GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 2: Novedades terapéuticas frente a dianas "clásicas"

18 de noviembre de 2021 - *Formato virtual*

Ensayos clínicos basados en alteraciones moleculares

Dra. María de Miguel

START Madrid-CIOCC HM Sanchinarro

- 1. Current situation of Precision medicine at Early Phase stages
- 2. Difficulties for clinical development in precision medicine
- 3. New approaches of trial designs

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Classical Objectives for Ph1 Trials

- Maximum Tolerated Dose
  - Acceptable, manageable, reversible toxicity in a reasonable percentage of patients
  - It assumes dose-dependent activity
- Phase 2 scheme
- Preliminary profile of side effects of the drug

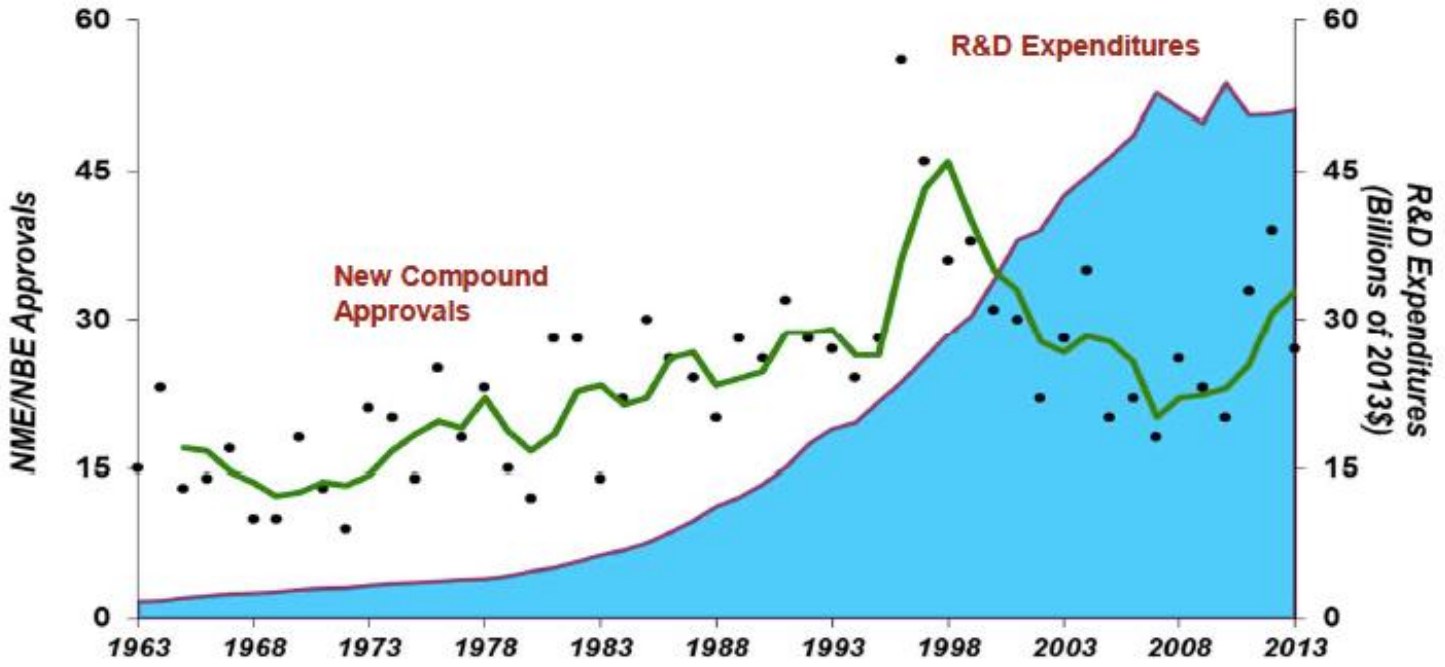
Drivers of Ph1 designs

- FDA responsibilites:
  - "advancing the public health by helping to *speed* innovations that make medicines *more effective, safer*, and more *affordable*"
    - Better drugs, sooner, at lower cost…
- Need for Early Phase trials to be more *informative*
- *Adaptation* of designs to the type of drugs in development

Drivers of Ph1 designs

- Transform Early Phase Clinical Trials to become more informative
- Starting point for rational clinical development
- Integration of preclinical pharmacokinetics, pharmacodynamics and toxicology
- ORR in the early phase (!)

New Drug and Biologics Approvals and R&D Spending



R&D expenditures are adjusted for inflation; curve is a 3-year moving average for NME/NBEs
Sources: Tufts CSDD; PhRMA, 2014 Industry Profile

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

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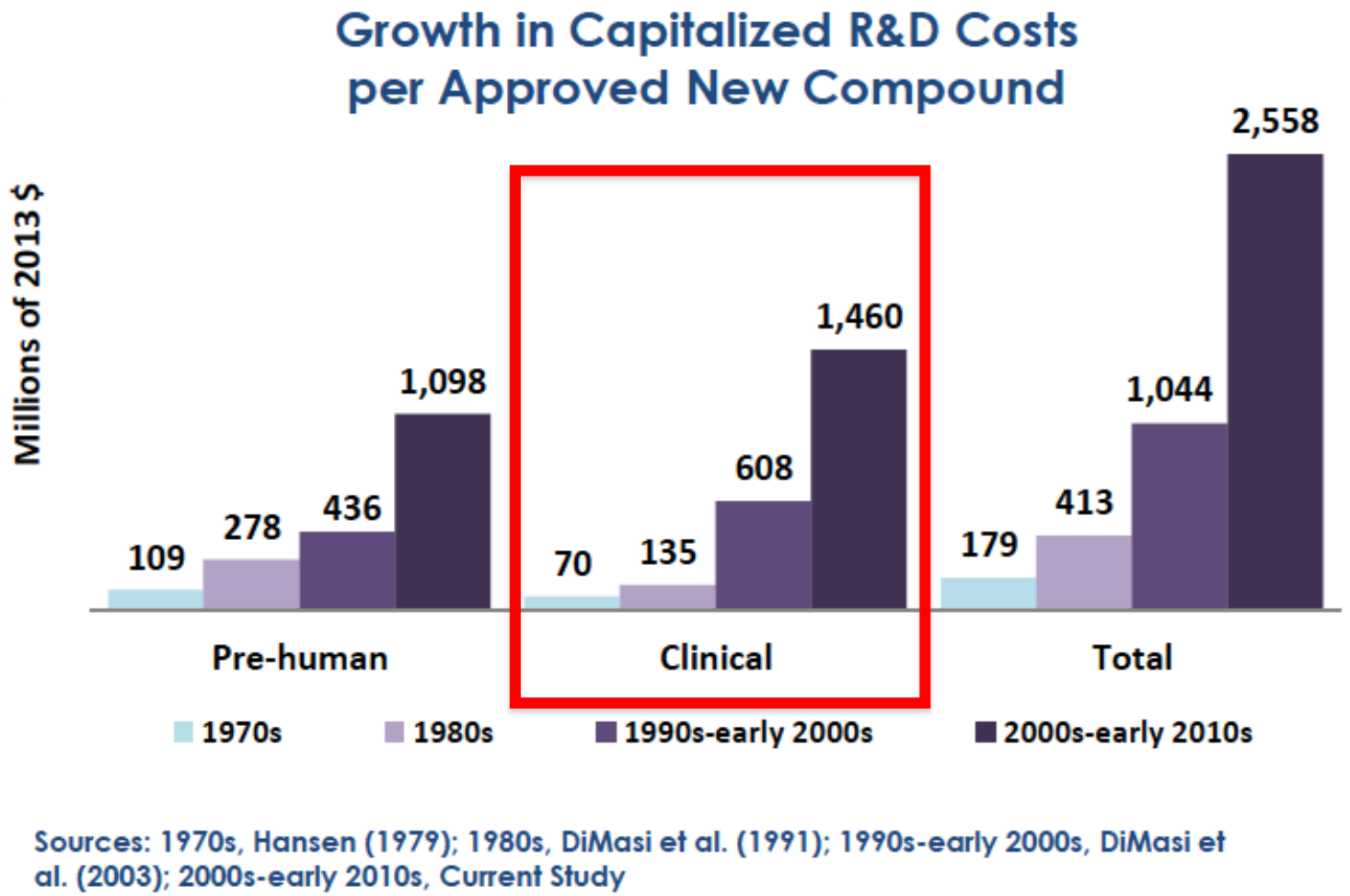


