

# Clinical genomics and cancer immunotherapy in renal cell carcinoma

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# Disclosures

- Consulting/Advisory
  - Tango Therapeutics
  - Genome Medical
  - Invitae
  - Foresite Capital
  - Illumina
  - Dynamo
- Research funding
  - Novartis
  - BMS
- Equity
  - Tango Therapeutics
  - Genome Medical
  - Syapse
  - Microsoft
- There will be discussion about the use of products for non-FDA approved indications in this presentation

# Outline

- Studying “immunogenomic” clinical biomarkers in RCC
- Expanding clinical cancer immunogenomics for discovery
- Casting a wider net to study RCC tumors in the immunotherapy era

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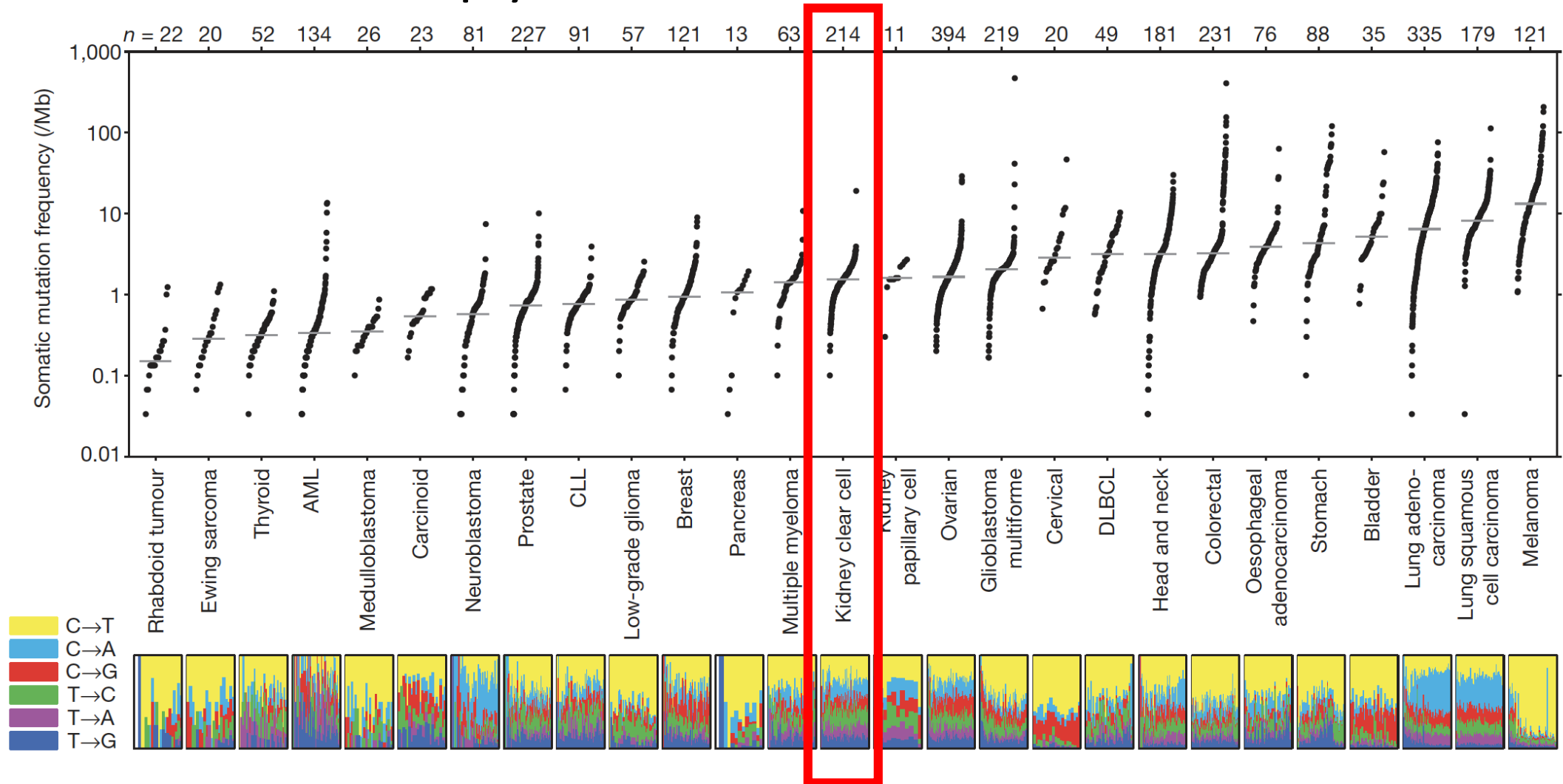
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# Clinical genomics and response to immune checkpoint blockade

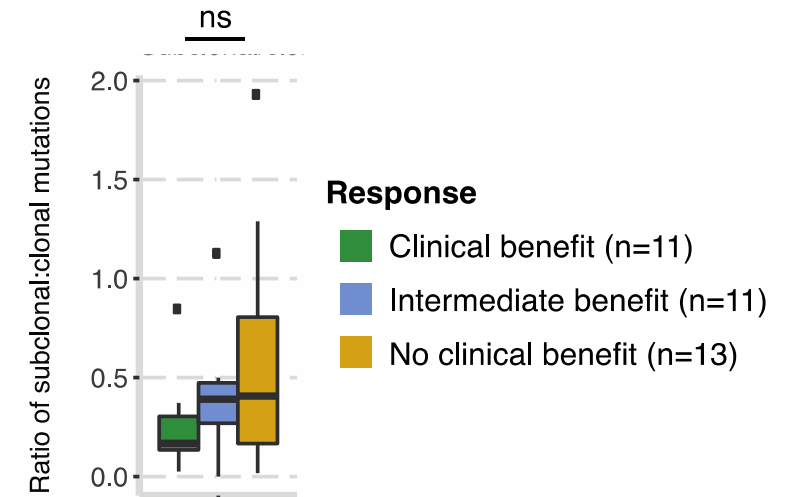
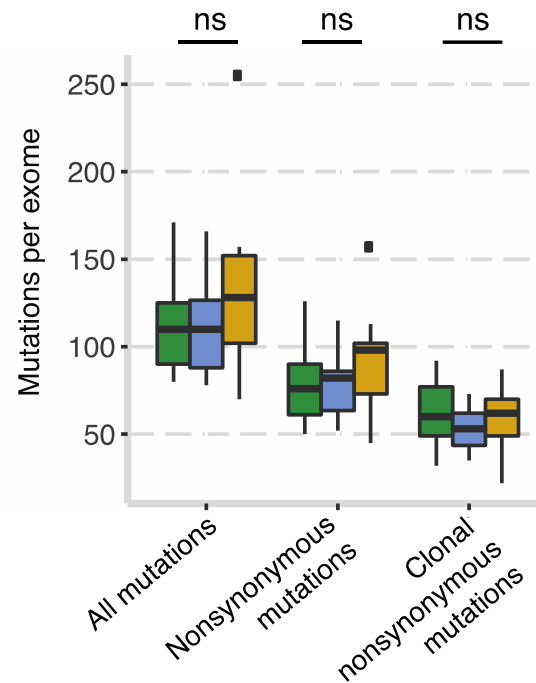
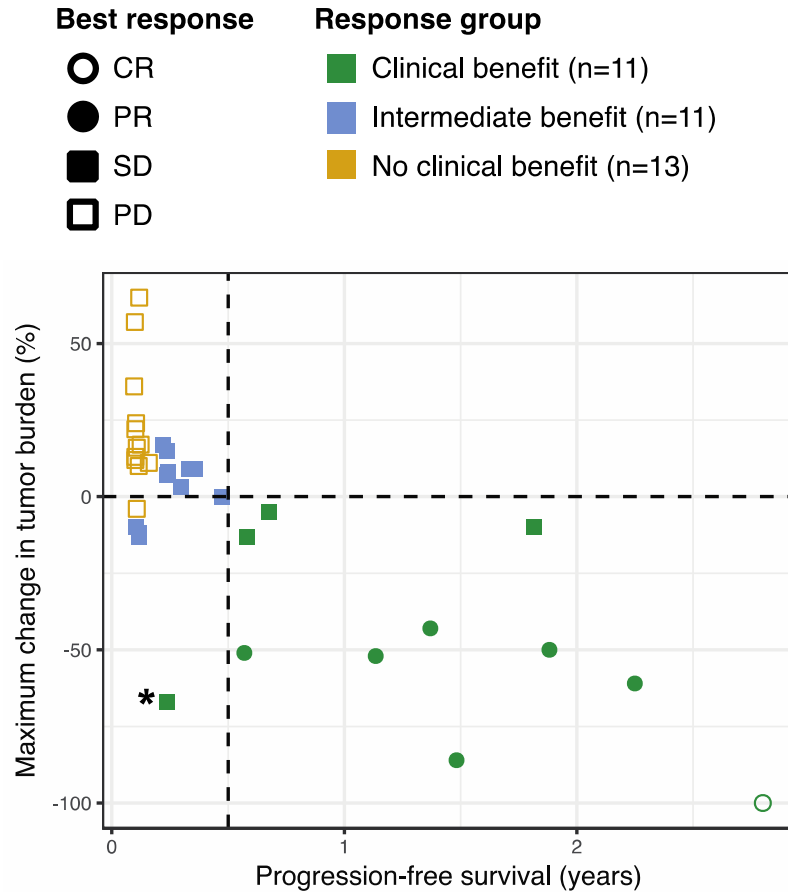
- Mutational load/neoantigens
  - Rooney et al *Cell* 2015; Snyder et al *NEJM* 2014; Rizvi et al *Science* 2015; Van Allen et al *Science* 2015; Le et al *NEJM* 2015/*Science* 2017; Luksza et al *Nature* 2017; McGranahan et al *Science* 2016; Rosenberg et al *Lancet*

