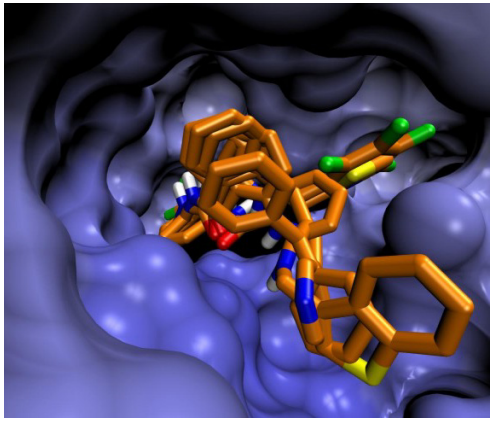
Genomics-Driven Clinical Trials in Oncology: Principles and Practice

Levi A. Garraway, M.D., Ph.D.

NCCTS Meeting

February 11, 2013



DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

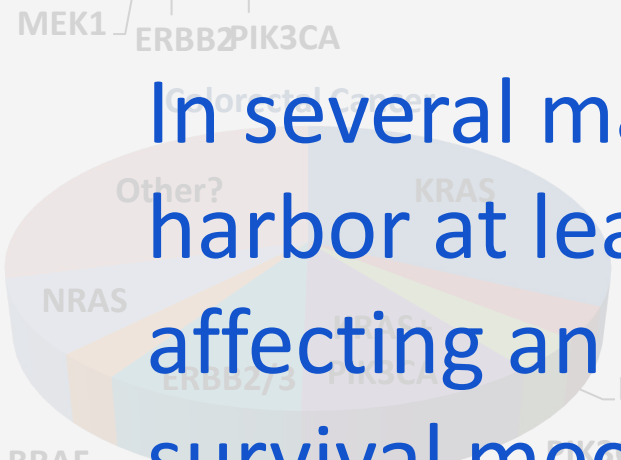
BWH BRIGHAM AND WOMEN'S HOSPITAL

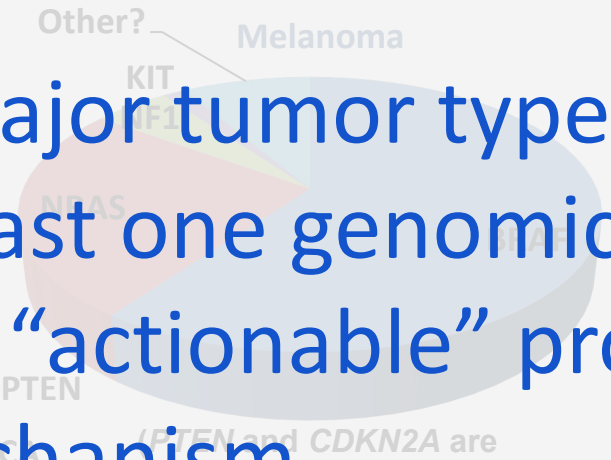
A Teaching Affiliate of Harvard Medical School

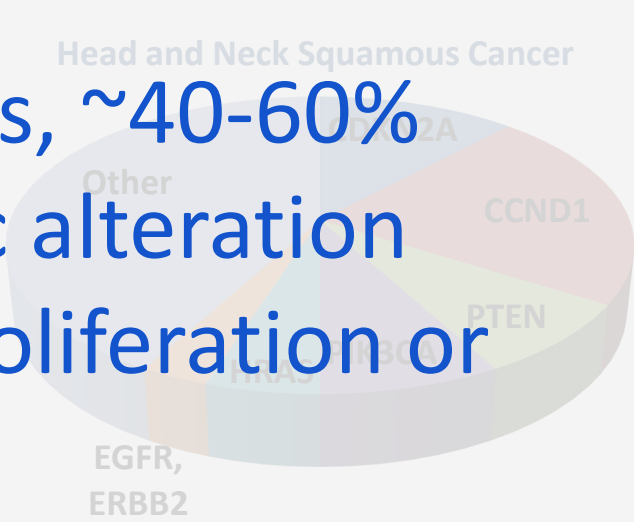
BROAD INSTITUTE

Genomics-Driven Cancer Medicine: Guiding Principles

<u>Principle #1</u>: Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.







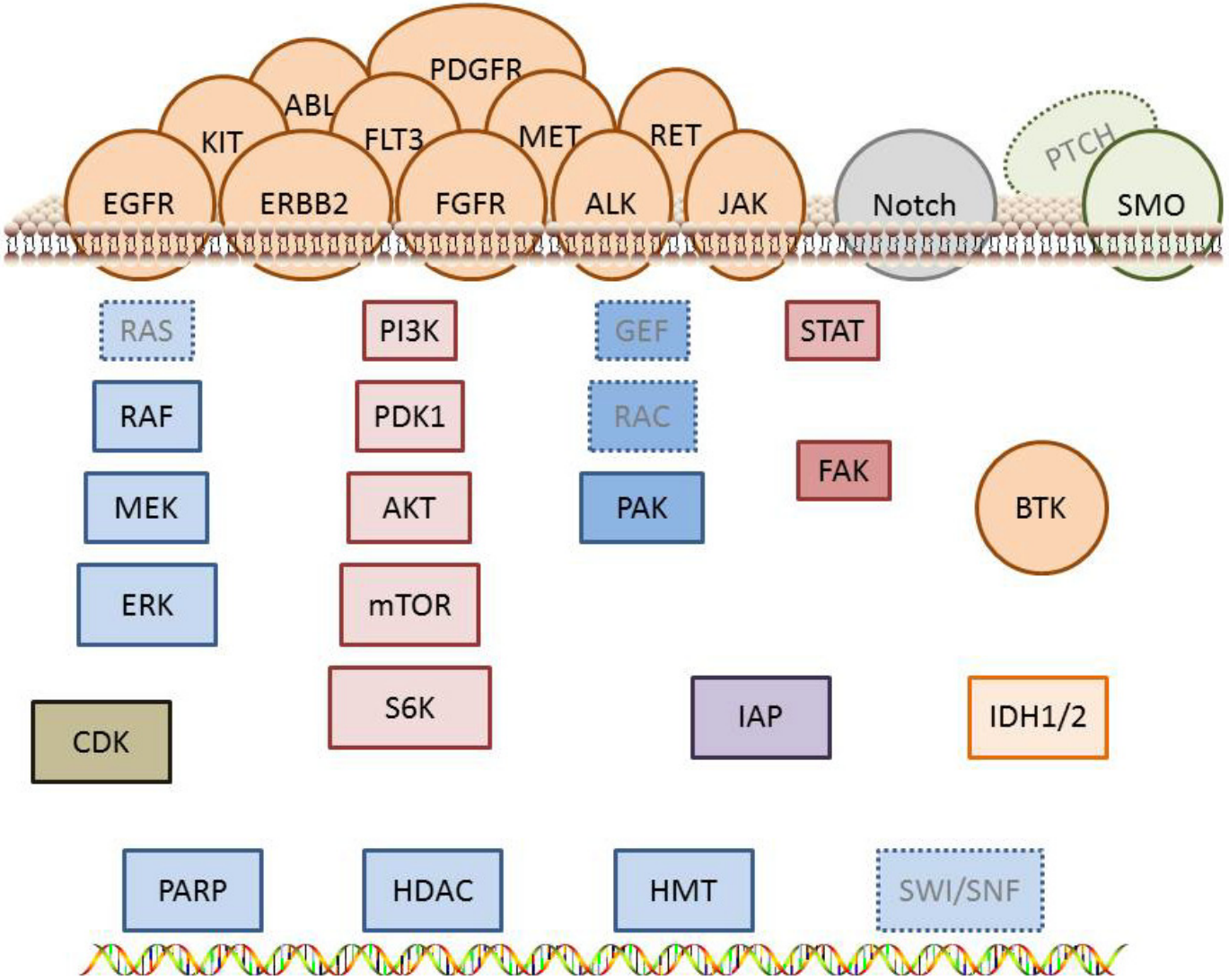
In several major tumor types, ~40-60% harbor at least one genomic alteration affecting an “actionable” proliferation or survival mechanism.

Genomics-Driven Cancer Medicine: Guiding Principles

Principle #1: Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.

Principle #2: Anticancer agents targeting many oncogenic pathways have entered clinical trials.

Spectrum of Targeted Anticancer Agents in Clinical Development



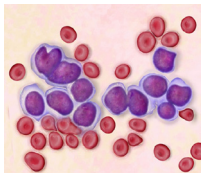
Genomics-Driven Cancer Medicine: Guiding Principles

Principle #1: Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.

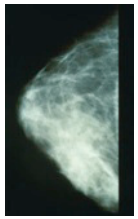
Principle #2: Anticancer agents targeting many oncogenic pathways have entered clinical trials.

