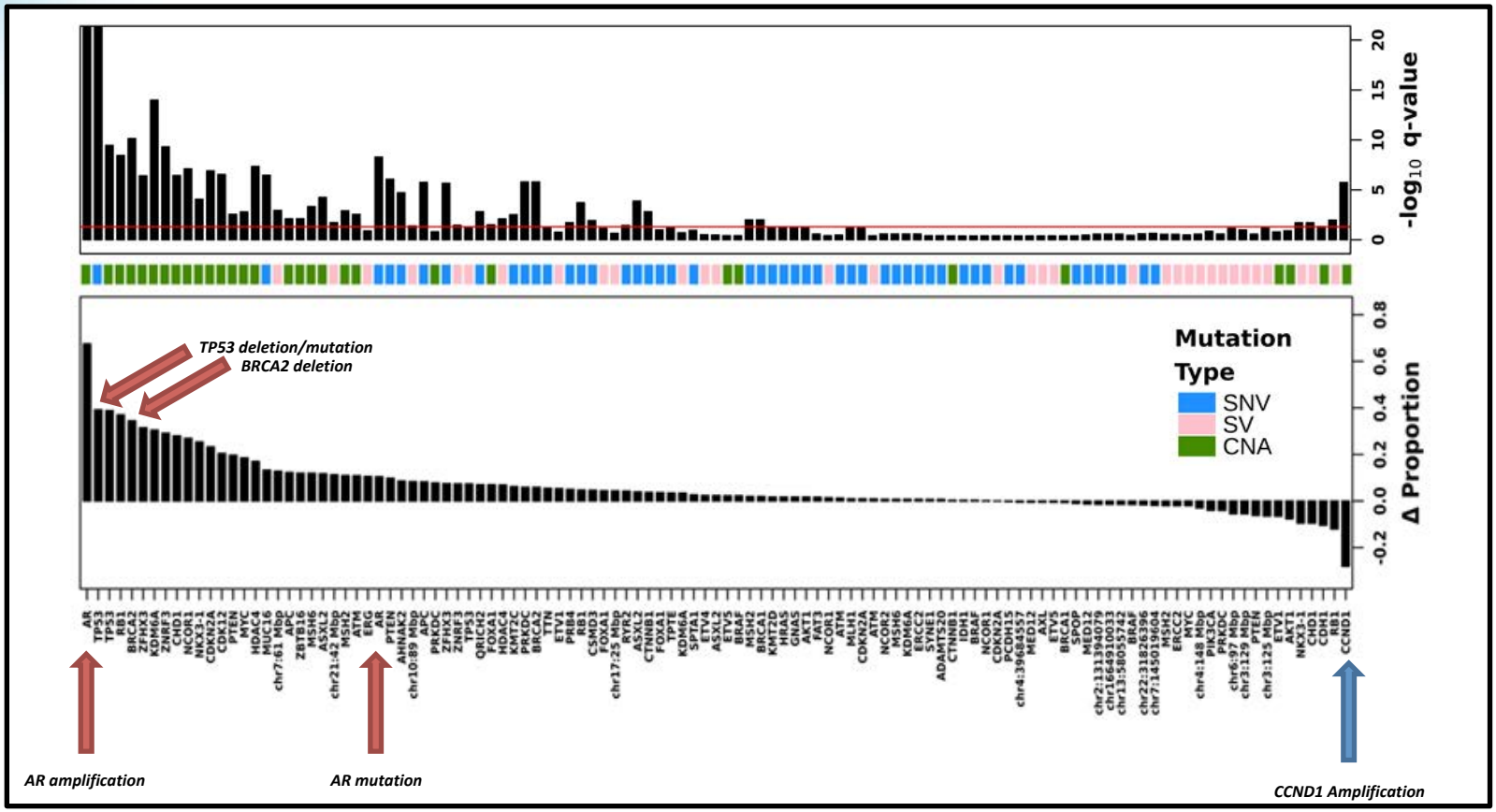
Espiritu et al, Cell, 2018

The Localized-Metastatic Axis

Hypothesis: Drivers of aggressive localized PC will be enriched in metastatic disease



Driver Enrichment in PC



Fraser et al, 2019 (under review)