*Can tumor genomics impact immunotherapy response in kidney cancer?*

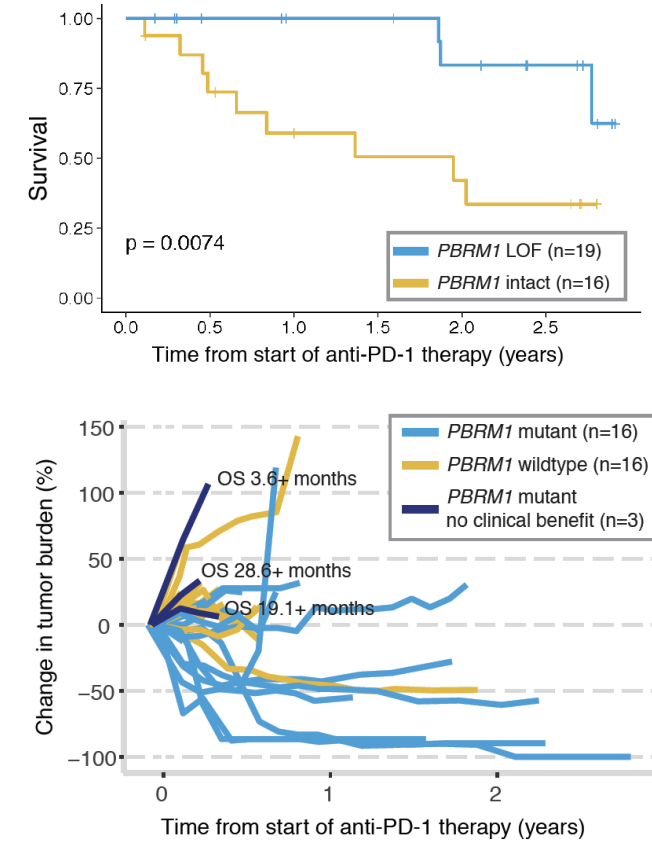
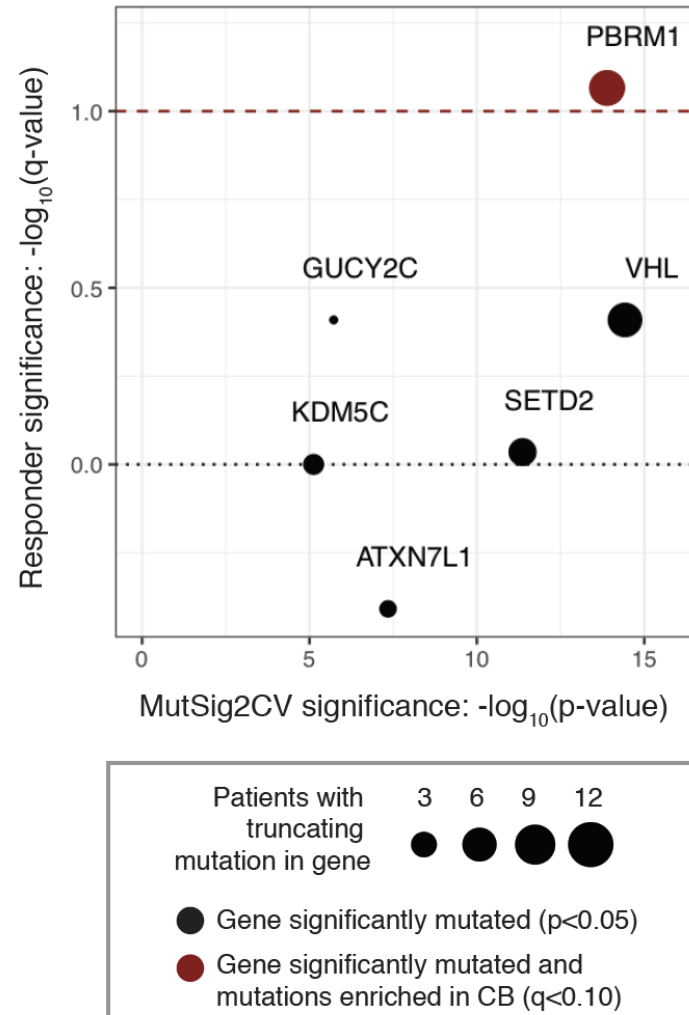
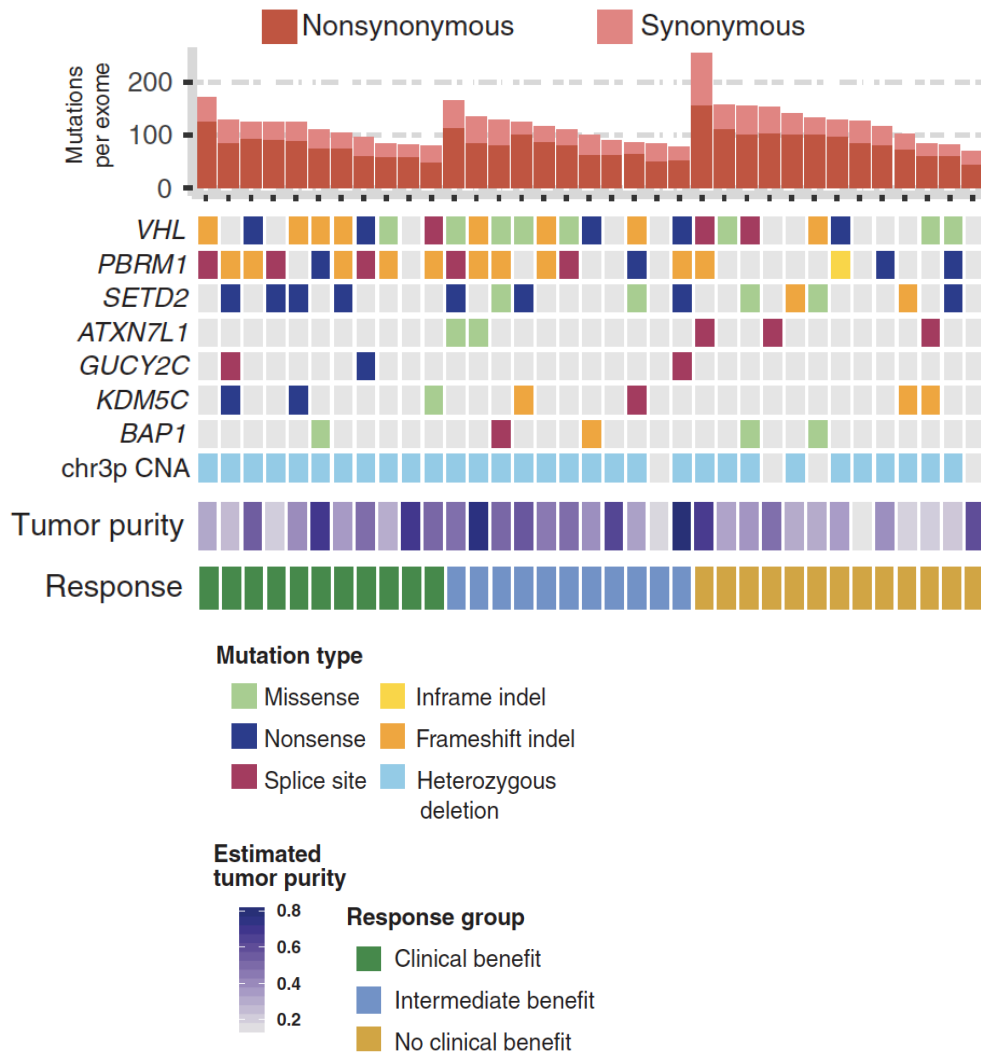
# Genomic mediators of response to cancer immunotherapy in RCC?



