Rigshospitalet

REGION

Cancer Crosslinks

25 October 2017, Lund

Innovative Trial Design in an Era of Personalized Cancer Therapy

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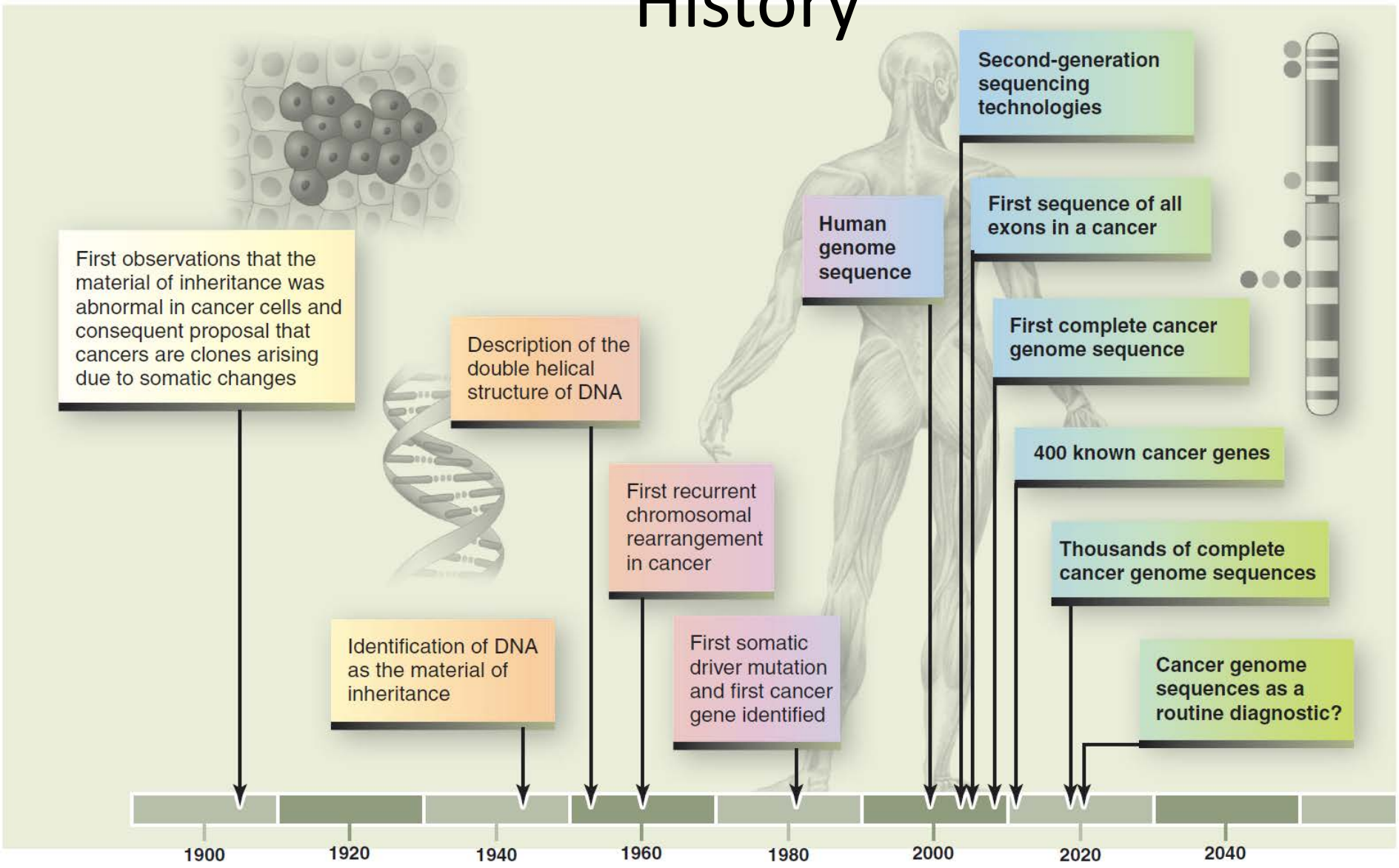
Phase 1 Unit, Rigshospitalet, Copenhagen

History



Exploring the Genomes of Cancer Cells: Progress and Promise
Michael R. Stratton
Science **331**, 1553 (2011);

Precision Medicine

- Personalized Medicine
  - tumor - targeted therapy
  - host - pharmacogenomics

What is targeted therapy

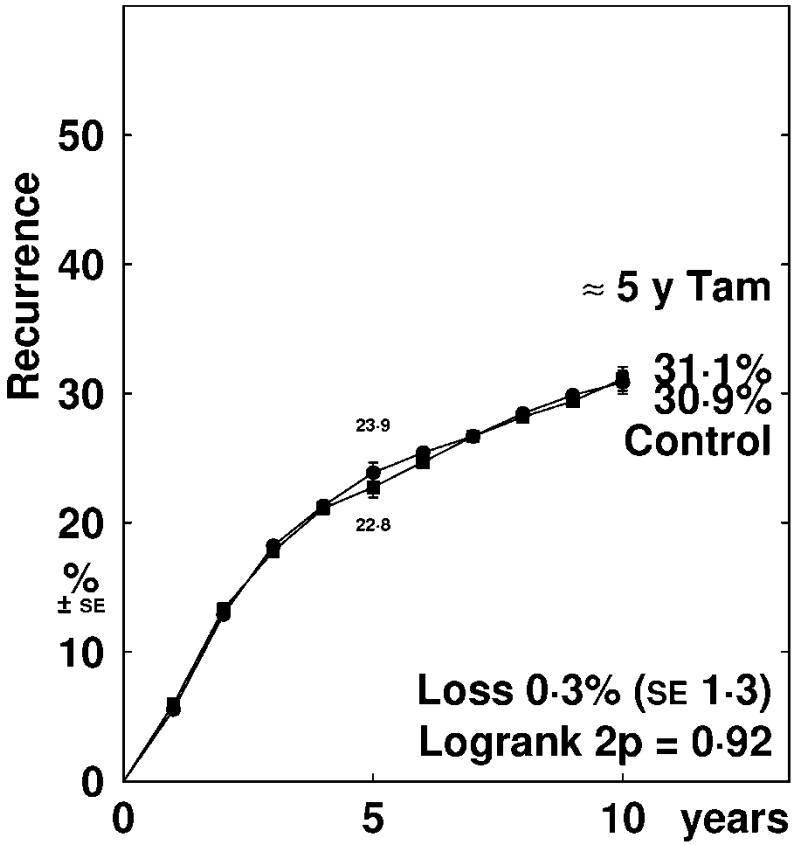
- Target – a defined process in cancer growth and/or development i.e hallmarks of cancer
- Target – measurable or identifiable in tumors in patients
- Outcome of targeted therapy is correlated to the presence or absence of target