Identifying Potential Prognostic Aberrations

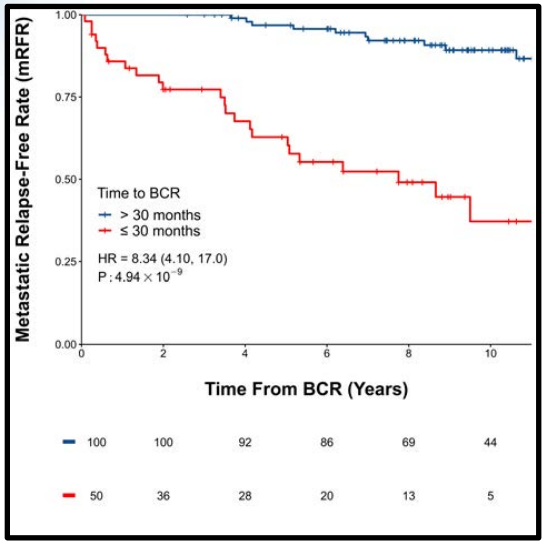
47/113
Enriched in mCRPC

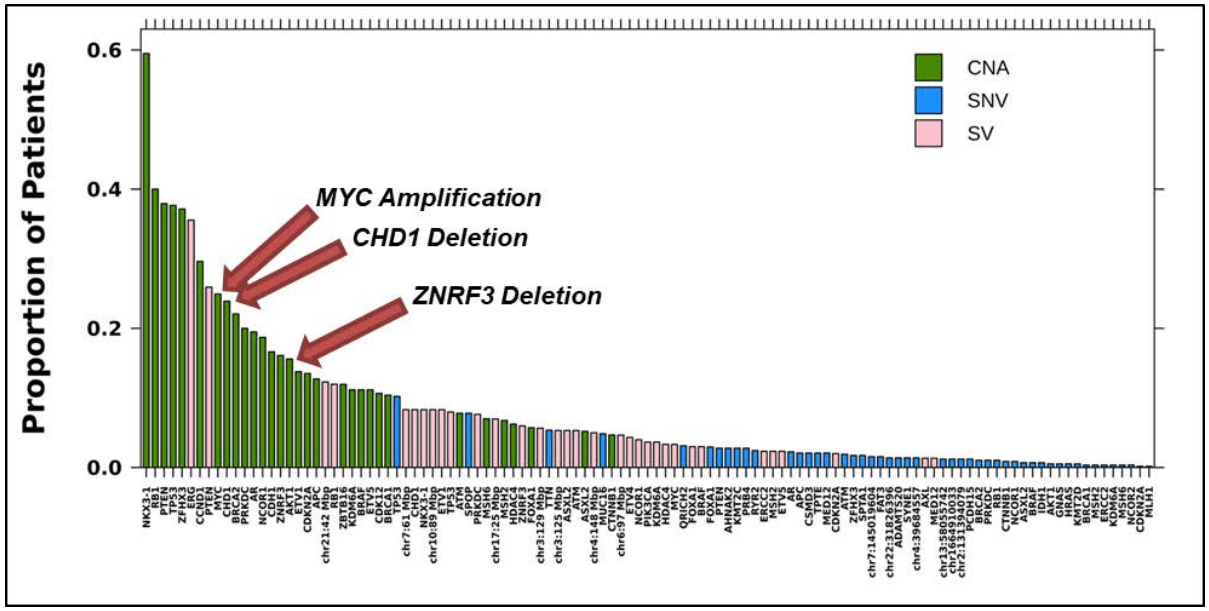
→

14/47
≥5% Localized

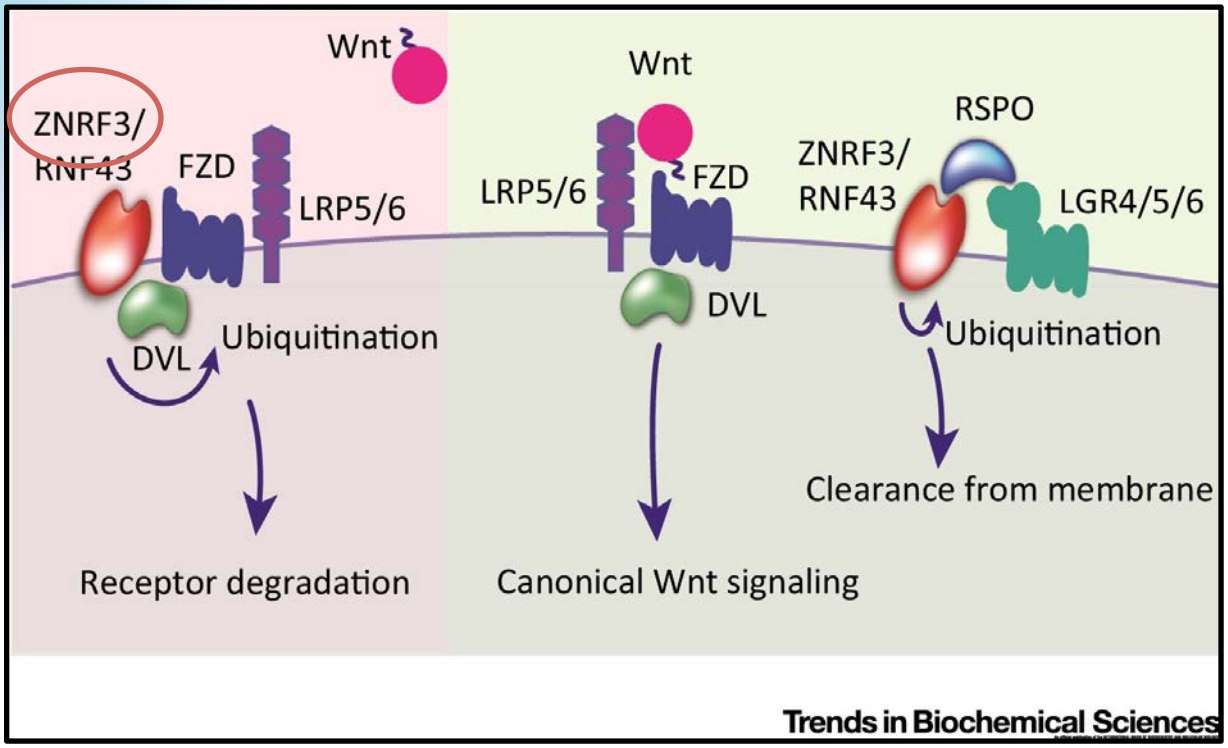
→

3/14
Associated with
30-month BCR

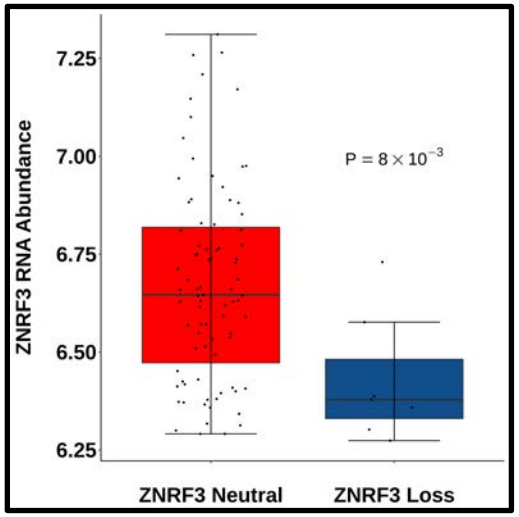




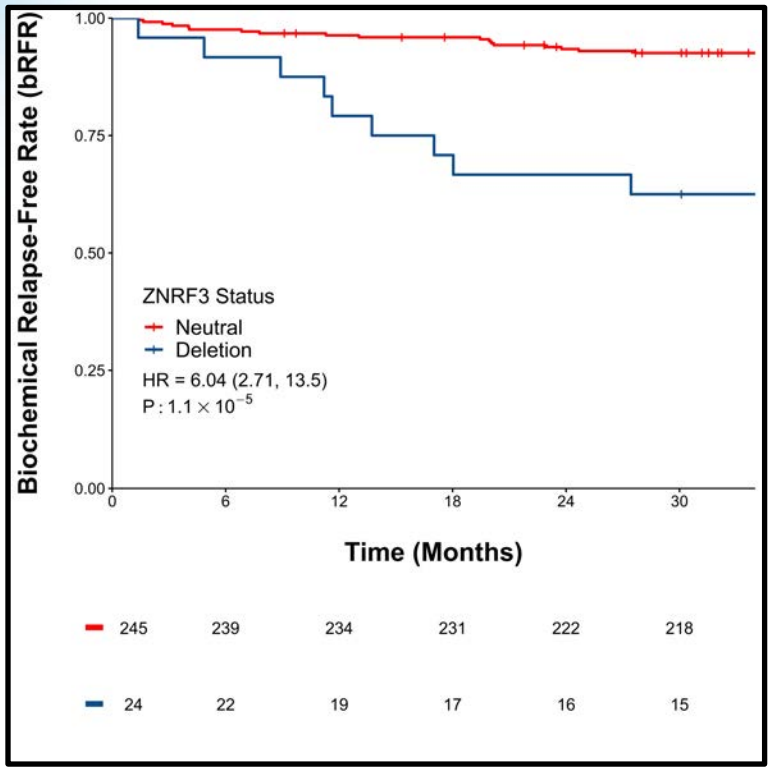
ZNRF3: A WNT Pathway Inhibitor

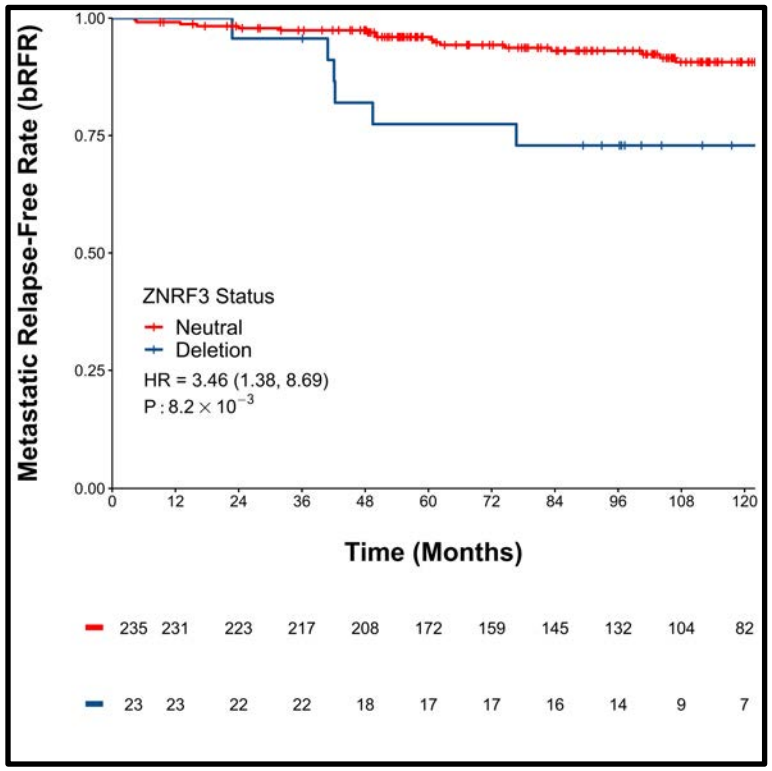


- Lost in 11% of localized PC
- Associated with WNT activation



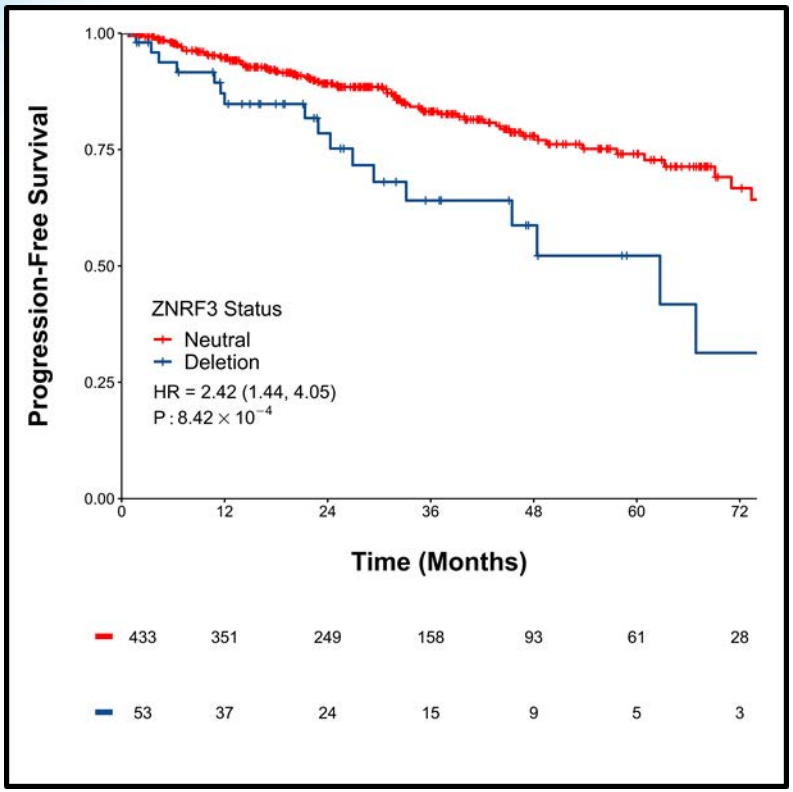
ZNRF3 Deletion is Associated With Poor Prognosis



