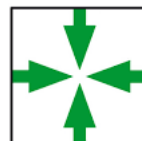


**II Giornata Nazionale  
della Ricerca  
Oncologica**



FONDAZIONE IRCCS  
ISTITUTO NAZIONALE  
DEI TUMORI



# Genoma e terapia dei tumori

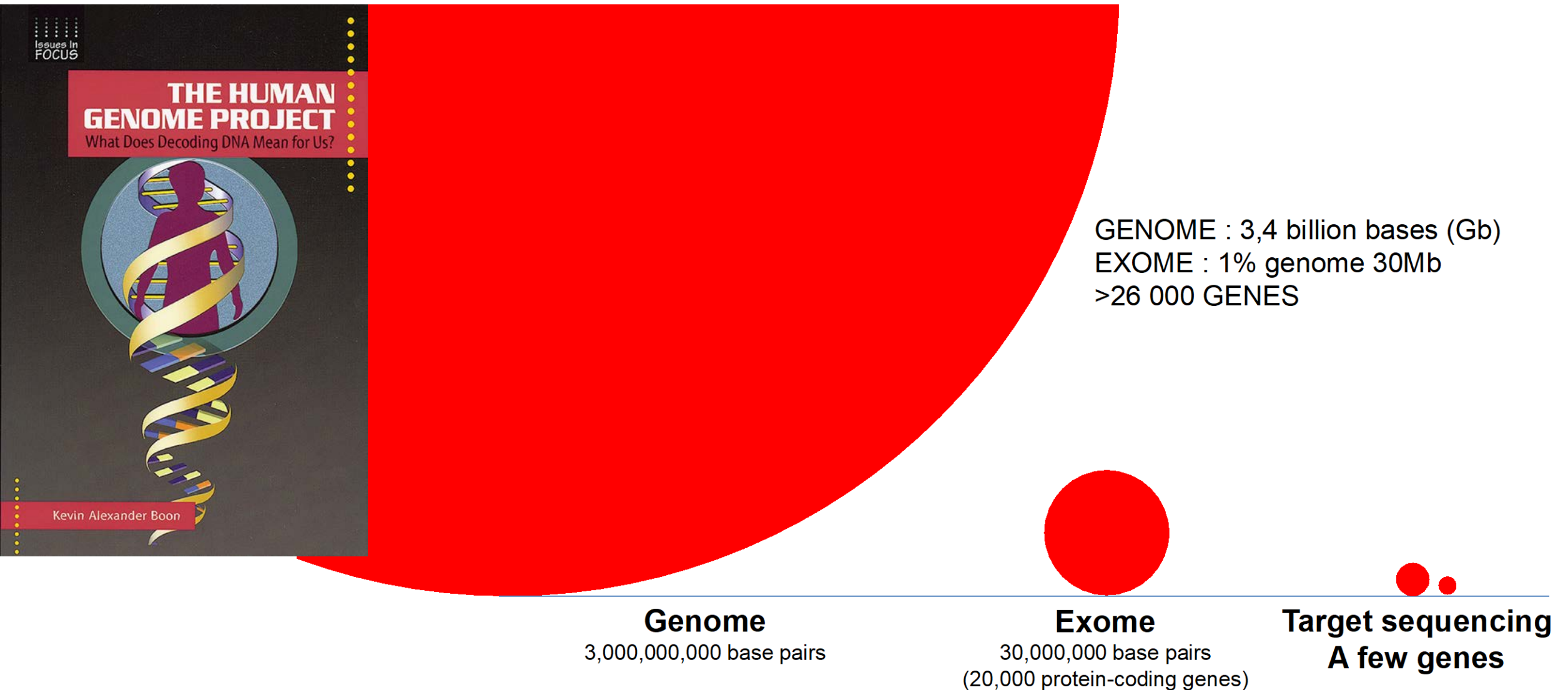
*Filippo Pietrantonio*

**II Incontro Nazionale FICOG**

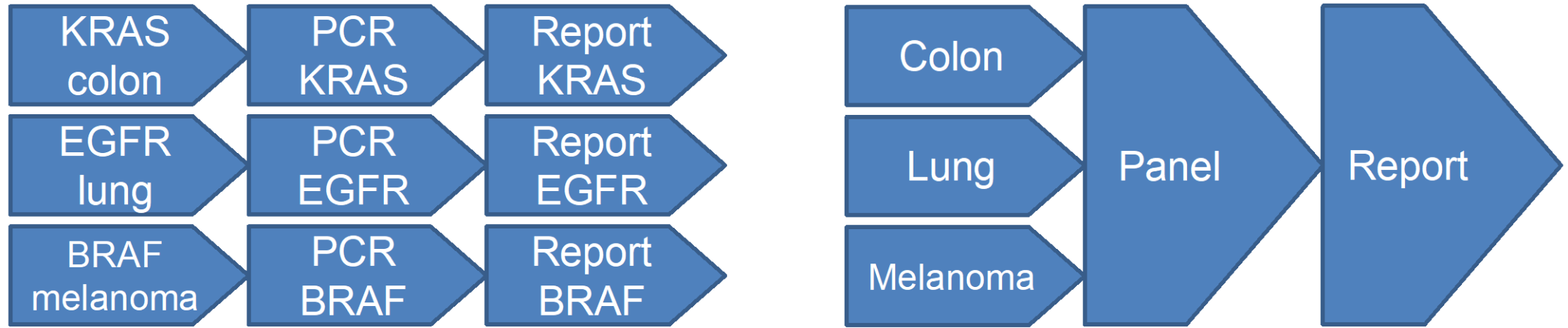
**I GRUPPI  
COOPERATIVI  
IN ONCOLOGIA**