Sledge, JCO editorial, p1614, 2013

~5 years Tamoxifen vs no tamoxifen

in estrogen pos and neg disease

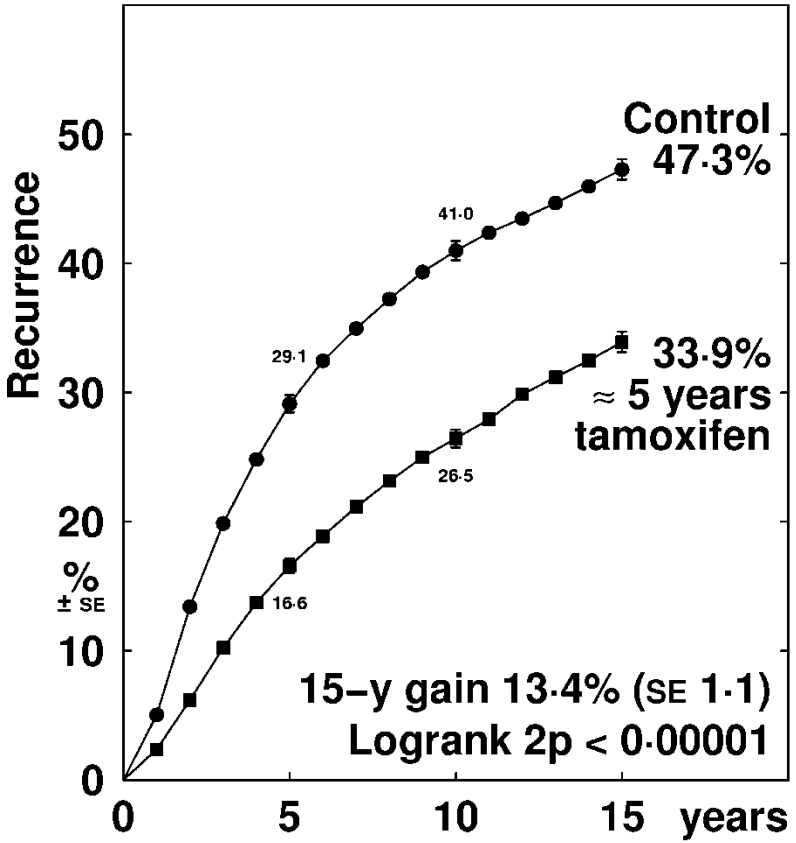
ER-poor disease



Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Year 10+
Tamoxifen	5·40 (721 / 13350)	2·35 (192 / 8172)	1·26 (49 / 3879)
Control	5·54 (741 / 13366)	1·93 (161 / 8343)	1·26 (52 / 4119)
Rate ratio, from	0·95 SE 0·05	1·20 SE 0·12	0·95 SE 0·20
(O–E) / V	–15·9 / 328·0	14·9 / 83·3	–1·2 / 24·1

ER+ disease

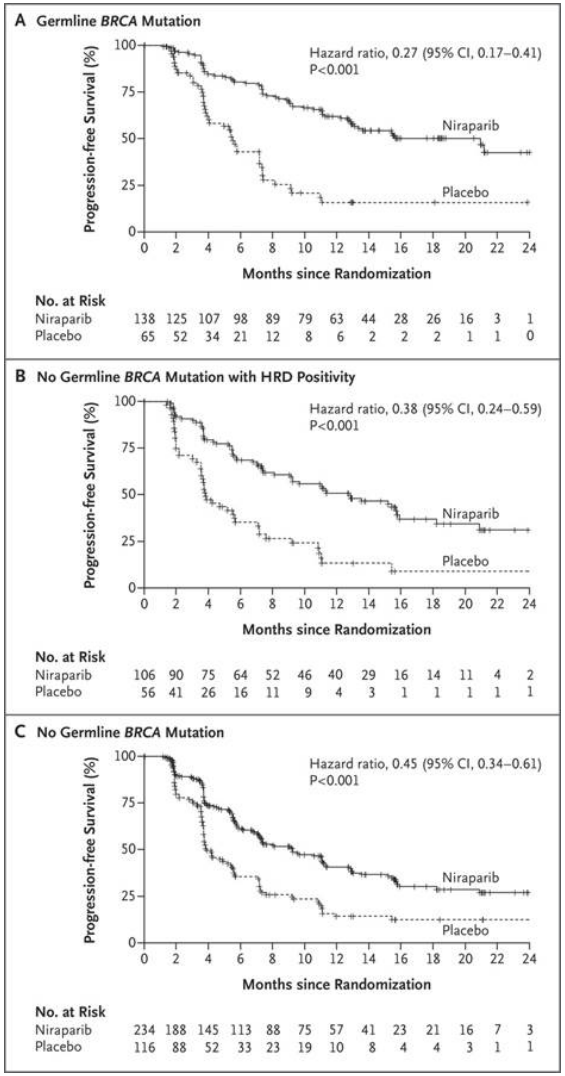


Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	3·75 (831 / 22144)	2·69 (440 / 16352)	2·20 (232 / 10550)	1·84 (92 / 5004)
Control	6·87 (1389 / 20221)	3·67 (497 / 13534)	2·20 (187 / 8514)	1·83 (72 / 3942)
Rate ratio, from	0·52 SE 0·03	0·68 SE 0·06	0·96 SE 0·10	0·92 SE 0·16
(O–E) / V	–328·7 / 507·7	–83·0 / 216·7	–3·8 / 97·2	–2·9 / 37·5

Peto SABCS 2007

Should PARP inhibitors be considered taregeted therapy
In BRCA pos/HRD pos ovarian cancer ?



