

Historical perspective and future directions: Computational science in immuno-oncology

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Disclosures

- Consulting/Advisory
 - Tango Therapeutics
 - Genome Medical
 - Genomic Life
 - Enara Bio
 - Janssen
 - Manifold Bio
 - Monte Rosa Therapeutics
- Research funding
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- Equity
 - Tango Therapeutics
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 - Genomic Life
 - Syapse
 - Enara Bio
 - Manifold Bio
 - Monte Rosa Therapeutics
 - Microsoft

Outline

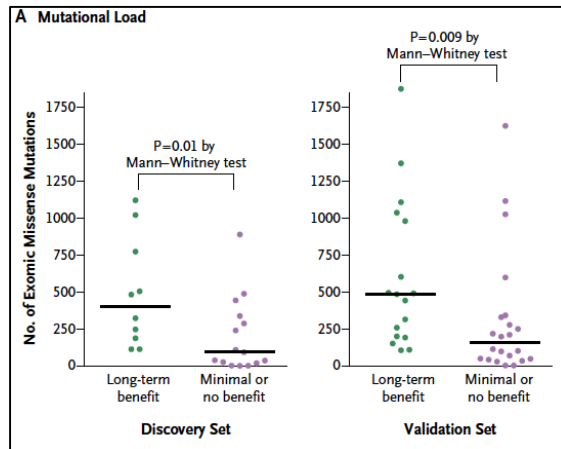
- Genomics and immuno-oncology biomarkers
- Pivoting to reverse translation and genomics
- Creating more complex molecular representations for discovery and prediction
- Next steps

Outline

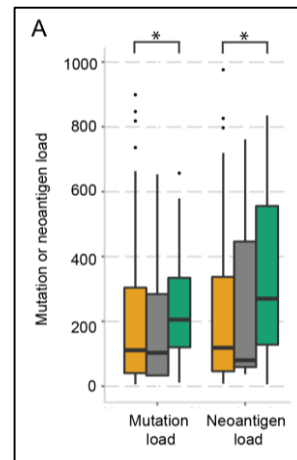
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Clinical genomics and cancer immunotherapy ca. 2015

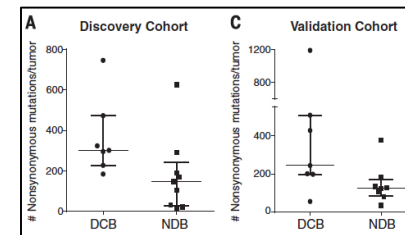
Tumor mutational burden



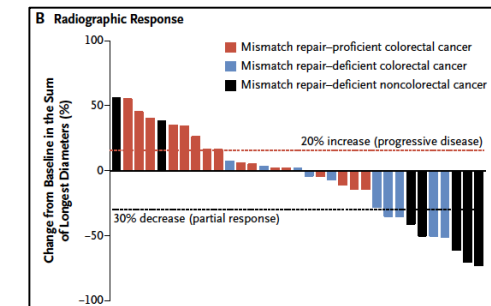
CTLA4 Ab
and melanoma



CTLA4 Ab
and melanoma

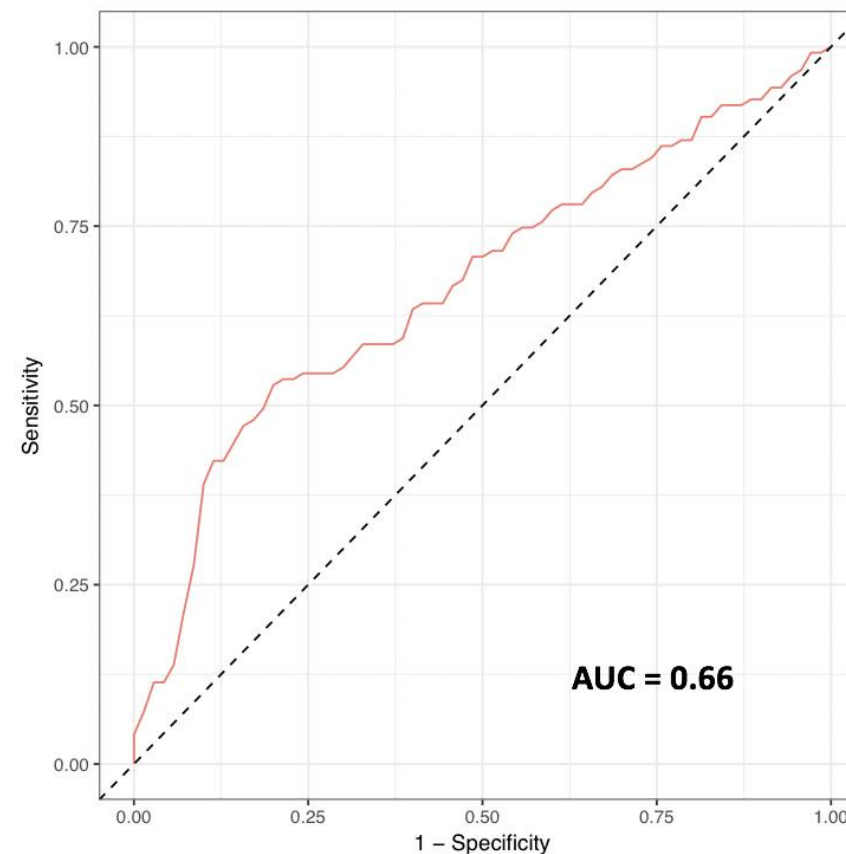
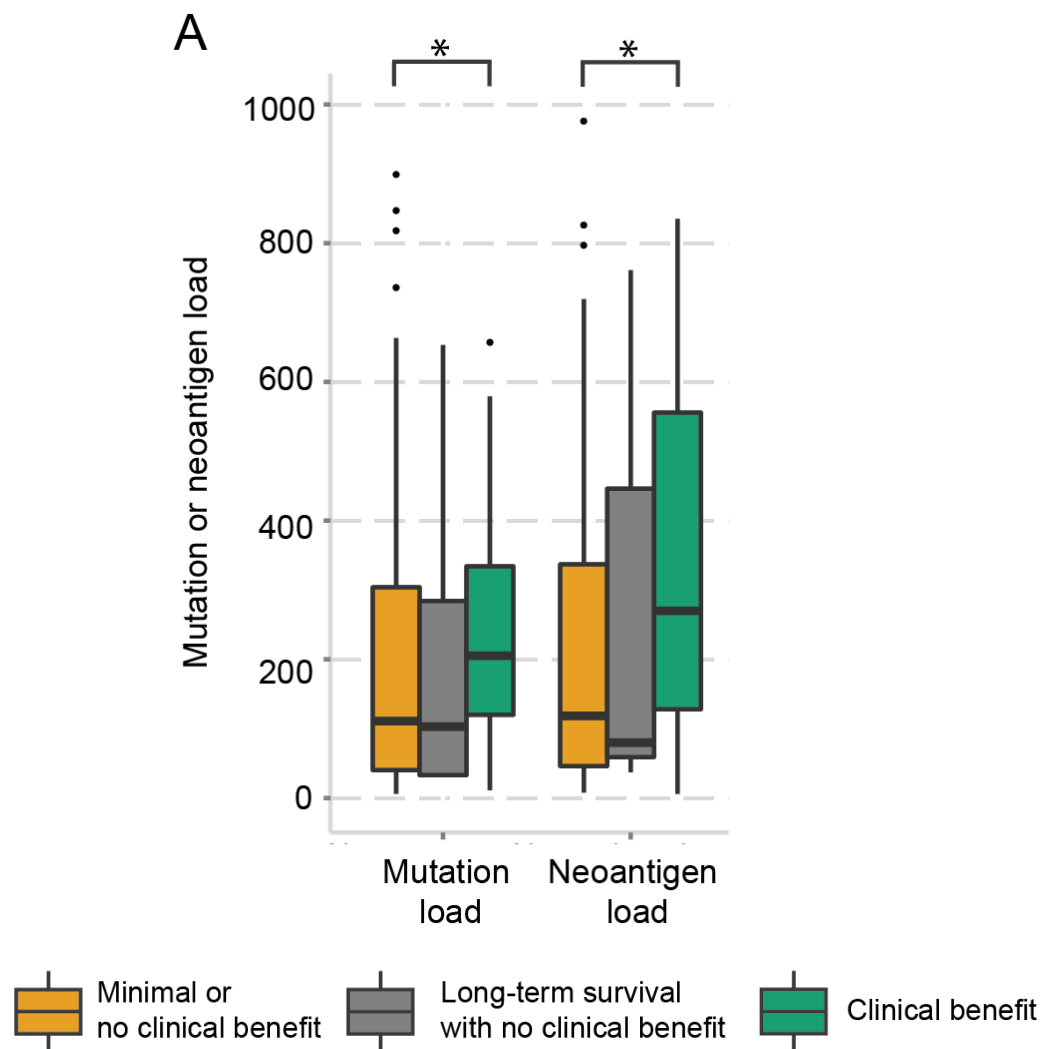


PD-1 Ab
and NSCLC



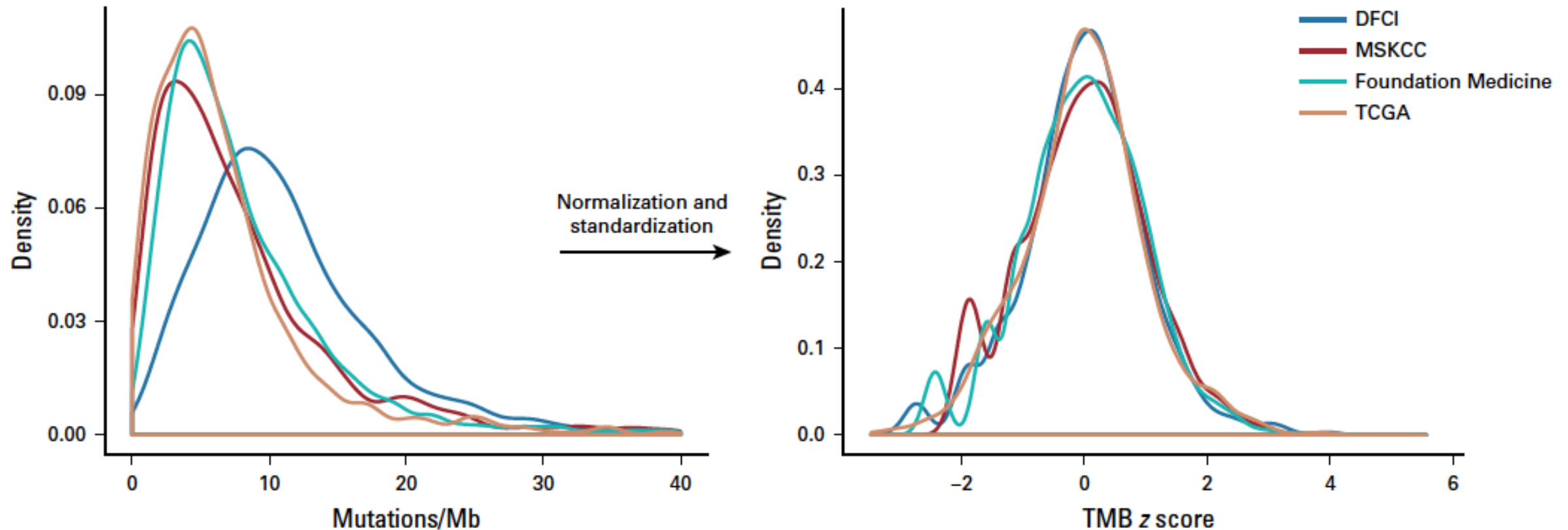
PD-1 Ab and
MSI-high tumors

Is TMB necessary and/or sufficient?



249 tumors across multiple histologies

Practical challenges with clinical use of TMB



Practical challenges with clinical use of TMB, cont.

