# Microsoft Research Faculty Summit 2014

15TH ANNUAL

Microsoft Research
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2014 15TH ANNUAL

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# Precision cancer medicine in the era of genomics

Microsoft

# Disclosures

~~None~~

Equity holder in Microsoft

Five shares for my bar-mitzvah in 1993

Thanks to the Gros family!

# Definitions

Clinical computational biology: the development and application of computational algorithms to analyze and interpret 'omic data from patient samples

Precision cancer medicine: The use of "pan-omic" technology to inform patient care and translational studies

# Precision oncology: A paradigm shift

Past → Present

Cancer → Non-specific chemotherapy

Present → Future

Cancer → *Test for tumor-specific genetic targets that can be "drugged"* → *Targeted therapy*

| | |
|---|---|
| EGFR | erlotinib |
| BCR-ABL | imatinib |
| ALK | crizotinib |
| HER2 | trastuzumab |
| … | … |

# Precision oncology: A paradigm shift

Past
Dacarbazine → 5% response rate

Present
*BRAF*$^{V600E}$
Vemurafenib

Wagle, Emery, et. al JCO 2011

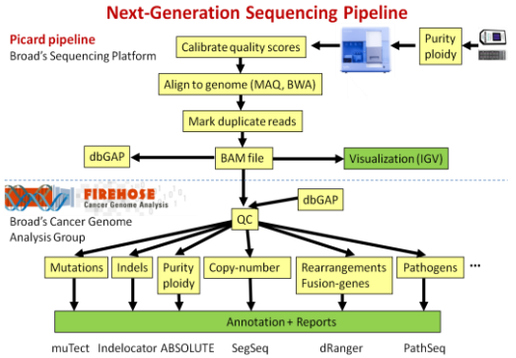
Big question: Can prospective knowledge of *all* alterations in a tumor genome impact patient care?

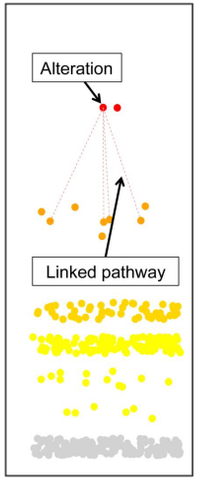
# Clinical interpretation needs

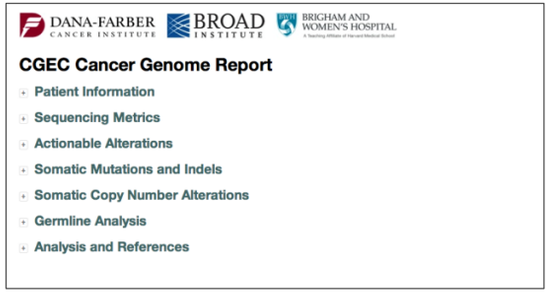
**Clinical Sequencing Pipeline Development**

**Clinical Genomics Data Interpretation**

**Data Representation for Clinicians**




Van Allen, et al ASCO oral abstract (2012)