# Mutational load and clear cell renal cell carcinoma

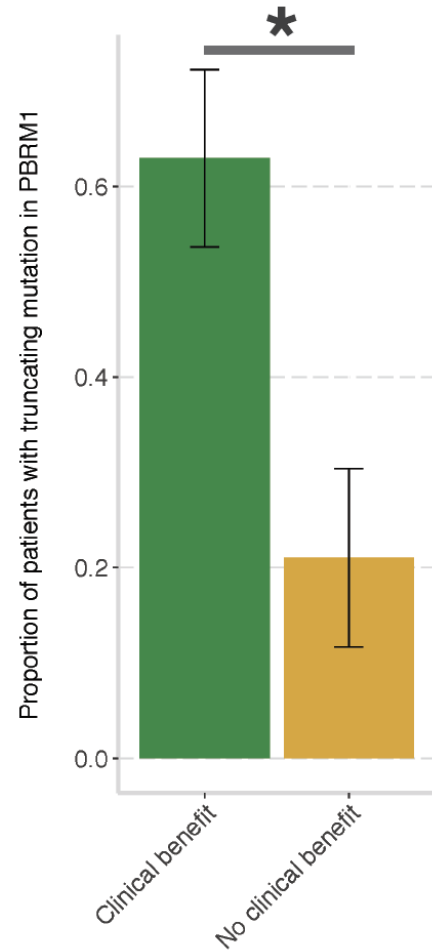


# Specific genes involved?

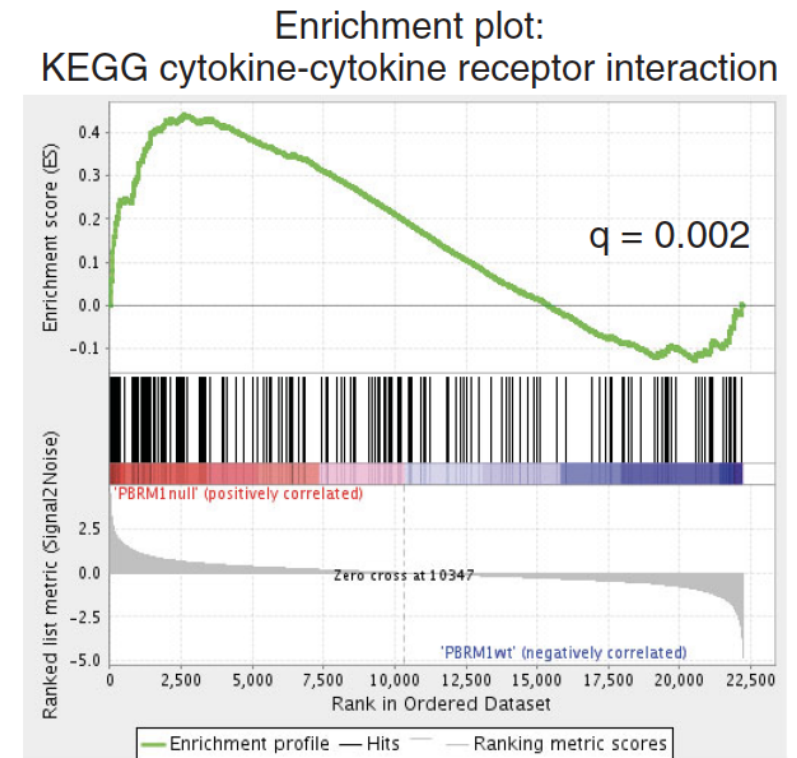
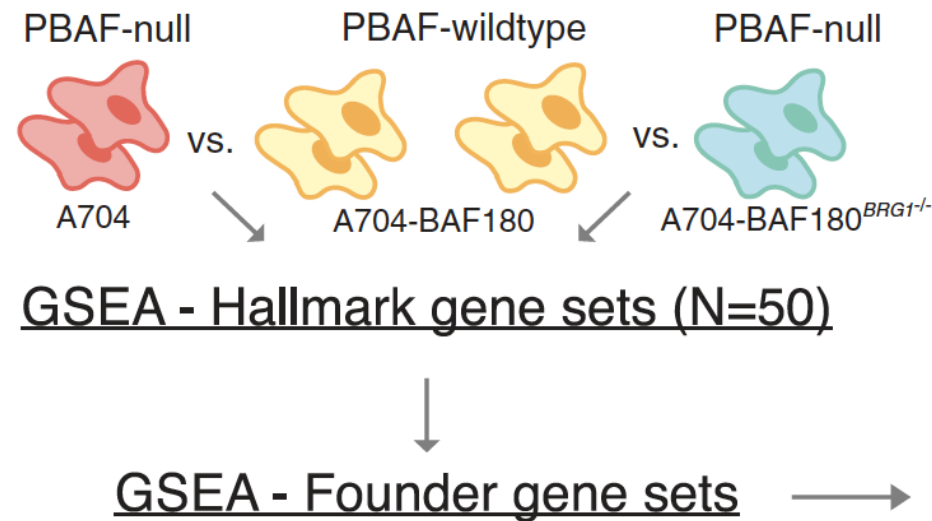




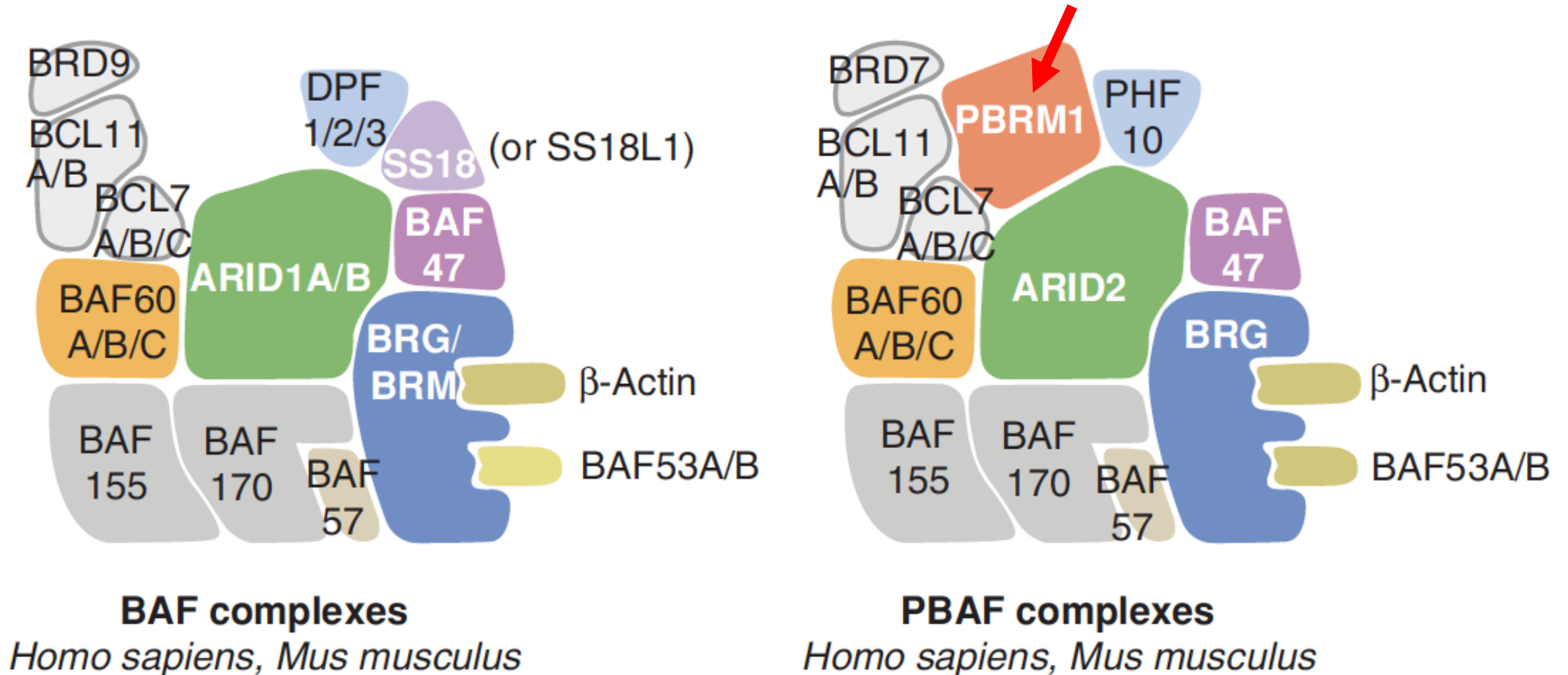
# Clinical and experimental validation?