Negative pts also derived benefit,
although to a smaller extent

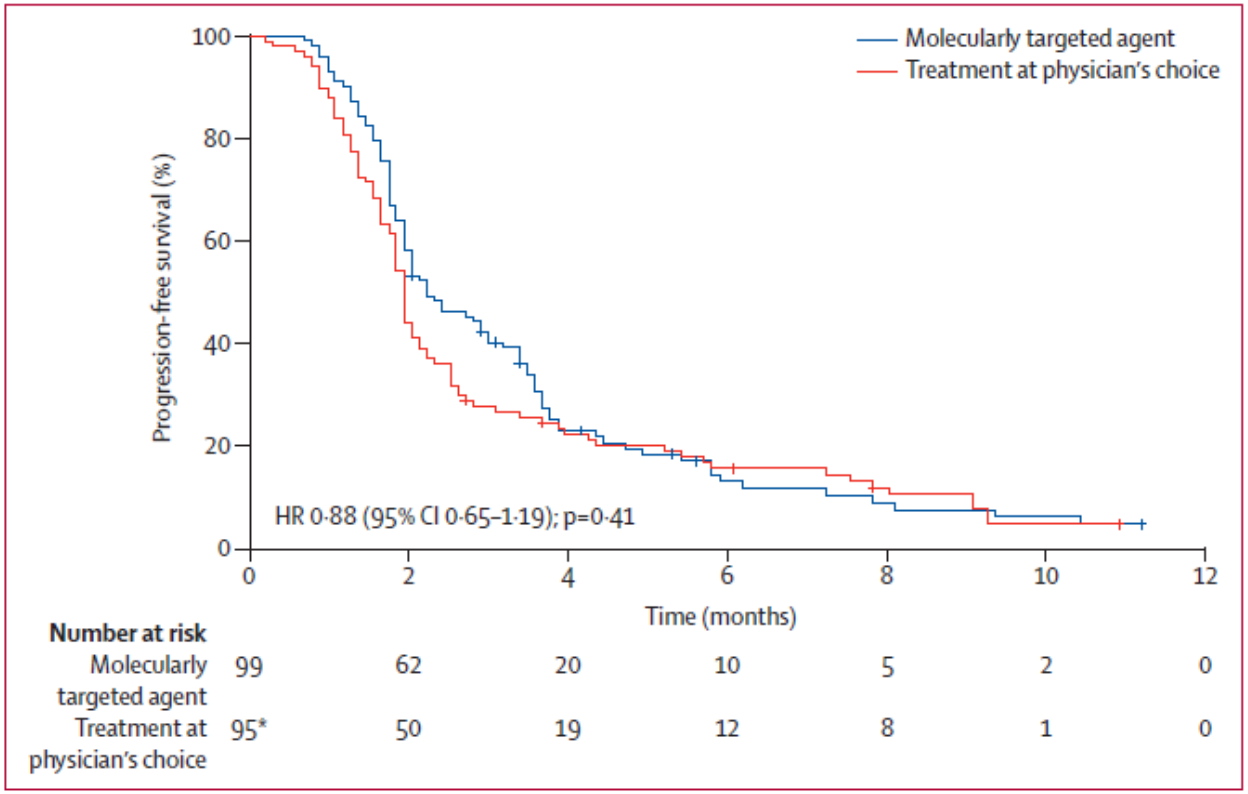
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer
Mansoor R. Mirza et al NEJM 2016

Question:

Does Personalized Therapy work ?

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

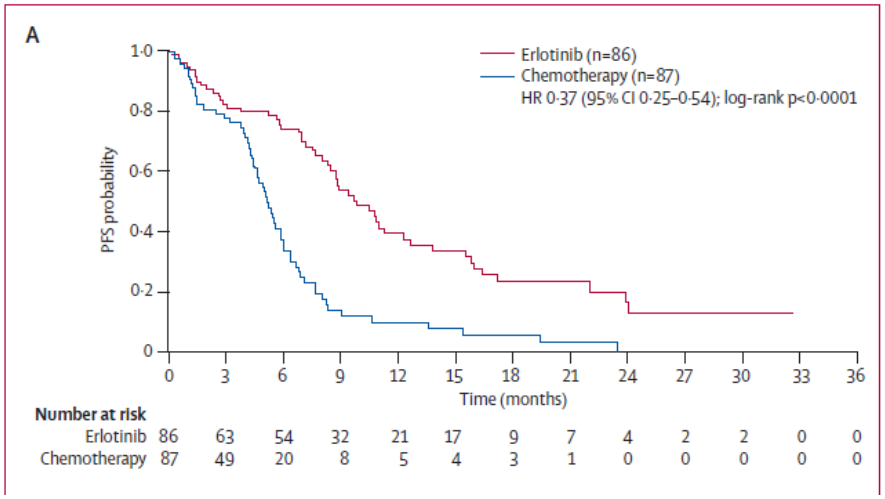
Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan,



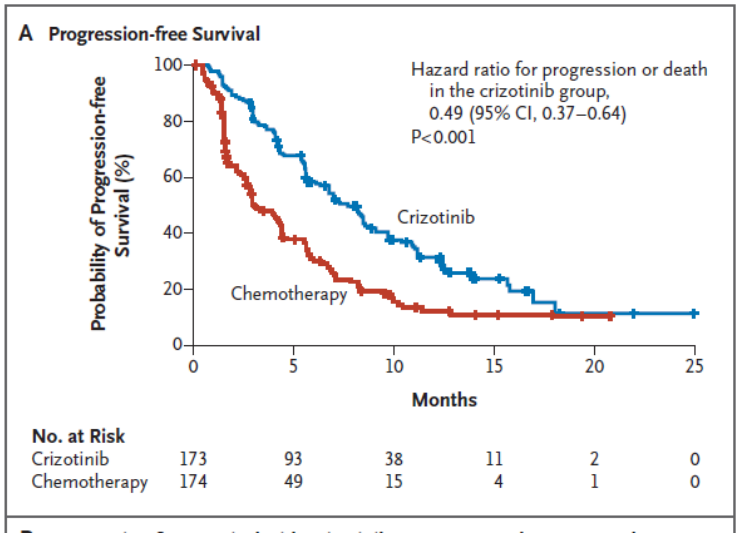
Answer: No

Question: However, was the evaluated therapy truely targeted ?
(abiraterone, letrozole, tamoxifen, everolimus, sorafenib)
Answer: No