**LE NUOVE SFIDE  
DELLA RICERCA INDIPENDENTE**

# The Human genome and the cancer-related genes



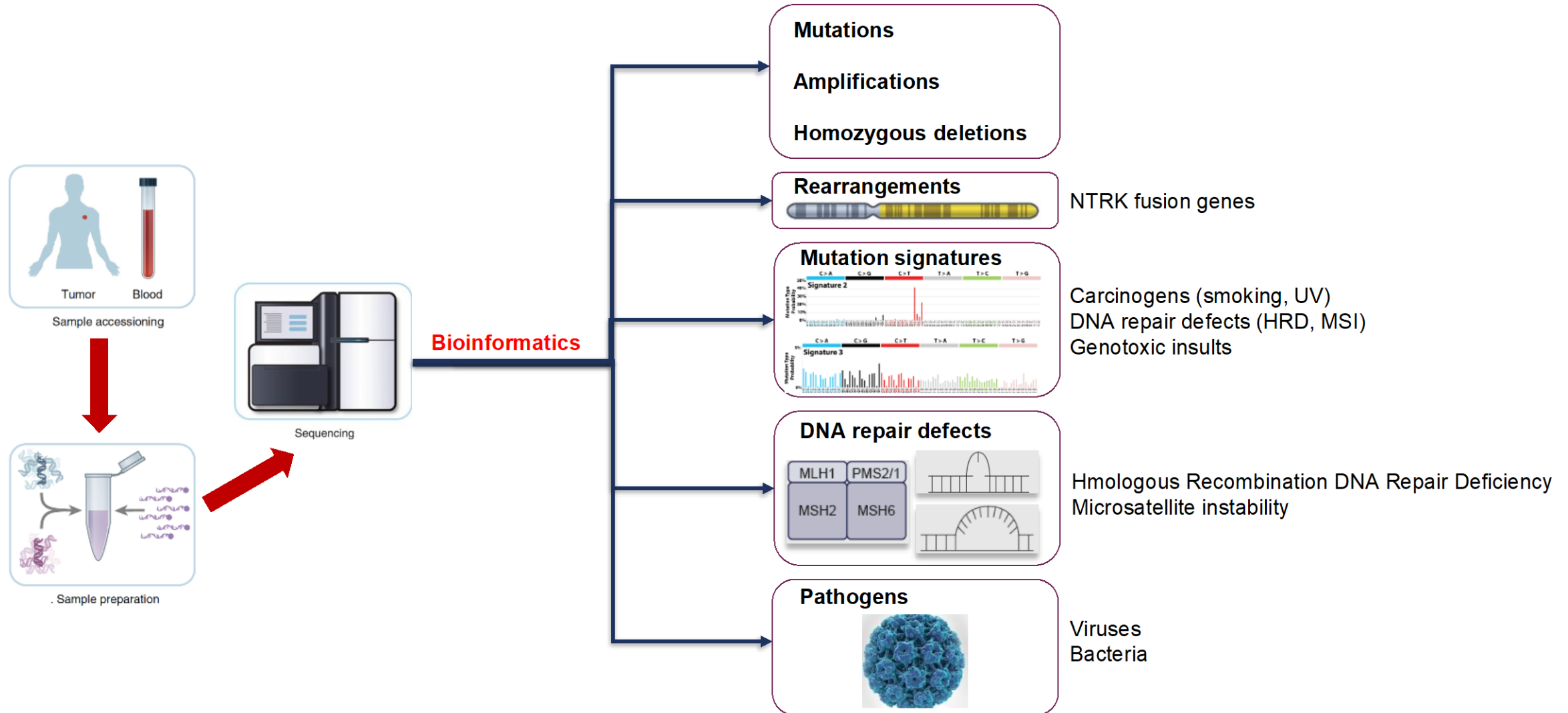
# Our clinical practice



## Implications

- Economy of scale
- Gain in the limit of detection  $\leq 1\%$  vs. 20% for sanger sequencing
- Bioinformatic limitation – capacity, database, filter bias
- Productivity limitation / number of samples per week – **PGM 318 < 30 samples per week**

# What can we detect by NGS?



# ESMO Scale for clinical actionability of molecular targets (ESCAT)

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo<sup>1</sup>, D. Chakravarty<sup>2</sup>, R. Dienstmann<sup>1</sup>, S. Jezdic<sup>3</sup>, A. Gonzalez-Perez<sup>4</sup>, N. Lopez-Bigas<sup>4,5</sup>, C. K. Y. Ng<sup>6</sup>, P. L. Bedard<sup>7</sup>, G. Tortora<sup>8,9</sup>, J.-Y. Douillard<sup>3</sup>, E. M. Van Allen<sup>10</sup>, N. Schultz<sup>2</sup>, C. Swanton<sup>11</sup>, F. André<sup>1,2\*</sup> & L. Puztai<sup>13</sup>

I-A: prospective, **randomised clinical trials** show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point

