Matching Drugs to Mutations for Treating Cancer

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I have the following financial relationships to disclose:

Consultant for: Boerhinger-Ingelheim (uncompensated), Regeneron (uncompensated), Merck (uncompensated), Novartis (compensated)

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Outline of Talk

- **Challenges and opportunities in the genomics era:**
  - **Technical**
  - **Clinical**
  - **Operational**
  - **Scientific**

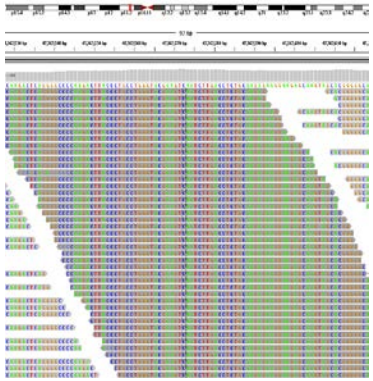
Technical Challenges in Precision Medicine

- Lack of infrastructure to perform large scale tumor biopsies
- Fast evolving technology
- Quality assurance (CLIA-CAP certification)
- Comparability across different labs
- Turnaround time

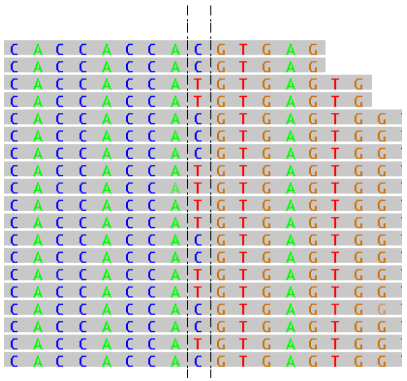
- Adequate coverage and depth – genotyping vs targeted exome vs whole exome or genome
- Complexity of NGS data analysis and bioinformatics
- Linkage of genomic and clinical data
- Elucidating the functional impact of variants and their prognostic/ therapeutic potential

From Reads to Report: Automated Analysis Pipeline with Systematic Human Review

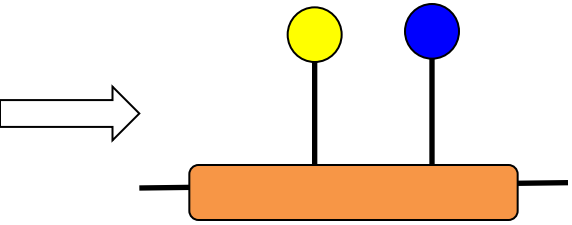
Sequencing device



Aligned Reads



Variant calls



Variant annotation

Interpretation

INCONCLUSIVE: The Thr70Ser variant in MYH7 has not been reported in the literature. Threonine (Thr) at position 70 is conserved across distant species, suggesting that a change would not be tolerated. This variant was also predicted to be pathogenic using a novel computational tool (a customized sarcomere-specific PolyPhen, which was validated using a set of cardiomyopathy variants with well-established clinical significance). This tool's pathogenic prediction is estimated to be correct 94% of the time, which suggests but does not prove that this variant is pathogenic.

Clinical report

Courtesy T Pugh

Comprehensive Variant Classification

		ACTIONABILITY*				
		Recurrent Mutation in Gene		Non-Recurrent Mutation in Gene		Unknown
		Same disease site	Different disease site	Same disease site	Different disease site	
CLASS	1					
	2					
	3					
	4					
	5					

**actionable = druggable/predictive/prognostic*

K. Craddock, M. Sukhai, S. Kamel-Reid, et al, Submitted

Linking an Alteration to a Clinical Action

CATEGORY:	LEVEL A	LEVEL B	LEVEL C	LEVEL D	LEVEL E
Predictive – FDA-approved therapies	There is a validated association between this alteration and response/resistance to this agent for this indication	There is limited clinical evidence (early or conflicting data) for an association between this alteration and response/resistance to this agent in this tumor type	There is clinical evidence for an association between this alteration and response/resistance to this agent in another tumor type ONLY	There is preclinical evidence for an association between this alteration and response/resistance to this agent	There is an inferential association between this alteration and response/resistance to this agent
Predictive – Therapies in clinical trials	This alteration is used or has been used as an eligibility criterion for clinical trials of this agent or class of agents	There is limited clinical evidence (early or conflicting data) for an association between this alteration and response/resistance to this agent or class of agents in this tumor type	There is clinical evidence for an association between this alteration and response/resistance to this agent or class of agents in another tumor type ONLY	There is preclinical evidence for an association between this alteration and response/resistance to this agent or class of agents	There is a inferential association between this alteration and response/resistance to this agent or class of agents
Prognostic	There is a validated association between this alteration and prognosis in this tumor type	There is limited evidence for an association between this alteration and prognosis in this tumor type			
Diagnostic	There is a validated association between this alteration and a diagnosis	There is limited evidence for an association between this alteration and a diagnosis			

Van Allen et al. Nat Med 2014

Clinical Challenges in Precision Medicine

- Keeping up with a fasting growing body of preclinical and clinical knowledge
- Return of results to patients, ensuring understanding of information (including incidental germline findings)
- Finding treatments (obtaining approved drugs or clinical trials of investigational drugs) to “match” mutations found
- Difficult to capture value generated through precision medicine in health care systems

Detailed Reporting with Annotation

MOLECULAR PROFILING CLINICAL STUDY REPORT

Summary of Findings:

Tumor cells were identified in the specimen: YES (70%)
Sufficient DNA for validated genomic analysis: YES

Overall result: Relevant somatic variant(s) identified.
NRAS (NM_004985.3). Heterozygous, c.181C>A (p.Q61K), Exon 8, Pathogenic.

The following somatic mutation(s) which may affect patient care have been identified in the patient's tumor sample:

Class 1 mutation: NRAS Q61K (34%)

The NRAS p.Q61K mutation results in an amino acid substitution at position 61 in NRAS, from a glutamine (Q) to a lysine (K). This is an activating, oncogenic mutation, leading to constitutive activation of NRAS signaling (mycancergenome.org). This mutation is most commonly found in melanomas and occurs at a frequency of 3-10% (COSMIC; TCGA: cbioportal.org). The role of NRAS mutations for selecting or prioritizing anti-cancer treatment, including cytotoxic chemotherapy and targeted agents, is unknown at this time (mycancergenome.org). Currently, there are no direct anti-NRAS therapies available. However in a phase II trial of a MEK inhibitor in melanoma patients with mutations of Q61, 20% of the patients exhibited a partial response (Ascierto et al Lancet Oncol, 2013, PMID: 23414587).

Analysis was successful for all mutations: YES
Overall mean depth of coverage[1]: 6060x
Overall quality threshold[2]: 90.3%
Hot spots quality threshold[3]: 87.2%

[1]Overall mean depth of coverage refers to the sequence mean read depth across the targeted region.
[2]Overall quality threshold refers to the percentage of the target region where read depth was at least 500x coverage to permit high quality variant base calling, annotation and evaluation.
[3]Hot spots quality threshold refers to the percentage of the hotspots listed below where read depth was at least 500x coverage to permit high quality variant base calling, annotation and evaluation.

Analysis was unsuccessful for the following hotspot mutations (list): None

Methodology:
Known mutations were identified using the Illumina MiSeq next-generation sequencing personal genomics platform, and verified by Sanger Sequencing and/or another validated test available in the CAP/CLIA Molecular Diagnostics Laboratory.

