Actionable Genome Consortium: Defining the actionable genome, Setting technical standards

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IOM Workshop Workshop:
Policy Issues in the Development and Adoption of Molecularly Targeted Therapies for Cancer
November 10, 2014

Memorial Sloan Kettering Cancer Center

How do we accelerate drug discovery?

1. Define the Targets
2. Identify a “drug”
3. Identify the Patient

If correct in correct patient why no response:

1. Bad drug → Develop better drug
2. Co-alterations
3. Adaptive/Selective resistance.
4. Sub-clonal/Tumor Heterogeneity

} Rational Combinations?

How do we define the targets?

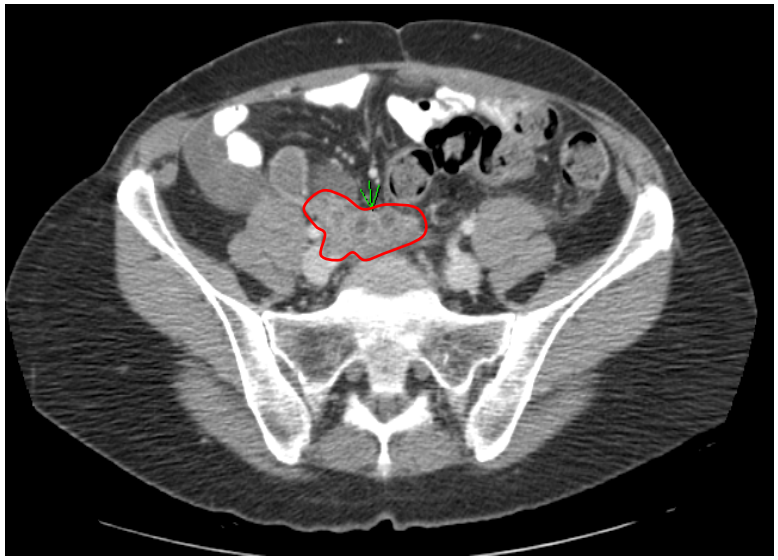
Genotype to Phenotype (G2P):

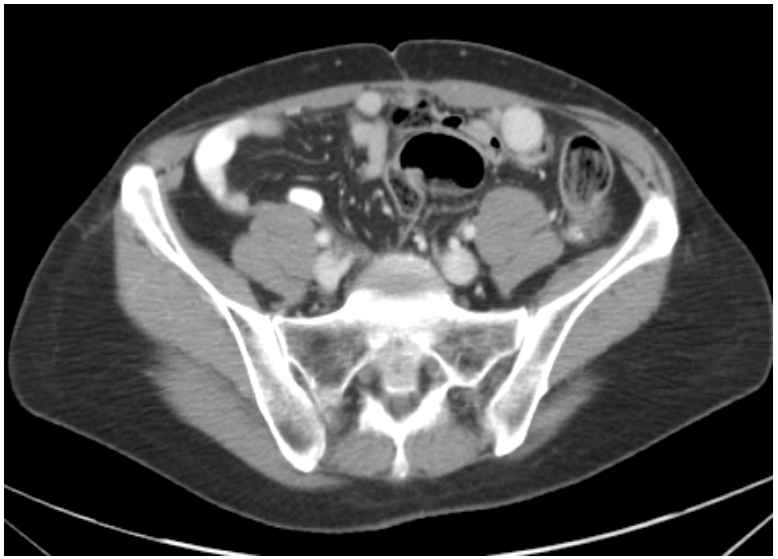
- Targets initially identified by retrospectively characterizing cohorts of tumors and cell lines.
- Many failures are due to inadequate target inhibition.
- Recent success with inhibitors of BRAF, ALK, etc.

Phenotype to Genotype (P2G):

- Can we identify the genetic basis for rare, extraordinary clinical responses?
- Would this then guide trials in select subpopulations.

Recurrent Ovarian Cancer



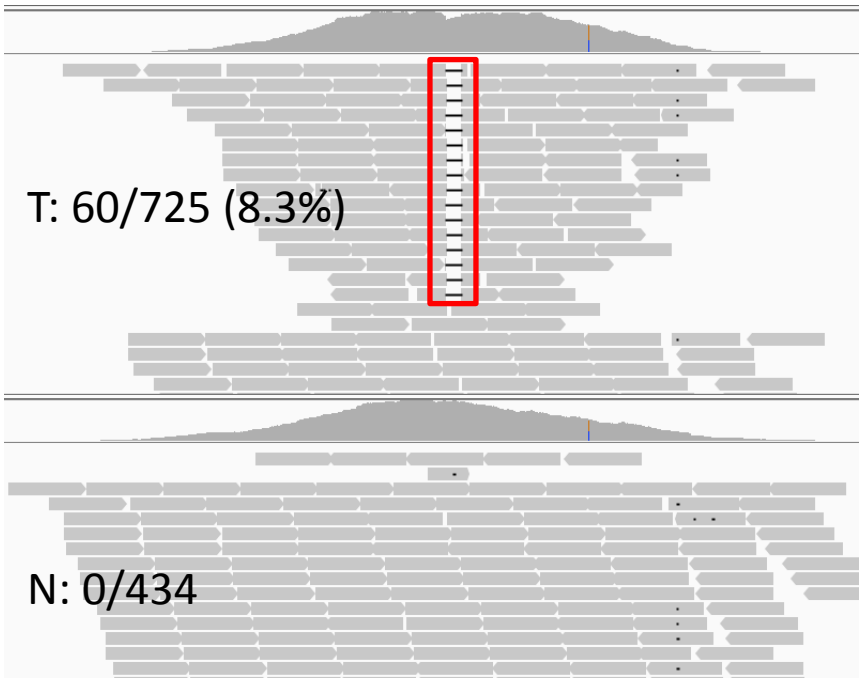


9/18/2009
2.8x4.2 cm vaginal cuff mass
Enrolled onto GOG 239 with AZD6244

11/19/2010
NED

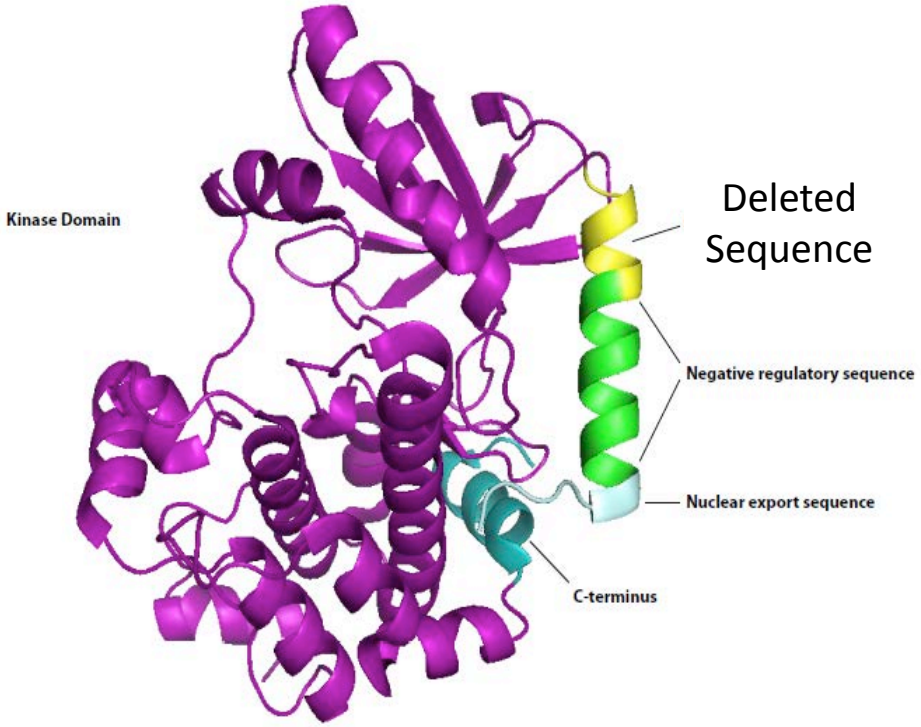
Last follow-up: 7/2013, still NED on drug