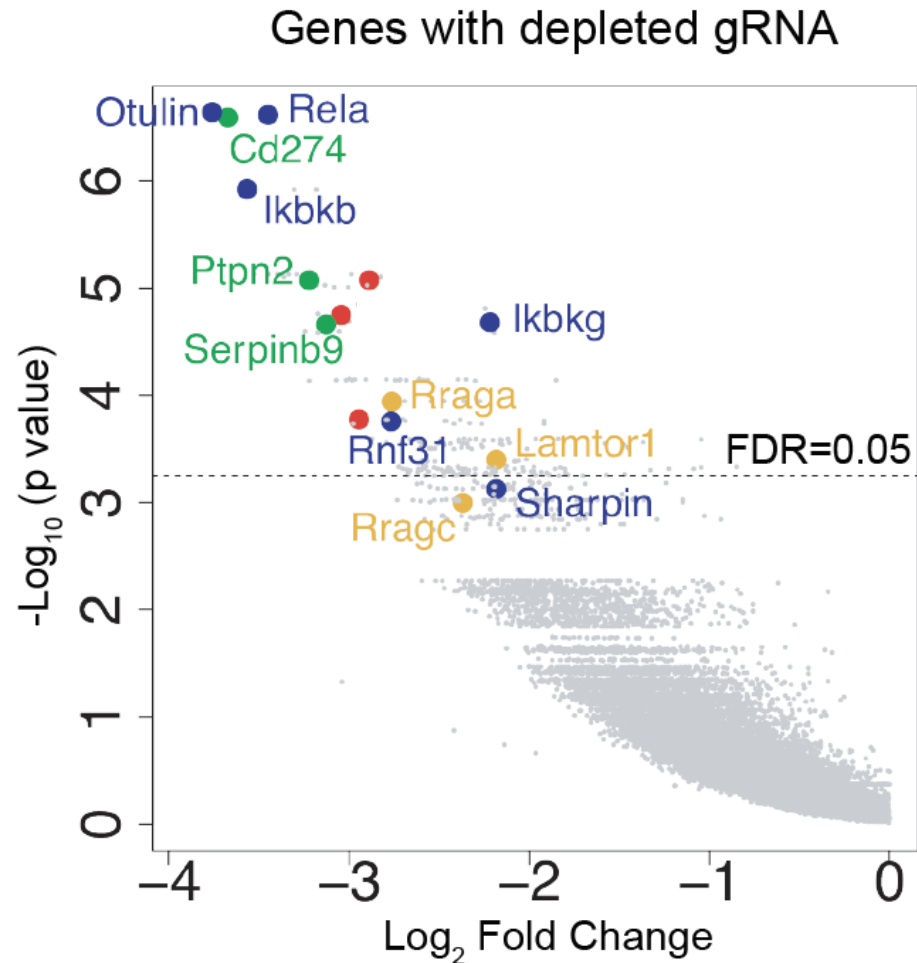
*RCC validation cohort*  
*PBRM1  $p < 0.01$*



# A role for SWI/SNF in cancer immunotherapy?

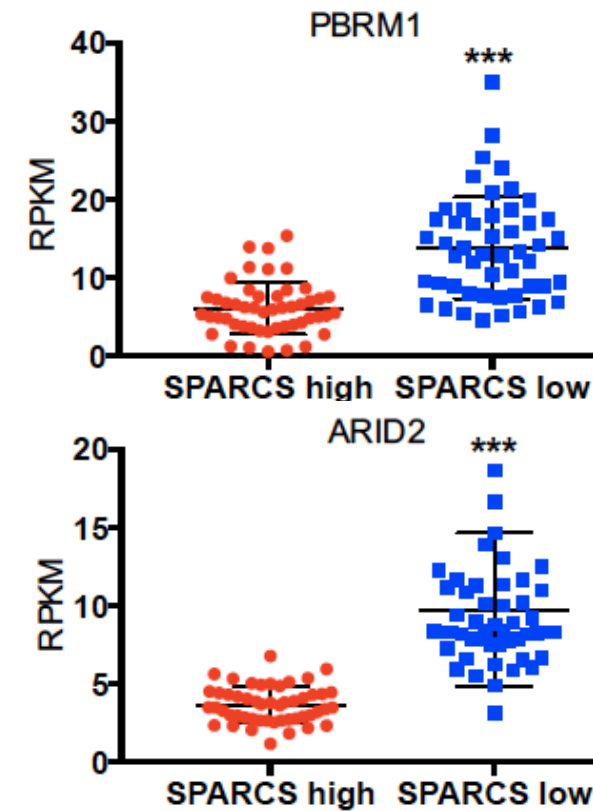


# Linking clinical genomics to functional and transcriptional findings



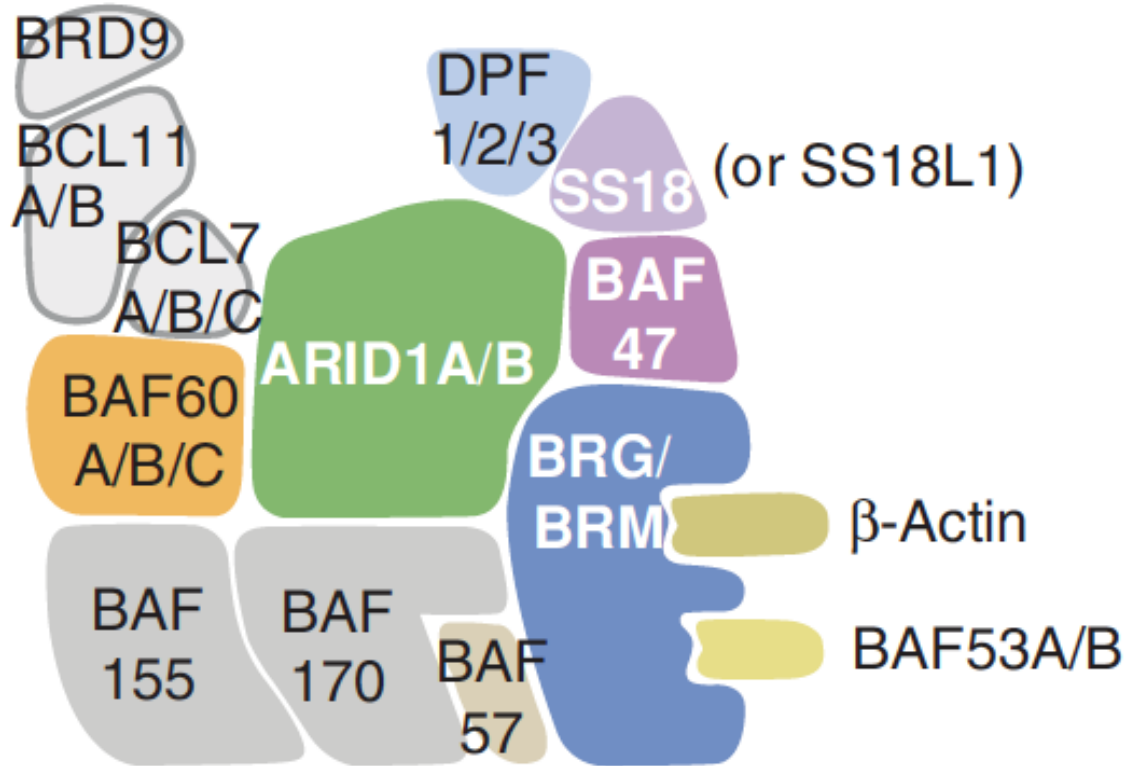
Pan, et al *Science* 2018

Endogenous retrovirus RNA signature (SPARCS)