Illumina MiSeq next-generation sequencing. Next-Generation Sequencing (NGS) is a technology platform that allows for parallel sequencing of the complete sequence of multiple genes. The Illumina MiSeq operates on the principle of amplicon sequencing, such that a library of PCR amplicons, each 150-200 base pairs, is

Addendum Diagnosis

MOLECULAR PROFILING CLINICAL RESEARCH STUDY REPORT

Summary of Findings:

Tumor cells were identified in the specimen: YES (80%)
Sufficient DNA for validated genomic analysis: YES

Overall result: Somatic variant(s) identified.
TP53 (NM_000546.4). Heterozygous, c.488A>G (p.Y163C), Exon 4
BRAF (NM_004333.4). Heterozygous, c.1406G>T (p.G469V), Exon 11
RB1 (NM_000321.2). Heterozygous, c.607+1G>A

The following somatic mutation(s) with unknown significance have been identified and verified in the patient's tumor sample:

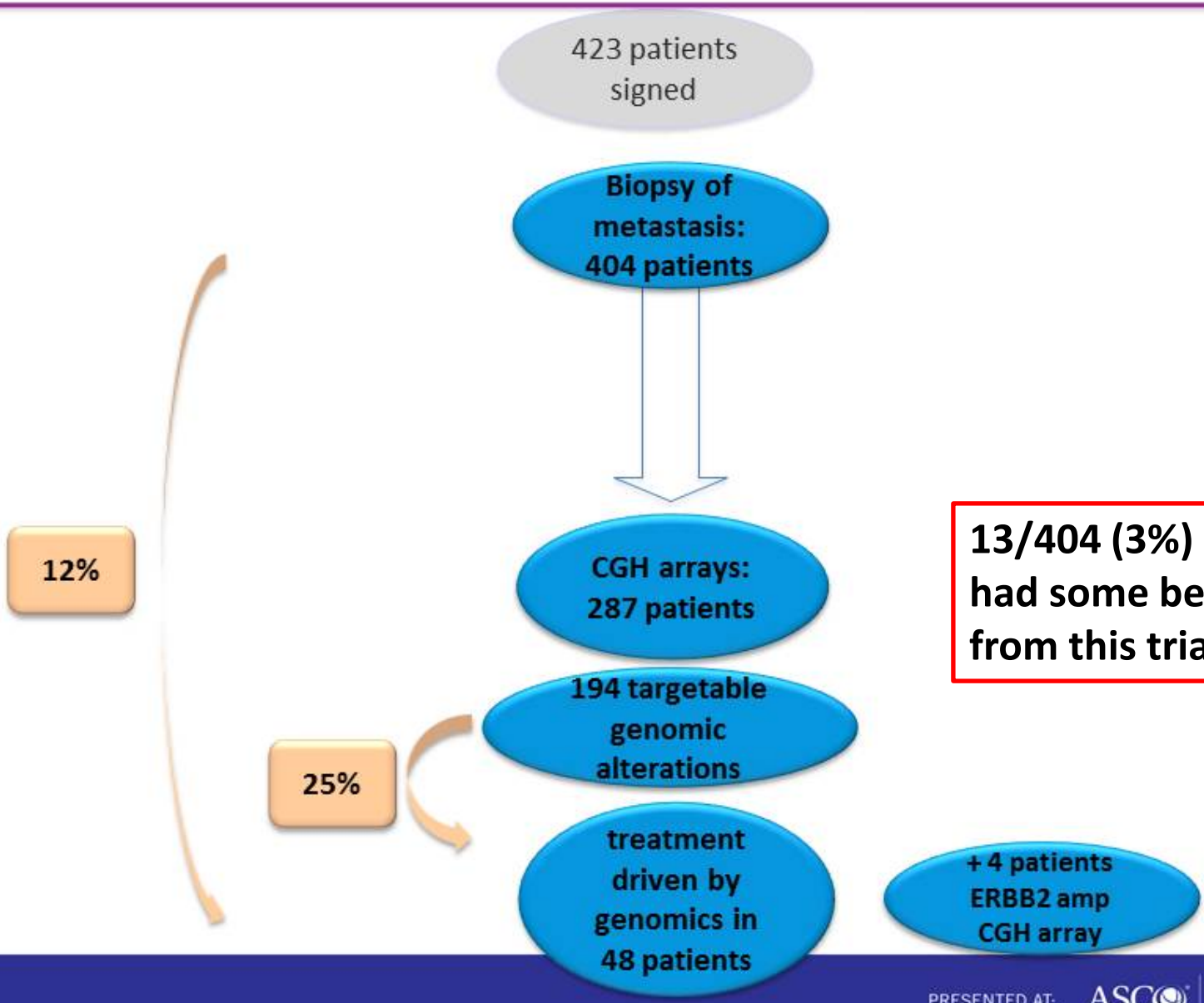
Class 3A mutation: TP53 Y163C (77%)
Y163C is a rarely occurring variant in ovarian cancers (< 1% frequency; IARC TP53 database), and is a missense mutation, leading to a nonfunctional protein product (IARC TP53 database). No data on correlation with patient outcome or response to therapy is as yet available in the literature for this variant. TP53 mutations are extremely frequent in this tumor site (COSMIC; TCGA).

Class 4A mutation: BRAF G469V (58%)
BRAF G469V is an extremely rare mutation in cancer generally (COSMIC), and has not been previously reported in ovarian serous carcinoma (COSMIC). BRAF is recurrently mutated in ovarian cancers, but is rarely mutated in high grade serous carcinoma (mycancergenome.org). The most common variant found in ovarian tumors is V600E (mycancergenome.org). Currently, the impact of this mutation on patient prognosis or treatment in this tumor site is unknown.

The following somatic mutation(s) with unknown significance have been identified but not verified in the patient's tumor sample:

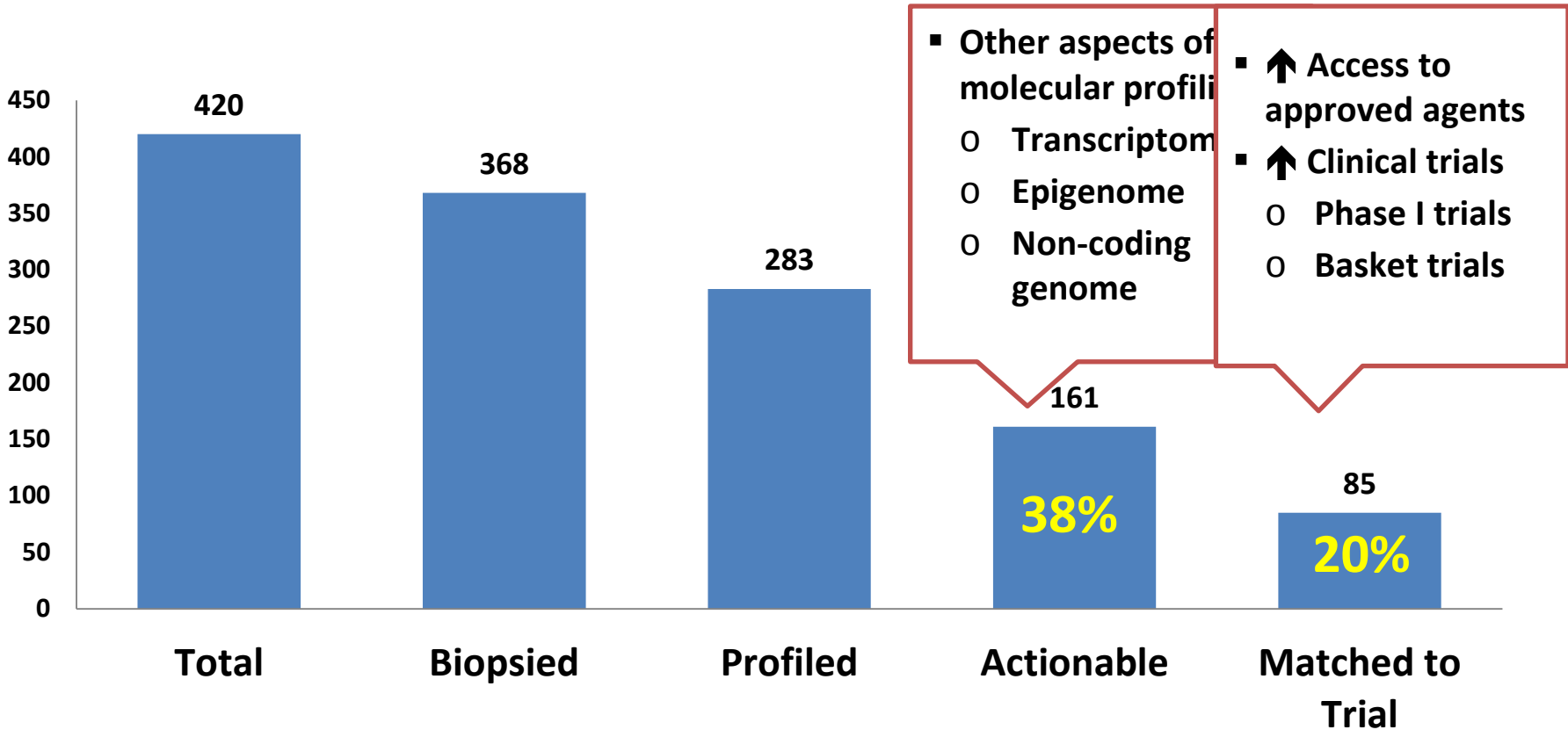
Treatment according to the genomic alterations

