

III USCAP
AACR HIGHLIGHTS

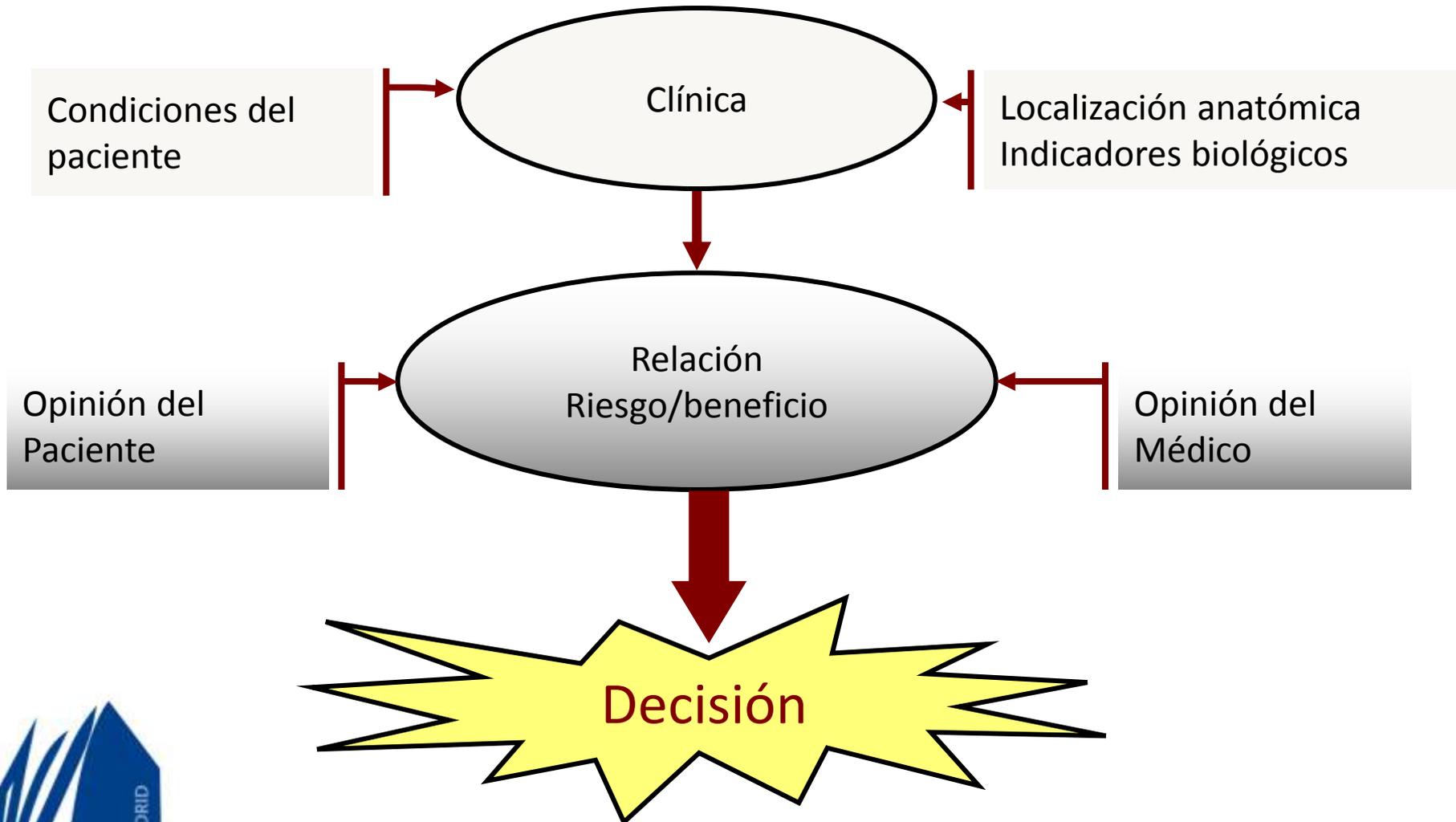
Actualización Congreso AACR 2014



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La decisión clínica



Contexts of Use Where Biomarkers Can Inform a Medical Decision

PRE-INTERVENTION:

Prediction	Identify subgroups of patients that differ in the benefit they receive from a particular form of therapy or the likelihood to a specific therapy (drug)
Therapy guiding	

POST-INTERVENTION:

Surrogate	A biomarker intended to substitute for a clinical efficacy endpoint (e.g. Survival): Clinical benefit (surrogate): how a patient feels, functions or how long he survives
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Analytical and Clinical Validation: A Complex Process With No Shortcuts

- Context of use: Context of use are the management treatment decisions influenced by the biomarker result.
- Analytical (Method) validation: The process of assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data.
- Clinical validation: The evidentiary process of linking a biomarker with biological processes and clinical endpoints-dedicated trials in a sequence.
- Clinical utility: Demonstrating that use of the test to direct management (therapy guiding) results in a favorable balance of benefits to harms leading to improved outcomes compared to non-use of the test





Precision Medicine

Biomarkers for Personalizing Cancer Therapy

- For patients who require systemic therapy, use molecular approaches
 - To determine which drugs will eradicate patient-specific minimal residual or significantly delay progress of metastatic disease
 - To perform real-time disease monitoring using methods that will provide actionable information



Multi-gen expression signatures from primary tumors are used for risk stratification –to decide who might benefit from chemotherapy

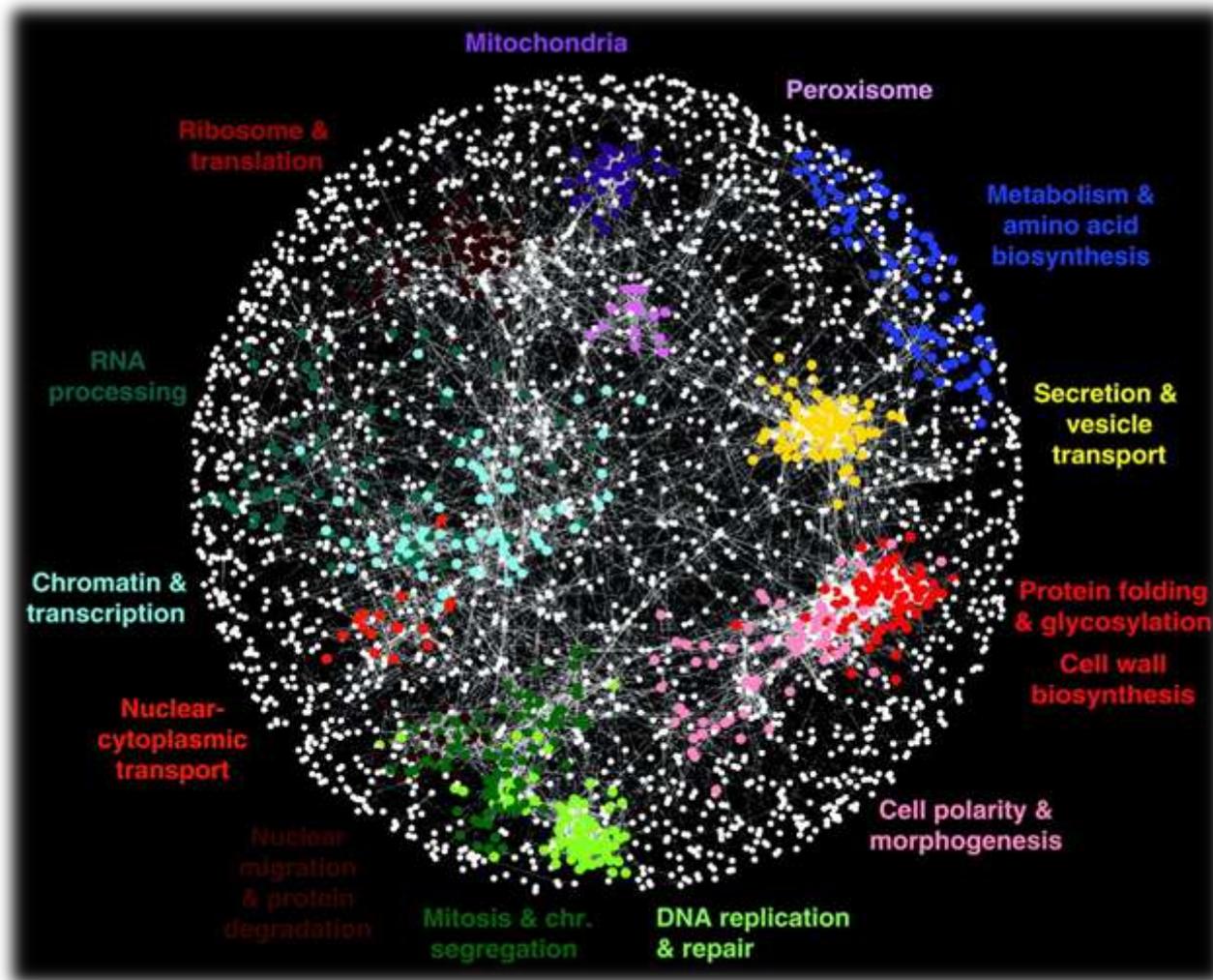
- OncoType Dx 21
- MammaPrint® 70 gene profile
- Rotterdam-Veridex 76 gene profile
- HOXB13:IL17BR
- PA; Prosigna™ gene signature assay

But risk stratification doesn't inform drug selection

To choose the “right” drugs for specific patients

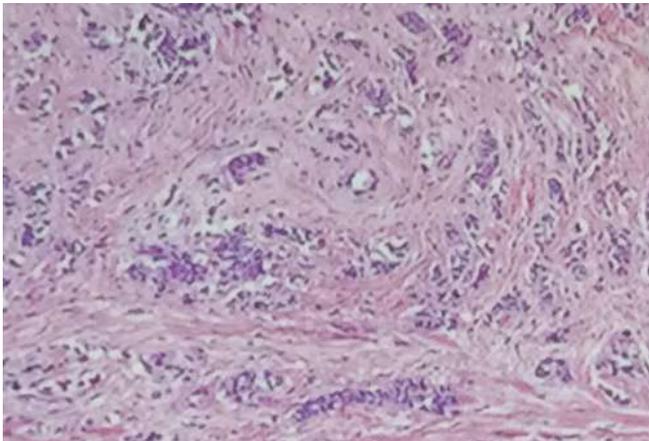
- **CURRENT APPROACH:** Assay/profile tumor for predictive molecular phenotype (DNA, RNA, Protein)
- **“NEXT GEN” APPROACH:** Perform drug challenge, rebiopsy, and determine change in biomarker assay (s)

Correlation-based network connecting genes with similar genetic interaction profiles.