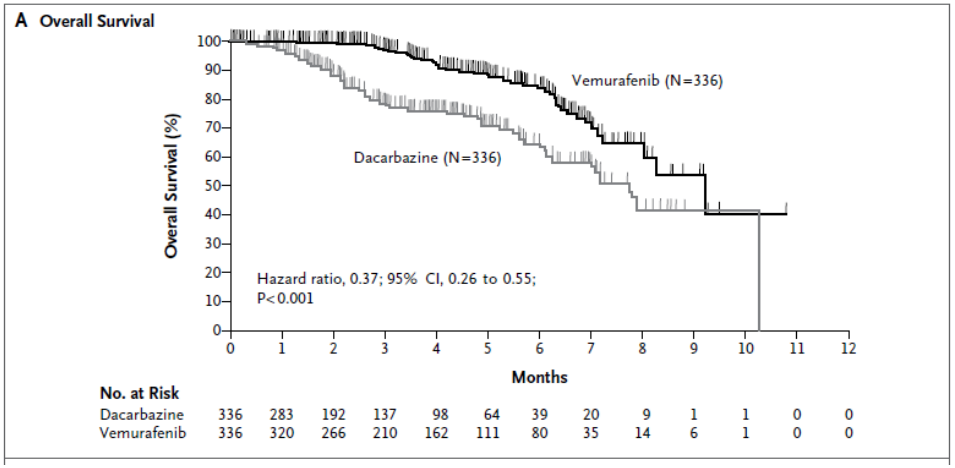
Erlotinib in EGFR mut lung cancer



Crizotinib in ALK pos lung cancer



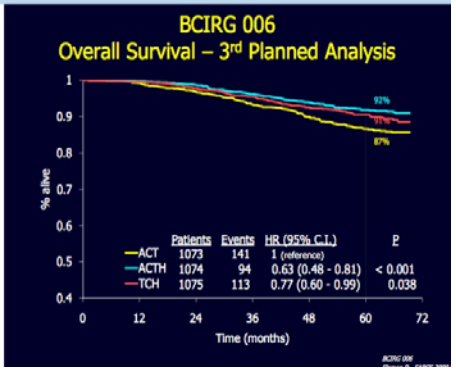
Vemurafenib in BRAFV600E mut malignant melanoma



Trastuzumab cures HER2 pos early BC

BCIRG 006 trial

- Overall survival:
- Conclusion: Addition of 1 year of adjuvant Trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer.



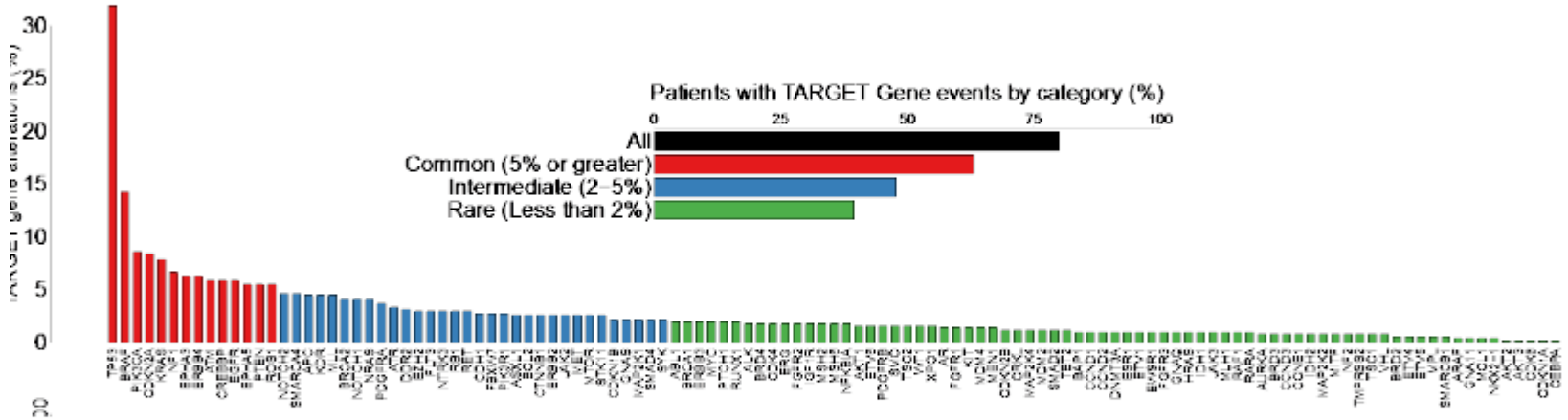
Question: Does personalized therapy work ?
Answer1: Yes, in certain rare indications
Answer2: Personalized therapy cures minimal disease HER2 pos early breast cancer

Question: Does personalized therapy work in cancer in general:
Answer: The jury is still out

Challenge: How to evaluate personalized therapy in several very small entities with rare driver mutations

Precision Medicine

- **Therapies designed to target the molecular alteration that aids cancer development**



- **A large proportion of cancers may contain at least one plausibly actionable genetic alteration**
- **The "long tail" means that the conventional clinical trial design approach may not be feasible**

Van Allen, Wagle et al., *Nature Med* 20, 682–688 (2014)