Safir01



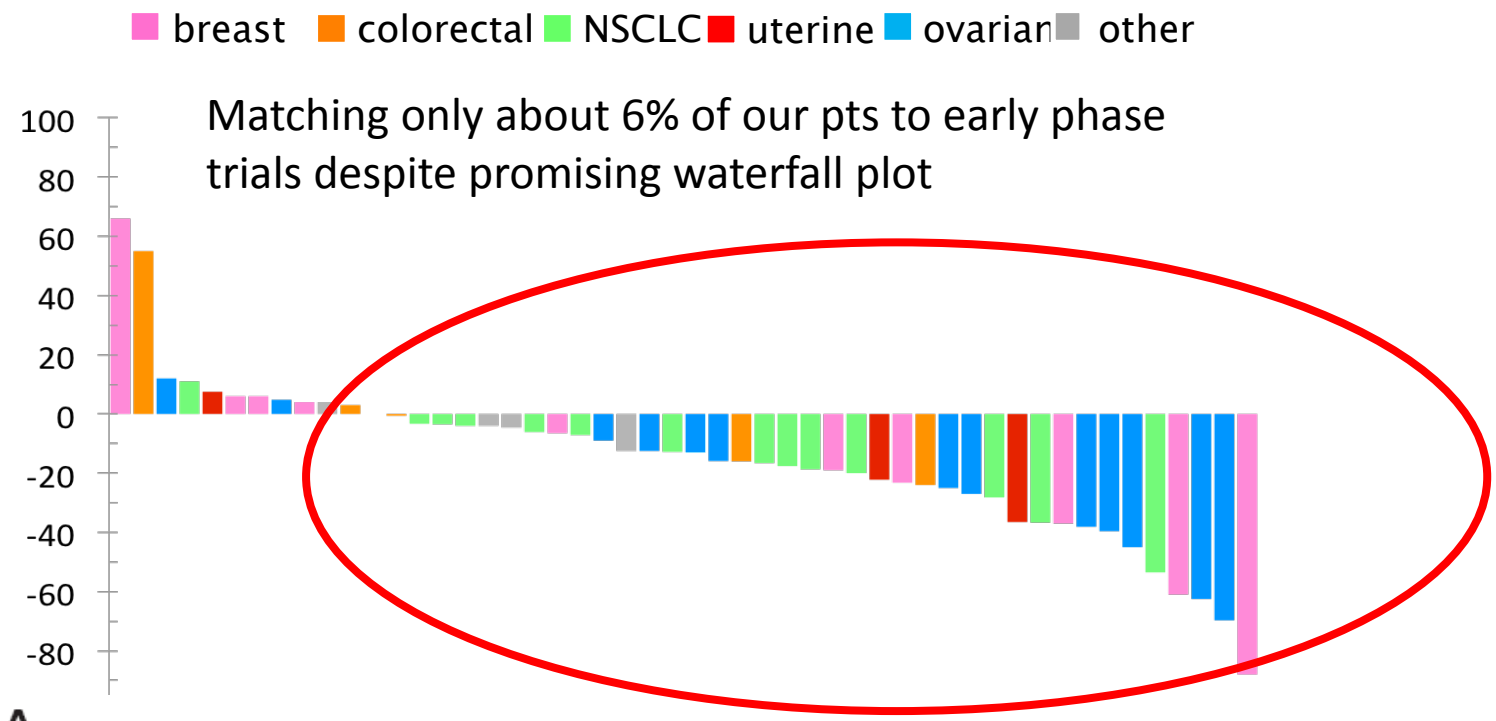
Andre et al 2013, Andre et al. Lancet Oncology 15 (3): 267 - 274

MOSCATO-01 –Gustave Roussy

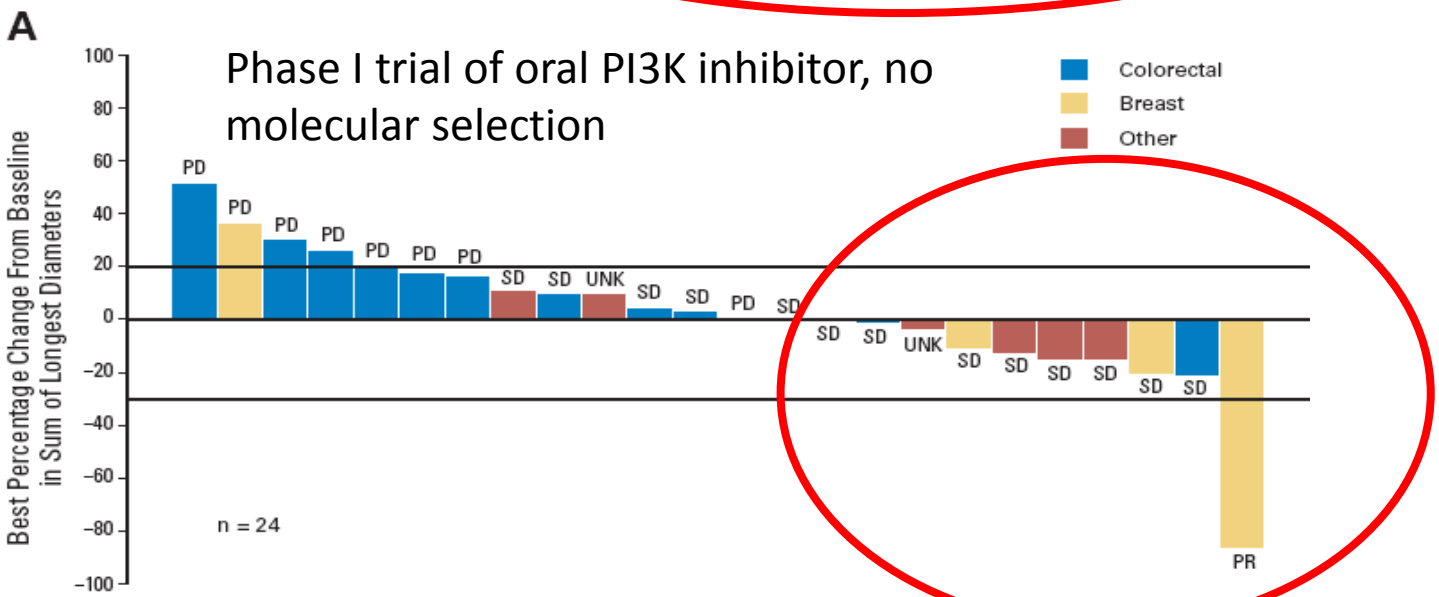


Ferte et al. AACR 2014

IMPACT and COMPACT at the Princess Margaret



Matching only about 6% of our pts to early phase trials despite promising waterfall plot