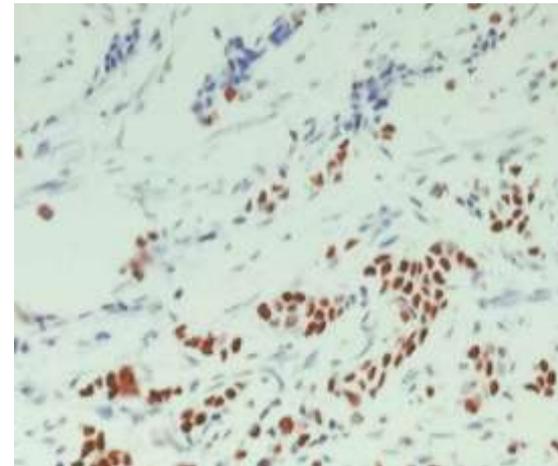


Concept of intratumoral heterogeneity

Which tumor cells metastasize?
(the “bad guys” – the “culprit cells”)



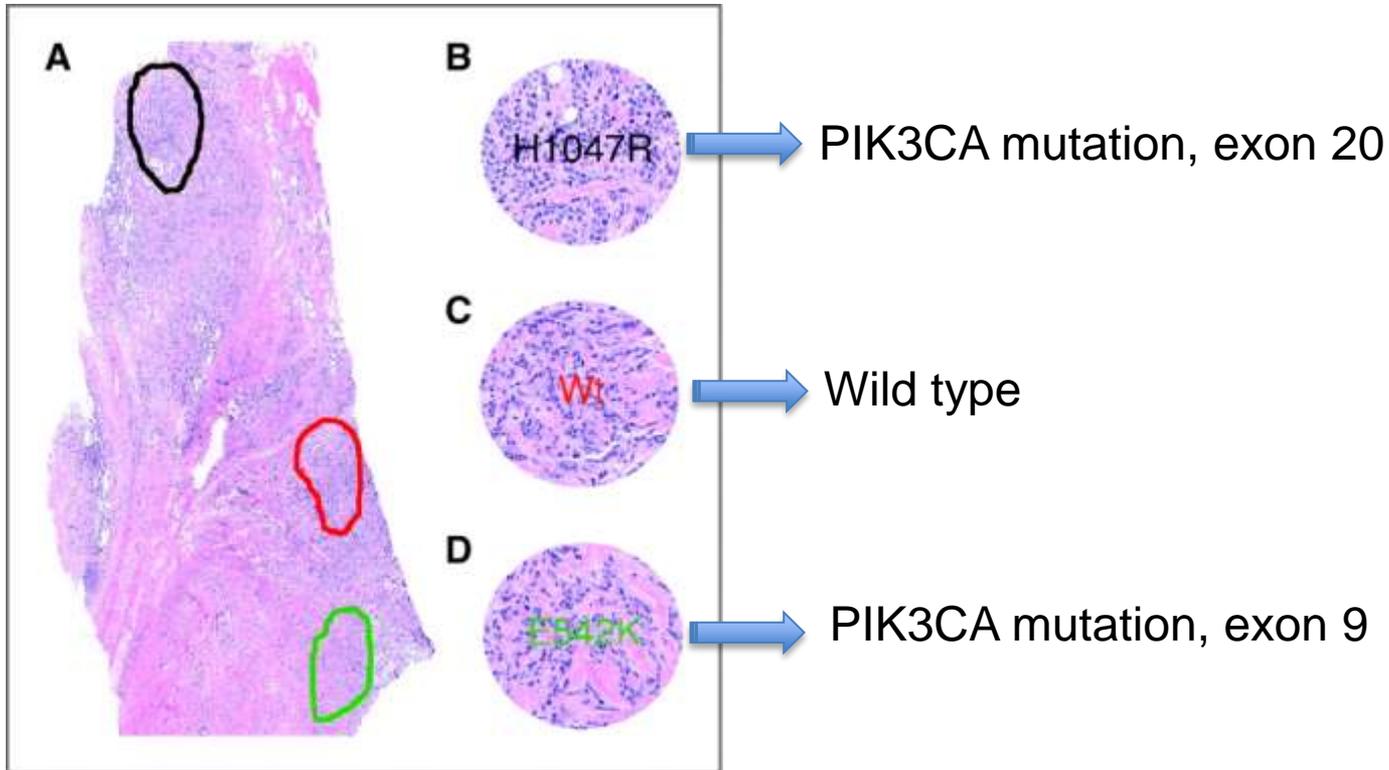
H&E of Grade II infiltrating ductal carcinoma (200x)



Higher power (400X) of same tumor, stained for estrogen receptor

Intratumoral heterogeneity: Biomarker discordance

Tumor cells within primary breast cancers often show different treatment-related biomarkers –Which metastasize?

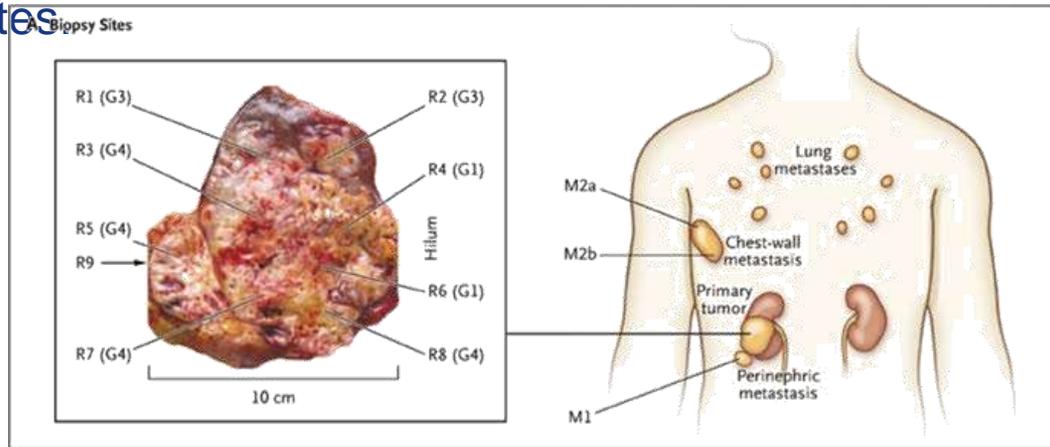


33% mutational discordance between primary tumor and asynchronous metastases in 100 pts – 40% (23/58) wild type tumors changed genotype to mutant; 24% (10/42) mutant tumors had wild type metastases

Intratumor Heterogeneity and Branches Evolution Revealed by Multiregion Sequencing

Premise: most biomarker discovery approaches rely on single tumor bx sample – is this representative of the tumor genomic landscape?

- Studied multiple spatially separated bx samples from primary renal-cell CA and associated metastases using exome sequencing.
- Single bx showed about 70 mutations=55% of all detected. Only 34% of all mutations were detected in all regions. 60% of mutations were NOT shared between primary tumor and chest wall metastases. Prognostic signature of metastases was clinically inconsistent and only matched 1/6 primary tumor samples sites.



Profiling metastasis – which sizes should be biopsied and characterized ?