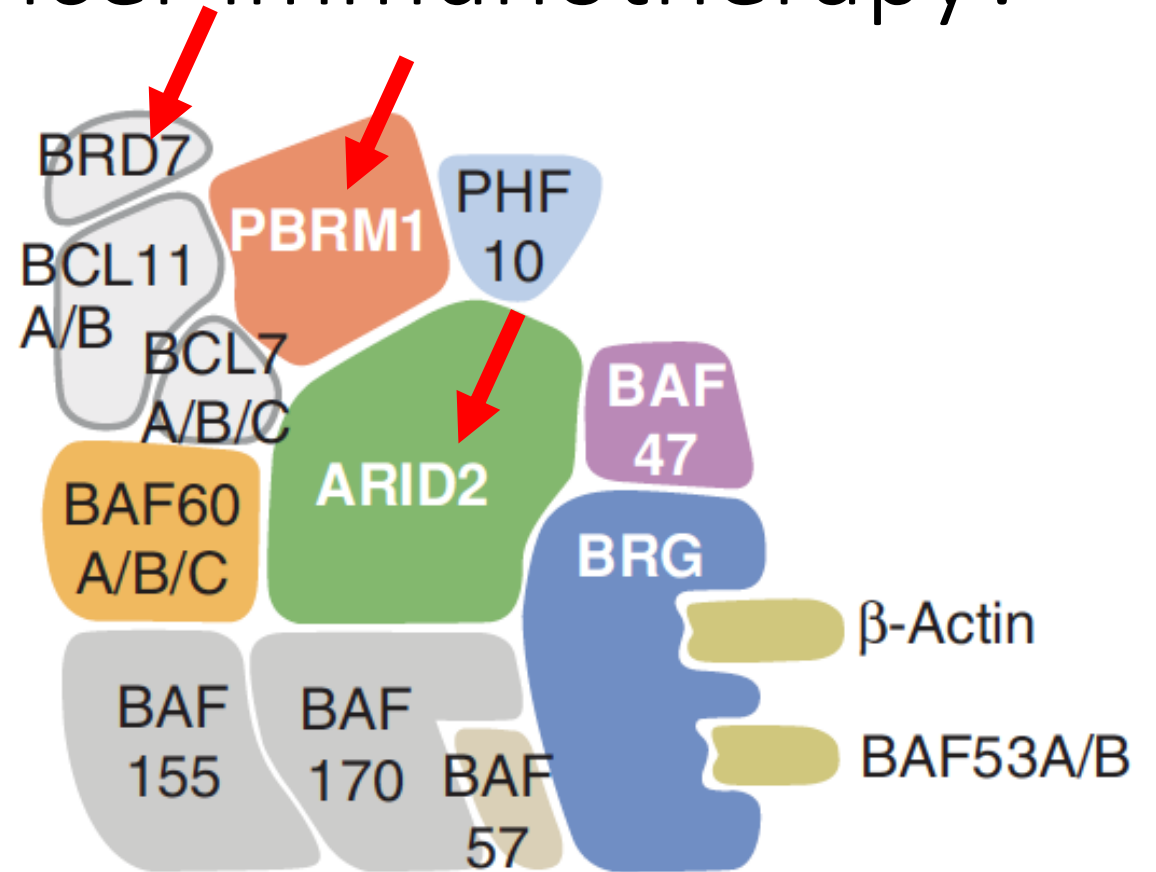
Canadas et al *Nature Med* 2018

# A role for SWI/SNF in cancer immunotherapy?



**BAF complexes**

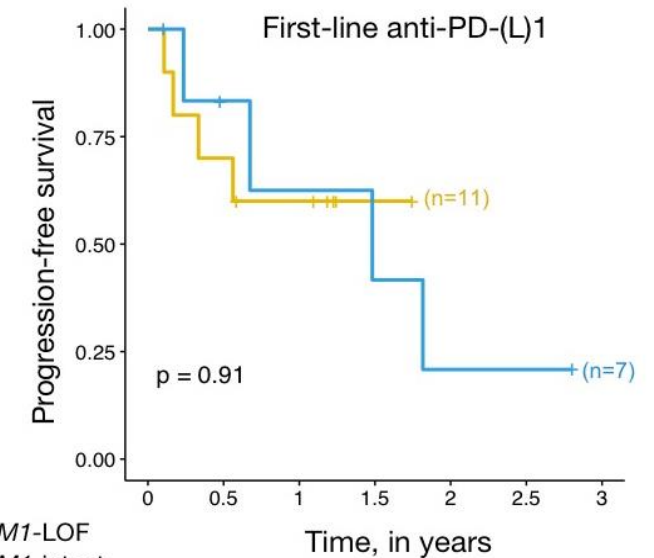
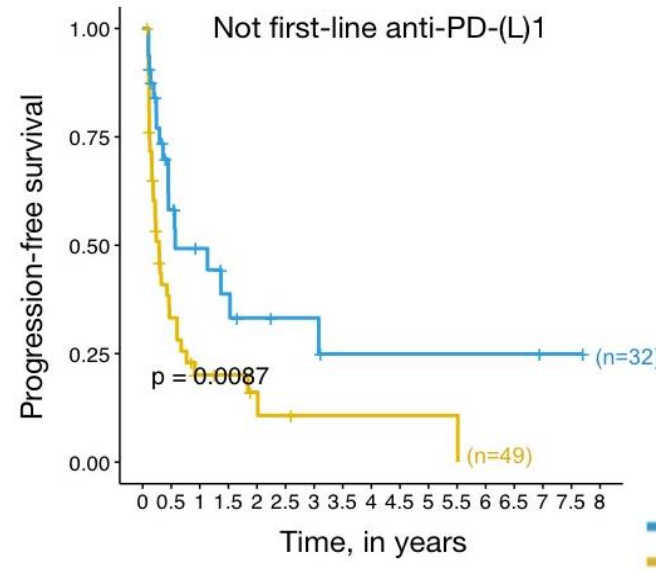
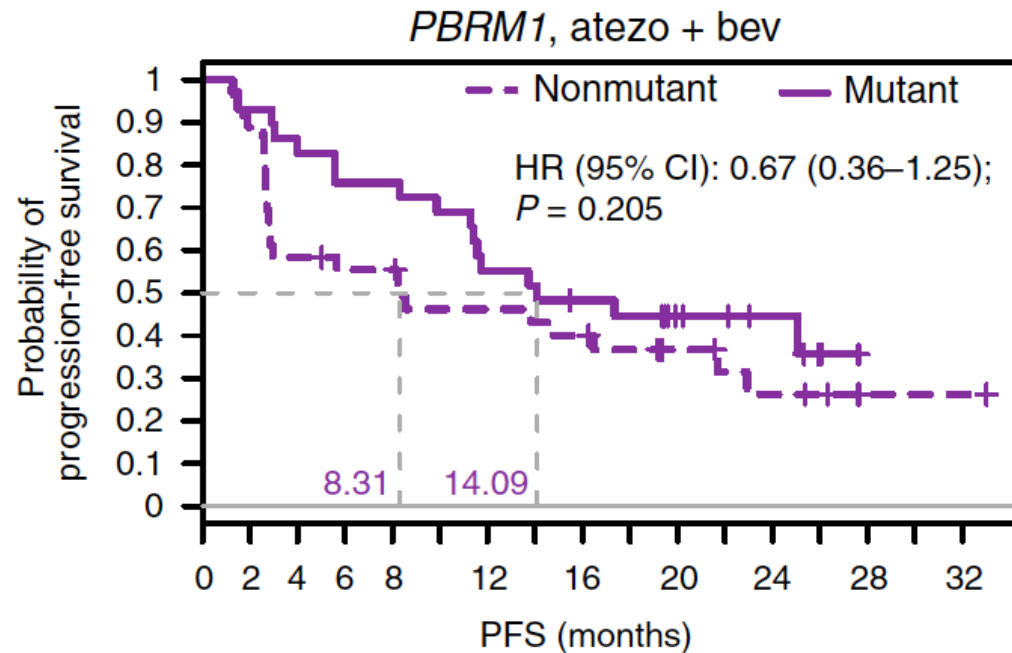
*Homo sapiens, Mus musculus*



**PBAF complexes**

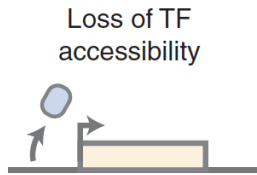
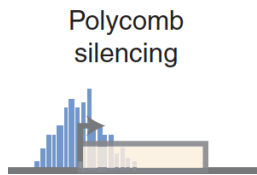
*Homo sapiens, Mus musculus*

# Complex biology of SWI/SNF in cancer

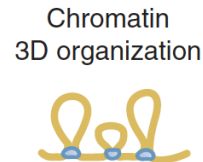
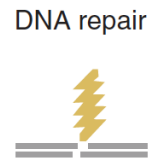