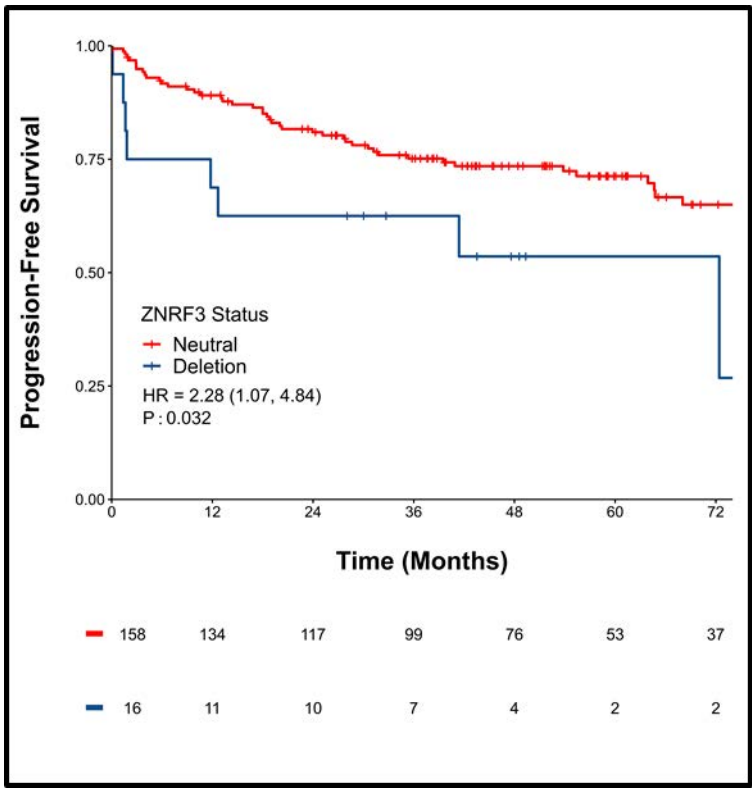


ZNRF3 Deletion is Associated With Poor Prognosis

TCGA (n = 486)

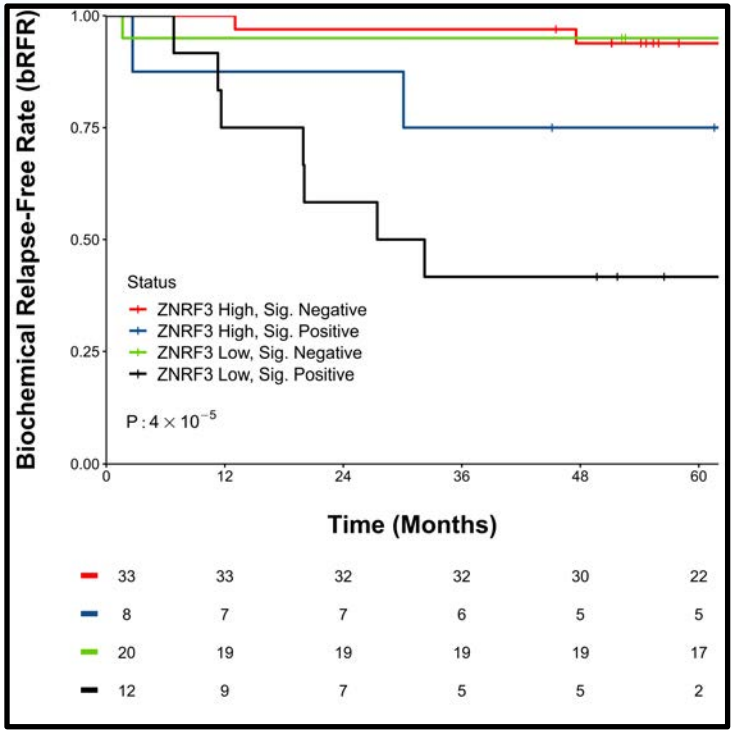


MSKCC (n = 174)

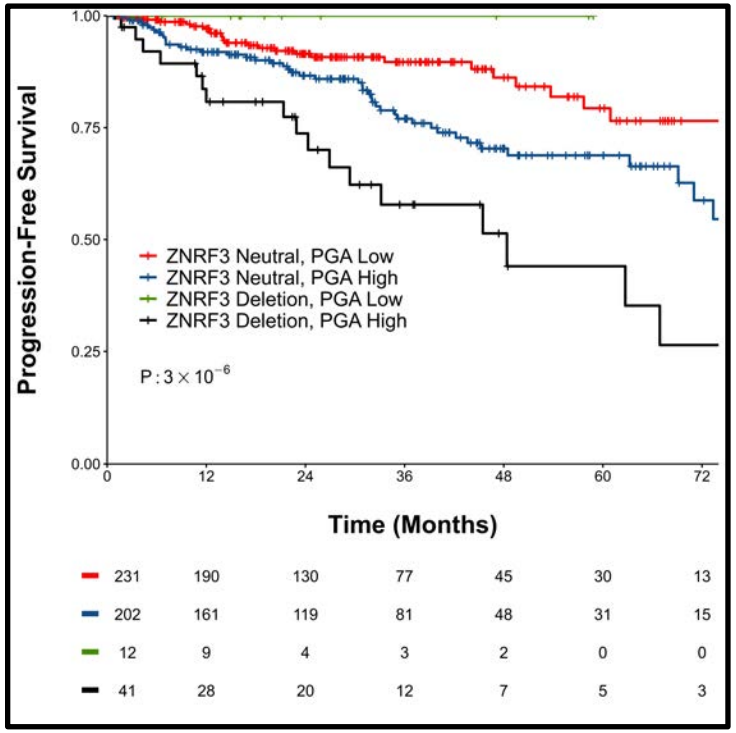


Interactions Between Prognostic Biomarkers

Fraser 6-Feature Clinico-Genomic Signature



Percentage Genome Alteration



Summary

- Localized PC genomes are highly heterogeneous within and between patient groups
- Multi-modal genomic/epigenomic indices can identify *clinically-important* subgroups
- Comparative genomics identifies rare drivers in localized disease that portend poor outcomes (tumour evolution!)
- What about the germline?
  - It matters. A lot. I'm around all day to chat…

How Do We Translate?

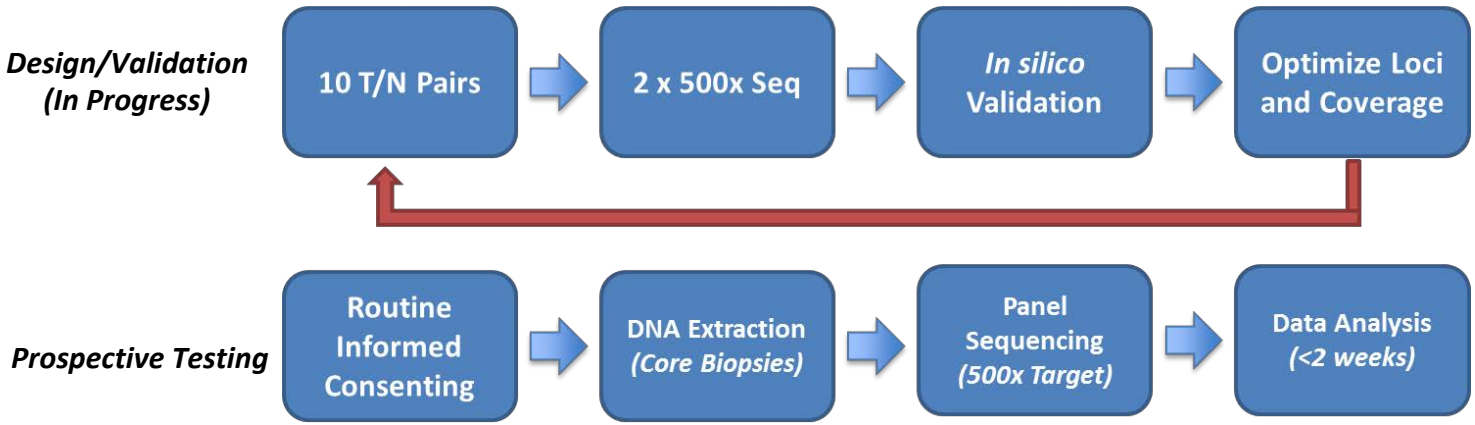
- **GOAL: Prevent progression to metastatic disease**
- Intensify or deintensify based on *individual* genomic risk profiles
- Test should be:
  - Accurate
  - Cheap*
  - Applicable across the risk spectrum
  - Capable of simultaneously capturing multiple analytes

* - Cost ≠ value. "Death is cheap."