- Discordance between primary tumor and biopsied metastasis
- Discordance between different metastasis
- Cannot biopsy all metastasis

**What is the best tissue source for
molecular characterization:
primary tumor, metastatic biopsy, plasma
ctDNA r CTCs?**

Primary tumor	Metastatic biopsy	Plasma ctDNA	CTCs
Intact cells	Intact cells	Fragmented DNA	Intact cells (few)
Accessible, most used	Invasive, not always accessible	Non-invasive, accessible, easy to process	Non-invasive, accessible, laborious to isolate
DNA, RNA, protein, cell culture, xenografts	DNA, RNA, protein, cell culture, xenografts	DNA	DNA, RNA, protein, cell culture, xenografts



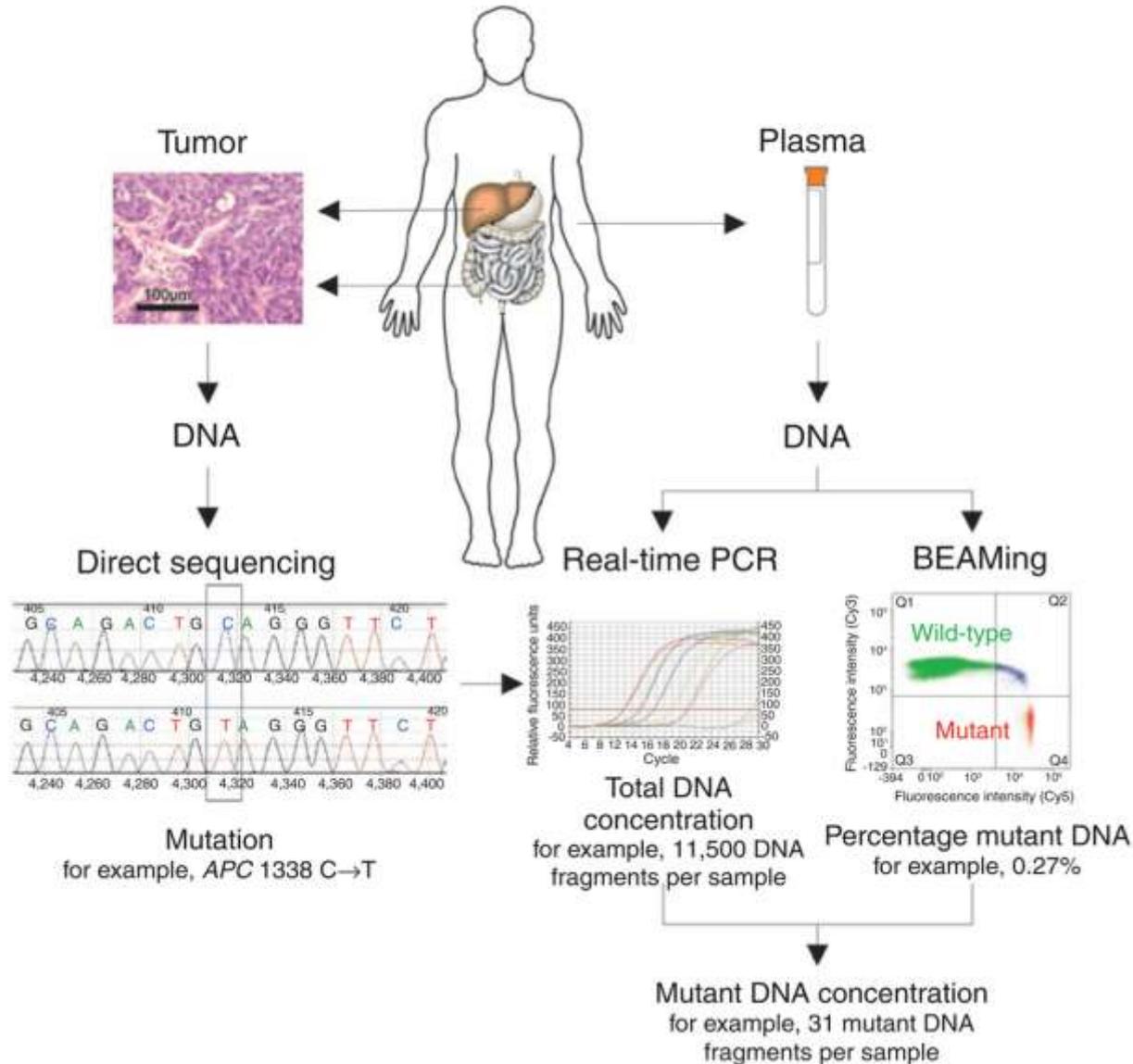
Detection of Circulating Tumor DNA in Human Malignancies



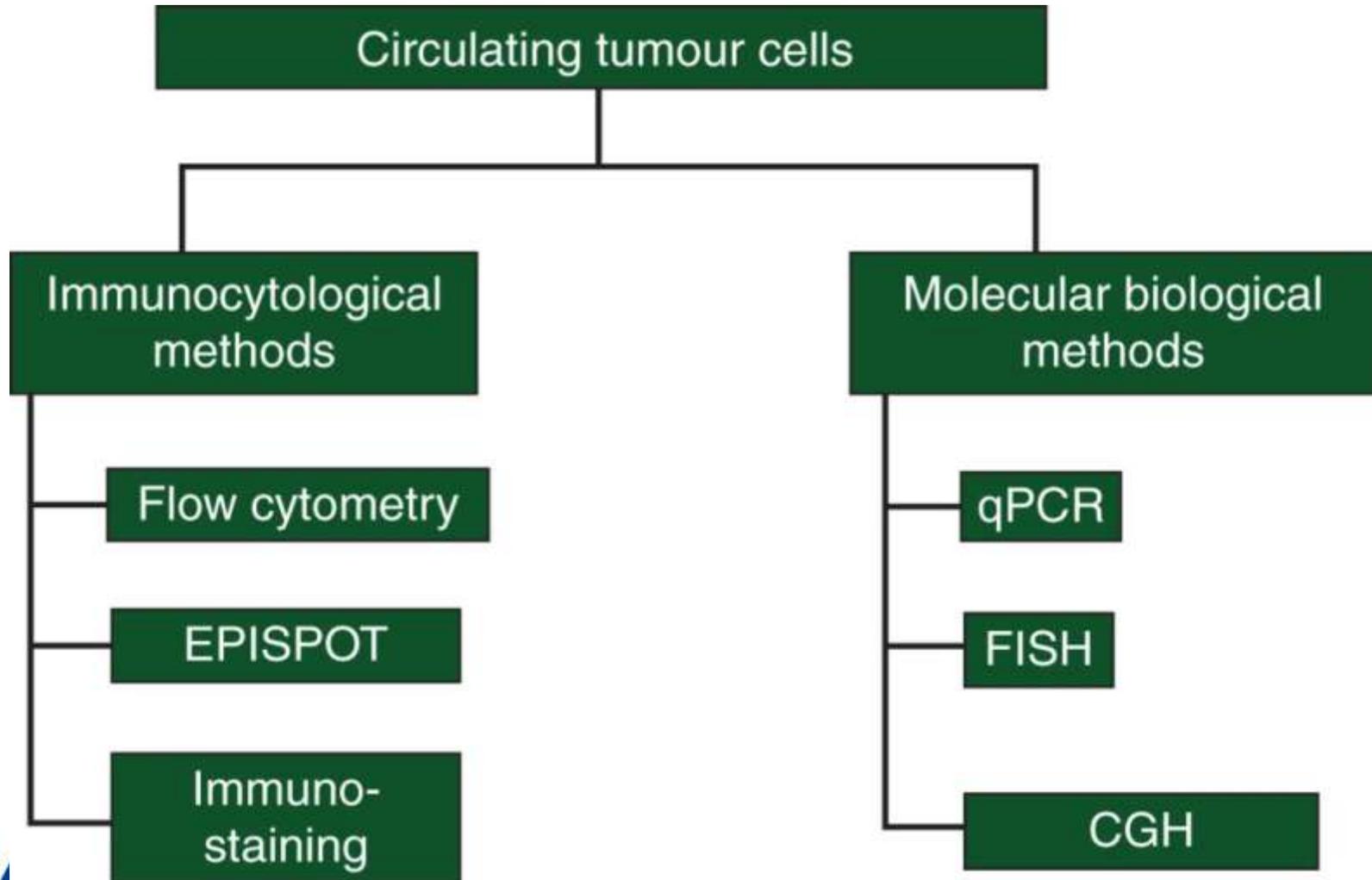
The development of noninvasive methods to detect and monitor tumors continues to be a major challenge in oncology. We used digital polymerase chain reaction–based technologies to evaluate the ability of circulating tumor DNA (ctDNA) to detect tumors in 640 patients with various cancer types. We found that ctDNA was detectable in >75% of patients with advanced pancreatic, ovarian, colorectal, bladder, gastroesophageal, breast, melanoma, hepatocellular, and head and neck cancers, but in less than 50% of primary brain, renal, prostate, or thyroid cancers. In patients with localized tumors, ctDNA was detected in 73, 57, 48, and 50% of patients with colorectal cancer, gastroesophageal cancer, pancreatic cancer, and breast adenocarcinoma, respectively. ctDNA was often present in patients without detectable circulating tumor cells, suggesting that these two biomarkers are distinct entities. In a separate panel of 206 patients with metastatic colorectal cancers, we showed that the sensitivity of ctDNA for detection of clinically relevant KRAS gene mutations was 87.2% and its specificity was 99.2%. Finally, we assessed whether ctDNA could provide clues into the mechanisms underlying resistance to epidermal growth factor receptor blockade in 24 patients who objectively responded to therapy but subsequently relapsed. Twenty-three (96%) of these patients developed one or more mutations in genes involved in the mitogen-activated protein kinase pathway. Together, these data suggest that ctDNA is a broadly applicable, sensitive, and specific biomarker that can be used for a variety of clinical and research purposes in patients with multiple different types of cancer.