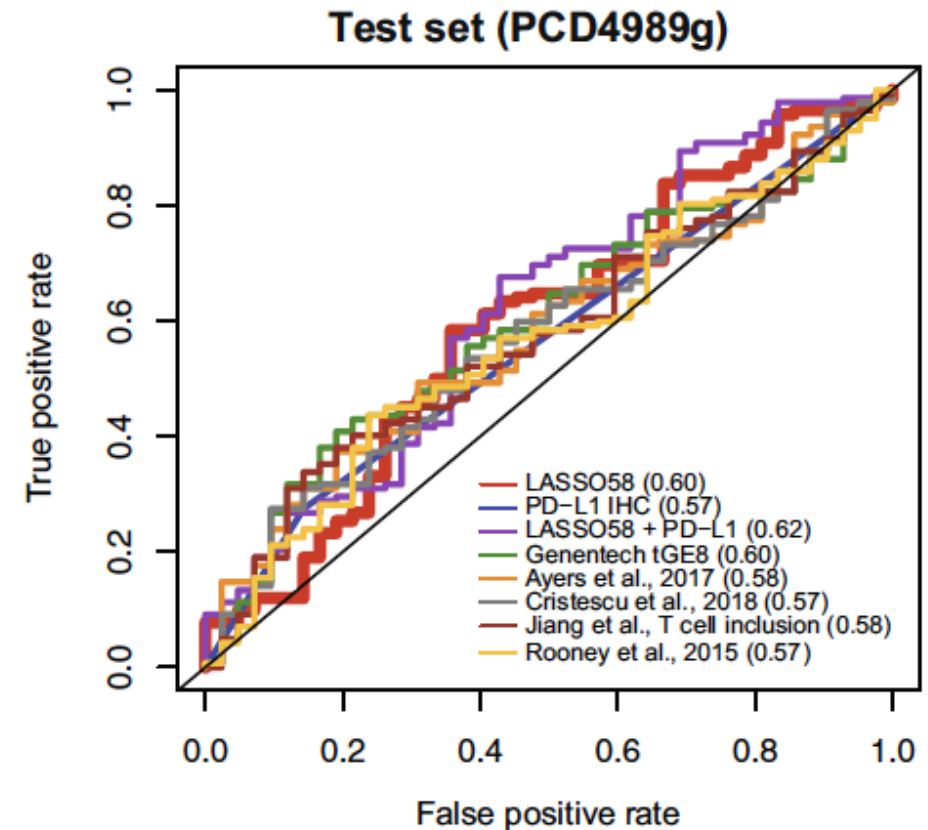
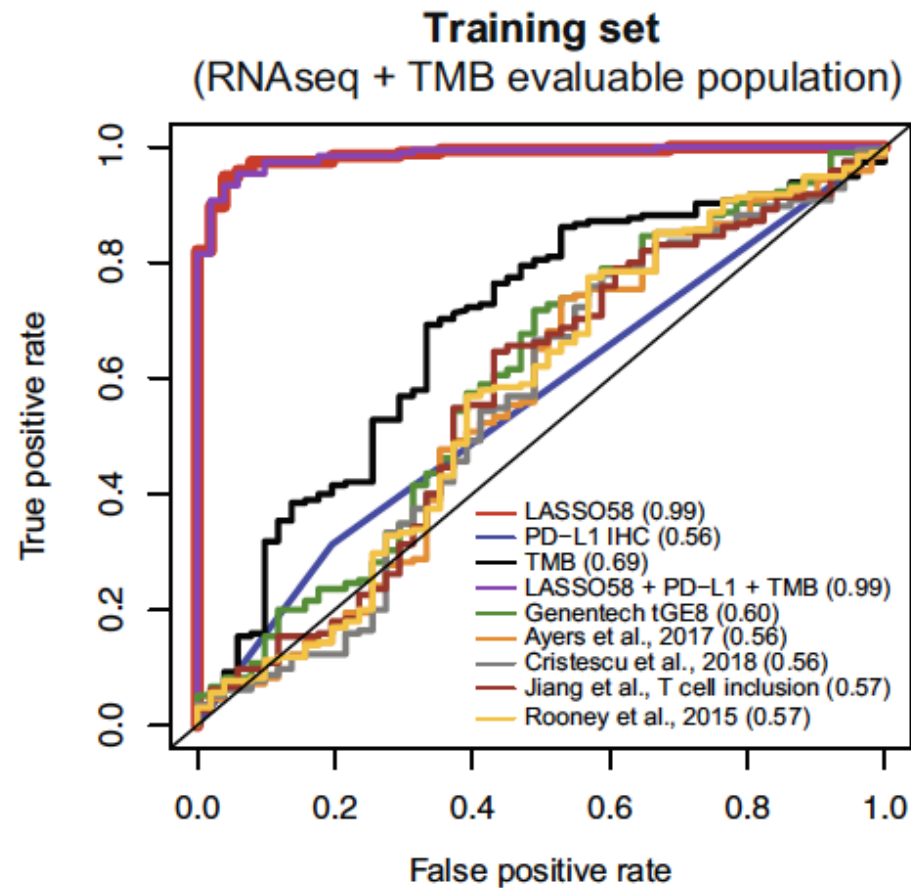
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer
with a High Tumor Mutational Burden

Of the 1739 randomly assigned patients, 1649 (94.8%) had tumor samples available to attempt assessment of tumor mutational burden, and 1004 (57.7%) had valid data for tumor mutational burden–based efficacy analyses (Table S2 in the Supplementary Appendix). Baseline char-

Practical challenges with clinical use of more complex signatures



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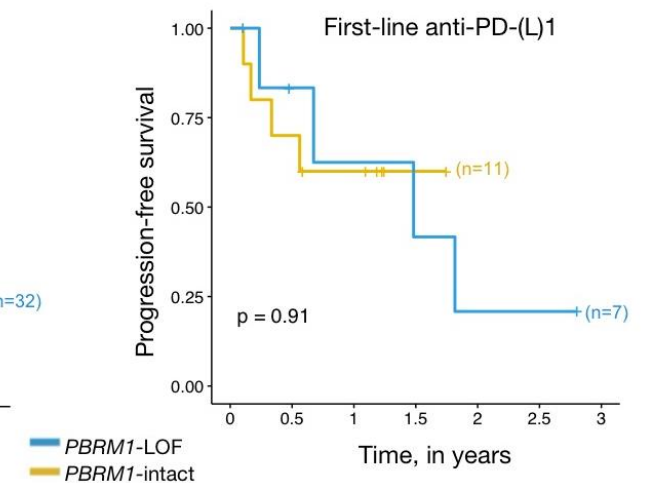
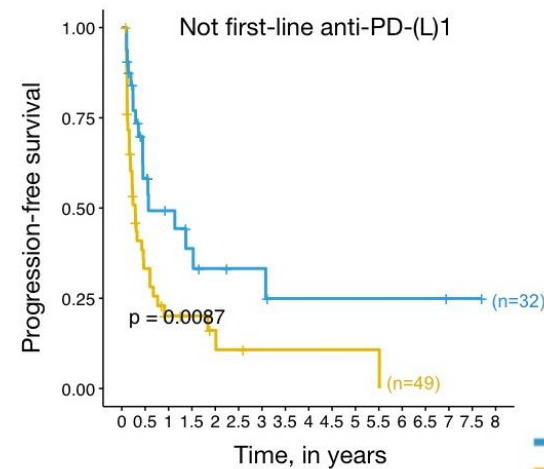
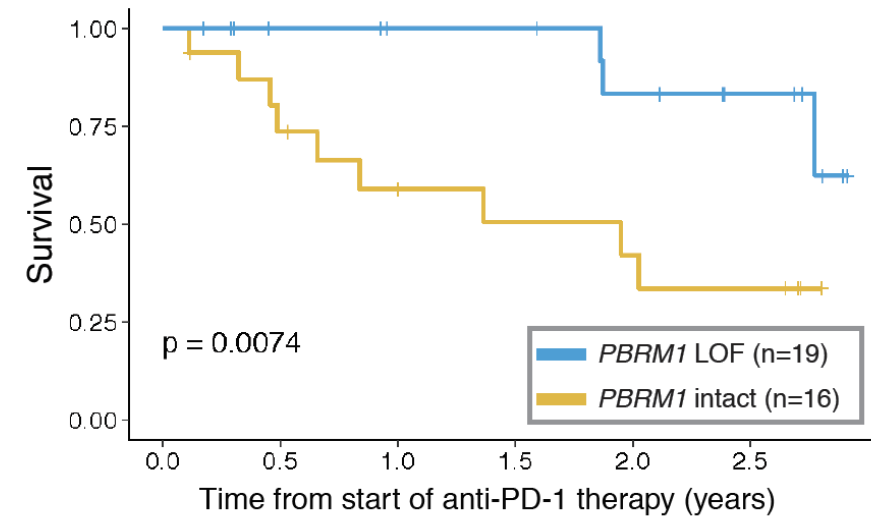
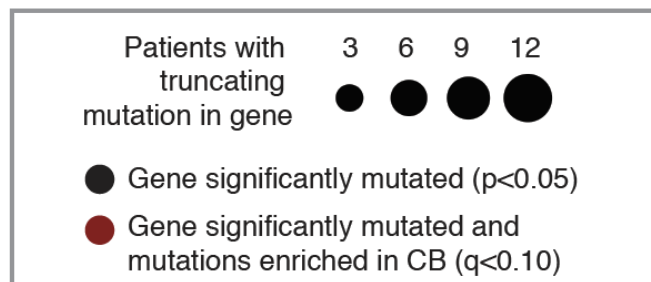
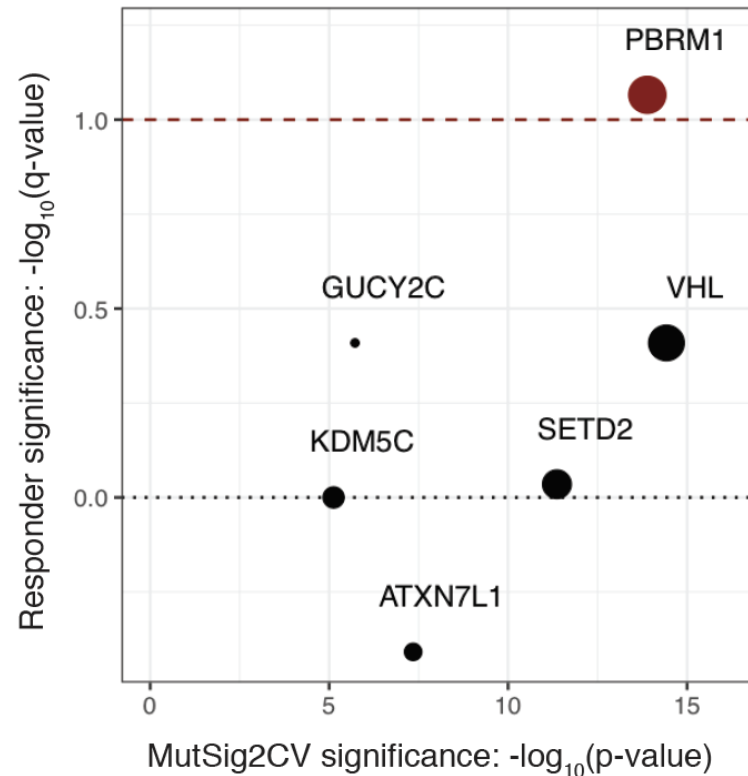
“First order” genomic events and response to immune checkpoint blockade?

Tumor cell (response mechanisms)	Tumor antigens ^{31,32,34-40,54,57,65,67}	Neoantigens, viral antigens
	Increased tumor mutation burden ^{9,37,48}	Mismatch repair deficiency