IMPACT assay of tumor (T) and peripheral blood (N)



***MAP2K1* in-frame deletion of 15 bp**

ACC CAG AAG CAG AAG GTG



*MAP2K1 plasmid tagged with GFP

Iyer/Aghaganian/Grisham

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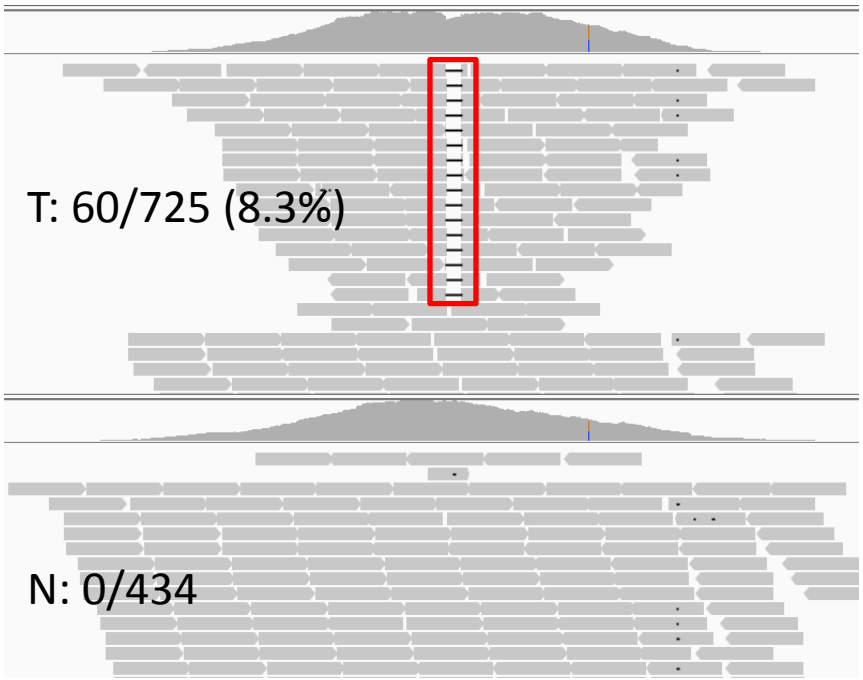

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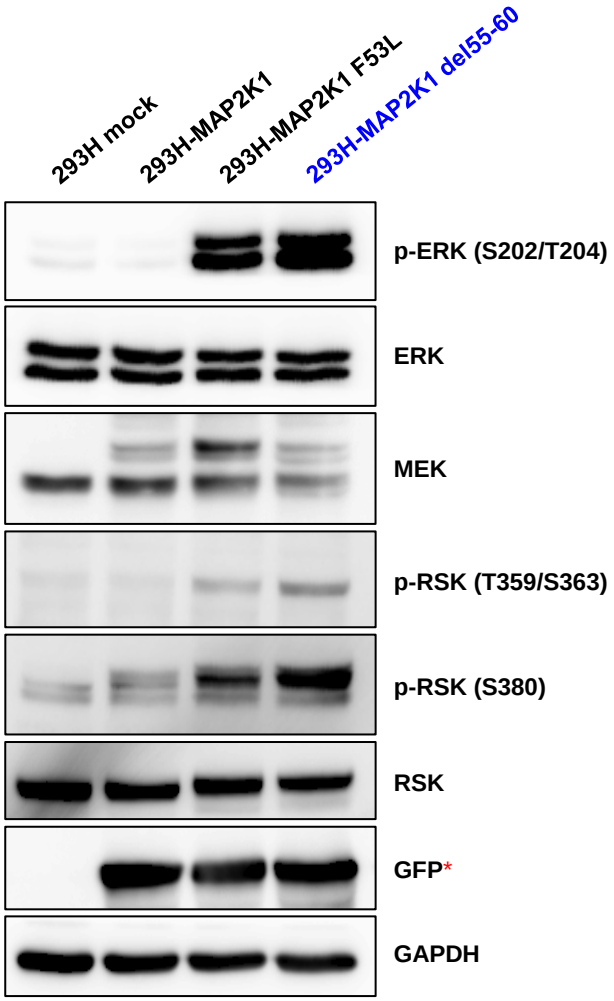
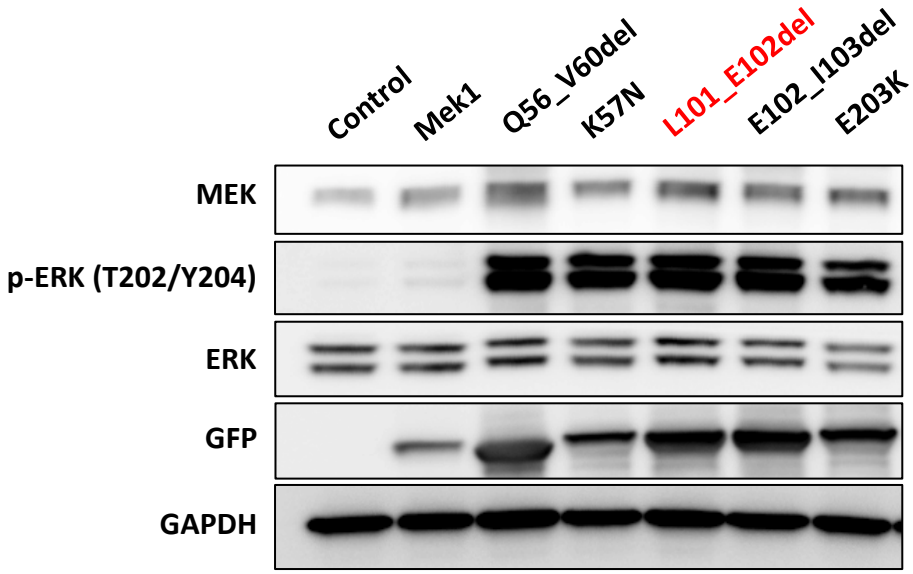