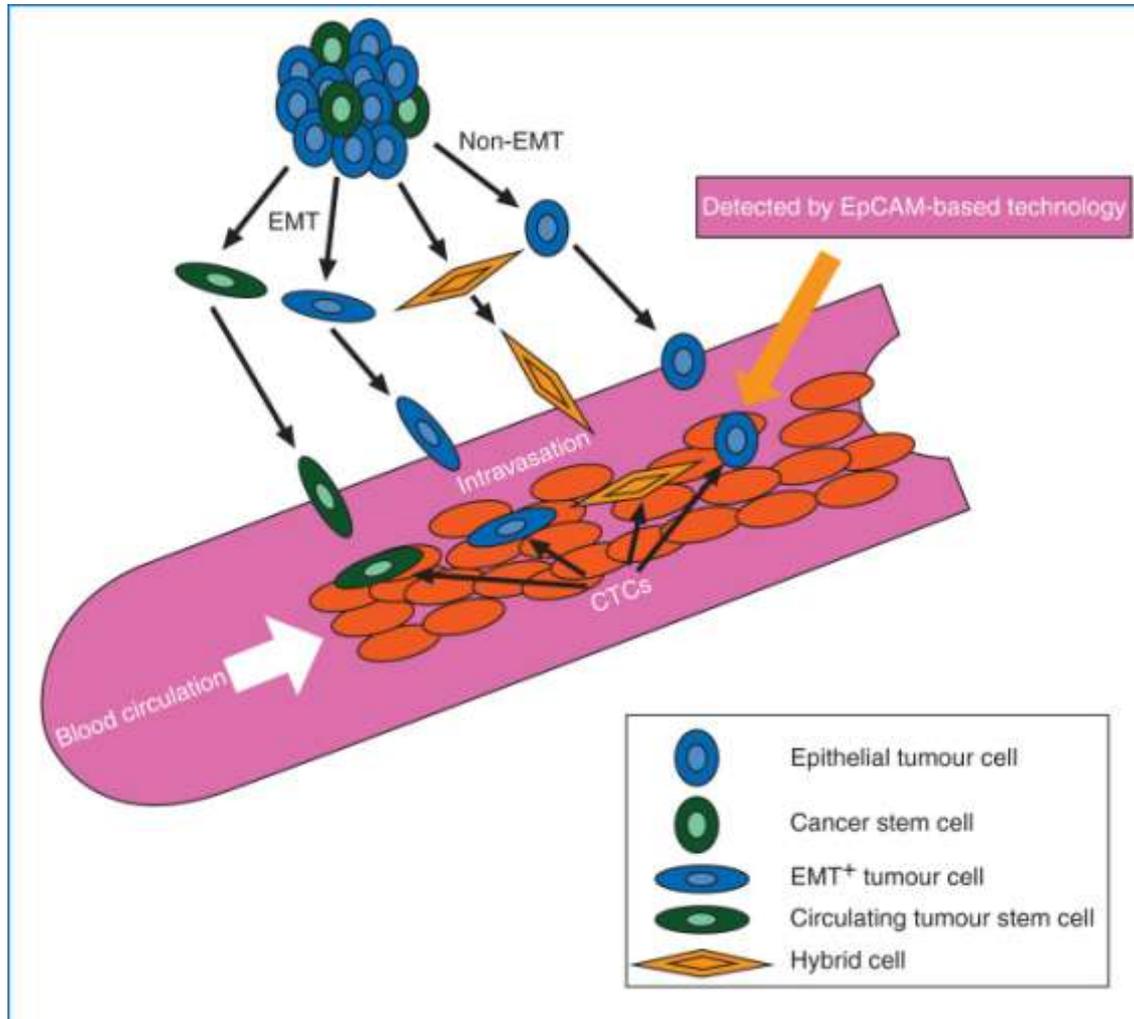
Measurement of ctDNA



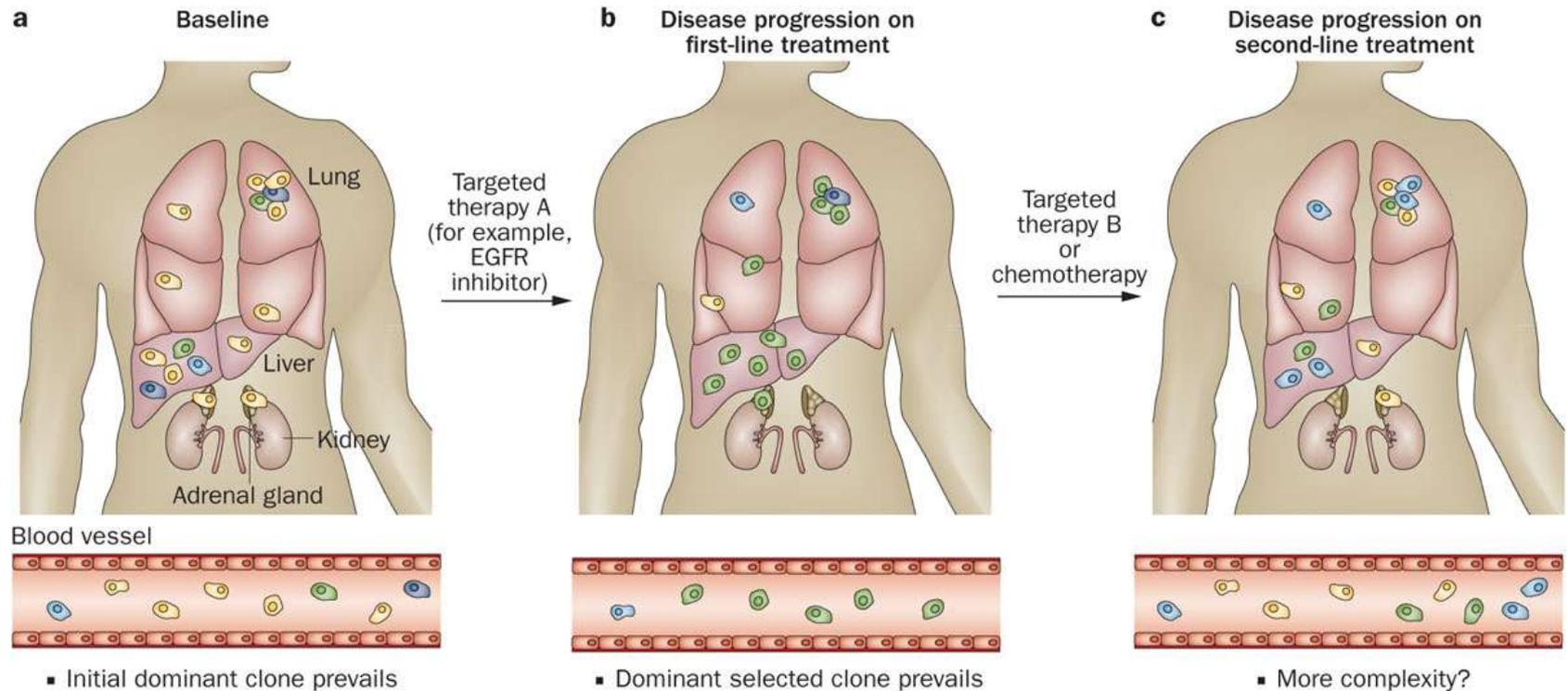
Methods of analysis of circulating tumour cells.



Subpopulations of cells from primary tumour circulating in the peripheral blood.

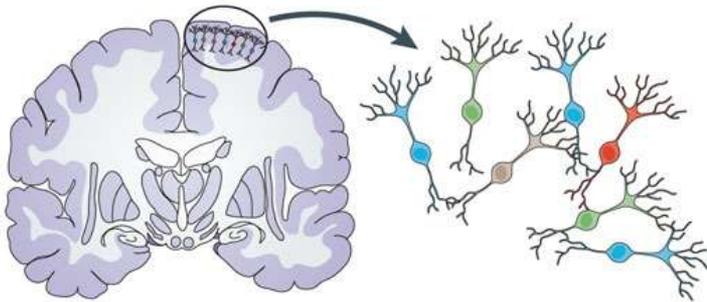


Potential of single CTC analysis to evaluate tumour heterogeneity and disease evolution

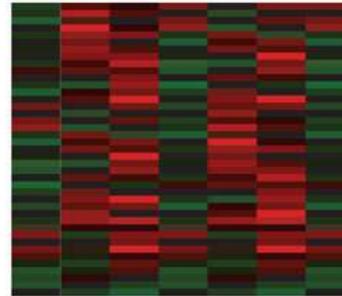


Single-cell sequencing

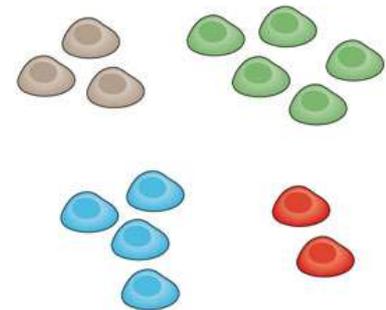
a Obtain an unbiased sample of single cells



