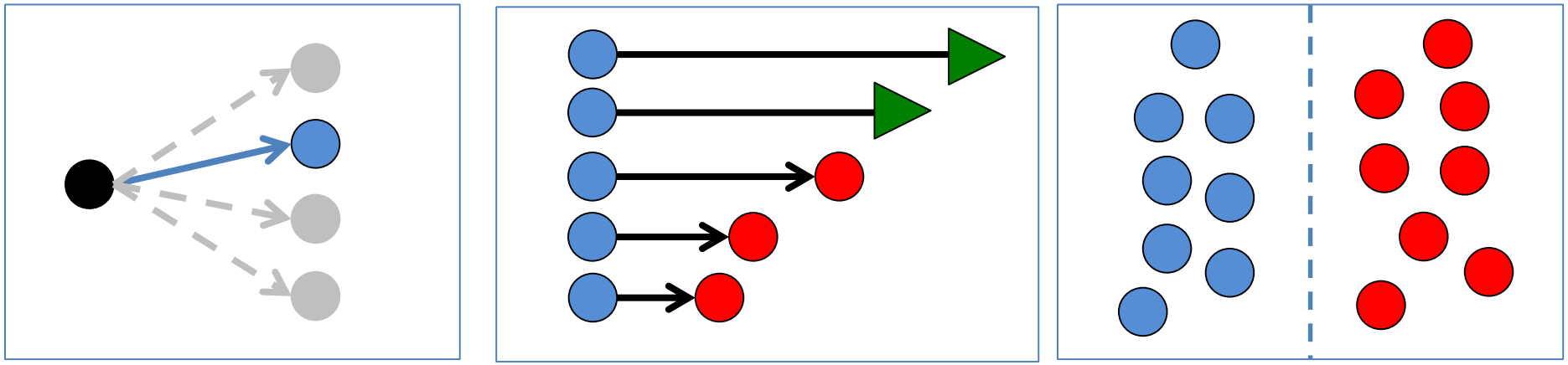
Clinical interpretation of the cancer genome for precision oncology



Eliezer (Eli) Van Allen, MD
Assistant Professor
Harvard Medical School
Dana-Farber Cancer Institute
Broad Institute of MIT and Harvard

June 13, 2016

vanallenlab.dana-farber.org

@VanAllenLab

DANA-FARBER CANCER INSTITUTE

BROAD INSTITUTE

Disclosures

- Consulting/Advisory
  - Syapse
  - Roche Ventana
  - Third Rock Ventures
- Equity holder in Microsoft
  - Five shares for my bar-mitzvah in 1993
  - Thanks to the Gros family!

Disclosures

STANFORD UNIVERSITY
SYMBOLIC SYSTEMS PROGRAM

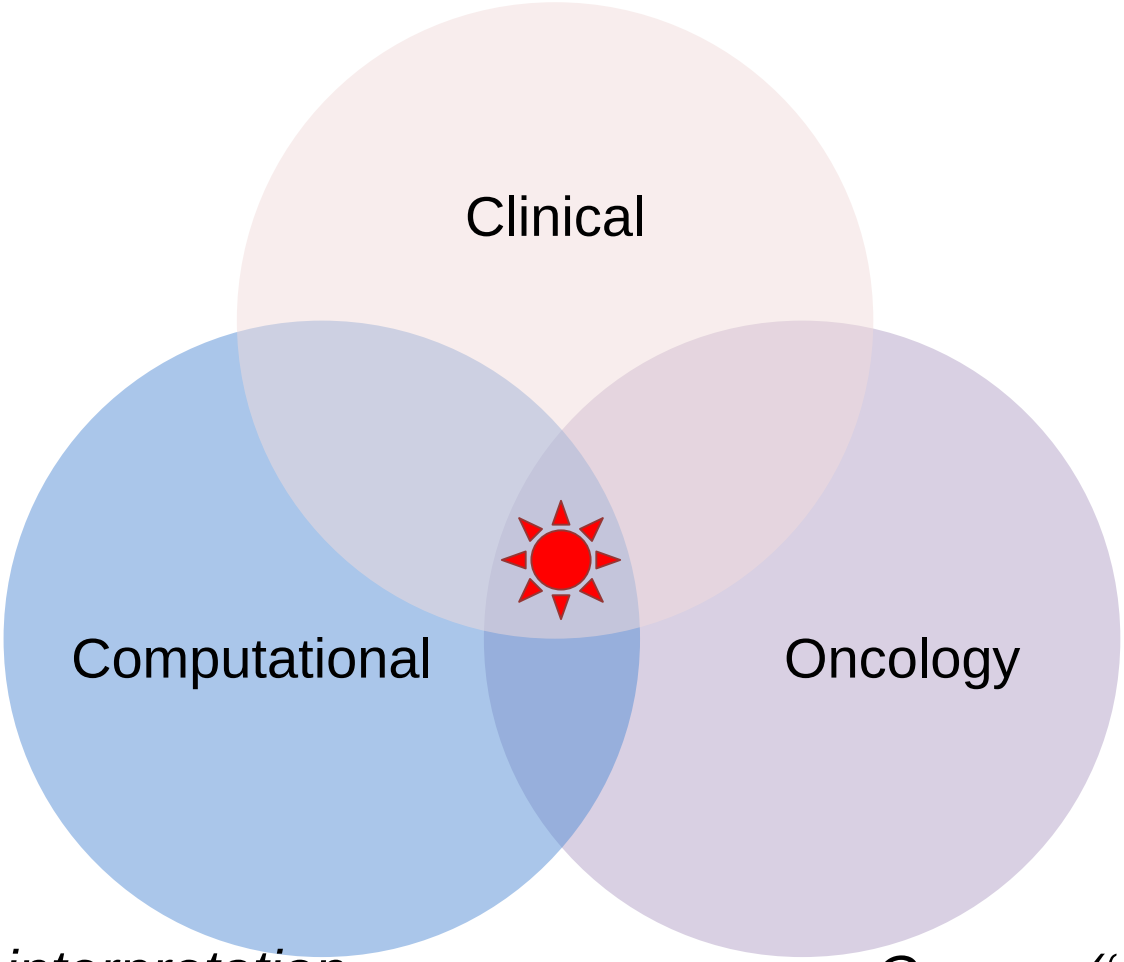
‘03

Google™

Camp Kesem

For children of patients who have/had cancer → …

Sampling patients directly



Analysis + interpretation algorithms

Cancer (‘omic) biology

Precision medicine

The use of:

genomic technology

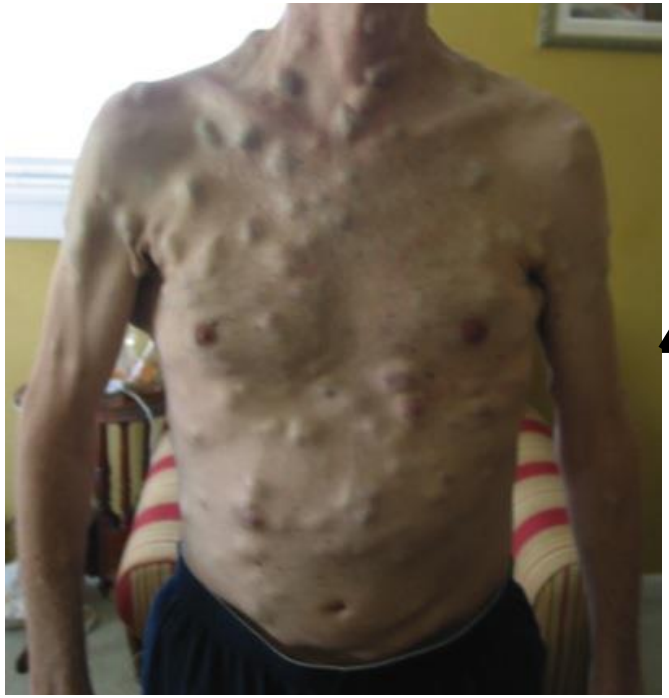
and

large-scale data

to guide:

1) individualized patient care
2) new discoveries

Precision cancer medicine: A paradigm shift

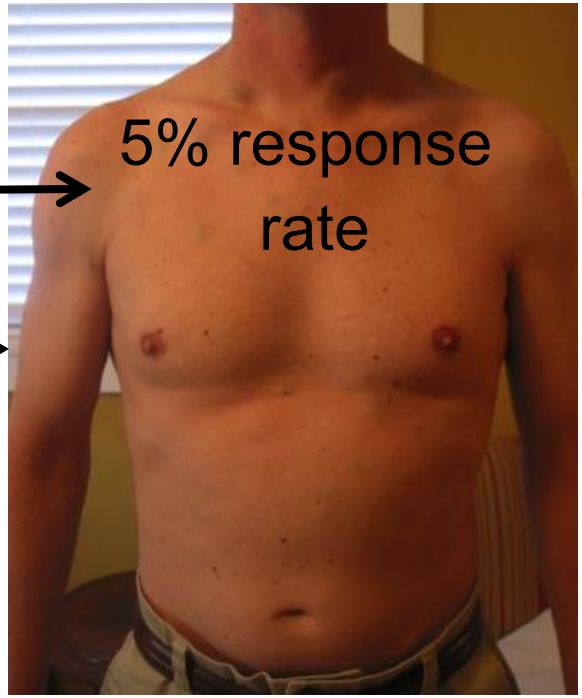


Past
Dacarbazine

5% response rate

Present

BRAF^{V600E}
Vemurafenib



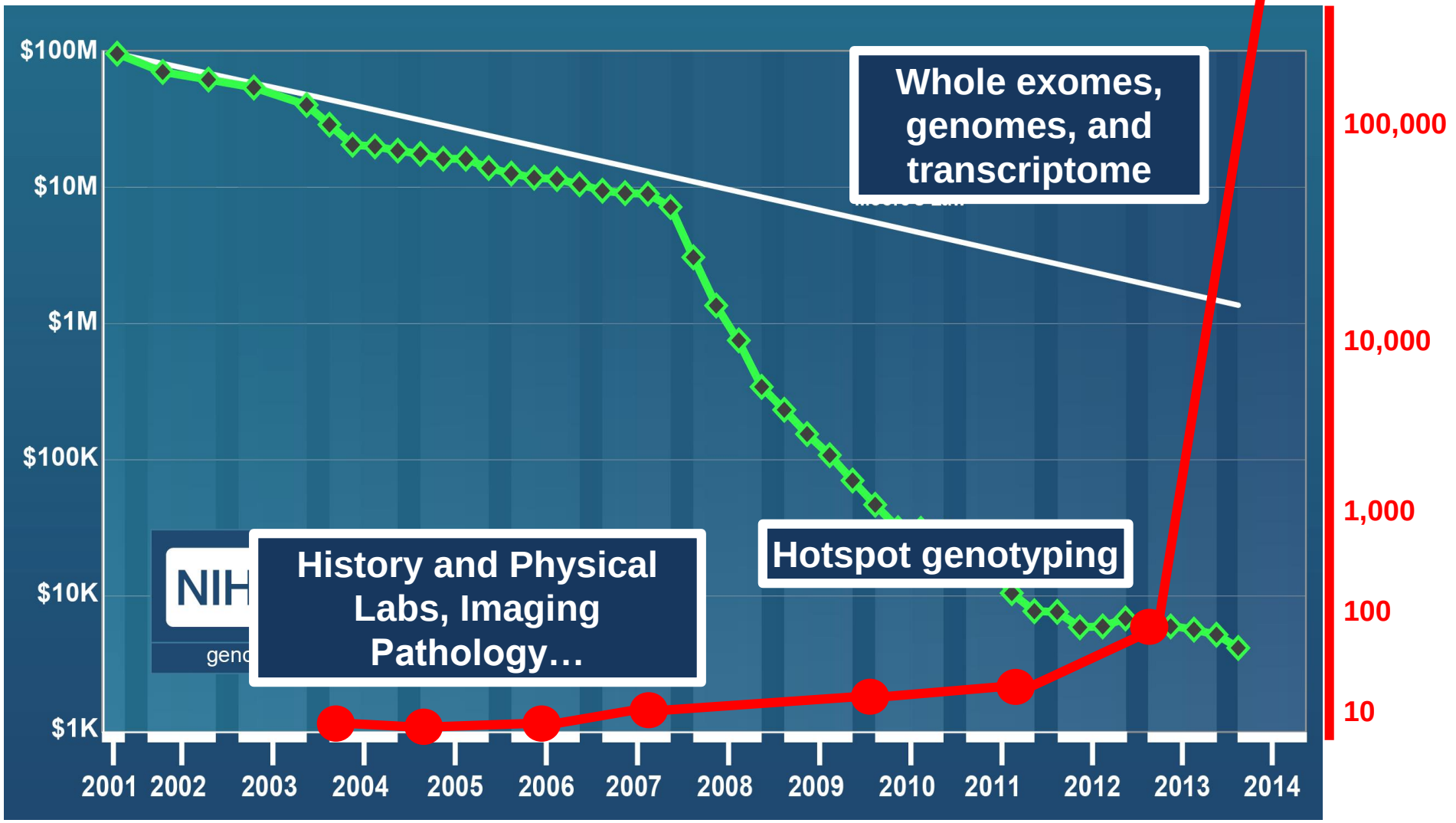
Wagle, Emery, et. al JCO 2011

Precision cancer medicine: A paradigm shift

EGFR	→	erlotinib
BCR-ABL	→	imatinib
ALK	→	crizotinib
HER2	→	trastuzumab
BRAF	→	vemurafenib
MEK1/2	→	trametinib
…		…