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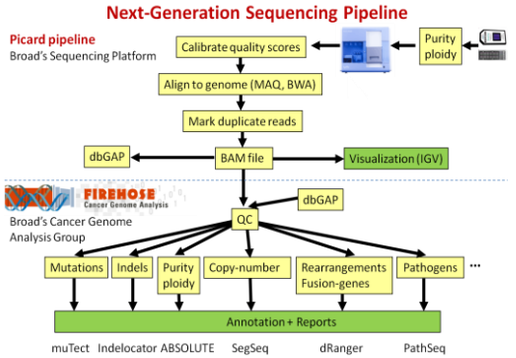
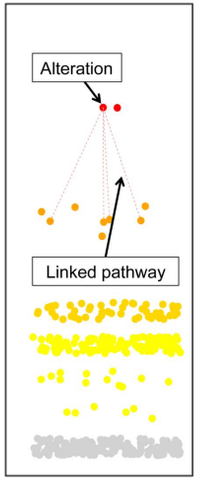
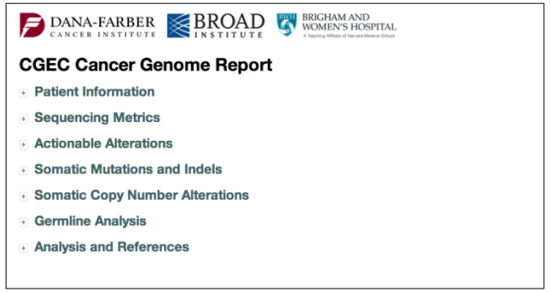
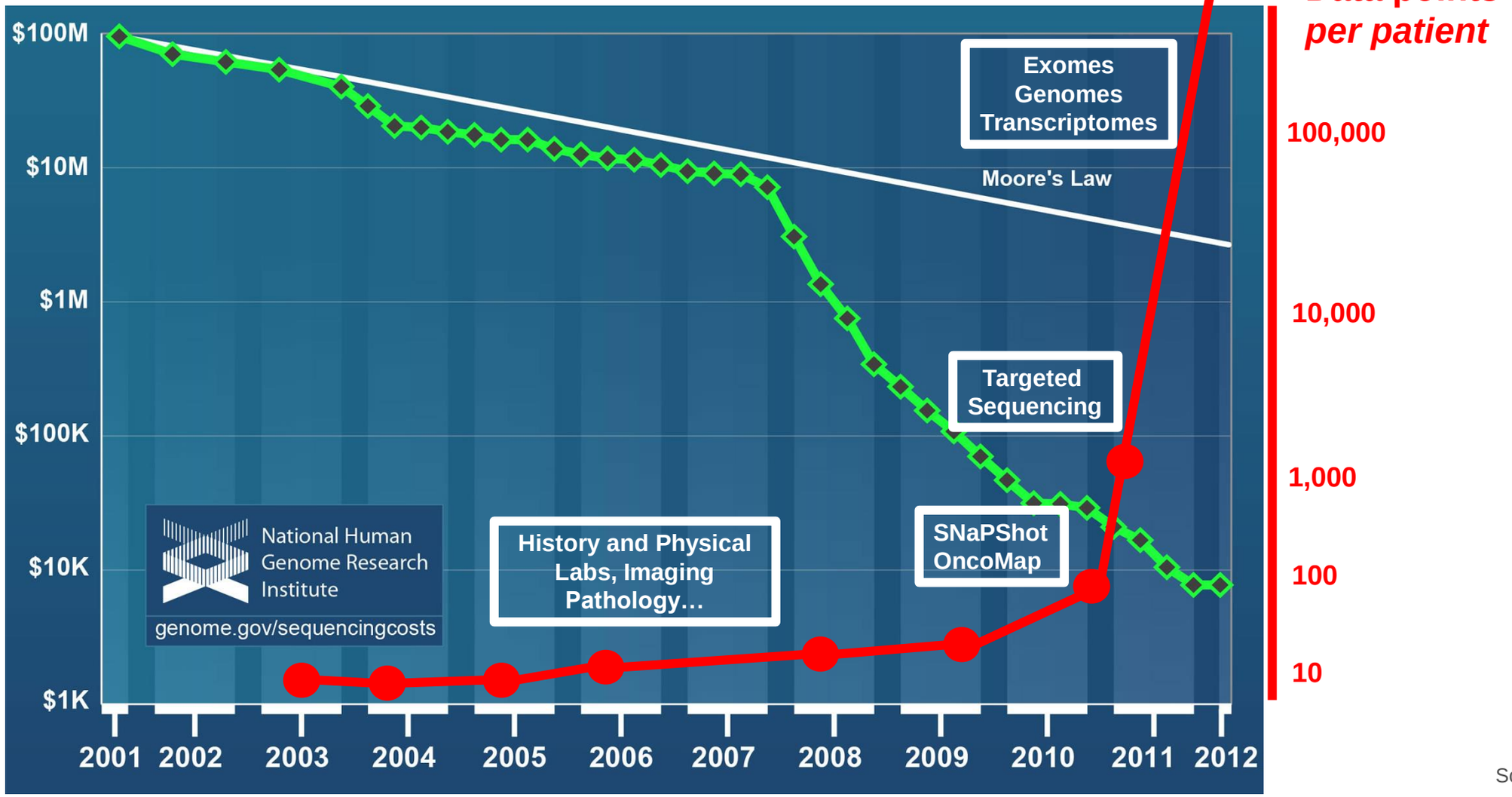