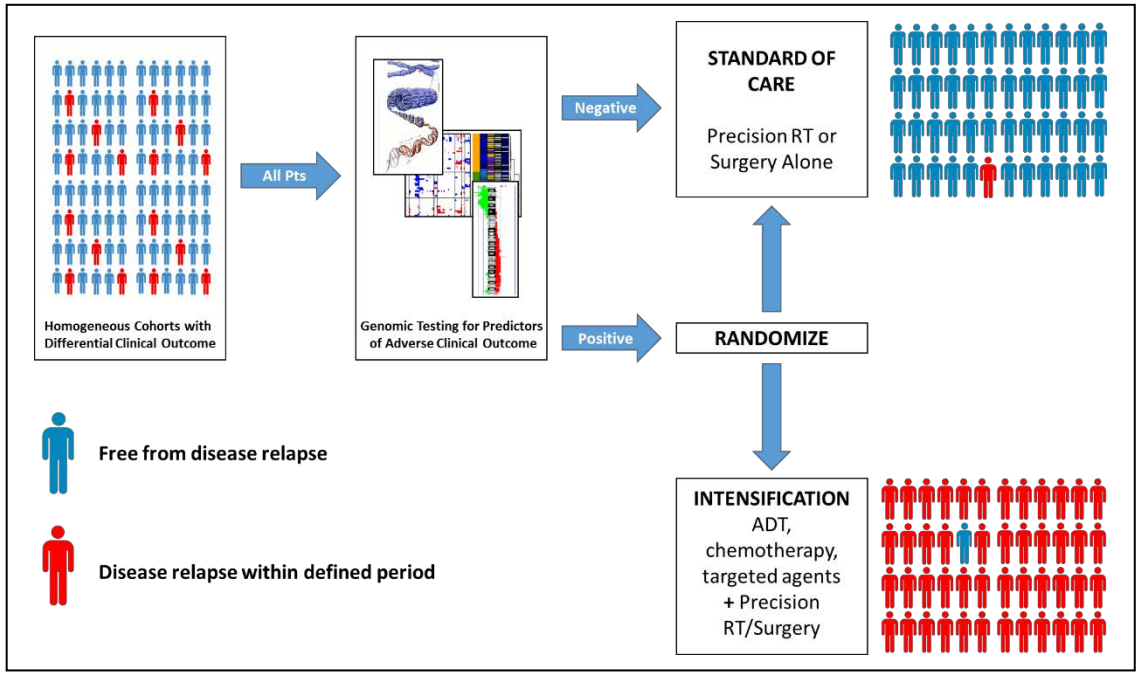
What Will The Test Look Like?

- Whole genome sequencing is (probably) not the answer
  - Storage and analysis overhead is huge!
- Identify relevant regions of the genome (NOT exomes) and go DEEP!

Mutation Type	Mutation Number	Size/Mutation (bp)	Total (bp)
Non-coding SNVs	100	500	50,000
Coding SNVs	100	50,000	5,000,000
Indels	100	500	50,000
Germline SNPs	1000	500	500,000
GRs (1Mbp bins)	15	1,000,000	15,000,000
GRs (100 kbp bins)	10	100,000	1,000,000
GRs (10 kbp bins)	100	10,000	1,000,000
CNAs	40,000	500	20,000,000
Mitochondrial Genome	1	16,569	16,569
TOTAL			**42,616,569**

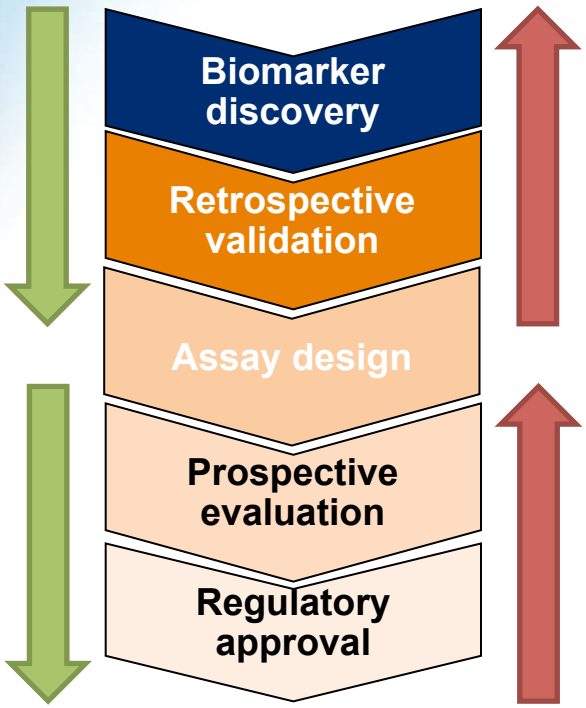


A Model for Genomics-Driven Clinical Trials



Fraser, JTGG, 2018

An Iterative Process



Acknowledgements

OICR

ICGC/PPCG

The 573 families (…and counting) who have trusted us with their tissues and private medical information – during the most difficult period of their lives.

NONE of this would be possible without them.

Michael Milosevic
Cynthia Menard
Jenna Sykes
Melania Pintile
Dominque Trudel
Neil Fleshner
Alex Zlotta
Brad Wouters

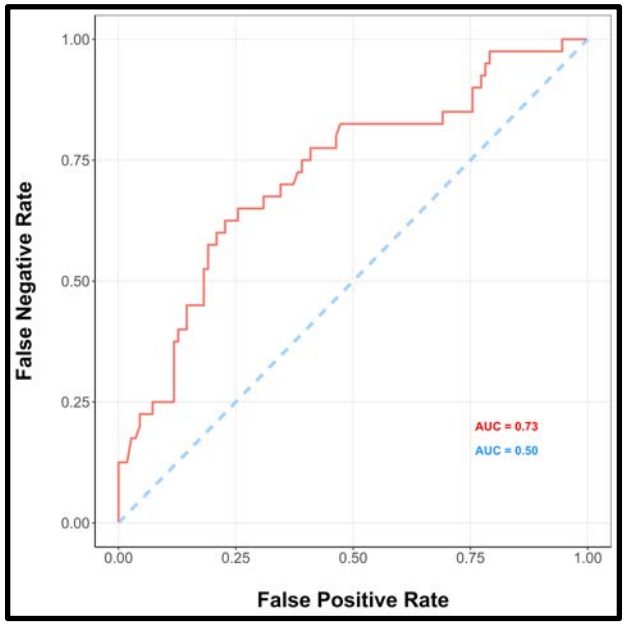
Colin Collins
Cenk Sahinalp

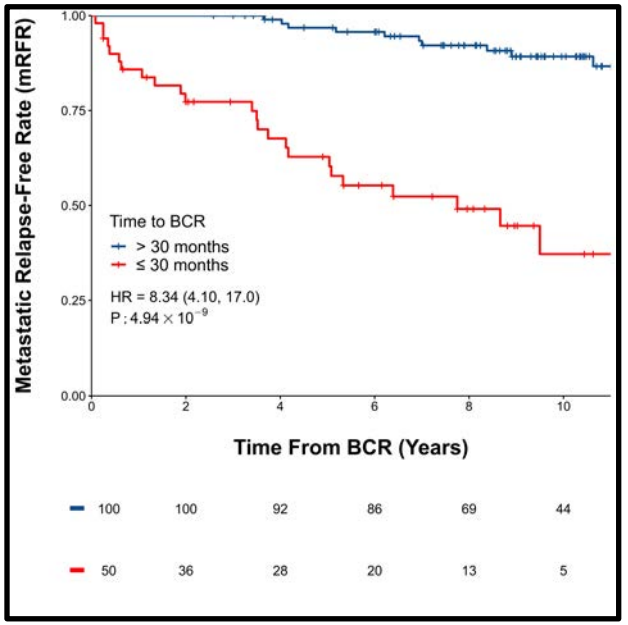
QUEBEC
Bernard Tetu
Yves Fradet
Alain Bergeron

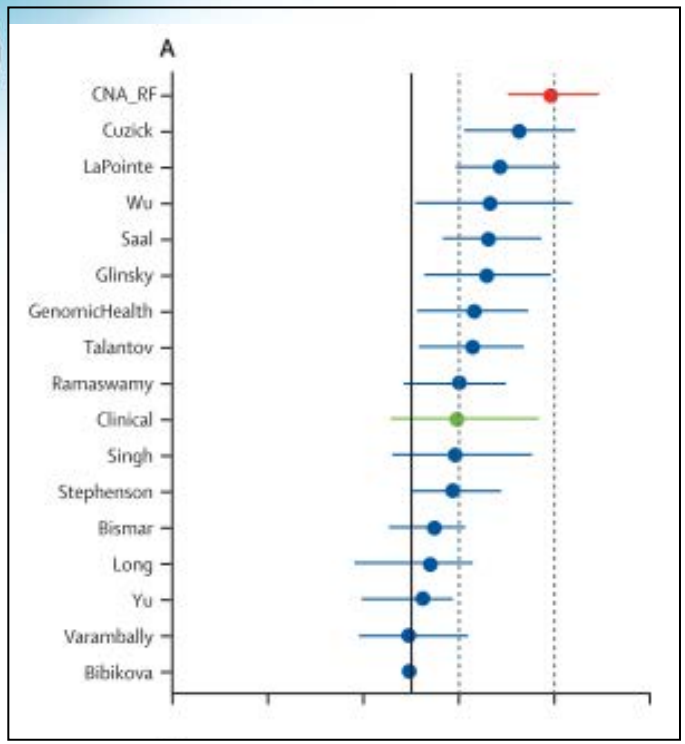
Gail Risbridger
Rebeca Taylor
Heather Thorne
Mitch Lawrence
Declan Murphy