I-B: prospective, **non-randomised clinical trials** show that the alteration-drug match in a **specific tumour type**, results in clinically meaningful benefit as defined by **ESMO MCBS 1.1**

I-C: clinical trials **across tumour types or basket clinical trials** show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types

II-A: **retrospective studies** show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients

II-B: **prospective clinical trial(s)** show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points

## ESCAT

### ESMO Scale for Clinical Actionability of Molecular Targets



*Mateo et al, Ann Oncol 2018*

# ESMO recommendations for NGS testing in clinical practice

Tumor types	General recommendations for daily practice
Lung adenocarcinoma	Tumor multigene NGS to assess level I alterations. Larger panels are acceptable if they induce acceptable incremental costs (drug included*) and report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.
Squamous cell lung cancers	No current indication for tumor multigene NGS
Breast cancers	No current indication for tumor multigene NGS
Colon cancers	Multigene tumor NGS can be an alternative option to PCR if it does not create additional cost.
Prostate cancers	Multigene tumor NGS to assess level I alterations. Larger panels are acceptable if they induce only acceptable incremental costs and report accurate ranking of alterations.
Gastric cancers	No current indication for tumor multigene NGS
Pancreatic cancers	No current indication for tumor multigene NGS
Hepatocellular carcinoma	No current indication for tumor multigene NGS
Cholangiocarcinoma	Multigene tumor NGS could be recommended to assess level I alterations. Larger panels are acceptable if they induce only acceptable incremental costs (drug included*) and report accurate ranking of alterations. RNA-based NGS can be used.



# Molecular tumor boards



## PATIENT PROFILE

Patients who are not responding to standard-of-care systemic therapies

Candidates for NGS studies

Histological context



## SPECIALISTS INVOLVED

**Clinical Oncologists, Pathologists,  
Geneticists, Bioinformaticians,  
Molecular Biologists**

Oncology Pharmacists, Bioethicists

Scientist/physicians

Research Clinical Trial Coordinator



## MOLECULAR ANALYSES

*Aim: Actionable alterations*

*Consider time and interpretation*

**NGS cancer-associated genes**

**Clinically Relevant gene fusions**



## MOLECULAR FINDINGS CLASSIFICATION

Standard Scales for classifying molecular aberrations based on potential Clinical Utility (JCR/**ESMO ESCAT**/OncoKB)

Functional Significance + Clinical actionability

Balanced Therapeutic Recommendations with potential immediate impact

MTBs are the result of introduction of Next Generation Sequencing (NGS) in Clinical practice leading to precision Oncology.

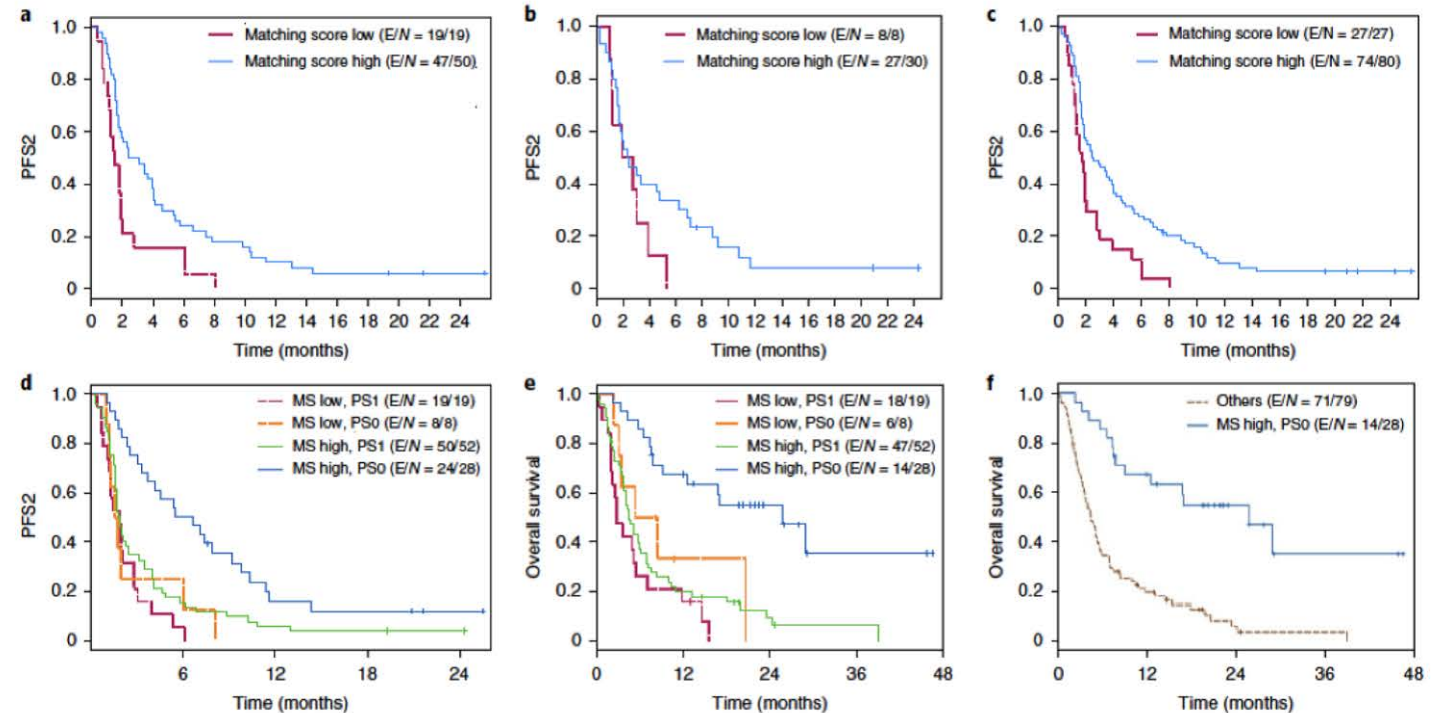
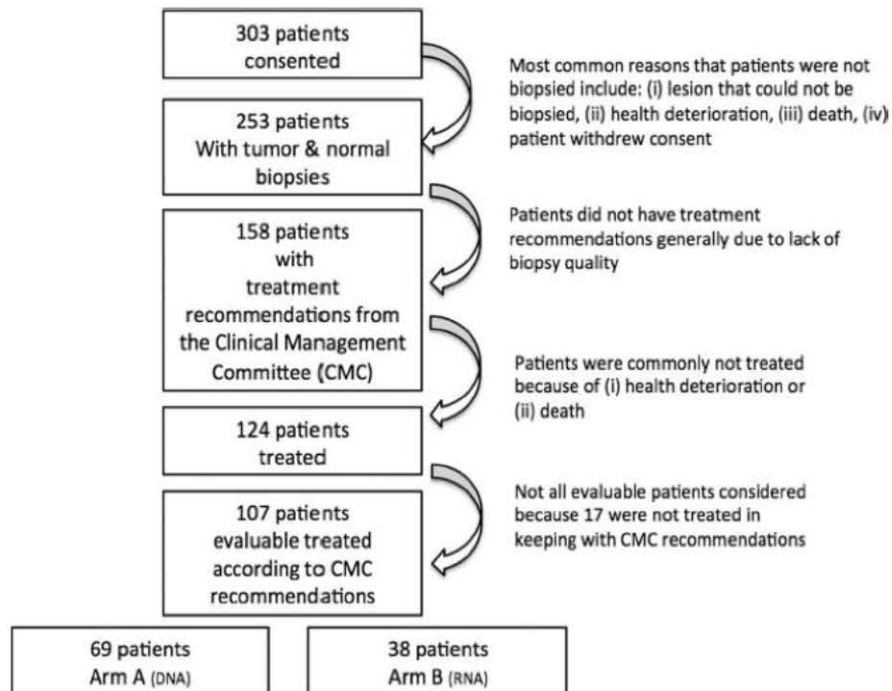
- Specific type of multidisciplinary tumour board in which cases are discussed on the basis of Clinical information and Modern molecular diagnostics.