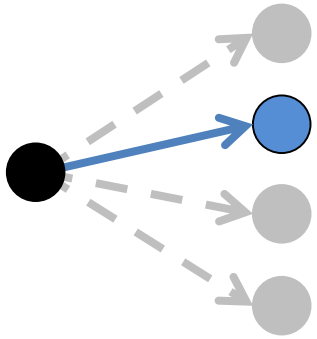
If one gene is good…

Clinical data explosion



Source: NHGRI

Question #1



Can large-scale genomics guide individualized patient care in oncology?

= one patient

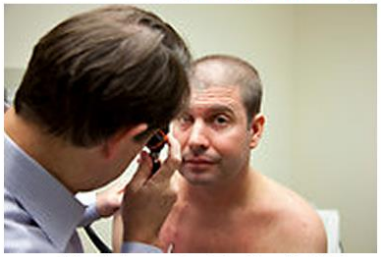
Clinical interpretation (ca. 2012)

In Treatment for Leukemia, Glimpses of the Future

Second Chance: Lukas Wartman, a leukemia doctor and researcher, developed the disease himself. As he faced death, his colleagues sequenced his cancer genome. The result was a totally unexpected treatment.

New York Times; July 7, 2012

Clinical interpretation (ca. 2012)



Dilip Vishwanat for The New York Times

Dr. Lukas Wartman, a leukemia patient in remission, being examined by his doctor, John DiPersio, in January in St. Louis.

Enlarge This Image

Sid Hastings for The New York Times

"I was definitely scared. It was so unreal," said Dr. Wartman on first suspecting that he had leukemia, the very disease he had devoted his medical career to studying.

Enlarge This Image

NOW PLAYING

Why not throw everything we have at seeing if we can find a rogue gene spurring Dr. Wartman's cancer, adult acute lymphoblastic leukemia, he asked? "It's now or never," he recalled telling them. "We will only get one shot."

Dr. Ley's team tried a type of analysis that they had never done before. They fully sequenced the genes of both his cancer cells and healthy cells for comparison, and at the same time analyzed his RNA, a close chemical cousin to DNA, for clues to what his genes were doing.

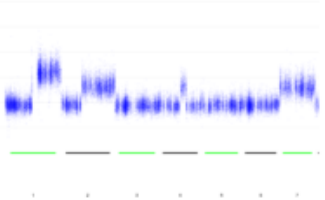
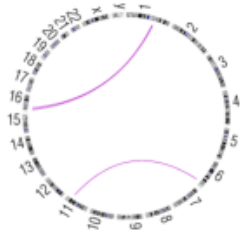
The researchers on the project put other work aside for weeks, running one of the university's 26 sequencing machines and supercomputer around the clock. And they found a culprit — a normal gene that was in overdrive, churning out huge amounts of a protein that appeared to be spurring the cancer's growth.

Even better, there was a promising new drug that might shut down the malfunctioning gene — a drug that had been tested and approved only for advanced kidney cancer. Dr. Wartman became the first person ever to take it for leukemia.

And now, against all odds, his cancer is in remission and has been since last fall.

New York Times; July 7, 2012

The deranged cancer genome

		Per patient
Mutations	…ACC… …TAG…	*10s– 1000s*
Insertion/ deletions	…TCG… …AACCC…	*1s– 1000s*
Copy number alterations		*10s– 1000s*
Rearrangements		*1s– 1000s*

Manual interpretation → not scalable

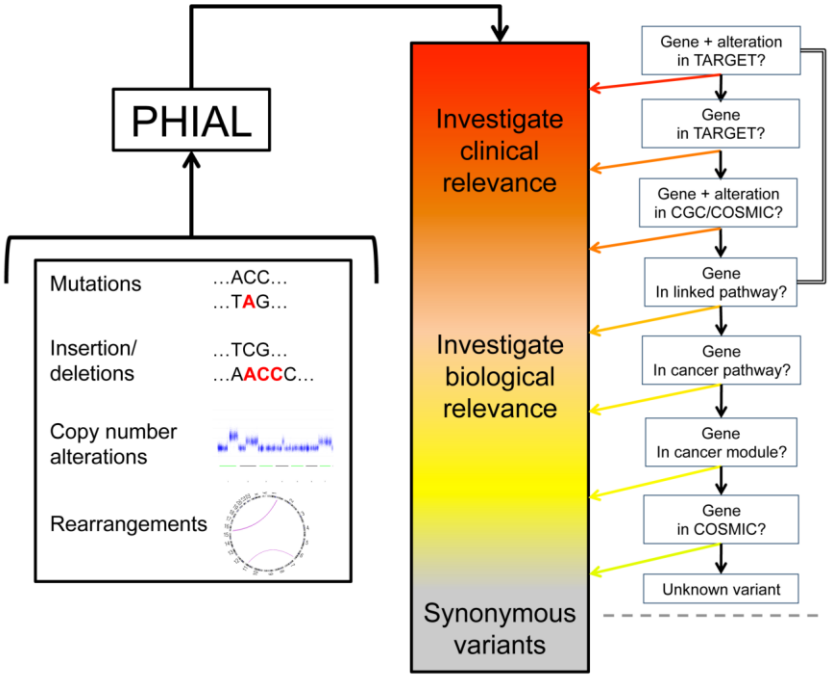
PHIAL

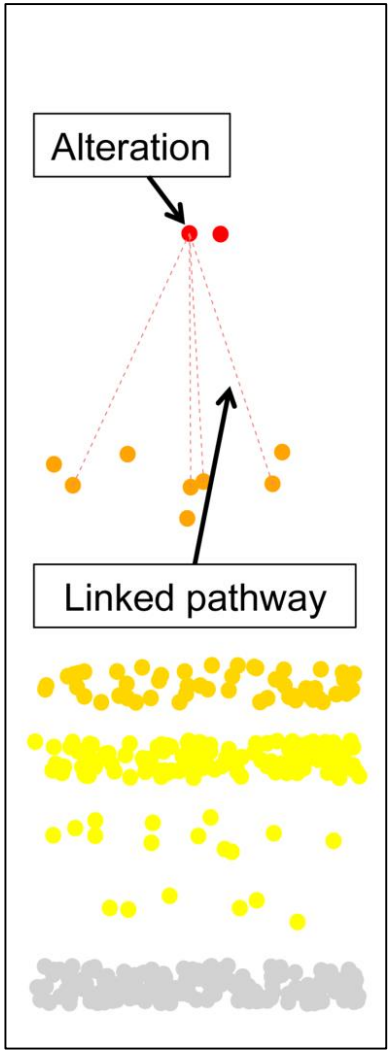
Precision **H**euristics for **I**nterpreting the **A**lteration **L**andscape

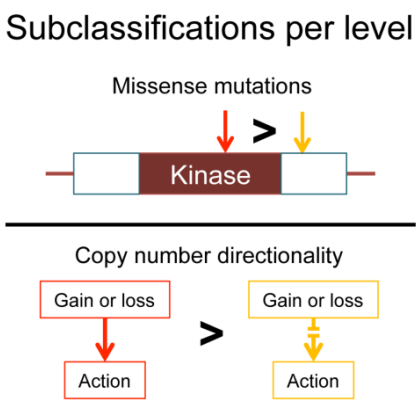
“May it be a light to you in dark places, when all other lights go out.”[1]

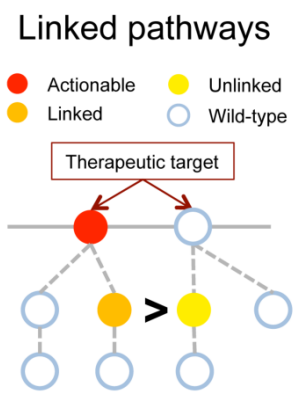
[1]Galadriel, *in* Tolkien, *The Fellowship of the Ring*

PHIAL





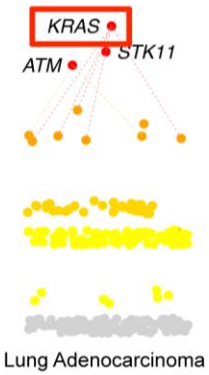




Van Allen, Wagle, et al. *Nature Medicine* 2014

Impact on clinical decision-making

a



KRAS A146V

- Rare activating alteration
- Not detected with deployed profiling technologies

Cancer Cell
Article

A Synthetic Lethal Interaction between K-Ras Oncogenes and Cdk4 Unveils a Therapeutic Strategy for Non-small Cell Lung Carcinoma

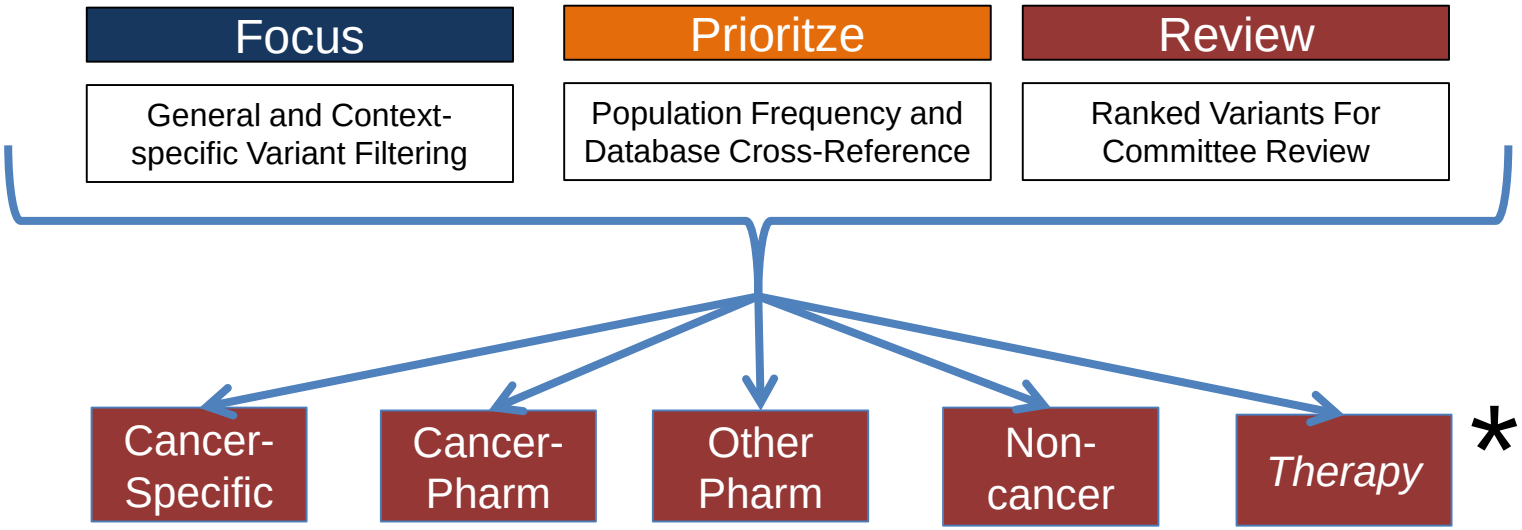
Cell PRESS

David Barbie
Leena Ghandi

Inherited genomics and interpretation

Tumor genome **-** Inherited genome **=** *Tumor-only mutations*

20,000-50,000 inherited variants per patient



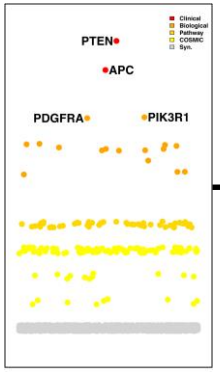
Van Allen et al AACR 2013

Role for inherited genomics in treatment decision-making

Metastatic prostate cancer patient

PHIAL

Tumor-only variants



PI3K inhibitor
AKT inhibitor
mTOR inhibitor

Exceptional responses in genomically-enriched cases!