Van Allen, et al ASCO oral abstract (2012)

# “Big (genomic) data” in oncology




Source: NHGRI

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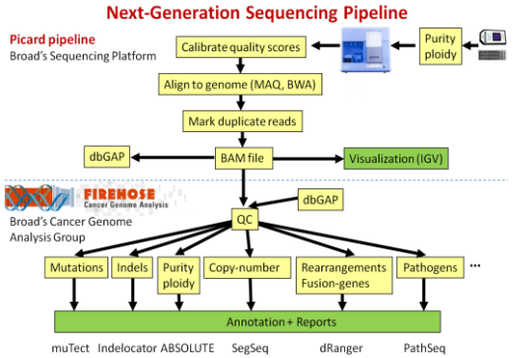
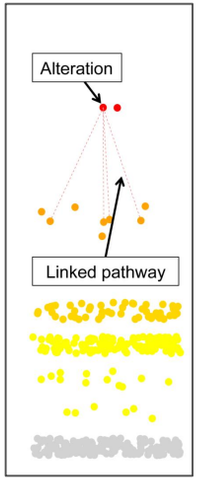
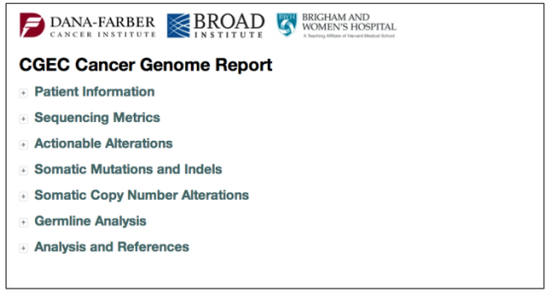



Van Allen, et al ASCO oral abstract (2012)