Unsustainable system: disproportionate R&D expenses…

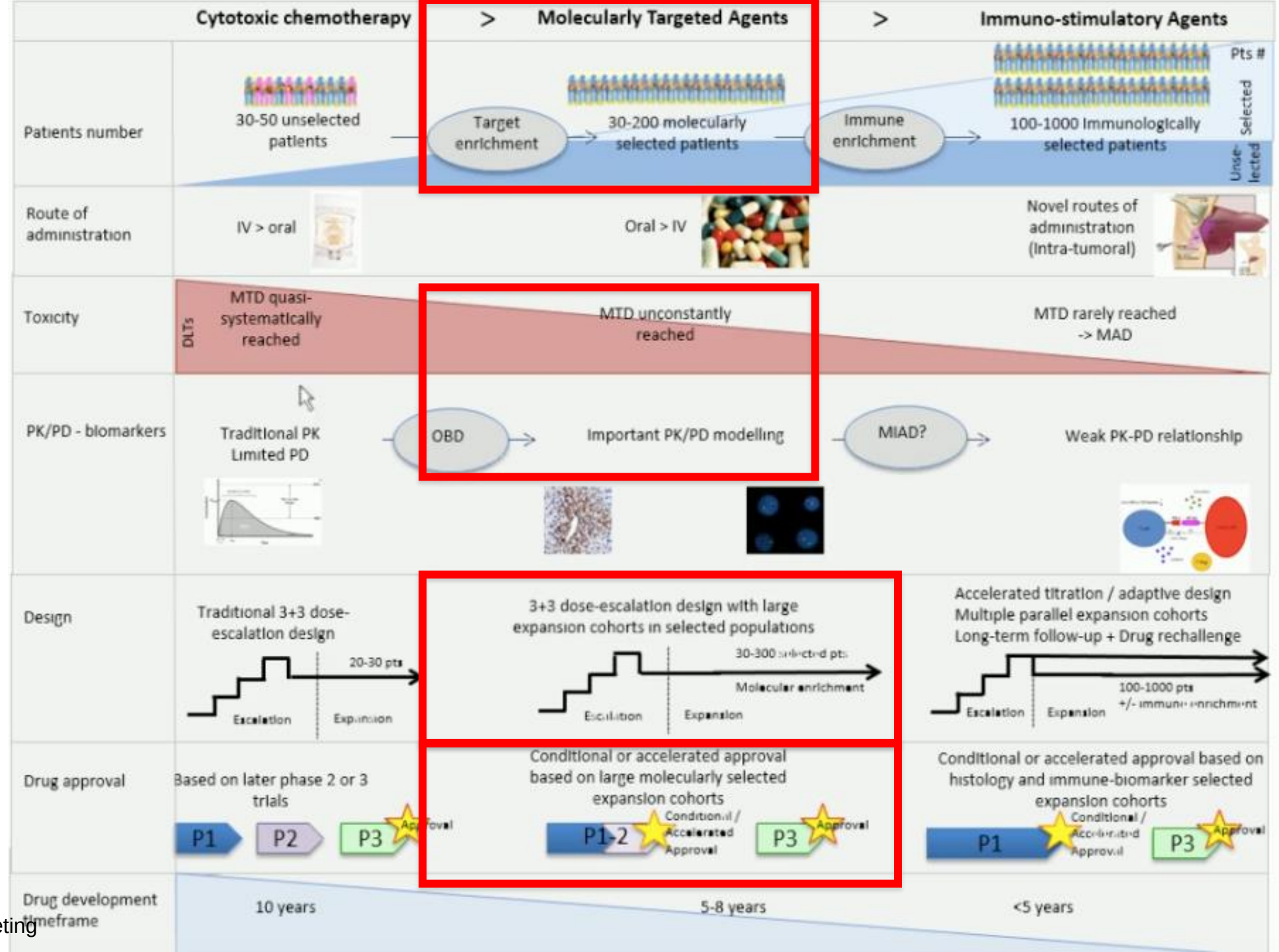
Classical Drug-to-patient process

	Discovery/ Preclinical Testing	File IND at FDA	Clinical Trials: Phase I	Clinical Trials: Phase II	Clinical Trials: Phase III	File NDA/BLA at FDA	FDA
Years	6.5		1.5	2	3.5		1.5
Test Population	Laboratory and animal studies		20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers		Review process/ approval
Purpose	Assess safety, biological activity and formulations		Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved

Darwinian *adaptation of early clinical trials designs* to the characteristics of the different families of drugs in early clinical development

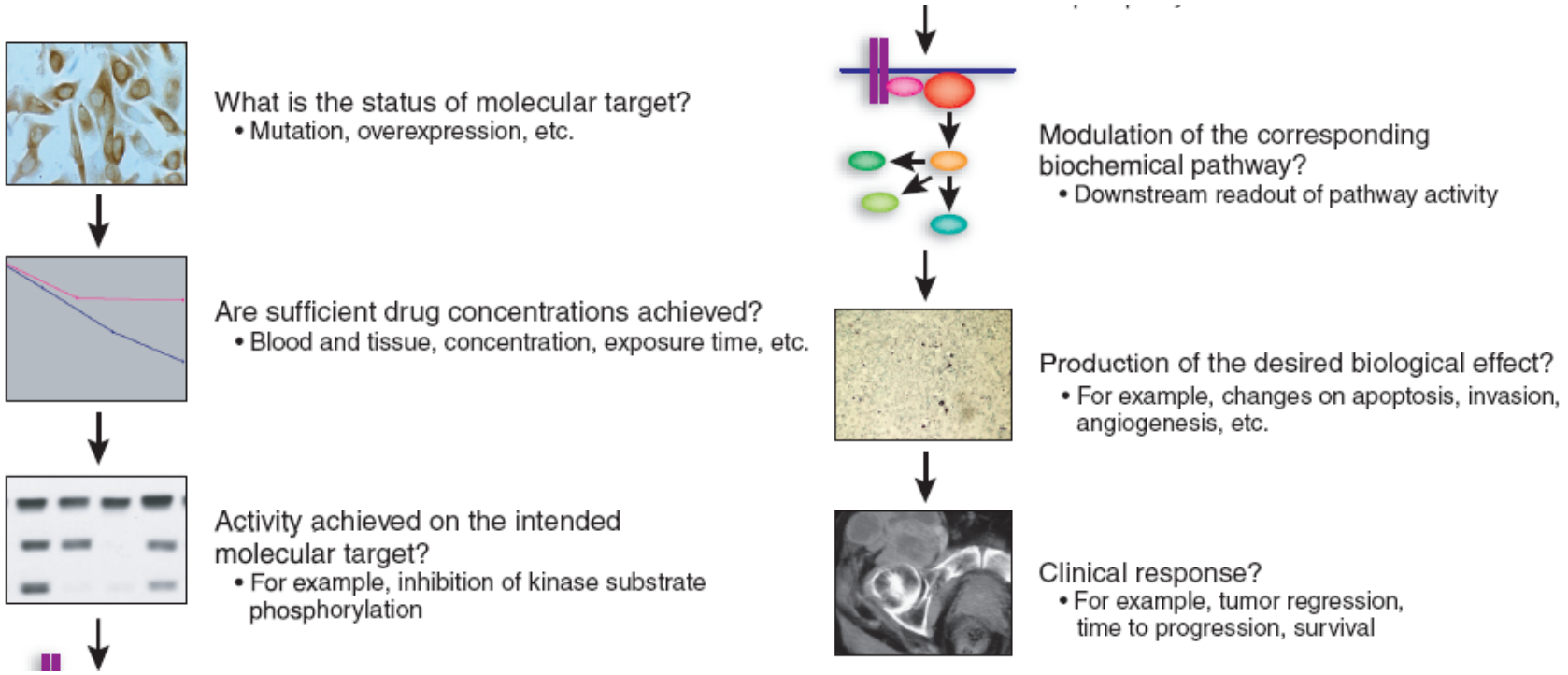
	CYTOTOXICS	"TARGETED"	IO
Early Clinical Trial DESIGN	**"Classical"**	**"Precision Medicine"**	**"Seamless"**
Paradigm	3+3	Basket, Umbrella, N of 1	Ph1b/2
What to do after RD is found?	Histology-specific Ph2	Target-based Ph2	Wide spectrum, octopus, Ph2
Goal	Ph3	Signal finding/ Fast-track	Signal finding and confirmation/ Registration