Inherited variant

BRCA2* K3326
nonsense

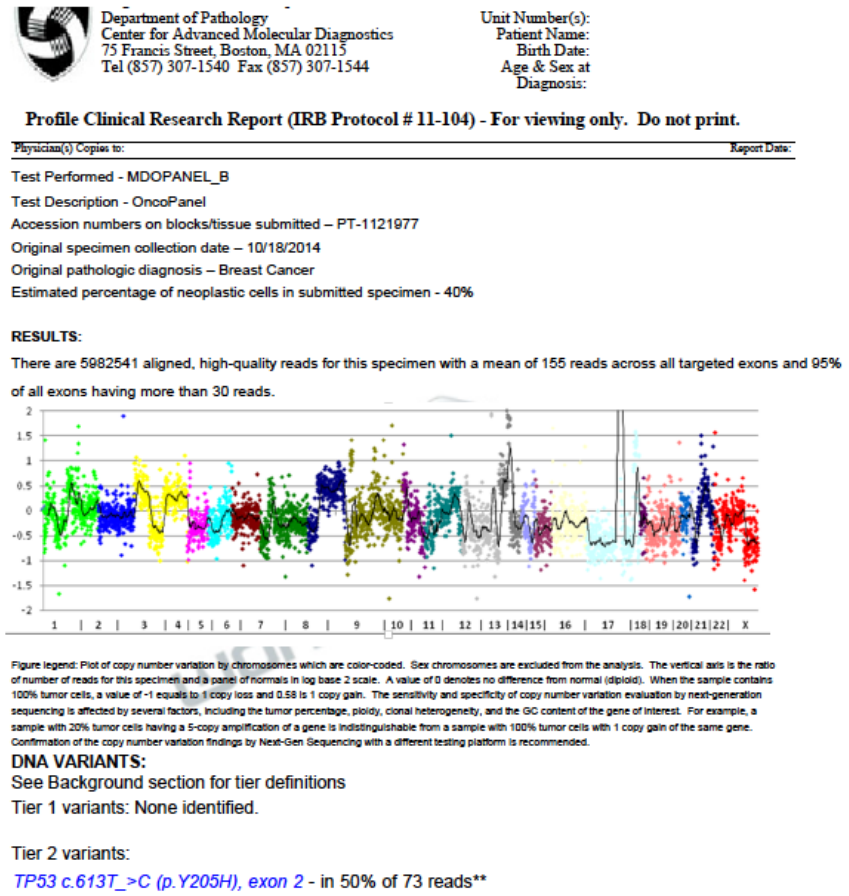
PARP inhibitor
Platinum chemotherapy

Van Allen, et al *Prostate Cancer Prostatic Dis*. 2014
Robinson, Van Allen, et al *Cell* 2015

Remember the consumer

Usability testing genomic reports

- “What do all those colors mean?”
- “Look at this actionable Tier 4 mutation!”
- “Which copy number events are important?”
- …



Department of Pathology
Center for Advanced Molecular Diagnostics
75 Francis Street, Boston, MA 02115
Tel (857) 307-1540 Fax (857) 307-1544

Unit Number(s):
Patient Name:
Birth Date:
Age & Sex at Diagnosis:

Profile Clinical Research Report (IRB Protocol # 11-104) - For viewing only. Do not print.

Physician(s) Copies to: Report Date:

Test Performed - MDOPANEL_B
Test Description - OncoPanel
Accession numbers on blocks/tissue submitted – PT-1121977
Original specimen collection date – 10/18/2014
Original pathologic diagnosis – Breast Cancer
Estimated percentage of neoplastic cells in submitted specimen - 40%

RESULTS:

There are 5982541 aligned, high-quality reads for this specimen with a mean of 155 reads across all targeted exons and 95% of all exons having more than 30 reads.

Figure legend: Plot of copy number variation by chromosomes which are color-coded. Sex chromosomes are excluded from the analysis. The vertical axis is the ratio of number of reads for this specimen and a panel of normals in log base 2 scale. A value of 0 denotes no difference from normal (diploid). When the sample contains 100% tumor cells, a value of -1 equals to 1 copy loss and 0.58 is 1 copy gain. The sensitivity and specificity of copy number variation evaluation by next-generation sequencing is affected by several factors, including the tumor percentage, ploidy, clonal heterogeneity, and the GC content of the gene of interest. For example, a sample with 20% tumor cells having a 5-copy amplification of a gene is indistinguishable from a sample with 100% tumor cells with 1 copy gain of the same gene. Confirmation of the copy number variation findings by Next-Gen Sequencing with a different testing platform is recommended.

DNA VARIANTS:

See Background section for tier definitions

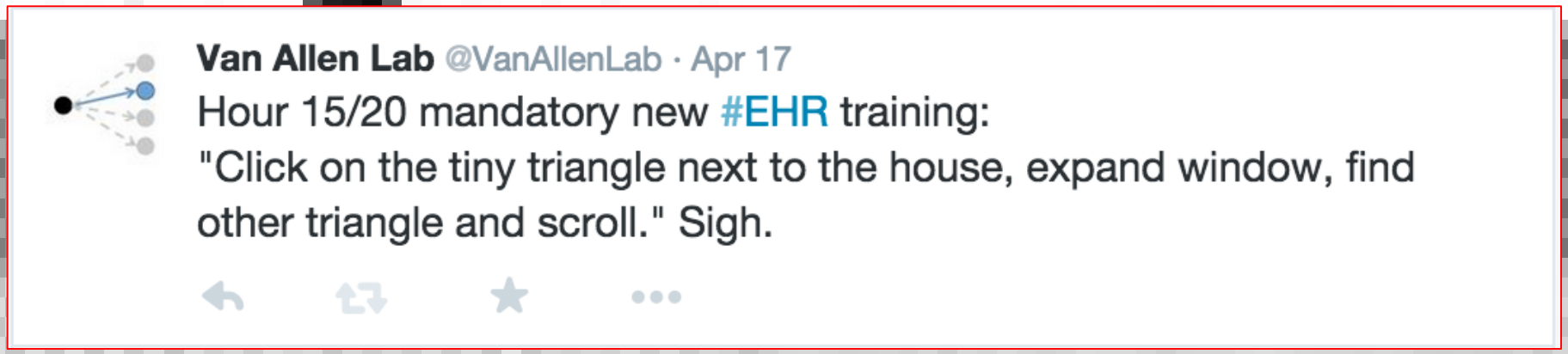
Tier 1 variants: None identified.

Tier 2 variants:

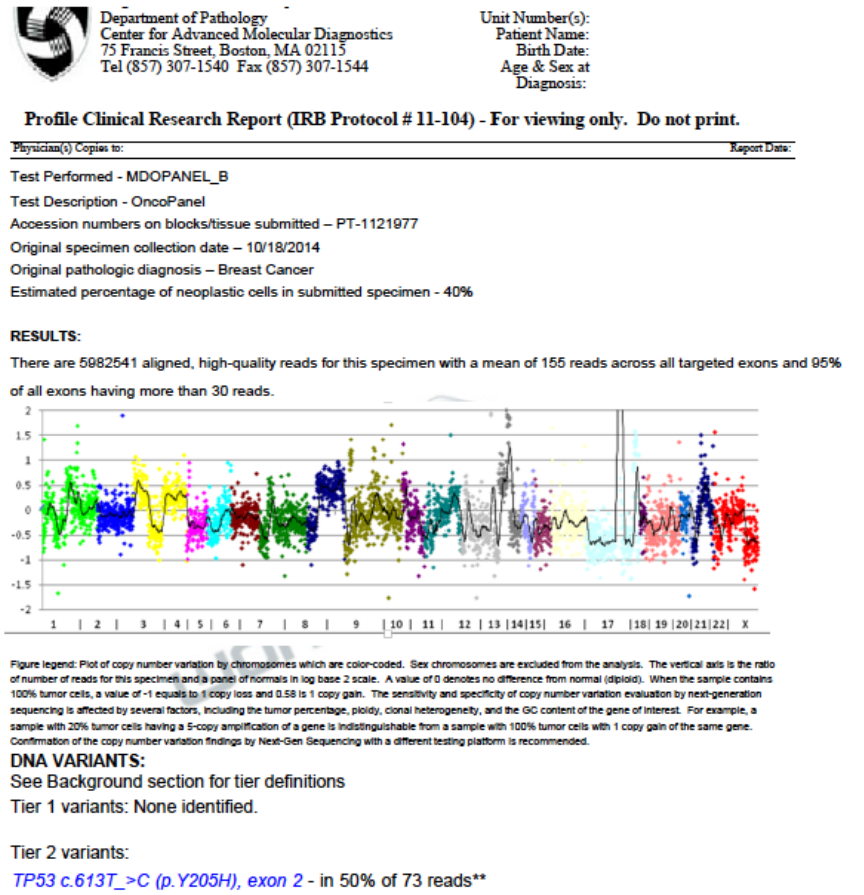
TP53 c.613T_>C (p.Y205H), exon 2 - in 50% of 73 reads**

State of the art in clinical informatics

dbye



Standard or web-based/interactive reporting



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DNA VARIANTS:

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Tier 1 variants: None identified.

Tier 2 variants:

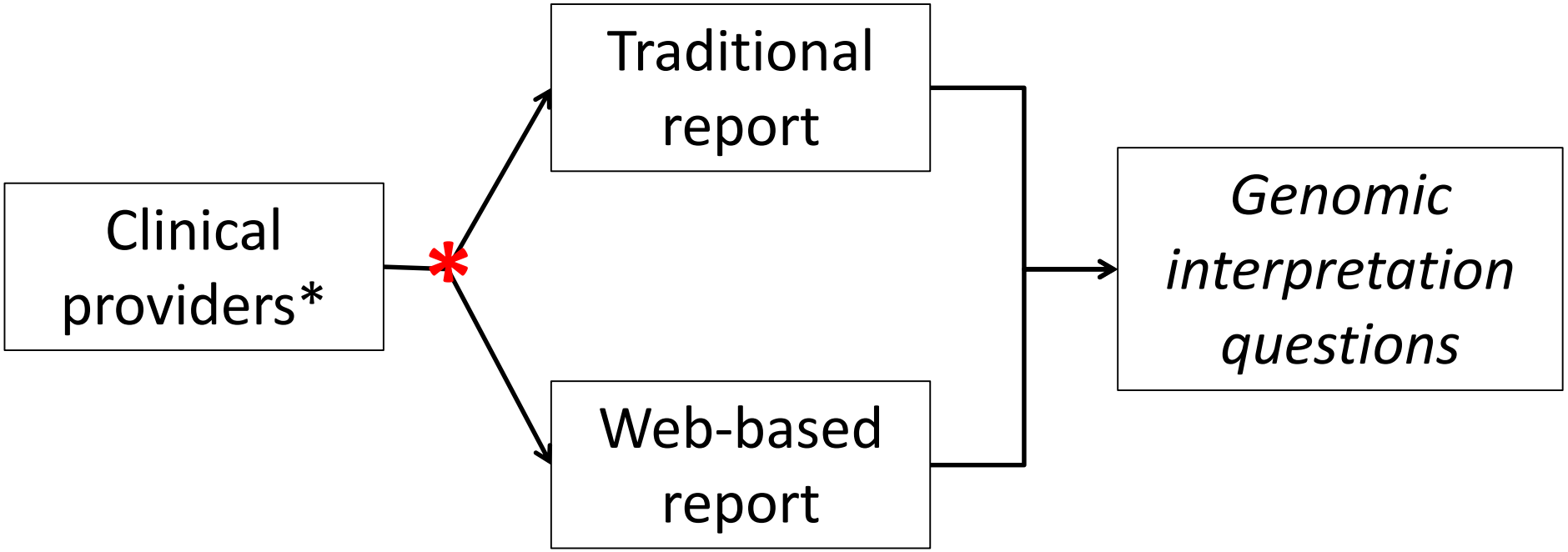
TP53 c.613T_>C (p.Y205H), exon 2 - in 50% of 73 reads**