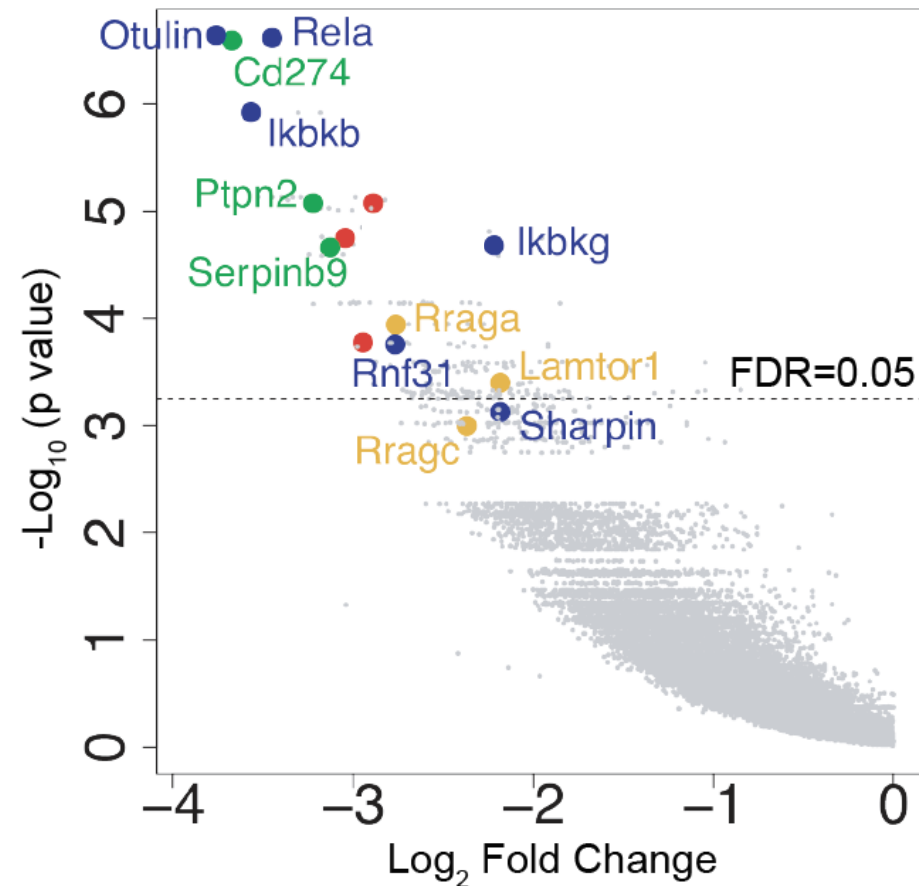
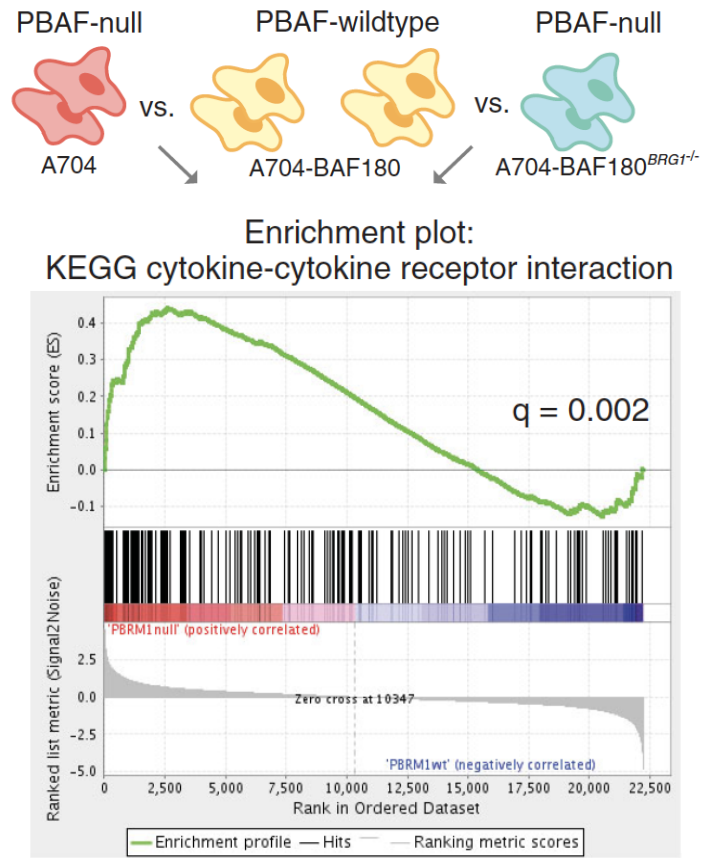


Keenan, Burke & Van Allen,
Nature Medicine 2019

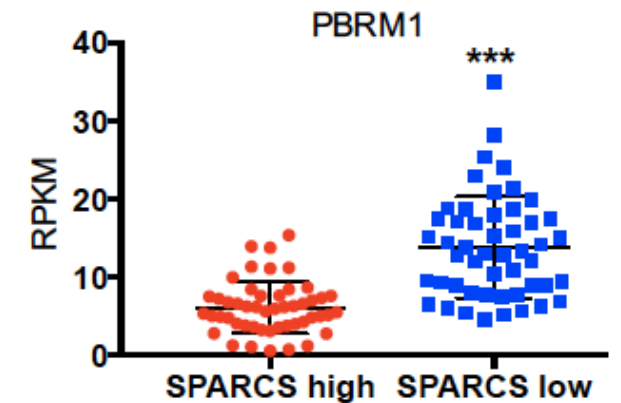
PBRM1 mutations and anti-PD-1 response



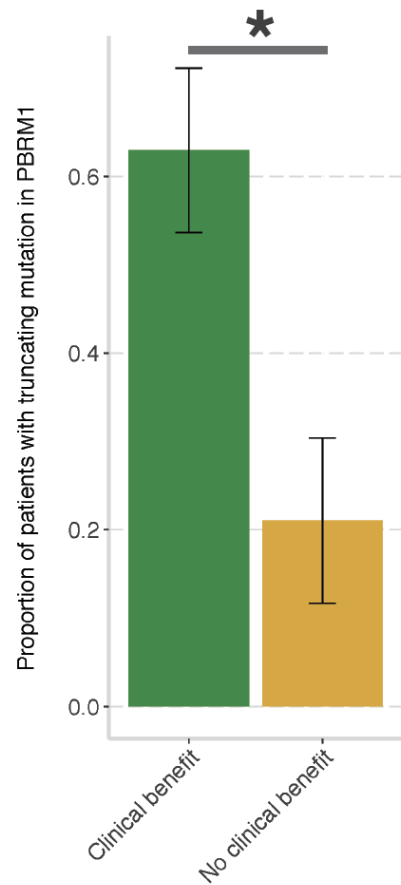
Linking clinical genomics to functional biology



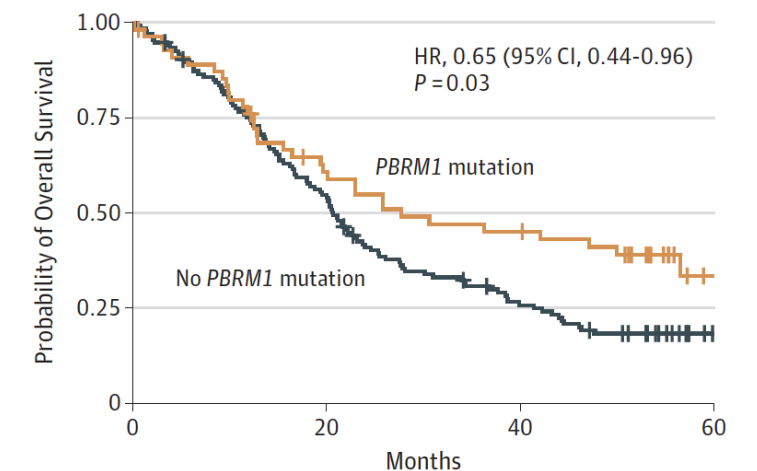
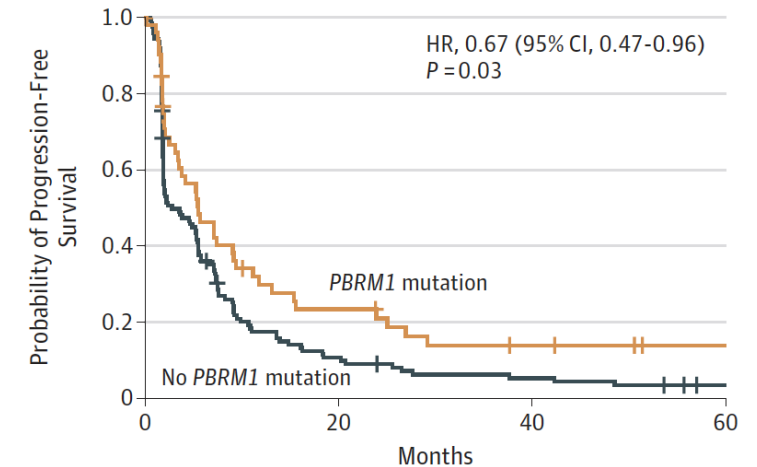
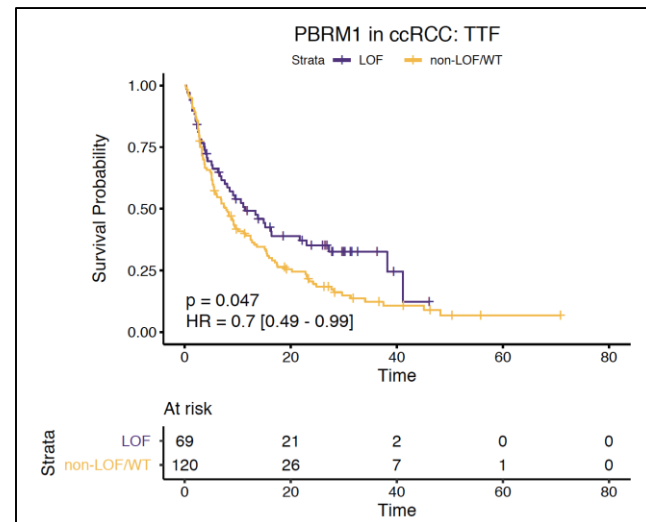
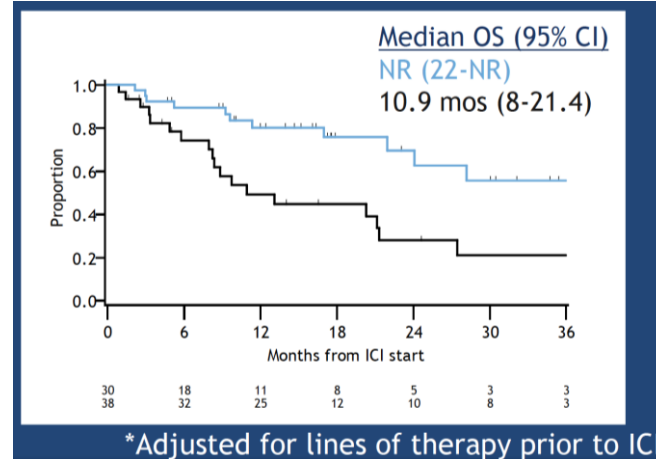
Endogenous retrovirus signature



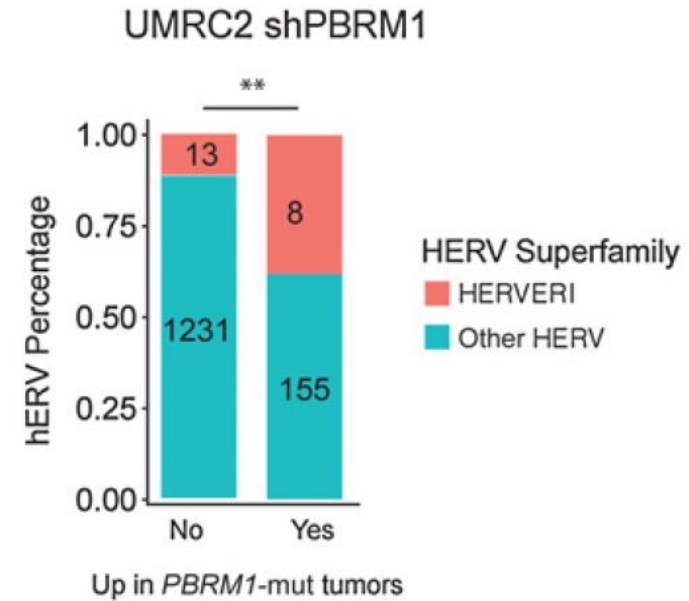
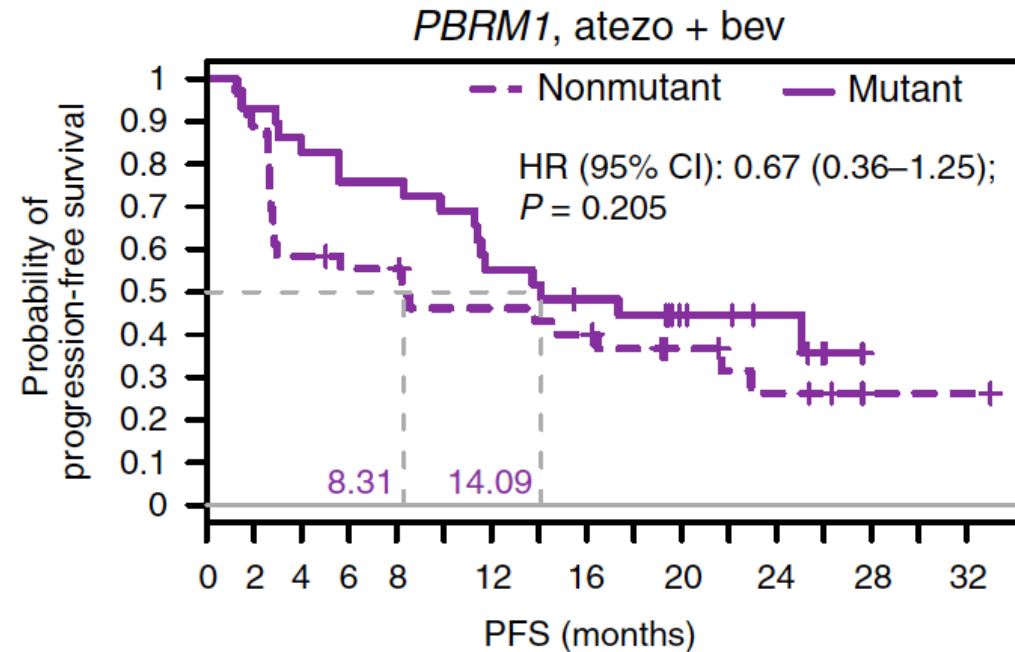
Clinical validation in similar clinical contexts in kidney cancer?