Courtesy of Dr. E. Calvo



Jean-Charles Soria
at 2015 ECCO meeting

"Pharmacological Audit Trail"



Workman P. Nature Chemical Biology 12, 689-700, 2006

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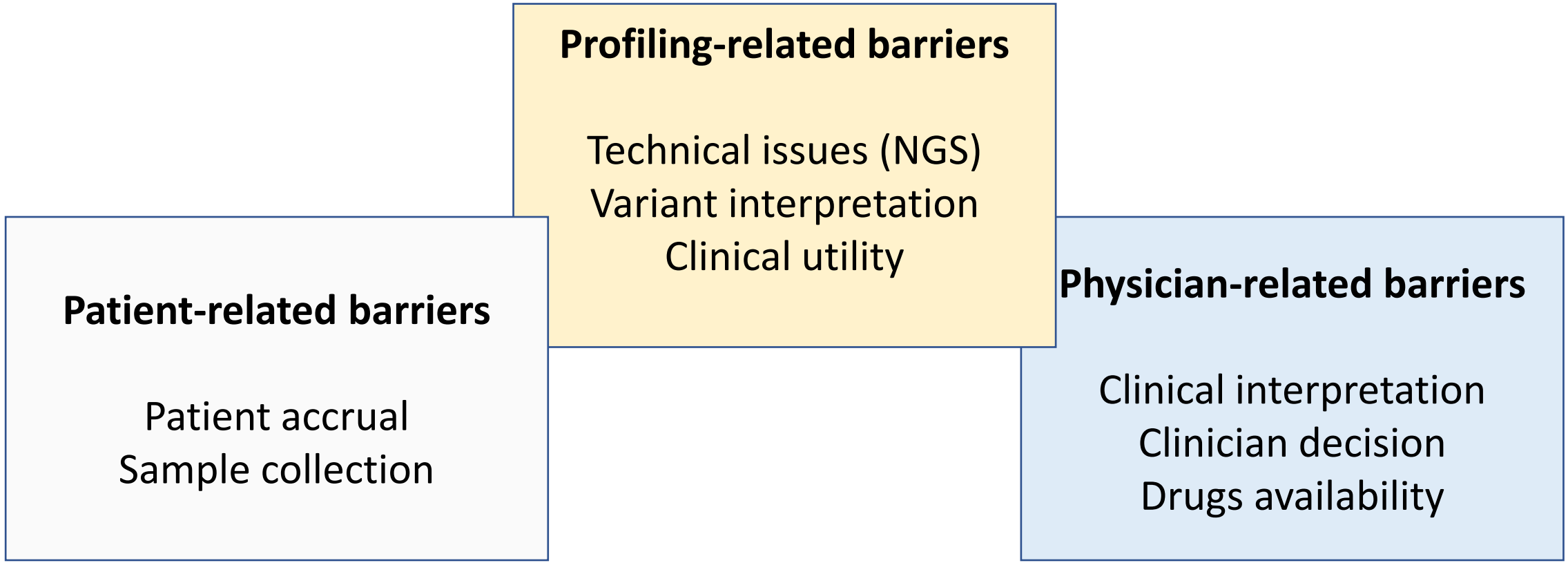
From molecular profiling to genotype-drug matching

Implementation barriers and knowledge gaps in practice



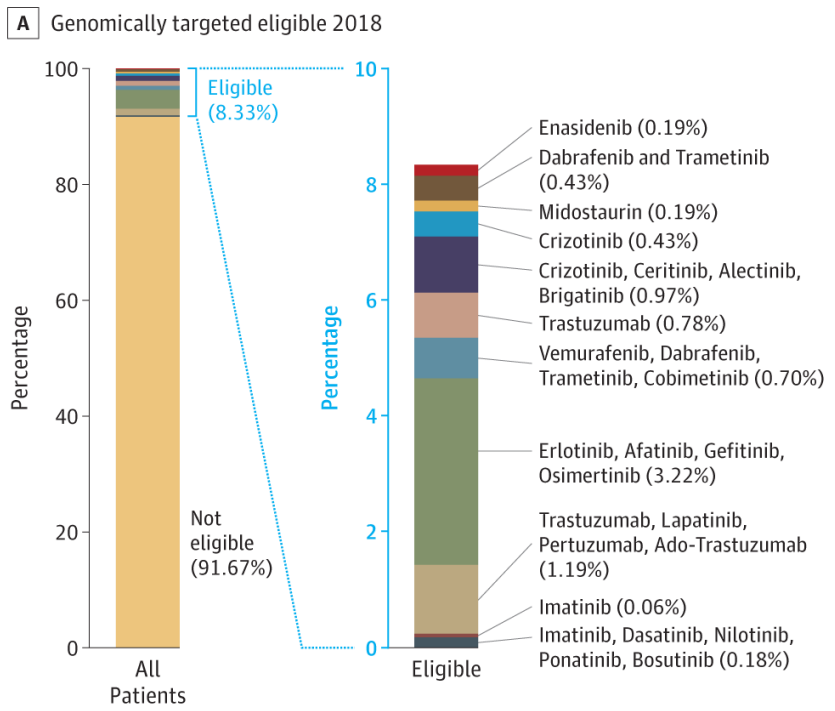
Eoghan R. Malone et al. Genome Medicine 2020;12:8