*MAP2K1 plasmid tagged with GFP

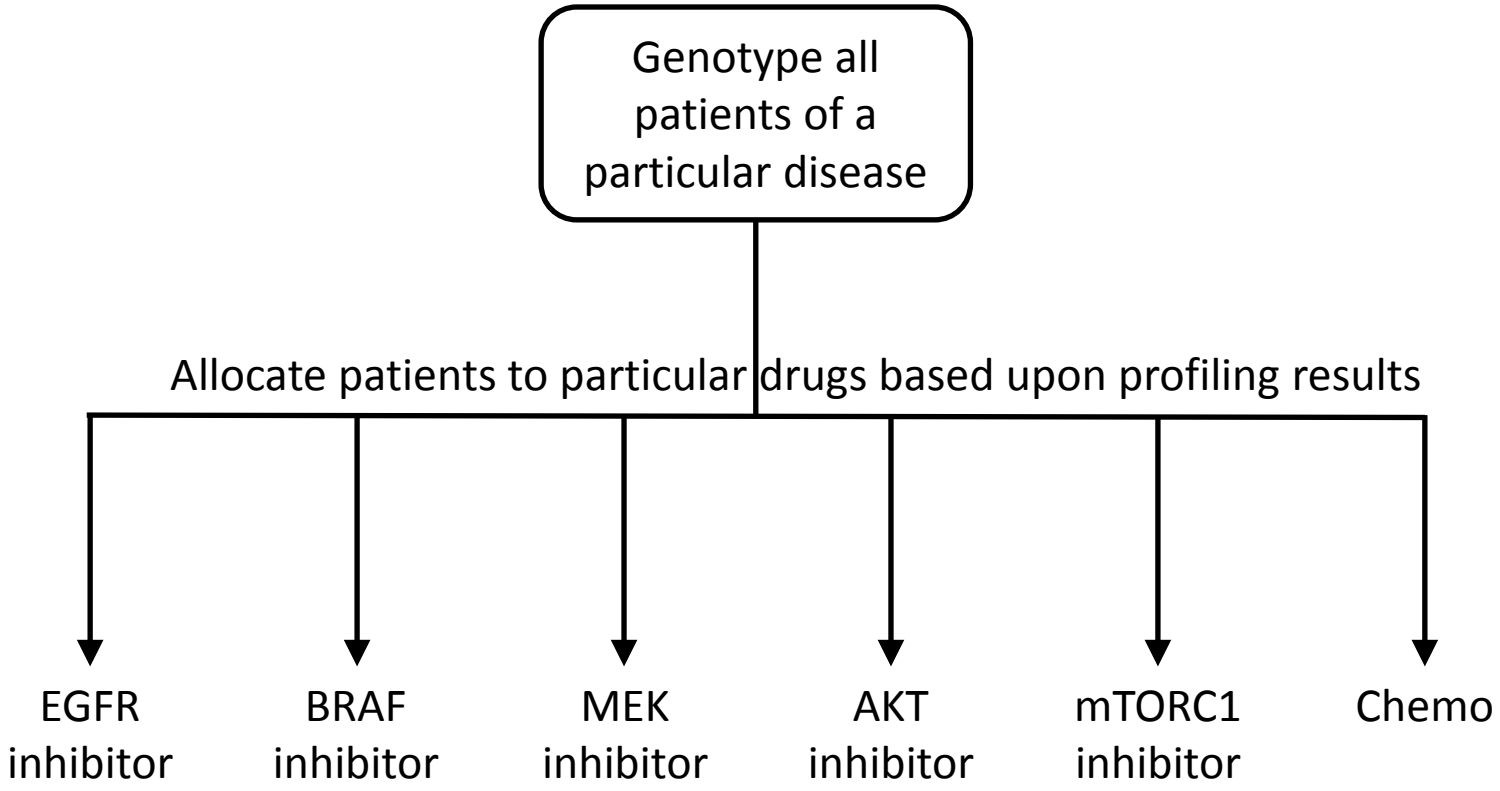
Iyer/Aghaganian/Grisham

5 mutations

Gene	Protein Change	Type	Allele Freq
PIK3CD	*N334K*	Missense	0.35
CDKN2AP16INK4A	*R112P*	Missense	0.28
ROS1	*S141R*	Missense	0.07
GATA3	*S370R*	Missense	0.07
MAP2K1	*LE101del*	Deletion	0.27