Original Miao et al validation cohort
PBRM1 $p < 0.01$

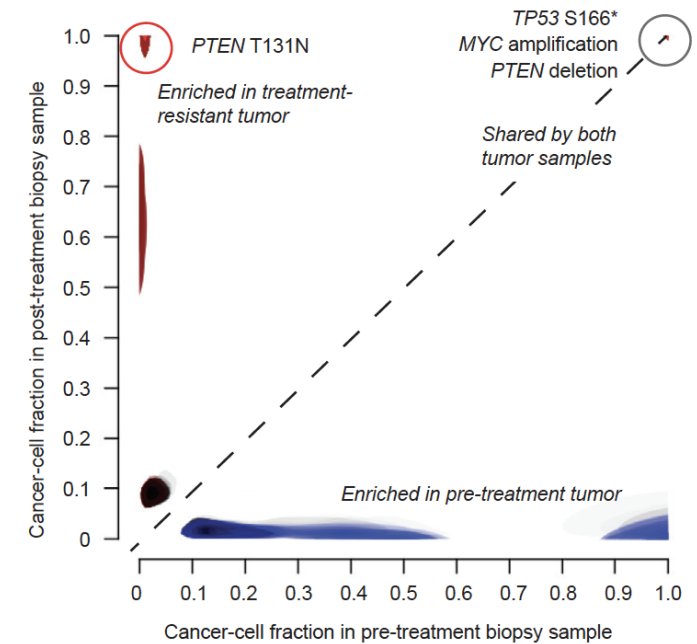
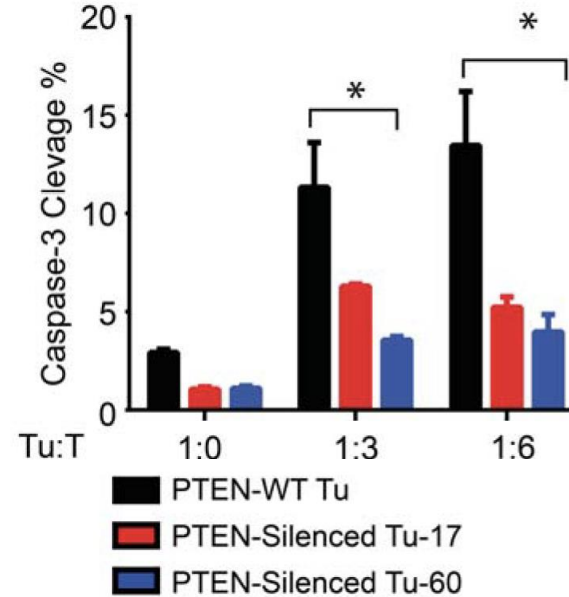
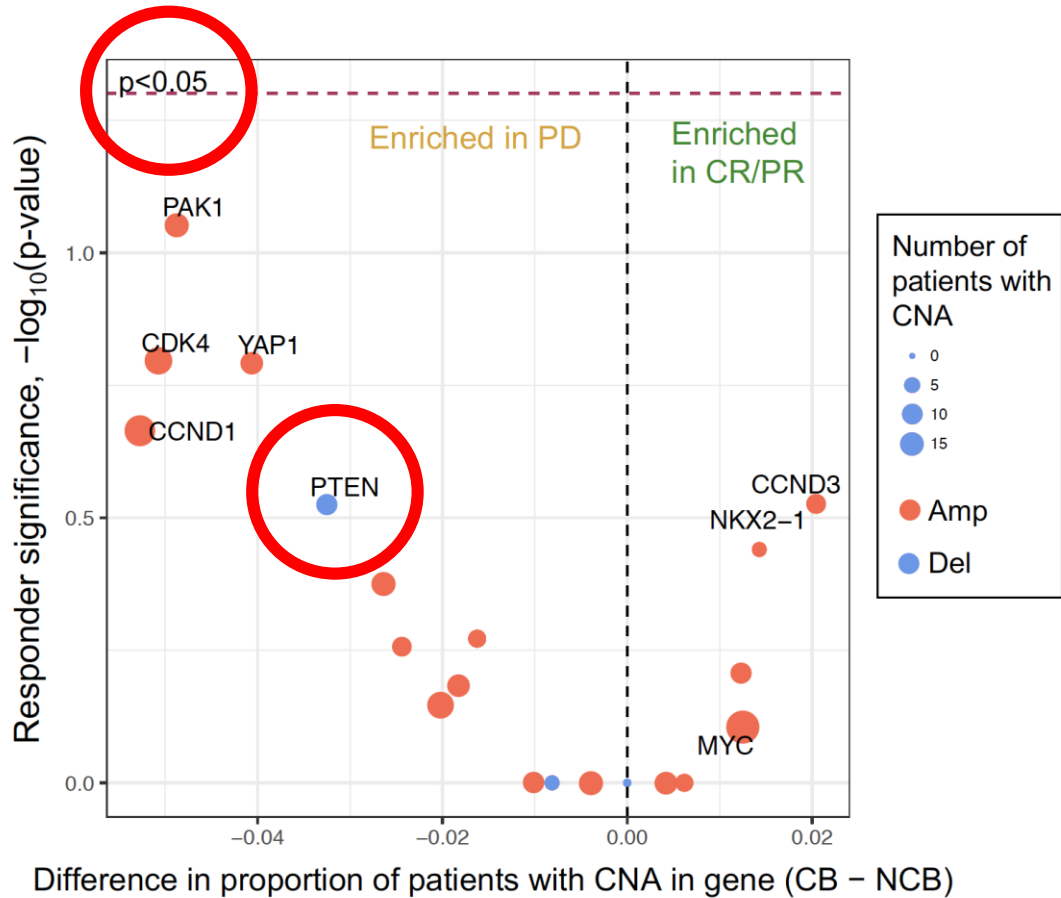


Biology vs. biomarker for immuno-oncology

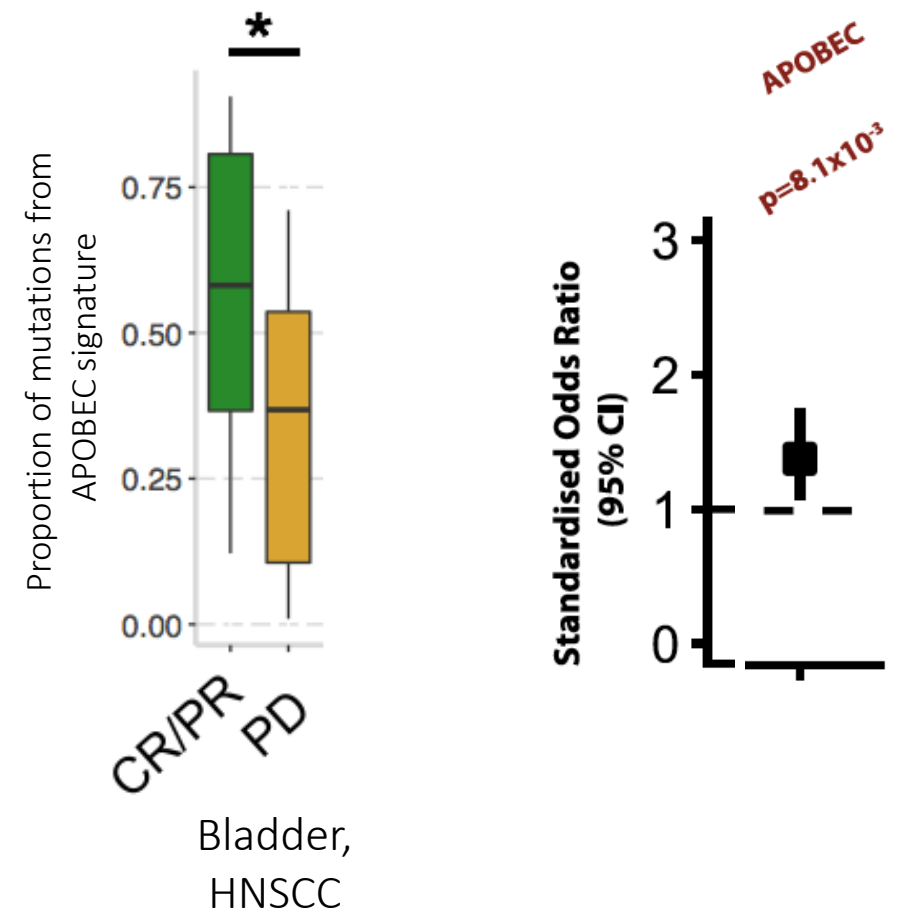
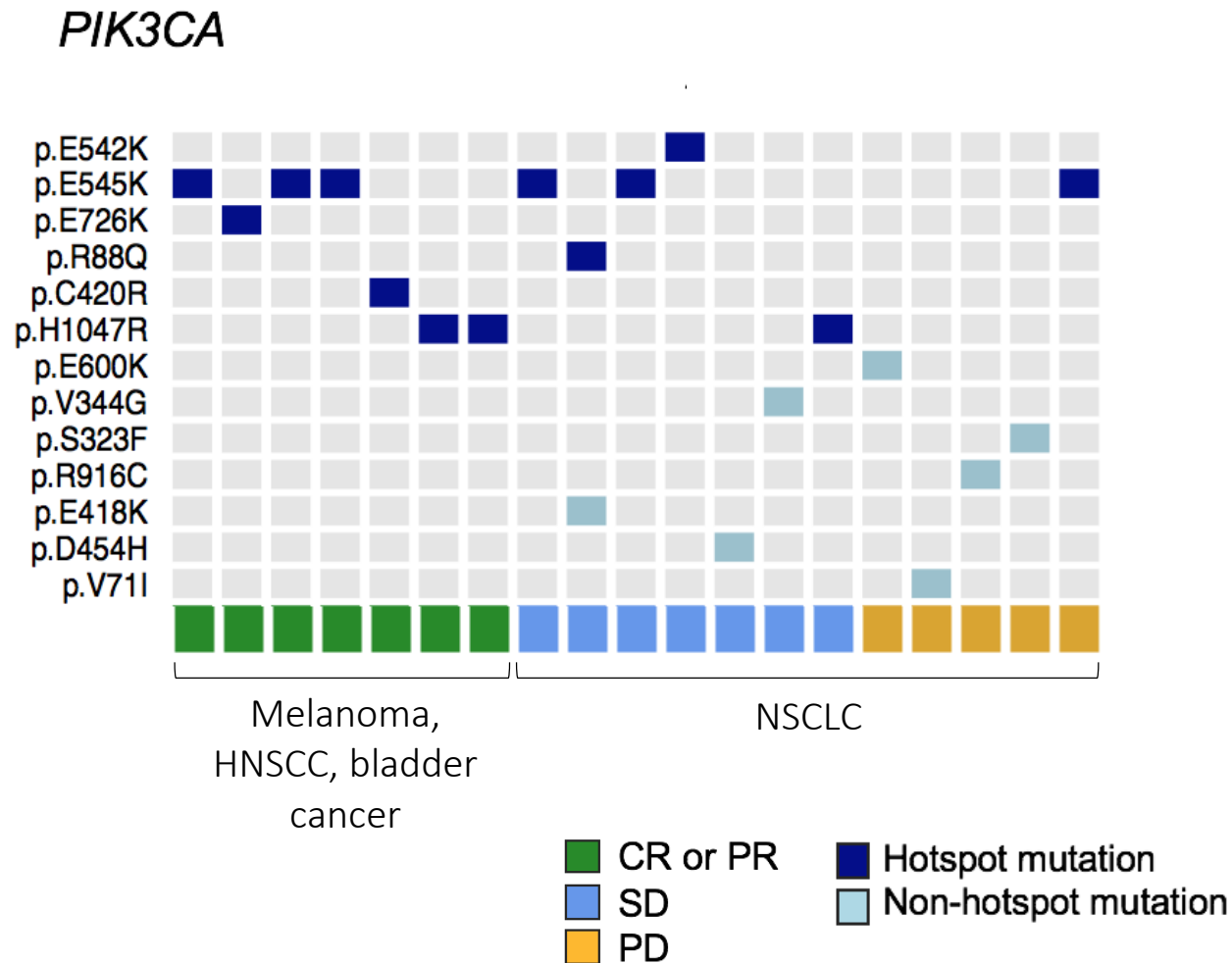


- Numerous interactions suggest complex interplay with other modifiers in distinct clinical contexts
- Additional lineage-specific, tumor heterogeneity, and microenvironmental factors at play
- Functional and larger clinical investigations needed/underway
- **NOT A CLINICAL BIOMARKER!**

PI3K/PTEN and cancer immunotherapy resistance?