Phase I trial of oral PI3K inhibitor, no molecular selection

Current Phase I Program Profile at the Princess Margaret n=33

Characteristic	Types	Number (%)
Sponsorship	NCI or NCIC Pharma	5 (15%) 28 (85%)
Disease Site Specific	Yes No	25 (76%) 8 (24%)
Molecular Selection Required	Yes No	10 (30%) 23 (70%)

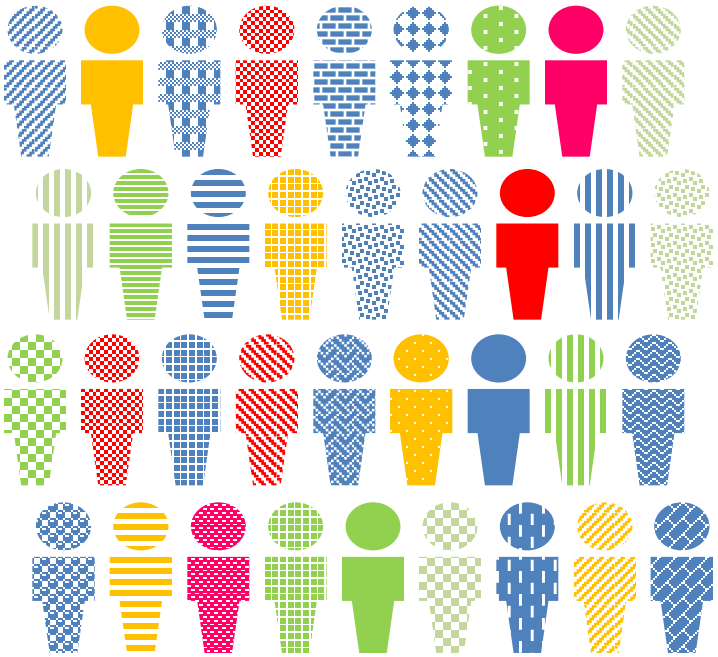
List of Clinical Trials Based on Genotypes: Development of an App

Trial Listing	Clinical Trial	D/E Ph2 Ph3	Colorectal			Ovarian					Breast						Melanoma			
			KRAS	BRAF	NOTCH1	KRAS	BRAF	PIK3CA	p53	BRCA	ER+	TNBC	HER2-	PIK3CA	NOTCH1	PTEN Null	BRAF	NRAS	RAS/ RAF	PIK3CA
1	[redacted]	E	x																	
		D	x	x		x	x										x		x	
		E	x																	
2		D															x Part B			
		E															x Part B			
3		D																		
		E	x	x								x							x Any	
4		Ph2							x											
5		Ph3									x (post-meno pause)									
6		Ph2																		x
7		D	WT																	
8		Ph2						x									x			
9		D		x																
		Ph2		x																
10		D																		
		E																		
11		Ph2											x							
12		Ph2									x		x							
13		D			x (Arm B)										x (Arm A, TNBC)					

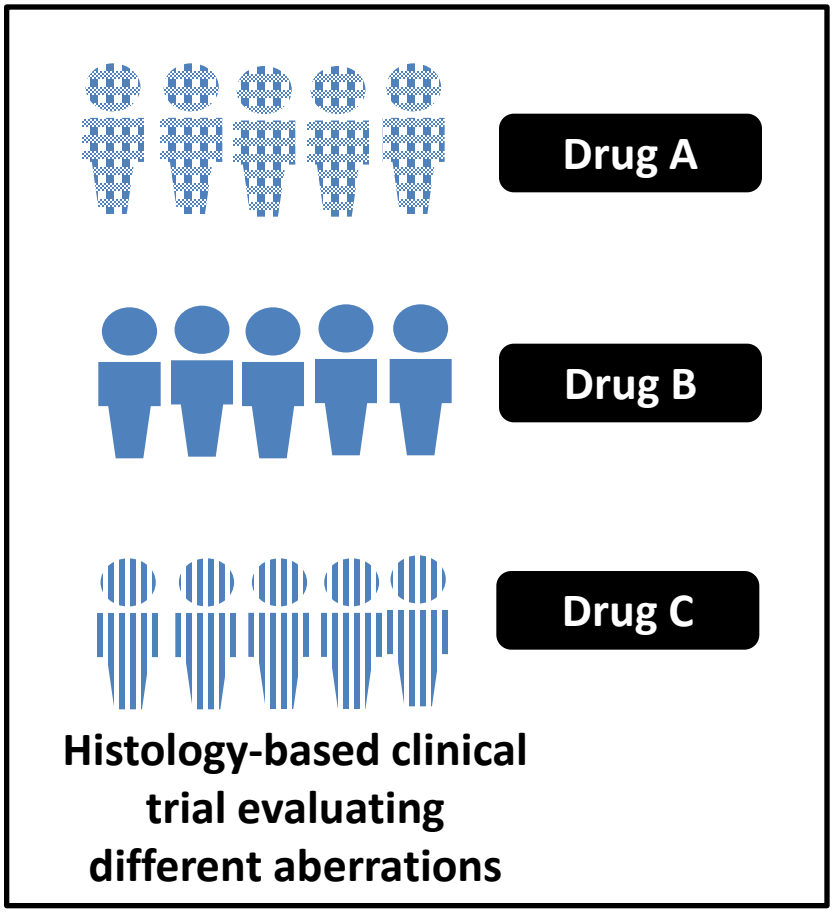
Operational Challenges Faced by Precision Medicine

Challenge	Potential Impact on Clinical Trial Conduct	Potential Solution
Molecular selection	▪ Archived tumor tissues requested by multiple sponsors, leading to exhaustion of tissues	▪ Local laboratory testing using validated multiplexed assay
Identification of rare subsets of patients	▪ ↑screening costs while number of eligible patients ↓, leading to a financial challenge to keep many trials open with few patients recruited per trial	▪ Support for screening ▪ Multiplexed screening ▪ Basket/Umbrella protocols
Large number of participating sites per trial	▪ Limited experience being accumulated per site	▪ Frequent investigator communications of study observations
Rational combinations made by different pharma companies	▪ Delay in design and execution of the 'best' combinations	▪ Pharma collaborations ▪ NCI-CTEP doing combo studies

Histology-based clinical trial design to evaluate multiple molecular aberrations ("umbrella" trials)