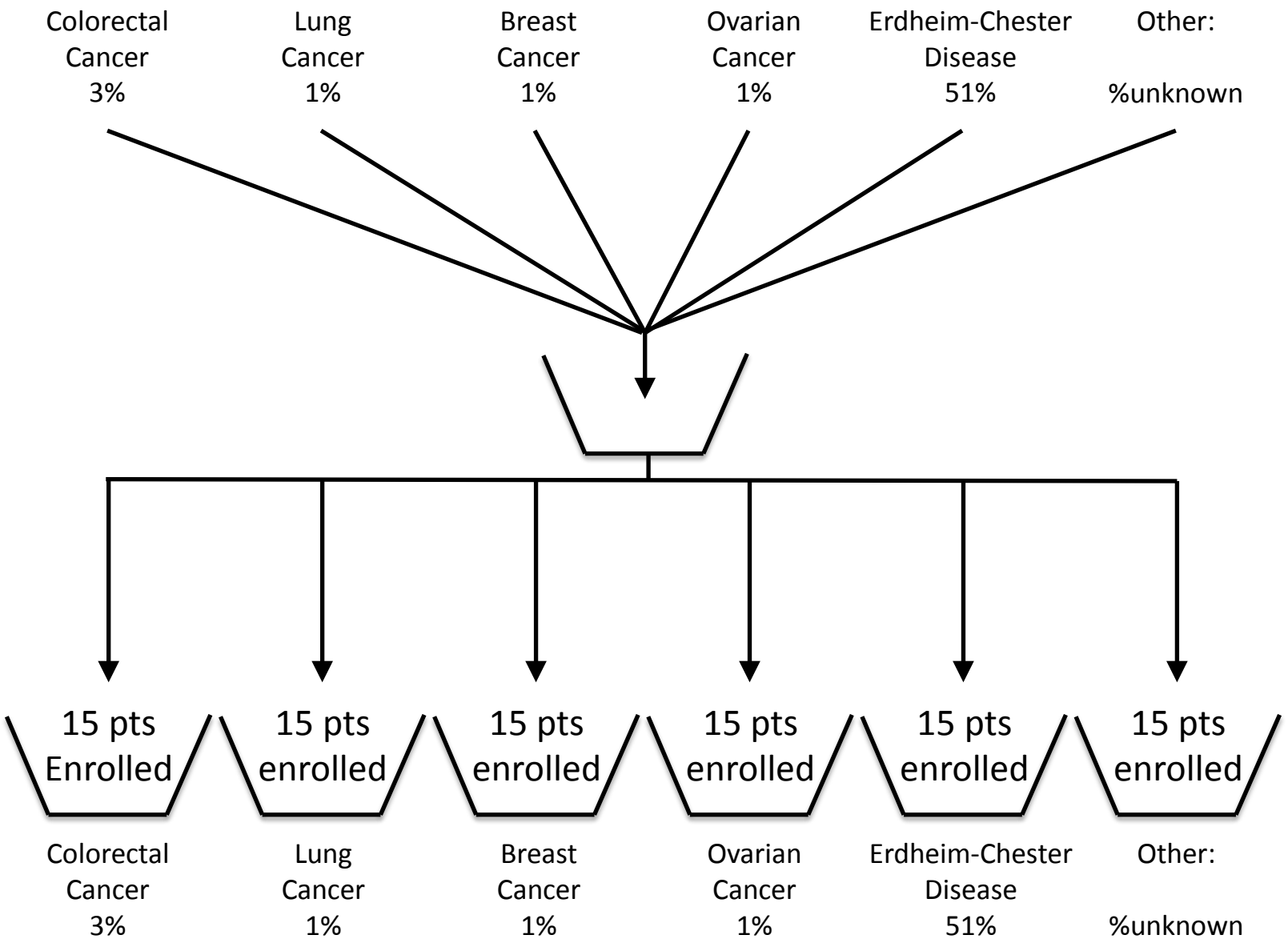
Umbrella/Master/Match study



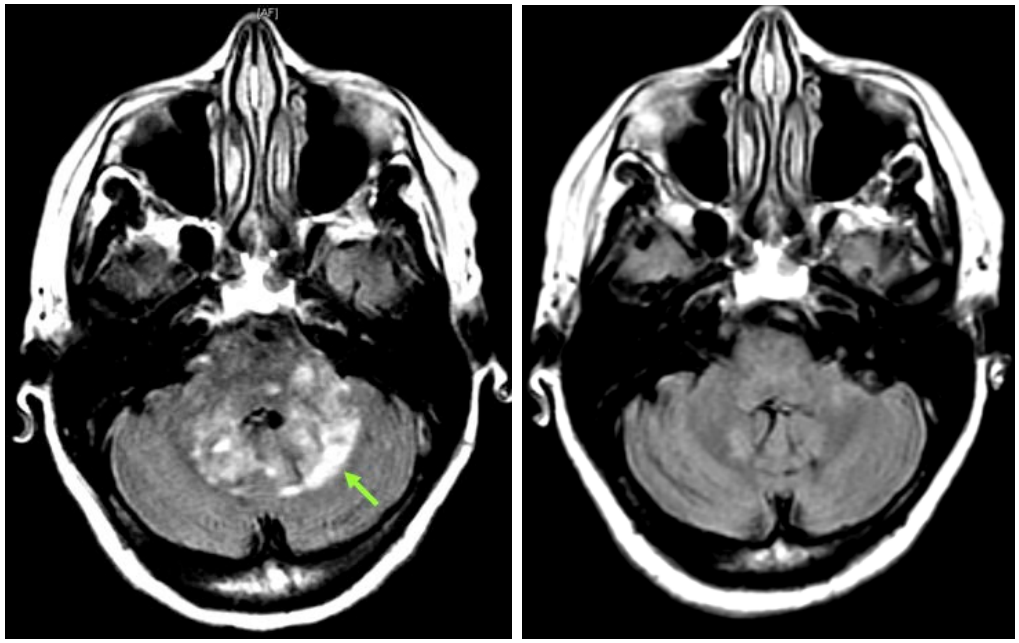
A few problems with this approach

- Drugs are often not best in class but what was available to the investigators at the time of study design.
- If an adaptive randomization design is used, it may become un-ethical during the coarse of the trial to randomize some patients. For example, EGFR mutants in NSCLC.
- The total number of patients is generally low and thus this design may not identify sufficient patients with “rare” mutations to test whether such mutations correlate with drug response (BRAF in Lung, MAP2K1 mutation in melanoma).

An alternative approach – The so-called "Basket" study



Basket Studies and Orphan Diseases - Erdheim-Chester Disease (ECD)



Pre-Tx

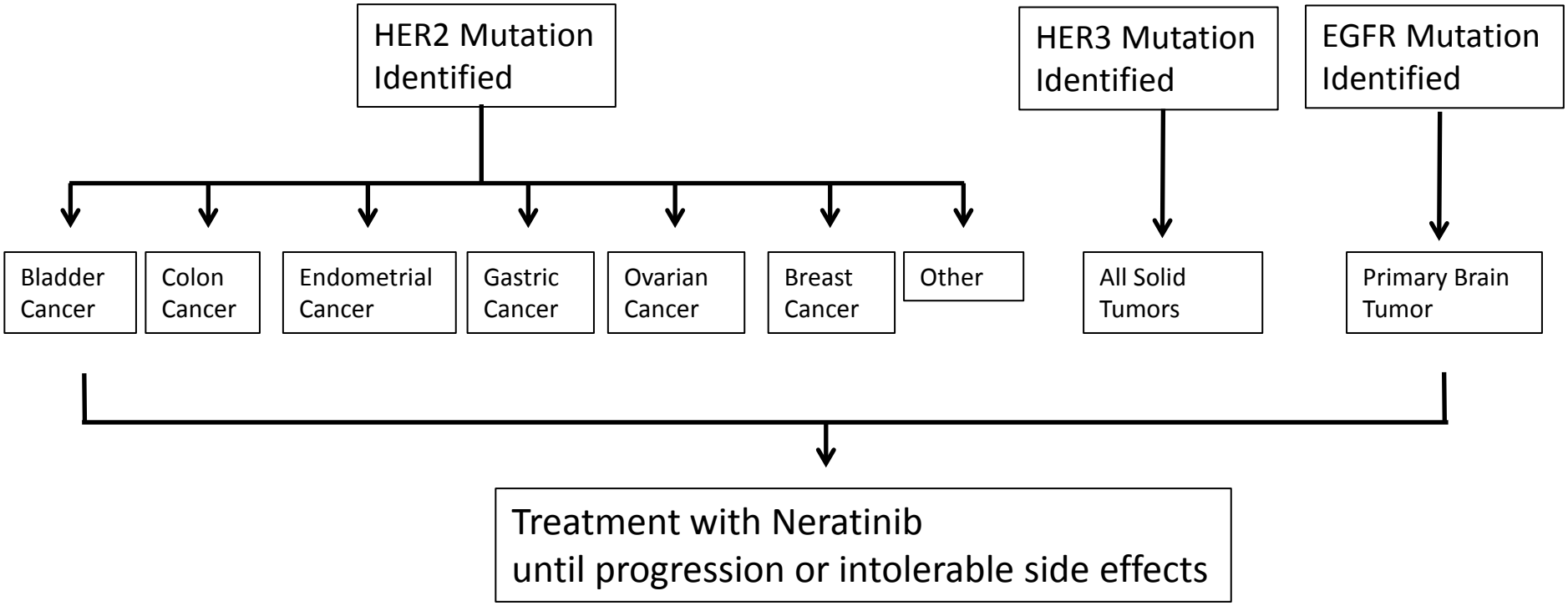
Post-Tx

- Rare histiocytic disorder

  (<500 pts in USA)
- Poor prognosis
- No prospective studies, no approved agents
- 50% BRAF mutation rate