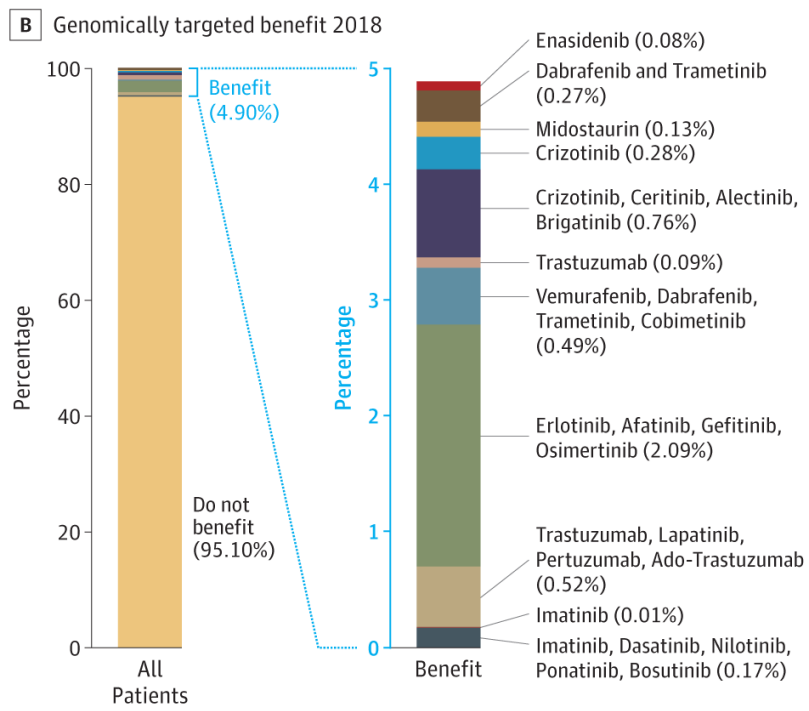
Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology

John Marquart, BA[1]; Emerson Y. Chen, MD[2]; Vinay Prasad, MD, MPH[2,3,4]

» Author Affiliations | Article Information

JAMA Oncol. 2018;4(8):1093-1098. doi:10.1001/jamaoncol.2018.1660





Number needed to analyze: biomarker-driven clinical research

$$NNS = \frac{1}{\text{(fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent)}}$$

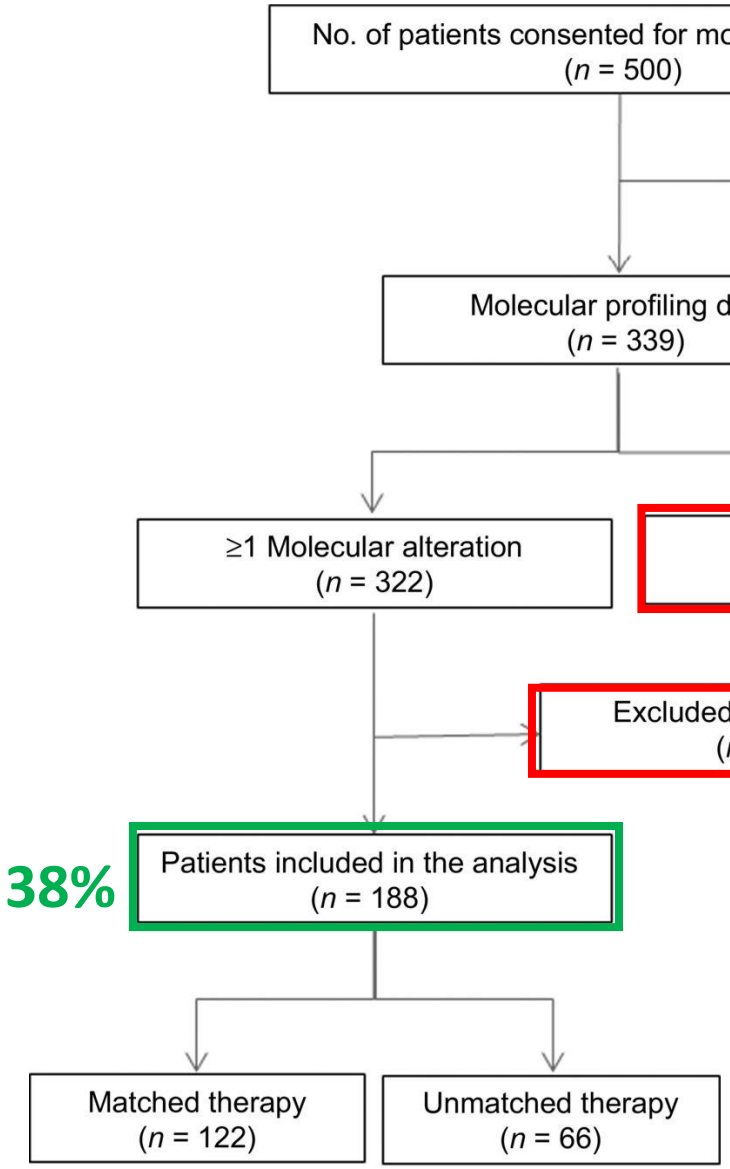
	Fraction with biomarker	Assay specificity	fraction trial-eligible	fraction accepting participation	Pt Needed to Analyze
HER2+ in Breast cancer	25%	90%	70%	50%	13
ALK fusion in NSCLC	5%	90%	70%	50%	63
FGFR fusion in GBM (freq 3-8%)	**3%**	90%	70%	50%	105

Clinical Studies

Cancer Research

Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study

Jennifer J. Wheler[1], Filip Janku[1], Aung Naing[1], Yali Li[2], Bettzy Stephen[1], Ralph Zinner[1], Vivek Subbiah[1], Siqing Fu[1], Daniel Karp[1], Gerald S. Falchook[3], Apostolia M. Tsimberidou[1], Sarina Piha-Paul[1], Roosevelt Anderson[1], Danxia Ke[1], Vincent Miller[2], Roman Yelensky[2], J. Jack Lee[4], David S. Hong[1], and Razelle Kurzrock[5]



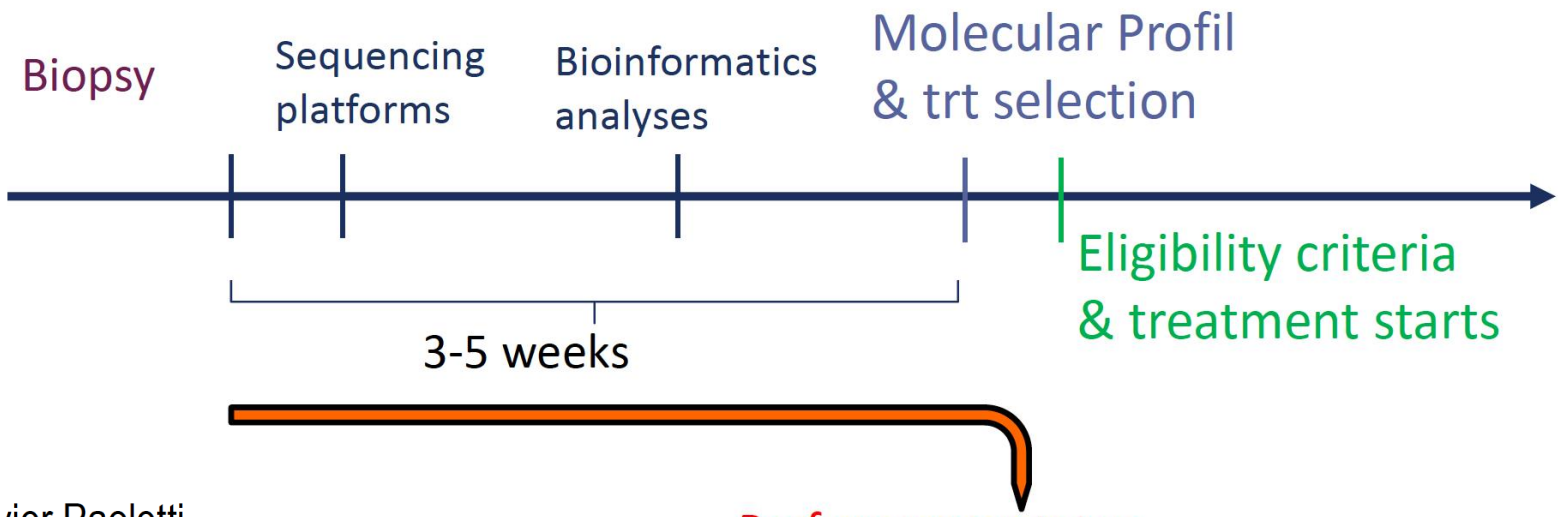
* Insufficient/no tissue, *n* = 111; expired/hospice before tissue could be obtained, *n* = 37; failed report/sequencing, *n* = 6; commercial NGS done (therefore excluded), *n* = 4; not willing to be treated, *n* = 2; withdrew from study, *n* = 1.