Principle #3: **Genomics technologies enable robust tumor genomic profiling in the clinical arena.**

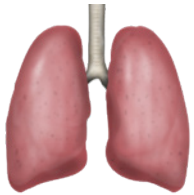
Molecular Profiling Today:
Single Genes with Specific Alterations



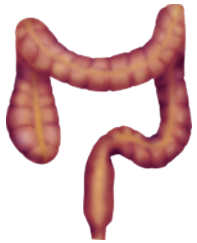
BCR-ABL → Imatinib, Dasatinib, Nilotinib



ERBB2 (Her2) → Trastuzumab, Lapatinib, Pertuzumab, T-DM1



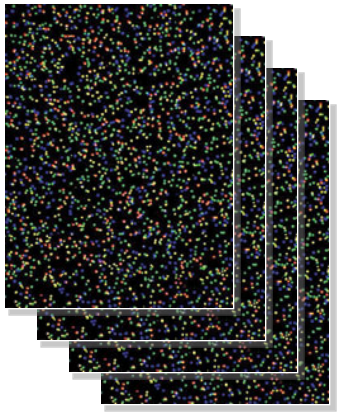
EGFR, ALK → Erlotinib, Crizotinib



KRAS → Cetuximab, Panitumumab

BRAF → Vemurafenib

Massively Parallel Sequencing in Cancer



Illumina Hi-Seq:

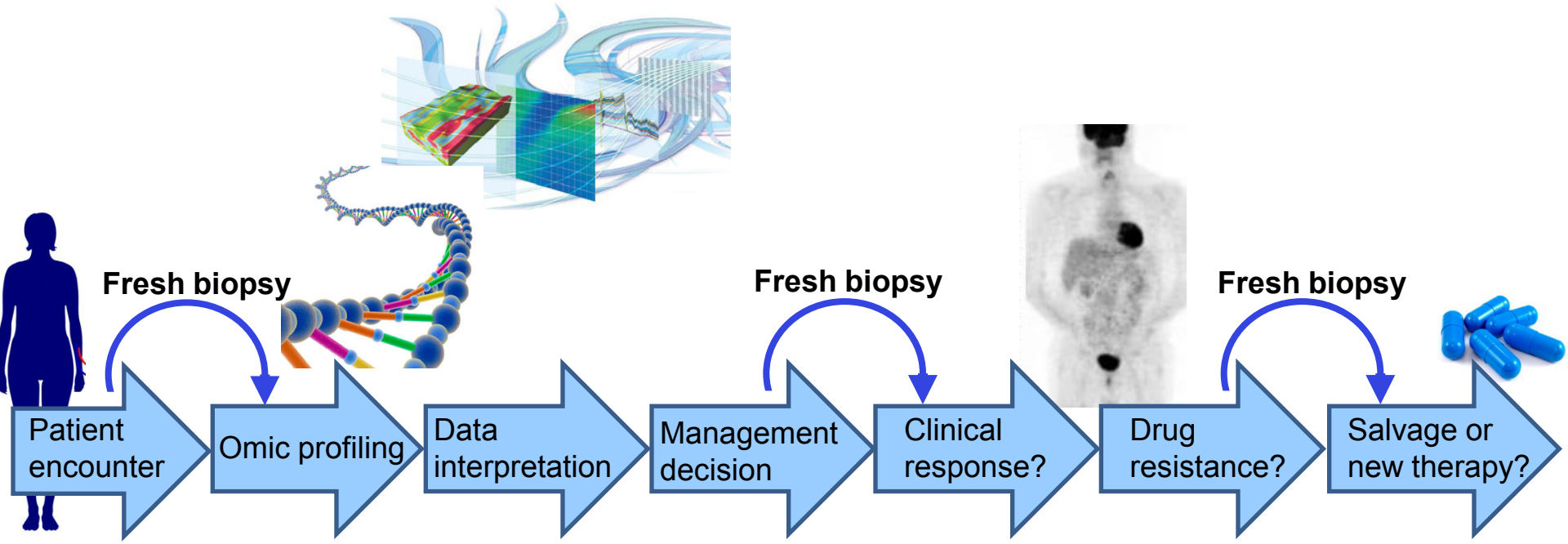
2 x 101 bp reads

>300 Gb per 8-day run

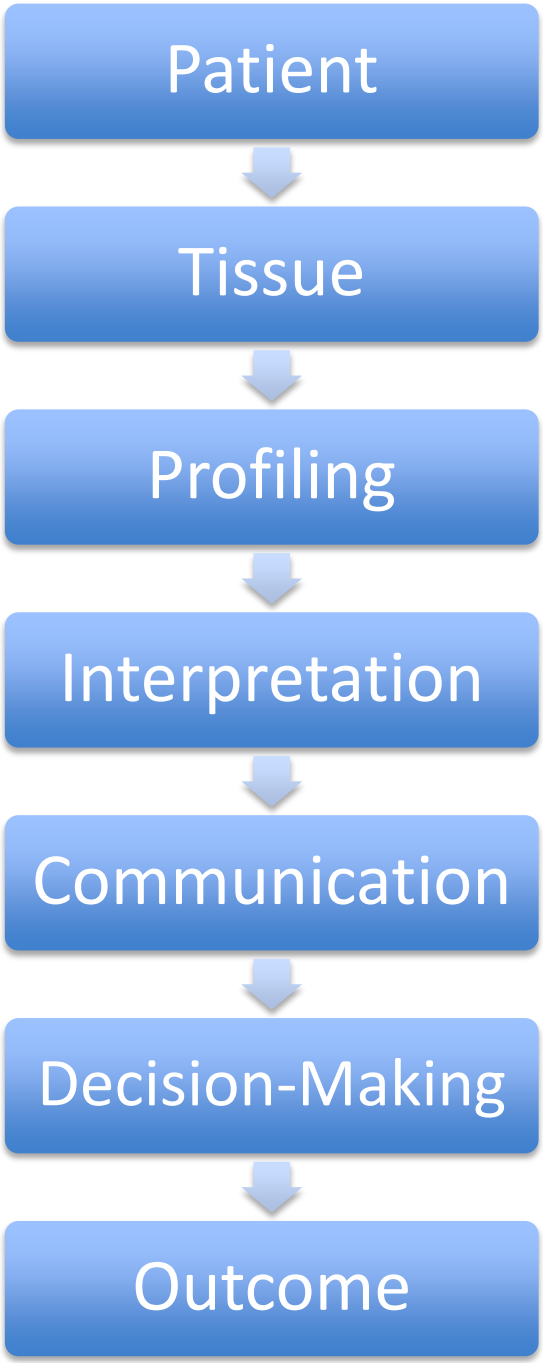
~40 Gb per day

(the human genome is 3 Gb)

The Engine of Precision Cancer Medicine



- Does genetic/molecular stratification identify patient subgroups that benefit from novel agents?
- Does the drug inhibit the relevant oncogenic pathway?
- What are the mechanisms of resistance to existing or emerging agents?
- What combinations hold promise to achieve more durable control?