# Complex biology of SWI/SNF in cancer

## Transcriptional effects



## Nontranscriptional roles

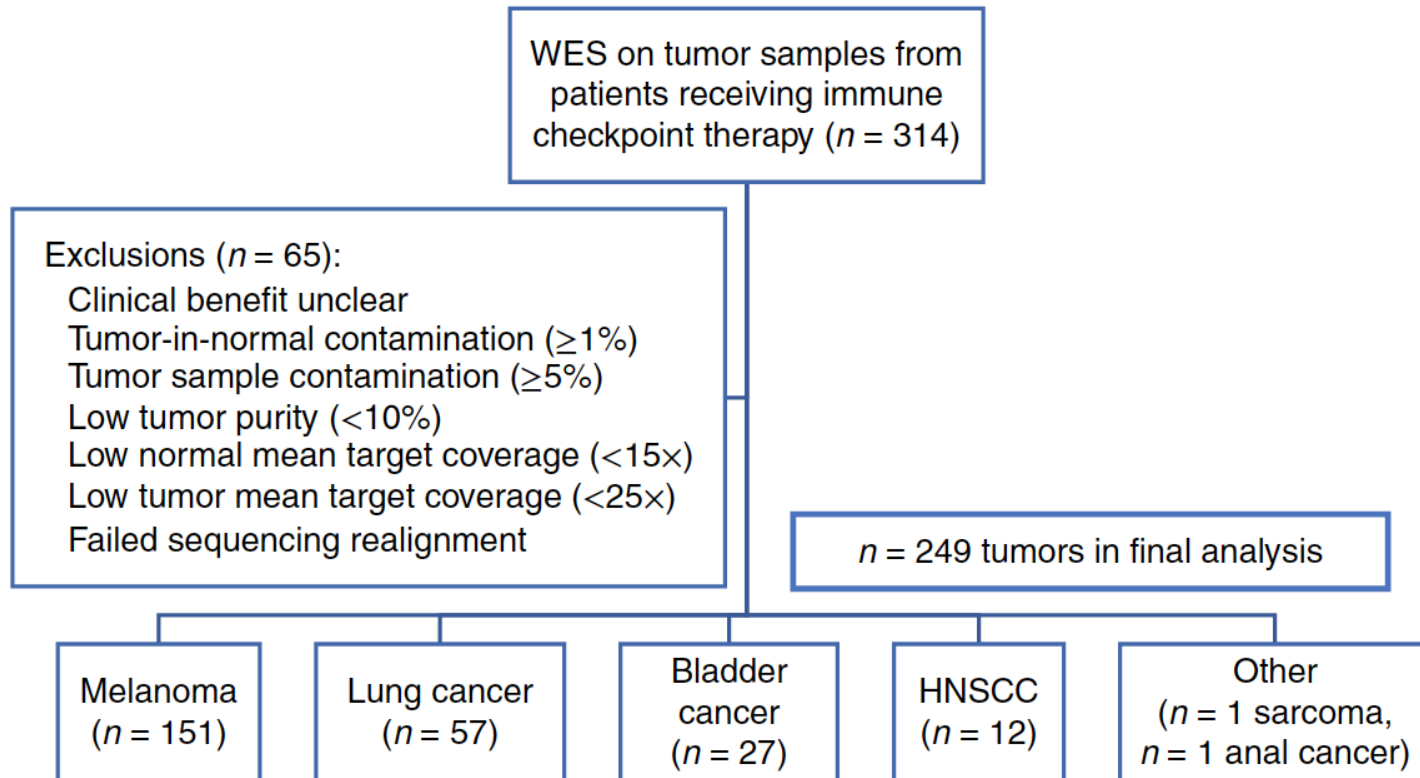


- Numerous interactions suggest complex interplay with other immuno-oncology modifiers
- Additional lineage-specific factors likely at play
- Functional and expanded clinical investigations underway
- **Not a clinical biomarker!**

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# Expanding clinical cohorts to match functional findings