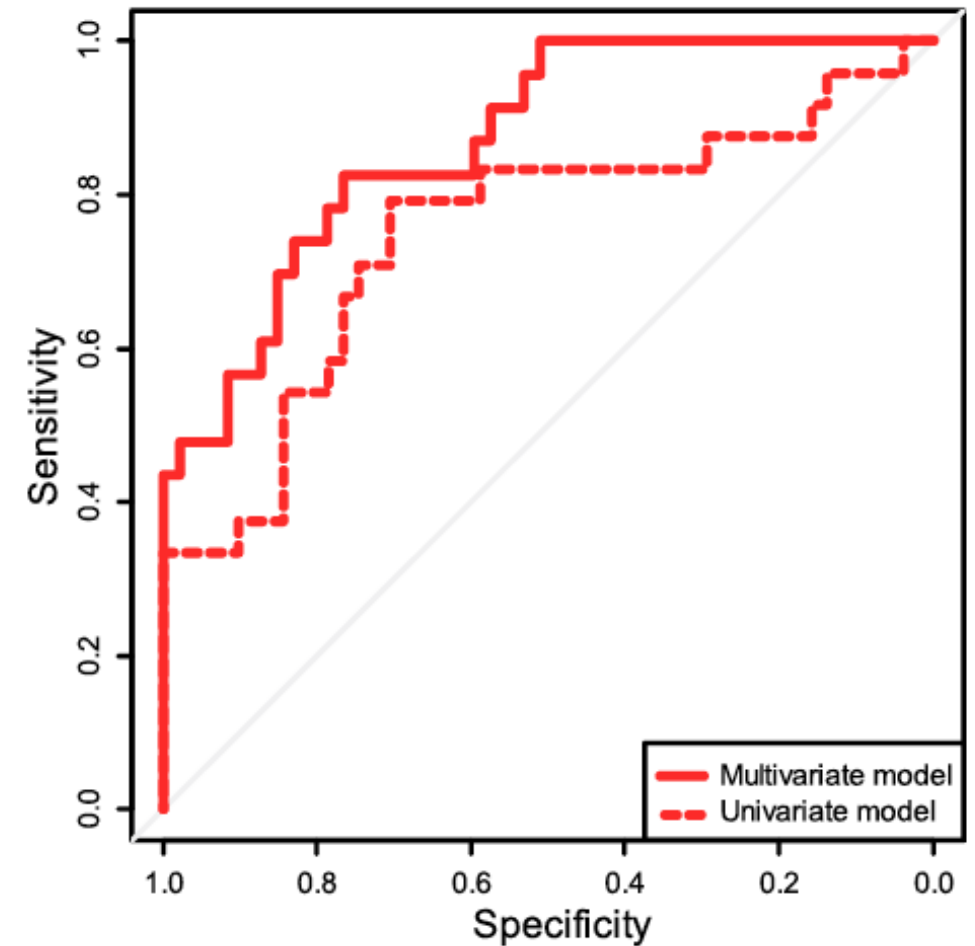
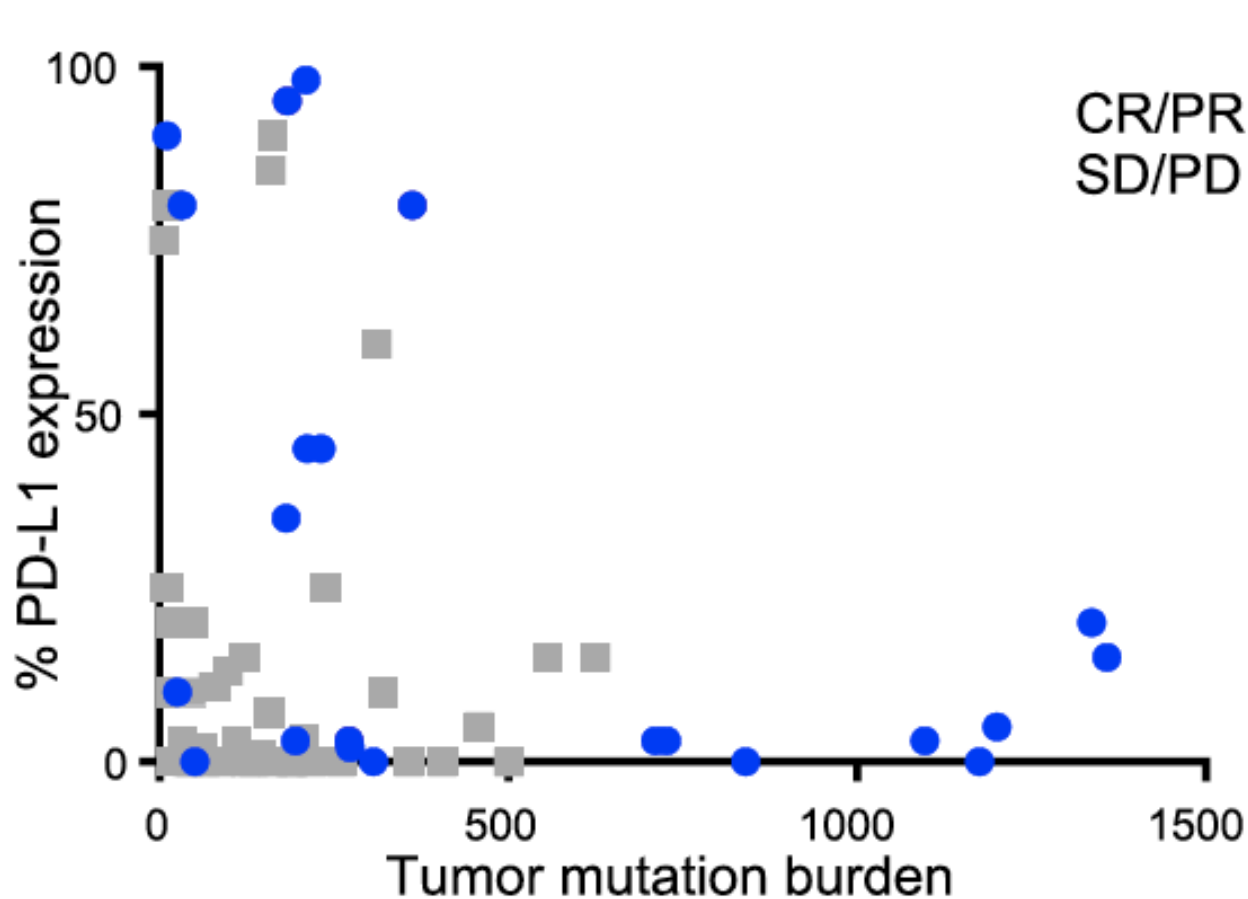
Placing single-gene correlates in broader molecular contexts



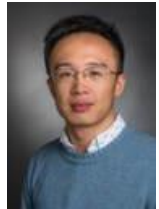
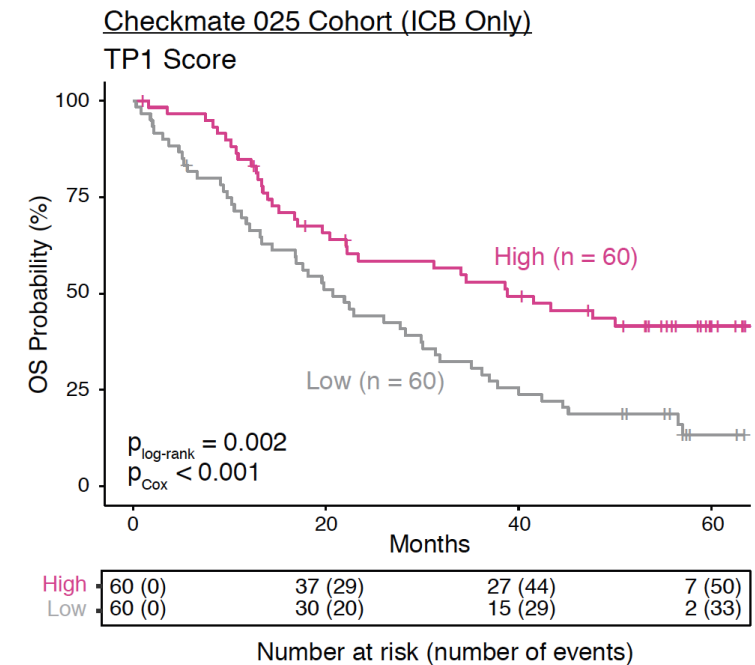
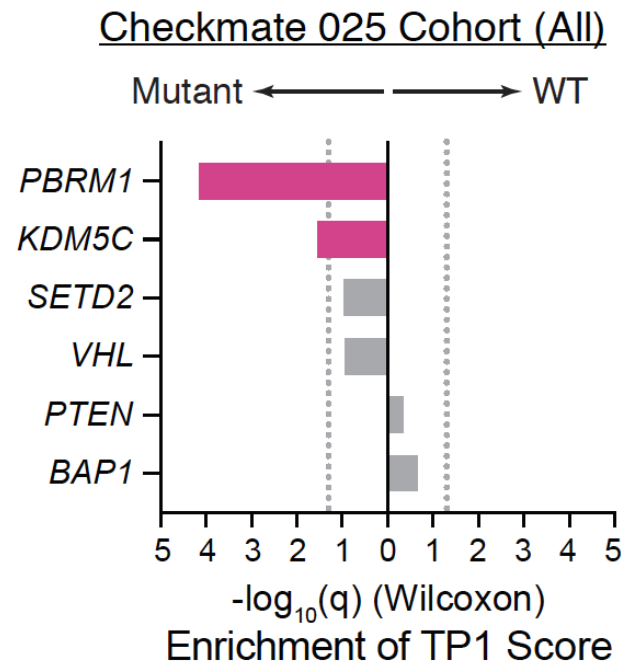
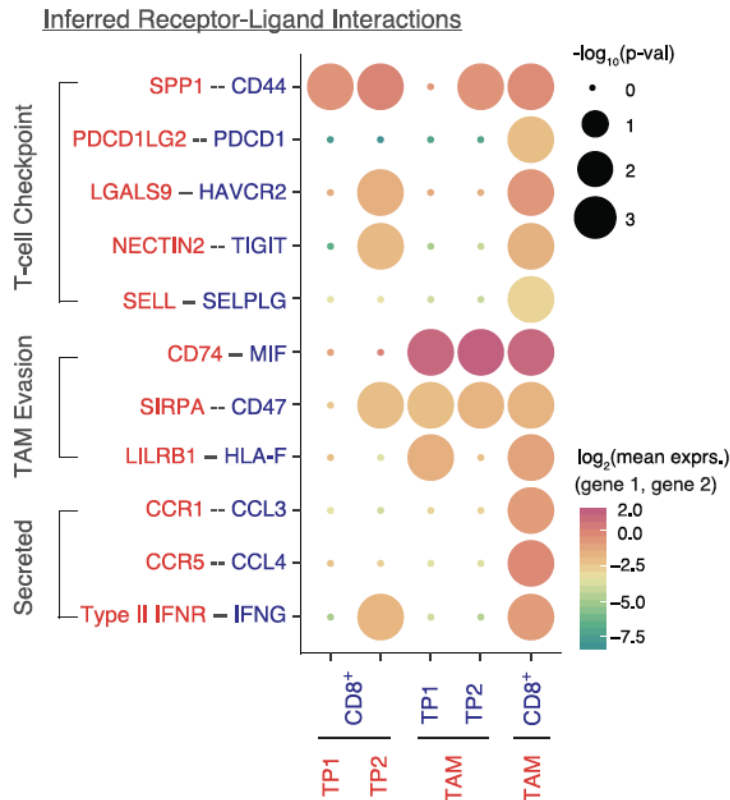
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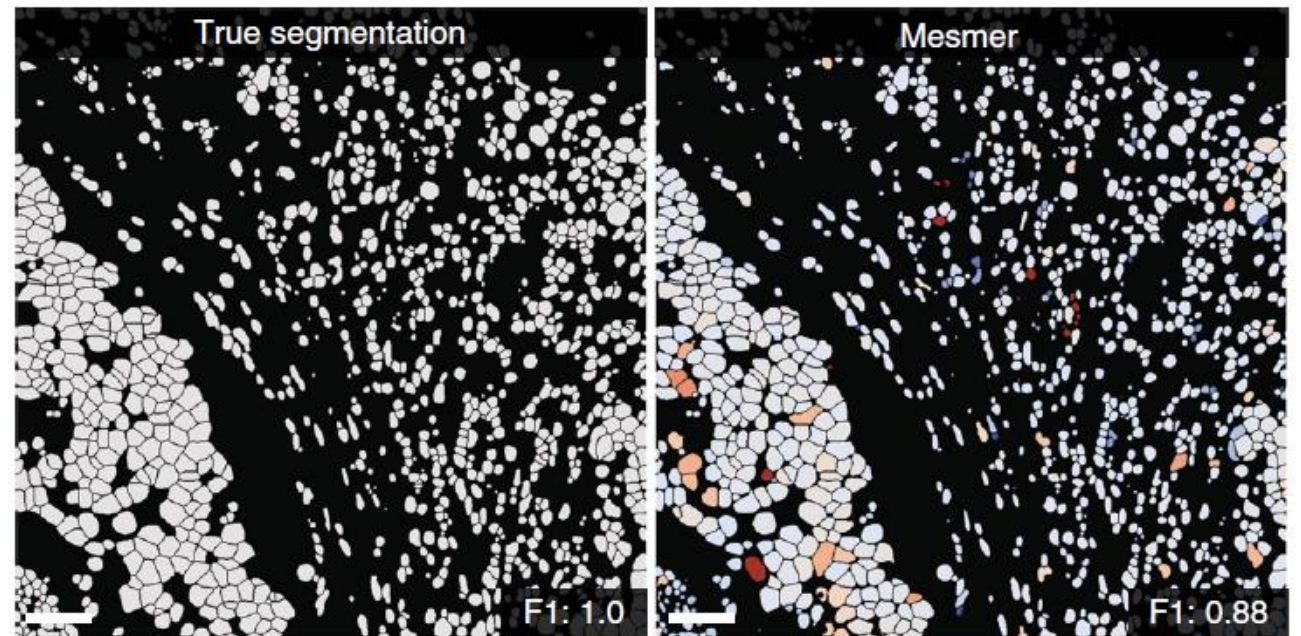
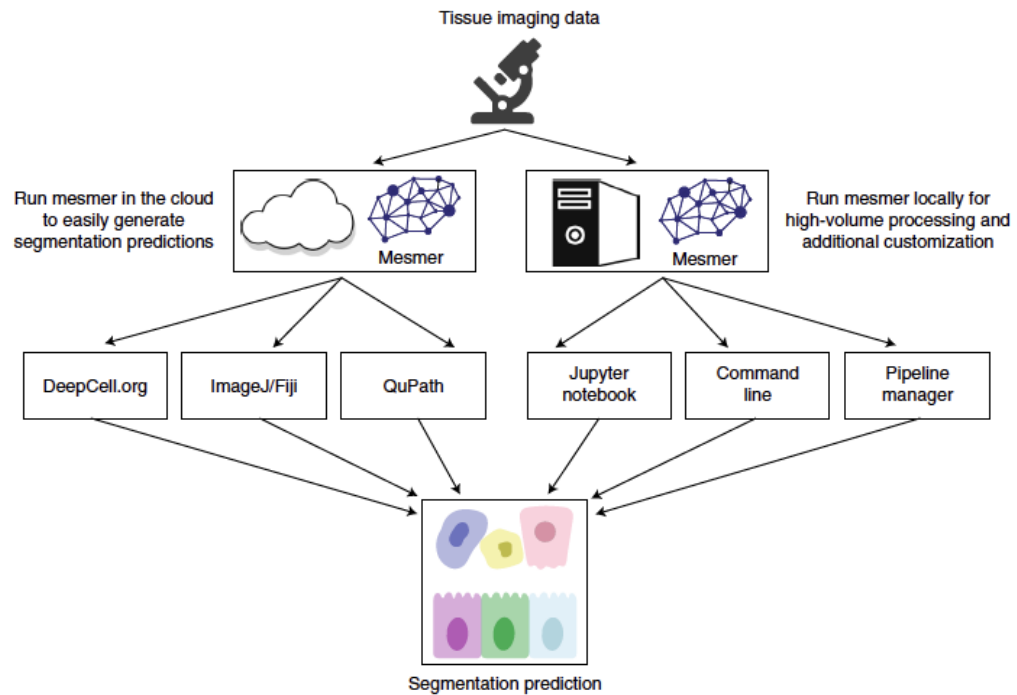
From “first order” genomics to integrated tumor-immune representations