Patient
Tissue
Profiling
Interpretation
Communication
Decision-Making
Outcome

Patient

Tissue

Profiling

Patient

Tissue

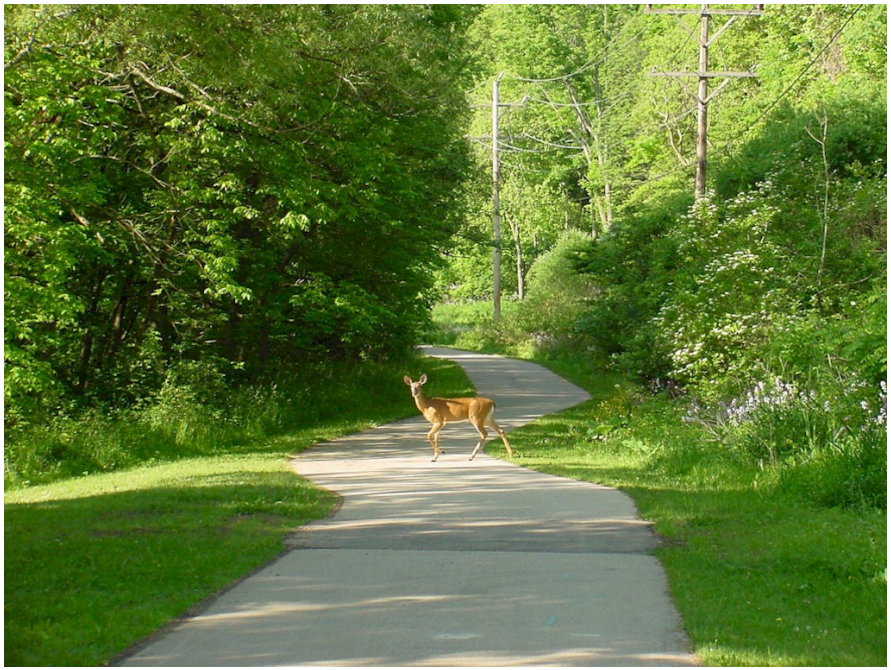
Profiling

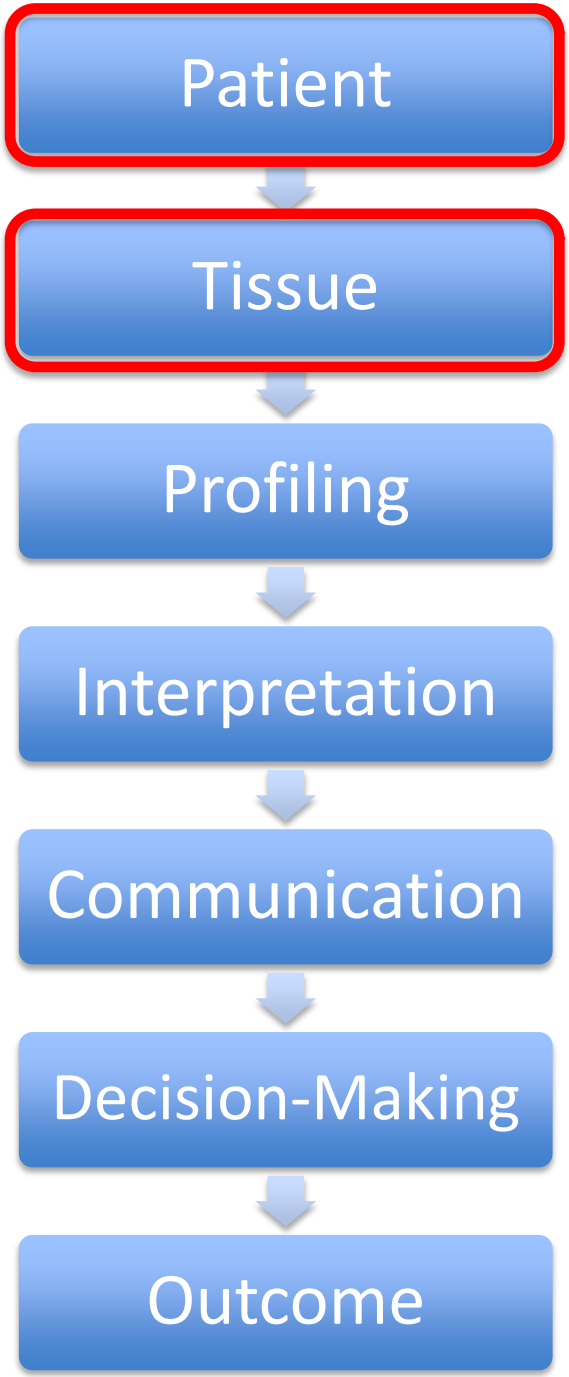
Interpretation

Communication

Decision-Making

Outcome

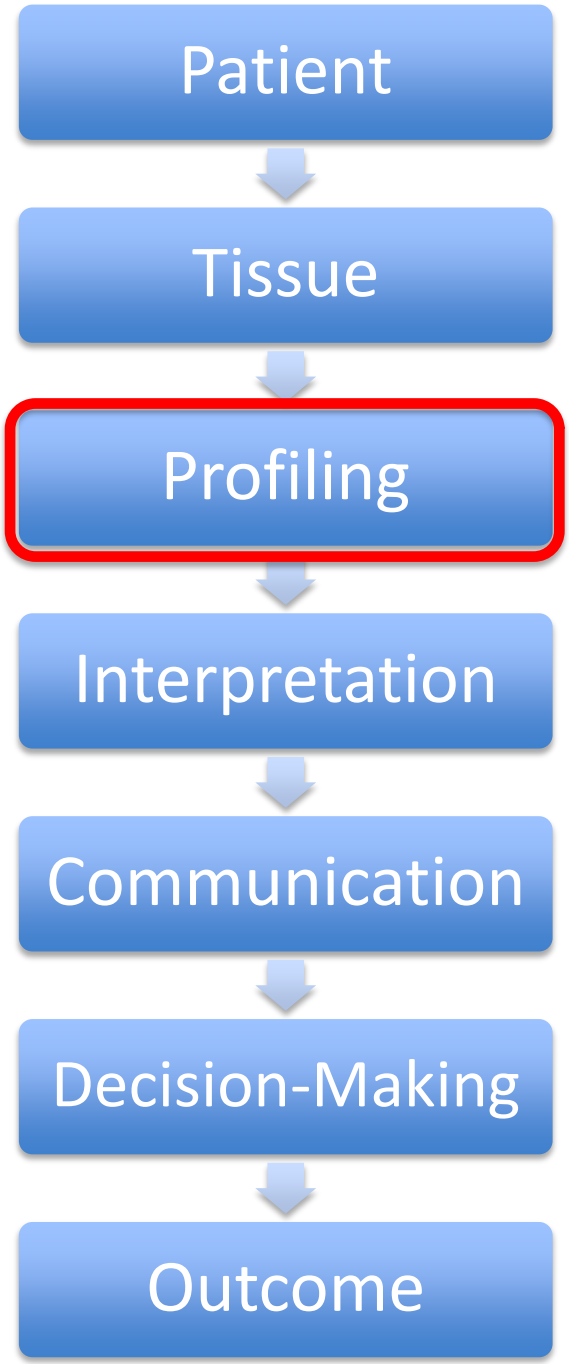




- Identification of patient
- Consent (genetics/data sharing)
- Genetic counseling

- Biopsies / Tissue Collection
- Quantity / Quality
- Sample tracking / LIMS
- Paired normal tissue / blood

Institutional Infrastructure



Tissue Processing

Profiling

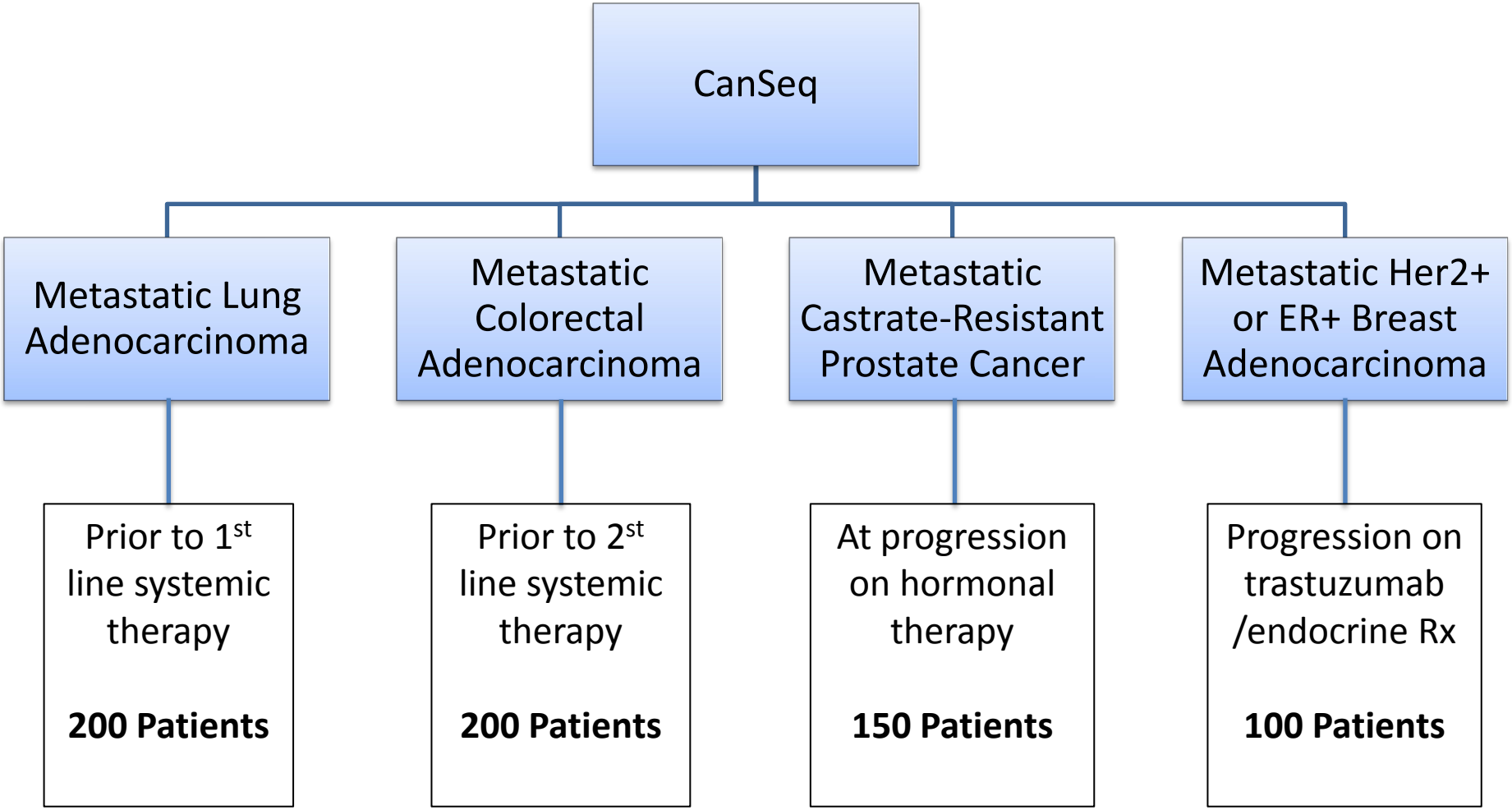
Basic Analysis

- Multiplexed genotyping
- Targeted sequencing
- Whole exome sequencing
- RNA-seq
- Whole genome sequencing
- Methylome studies

- Build internal capabilities or outsource?