- Aims:

- Provide Clinical recommendations
- Provide guidance based on the best available evidence
- Guide patients towards innovative Clinical trials

# Clinical validity versus clinical utility

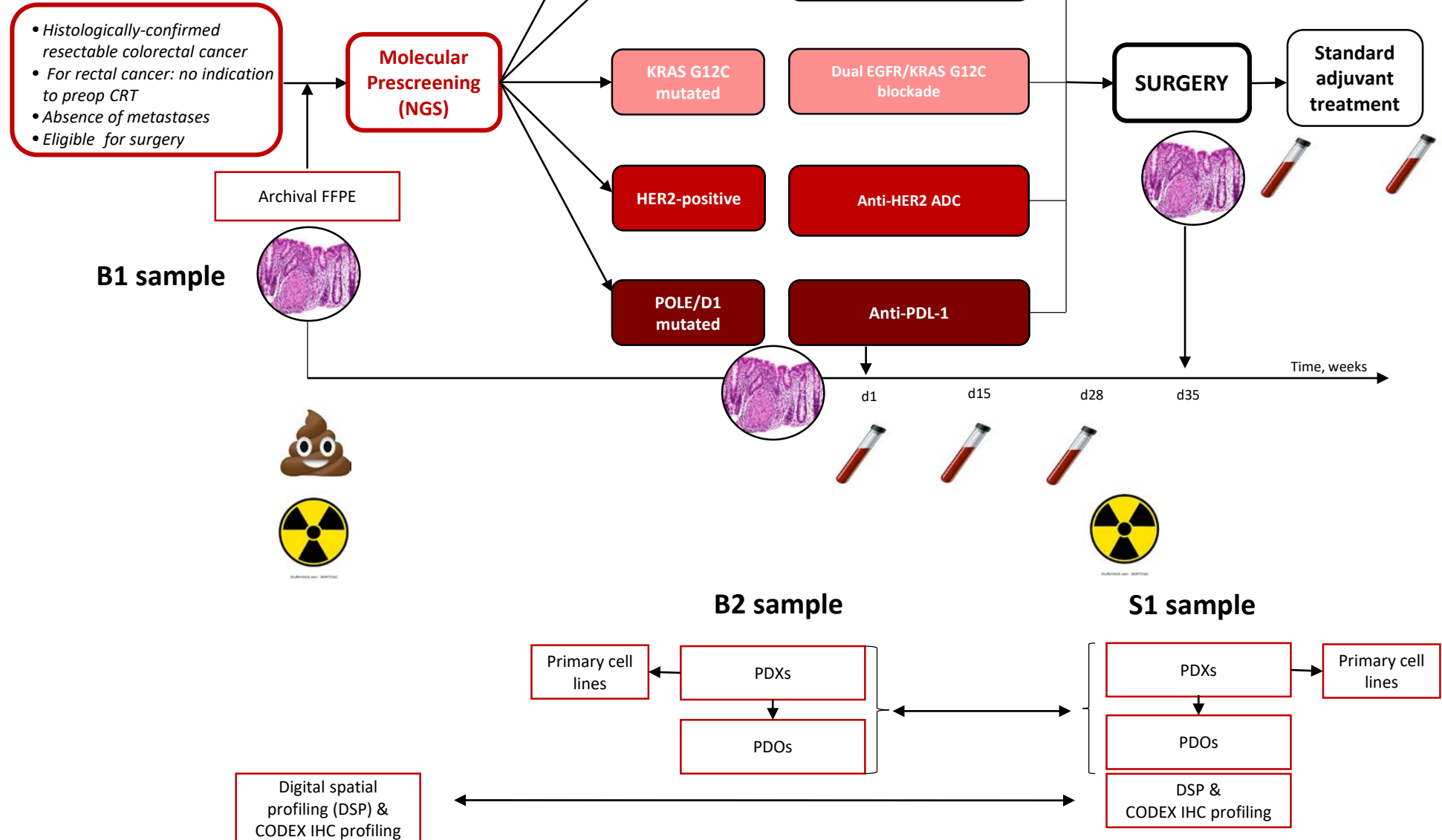
Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial



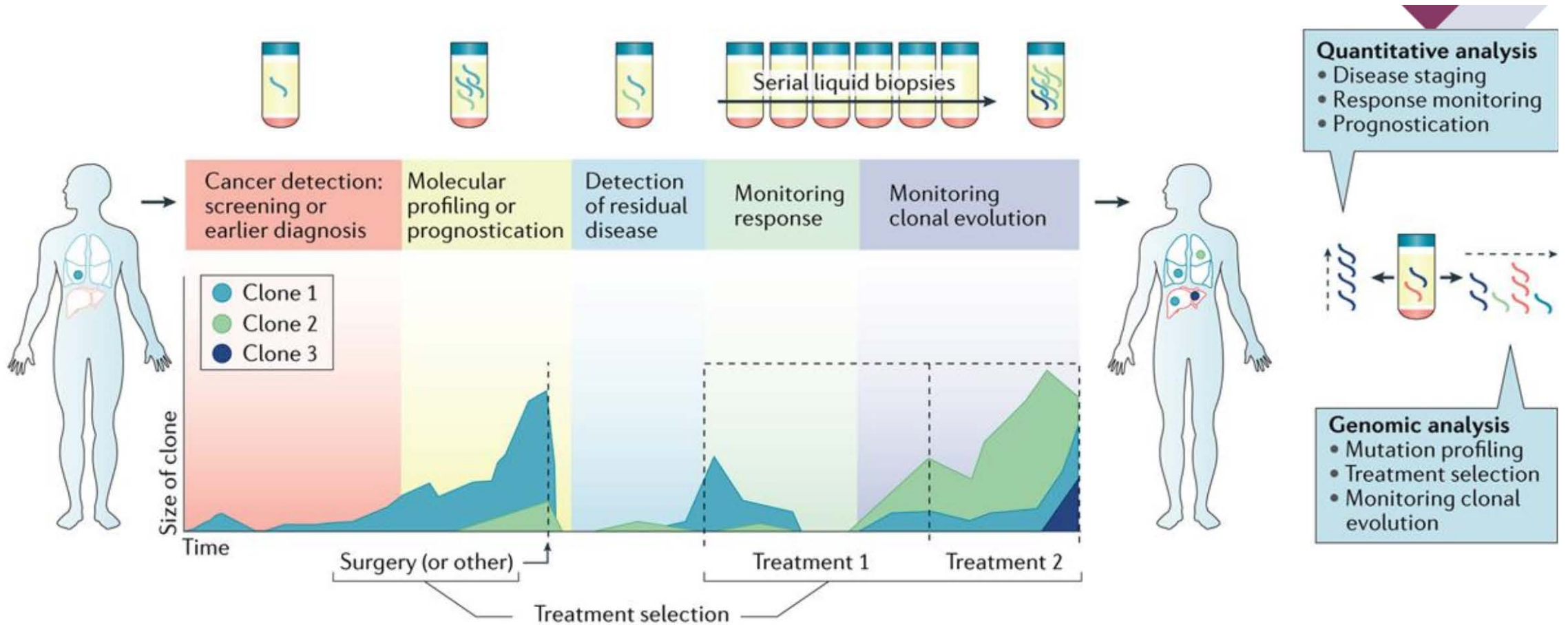
*Rodon et al, Nat Med 2019*



# UNICORN: Study Design



# The role of liquid biopsy



Wan et al, Nature Reviews Cancer 2017

Nature Reviews | Cancer

- ✓ **Quantitative information:** changing ctDNA levels, monitoring and prognostication
- ✓ **Qualitative information:** selection of targeted therapies, resistance mechanisms, clonal evolution