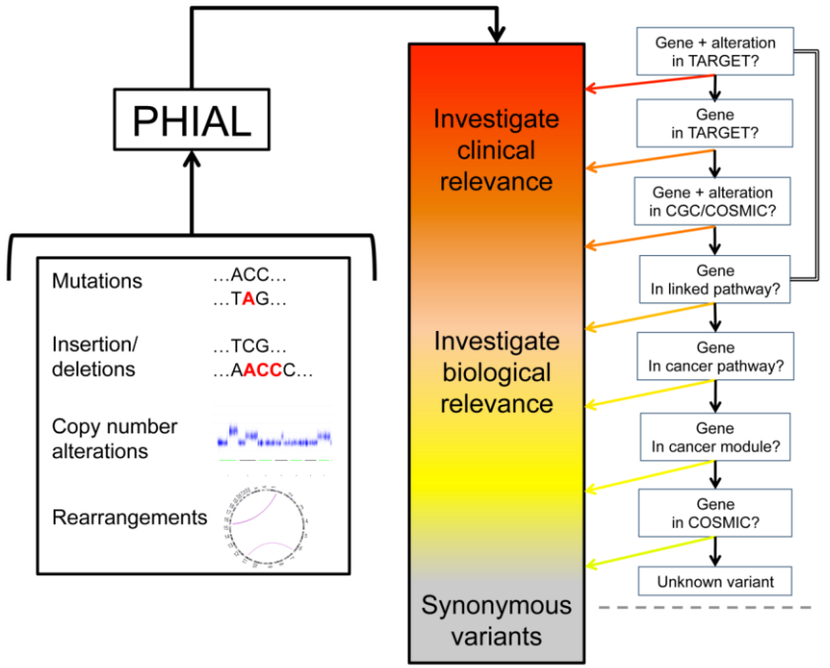
# PHIAL

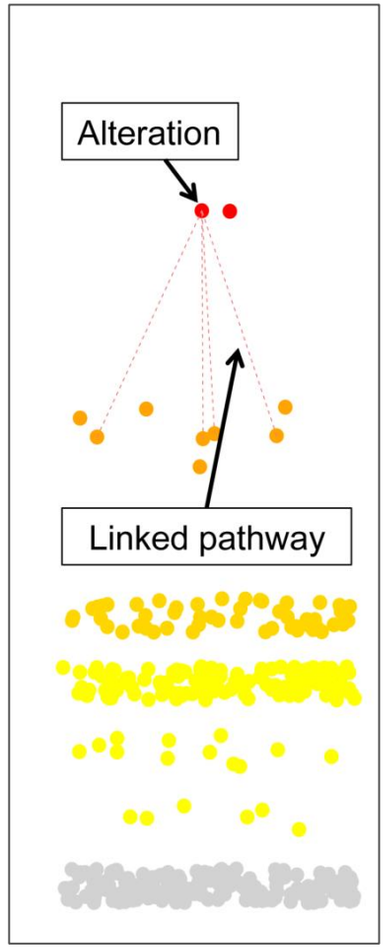
## **P**recision **H**euristics for **I**nterpreting the **A**lteration **L**andscape

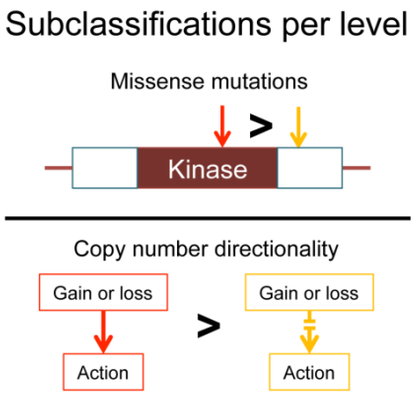
"May it be a light to you in dark places, when all other lights go out."[1]

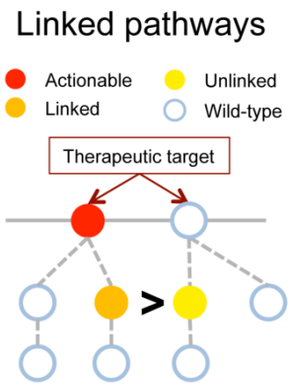
[1]Galadriel, in Tolkien, The Fellowship of the Ring

# PHIAL



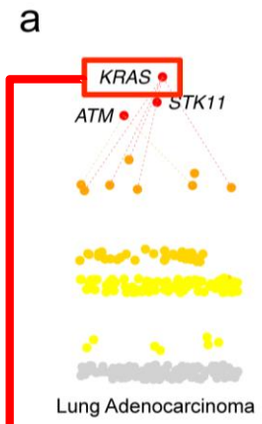



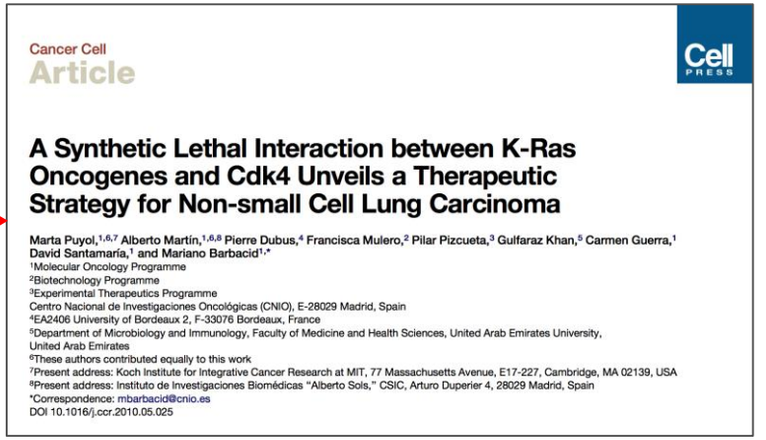

Van Allen, Wagle et al. Nature Medicine 2014

# Impact on clinical decision-making




*KRAS* A146V

- Rare activating alteration
- Not detected with deployed profiling technologies (at that time)