CanSeq: Prospective Whole Exome Sequencing

Prospective whole-exome sequencing on patients at DFCI/BWH with return of clinically actionable results to clinical care team

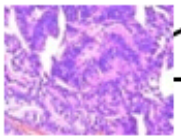


Target of ~200 patients in year 1

CanSeq: Sequencing Production Overview

Consented patient

Specimen retrieval



Pathology processing

Normal (uninvolved tissue)

tumor

DNA extraction

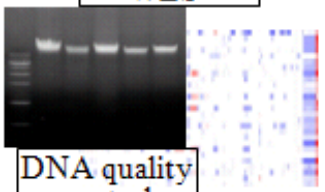
OncoMap (top-tier "actionable" events, CLIA lab)

Sample transfer for WES

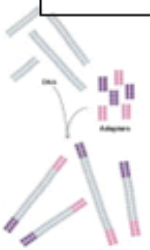
Neal Lindeman (BWH Path.)

DFCI/BWH

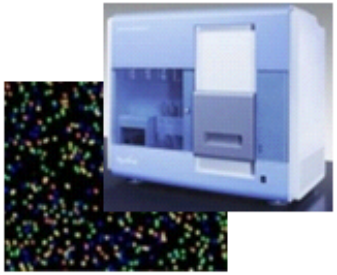
Broad Inst.



DNA quality control



Library construction and hybrid selection



Whole exome sequencing and analysis

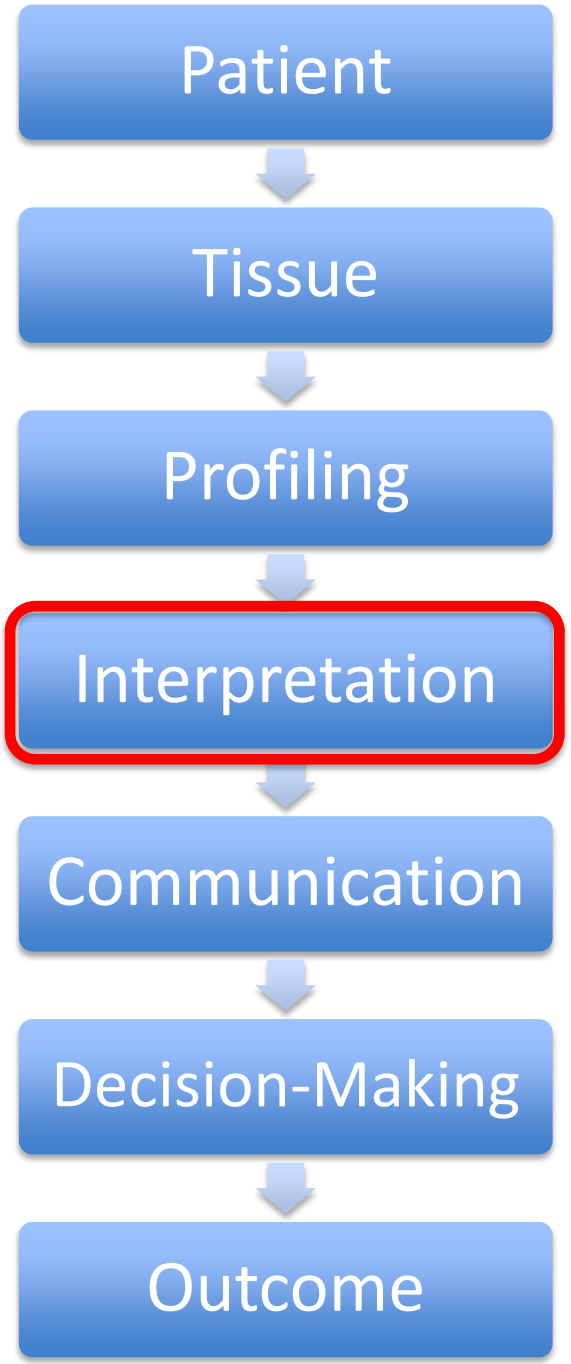
Identification of somatic and germline alterations (Aim 1)

List of potentially "actionable" and "consequential" variants (Aim 2)

Prioritized events for oncology evaluation (Aim 3)

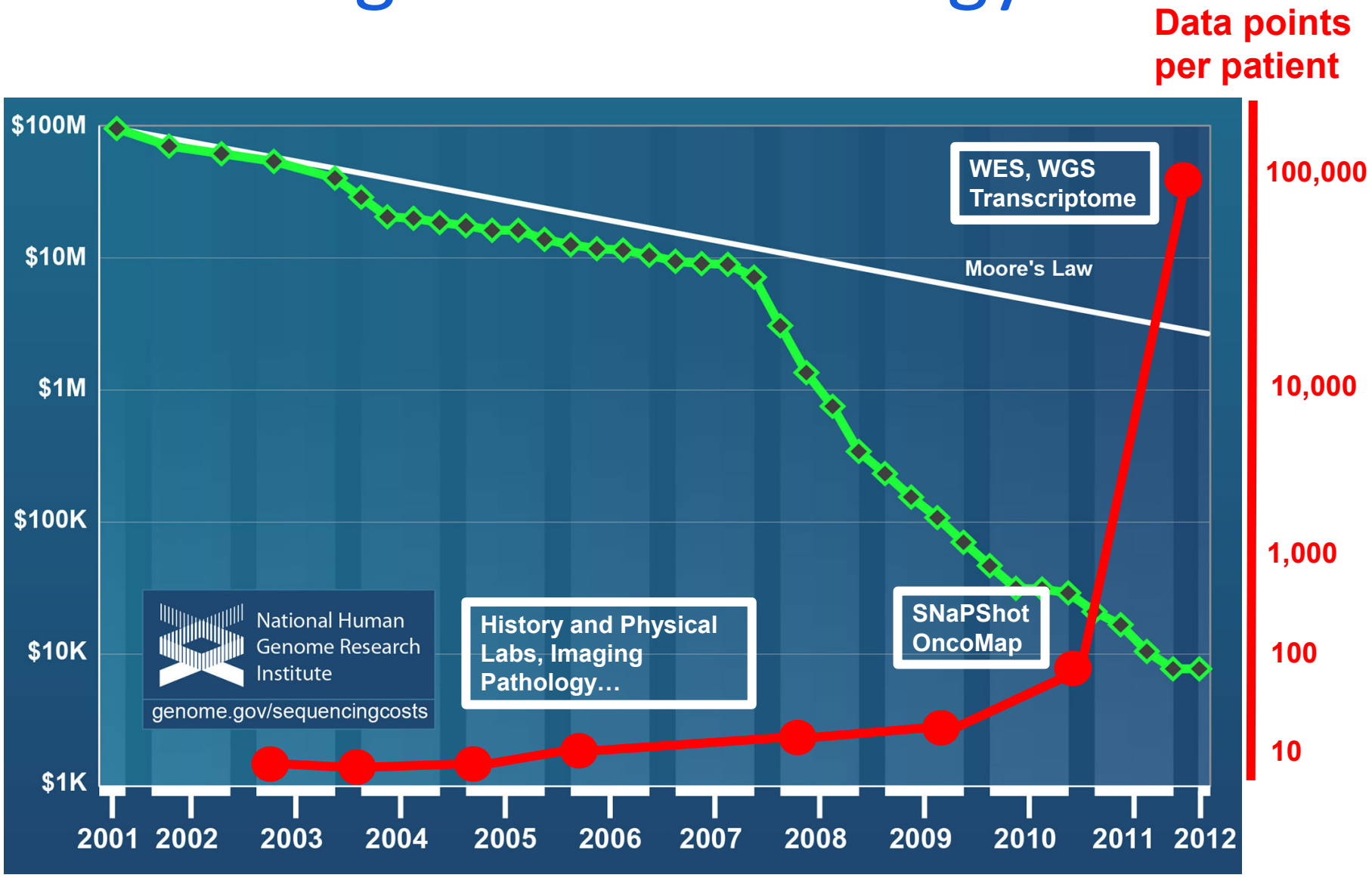
Cancer Genome Evaluation Committee (CGEC), DFCI (***Judy Garber***)