** Never received new evaluable treatment after consent, *n* = 124 (hospice/expired before treatment could be initiated, *n* = 79; still on prior therapy, *n* = 32; lost to follow-up, *n* = 8; refused *n* = 4; watchful waiting only, *n* = 1); prior immunotherapy, *n* = 6; unclear action of drug, *n* = 3; stem cell transplant, *n* = 1.

Jennifer J. Wheler et al. Cancer Res 2016;76:3690-3701

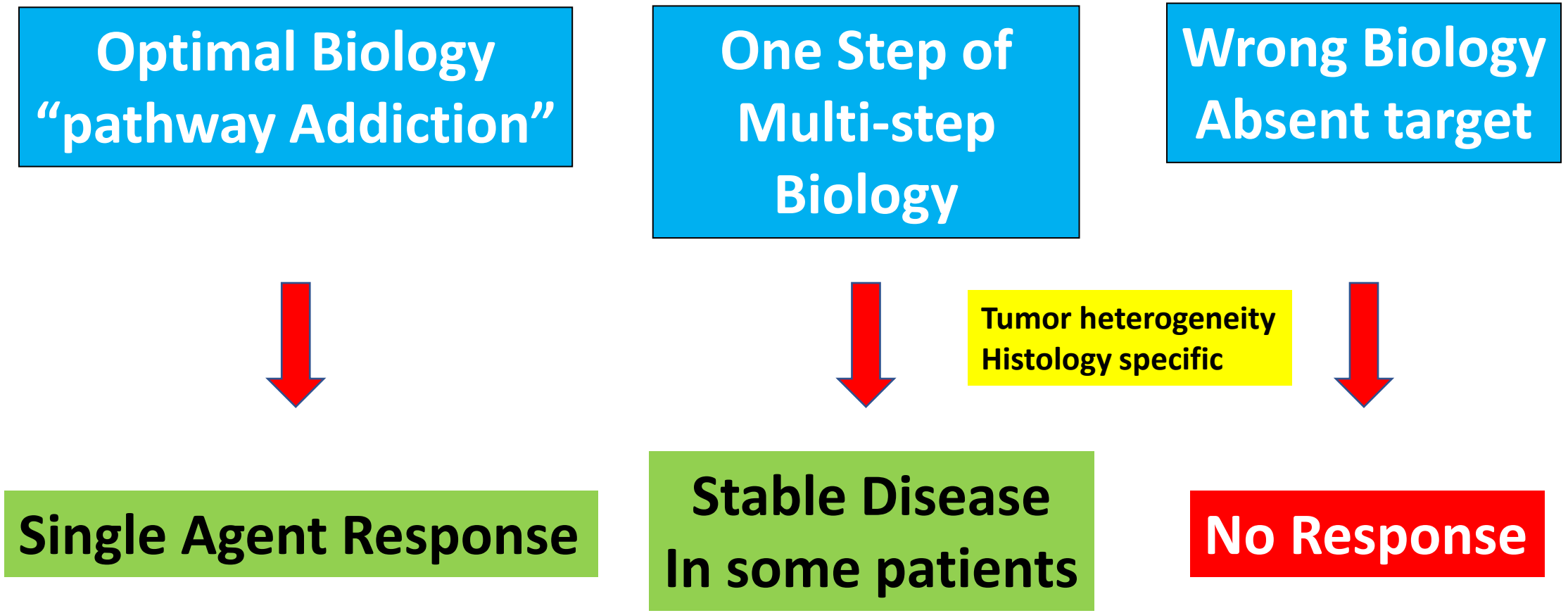
A closer look at non randomized trials
Risk of attrition (selection) bias

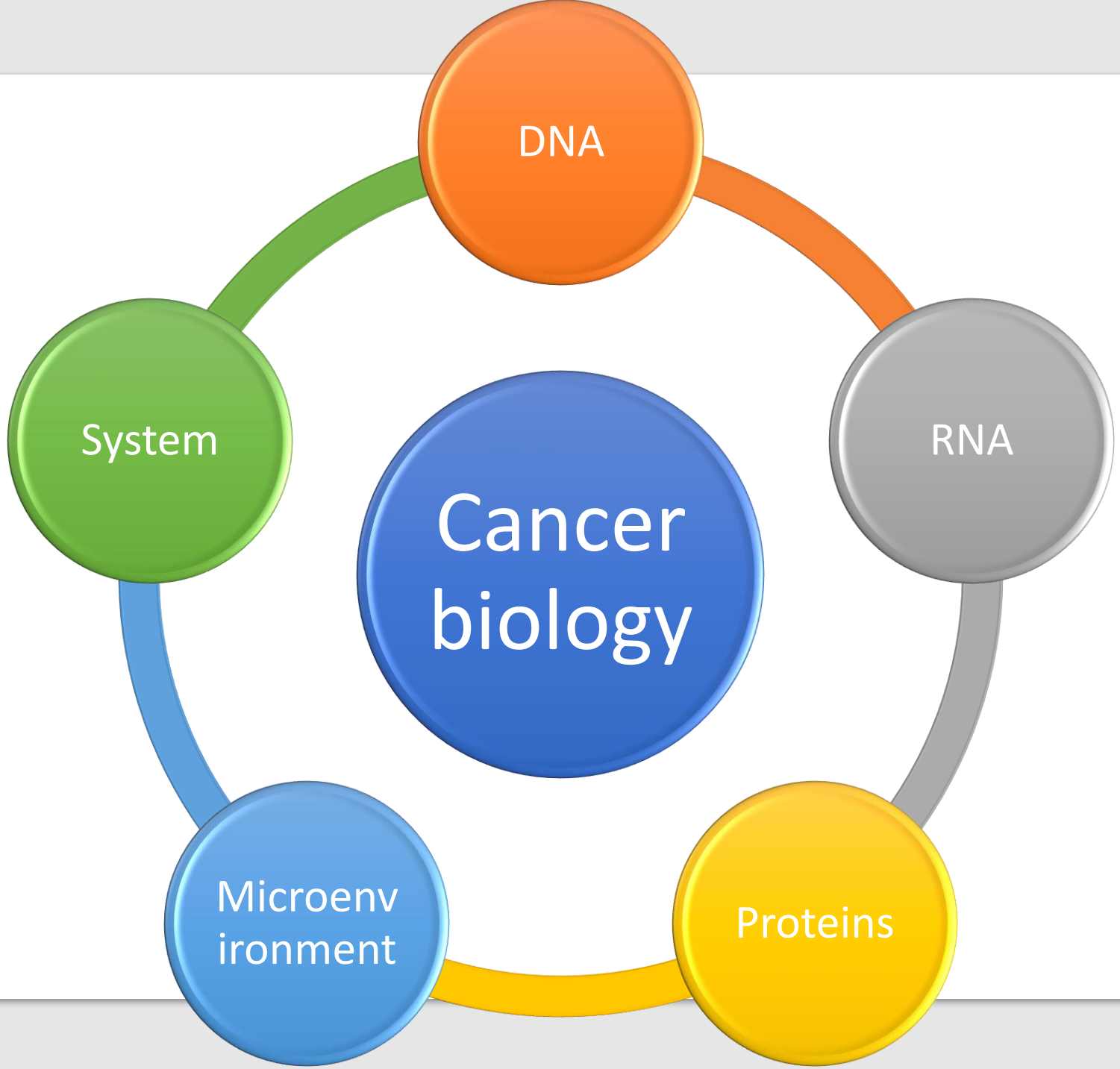
- In practice, molecular profile takes time !