b Generate single-cell expression profiles



c Identify cell types by clustering



Nature Reviews | **Genetics**

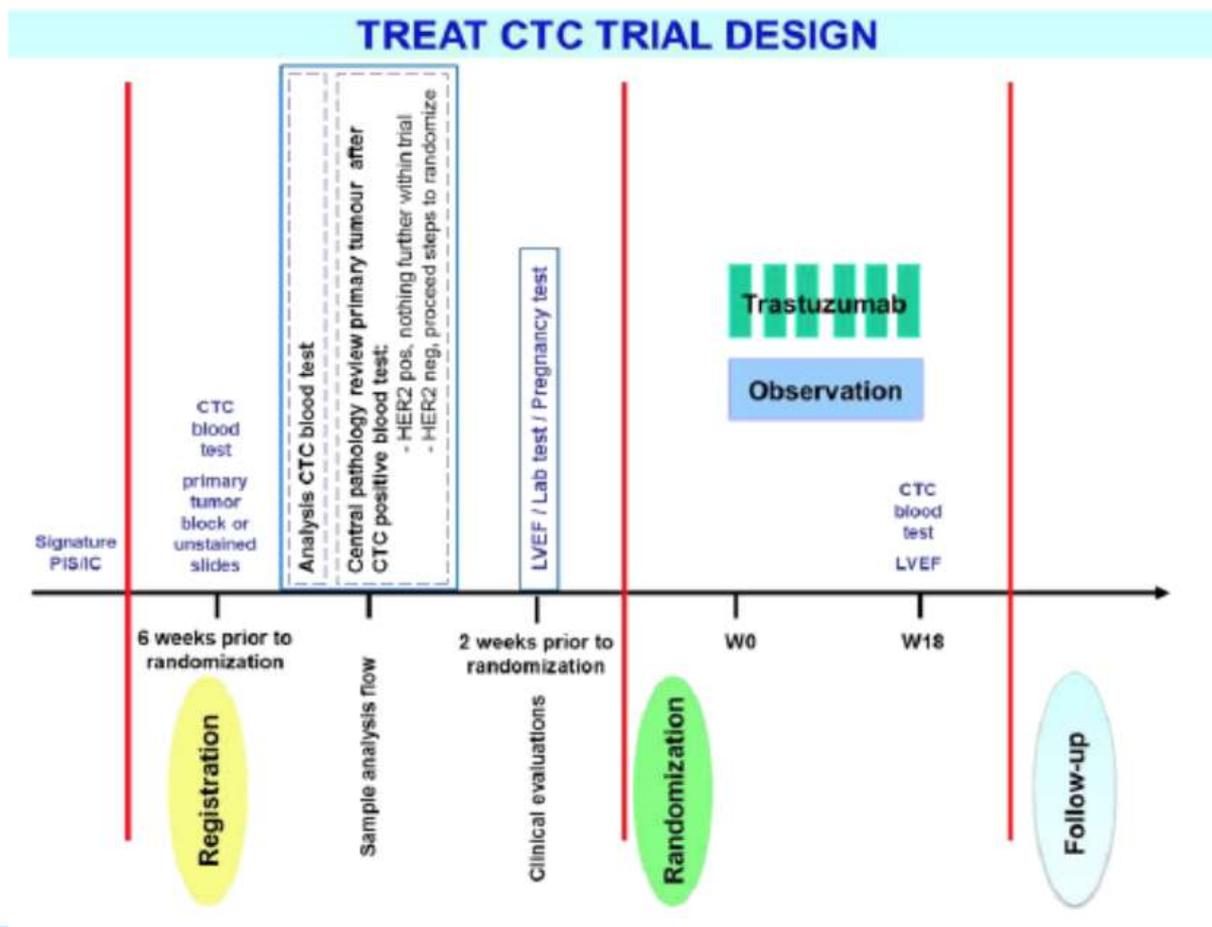


Future applications of ctDNA/CTCs (?)

1. Monitor drug response with ctDNA if able to identify a tumor-associated variant
2. CTCs for monitoring patients without easily identifiable tumor-associated variants
3. CTCs for “real-time” in vitro and in vivo drug testing: drug discovery



Trastuzumab in HER2-negative Early breast cancer as secondary Adjuvant



Primary objective

- To evaluate whether trastuzumab eliminates CTC in patients with HER2-negative primary BC

Secondary objectives

- To evaluate feasibility, reliability, within patient reproducibility of the CTC assay
- To evaluate the safety of trastuzumab in these women
- To compare clinical outcomes between the trastuzumab and observation arms
- To perform translational Research



Experimenting with Experiments



- It is ironic that as clinical trials investigate therapies with ever greater biological complexity, clinical trial designs have remained largely unchanged for 65 years
- ...except that they keep getting bigger, not more successful, just bigger

 COMMENTARY

A Historical Perspective on Clinical Trials Innovation and Leadership Where Have the Academics Gone?

David L. DeMets, PhD

Robert M. Califf, MD

THE RANDOMIZED CONTROLLED TRIAL (RCT), THE GOLD standard for evaluating the balance of risk and benefit in medical therapies, first emerged as a key clinical research tool in the mid-20th century thanks to visionary leadership of agencies such as the US National Institutes of Health (NIH), the UK Medical Research Council, and academic research institutions. Since then, clinical trials activity has shifted from the NIH and academia into the purviews of the medical products industry and regulatory authorities. Recent emphasis on evidence-based medicine, patient-centered outcomes research,¹ and learning² and accountable³ health care systems underscores the fact that most clinical trials fail to provide the evidence needed to inform medical decision-making. However, the serious in-

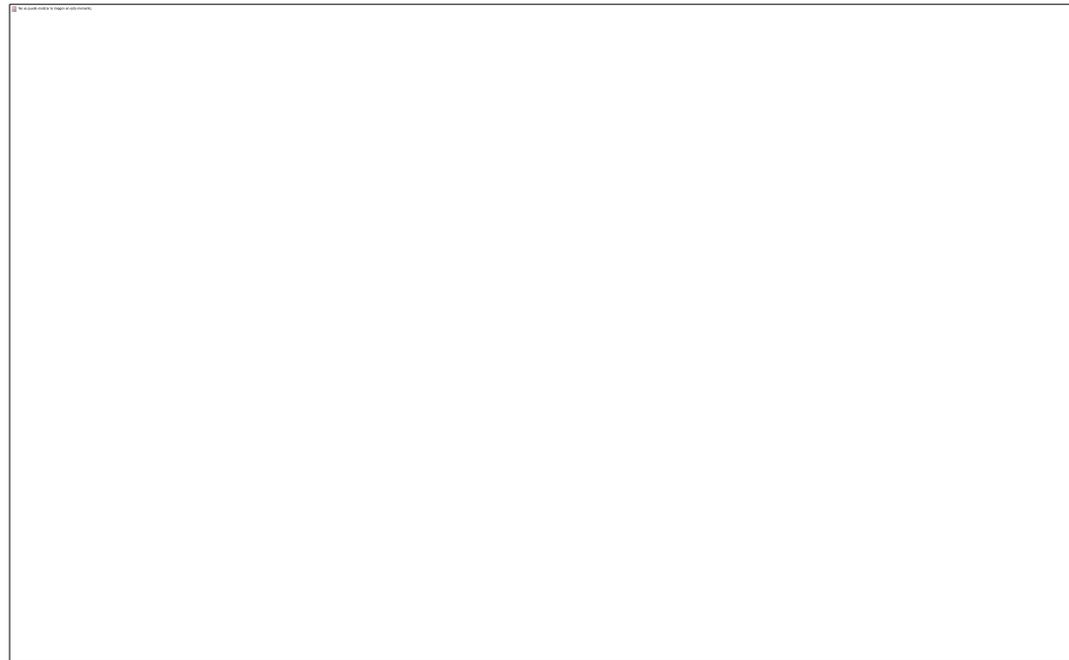
When fundamental trials methodologies were being developed at the NIH in the 1960s, an NIH-commissioned task force delineated recommendations for organizing and conducting RCTs.⁴ One significant early example is the Coronary Drug Project,⁵ a joint effort among NIH sponsors, an academic coordinating center, and a steering committee of academic leaders. In the 1970s and 1980s, the NIH often convened academic leaders to identify knowledge gaps and prioritize and conduct specific trials as funding permitted.

During the 1960s, there was scant statistical literature examining clinical trials methodologies. Researchers learned by doing trials, noting successes and failures, and iterating to advance the field. In a series of discussions in the 1970s, ideas were debated and solutions to immediate problems were proposed.⁶ Throughout the 1970s and 1980s, NIH and academic biostatisticians developed many methods now in routine use, including sample size estimation, interim data monitoring, and sequential measures methods for analysis.



The Approaching Wall

- Ever finer grid of biomarker categories: Within 10 years every cancer patient will have an orphan disease
- How to develop drugs in diseases with ever decreasing prevalence?
- Traditional statistical considerations do not include disease prevalence.