Linking transcriptional programs, mutations, and clinical outcomes

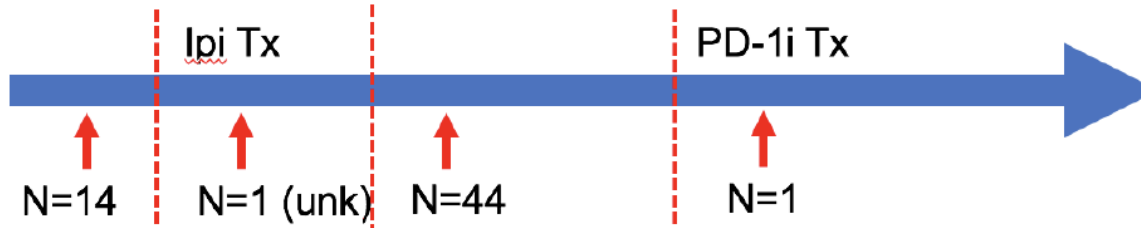


Toward convergent spatial representations of integrated molecular states

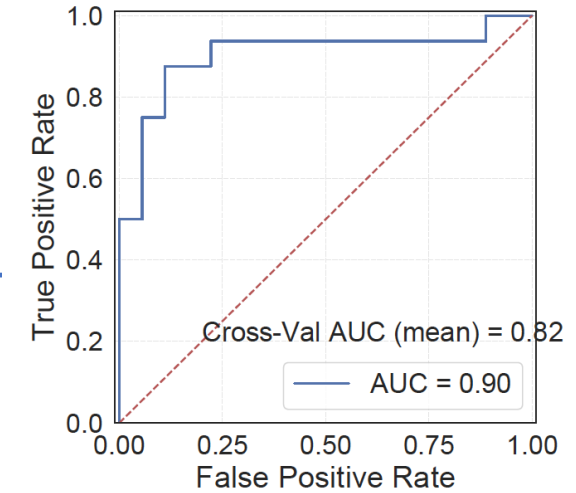
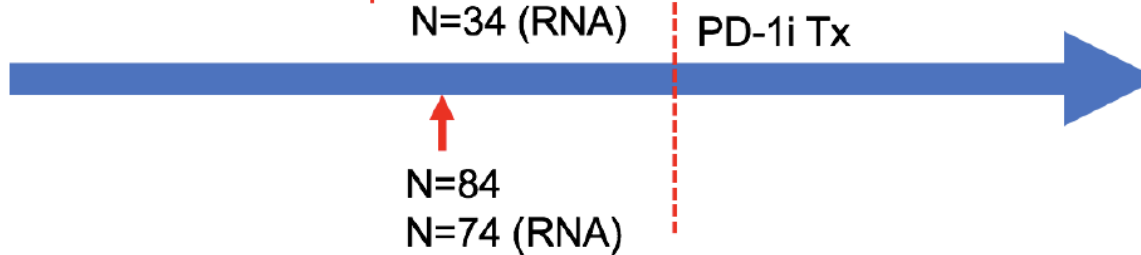


Linking integrated molecular representations with complete clinical features

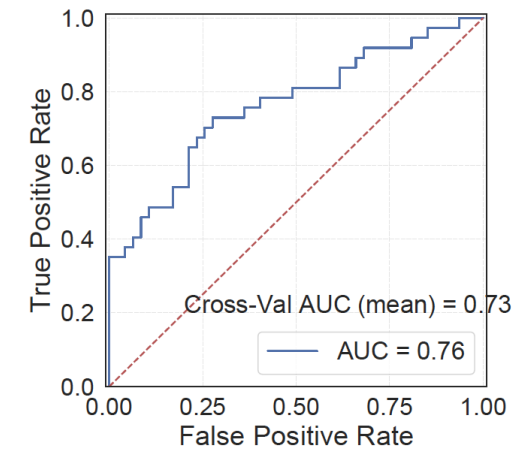
Ipilimumab-
Pretreated
(n=60)



Ipilimumab-
Naive
(n=84)



(MHC-II, LN Met, LDH)

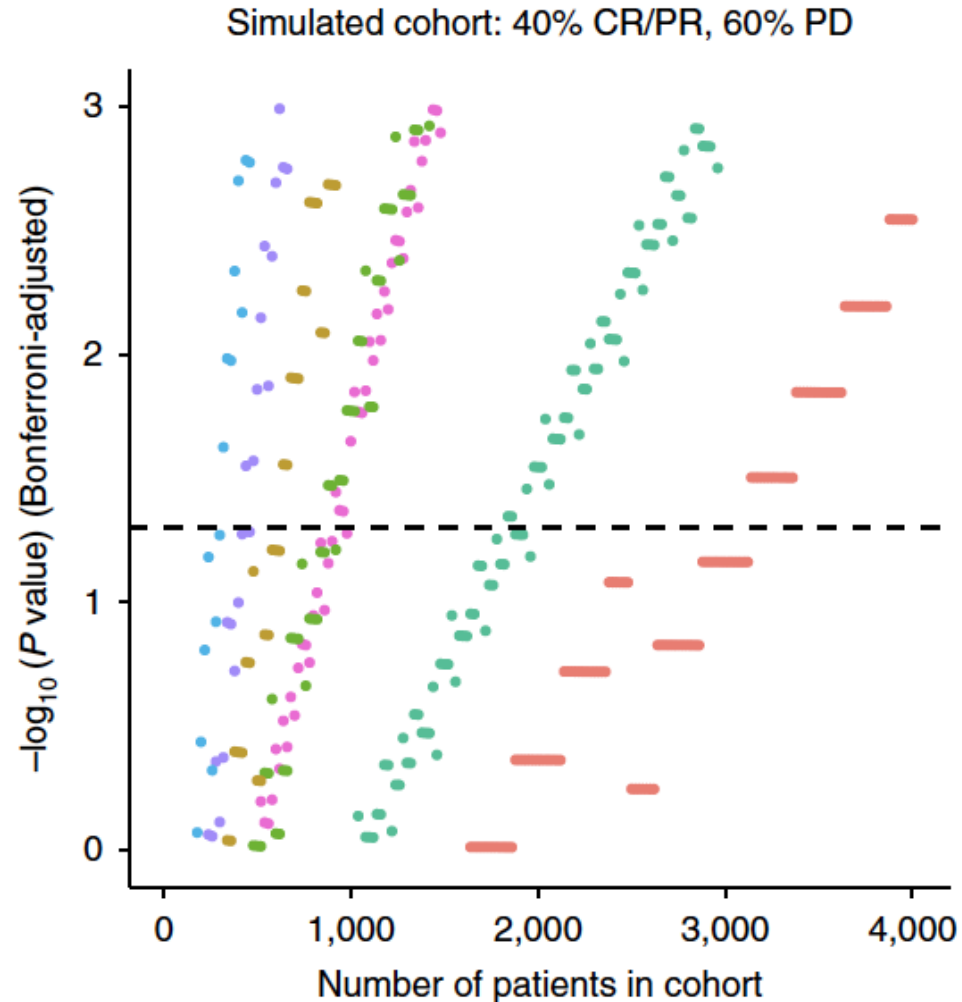


(heterogeneity, ploidy, purity)

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More (and better!) data needed