Cancer Cell
Article

Cell PRESS

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

Marta Puyol,[1,6,7] Alberto Martín,[1,6,8] Pierre Dubus,[4] Francisca Mulero,[2] Pilar Pizcueta,[3] Gulfaraz Khan,[5] Carmen Guerra,[1] David Santamaría,[1] and Mariano Barbacid[1,*]
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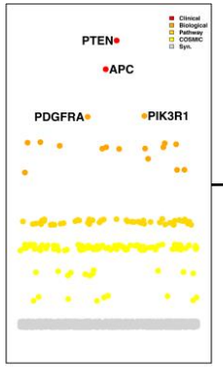
DOI 10.1016/j.ccr.2010.05.025

# Impact on clinical decision-making

Metastatic *advanced* prostate cancer patient

**PHIAL**

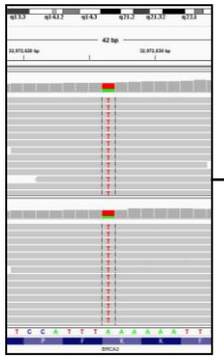
Tumor-only variants




PI3K inhibitor
AKT inhibitor
mTOR inhibitor

***Responds to cisplatin!***

Inherited ("germline") variant



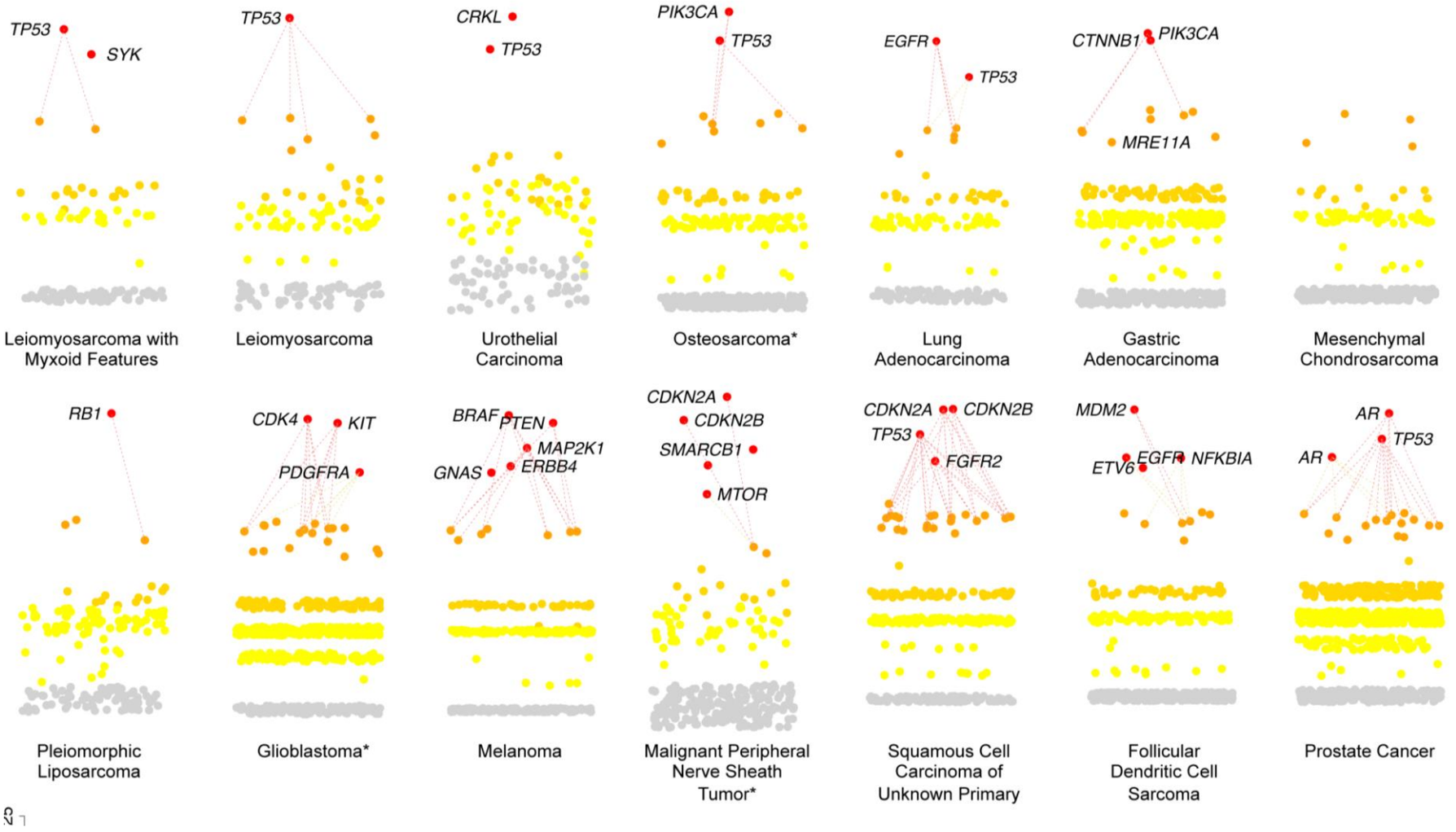
BRCA2 K3326* nonsense

PARP inhibitor
Platinum chemotherapy