Molecularly profiled patients with different histologies

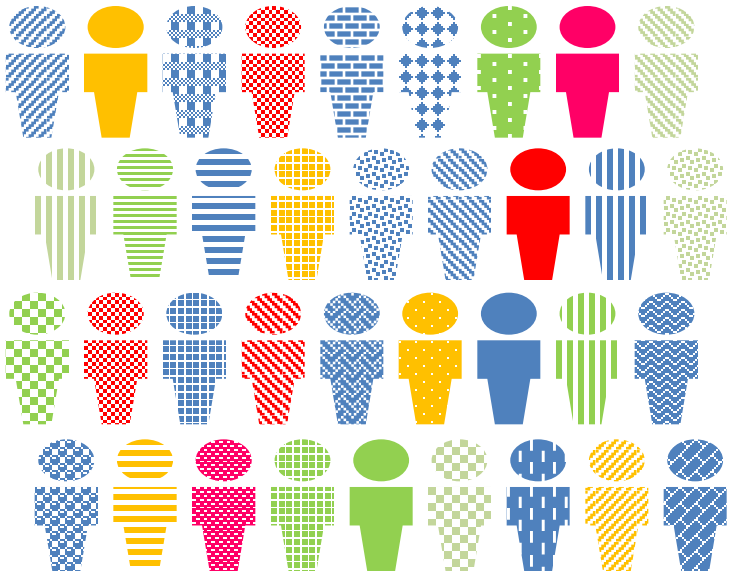


Sleijfer S, Bogaerts J, Siu LL, J Clin Oncol 2013

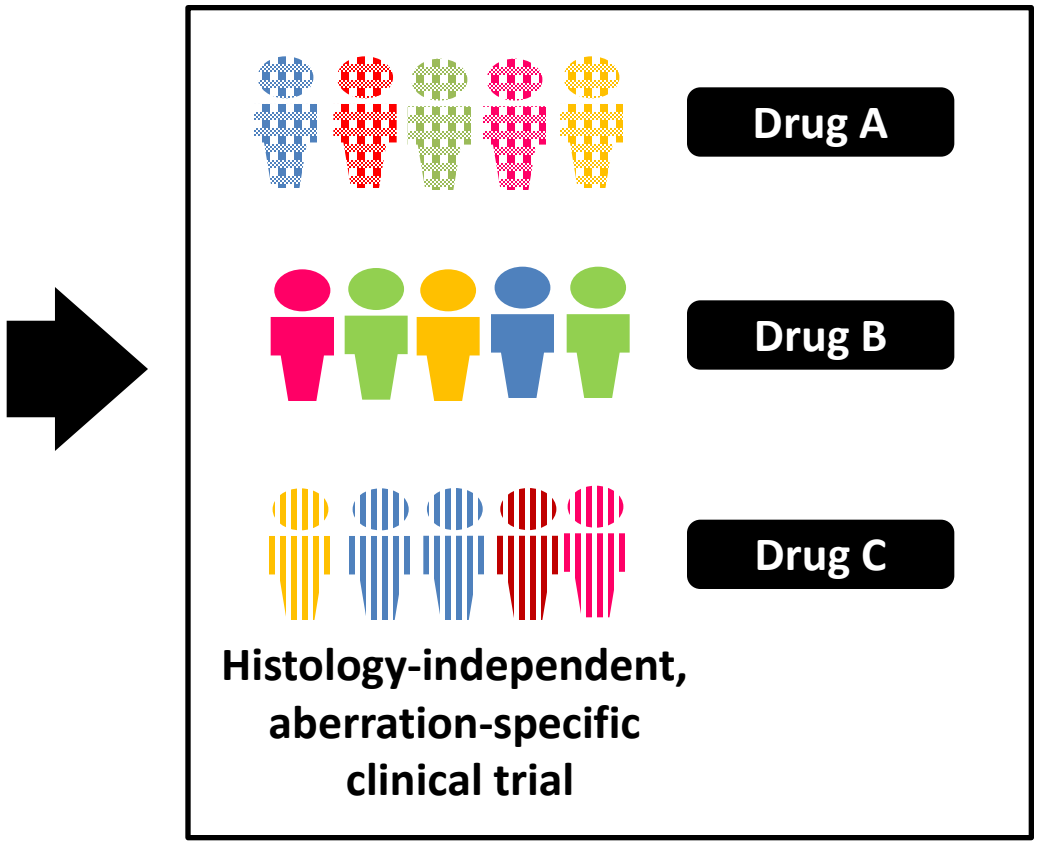
Selected Examples of International Trials to Match Patients based on Molecular Profiles

Program Name	Led By	Tumor Types	Trial Type
I-SPY 2	**US National Institutes of Health**	**Breast**	**Umbrella**
LUNG-MAP	**US National Cancer Institute**	**Squamous lung**	**Umbrella**
ALCHEMIST	**US National Cancer Institute**	**Adenocarcinoma lung**	**Umbrella**
FOCUS 4	**Cancer Research UK**	**Colorectal**	**Umbrella**
ASSIGN	**NCTN**	**Colorectal**	**Umbrella**
SAFIR-01	**Gustave Roussy**	**Breast**	**Umbrella**

Histology-agnostic, aberration-specific clinical trial design ("basket" trials)