Diana  
Miao



Claire  
Margolis

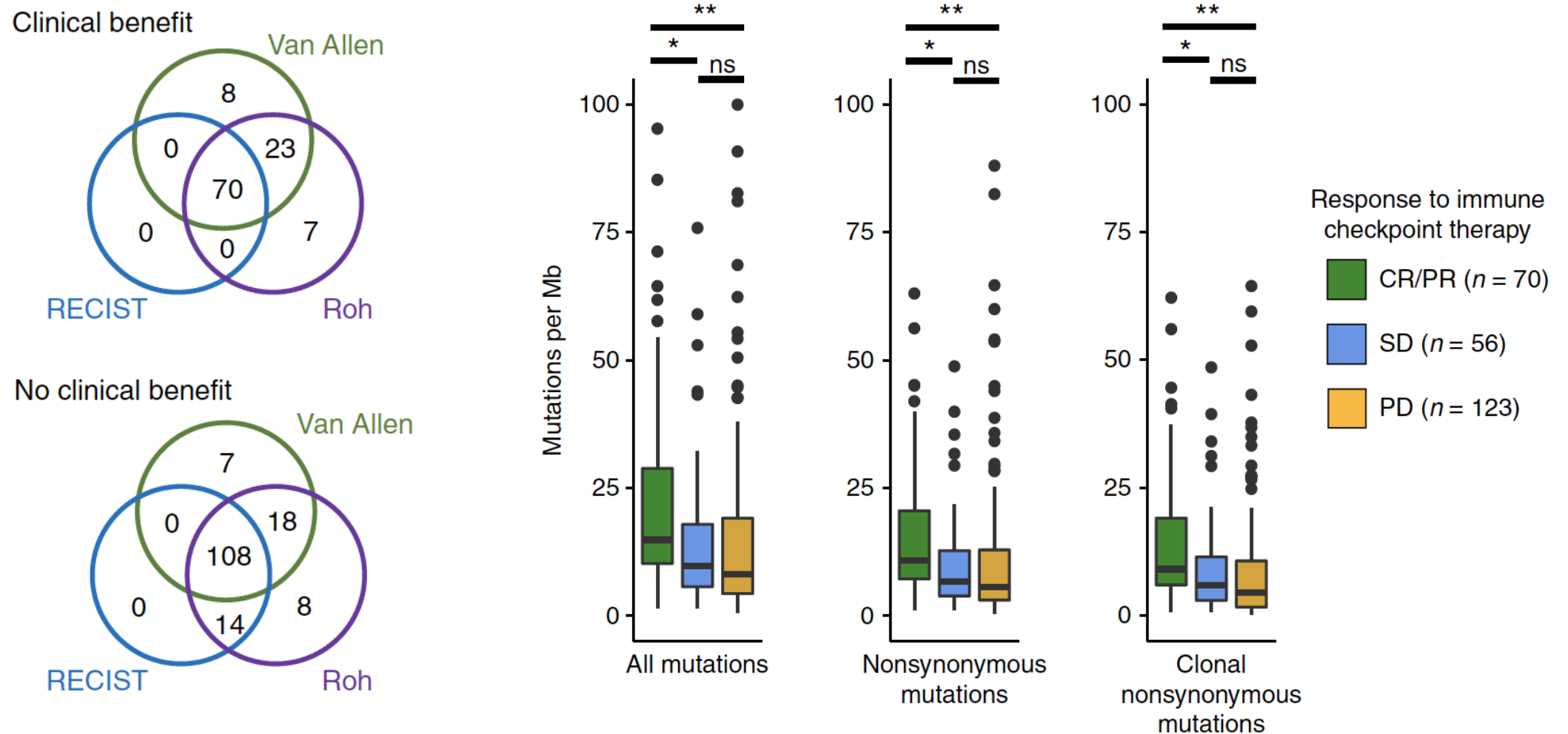


Natalie  
Vokes

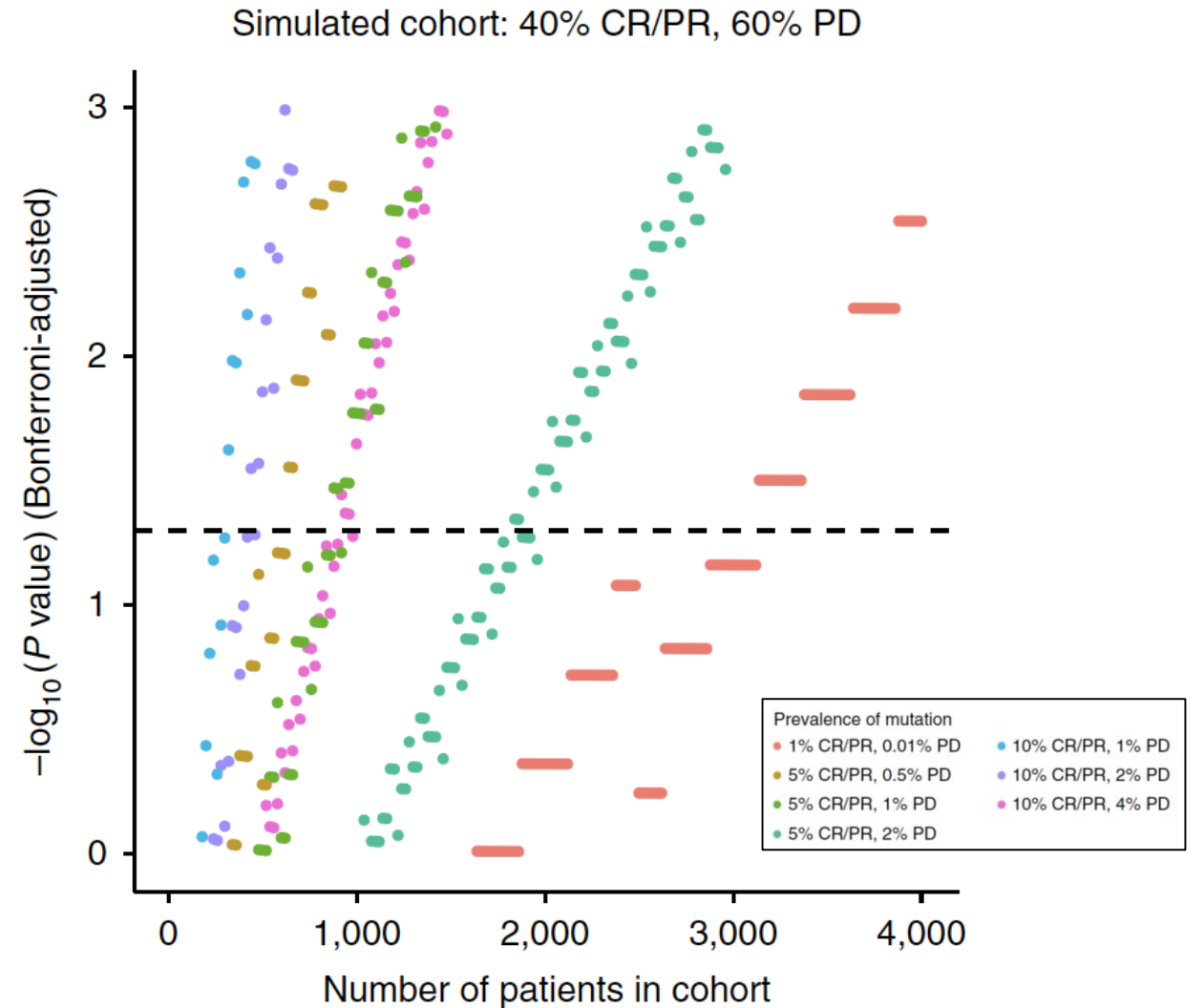
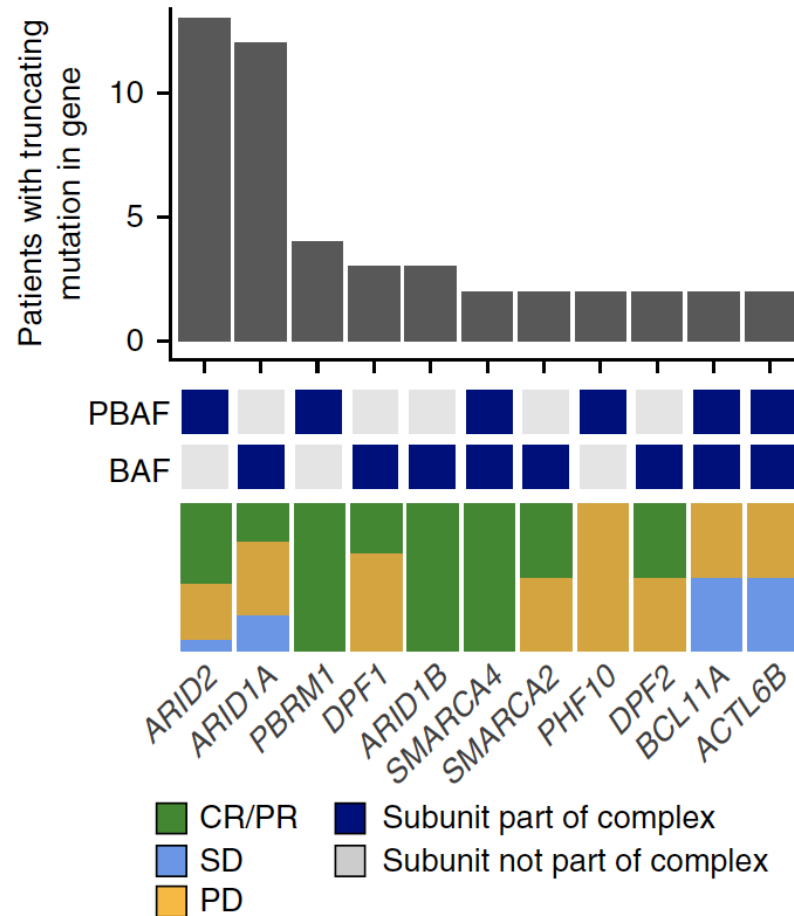
*Opportunities to inform clinical  
and functional genomics  
across cancer types*



# Linking genomics with outcomes remains major barrier to discovery



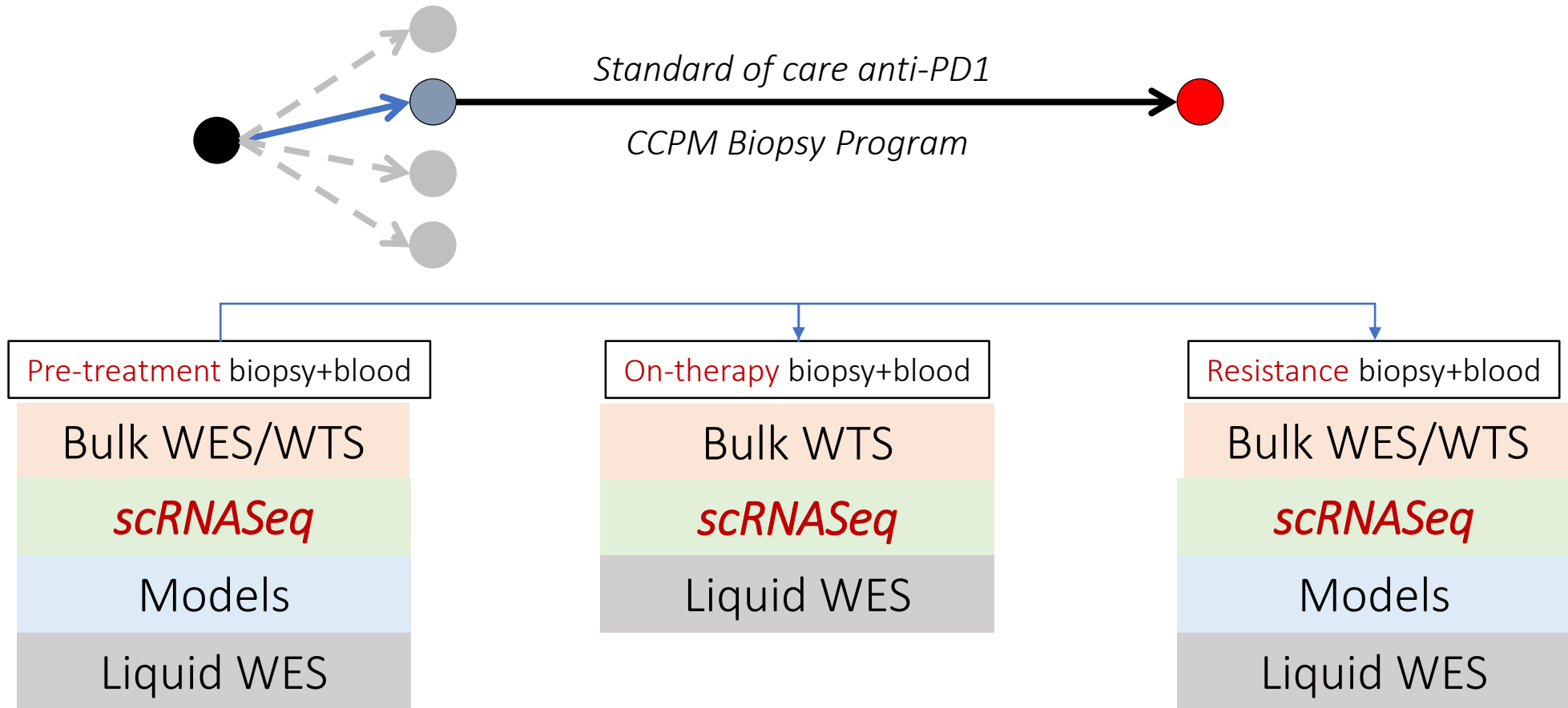
# Power to detect single gene correlates of response is still limited due to sample size