***Five potential therapies for a patient who exhausted standard-of-care options!***

Van Allen, et al, Prostate Cancer Pros. Dis., 2014

# PHIAL applied to diverse cancer types



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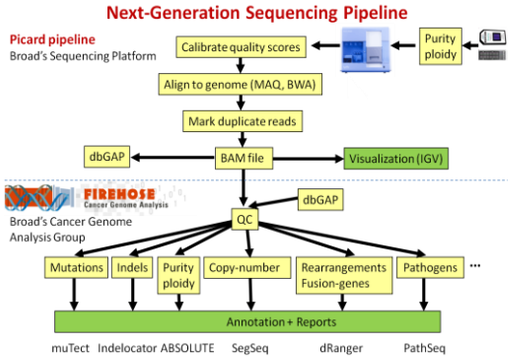
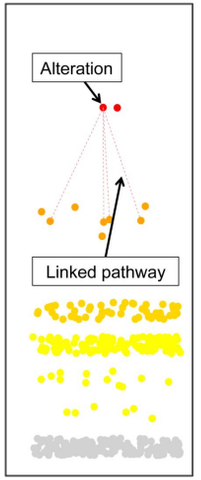
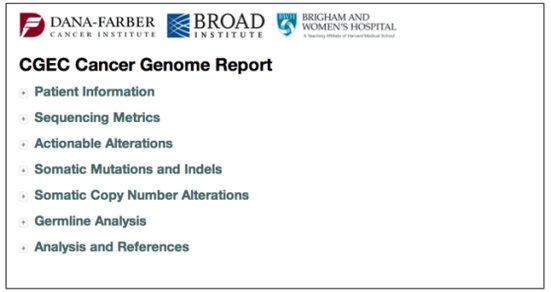



Van Allen, et al ASCO oral abstract (2012)

# The challenge of representation

## Microsoft phone interview (~2002):

"Describe how you might make a mouse from scratch?

Eli: "I would start with a white-ish color, shaped around the palm of my hands…"

*Did not get call back for second interview*

# The challenge of representation

## True stories from oncology clinic (12/9/2013):

Patient's genomic testing reveals *PIK3CA*$^{E545K}$ mutation

Specific inhibitors of this gene and pathway ("PI3K inhibitors") are in clinical trials