Or

Web-based report (revealed in survey)

Stacy Gray, Jordan Bryan

OncoSkins survey study



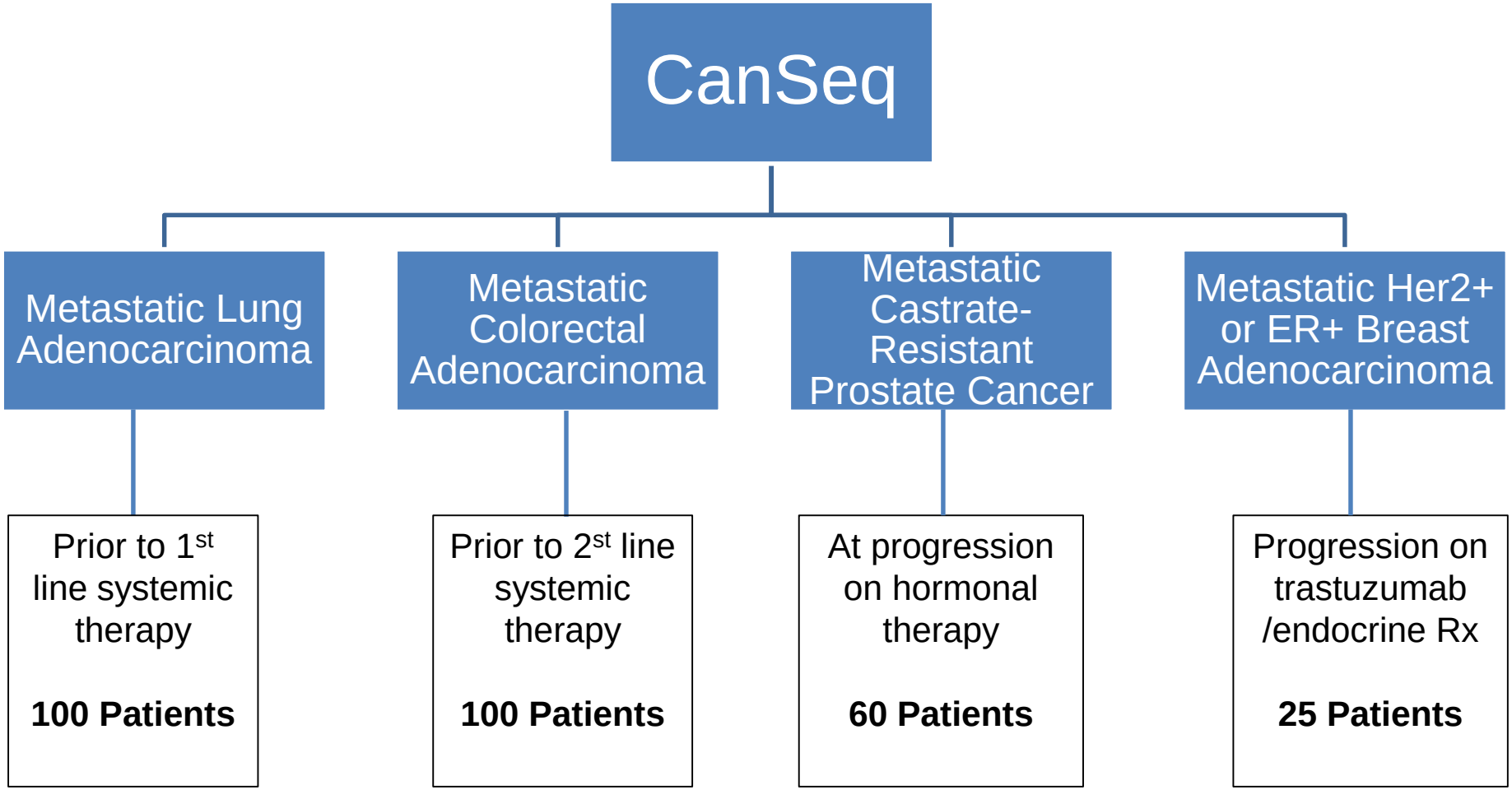
We cannot improve the system without <u>your</u> contribution

There are incentives for completing the report!

Coming soon (Protocol #16-101)

*Medical, radiation, surgical, and pediatric oncology

Expanding whole exome clinical sequencing

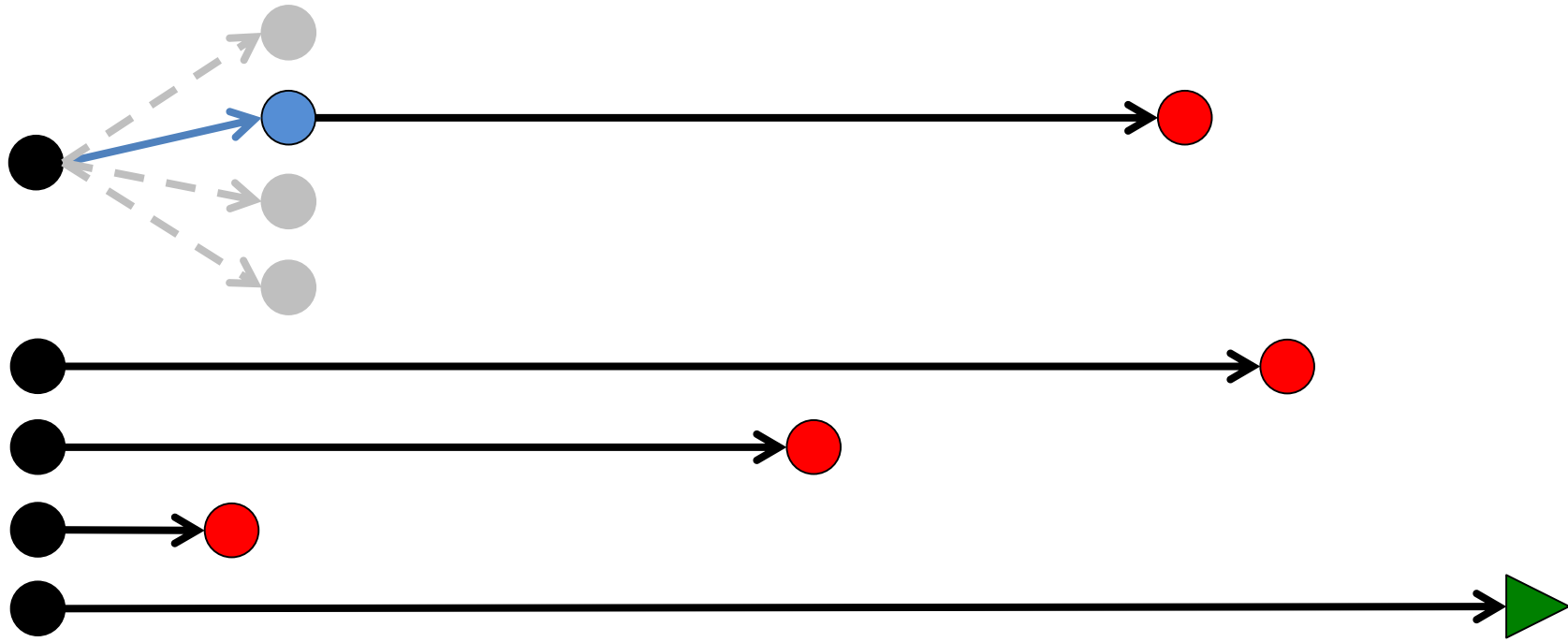


Levi Garraway, Nikhil Wagle, Stacy Gray, Judy Garber, Pasi Janne, Nelly Oliver, Philip Kantoff, Mary-Ellen Taplin, *many others*

PHIAL in a CLIA lab!

CLINICAL RESEARCH SEQUENCING PLATFORM
BROAD INSTITUTE OF HARVARD & MIT

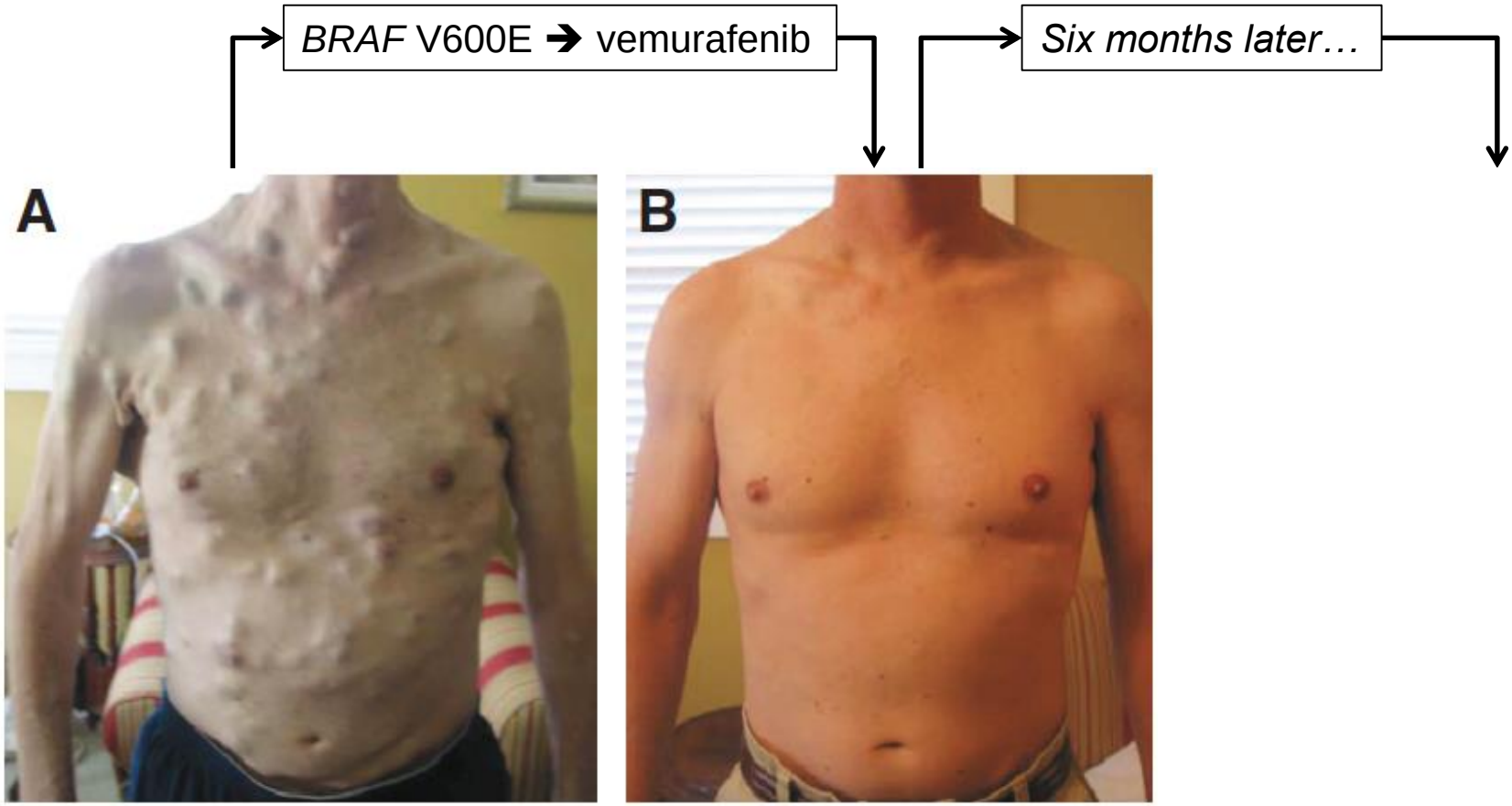
Question #2



Can genomics explain clinical resistance to cancer therapies?