Xavier Paoletti
Institut Curie / UVSQ
St Cloud, France

Target specific agents: three types of potential outcomes




DNA
RNA
Proteins
Microenv
ironment
System
Cancer
biology

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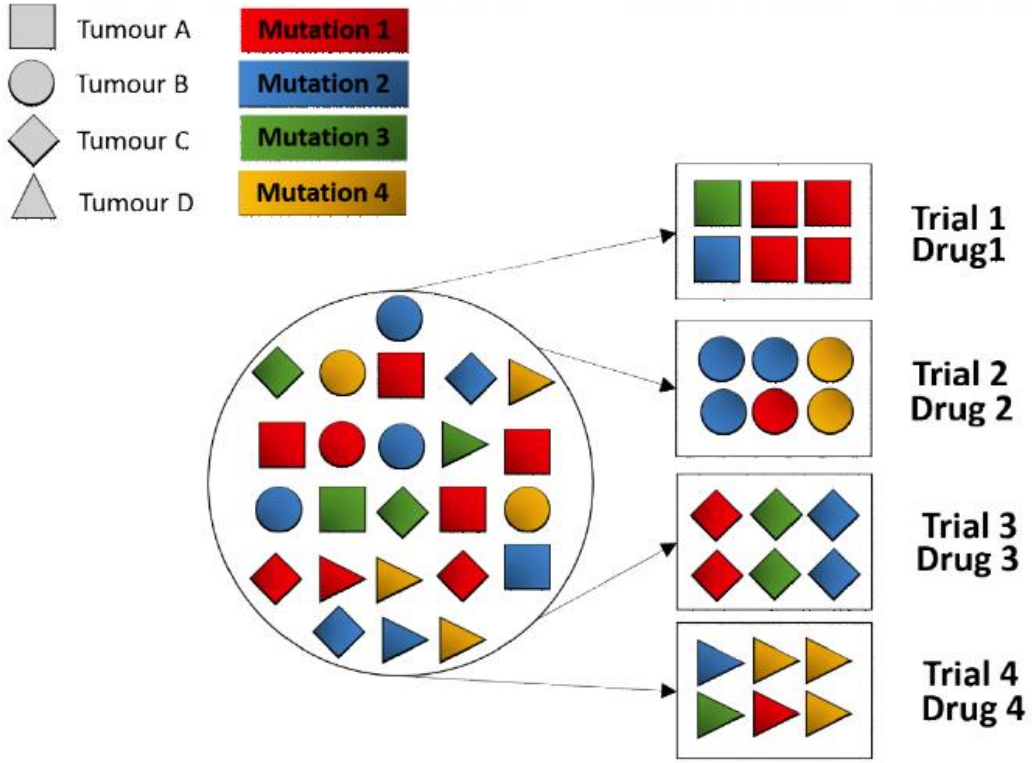
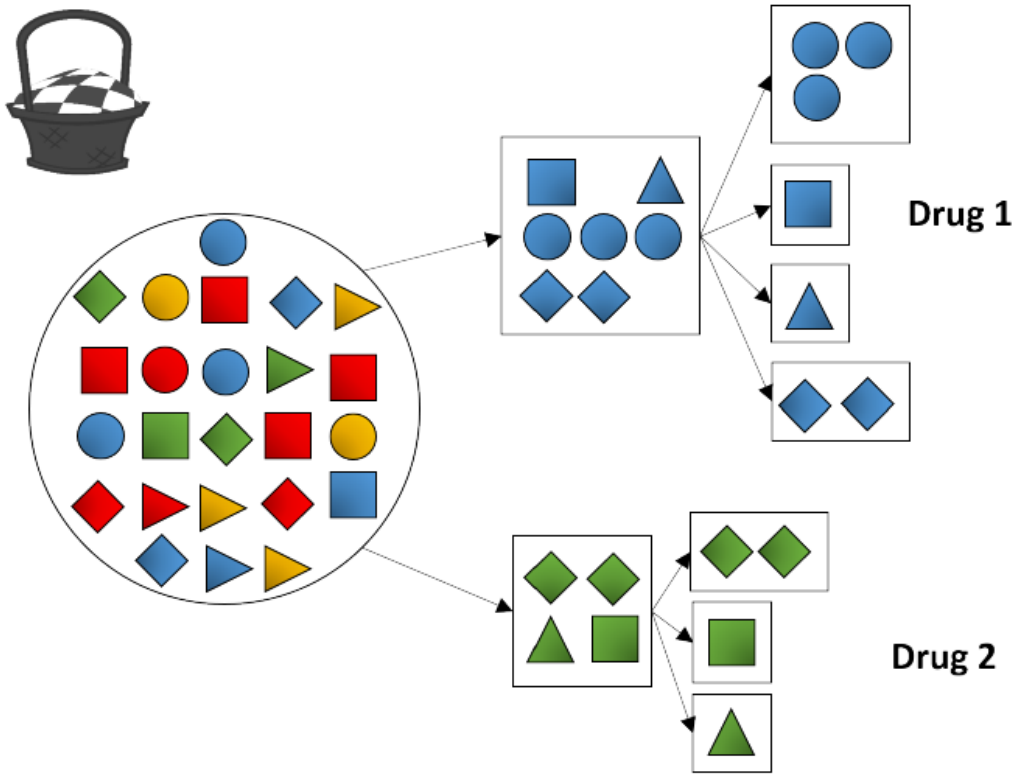
Traditional histology-determined treatment allocation