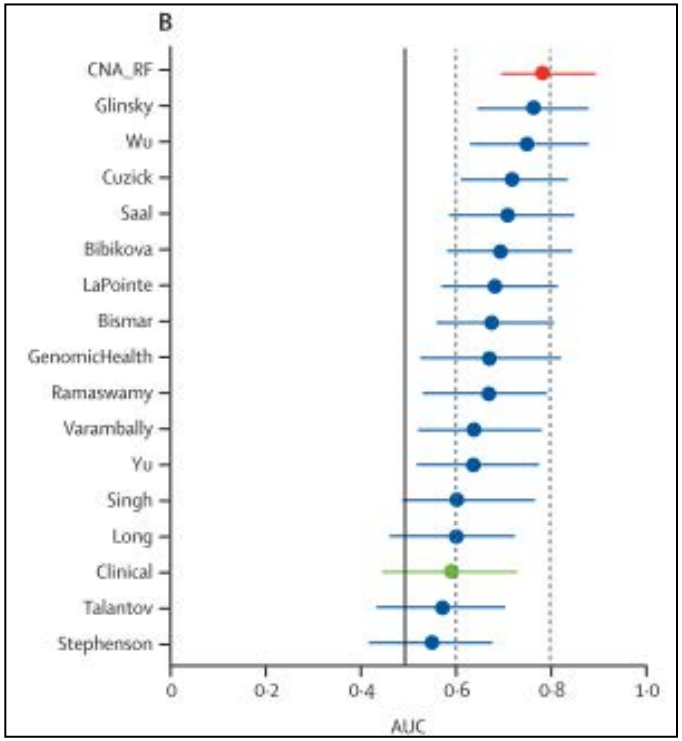
A Short Digression on BCR…

- PPV for 10-yr mets = 27%
- What about ‘time to BCR’?









Lalonde et al, Lancet Oncology, 2014

oncotype DX® Genomic Prostate Score

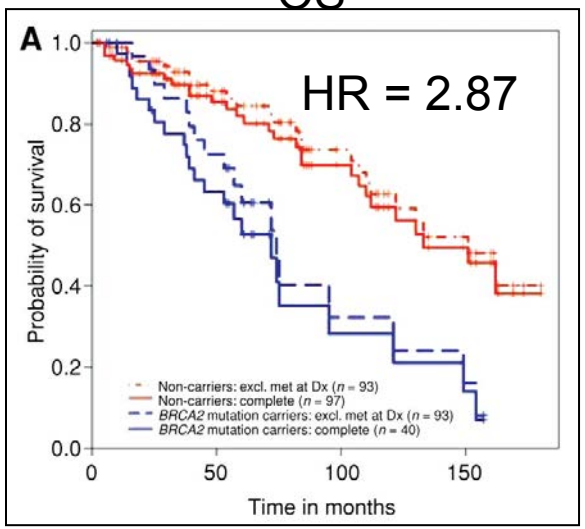
Prolaris® PROSTATE CANCER

DECIPHER BY GENOME DX

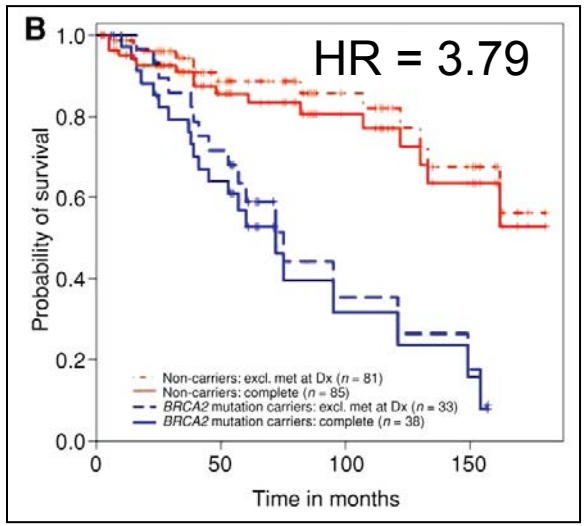
The Germline

- Germline *BRCA2* mutations are associated with v. poor clinical outcomes
  - 5yr OS ~60%