TAPUR Targeted Agent and Profiling Utilization Registry Study | ASCO

Conventional trials based on histology

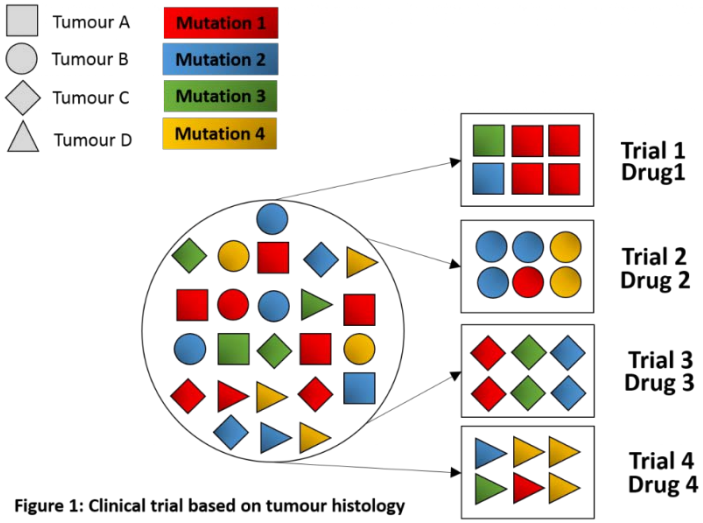


Figure 1: Clinical trial based on tumour histology

Basket trials – multiple histologies
One driver mutation – one drug

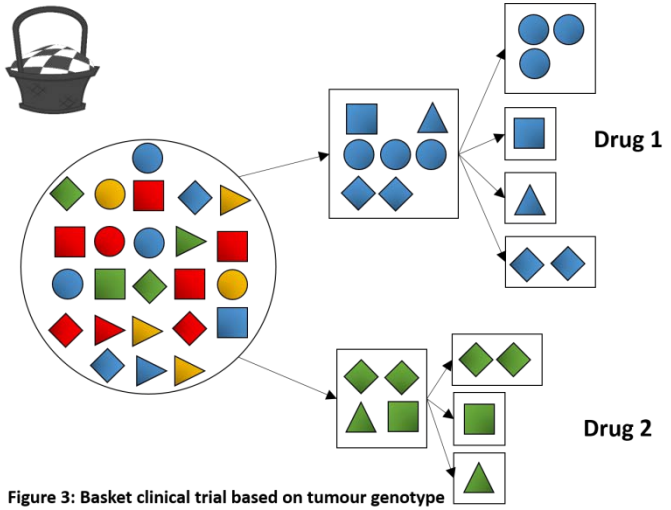


Figure 3: Basket clinical trial based on tumour genotype

Umbrella trials – one histology
Several driver mutation treated with one drug each

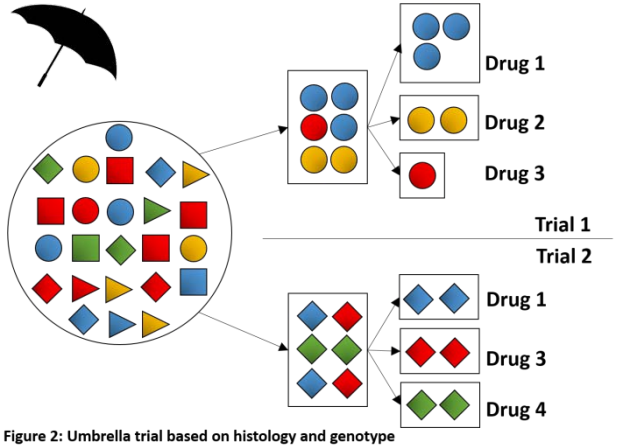


Figure 2: Umbrella trial based on histology and genotype

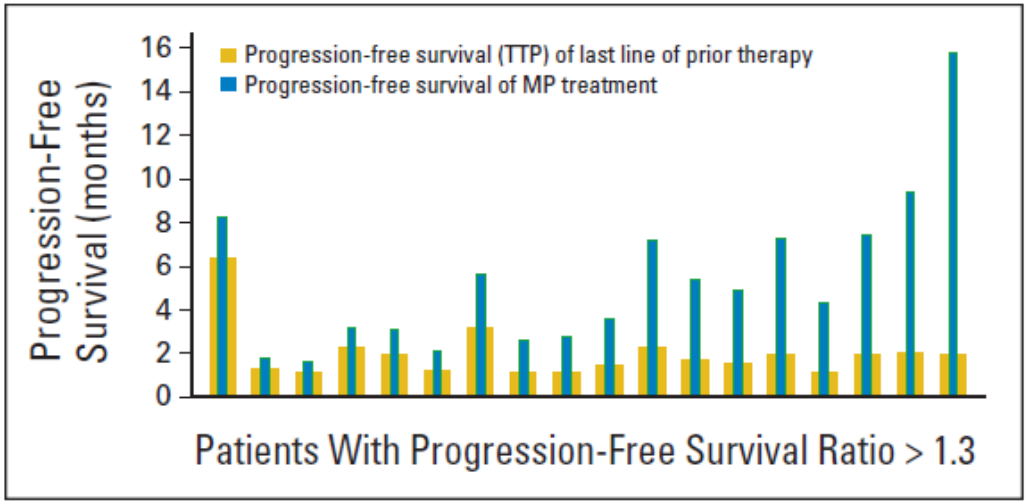
N-of-1 trials

- Recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between

- Each involved patient serves as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives

Pilot Study Using Molecular Profiling of Patients' Tumors to Find Potential Targets and Select Treatments for Their Refractory Cancers

Daniel D. Von Hoff, Joseph J. Stephenson Jr, Peter Rosen, David M. Loesch, Mitesh J. Borad, Stephen Anthony,