Design of a Phase II POC Study

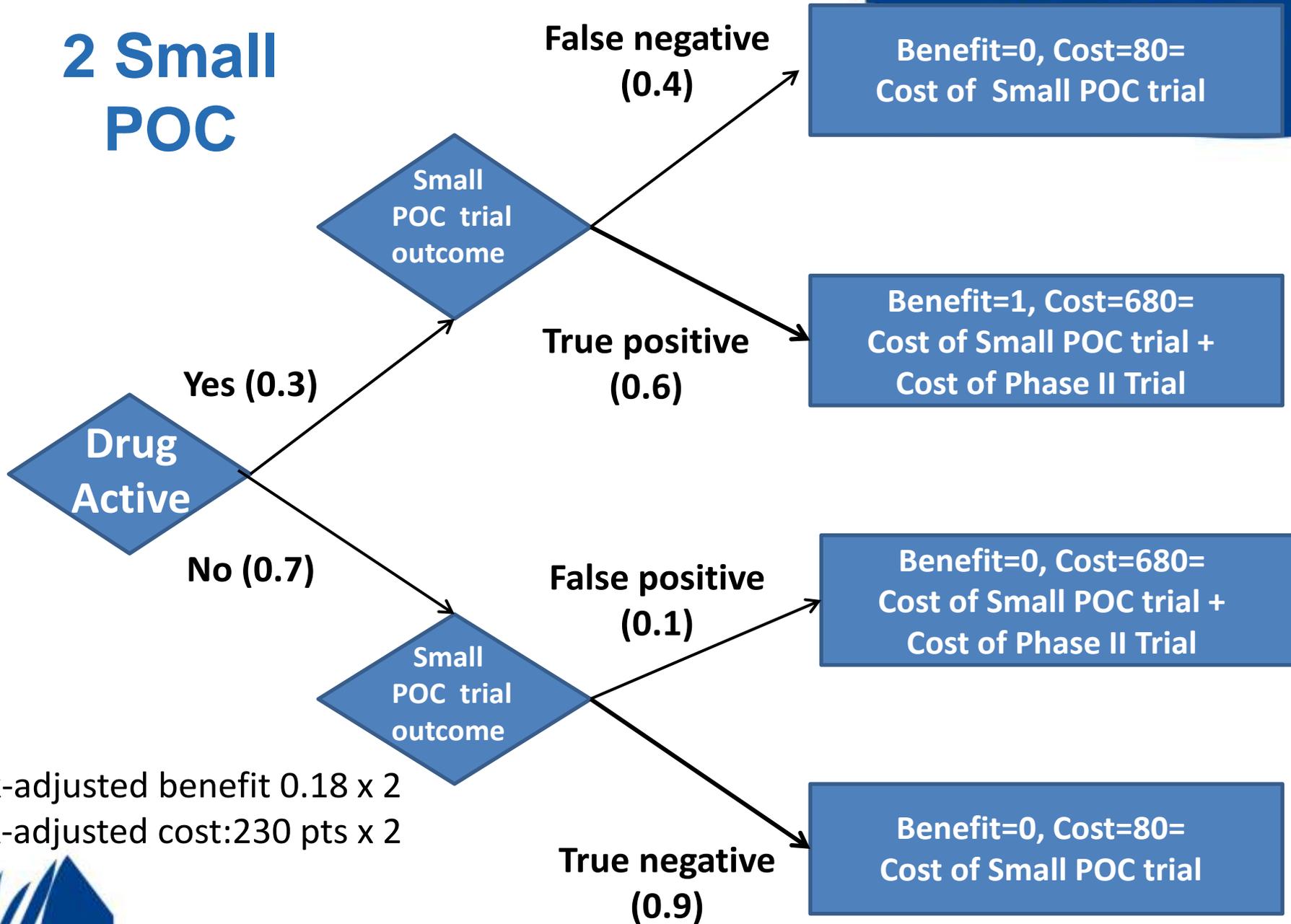
- Sized for detecting an effect size of clinical interest on a surrogate marker (eg. PFS and RR)
 - Blinded and randomized designs preferred

	Drug Active	Drug Inactive
Outcome positive	True positive (Power)	False positive (Type I error/alpha)
Outcome negative	False negative (Type II error)	True negative

- What about those trials that would have been successful but were not performed (Type III error)?



2 Small POC



Risk-adjusted benefit 0.18×2
Risk-adjusted cost: $230 \text{ pts} \times 2$

1.278 pts in Phase II/III per indication



**The two-small trial strategy is 12%
more efficient than the one-large trial
strategy!**

The challenge to bring personalized cancer medicine from clinical trials into routine clinical practice: The case of the Institut Gustave Roussy

Monica Arnedos, Fabrice André, Françoise Farace, Ludovic Lacroix, Benjamin Besse, Caroline Robert, Jean Charles Soria and Alexander M.M. Eggermont

Molecular Oncology
[Volume 6, Issue 2, Pages 204-210](#) (April 2012)
DOI: 10.1016/j.molonc.2012.02.008

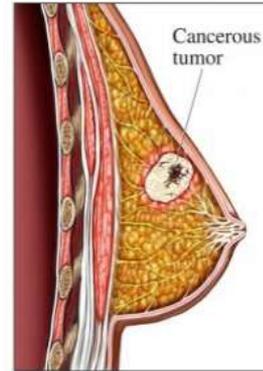
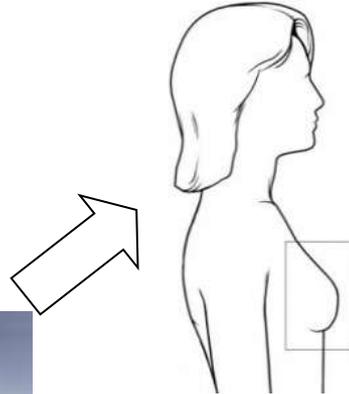


Precision Medicine

Concept: Identify the targets to be treated in each patient

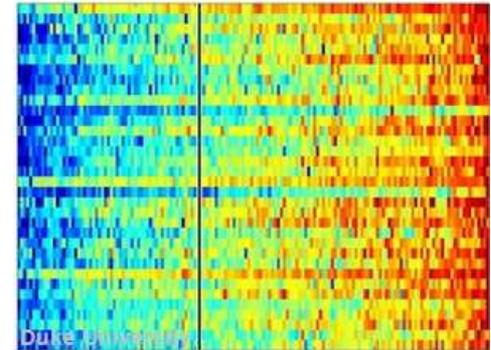
Clinical evidence

Therapy matched to genomic alteration



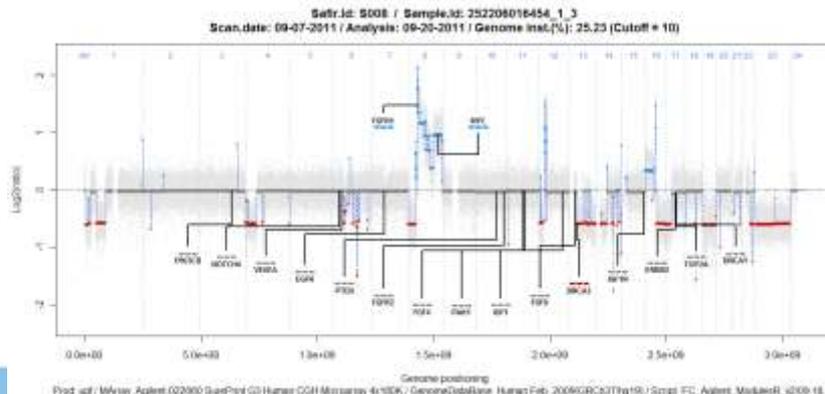
What is the optimal Biotechnology ?

Molecular analysis



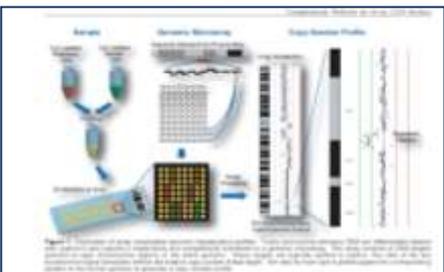
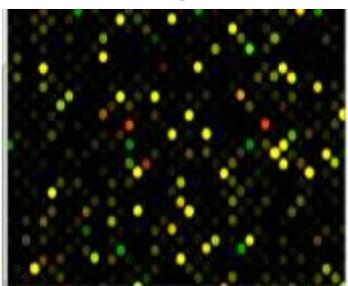
What is the optimal Algorithm ?

Target identification



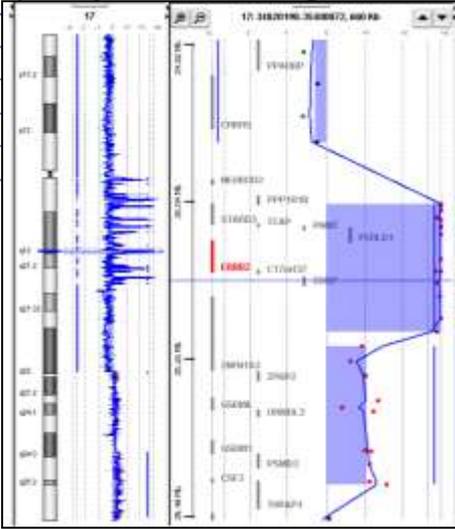
Molecular screening programs: to identify patients eligible for phase I/II trials