Histology-agnostic enrollment of marker-defined cohorts



Benner, 2016

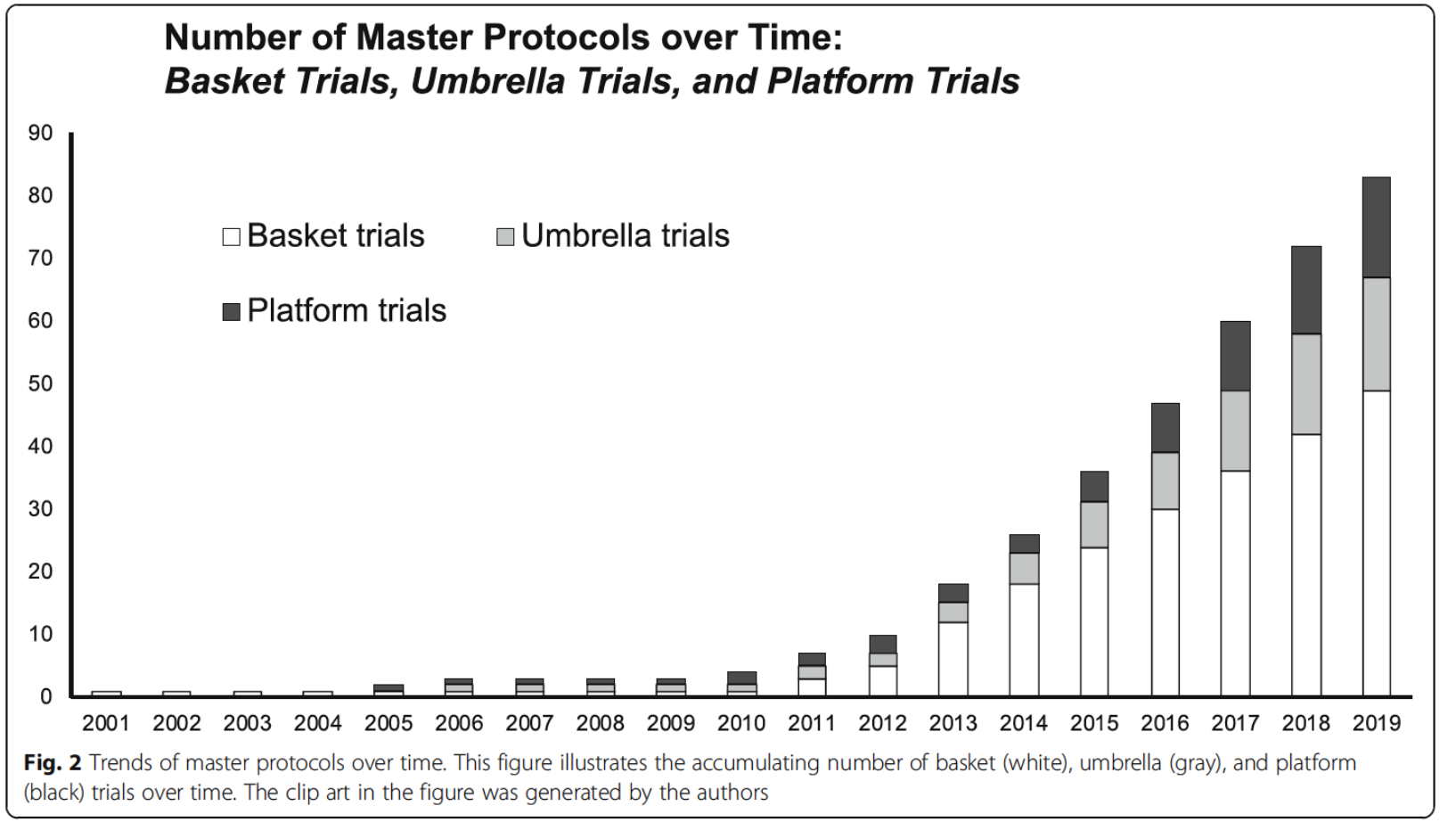
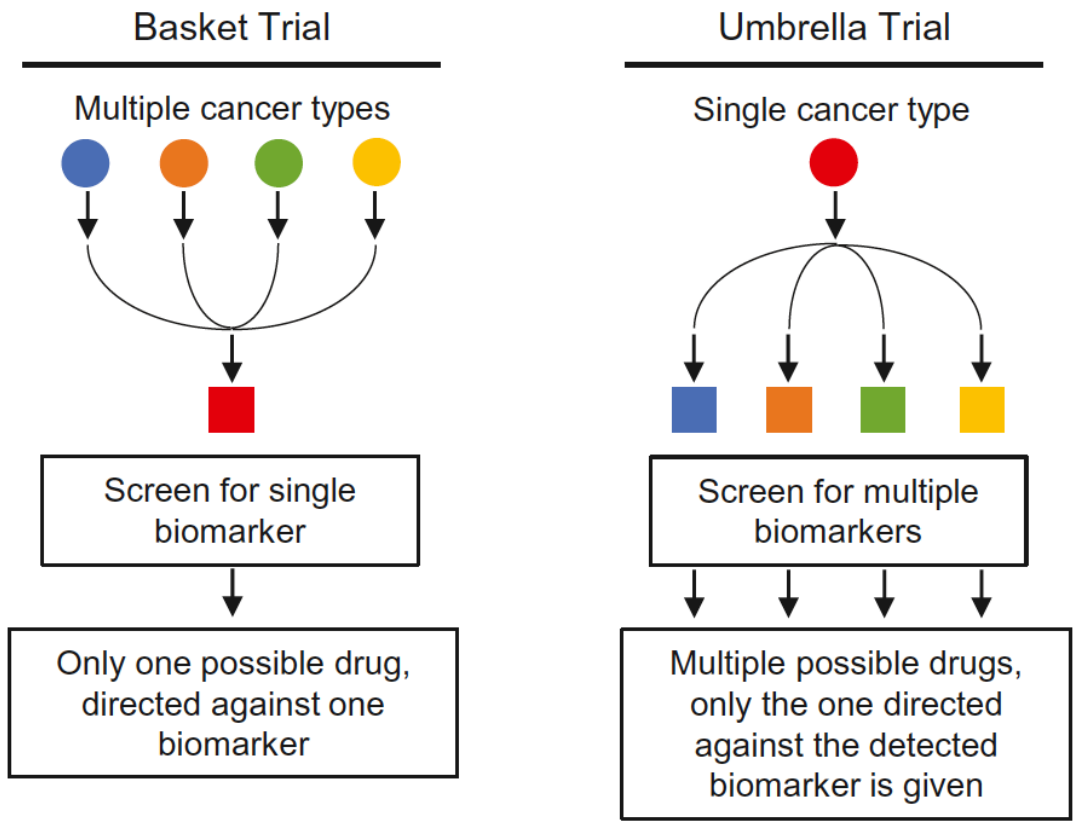


Fig. 2 Trends of master protocols over time. This figure illustrates the accumulating number of basket (white), umbrella (gray), and platform (black) trials over time. The clip art in the figure was generated by the authors

Park *et al. Trials* (2019) 20:572
https://doi.org/10.1186/s13063-019-3664-1

Master/Main protocols

CT with a molecular screening process and the ability to evaluate multiple regimens in parallel



Cancer
Review Article | Open Access

Clinical trial design: Past, present, and future in the context of big data and precision medicine

Allen Li MD, MS, Raymond C. Bergan MD

PROS

- Improve screen success rate
- Therapeutic benefit for patients
- Regulatory input for early approval
- More efficient designs
- Umbrella: specific tumor type conclusions
- Basket are interesting for rate tumor

CONS

- Multiple endpoints = increase of % of false-positive findings
- Ensure type I error is controlled at 2.5%
- Include prespecified endpoints and specifications for interim analysis
- Molecular profiling better than histological typing for treatment?
- High number of patients to be screened
- Possible new standards of care during the trial