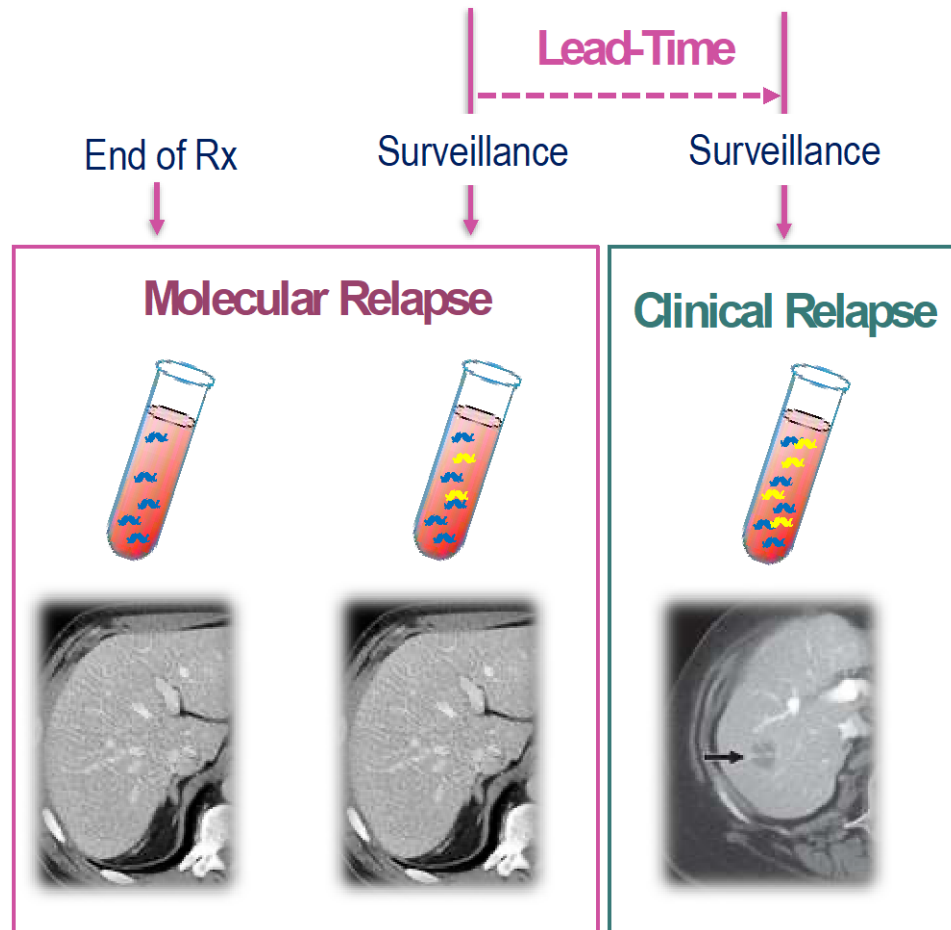
# Two different approaches for minimal residual disease

	Tumour-Agnostic
Method	Detect mutations de novo from <u>plasma</u> (one assay for all)
Key Advantage	Does not require tumour tissue
Key Disadvantage	Lower sensitivity due to multiple hypothesis testing
Applications	Non-invasive genotyping Detect emerging resistant mutations Cancer screening

Tumour-Informed
Identify mutations in <u>tumour</u> tissue → track mutations in plasma (customised)
Higher Sensitivity
Requires tumour tissue
<u>Minimal residual disease detection</u> Surveillance – monitor recurrence Response monitoring

# The fourth dimension: time

## Lead-Time to Clinical Recurrence



**Lead-Time:** Time between first detection of ctDNA from the end of definitive treatment and clinically detectable recurrence