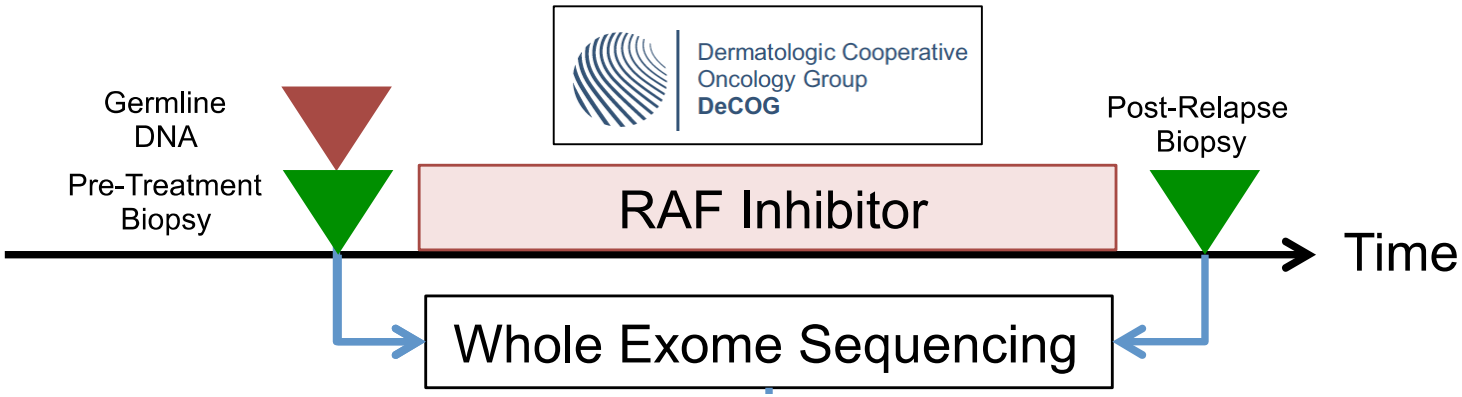
= one patient

Targeted therapies and resistance



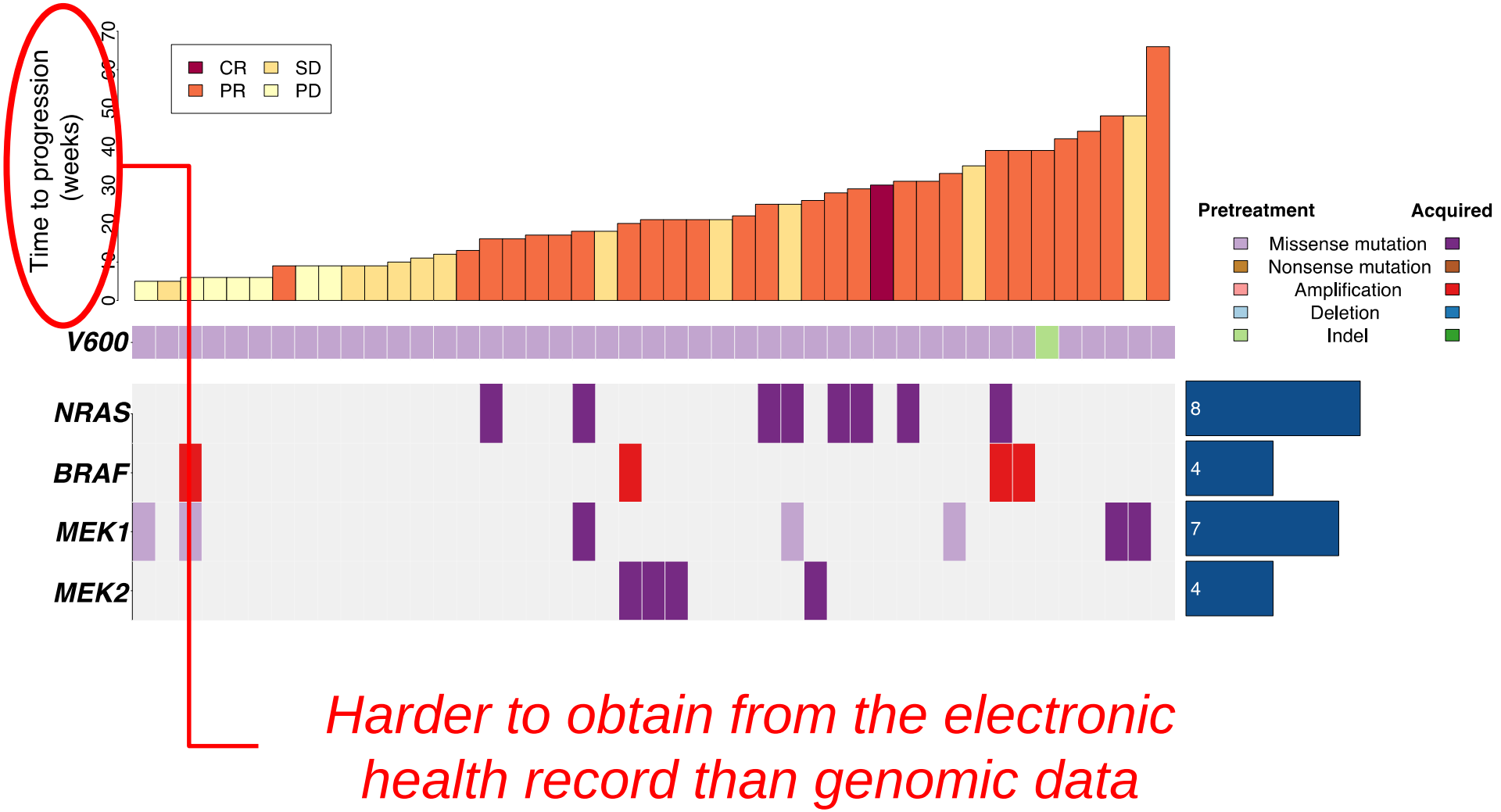
Wagle et al *JCO* 2011

Studying clinical resistance



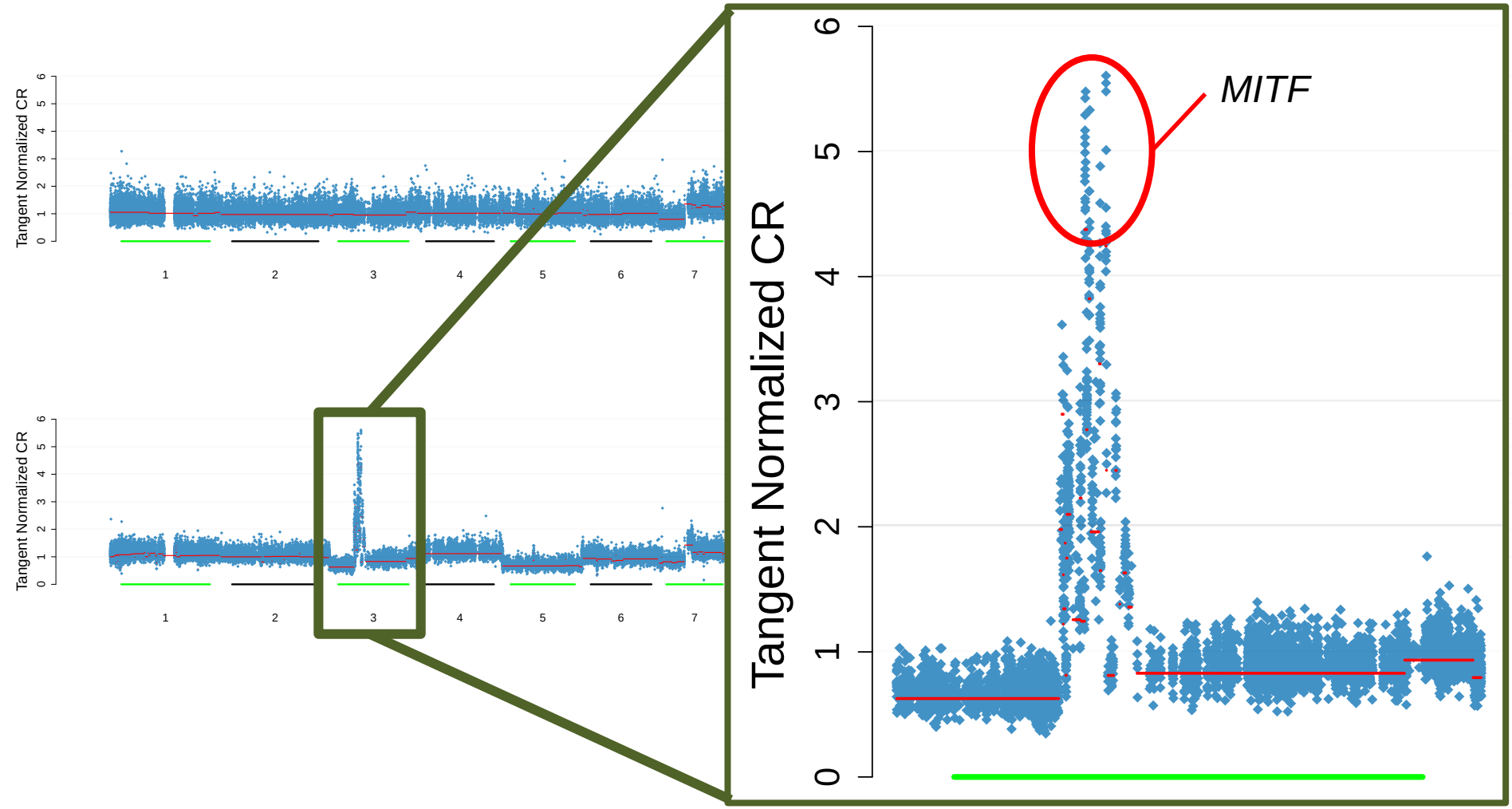
Whittaker et al *Cancer Discovery* 2013
Johannessen et al *Nature* 2013
Van Allen, Wagle et al, *Cancer Discovery* 2014

Linking clinical data to genomics



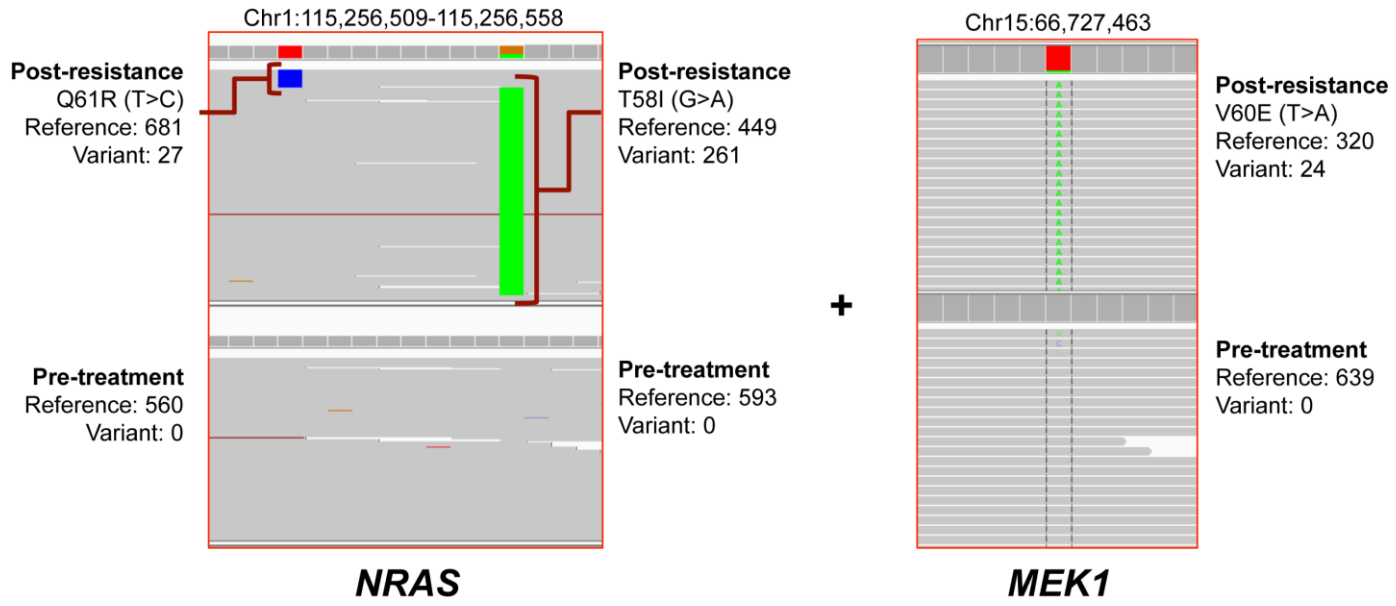
Harder to obtain from the electronic health record than genomic data