OS

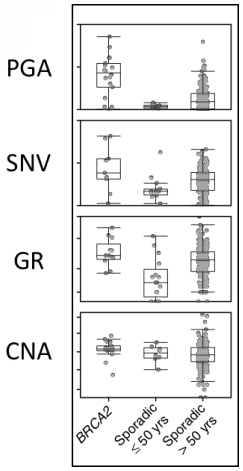


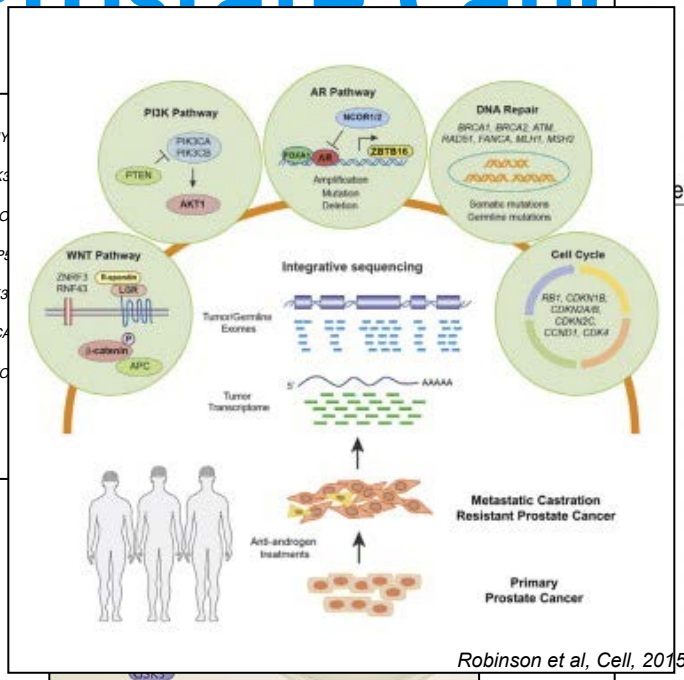
PCSM



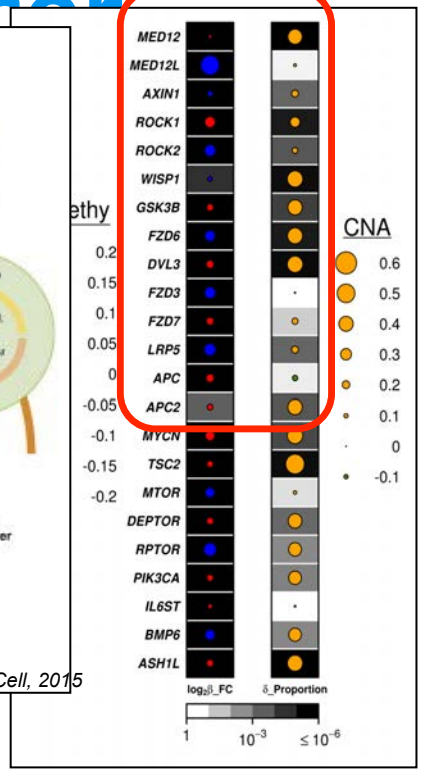
Thorne et al, 2011

BRCA2-Associated Prostate Cancer



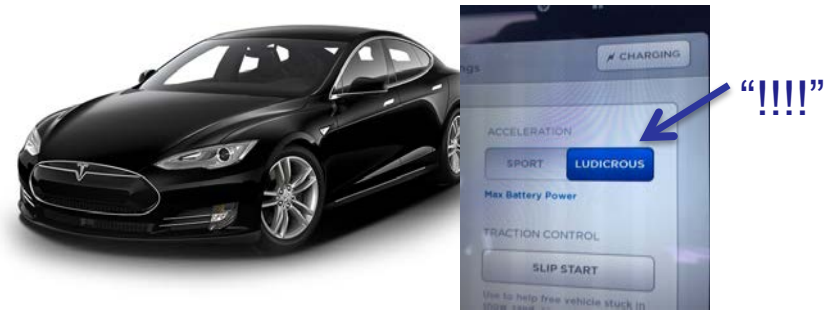


Robinson et al, Cell, 2015

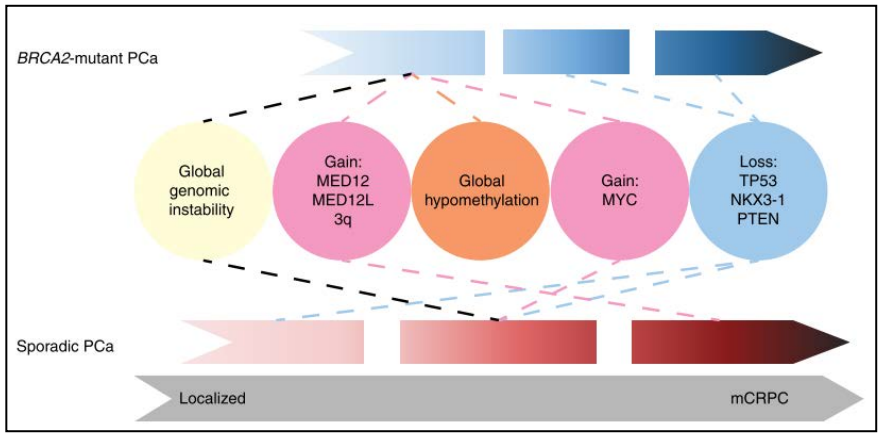


Taylor, Fraser, Boutros, Bristow, Nat Comms, 2017

BRCA2-Mutant Cancers: Ludicrous Mode

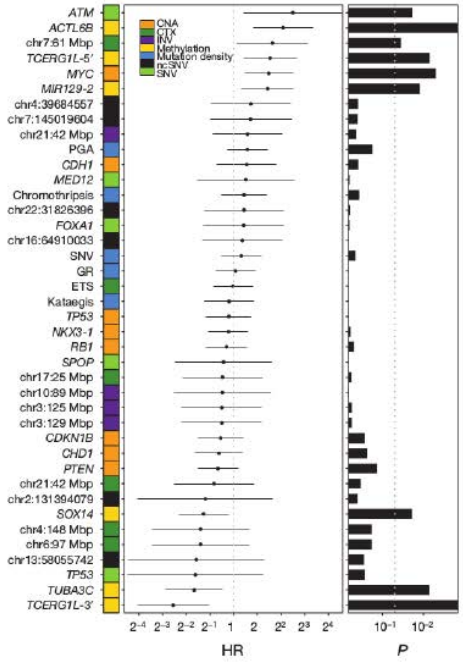


"!!!!"



Fraser, Taylor, Boutros, Bristow, ***Nat Comms****, 2017*

Can We Do This for Sporadic Tumours?

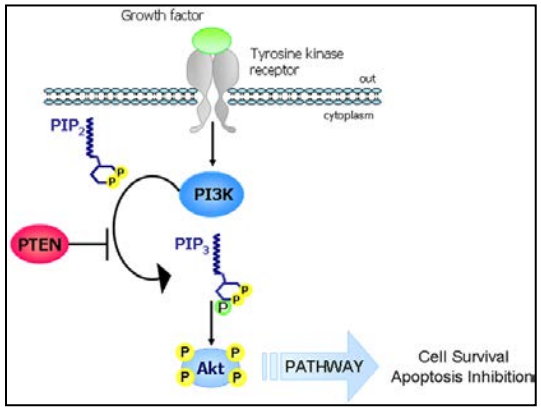


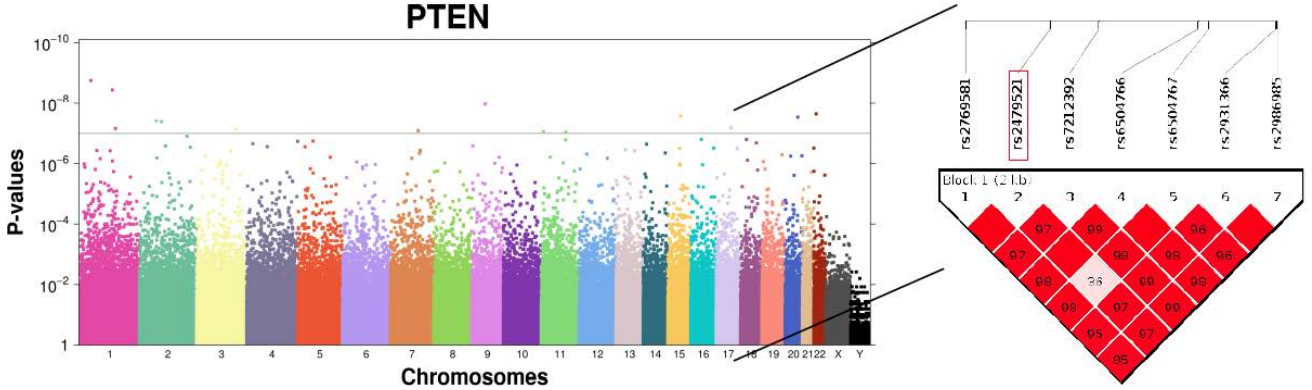
Fraser *et al.*. *Nature* 2017

Discovery:

- 230 intermediate-risk prostate cancer genomes
- ~ 560,000 SNPs (LD pruned)
- 34 somatic events
  - Copy Number Aberrations
  - Coding and Non-coding SNVs
  - Genomic Rearrangements
  - Methylation

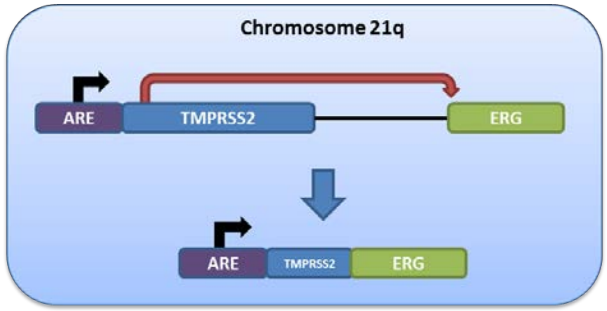
Consider *PTEN* Deletions

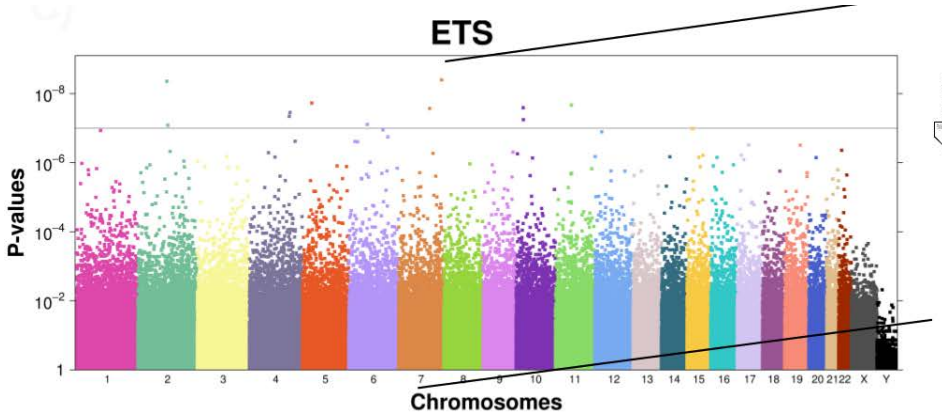


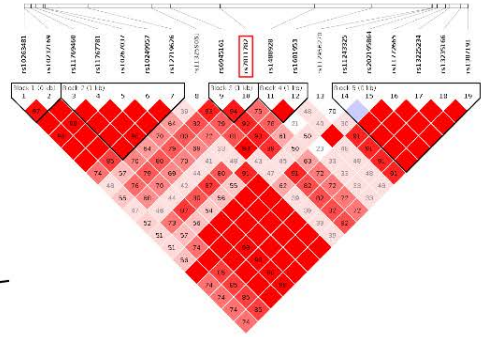


Houlahan *et al.* Nature Genetics, in press

Or ETS Fusions (TMPRSS2:ERG)