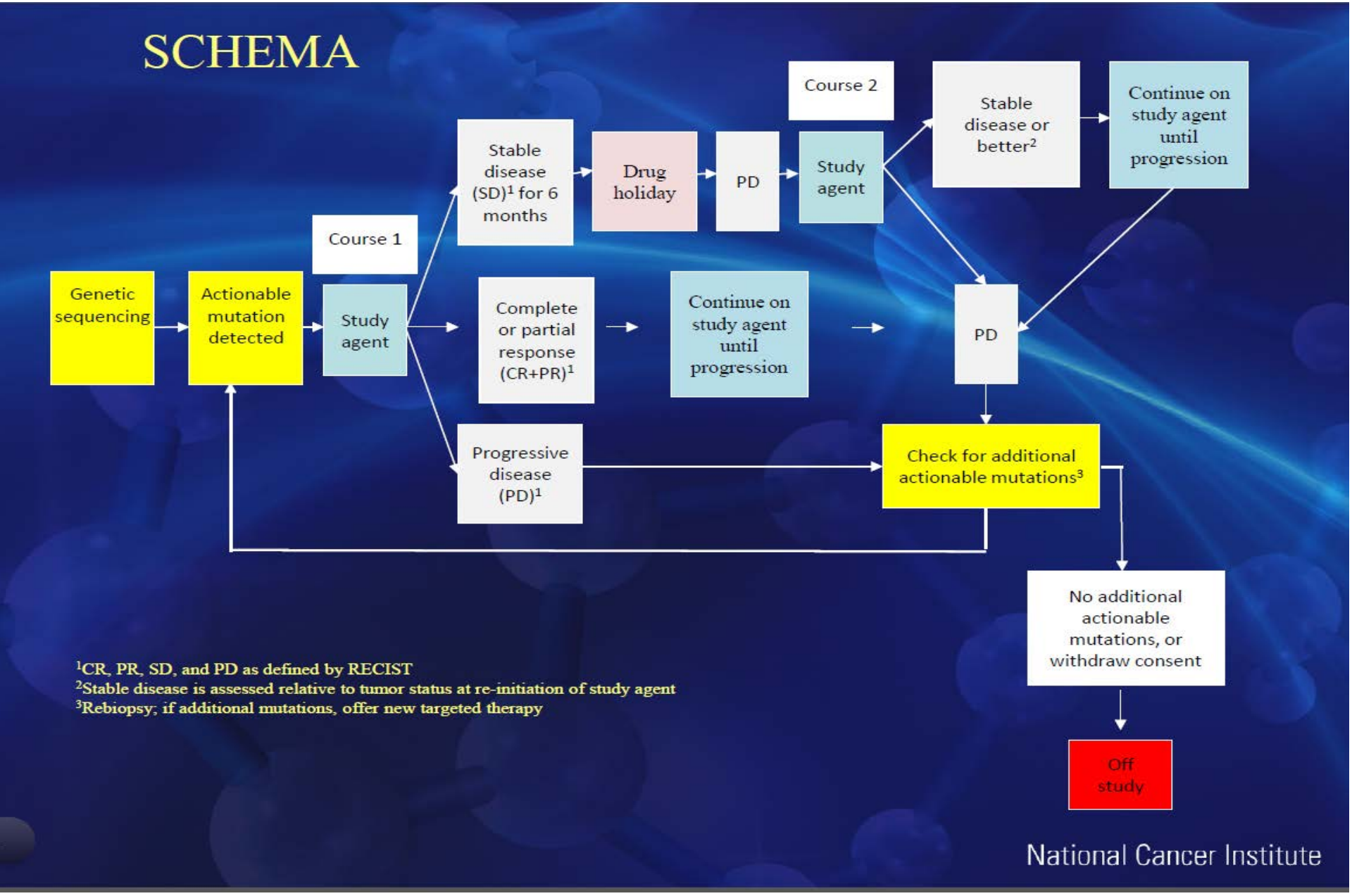


Molecularly profiled patients with different histologies



Sleijfer S, Bogaerts J, Siu LL, J Clin Oncol 2013

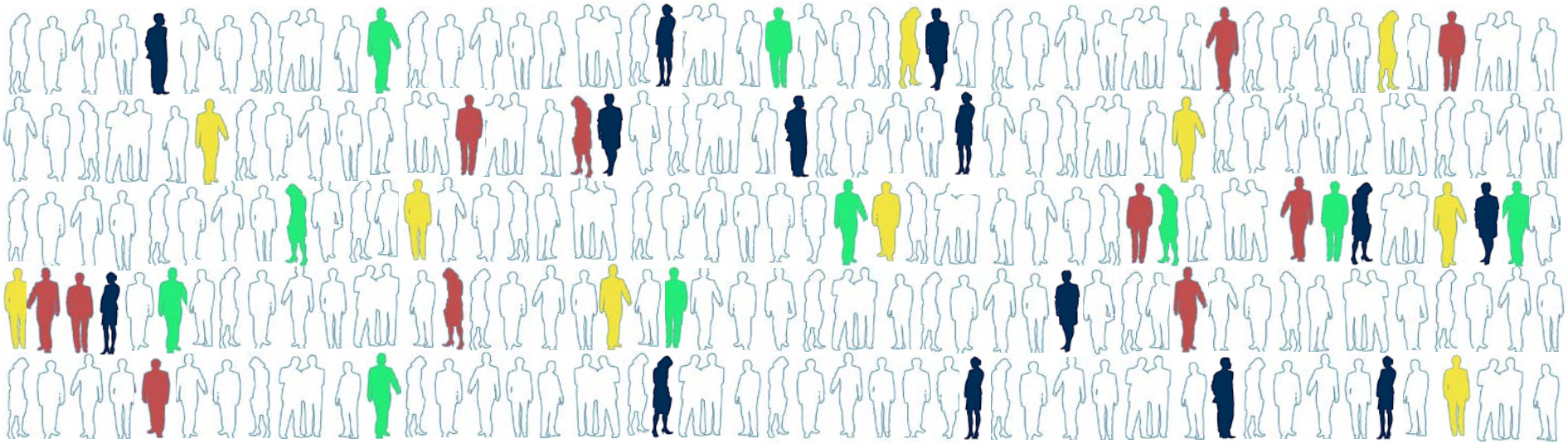
NCI MATCH Trial – Conley et al.



Selected Examples of International (and Local) Trials to Match Patients based on Molecular Profiles

Program Name	Led By	Tumor Types	Trial Type
NCI-MATCH	**US National Cancer Institute**	**Advanced solid tumors**	**Basket**
NCI-M-PACT	**US National Cancer Institute**	**Advanced solid tumors**	**Basket**
Signature	**Novartis**	**Advanced solid tumors**	**Basket**
My Pathway	**Genentech**	**Advanced solid tumors**	**Basket**
Princess Margaret Mobility Series	**002 – Bedard (GSK)** **003 – Razak (BI)**	**Pancreas/GI Advanced solid tumors**	**Basket**

Finding the Right Treatment for Each Individual Patient



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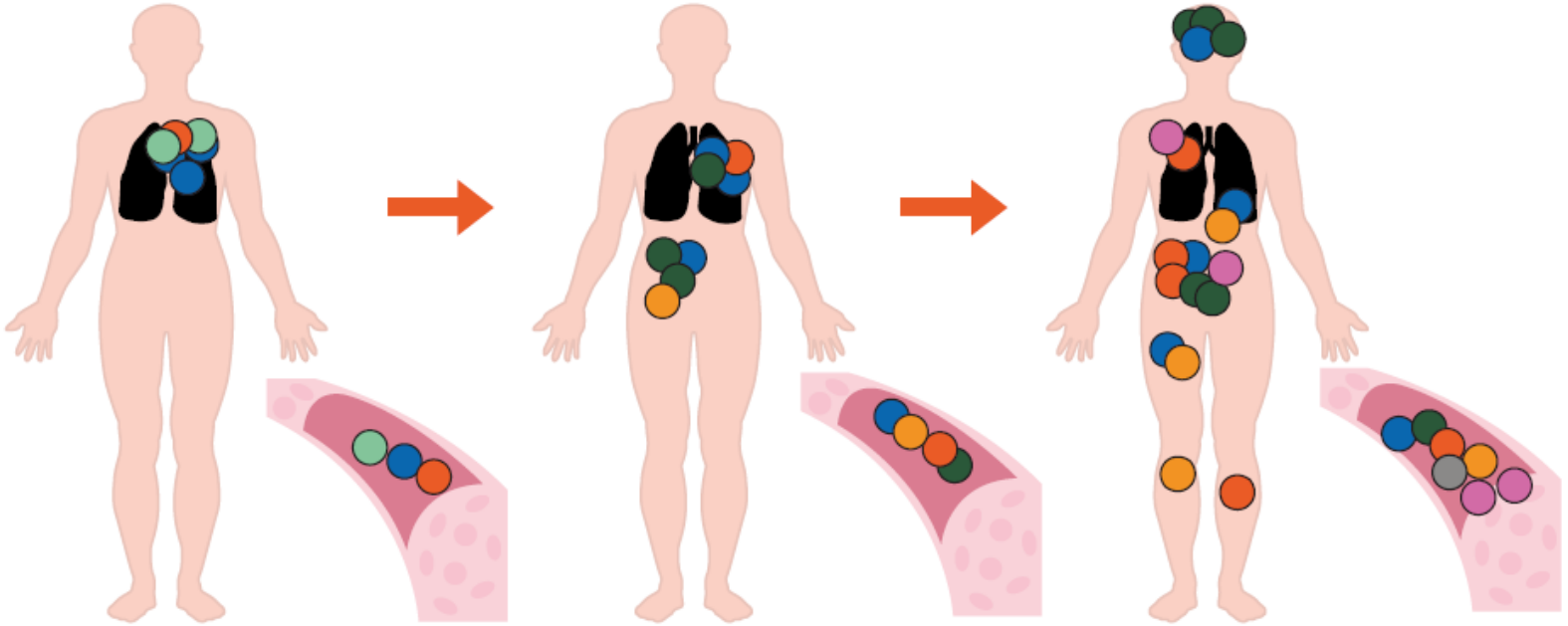
Foundation Medicine Partners with EmergingMed to Offer Clinical Trial Navigation Services for Physicians and Patients

Foundation Medicine facilitates patient access to clinical trials by offering personalized guidance through the selection and enrollment process