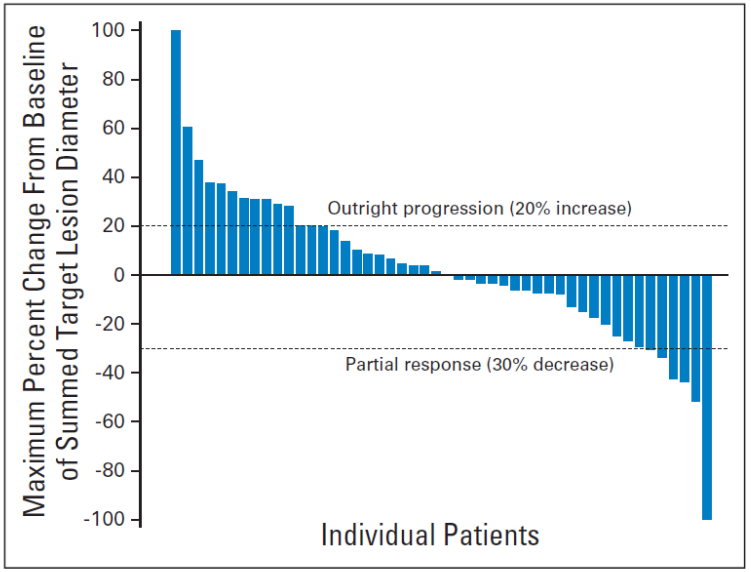
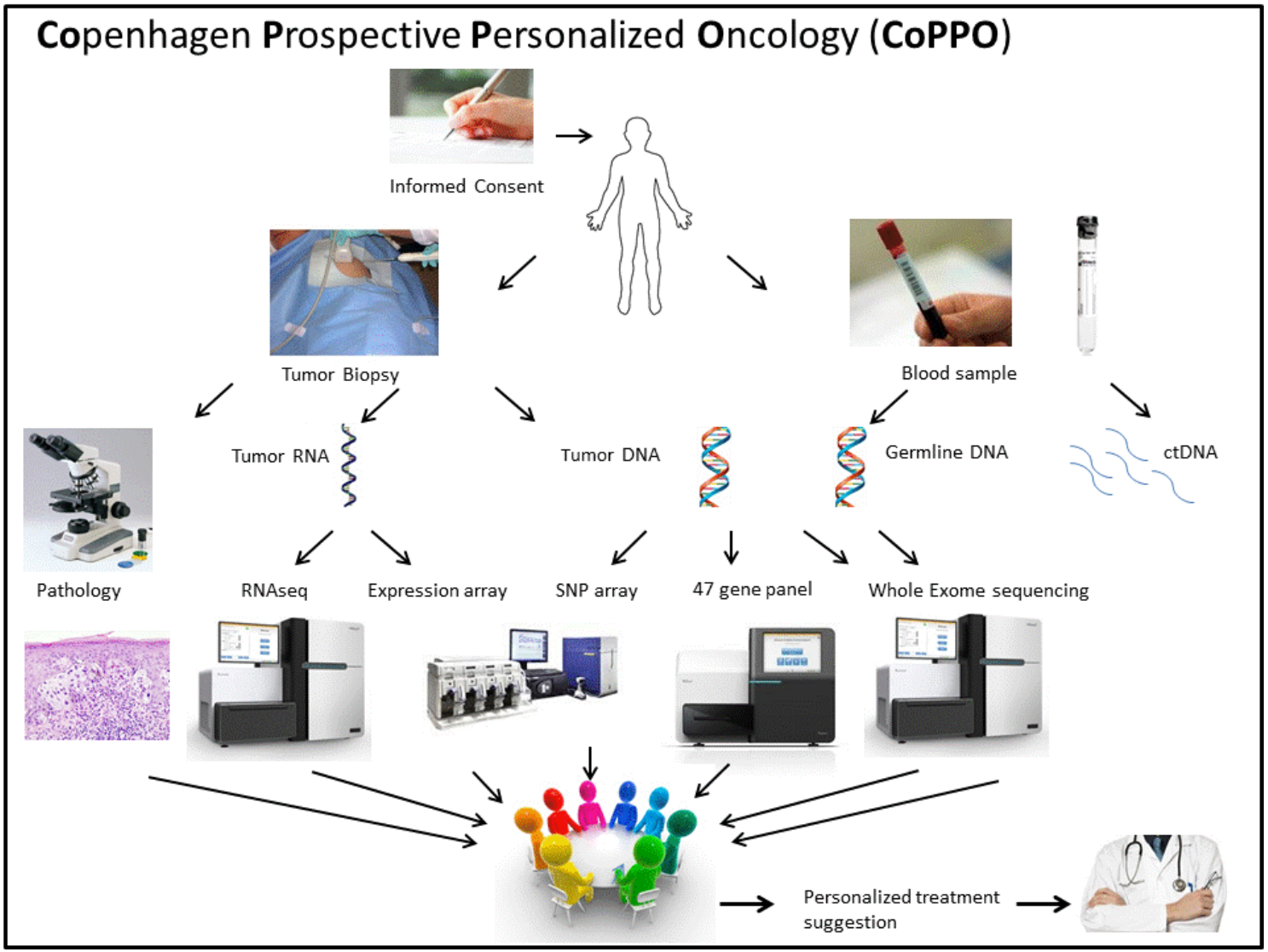


Fig 4. Waterfall plot in all patients for maximum percent change of summed diameters of target lesions with respect to baseline diameters.

of the 84 patients were treated according to MP results. Eighteen (27%) of 66 patients had a PFS ratio of ≥ 1.3 (95% CI, 17% to 38%; one-sided, one-sample $P = .007$). Therefore, the null hypothesis (that ≤ 15% of this patient population would have a PFS ratio of ≥ 1.3) was rejected.

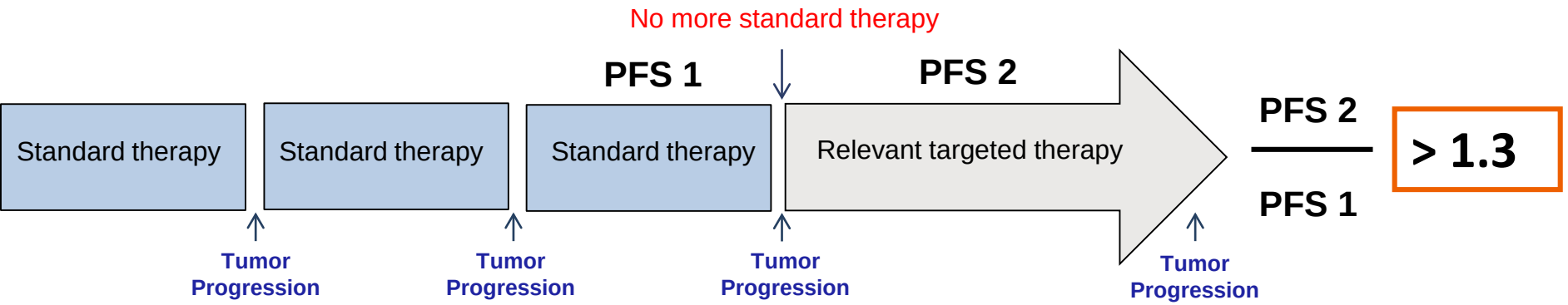


Tuxen et. al, APMIS 2014

Copenhagen **P**rospective **P**ersonalized **O**ncology (CoPPO)

Primary Objectives:

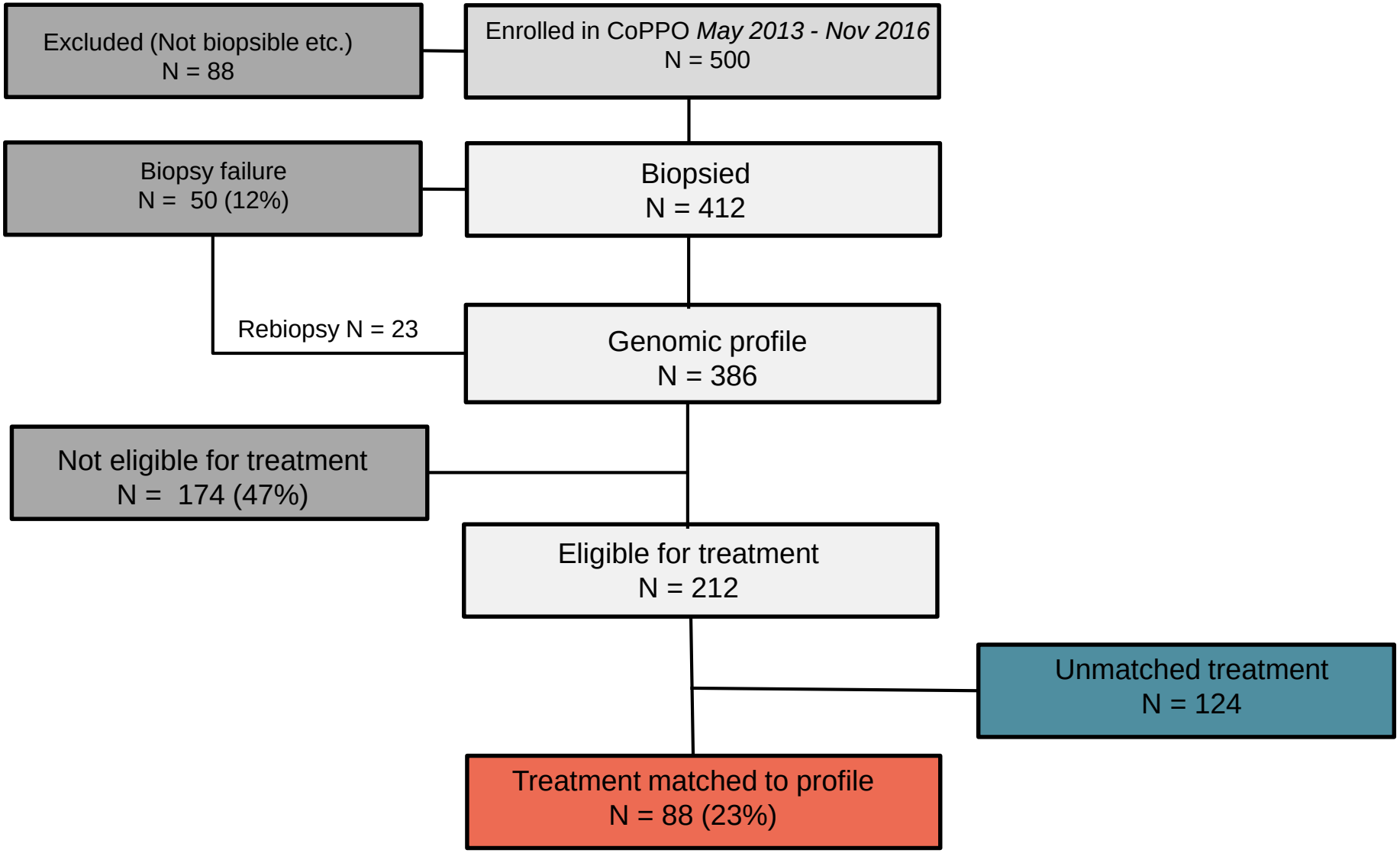
- ✓ To obtain new biological knowledge
- ✓ To show that a genomic screening approach improves outcome



Secondary Objective:

- ✓ To enrich Phase 1 trials with appropriate patients
- ✓ To attract trials to the Phase 1 unit
- ✓ To accelerate drug development

Copenhagen **P**rospective **P**ersonalized **O**ncology (CoPPO)



Genotype-driven clinical trials : Pros and cons

Pros

- New and selective therapeutic options for patients
- Better outcome

Cons

- Absence of agents in some detected driver targets
- No direct clinical implication or benefit in a large proportion of screened patients
- Difficulties to discriminate drivers from passengers targets

Future precision medicine: From sequencing to functionality in PDX and organoid models

More efforts is needed on :

- - Networking between institutions to render molecular tumor board accessible to the majority of centers and consequently to clinical trials and new drugs

- - More collaboration between pharmaceutical companies due to the need of drugs (including off label drugs) with the different mechanisms of action to be used in precision medicine

- -Role of liquid biopsy in determining the biological heterogeneity and evolution of the tumor

How does TAPUR work?

A patient's treating physician has results of a genomic profile of the patient's tumor and determines that a study drug may benefit the patient.

The patient decides to participate in TAPUR and gives informed consent.

The Molecular Tumor Board —a group of experts convened by ASCO— is available for consult regarding the proposed treatment or to provide alternate treatment options.

A participating pharmaceutical company provides the study drug at no cost to the patient.

The patient is followed for standard toxicity and efficacy outcomes and data are collected for analysis.

The study's Data and Safety Monitoring Board reviews results and determines whether a treatment is promising for a particular cancer and genomic variant.

ASCO publishes study findings in peer reviewed journals to inform clinical practice and future research.