### Lead-Time Affected by:

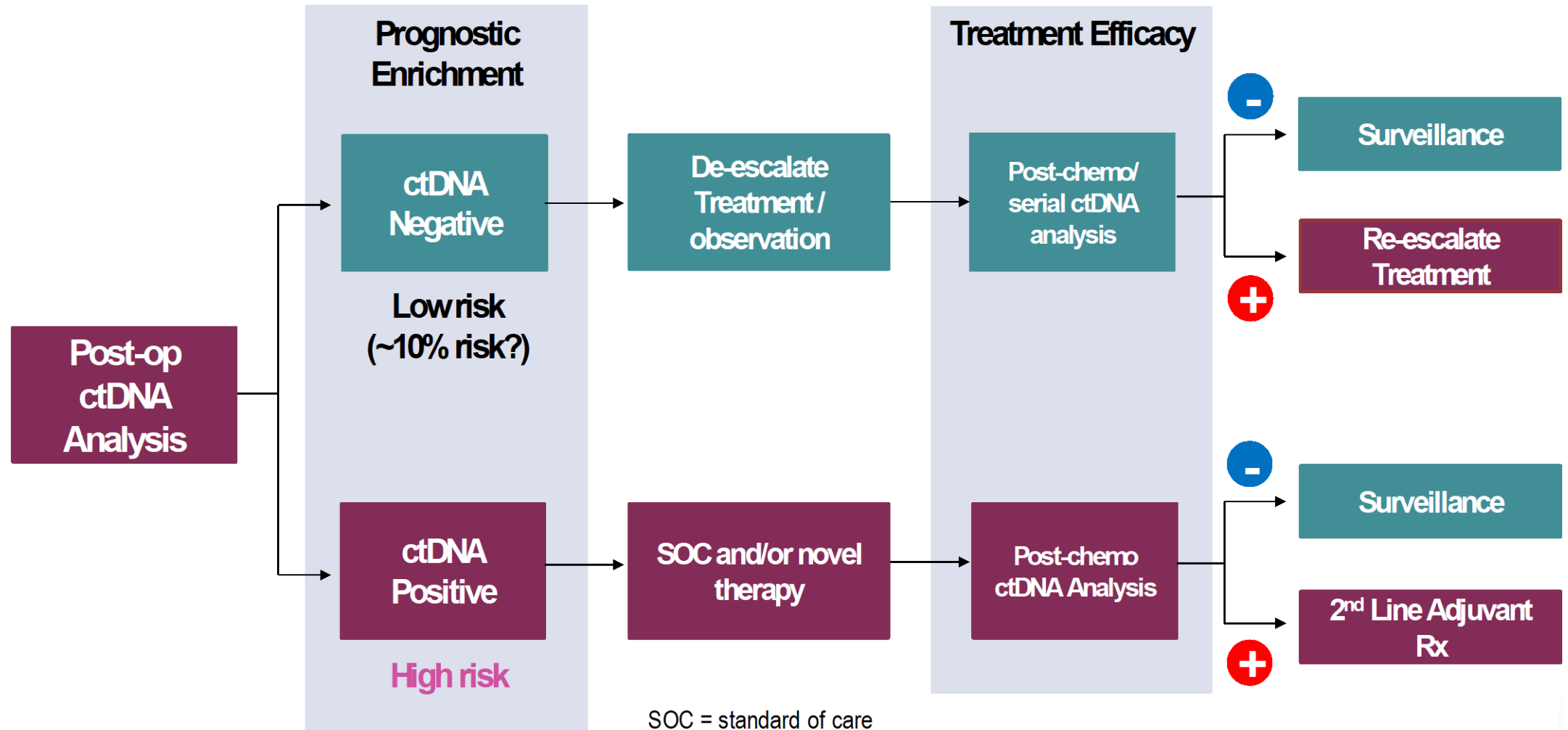
- frequency of ctDNA testing and imaging
- sensitivity of ctDNA assay and imaging modality
- tumour biology / site of relapse

**Increasing ctDNA detection rate with increasing time after surgery**

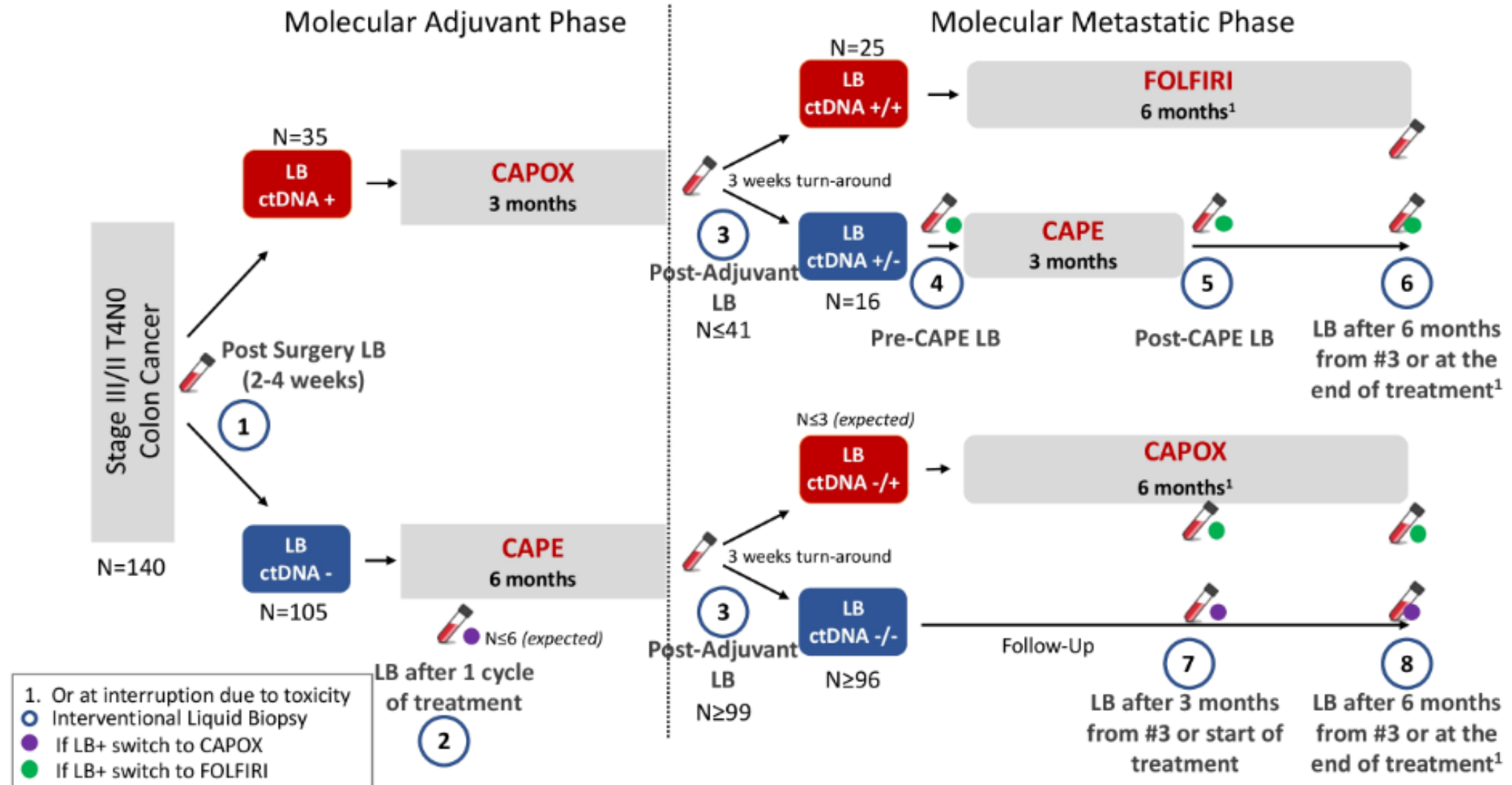
Study	Frequency of Testing		Lead-Time median (range)
	ctDNA	CT scan	
Tie J, <i>et al.</i> (SII)	Q3M	Q6M	5.6M (IQR 2.7-9.3)
Tie J, <i>et al.</i> (SIII)	Q3M	1M + Q12M	1.7M (0.3-15.7)
Tarazona N, <i>et al.</i>	Q4M	Q6M	11.5M (3-18)
Chen G, <i>et al.</i>	Q3M	Q12M	5.1M (not reported)
Wang Y, <i>et al.</i>	Q3-6M	not reported	4M (2-31)
Henriksen TV, <i>et al.</i>	Q3M	12M + 36M	8M (0.56-21.6)