Hyman, Baselga, et al, ASCO 2014

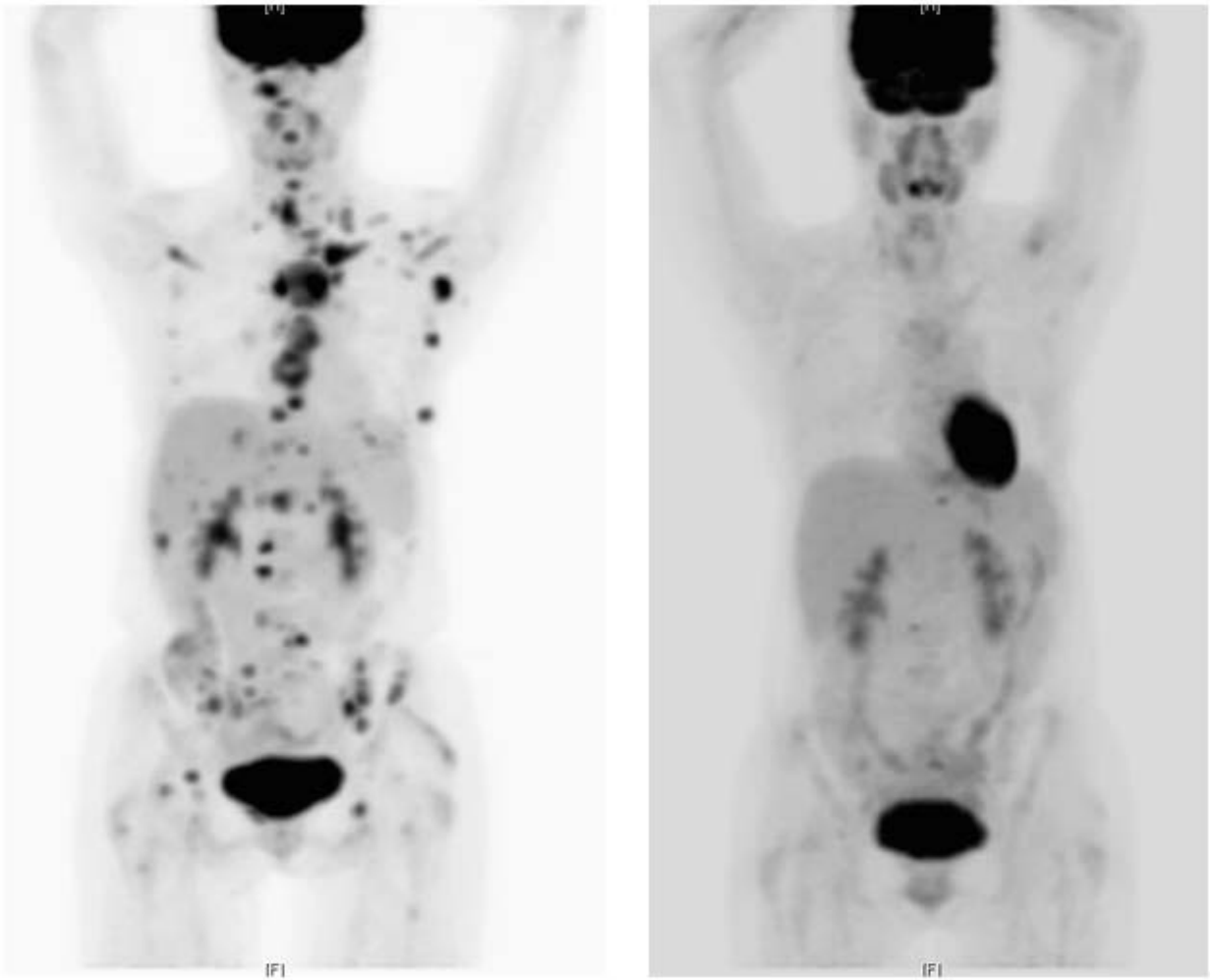
Neratinib Basket Study Schema



Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoints: PFS, OS

Multinational Study, MSKCC Lead Site
MSKCC Central Repository for All Biospecimens

HER2 non-amplified, V777L Breast Cancer



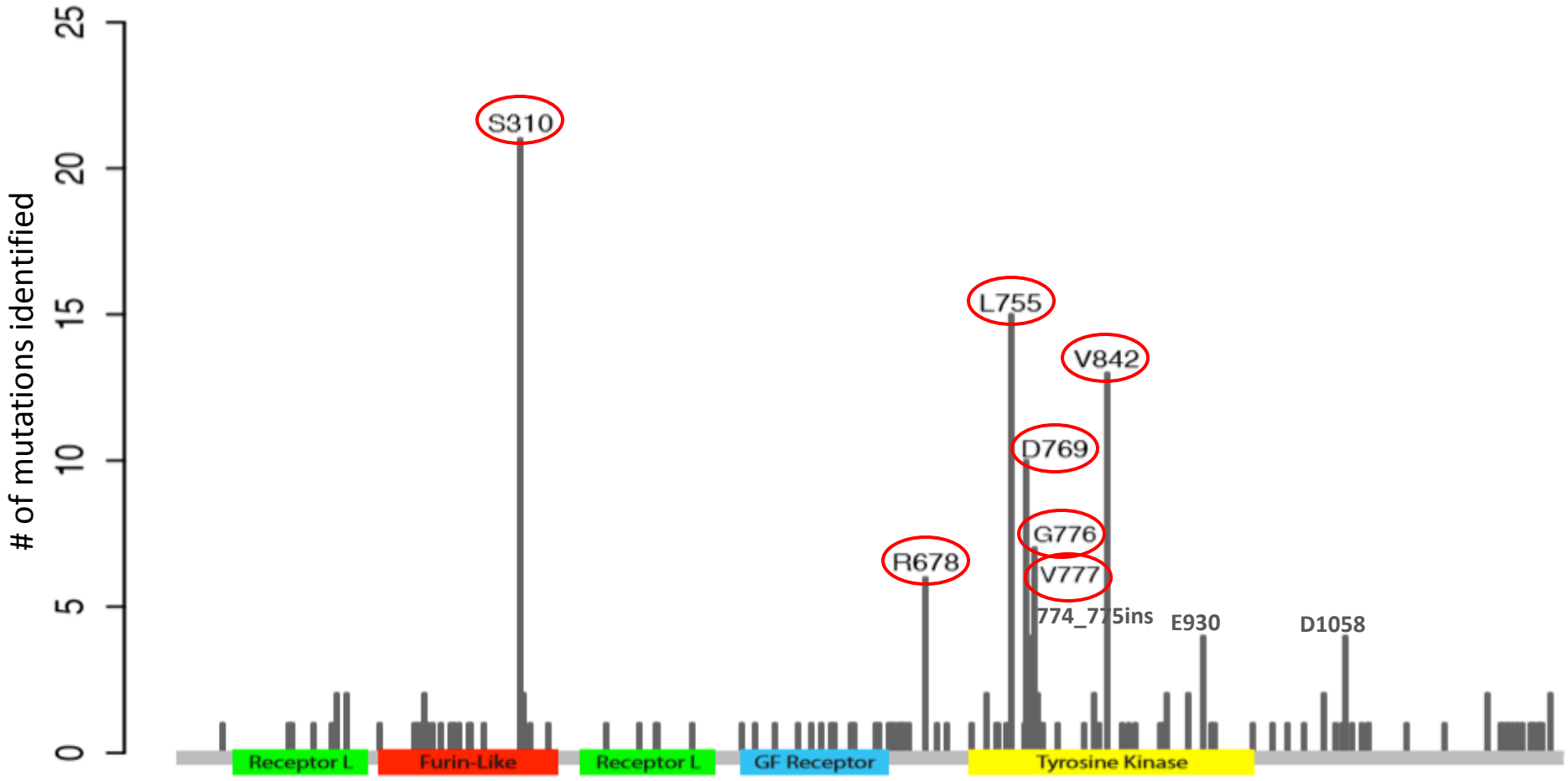
Baseline 8 weeks

Almost all patients with V777L ERBB2 mutations are unaware that they have this mutation as ERBB2 mutational testing is not SOC.

Advantages of this approach

- **Allows for testing a defined biologic hypotheses.**
  - Do patients with ERBB2 mutations respond to neratinib? Estimate that 30-40,000 patients will need to be screened to complete full enrollment to 8 cohort.
  - Does lineage matter?
  - Does the specific mutant allele impact RR.
- Tissue can be collected to determine the basis for heterogeneity of response.
- Co-Clinical trial concept: Allow enrollment of uncharacterized mutations but generate constructs in parallel.