Scientific Challenges in Precision Medicine
Tumor Heterogeneity

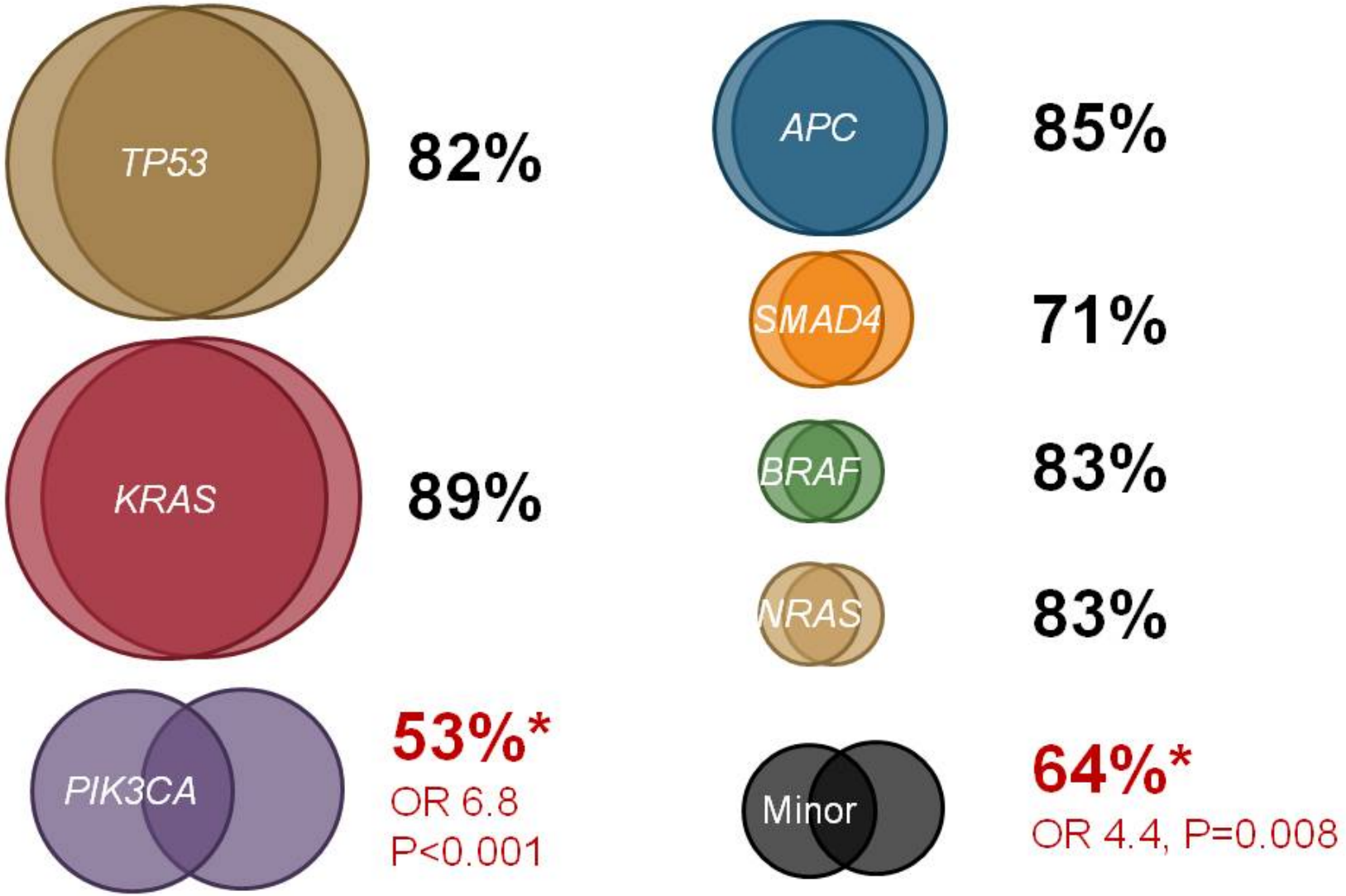


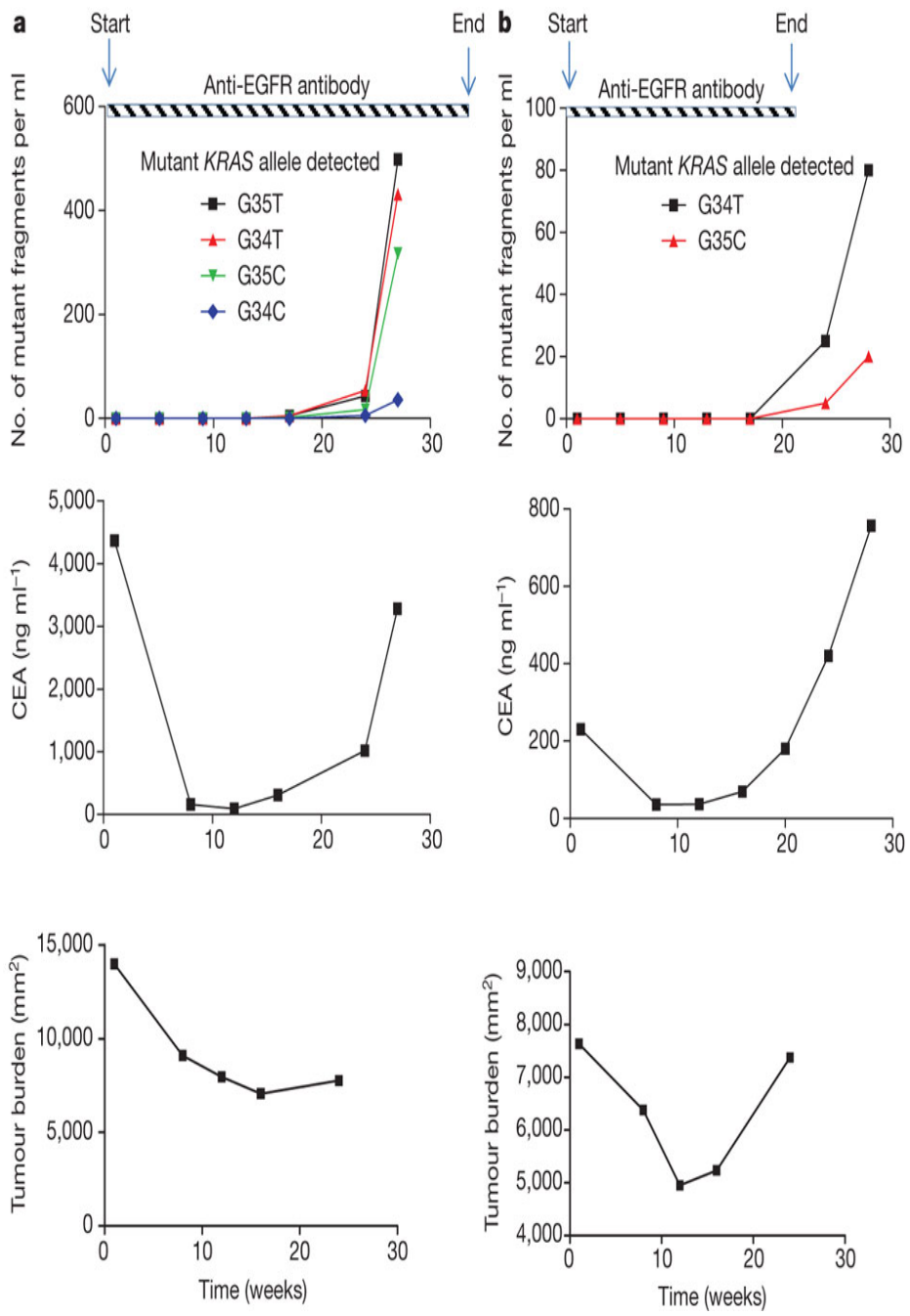
Focus of clinical trial	Therapeutic strategy
Histology-based, no molecular profiling	
Molecular profiling of one tumour sample	
Molecular profiling of multiple tumour samples across space and time	