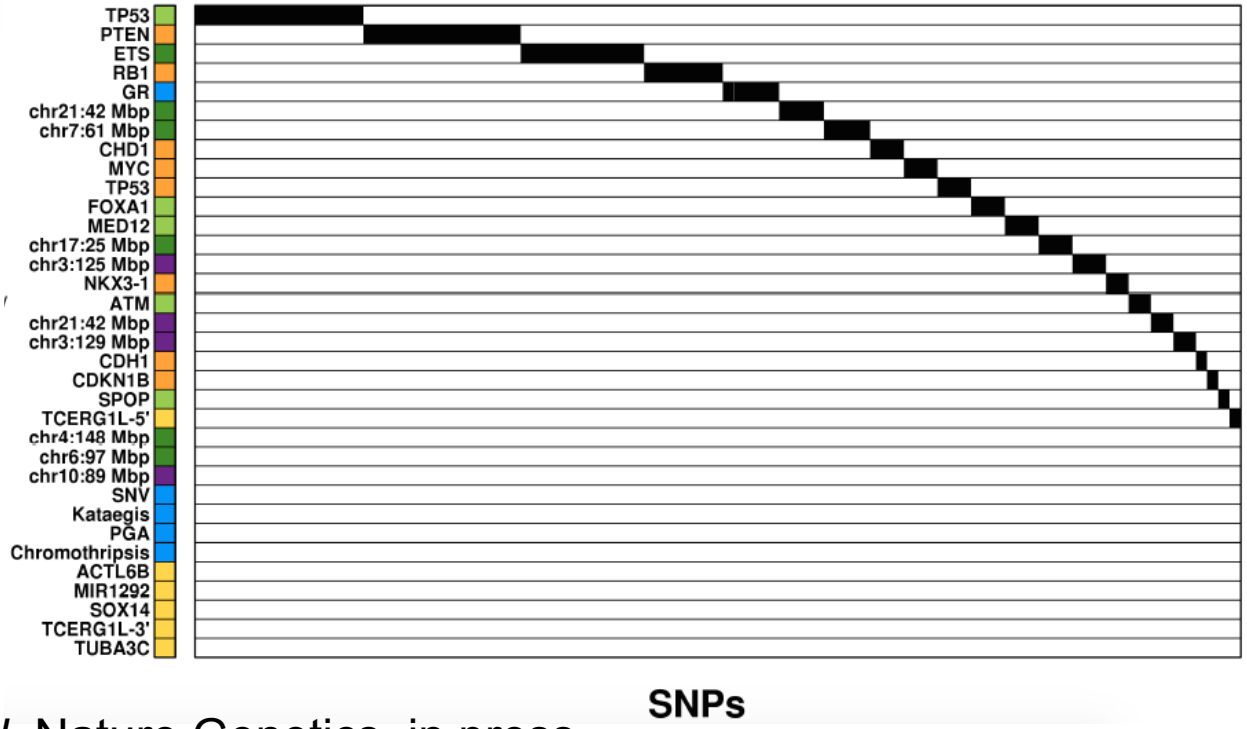






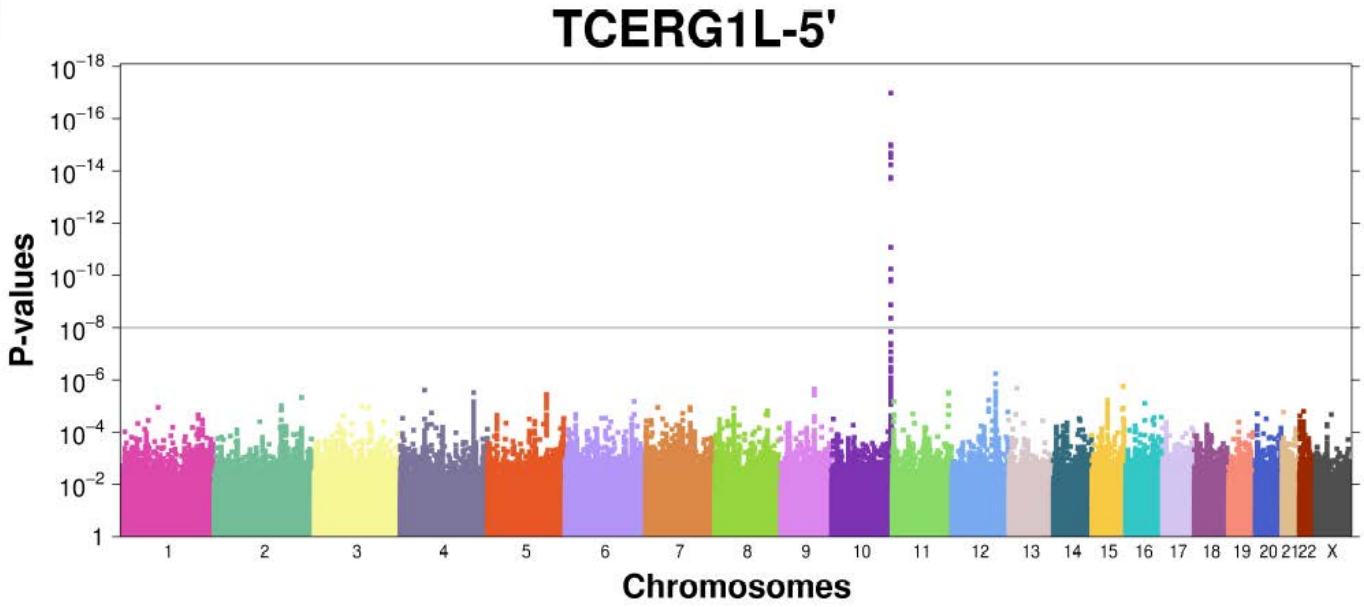
Houlahan *et al.* Nature Genetics, in press

Hundreds of Germline-Somatic Interactions



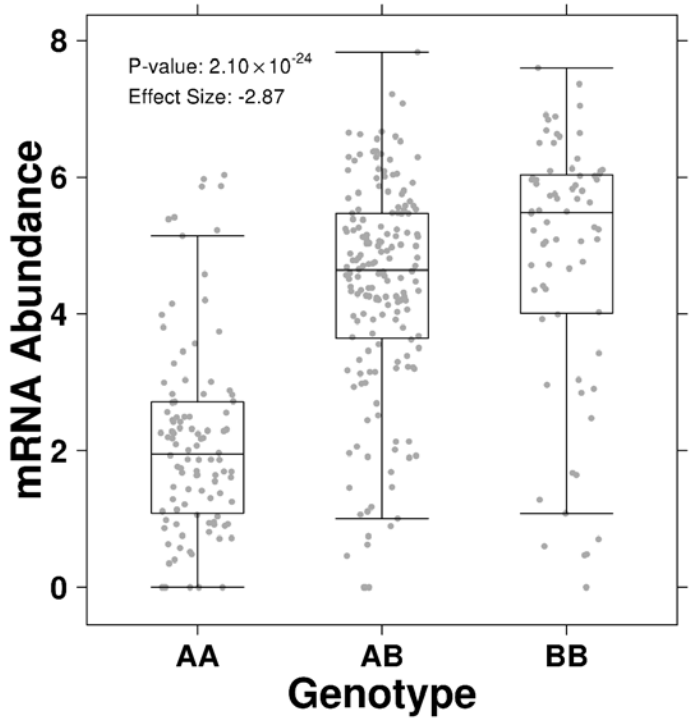
Houlahan *et al.* Nature Genetics, in press