Final report to treating oncologist



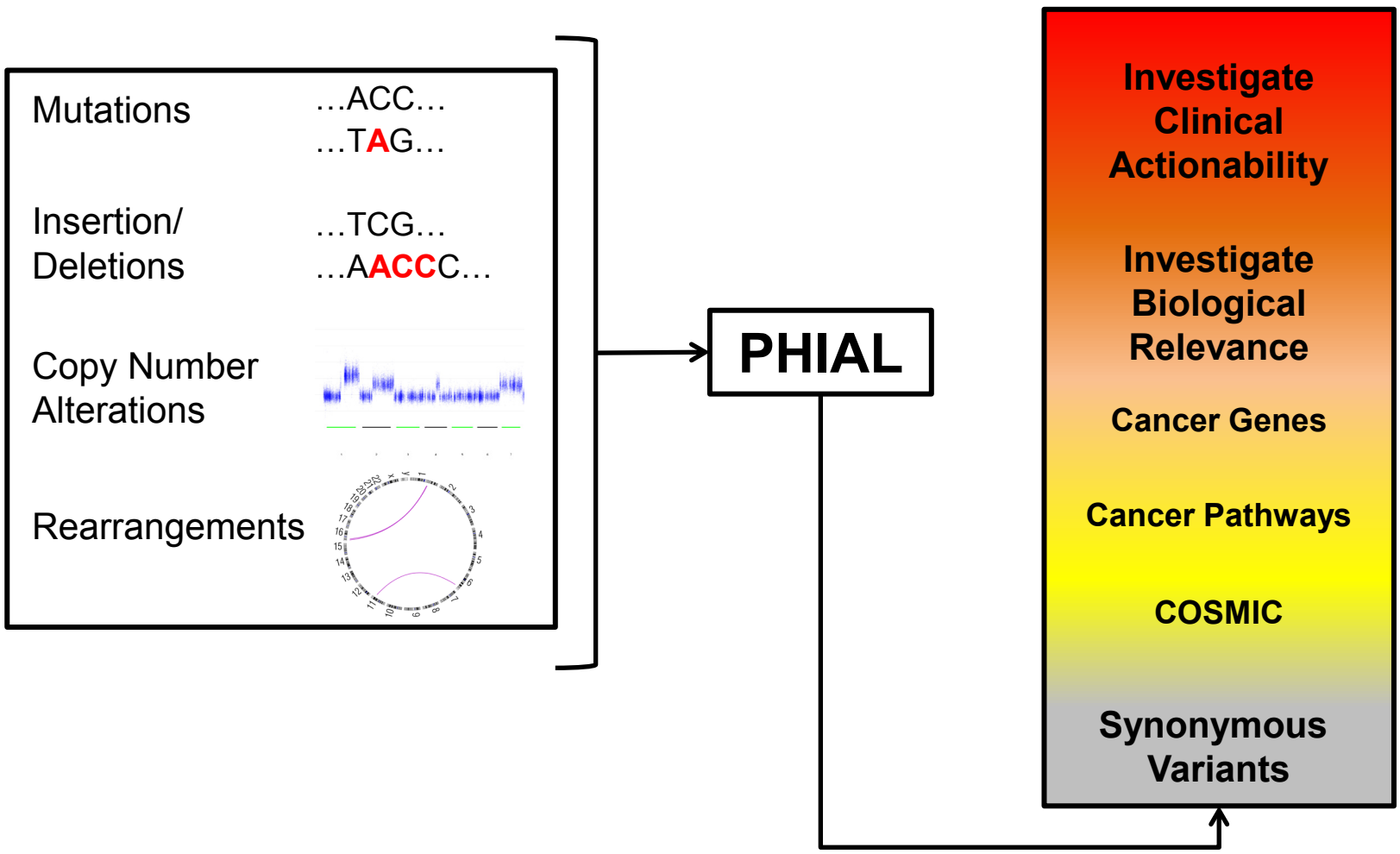
How can you interpret the profiling data for use by a clinician and patient?

Big Data in Oncology



Source: NHGRI

Precision Heuristics for Interpreting the Alteration Landscape (PHIAL)



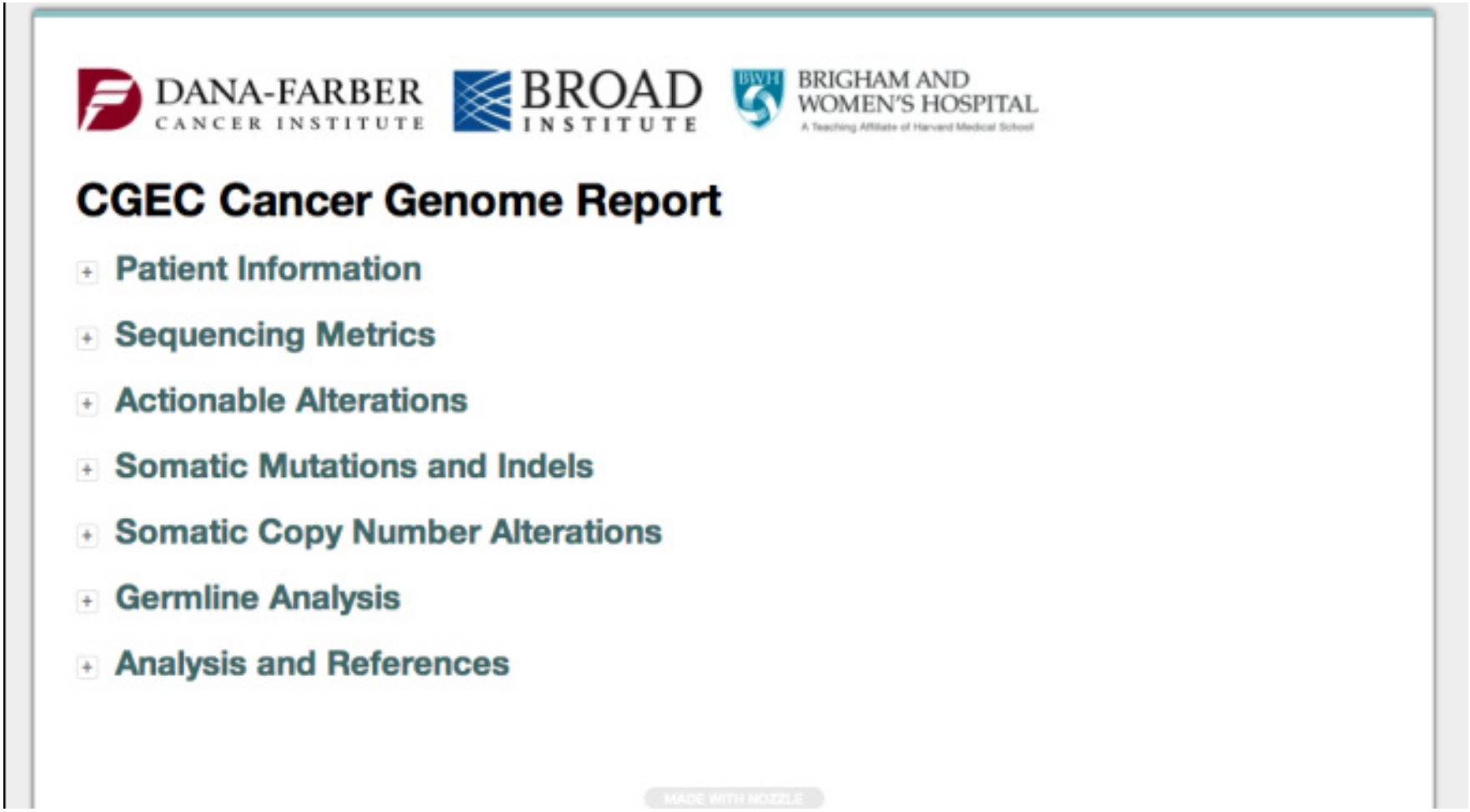
Eli Van Allen

Evidence Levels for Somatic Alterations

	Tier 1 (FDA-Approved / Standard Therapies)	Tier 2 (Clinical Trials / Experimental Therapies)	Prognostic / Diagnostic
A	Clinically Validated	Eligibility Criteria for Trial	Clinically Validated
B	Limited Evidence	Limited Evidence	Limited Evidence
C	Evidence in another tumor type *only*	Evidence in another tumor type *only*	
D	Pre-clinical Evidence	Pre-clinical Evidence	
E	Theoretical	Theoretical	

Wagle, Berger *et al*., *Cancer Discovery*, November 2011

Evaluating Actionable Alterations



Eli Van Allen

Evaluating Actionable Alterations

Actionable Table and Details

Table 4. Actionable findings with details, sorted by actionability score

Gene	Alteration	Variant	Coverage	Allelic_fraction	Tier	Trials
KRAS	p.A146V	Missense_Mutation	248	0.61	Actionable: Tier 2-A, Plausibly Actionable, Tier 1-B(R), Prognostic/Diagnostic-B	Click here
STK11	p.G279fs	Frame_Shift_Del	23	0.48	Plausibly Actionable: Tier 1-C, 1-D, and 2-B	Click here
ATM	p.K208fs	Frame_Shift_Ins	39	0.36	Plausibly Actionable: Tier 2-B	Click here
BCL6	p.E419V	Missense_Mutation	112	0.53	Theoretically Actionable: Tier 2-E	Click here

KRAS p.A146V: Activating mutations in KRAS are among the most common genetic alterations in human tumors. KRAS mutations play a central role in tumor progression in multiple cancer types, and have been implicated in poor prognosis and resistance to therapy.