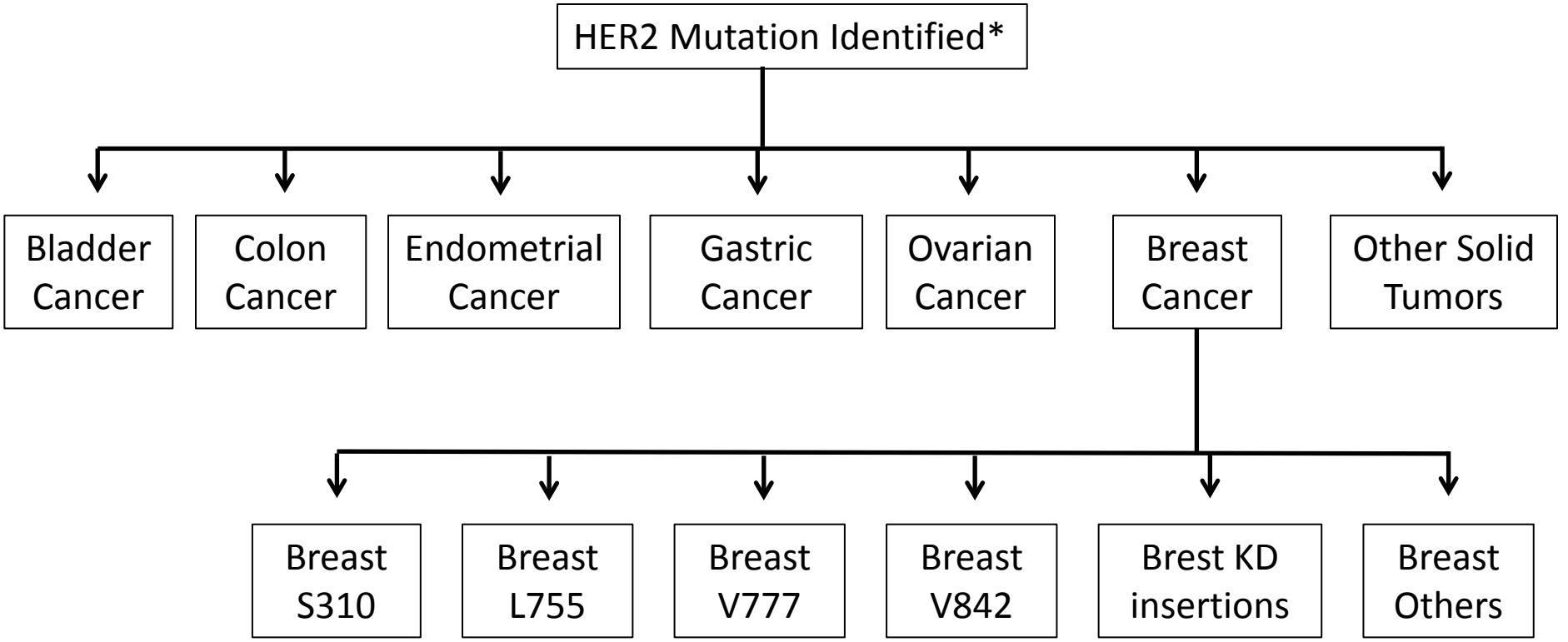
Structural localization and frequency of ERBB2 mutations identified across all cancers (TCGA)



Data from 49 studies included in the cbio portal

Ricardo Ramirez

Is a phase 3 trial required for regulatory approval?



Can we find mutation/disease combinations where the response rate and durability of response is sufficiently high to warrant an immediate change in clinical practice?

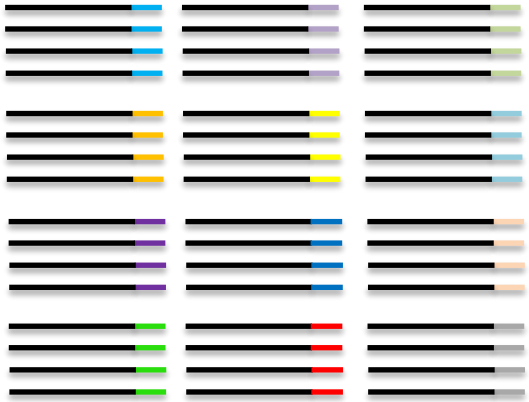
Challenges with this approach

- Primary criticism from clinicians/companies/regulators: You fail to identify patient who may potentially respond but lack the biomarker being tested.
- Sad fact: Getting multiple disease teams to work together has been a challenge.
- Primary hurdle: Identifying patients remains a challenge.

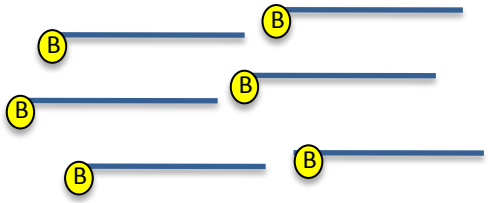
The screening protocol should be separated from the treatment protocol (this is a polarizing concept).

IMPACT: Integrated Mutation Profiling of Actionable Cancer Targets

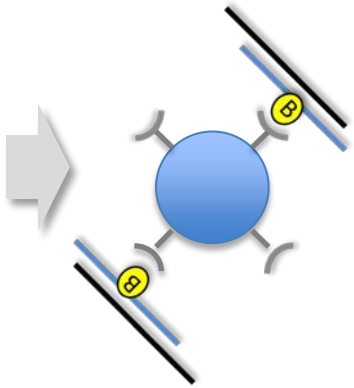
Prepare **24-48 libraries**



Probes for **341 cancer genes**

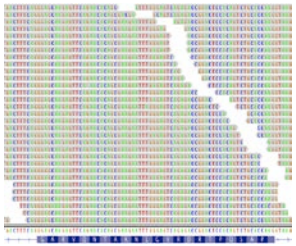


Hybridize and select
(NimbleGen SeqCap)



Sequence to 500-1000X
(HiSeq 2500)