Molecular screening with High Throughput Genomics



IF Progressive disease

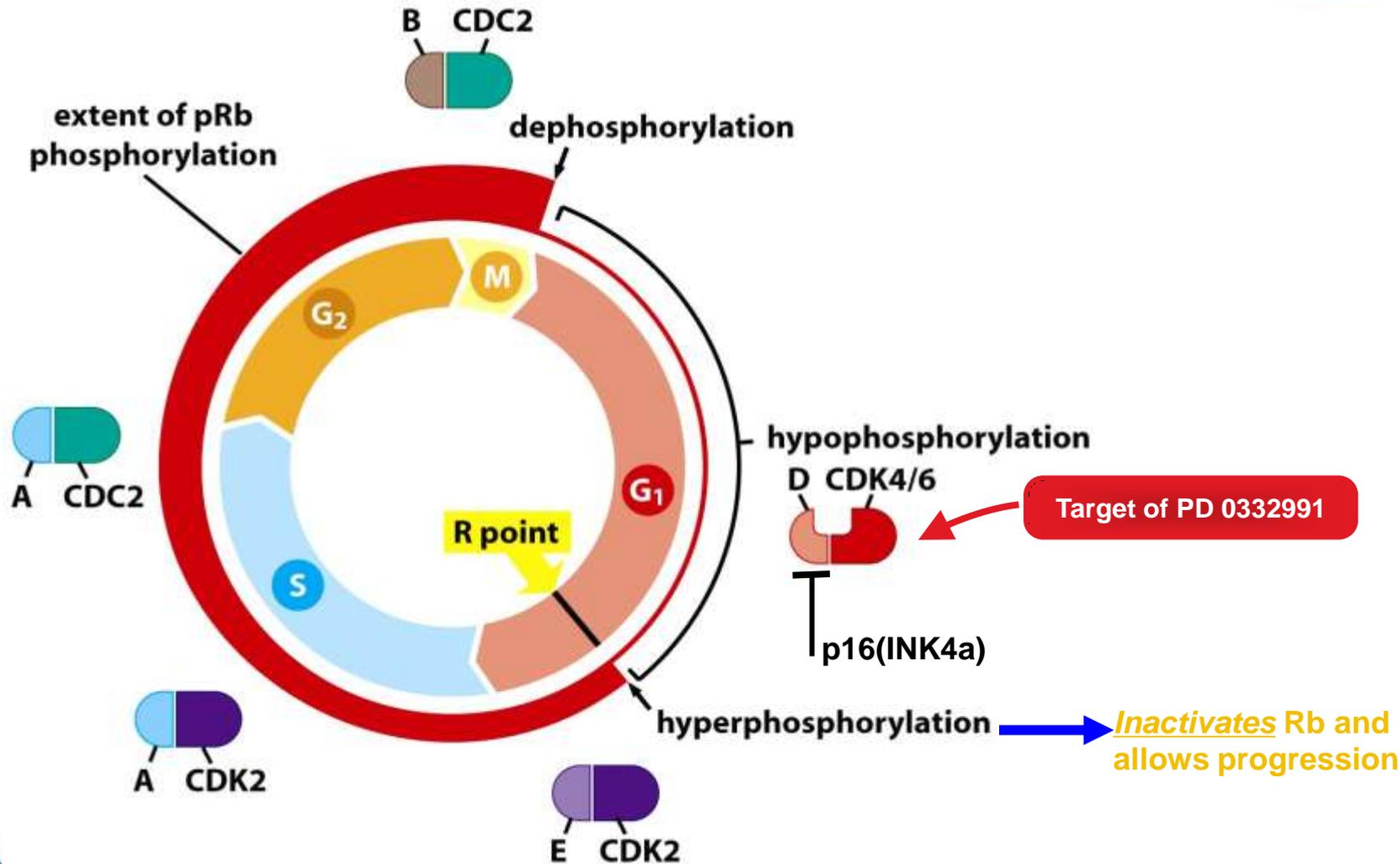
Target identification



- Trial A
- Trial B
- Trial C
- Trial D
- Trial E
- Trial F



Rb as Master-Regulator of the R Point



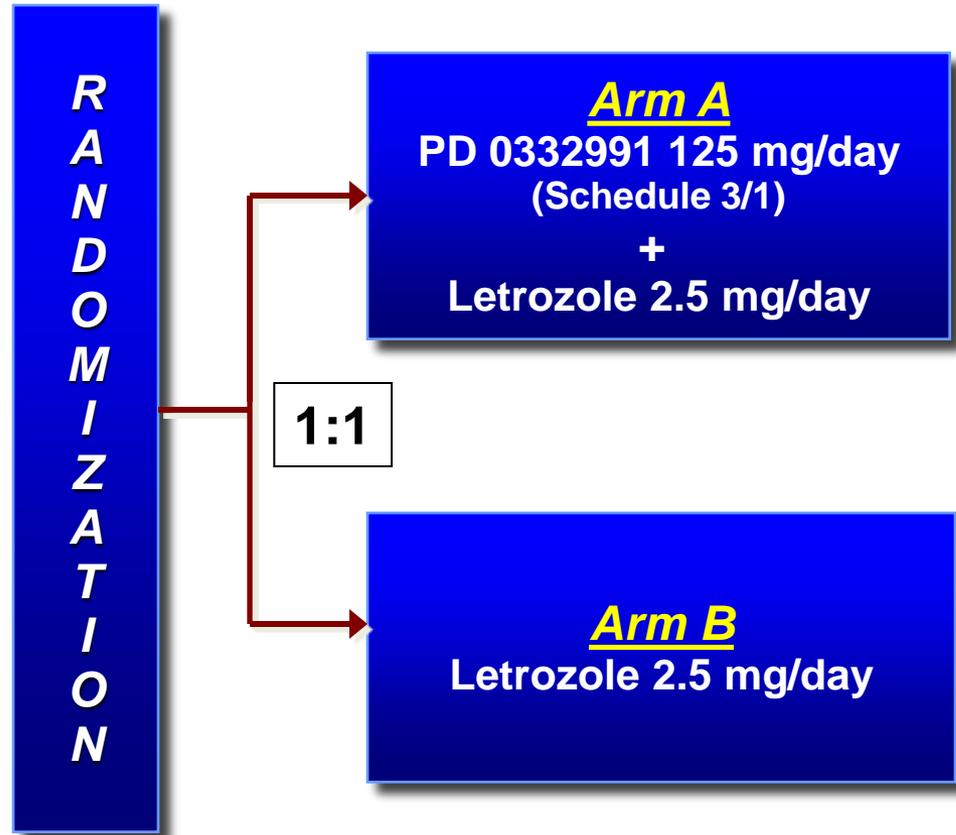
Phase II Study Design (Part II)