New mechanisms of clinical resistance

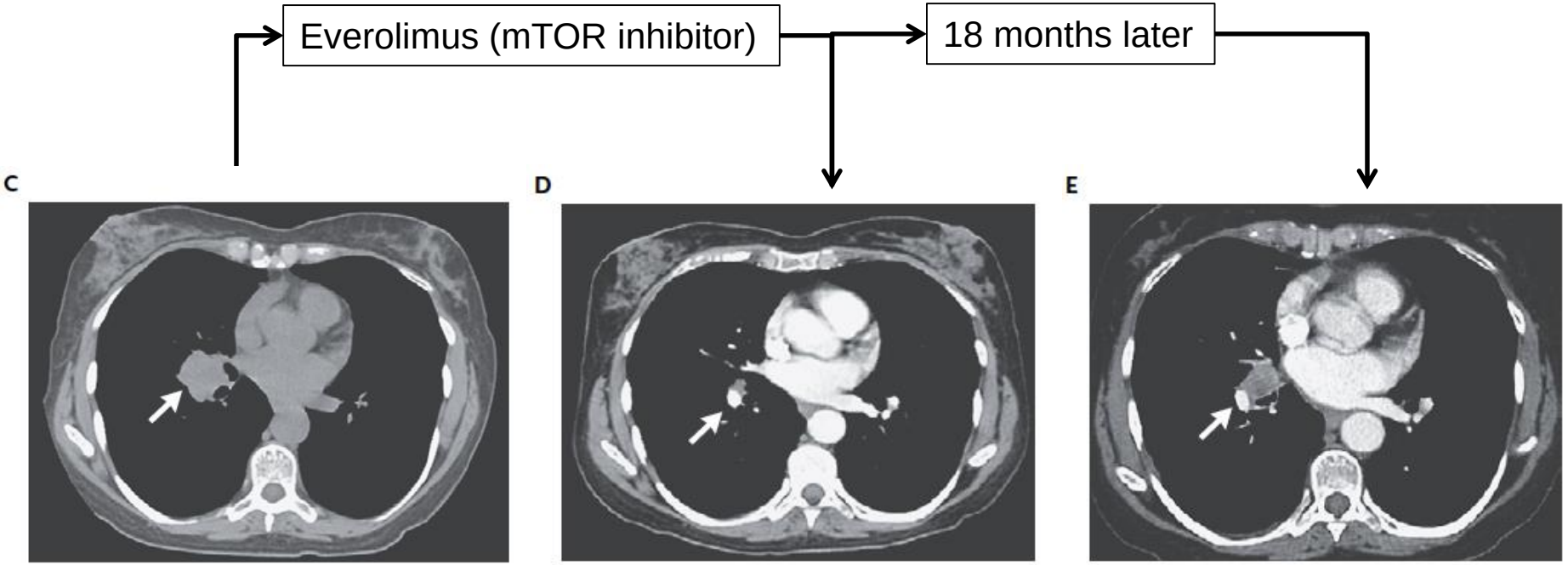


Resistance heterogeneity

A



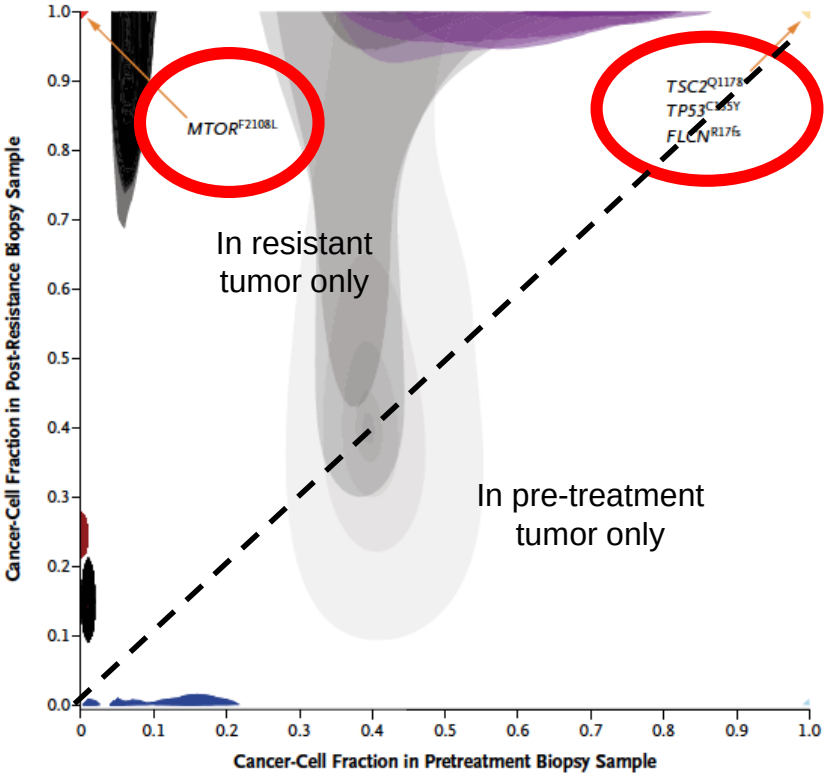
Genomics and exceptional response/resistance



Anaplastic thyroid cancer

Wagle et al *NEJM* 2014

Genomics and exceptional response/resistance

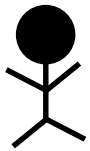


HEALTH

Finding Clues in Genes of 'Exceptional Responders'

By GINA KOLATA OCT. 8, 2014

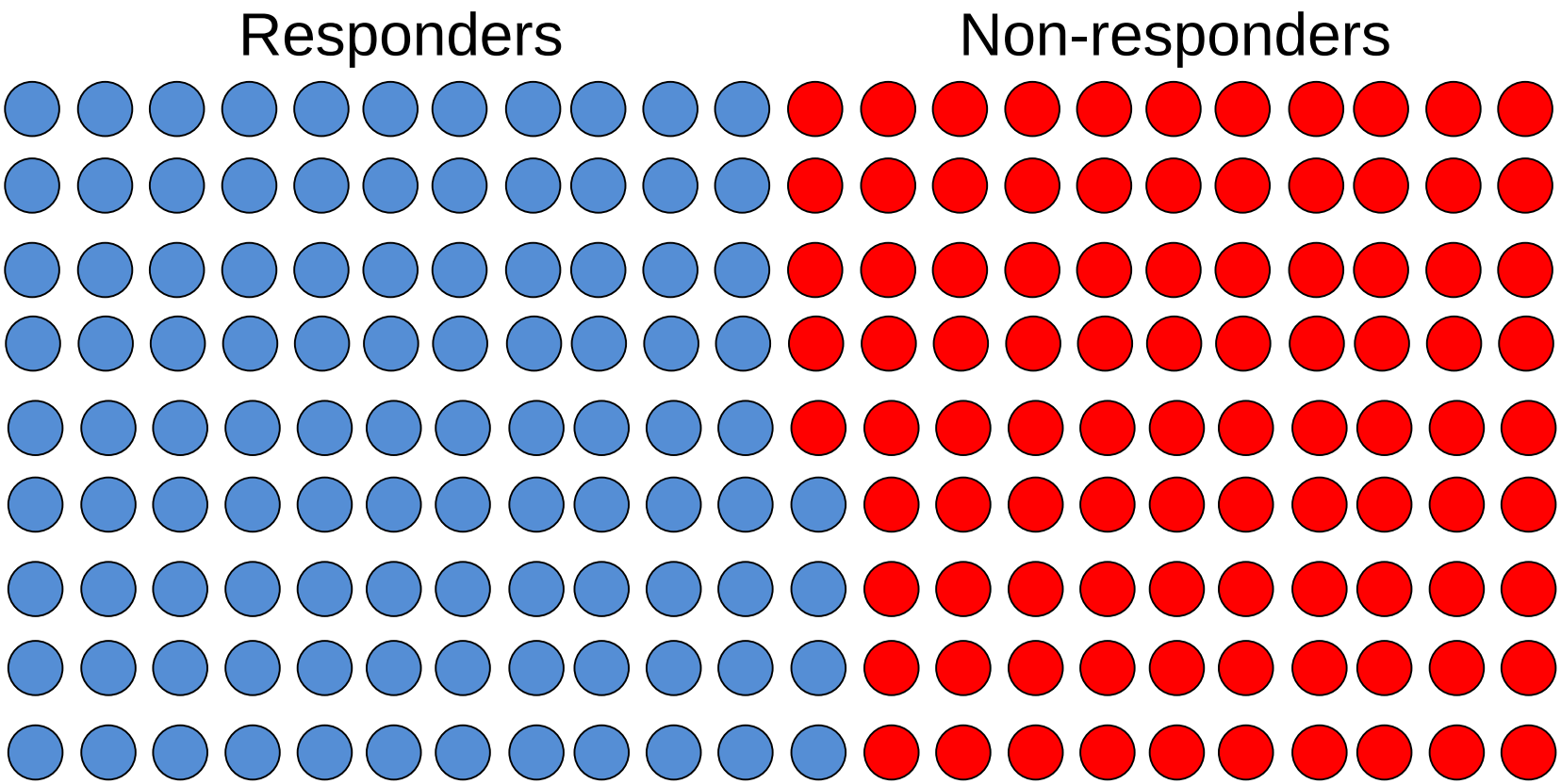
Grace Silva of Dartmouth, Mass., has a form of thyroid cancer that is considered untreatable, but she responded well to a drug. Kayana Szymczak for The New York Times