KRAS alterations are common across numerous malignancies. Activating KRAS mutations are found in 15 to 30% of all patients with non-small cell lung cancer (NSCLC).

This alteration has rarely been found in other cancer types. This alteration has only been reported in 15 colorectal cancer cases in the COSMIC database. An additional 68 cases of A146T have been reported in colorectal cancer in the COSMIC database. However, one systematic study of exon 4 mutations in conorectal cancer demonstrated the presence of A146 mutations in 5% of colon cancers.

This alteration is a known activating mutation, though may be less potent than the more common codon 12 and 13 mutations.

Activating mutations in KRAS predict poor survival in patients with NSCLC, though these studies have generally only included codon 12 and 13 mutations. Activating mutations in KRAS may predict sensitivity to inhibitors of the RAS/RAF/MEK/ERK pathway. Preclinical studies have shown that MEK inhibitors, in particular, may be effective for KRAS mutant tumors, and these agents are in clinical trials for patients with KRAS mutant cancers. Activating KRAS mutations may also predict resistance to anti-EGFR therapies.

STK11 p.G279fs: STK11 is a well-known tumor suppressor (also known as LKB1) that is commonly inactivated in several cancers. Germline mutations in STK11 cause Puetz-Jeghers Syndrome (PJS).

This gene has been implicated in NSCLC. In addition, it is commonly seen in conjunction with KRAS mutations

This gene has been implicated in NSCLC. This specific alteration has not been reported in the COSMIC database for NSCLC, though inactivating mutations in STK11 are common in this tumor type, ocurring at a rate of 5-15% of NSCLC. They commonly co-occur with KRAS mutations.

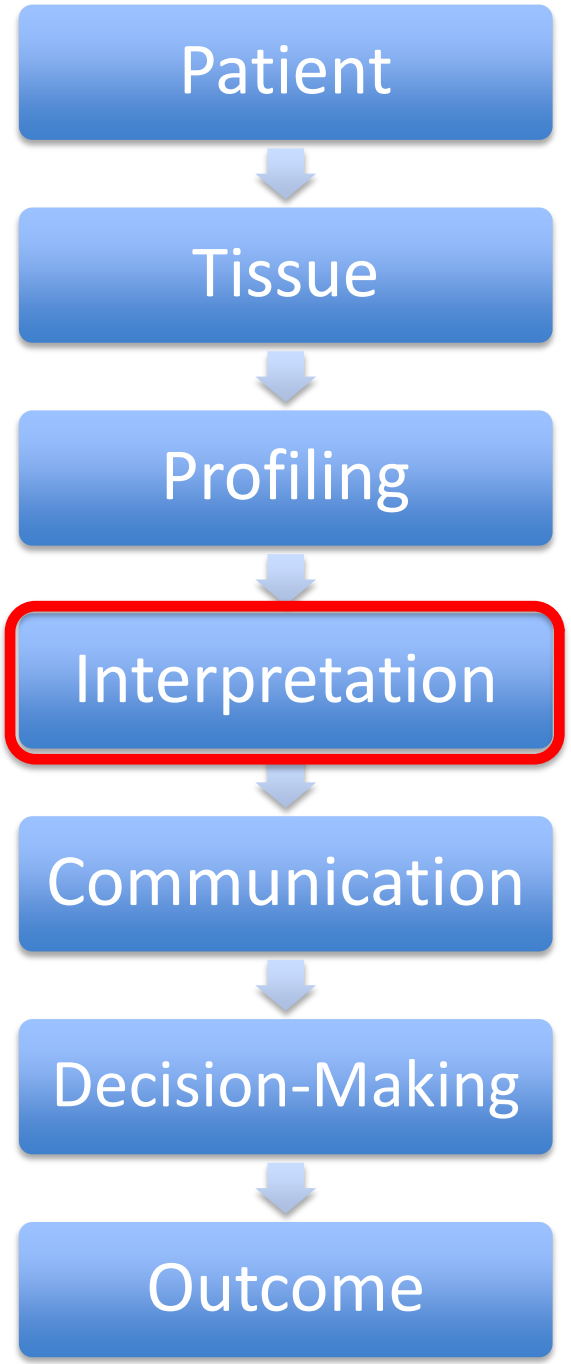
This alteration is likely inactivating, since it is a frameshift mutation that occurs at codon 279 out of 434.

Loss of STK11 activates the MTOR pathway and therefore may predict sensitivity to inhibitors of this pathway. Preclinical evidence suggests that MTOR

Eli Van Allen

Cancer Genome Evaluation Committee (CGEC)

- Judy Garber, *Co-chair*
- Pasi Janne, *Co-chair*
- George Demetri
- Matthew Freedman
- Charles Fuchs
- Levi Garraway
- Gad Getz
- Monica Giovanni
- Stacy Gray
- Elaine Hiller
- Franklin Huang
- Katherine Janeway
- Steven Joffe
- Ian Krop
- David Kwiatkowski
- Neal Lindeman
- Jeffrey Meyerhardt
- Cynthia Morton
- Michael Murray
- Giovanni Parmigiani
- Mark Pomerantz
- Irene Rainville
- Huma Rana
- Scott Rodig
- Barrett Rollins
- Geoffrey Shapiro
- Sapna Syngal
- Eliezer Van Allen
- Nikhil Wagle
- Brian Wolpin
- Matthew Yurgelun

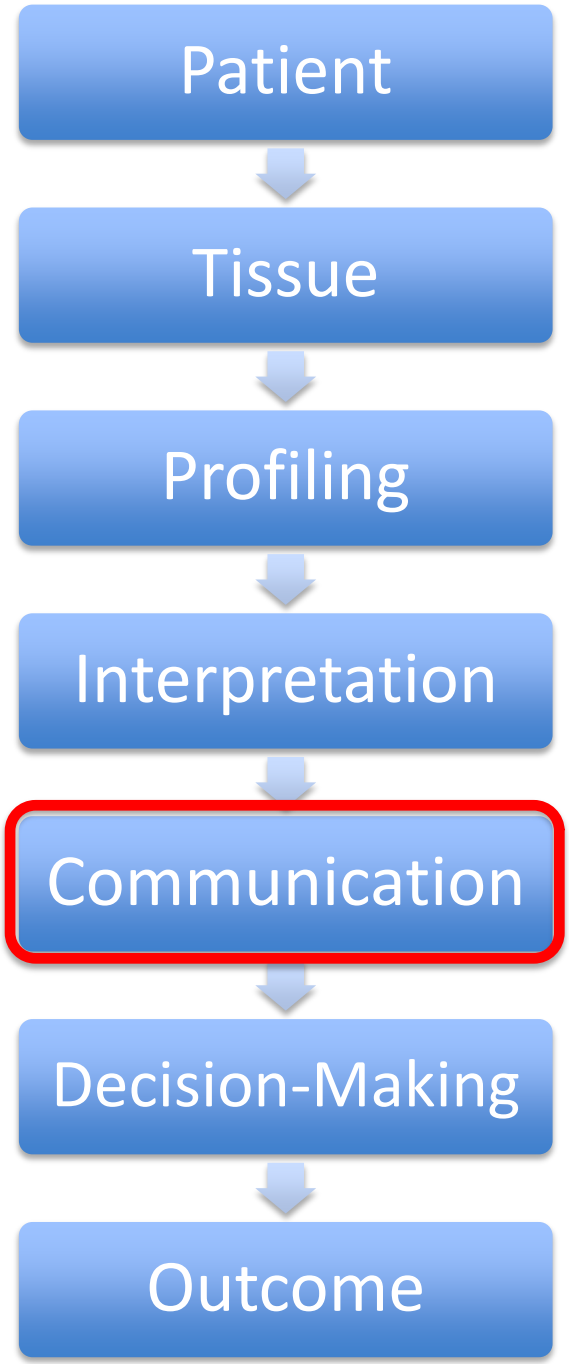


- **Heuristic Tools**
- **Curation / Annotation Teams**
- **Genomics Tumor Boards**
- **Knowledgebase**

- VUS investigative team
- Patient-derived cancer cell lines

- Outcomes database
- Genomics registry

- Integrative analyses
- Machine learning



Once the data has undergone clinical interpretation, how do you effectively communicate the information to the clinical team & patient in a usable way?