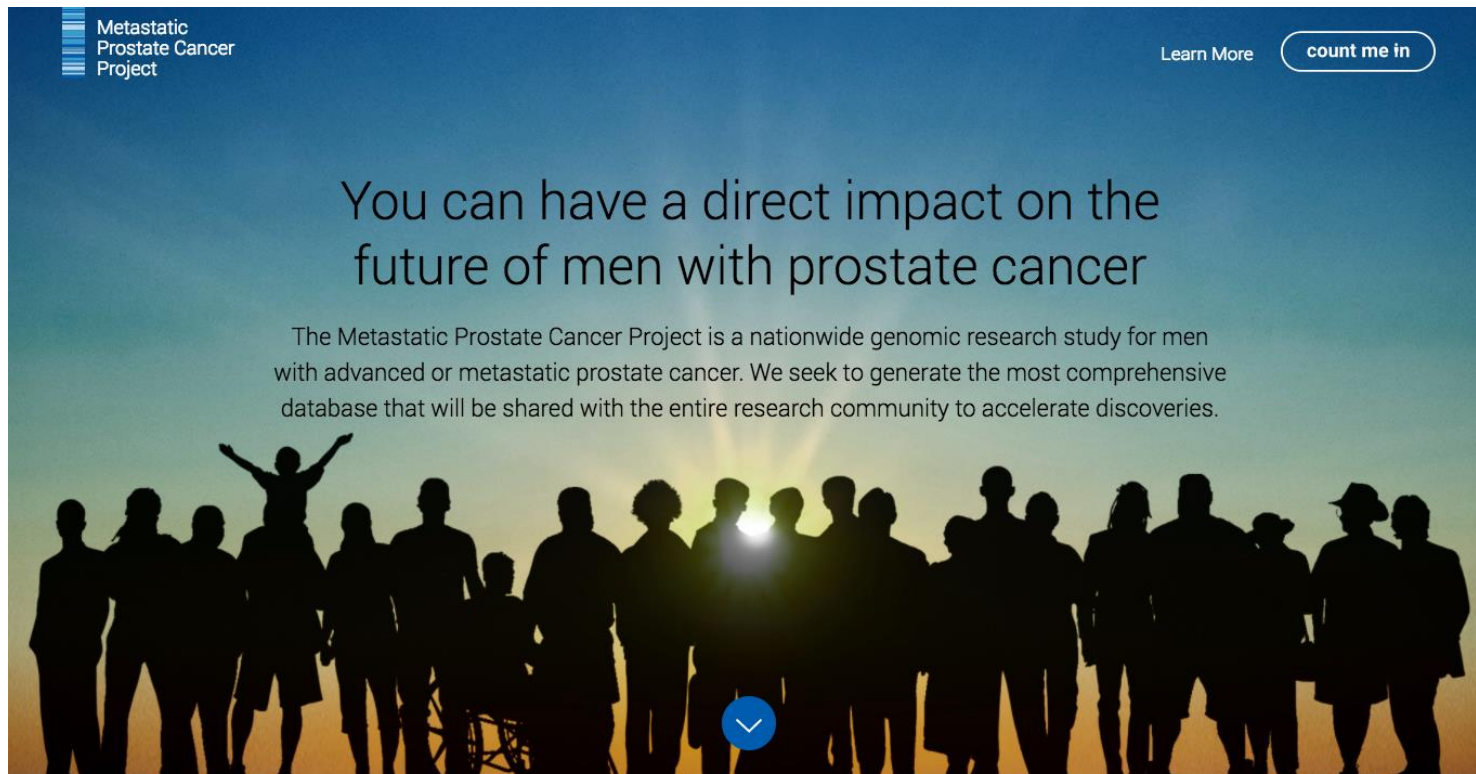
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# DFCI/Broad Center for Cancer Precision Medicine: Capturing tumor, immune, and stromal programs



# Direct to patient approaches to study immunotherapy-treated RCC?



The banner features a blue header with the project name and a 'count me in' button. The main text encourages participation, stating that the project is a nationwide genomic research study for men with advanced or metastatic prostate cancer. The background shows silhouettes of a diverse group of people against a sunset sky.

Metastatic Prostate Cancer Project

Learn More [count me in](#)

You can have a direct impact on the future of men with prostate cancer

The Metastatic Prostate Cancer Project is a nationwide genomic research study for men with advanced or metastatic prostate cancer. We seek to generate the most comprehensive database that will be shared with the entire research community to accelerate discoveries.



The Metastatic Prostate Cancer Project  
[mpcproject.org](http://mpcproject.org)

## MPCproject Patient Reported Medications (N=480)

|                     |     |
|---------------------|-----|
| LUPRON              | 361 |
| CASODEX             | 243 |
| ZYTIGA_ABIRATERONE  | 135 |
| DOCETAXEL_TAXOTERE  | 127 |
| DEGARELIX           | 78  |
| XTANDI_ENZALUTAMIDE | 76  |
| XGEVA               | 65  |
| EXP_CLINICAL_TRIAL  | 56  |
| PROVENGE            | 42  |
| OTHER_THERAPY       | 38  |
| ZOLADEX             | 36  |
| ZOMETA              | 34  |
| XOFIGO              | 19  |
| CARBOPLATIN         | 15  |
| JEVTANA_CABAZITAXEL | 13  |
| KEYTRUDA            | 6   |
| LYNPARZA_OLAPARIB   | 6   |
| NILANDRON           | 5   |
| ETOPOSIDE           | 4   |
| PACLITAXEL_TAXOL    | 4   |
| PROSTAP             | 4   |
| YERVOY_IPILUMIMAB   | 4   |
| DROGENIL            | 3   |
| ESTRAMUSTINE        | 3   |
| DECAPEPTYL          | 2   |
| OPDIVO_NIVOLUMAB    | 1   |
| RUBRACA_RUCAPARIB   | 1   |



# Acknowledgements



Let's work together!  
[vanallenlab.dana-farber.org](http://vanallenlab.dana-farber.org)  
[@vanallenlab](https://twitter.com/vanallenlab)

## The Patients

### Clinical computational oncology team

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Claire Margolis  
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Brendan Reardon  
Shirley Mo  
Meng Xiao He  
Jihye Park  
Saud AlDubayan  
Jake Conway  
Haitham Elmarakaby  
Eric Kofman  
Tanya Keenan  
Amaro Taylor-Weiner  
Sophia Kamran  
Jackson Nyman  
Seunghun Han

### Broad Institute

Gad Getz  
Catherine Wu  
Sachet Shukla  
John Doench  
Genomics Platform  
Picard Team  
Firehose Team  
Adam Tracy  
Kris Cibulskis  
Carrie Cibulskis  
Will Gibson  
Scott Carter  
Will Gibson  
Jesse Boehm  
Cory Johannessen  
Many others...

### DFCI + Center for Cancer Precision Medicine

Entire GU Oncology team  
Entire CCPM team  
Toni Choueiri  
Kai Wucherpfennig  
Bruce Johnson  
F. Stephen Hodi  
Chris Sweeney  
Bruce Johnson  
W. Nicholas Haining  
William Kaelin Jr.  
Sabina Signoretti  
Peter Hammerman  
Mary-Ellen Taplin  
George Demetri  
Suzanne George  
Lynette Sholl  
David Barbie  
Many others...

### BMS

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Christine Horak  
Megan Wind-Rotolo  
  
MSKCC  
Martin Voss  
Alex Snyder  
Robert Motzer  
Matthew Hellmann

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Mo Allaf  
Charles Drake

### Mayo Thai Ho

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BMS IION  
BroadIgnite | BroadNext10