= one patient

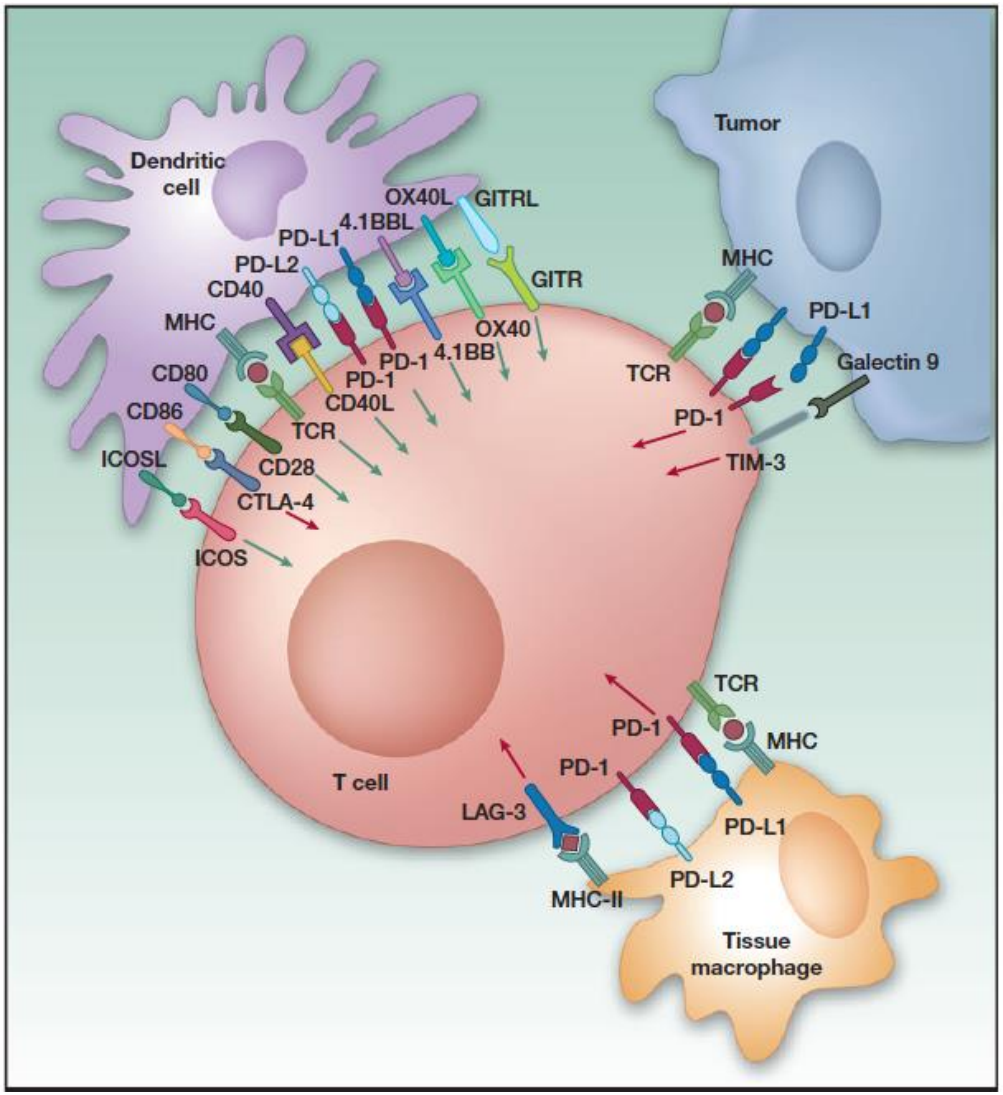
Scott Carter
Ali Amin-Mansour
Amaro Taylor-Weiner

Question #3



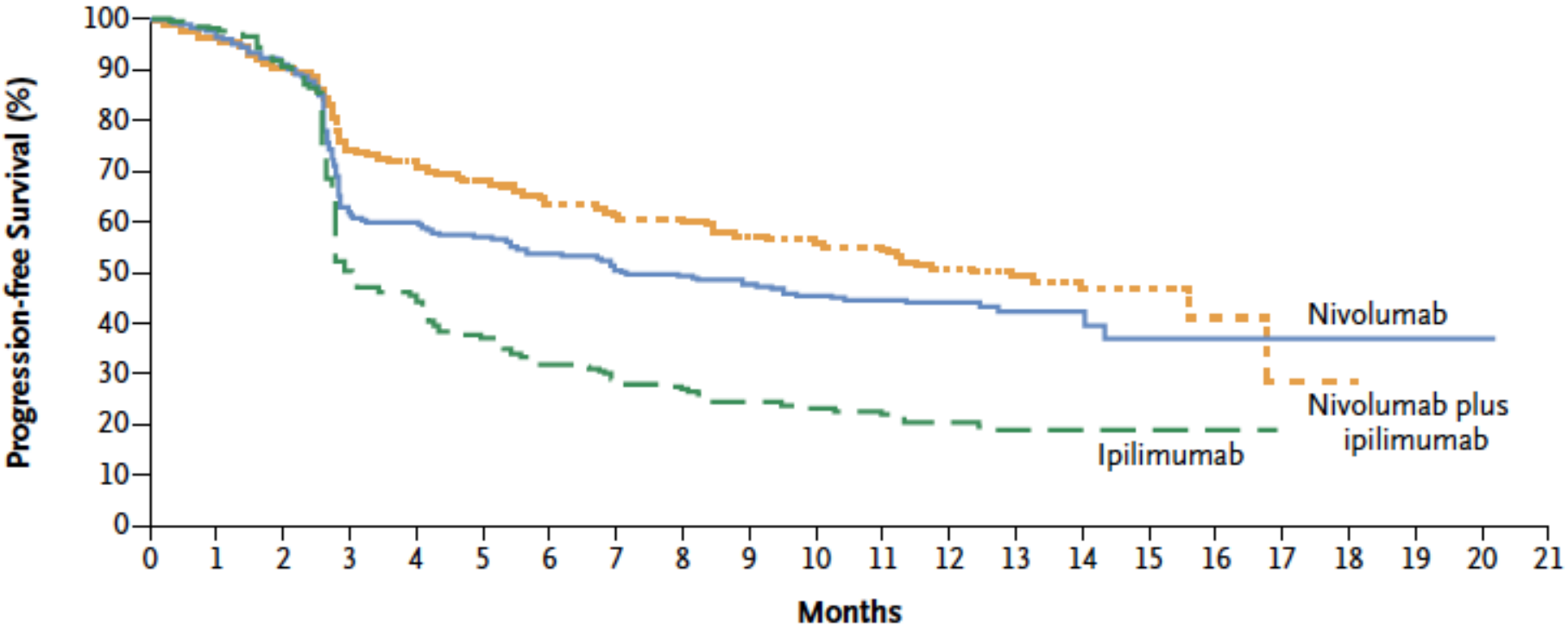
Can computational oncology enable discovery of genomic mechanisms of response to cancer therapies?

The rise of immunotherapies



Ott et al *Clin Cancer Res* 2013

Combining immunotherapies



Do genomic features drive selective response?

Larkin et al *NEJM* 2015

Mutations and “neo”-antigens

Pieces of protein presented to immune cells = antigens

Wild-type	$Patient_1$	$Gene_1$	→ $Protein_1$	…YLFSSYSAS…
Mutant	$Patient_1$	$Gene_1$*	→ $Protein_1$*	…YLFSSYS**S**S…

Can be a passenger or a driver…

Mutation causes “neo”-antigens

May appear foreign to immune cells

Drive response even if altered protein itself has no function?

Sachet Shukla
Catherine Wu

Searching for melanoma neoantigens

Diana Miao

Clinical cohort consolidation

Cohort development

Dermatologic Cooperative Oncology Group
DeCOG

Whole exome sequencing
tumor and germline
(n = 150)

Transcriptome sequencing
(n = 62)

Quality control

Quality control

DNA sequencing
(n = 110)

RNA sequencing
(n = 42)

Somatic mutation calling (MuTect)
HLA-typing (Polysolver)

Microenvironmental signature

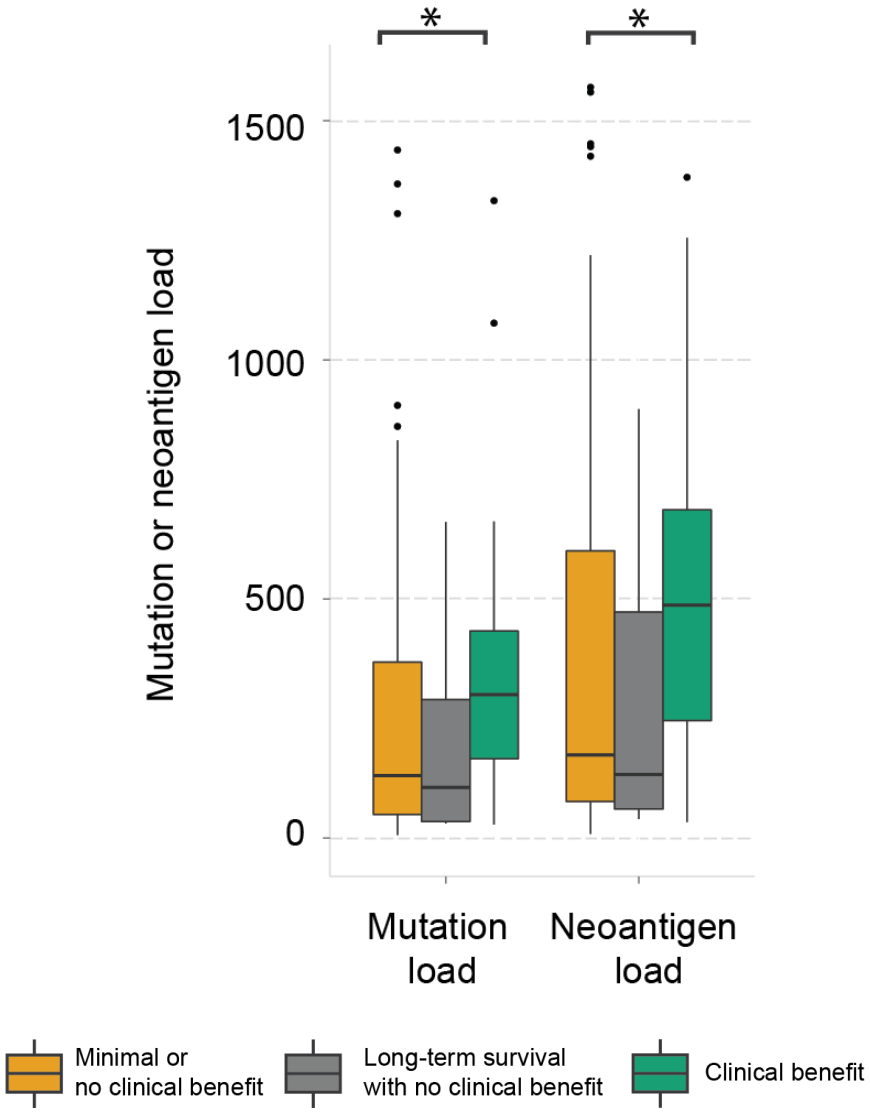
Mutational load
Neoantigen load
Gene-specific enrichment
n-mer signature

Integrated molecular analysis
(n = 40)

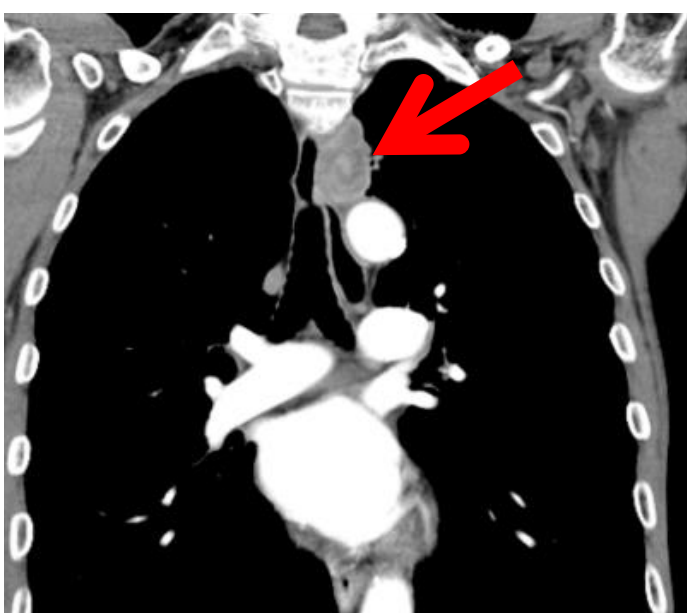
Enhanced neoepitope selection

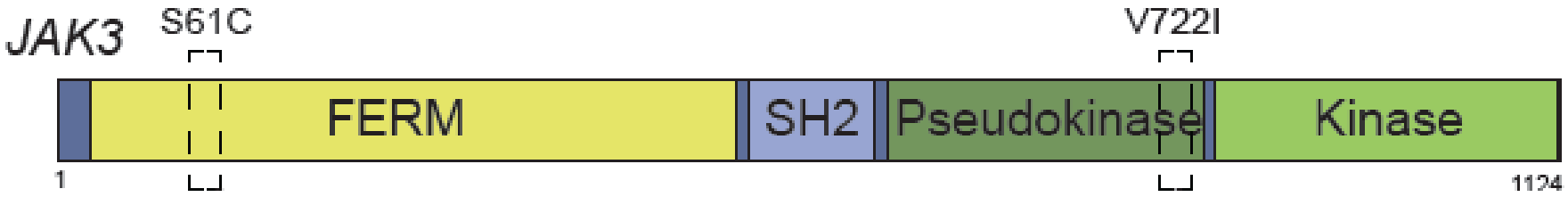
Van Allen, Miao, Schilling et al, *Science* 2015