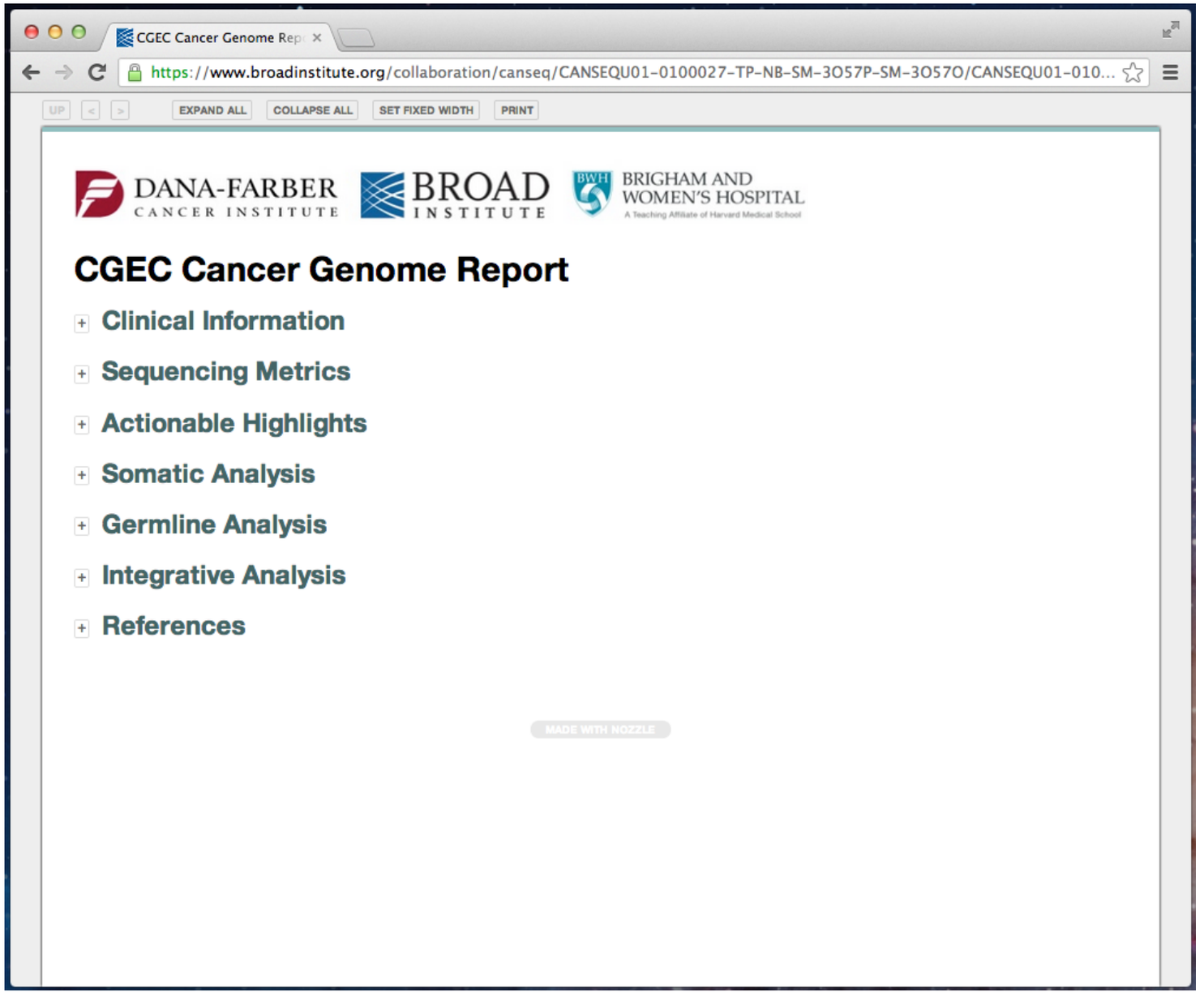
"Why might you suggest PI3K inhibitor?" - Doc