Andre, Mardis, Salm, Soria, Siu, Swanton, In Press Ann Oncol

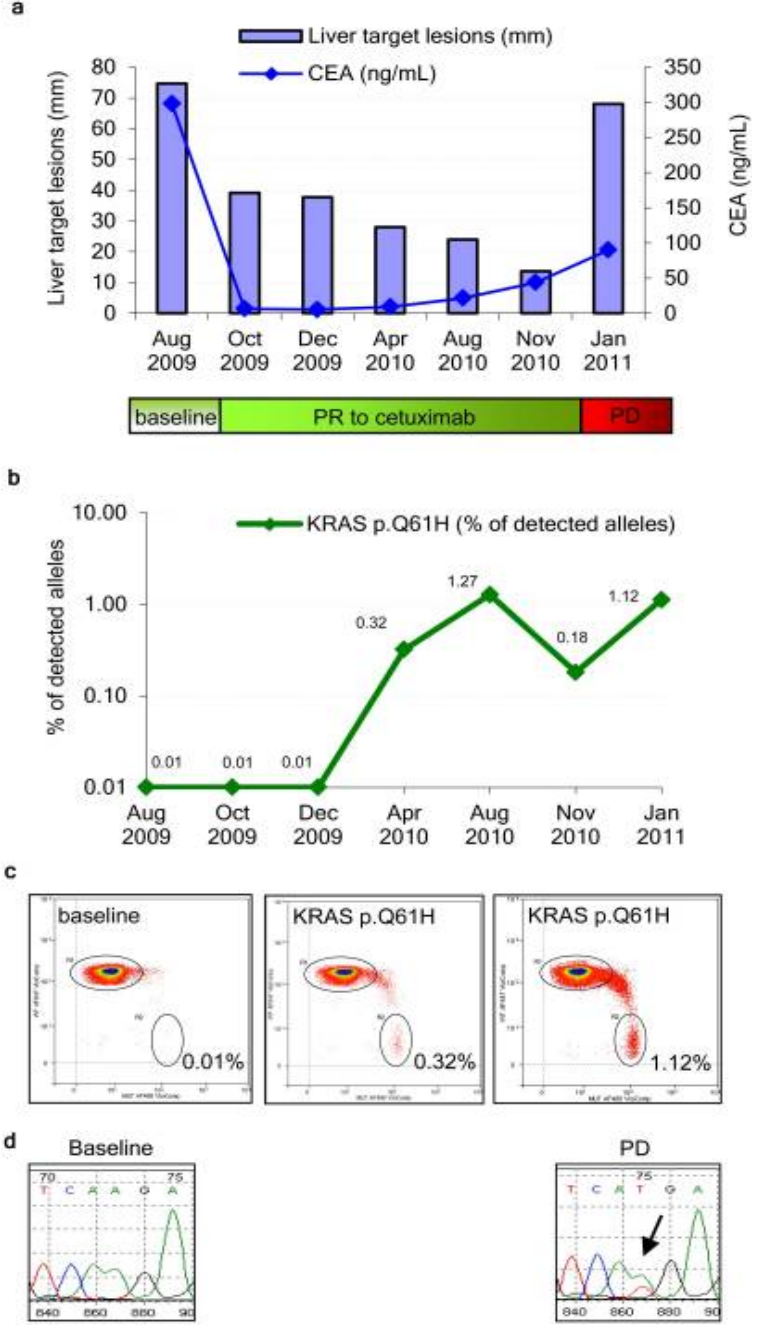
Low Concordance Between Primary and Metastases for *PIK3CA* and Minor Genes

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center



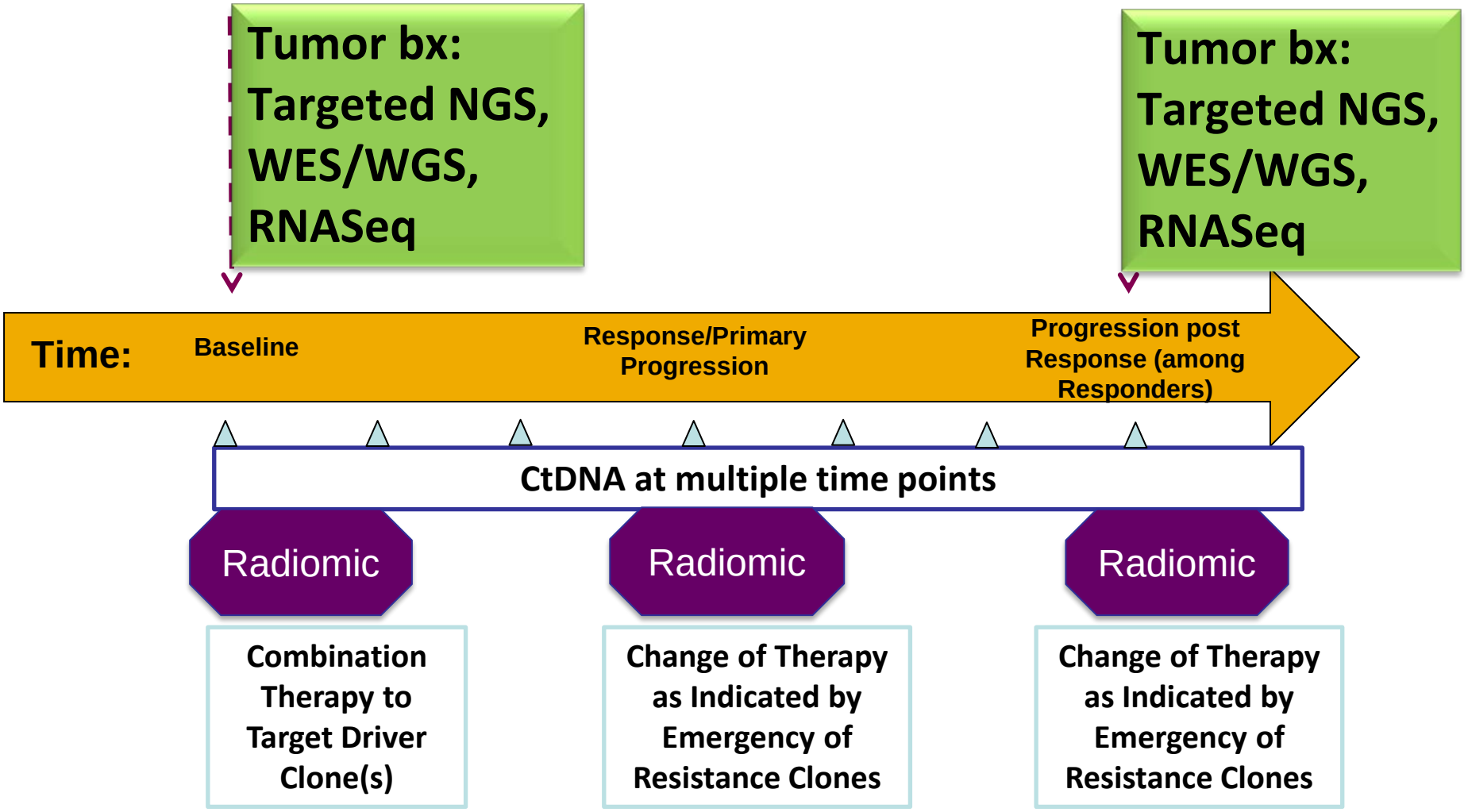


Diaz LA Jr *et al. Nature* 486, 537–540



Misale et al. *et al. Nature* 486, 532-536

Sampling Strategies on a Genomic-Driven Trial



Conclusions

- Molecular characterization of tumors at point-of-care is now feasible and affordable
- Challenges (and opportunities) ahead:
  - Bioinformatics needs and data overload
  - Prioritization of targets (oncogenic drivers)
  - Finding drugs to match genotypes
  - Capture value of genotype-drug matching
  - Designing trials taking into account tumor heterogeneity (inter and intra)
  - Data sharing and learning

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