Consider A Driving (and Prognostic!) Methylation Event

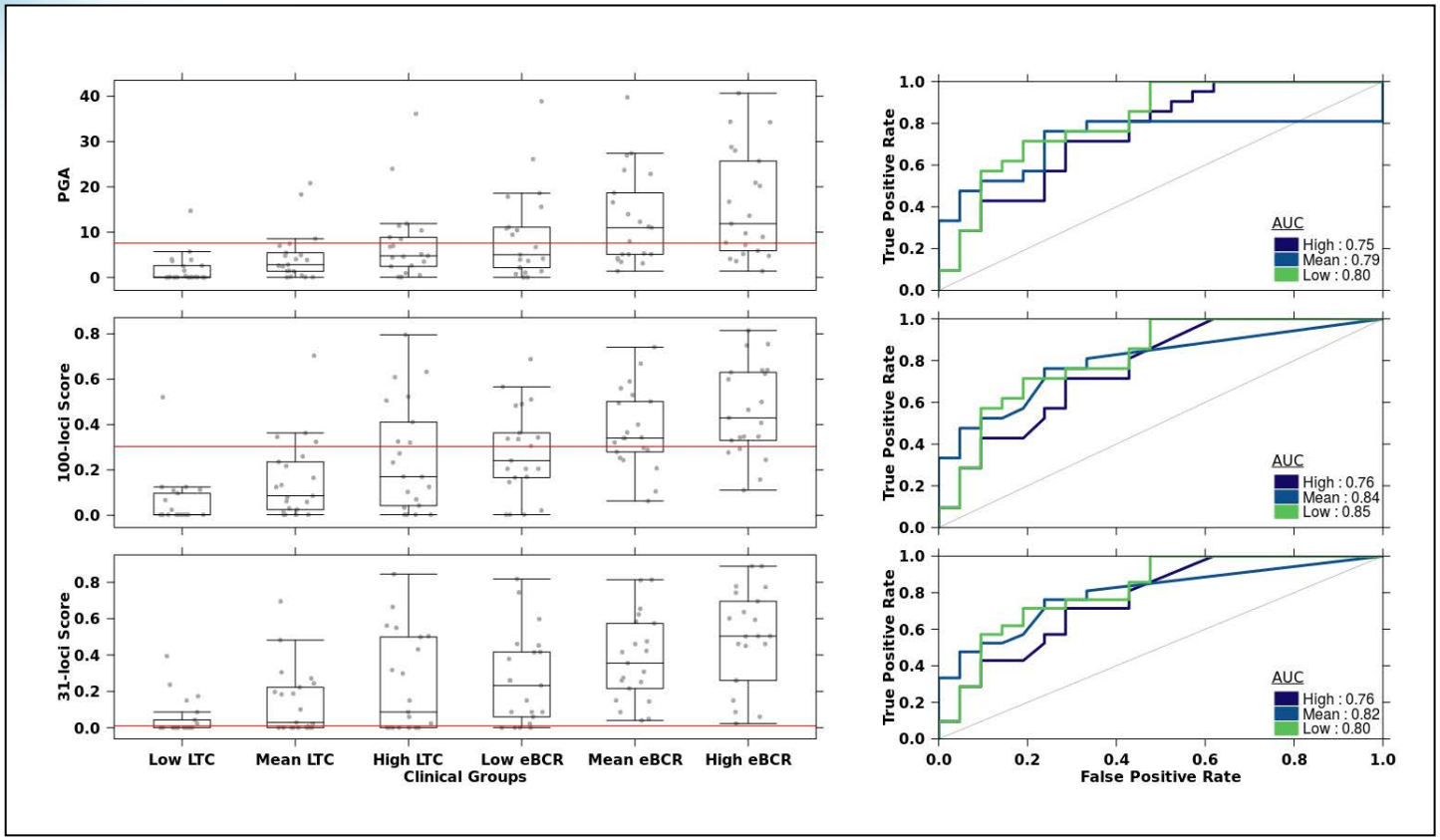


Houlahan *et al.* Nature Genetics, in press

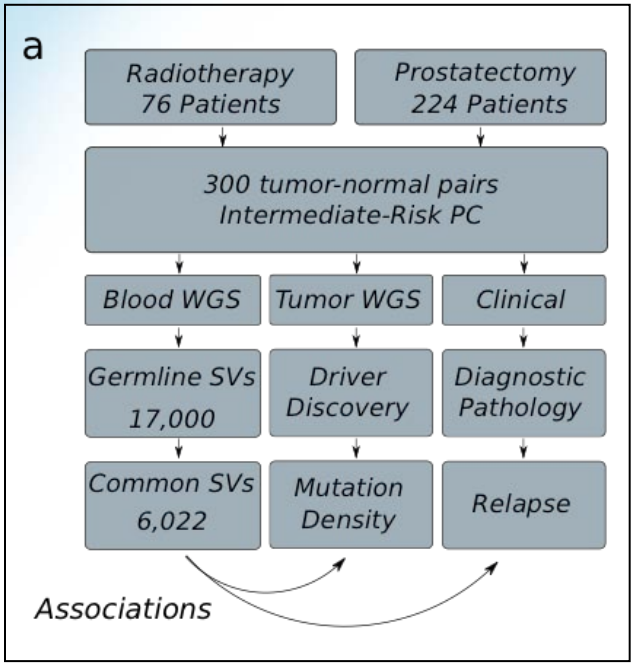
Allele-Specific Expression Differences

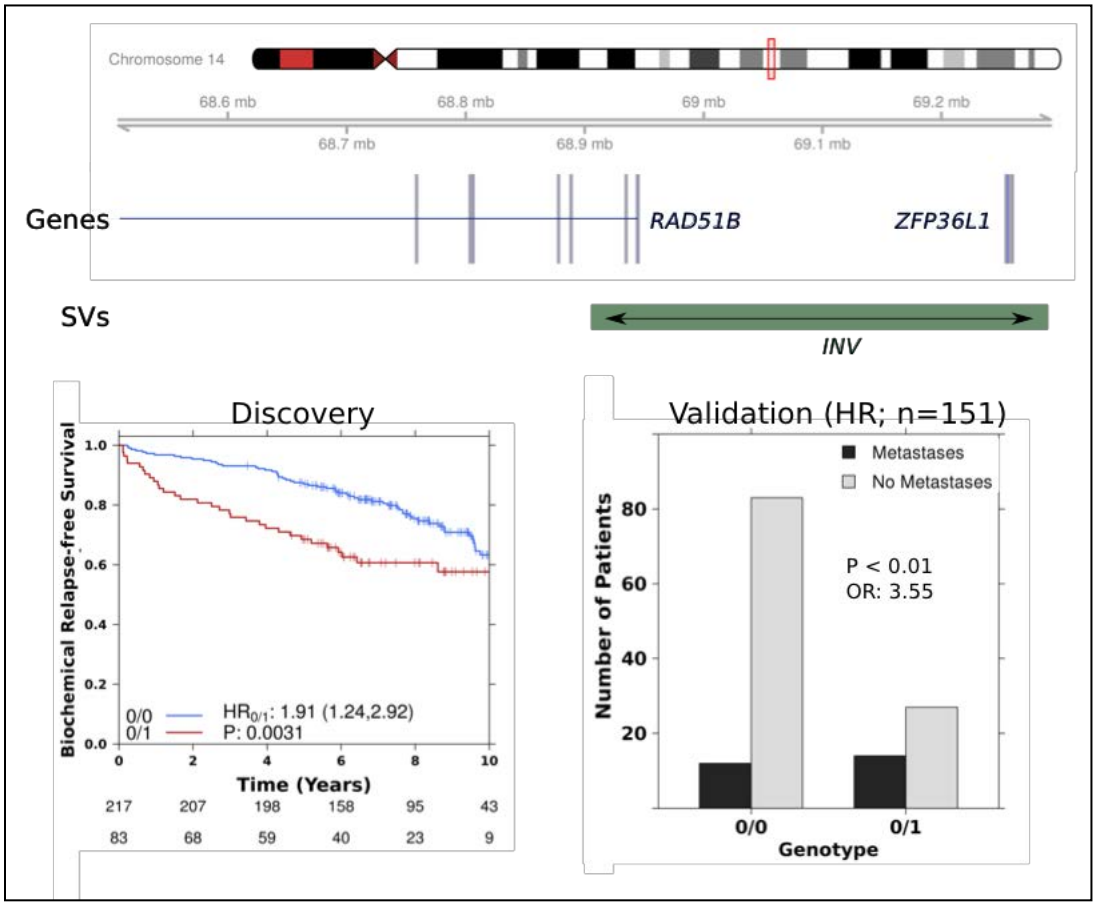


Houlahan *et al.* Nature Genetics, in press

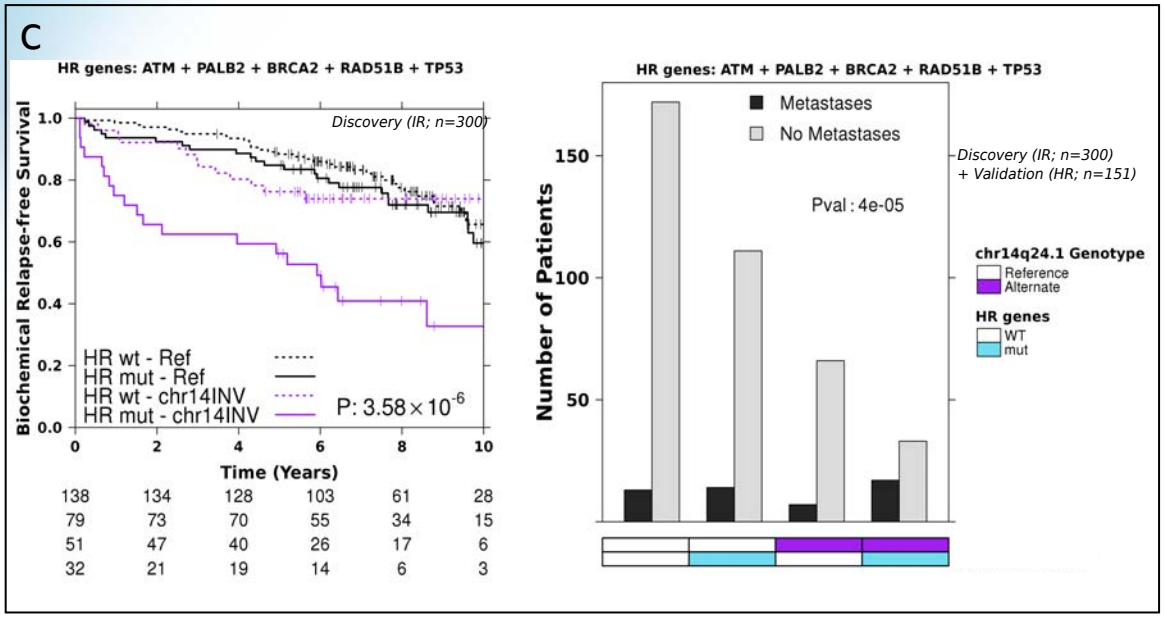


Brastianos et al, under review





Rouette, Fraser, Boutros, Nat Gen (under review)



Rouette, Fraser, Boutros, Nat Gen (under review)