"There is an activating PIK3CA mutation." - Eli

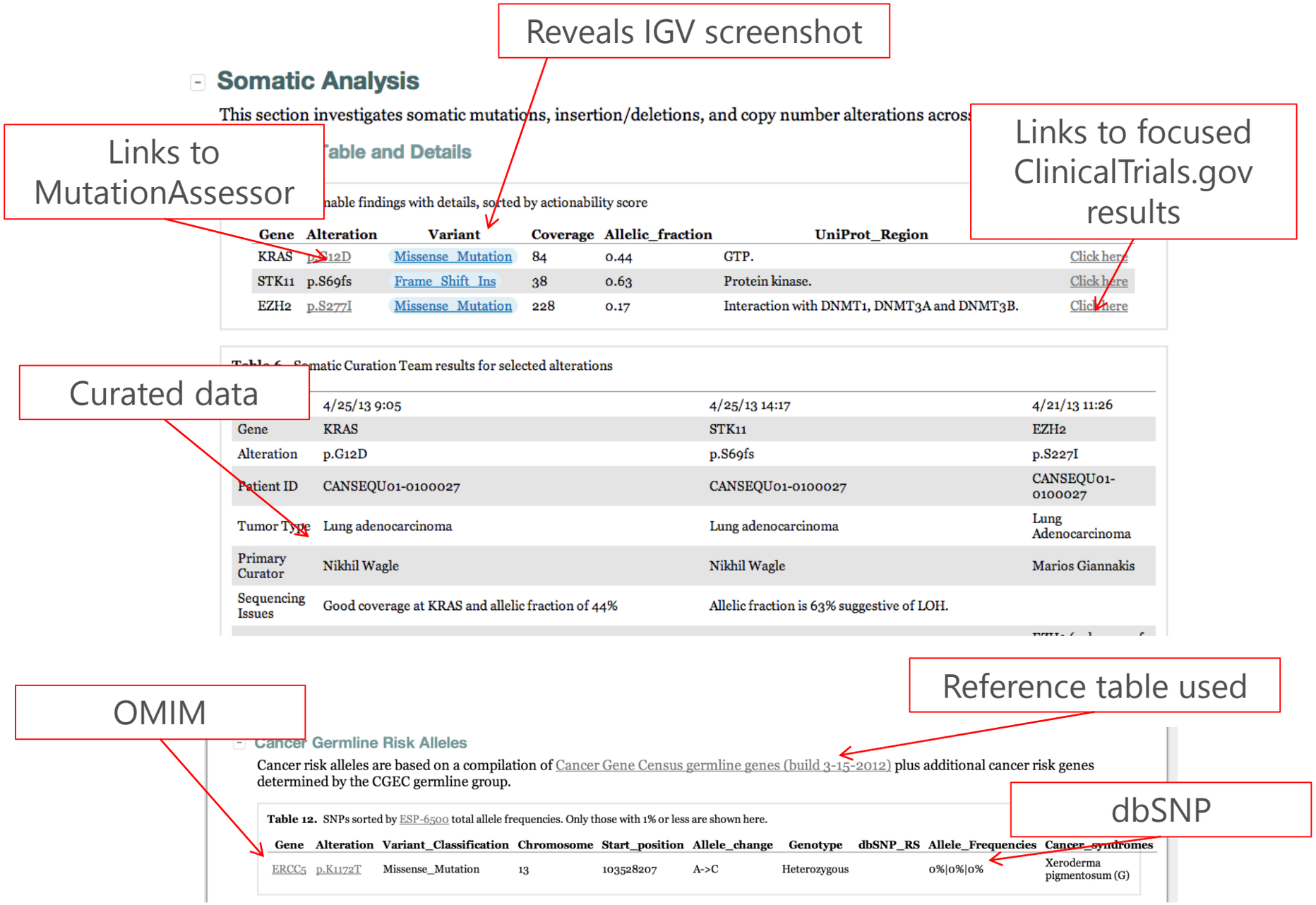
"Oh, is PIK3CA part of the PI3K pathway?" – Doc

# The state of clinical informatics

# Digital genomics report



# Digital genomics report



Big question: Can prospective knowledge of *all* alterations in a tumor genome impact patient care?

*With the right computational approaches, we can study this on growing numbers of patients*

# What are we missing?

A lot.

"Clinical" computational oncology is in its infancy

Much room for improvement

Open/eager for collaboration

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# Acknowledgements

**The patients**


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Save the planet and return
your name badge before you
leave (on Tuesday)

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