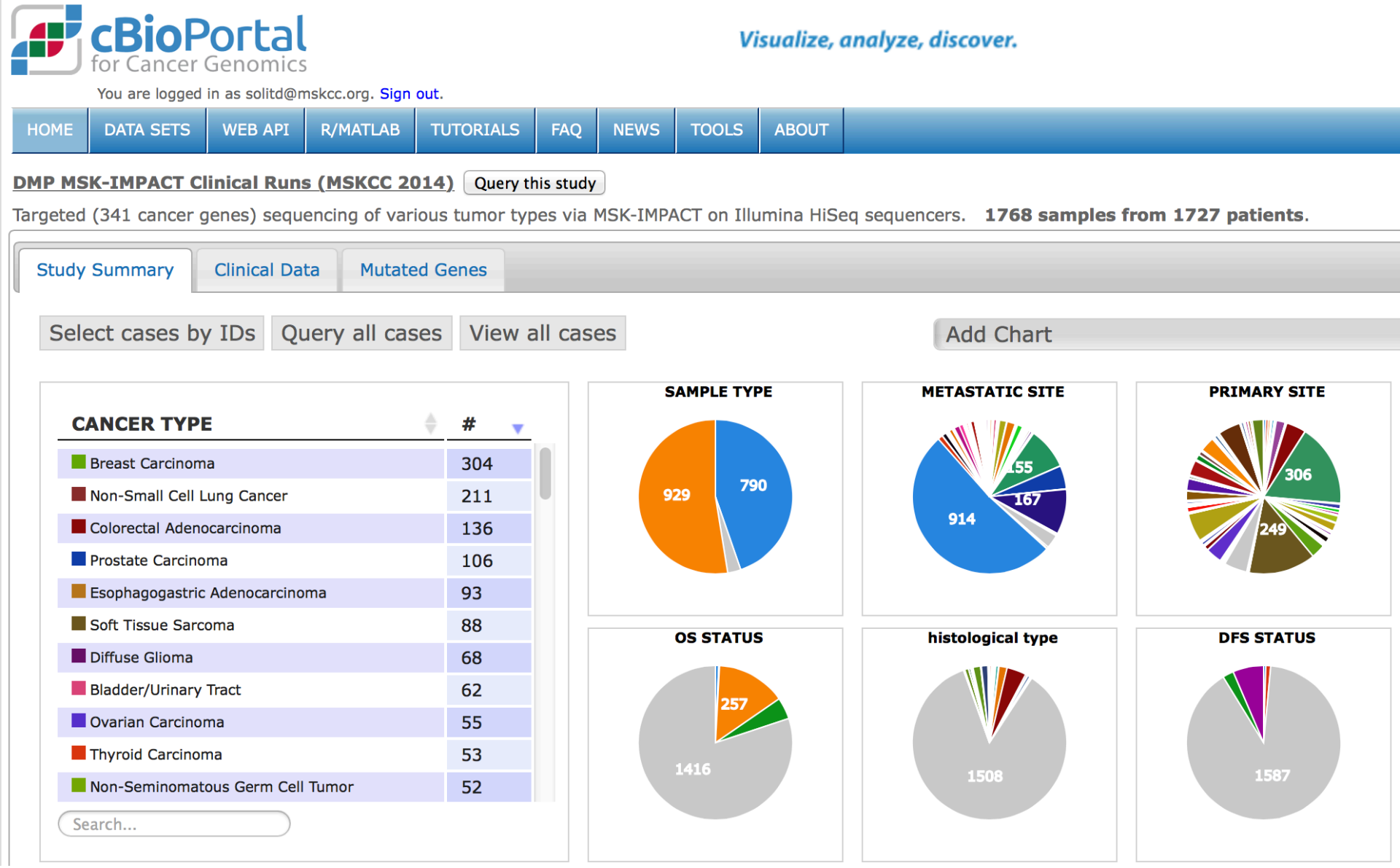
Align to genome
and analyze



Adapted from *Wagle, Berger et al., Cancer Discovery, 2:82-93, 2012*

Somatic Mutations (Tumor-Normal Pairs):
Base Substitutions
Small Indels
Copy Number Alterations
Select Rearrangements

DMP study summary



ERBB2 mutations identified by MSK-IMPACT

Show / hide columns | Showing 50 mutation(s)

Sample ID	Cancer Type	AA change		Type	Copy #	COSMIC	Mutation Assessor
DMP1179	Non-Small Cell Lung Cancer	*775_776insYVMA*	3D	IF ins	diploid	63	
DMP0811	Breast Carcinoma	*L755S*	3D	Missense	diploid	23	Medium
DMP0772	Breast Carcinoma	*L755S*			diploid	23	Medium
DMP0407	Endometrial Carcinoma	*L755S*			diploid	23	Medium
DMP0513	Breast Carcinoma	*L755S*	3D	Missense	diploid	23	Medium
DMP0411	Cervical Adenocarcinoma	*S310Y*	3D	Missense	diploid	13	Medium
DMP1100	Non-Small Cell Lung Cancer	*S310F*	3D	Missense	AMP	13	Medium
DMP0297	Cancer of Unknown Primary	*S310F*	3D	Missense	diploid	13	Medium
DMP0270	Bladder/Urinary Tract	*S310F*			diploid	13	Medium
DMP0842	Bladder/Urinary Tract	*S310F*			diploid	13	Medium
DMP0856	Skin Squamous Cell Carcinoma	*S310F*	3D	Missense	diploid	13	Medium
DMP0853	Bladder/Urinary Tract	*S310F*	3D	Missense	diploid	13	Medium
DMP0913	Biliary Cancer	*S310F*	3D	Missense	diploid	13	Medium
DMP1632	Non-Small Cell Lung Cancer	*776_776G>AVGC*	3D	IF ins	diploid	12	
DMP1758	Breast Carcinoma	*V777L*	3D	Missense	diploid	11	Neutral
DMP0898	Colorectal Adenocarcinoma	*V842I*	3D	Missense	AMP	10	Neutral
DMP1739	Colorectal Adenocarcinoma	*D769Y*	3D	Missense	diploid	8	Low
DMP0050	Esophagogastric Adenocarcinoma	*D769Y*	3D	Missense	AMP	8	Low
DMP0407	Endometrial Carcinoma	*R678Q*	3D	Missense	diploid	5	Low
DMP1224	Breast Carcinoma	*R678Q*	3D	Missense	diploid	5	Low
DMP1449	Breast Carcinoma	*I767M*	3D	Missense	diploid	3	Neutral
DMP0705	Colorectal Adenocarcinoma	*I767M*	3D	Missense	diploid	3	Neutral

4 L755 mutations

8 S310 mutations

Finding rare mutations is not difficult if you are testing all patients.

How do we interpret co-mutations?

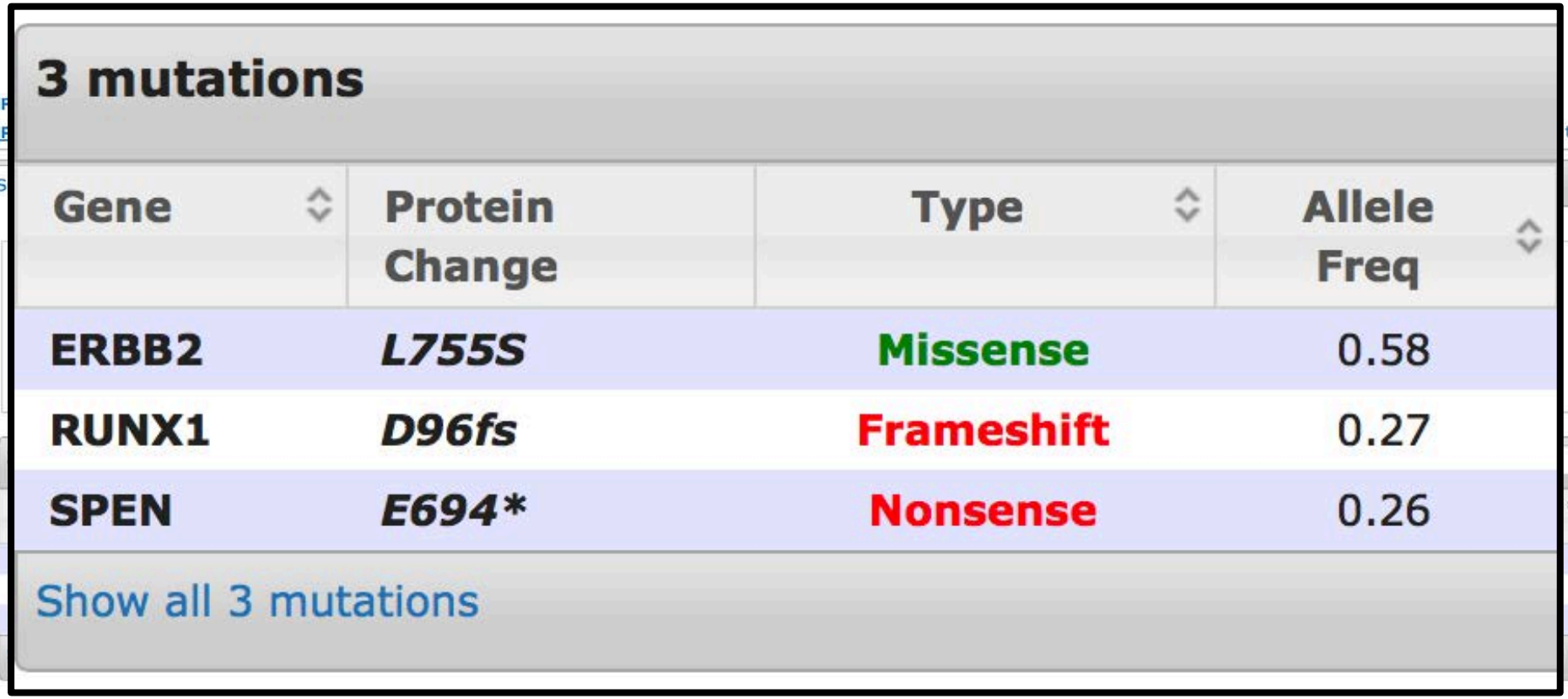
7 mutations

Gene	Protein Change	Type	Allele Freq
KRAS	*G12D*	Missense	0.34
TP53	*V272L*	Missense	0.27
APC	*S1426fs*	Frameshift	0.40
ERBB2	*I767M*	Missense	0.28
PTPRS	*R1919W*	Missense	0.28

Does co-mutation of KRAS confer resistance to ERBB2 inhibition in a patient with an ERBB2 mutation?