Reporting Results to Clinicians

DANA-FARBER CANCER INSTITUTE | BROAD INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL

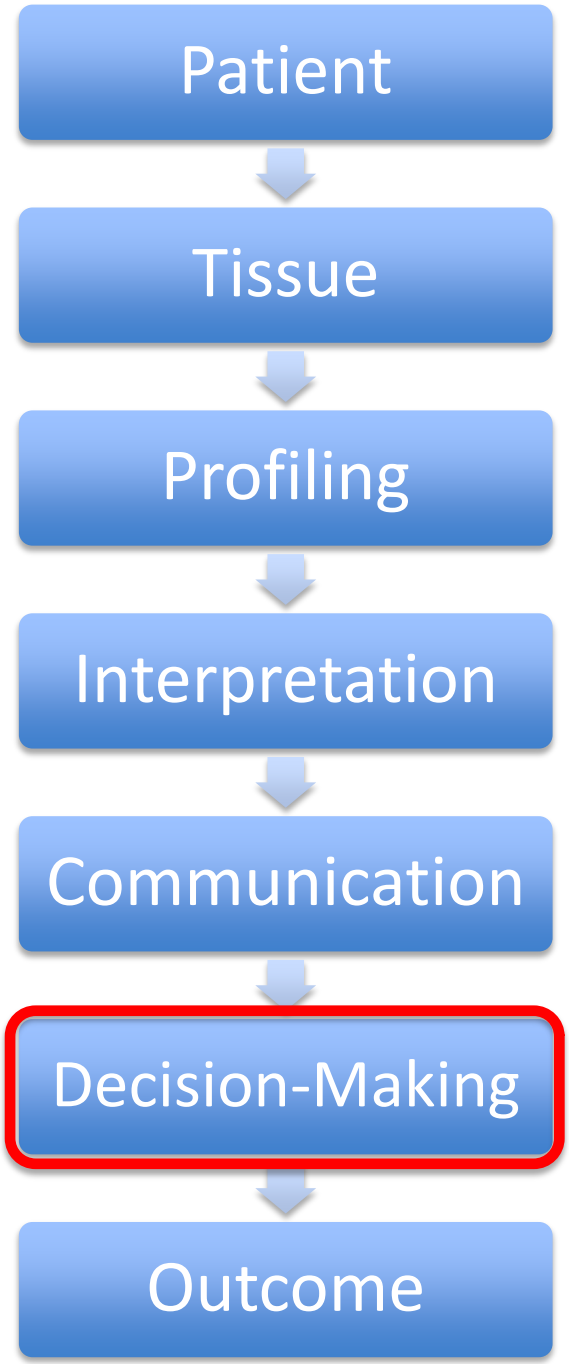
CanSeq Cancer Genome Report

Patient ID: xxxxxxx
DOB: xxxxx
Diagnosis: Lung Adenocarcinoma

ACTIONABLE SOMATIC ALTERATIONS				
Alteration	Action / Agent	FDA Approved?	Level of Evidence	Validated by:
KRAS A146V	MEK Inhibitors Resistance to EGFR inhibitors Poor prognosis		Eligibility Criteria Limited Clinical Theoretical	IonTorrent Seq
STK11 G279fs	Everolimus Temsirolimus mTOR Inhibitors Dasatinib FAK inhibitors	Yes Yes Yes 	Other tumor type Other tumor type Pre-clinical Pre-clinical Pre-clinical	IonTorrent Seq
ATM K208fs	PARP inhibitors		Pre-clinical	IonTorrent Seq

***KRAS* A146V**

- Activating mutations in KRAS are among the most common genetic alterations in human tumors. KRAS mutations play a central role in tumor progression in multiple cancer types, and have been implicated in poor prognosis and resistance to therapy.
- KRAS alterations are common across numerous malignancies. Activating KRAS mutations are found in 15–30% of all patients with non-small cell lung cancer (NSCLC).
- **This alteration is a known activating mutation**, though may be less potent than the more common codon 12 and 13 mutations (PMID: 20570890).
- **This alteration has not been reported in the COSMIC database for NSCLC.** Furthermore, A146 mutations in KRAS were not found in 2 studies comprised 449 cases of NSCLC in which KRAS was sequenced in its entirety (PMID: 18948947, 18632602).
- **This alteration has rarely been found in other cancer types.** This alteration has only been reported in 15 colorectal cancer cases in the COSMIC database. An additional 68 cases of A146T have been reported in colorectal cancer in the COSMIC database. However, one systematic study of exon 4 mutations in colorectal cancer demonstrated the presence of A146 mutations in 5% of colon cancers (PMID: 20570890).
- **Activating mutations in KRAS predict poor survival in patients with NSCLC**, though these studies have generally only included codon 12 and 13 mutations.
- **Activating mutations in KRAS may predict sensitivity to inhibitors of the RAS/RAF/MEK/ERK pathway.** Preclinical studies have shown that MEK inhibitors, in particular, may be effective for KRAS mutant tumors, and these agents are in clinical trials for patients with KRAS mutant cancers.
- **Activating KRAS mutations may also predict resistance to anti-EGFR therapies.**



Does the information provided impact clinical decision-making?

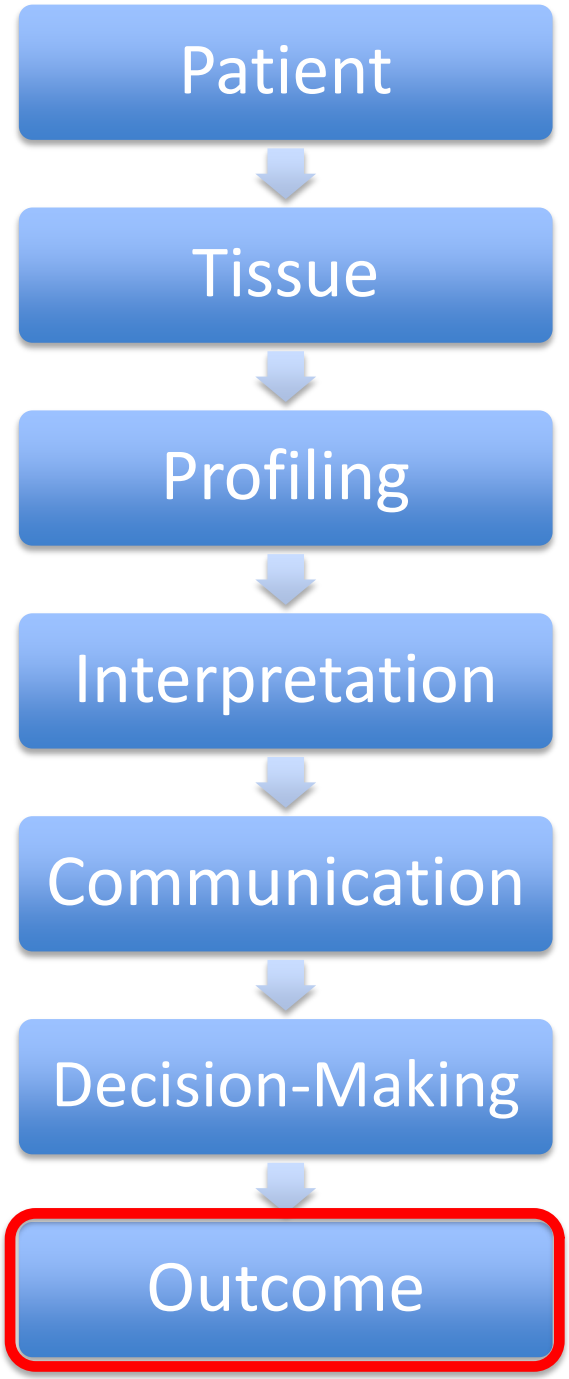
CanSeq: Patient with Lung Adenocarcinoma

- 61 year old man with a history of breast cancer who then developed lung adenocarcinoma
- Initially surgically resected but rapidly recurred as metastatic disease
- Progressed rapidly through standard chemotherapy
- Tested negative for *EGFR, KRAS, ALK*, *ROS* alterations