ER+, HER2- breast cancer

Biomarker Selection

- CCND1 amp
- And/or loss of p16

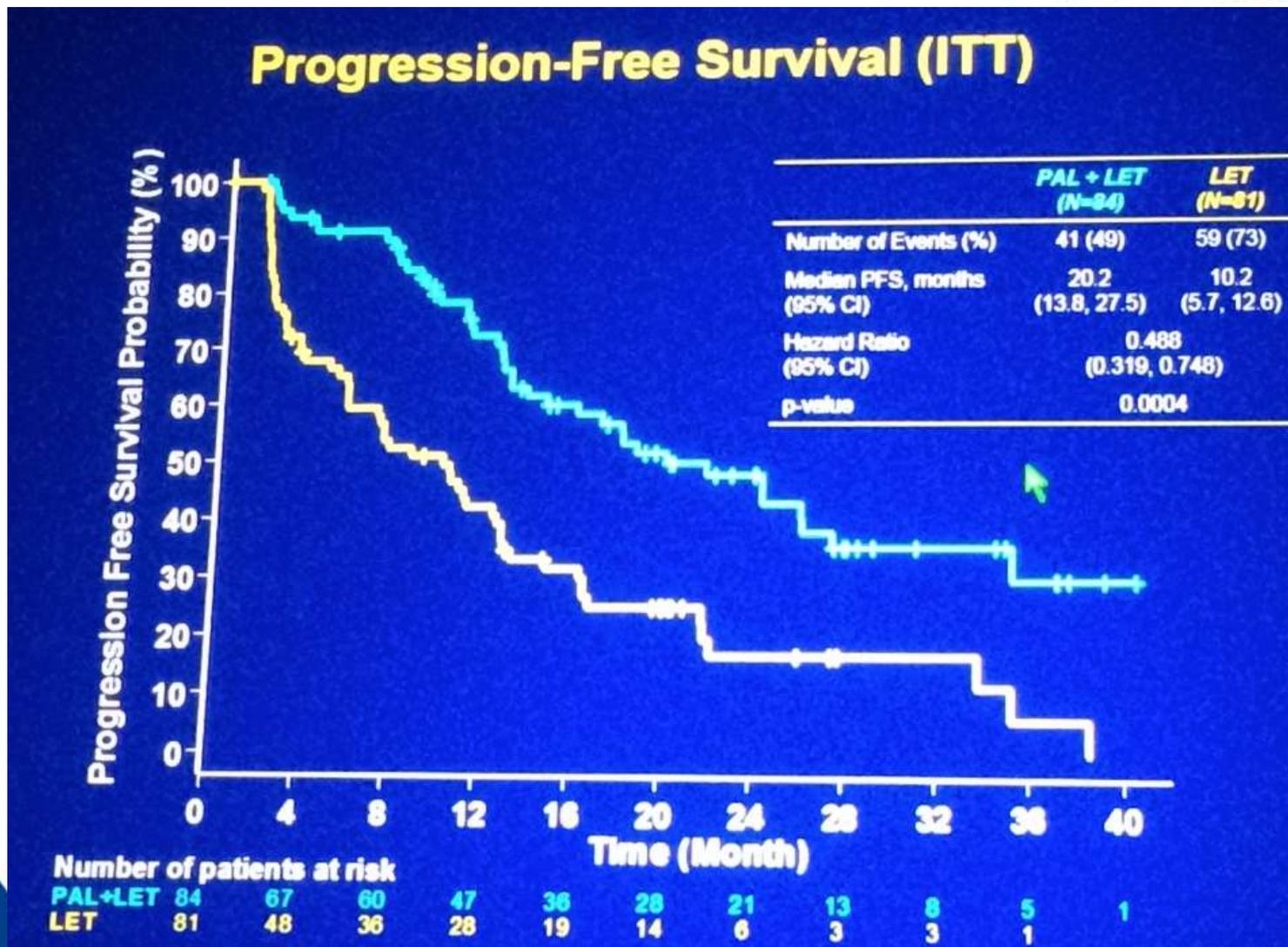
Primary endpoint: PFS



N = 150

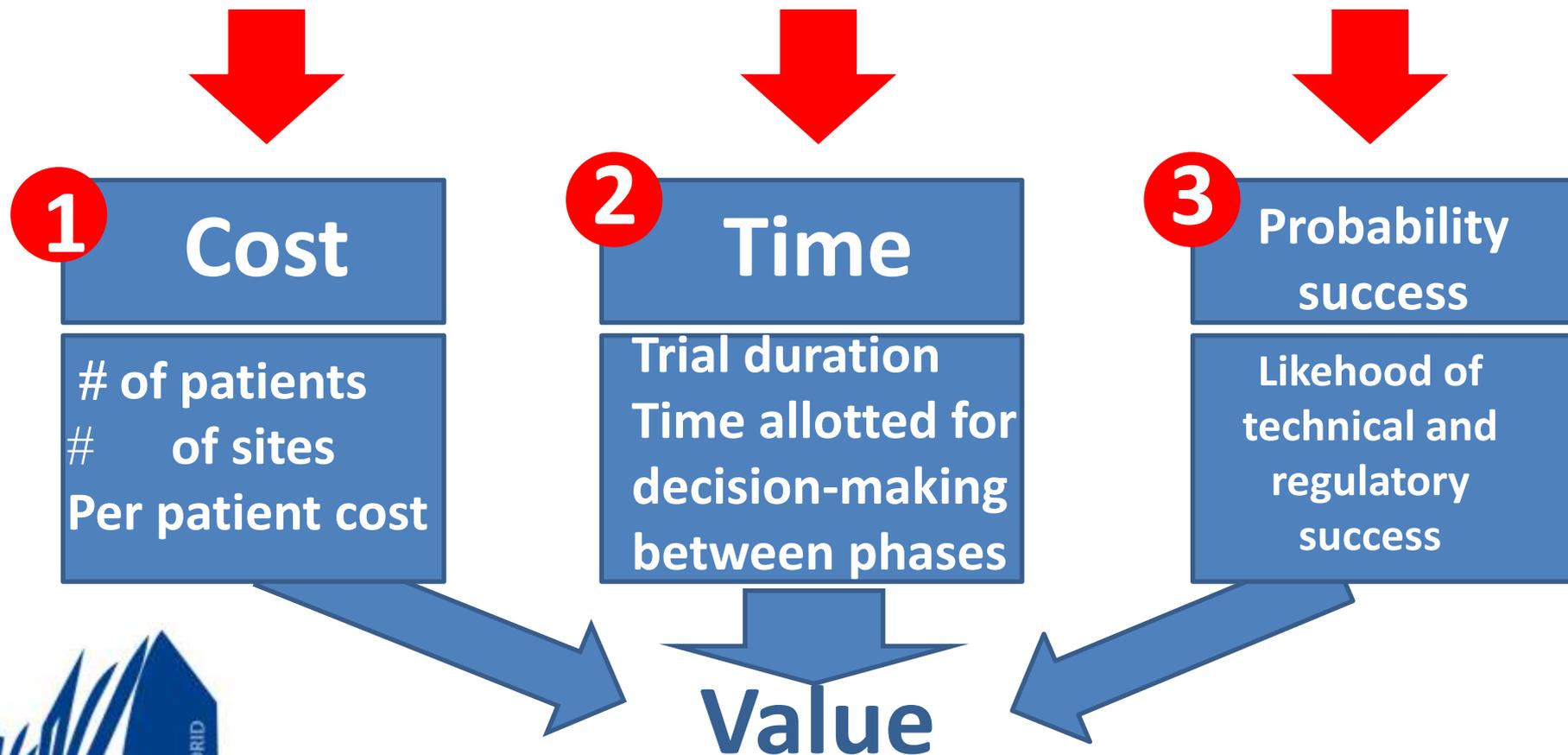


PALOMA-1 (Palbociclib)



To improve R&D productivity, we can use adaptive trials to optimize three key variables that ultimately drive value and thus productivity of R&D

Adaptive trials

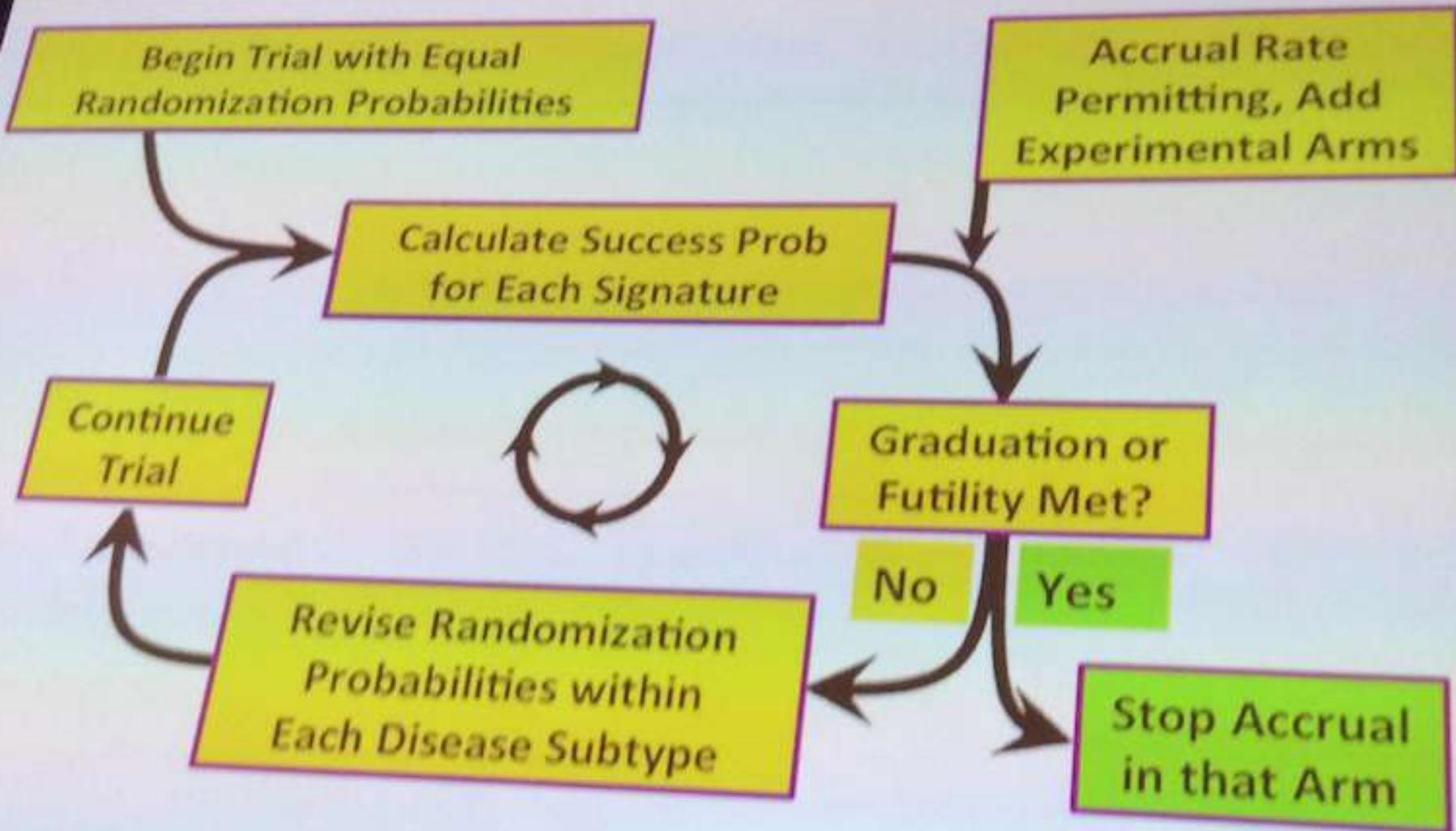


In our alternative designs, we leveraged basic adaptations to create designs with more flexibility, optionality and value vs. base care

Adaptation	Potential benefits
Phase 2/3 Hybrid	➤ Faster and often cheaper: eliminates need to re-recruit patients, create additional study protocols, etc..
Interim Analyses	➤ Faster: creates potential for skipping phases or stopping early if effect size is better or much smaller than expected ➤ Less risky: improves PoS by increasing Phase 2/3 sample sizes while keeping costs or below prototypical designs
Sample Size Re-estimation	➤ Less risky: creates potential to adjust sample size to match observed effect size

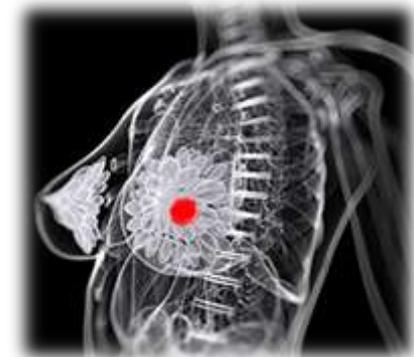
These design enhancements can be applied to a variety of different programs, depending on specific characteristics.

I-SPY 2 Adaptive Process



Precision Medicine Biomarkers for Personalizing Cancer Therapy

- For patients who require systemic therapy, use molecular approaches
 - To determine which drugs will eradicate patient-specific minimal residual or significantly delay progress of metastatic disease
 - To perform real-time disease monitoring using methods that will provide actionable information
 - Optimize clinical trial design





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Muchas Gracias