# Clinical applications of MRD

## Opportunities to Improve Outcome

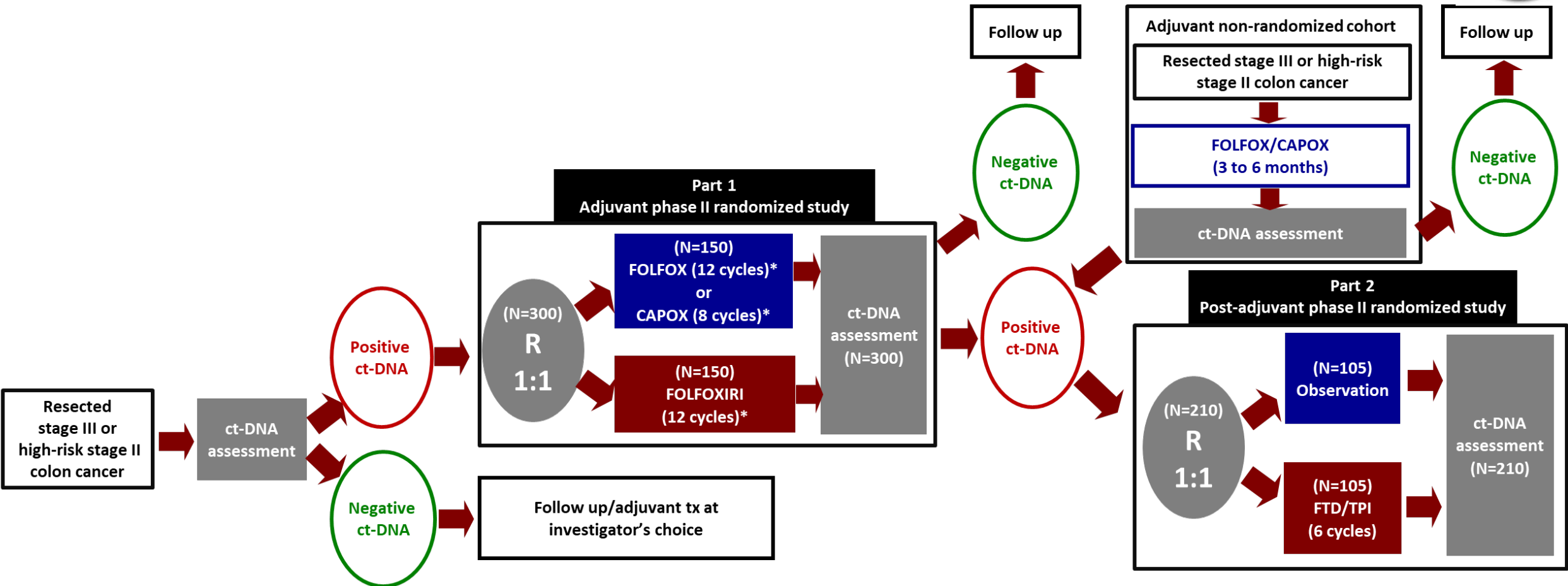


# Pegasus trial





# ERASE-CRC trial



## Part 1, adjuvant randomized study:

- ✓ **Stratification factors:**
  - High risk stage III vs low-risk stage III vs high-risk stage II
  - Center
- ✓ **Primary endpoint:** rate of ct-DNA clearance
- ✓ **Target accrual:** 300 patients

## Part 2, post-adjuvant randomized study:

- ✓ **Stratification factors:**
  - Previous adjuvant therapy (FOLFOX/CAPOX vs FOLFOXIRI)
  - High risk stage III vs low-risk stage III vs high-risk stage II
- ✓ **Primary endpoint:** rate of ct-DNA clearance
- ✓ **Target accrual:** 210 patients

\* pending the results of ct-DNA analysis, up to 2 cycles of FOLFOX/CAPOX are allowed to start the adjuvant treatment within 8-10 weeks after surgery

Grazie



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