Prevalence of mutation

1% CR/PR, 0.01% PD

5% CR/PR, 0.5% PD

5% CR/PR, 1% PD

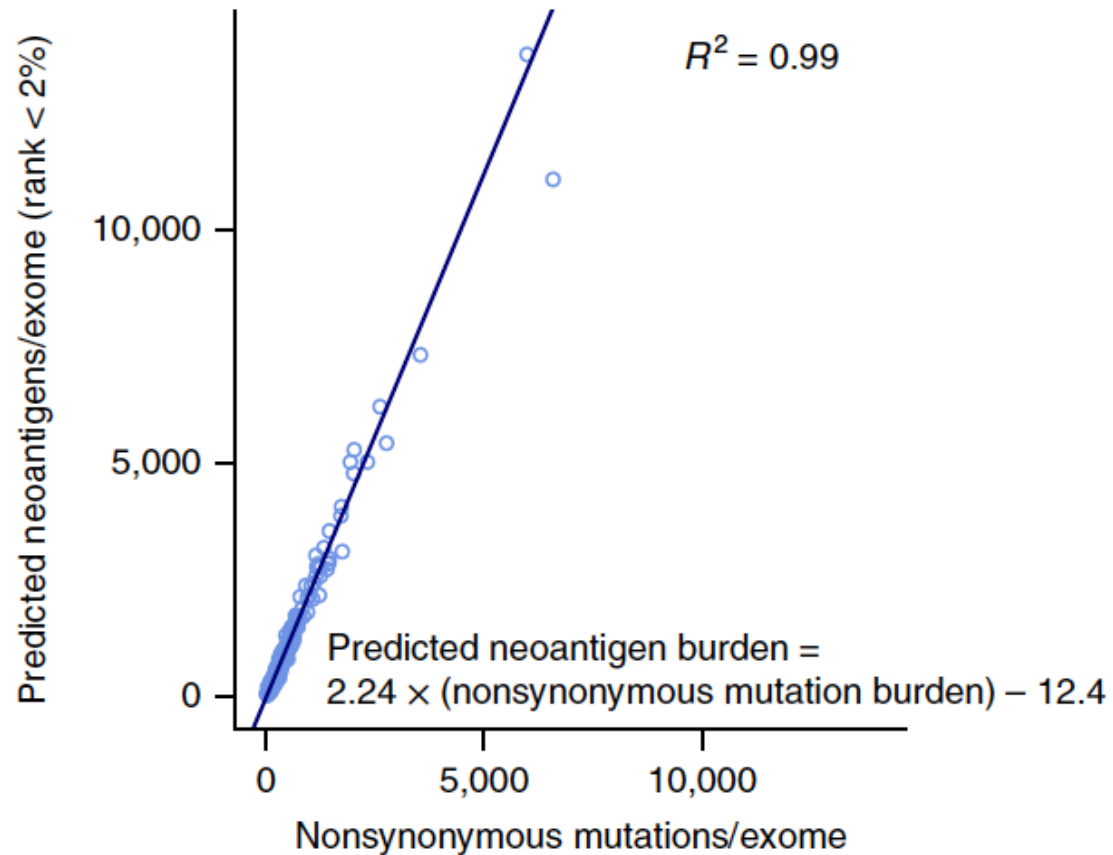
5% CR/PR, 2% PD

10% CR/PR, 1% PD

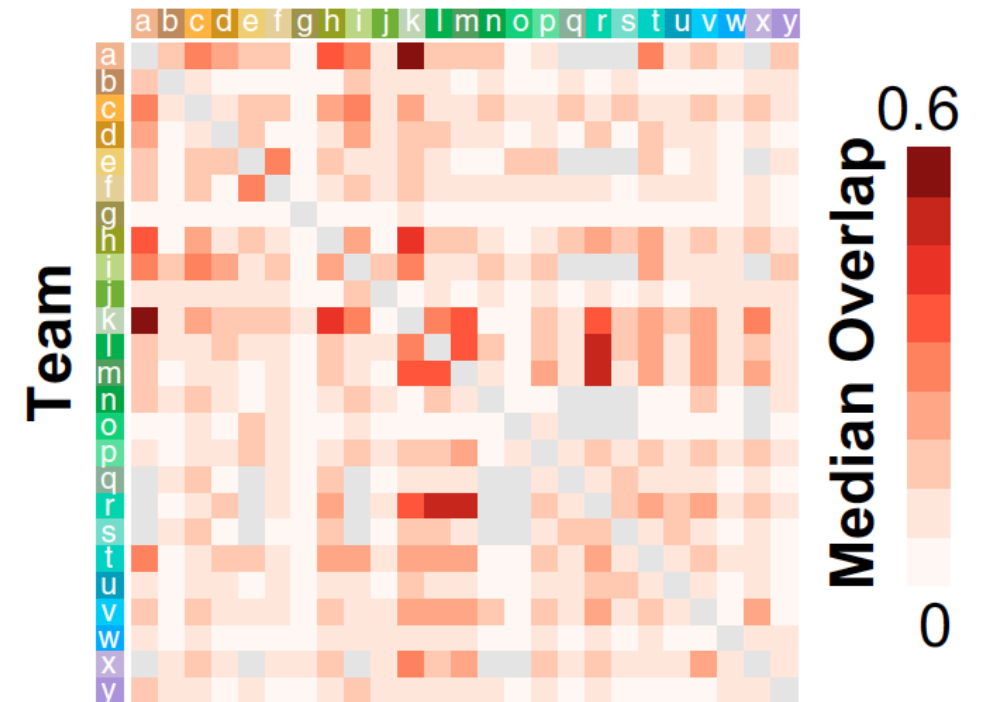
10% CR/PR, 2% PD

10% CR/PR, 4% PD

Considering genomics and neoantigen discovery

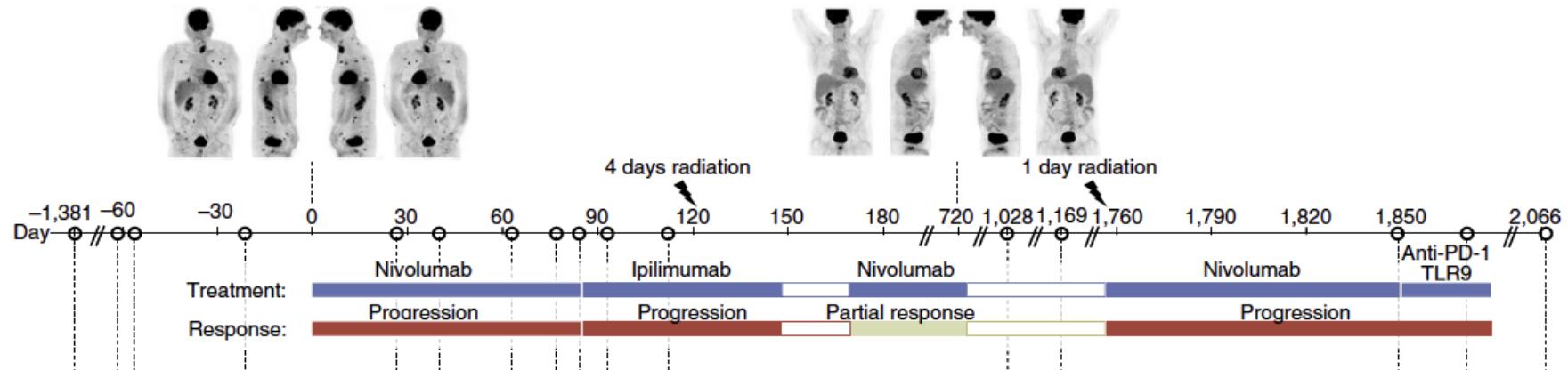


Miao, Margolis, Vokes et al *Nature Genetics* 2018

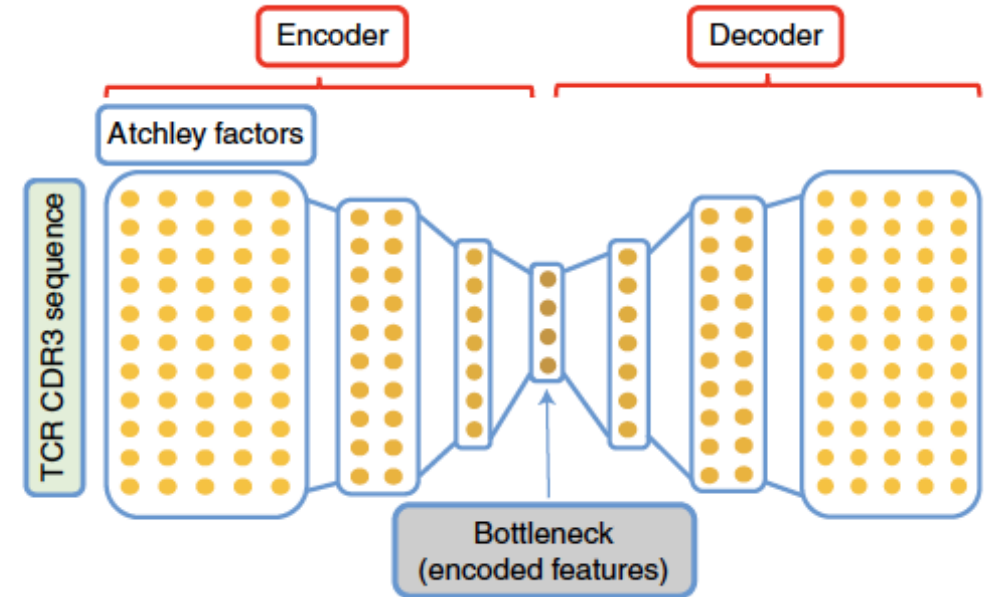
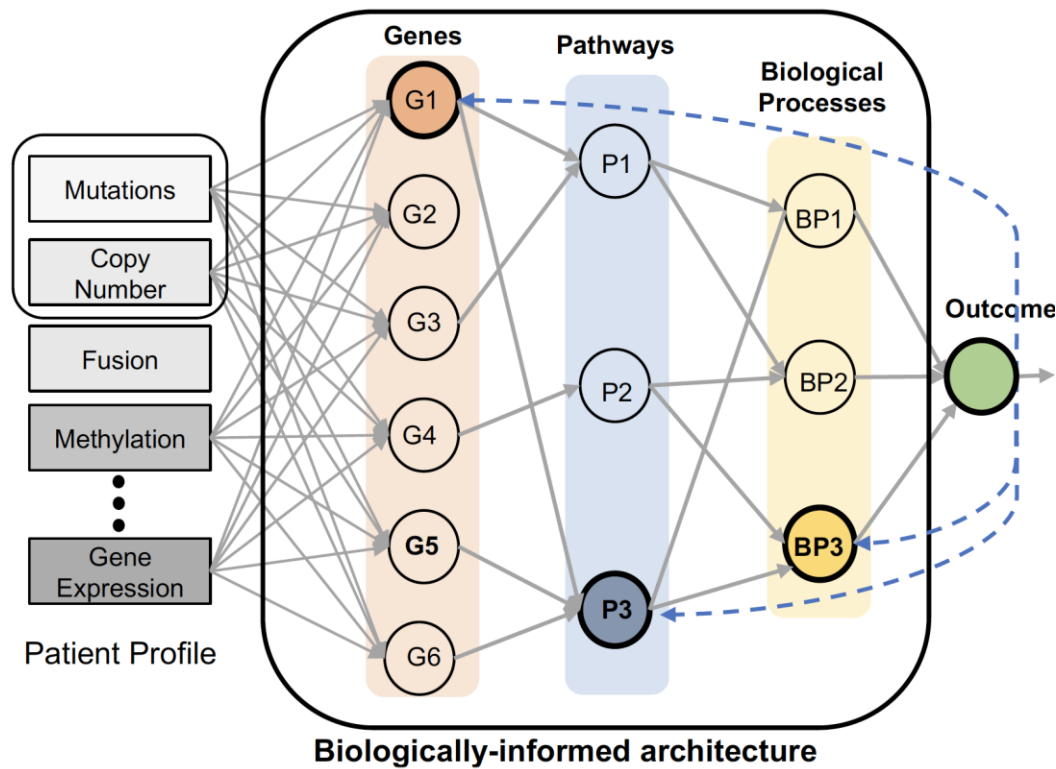