nature medicine

LETTERS

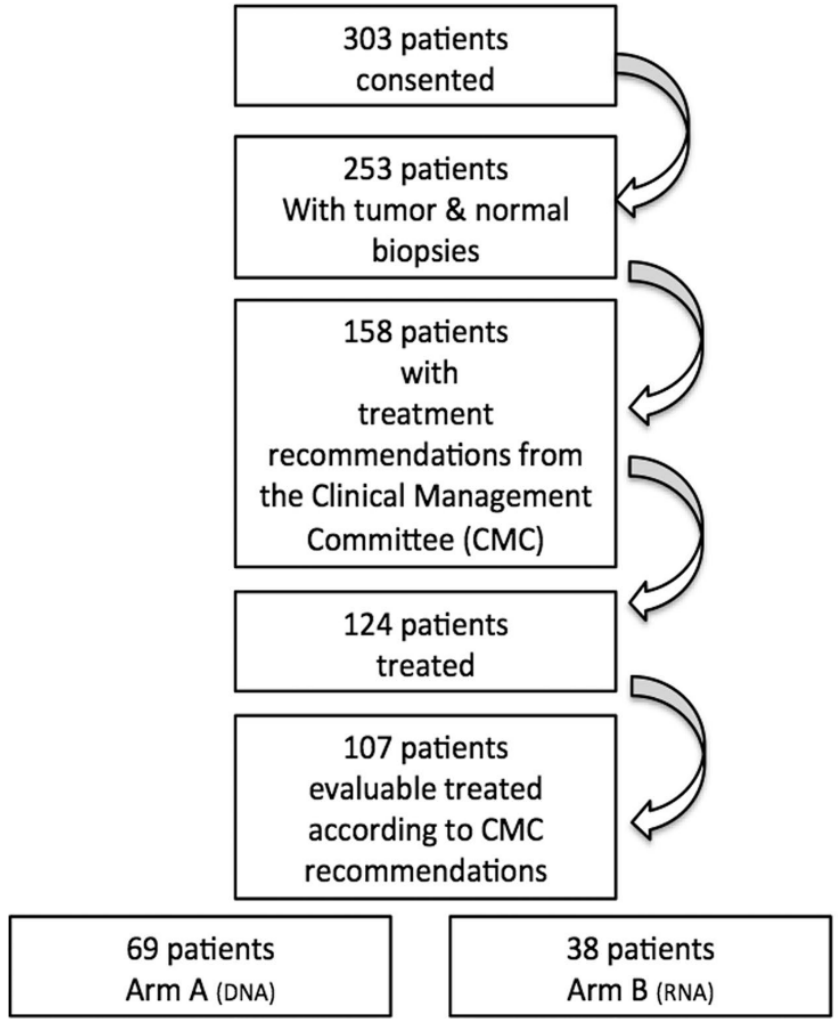
https://doi.org/10.1038/s41591-019-0424-4

Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial

Jordi Rodon[1,2,17], Jean-Charles Soria[3,17], Raanan Berger[4,17], Wilson H. Miller[5,17], Eitan Rubin[6],

Endpoint:
ratio of PFS2/PFS1>1,5

Based on Von Hoff model

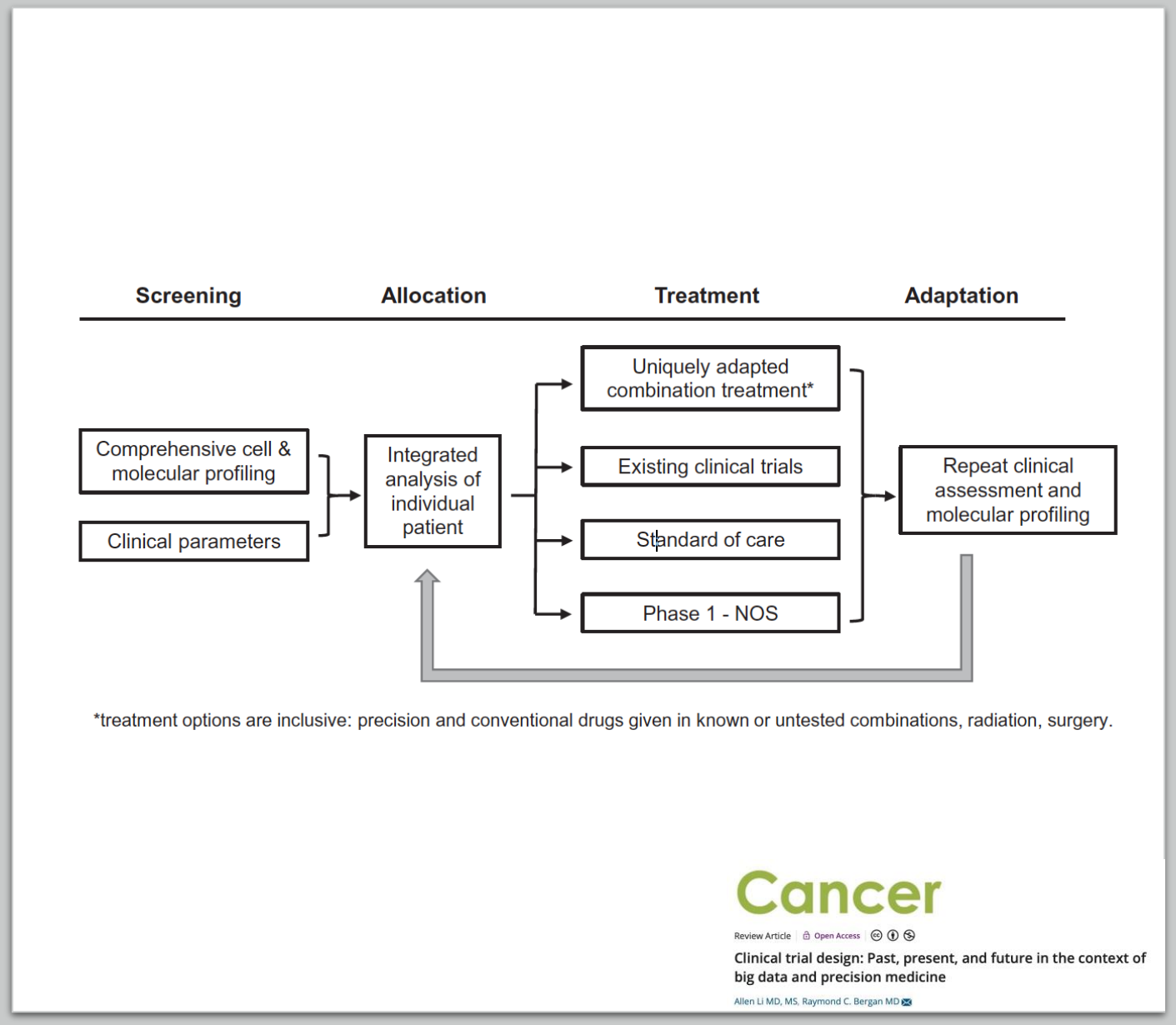


Objective: 50% pts
Achieved: 20.3% pts

Objective: 50% pts
Achieved: 26.3% pts

Platform trials

- Evaluate multiple TT for one disease through different substudies
- Typically contain a shared control arm and multiple experimental arms
- Allow for the introduction of new treatment arms.



FDA	EMA
Fast Track Preliminary nonclinical, mechanistic, or clinical data	**Conditional MA** Are unmet medical needs The benefit to public health outweighs the potential risks
Breakthrough Therapy Substantial improvement on clinically significant endpoint(s) over available therapies	
Accelerated approval Meaningful advantage over therapies Demonstrates effect on a surrogate endpoint	**MA exceptional circumstances** -Rare conditions -Full information is not posible/unethical.

FDA Grants AMG 510 Fast Track Designation for KRAS G12C+ NSCLC

September 9, 2019
Lisa Astor

The FDA has granted a fast track designation to AMG 510 for t
non–small cell lung cancer harboring a KRAS

Novartis announces MET inhibitor capmatinib (INC280), the first potential treatment for METex14 mutated advanced non-small cell lung cancer, granted priority FDA review

2 min read

FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion

FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC

Blueprint Medicines Announces FDA Approval of GAVRETO™ (pralsetinib) for the Treatment of Adults with Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

September 4, 2020 at 7:00 PM EDT

Conclusions

- Accessible holistic molecular screening for patients
- Better knowledge of tumor biology and drug discovery
- There are still many different barriers to overcome
- Novel drugs need novel designs, adaptive desings
- Appropriate measures are required to ensure validity
- Regulatory agencies lately allow for breakthrough designations or conditional approvals earlier.
  - More patients being treated faster
- Still, faster approval does not bring lower prices and wider access to drugs

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