Example: Patient with Lung Adenocarcinoma

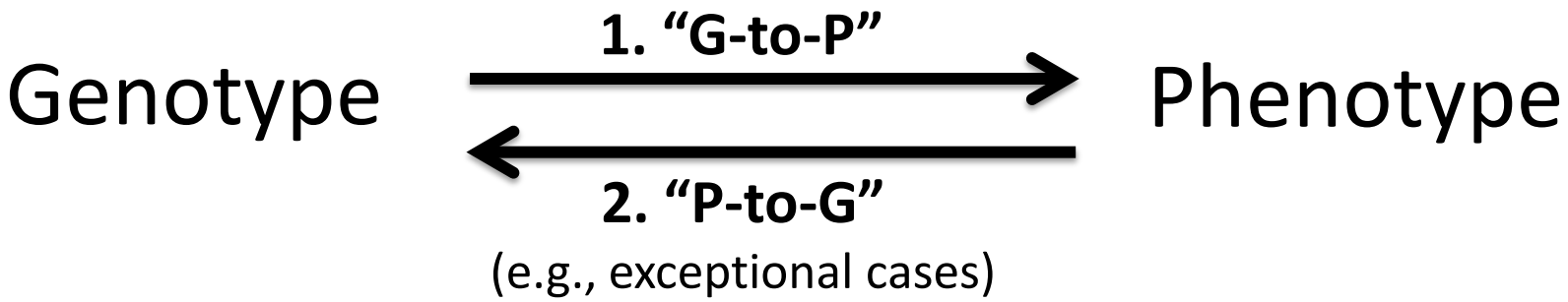
Patient 11-104.03: Lung Adenocarcinoma				
Alteration	Action / Agent	Category	Tier	Level of Evidence
KRAS A146V	MEK Inhibitors	Predictive	II	Eligibility Criteria
	CDK4/6 Inhibitors	Predictive	II	Pre-clinical
STK11 G279fs	Everolimus	Predictive	IIb	Other tumor type
	Temsirolimus	Predictive	IIb	Other tumor type
	mTOR Inhibitors	Predictive	II	Pre-clinical
	Dasatinib	Predictive	IIb	Pre-clinical
	FAK inhibitors	Predictive	II	Pre-clinical
ATM K208fs	PARP inhibitors	Predictive	II	Pre-clinical

Enrolled on a clinical trial based on his activating KRAS mutation



Does genomic profiling improve care and outcomes for patients with cancer?

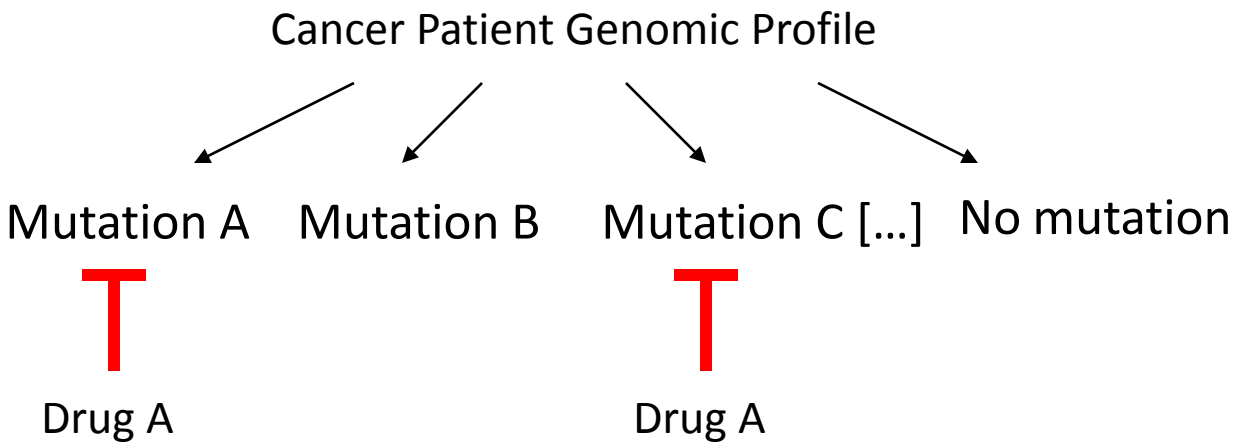
Categories of Genomics-Driven Clinical Studies in Cancer



3. Decision impact (switch rate)

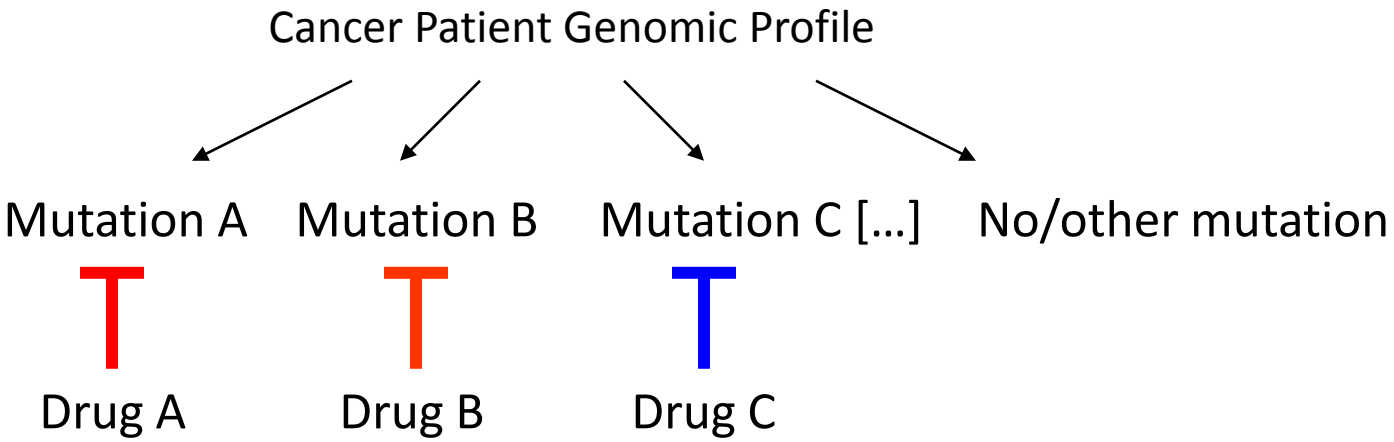
4. Platform/algorithm comparisons

Mutation-based Clinical Trials: "Drug-Centered" or "Basket" Approach



Test cohort: 100% with mutant A or C
Control cohort: at-large randomization (?)
Endpoints: Drug A survival, response rates in test versus control cohort

"Genomics Driven" Clinical Trials: "BATTLE-like" Approach



Patient Group #1: "Targeted group"
Mutation A + Drug A
Mutation B + Drug B
Mutation C + Drug C

Patient Group #2: "Empiric group"
Randomized agnostic to mutation status but controlled for tumor type

Endpoints: tumor response rate, survival in targeted versus empiric groups

Design integrated phase I/II trials to test "genomics-driven" hypotheses
Incorporation of correlative science (pharmacodynamics, imaging, additional omics)
Plan deep characterization of relapsing tumors

Acknowledgements

- **Nikhil Wagle**
- Pasi Janne
- Judy Garber
- Steve Joffe
- Stacy Gray
- Barrett Rollins
- Neal Lindeman
- Nelly Oliver
- **Eli Van Allen**
- Franklin Huang
- Julie Najita
- Lisa Digianni
- Carol Lowenstein
- Yolanda Martins
- Debra Morley
- Alanna Church

- Garraway Lab Members

- Irene Raineville
- Elaine Hiller
- Huma Rana
- Peter Lo
- Christine Lydon
- Lauren Brais
- Megan Gorman
- Caitlin Brennan
- Alanna Church
- Susanne Hooshmand
- Jessica Baroni
- Elizabeth Bair
- Angela Stroup
- Daniel Treacy
- Erru Yang
- Matthew Meyerson
- William Hahn

- Laura MacConaill
- Jane Song
- John Orechia
- Frank Kuo
- CCGD / PROFILE
- Daniel Auclair
- Lauren Ambrogio
- Deb Farlow
- Denielle Perrin
- Sheila Fisher
- Kristin Thompson
- Clint Chalk
- Kristin Ardlie
- Sara Chauvin
- Jane Wilkinson
- Brendan Blumenstiel
- Matthew Defelice
- BSP / GSP

- Gaddy Getz
- Gregory Kryukov
- Alexis Ramos
- Aaron McKenna
- Adam Keizun
- Pablo Tamayo
- Michael Lawrence
- Kristian Cibulskis
- Nils Gehlenborg
- Scott Carter
- David DeLuca
- Andrey Sivachenko
- Yotam Drier
- CGA
- Stacey Gabriel
- Todd Golub
- Eric Lander

DANA-FARBER CANCER INSTITUTE

The Patients

BROAD INSTITUTE

BWH BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

HARVARD MEDICAL SCHOOL