Well et al *Cell* 202

Considering resistance heterogeneity

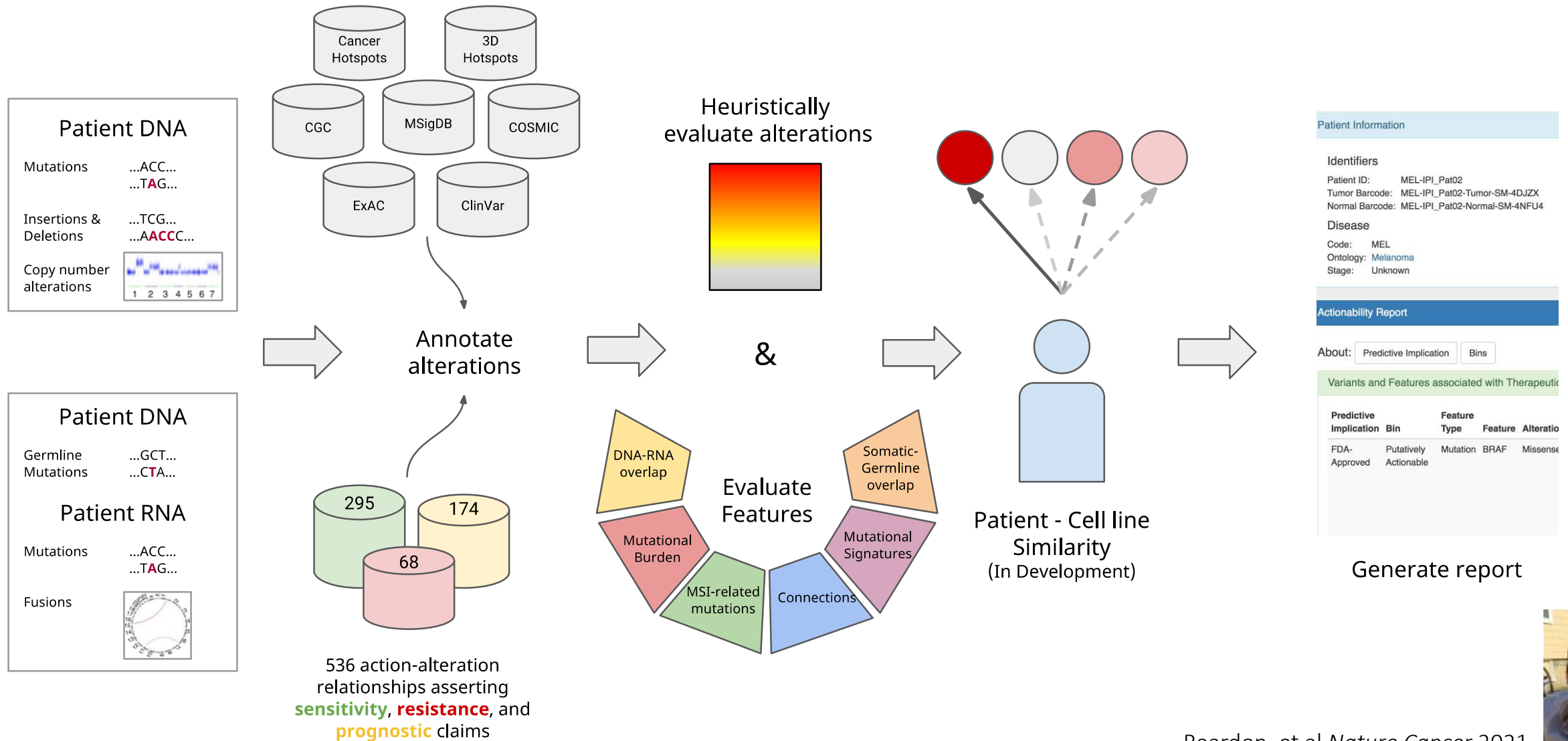


Toward integrating biology and machine learning for immunogenomics discovery



A Molecular Oncology Almanac

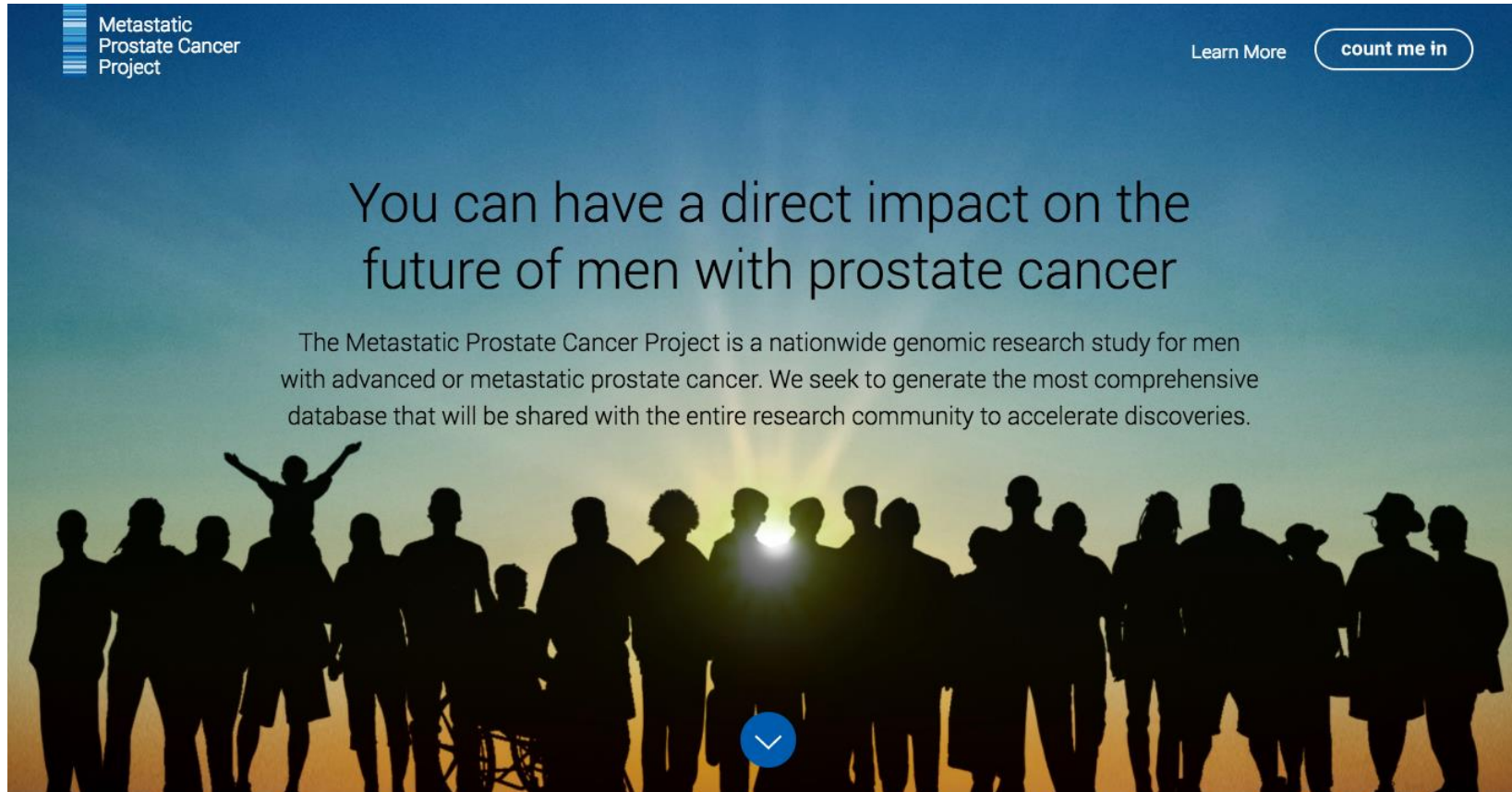
www.moalmanac.org



Reardon, et al *Nature Cancer* 2021



Toward representative clinicogenomic cohorts: The Metastatic Prostate Cancer Project & Count Me In

A banner for the Metastatic Prostate Cancer Project. The background is a blue-to-orange gradient with silhouettes of a diverse group of people at the bottom. The text is centered and reads: "You can have a direct impact on the future of men with prostate cancer". Below this, a paragraph states: "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." In the top left corner is the "Metastatic Prostate Cancer Project" logo. In the top right corner are links for "Learn More" and "count me in". A blue downward arrow icon is centered near the bottom of the banner.

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.



www.mpcproject.org

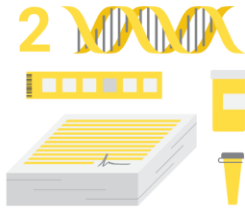
joincountmein.org

The Metastatic Prostate Cancer Project

MPCProject.org



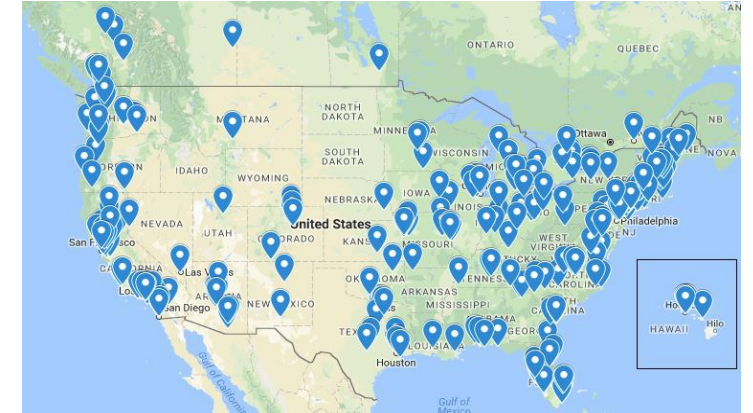
Step 1.
Tell us about yourself



Step 2.
Give us permission to collect your samples and data



Step 3.
Learn with us along the way

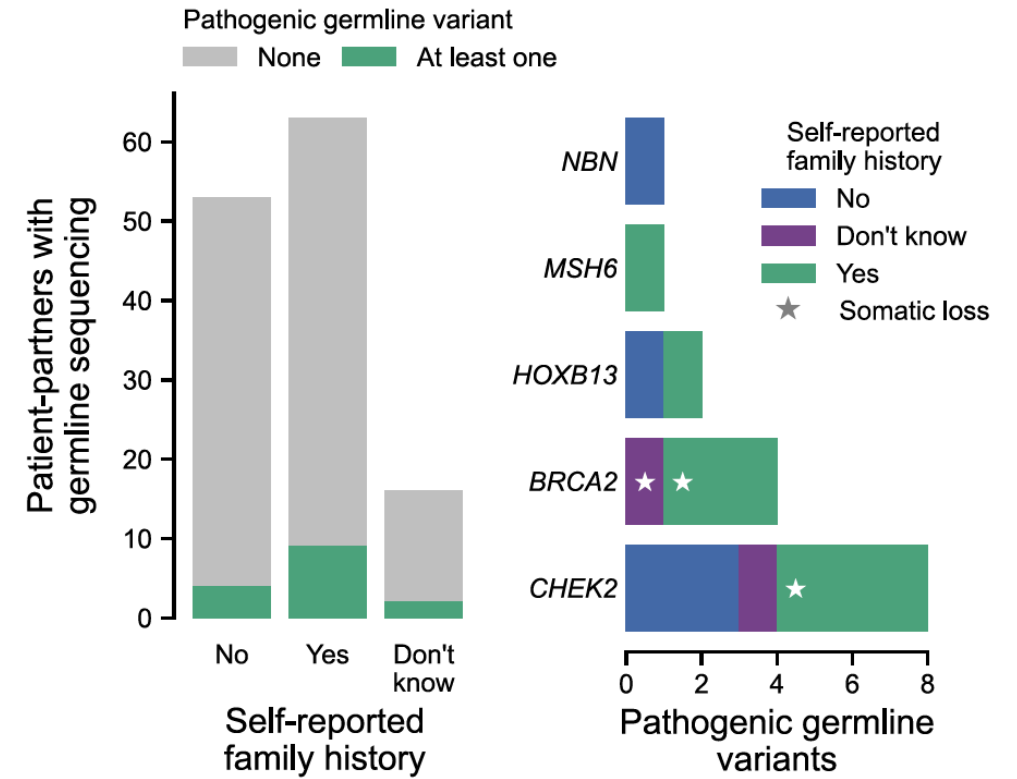
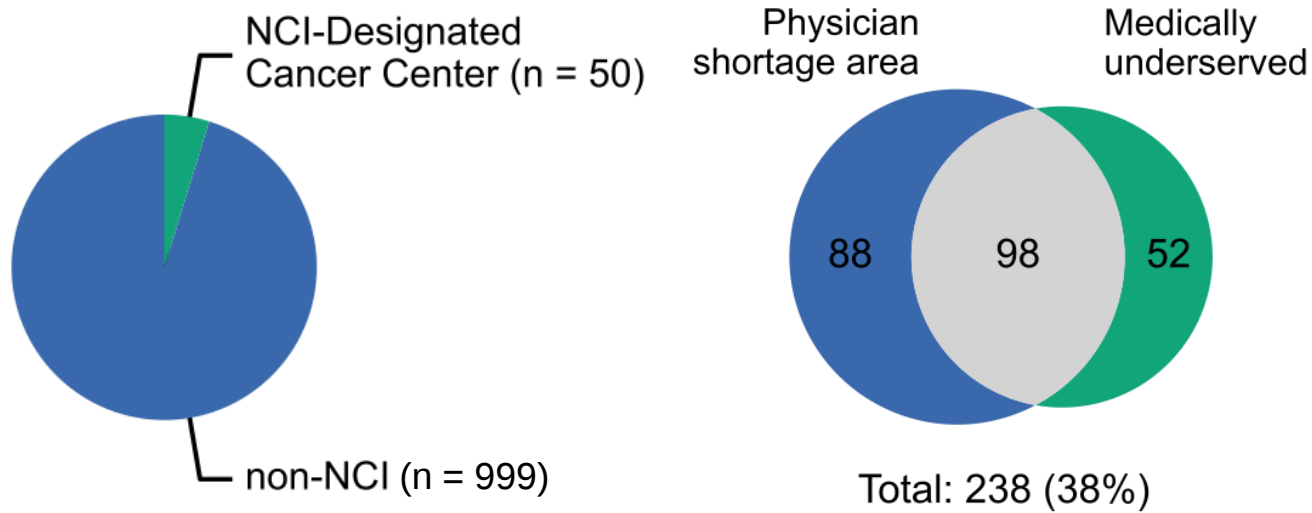


*Over 1100 men with
metastatic prostate cancer
have joined the MPCproject
since our launch in January
2018*

<http://www.mpcproject.org>
@PrCaProject

The Metastatic Prostate Cancer Project

MPCproject.org



Acknowledgements

The Patients



Let's work together!
vanallenlab.dana-farber.org
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Van Allen Lab

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+ Alumni!

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Firehose Team
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Kris Cibulskis
Carrie Cibulskis
Will Gibson
Jesse Boehm
Many others...



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Entire CCPM team
Entire HTAN team
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Matthew Mossanen
Steve Chang
Mark Preston
Chris Sweeney
Many others...



Friends Near & Far

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Elizabeth Plimack
Phil Abbosh
Leandro Colli
Many others...

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- Type your question in the Q&A box, then click “Send”
- Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)