Likely but no actual clinical data.

A likely clonal ERBB2 mutation



3 mutations

Gene	Protein Change	Type	Allele Freq
ERBB2	*L755S*	Missense	0.58
RUNX1	*D96fs*	Frameshift	0.27
SPEN	*E694**	Nonsense	0.26

Show all 3 mutations

A sub-clonal ERBB2 mutation in a tumor with a likely clonal TSC1 mutation

8 mutations

Gene	Protein Change	Type	Allele Freq
ERBB2	***S310F***	**Missense**	0.03
TP53	***E336****	**Nonsense**	0.57
AXL	***A273V***	**Missense**	0.38
TSC1	***Q516****	**Nonsense**	0.62
TERT	***Promoter***	**5'Flank**	0.17
CDKN2AP16INK4A	***19_20insTA***	**Insertion**	0.20
ERBB4	***F1102C***	**Missense**	0.18
NOTCH3	***R103****	**Nonsense**	0.15

The Actionable Genome Consortium (AGC)

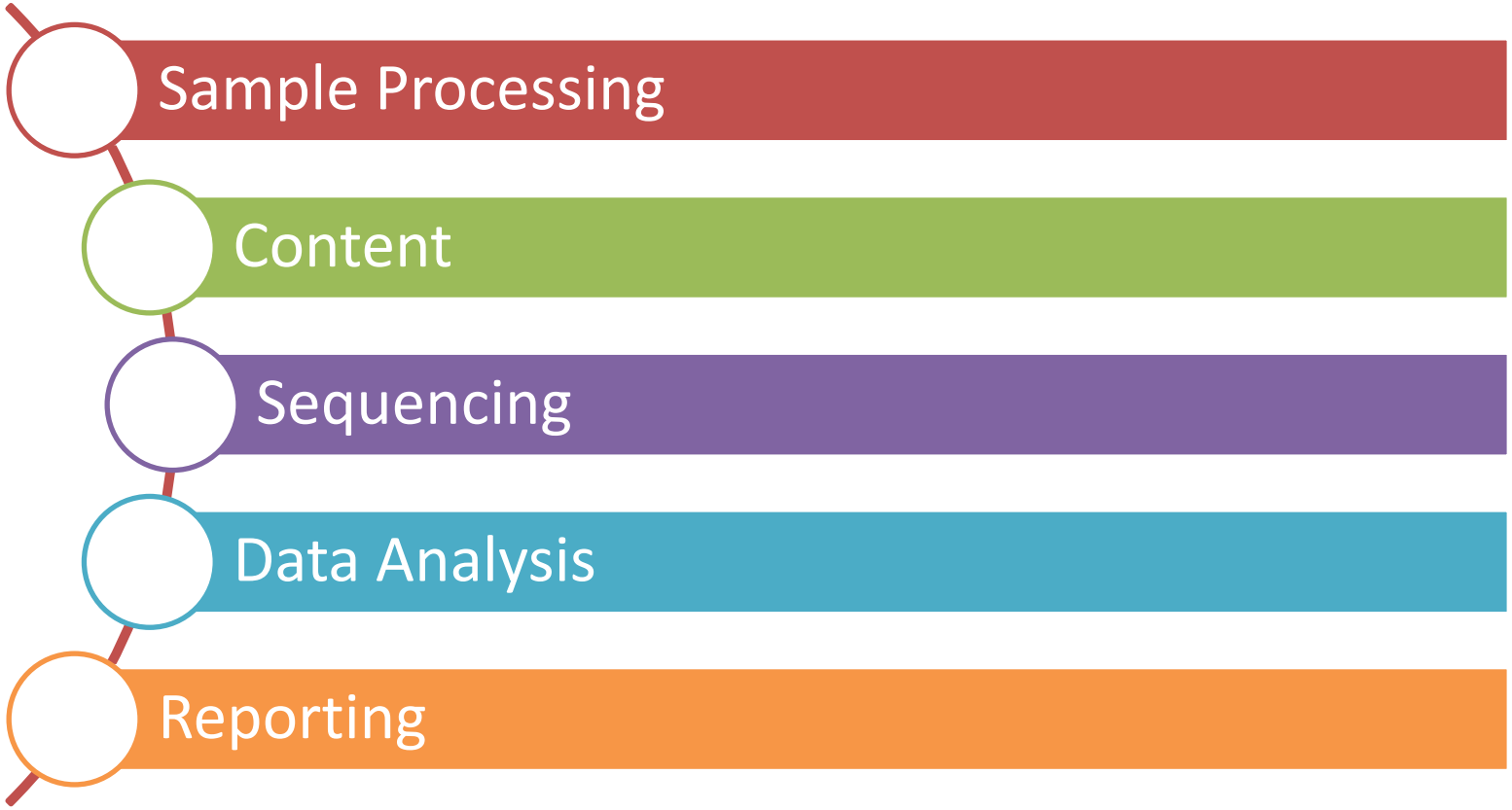
Advancing Clinical Decision-making in Oncology

Representation from: NCI, MSKCC, MDACC, Broad, Cancer Research UK, Fred Hutchinson Cancer Research Center, Princess Margaret Cancer Center

Charge to the AGC: All Aspects of NGS in Oncology

- Demonstrate clinical utility
- Democratize genomic testing
  - Becoming widely available and implemented
  - Currently primarily covered through philanthropy, patient self-pay.
- Contain costs
- Define Actionability
  - Critical to define the actionable genome
    - Must be flexible due to changing landscape and information
- All conclusions published and available to the community
  - No restrictions

A Suite of Standards



All of the output of the Consortium including standards, SOPs, analytic tools and results will be published and made available to any and all who want access to the information.

** See notes section*

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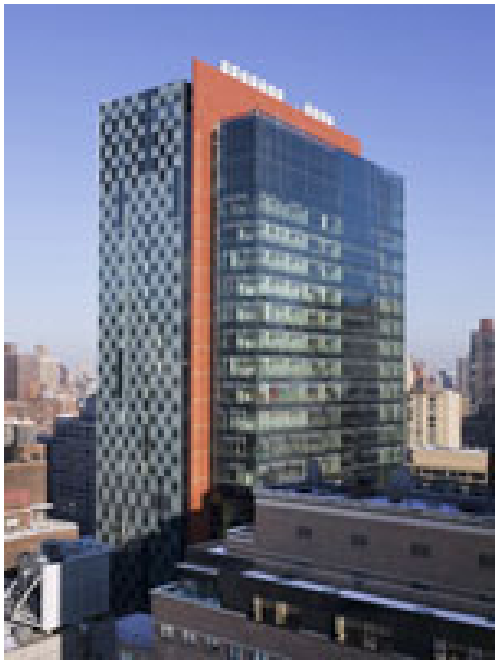

NIH/NCI

Marie Josée and Henry Kravis

Cycle for Survival

Melanoma Research Alliance

SU2C

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