Neoantigen load and clinical benefit



Immunotherapy exceptional responders

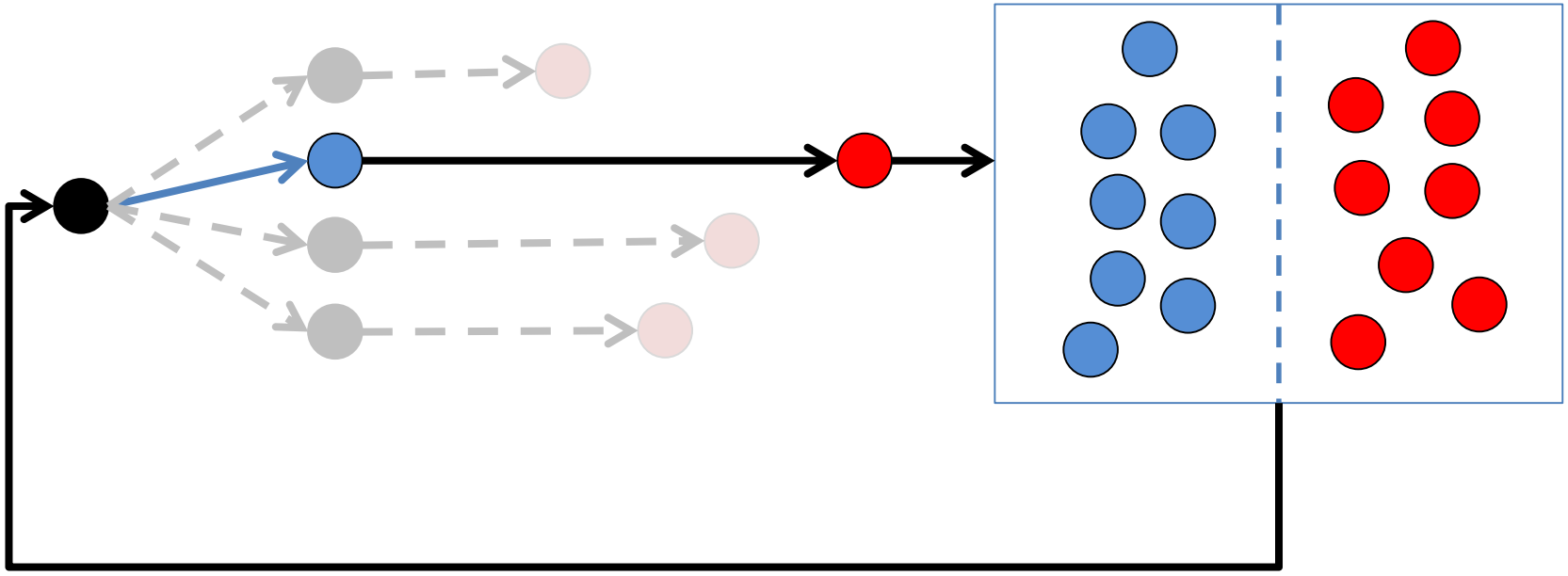




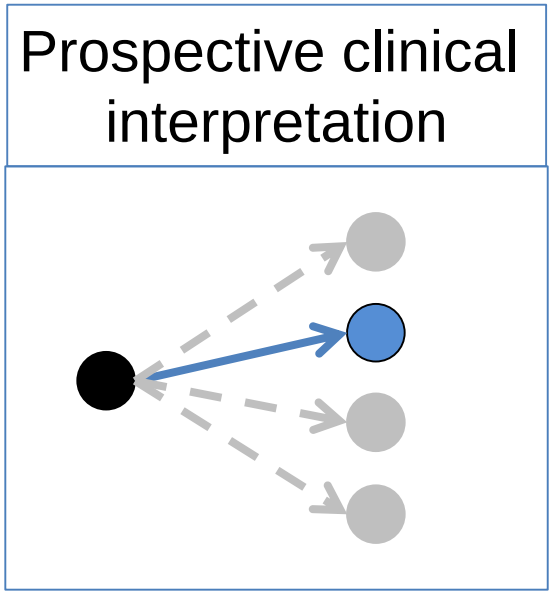
Van Allen, et al. *Cancer Immunol. Res.* 2015

BroadIgnite

Clinical computational oncology



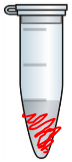
Question #1 (Interpretation): Next Steps



- Improve integrative analyses
- Expanding tumor types
- Expanding clinical scenarios
- …

Question #1 (Interpretation): Next Steps

Patient data



Current best practices:
"First order" clinical interpretation

Multiple actionable targets?
No actionable targets?
Functional readout?

Clinical interpretation methodology for precision cancer medicine

Tumor Cellular State

Clinical-Preclinical Matchmaker

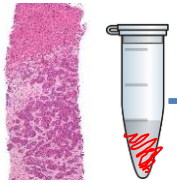
Prioritize actionable targets
Identify new lesions
Match with preclinical models

Machine learning methodologies

R21 ITCR Grant!

Question #1 (Interpretation): Transcriptional state finder

Patient data

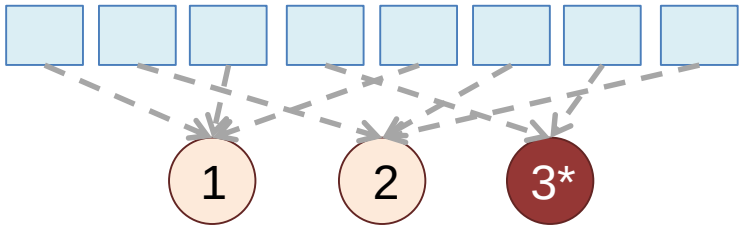


DNA $[g_1v_1 \ldots g_nv_n, f_1 \ldots f_m]_{DNA}$

RNA $TCGA[g_1v_1 \ldots g_nv_n, f_1 \ldots f_m]_{RNA}$ Histology-matched$_{RNA}$

Lasso-based feature compression

Bayesian mixture model

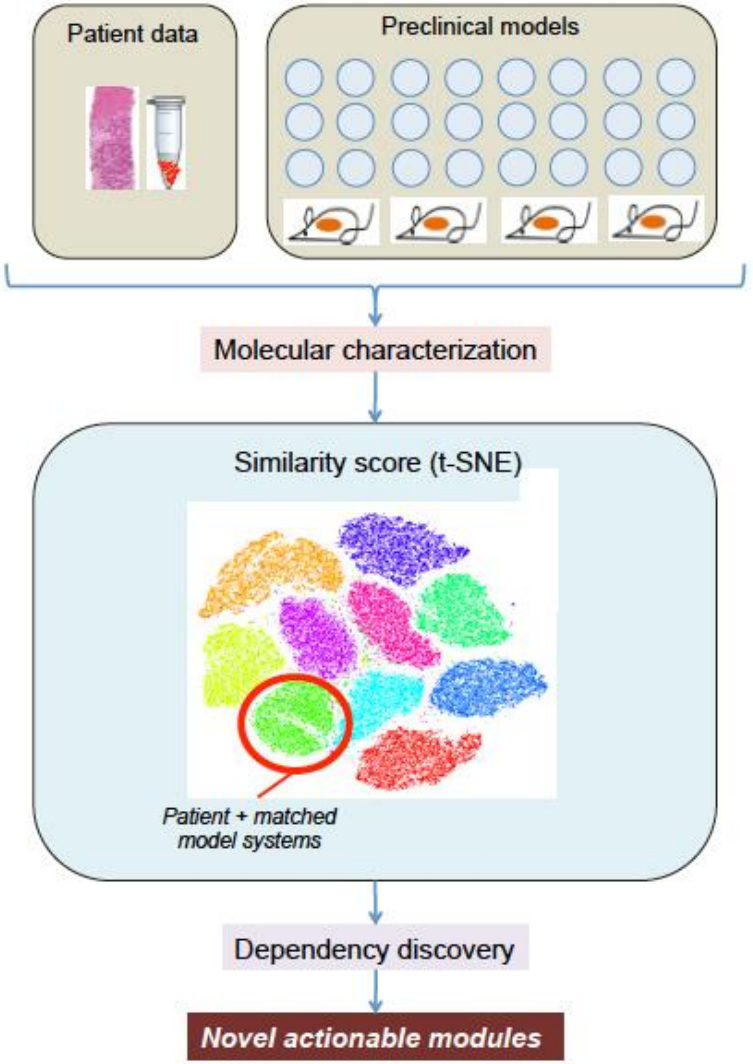


g = gene
v = variant
f = feature
*Denotes cellular state including patient

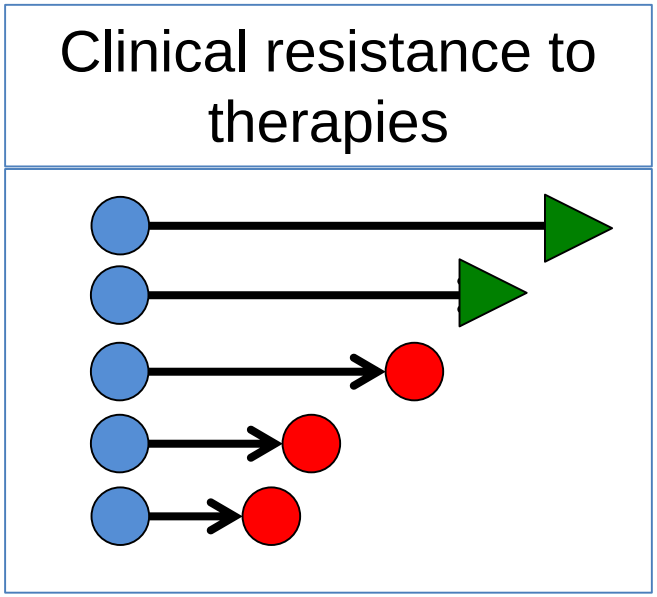
Towards "second order" interpretation

Prioritize patient-specific actionable cellular states

Question #1 (Interpretation): Clinical-preclinical matchmaker

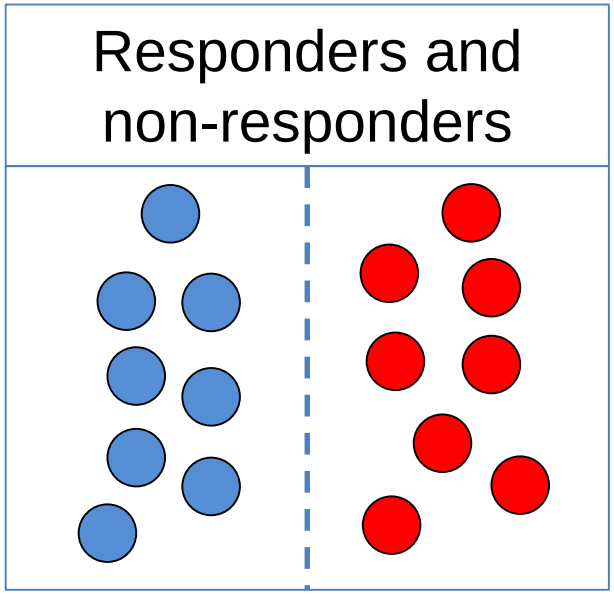


Question #2 (Resistance): Next steps

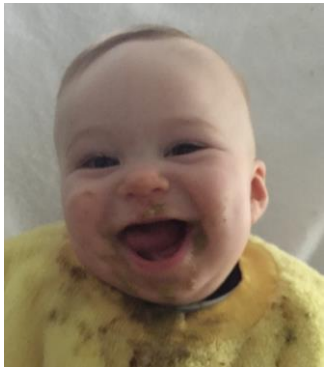


- More biopsies
- More cohorts
- More therapies
- More!

Question #3 (Response): Next steps



- **Studying response to all therapy types (targeted, chemo, immuno)**
- **Integration into trials**
- **Algorithm enhancement**



Let's work together!

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Many others…

The Patients

Funding

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