TAPUR Targeted Agent and Profiling Utilization Registry Study | ASCO

Personalized therapy

Conclusions

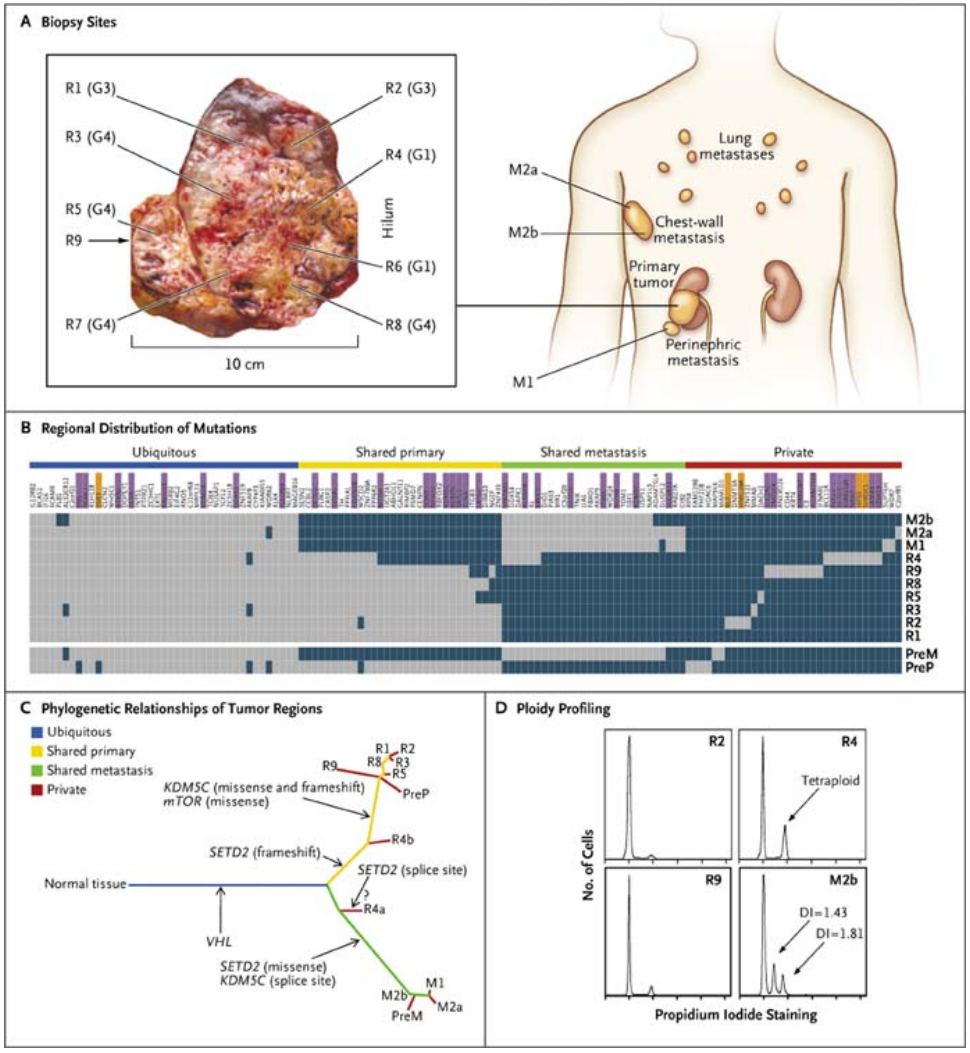
- Proof of Consept in tumors with rare drivers
- *Personalized therapy can cure cancer (HER2+ early BC)*

Challenges

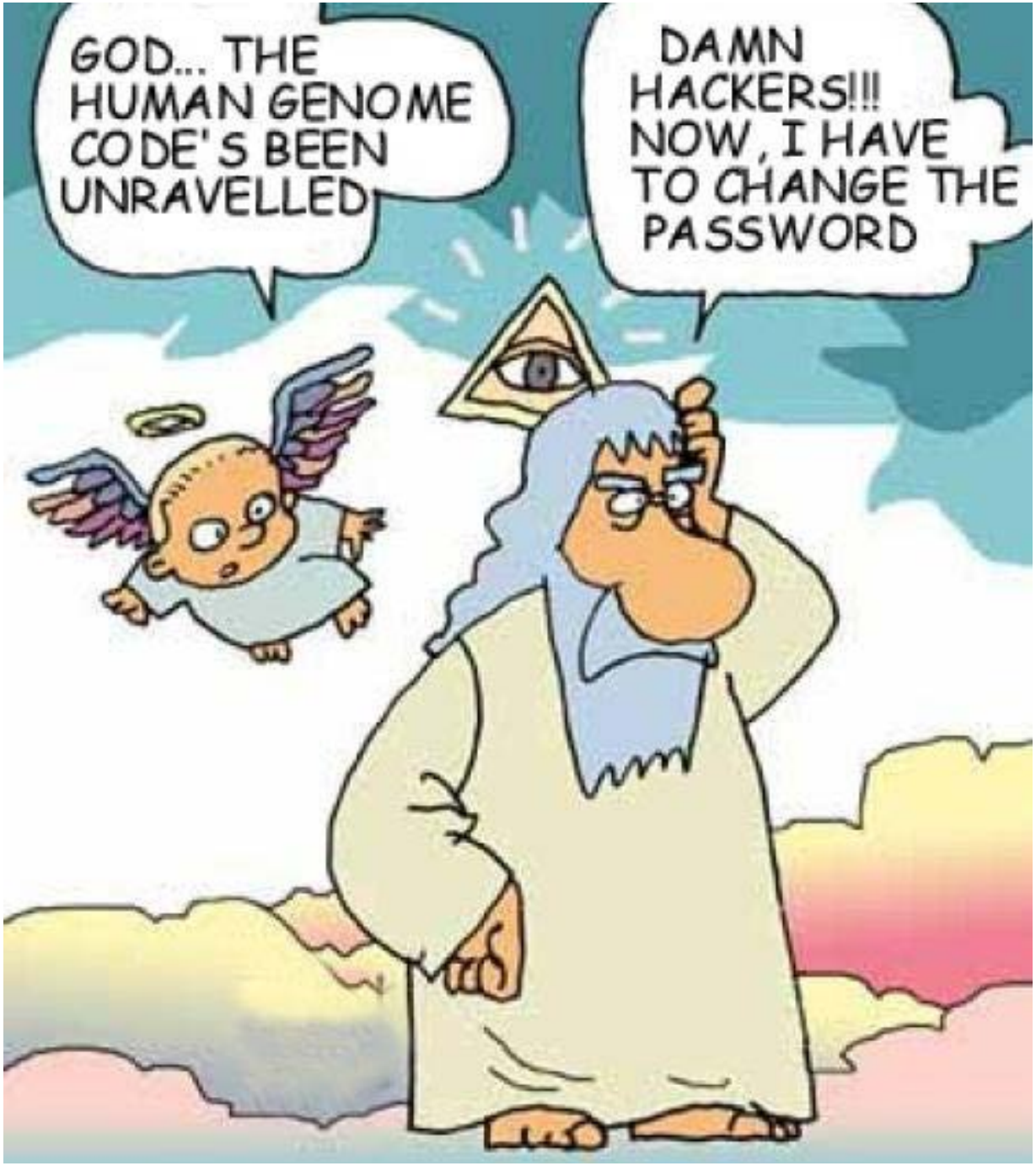
- *Discern between driver and passager mutation*
- *Development of truely targeted therapies*
- *Evaluation of targeted therapy in histologically agnostic small entities driven by rare mutations*

Tumor heterogeniety remains a challenge

Why do pts on targeted therapy eventually fail
Genetic Intratumor Heterogeneity



Gerlinger M et al. N Engl J Med 2012;366:883-892


GOD... THE HUMAN GENOME CODE'S BEEN UNRAVELLED
DAMN HACKERS!!! NOW, I HAVE TO CHANGE THE PASSWORD

Rigshospitalet

Acknowledgements

Nurses and staff at the Phase I unit

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And all the patients

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