Piattaforme di Analisi e Bioinformatica

Giovanni Crisafulli, PhD

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Who I am…

Education

Apr 2012	Ph.D. in Mathematical logic, Computer Science and Bioinformatics (Bioinformatics field), University of Siena, Italy
Dec 2008	Master course in Bioinformatics "Alberto Del Lungo", University of Siena, Italy
Jan 2008	Biologist Qualification
Jul 2007	MD in Biological Sciences (Biomolecular field). Grade: 110/110 cum laude.

Candiolo Cancer Institute (Candiolo, TO)

2014-2022

IFOM, The AIRC Institute of Molecular Oncology (Milano, MI)

2022-2026

Istituto S. Raffaele Giglio (Cefalù, PA)

2013-2014

Computational Oncology and Bioinformatics

Novartis Vaccines & Diagnostics (Siena, SI)

2008-2013

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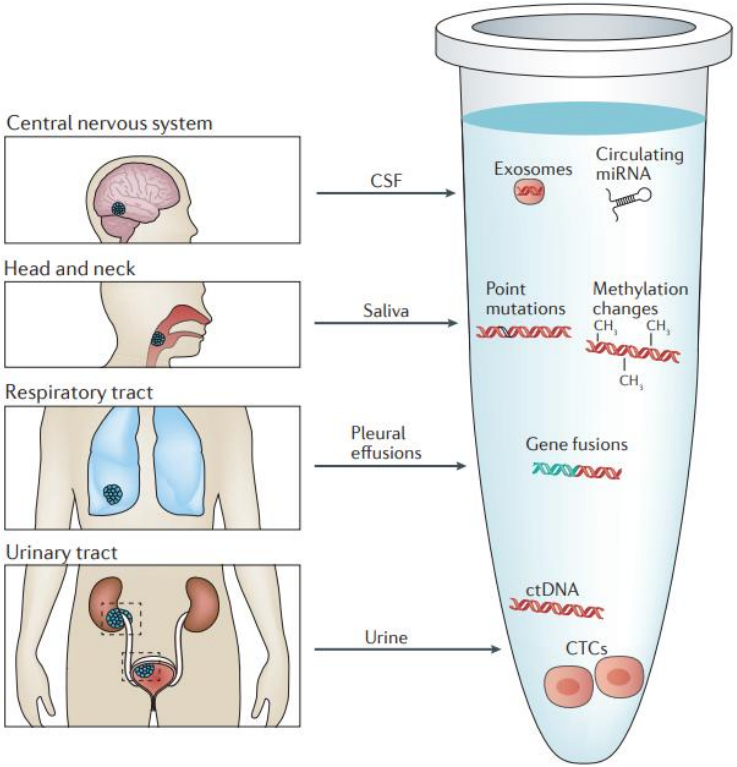
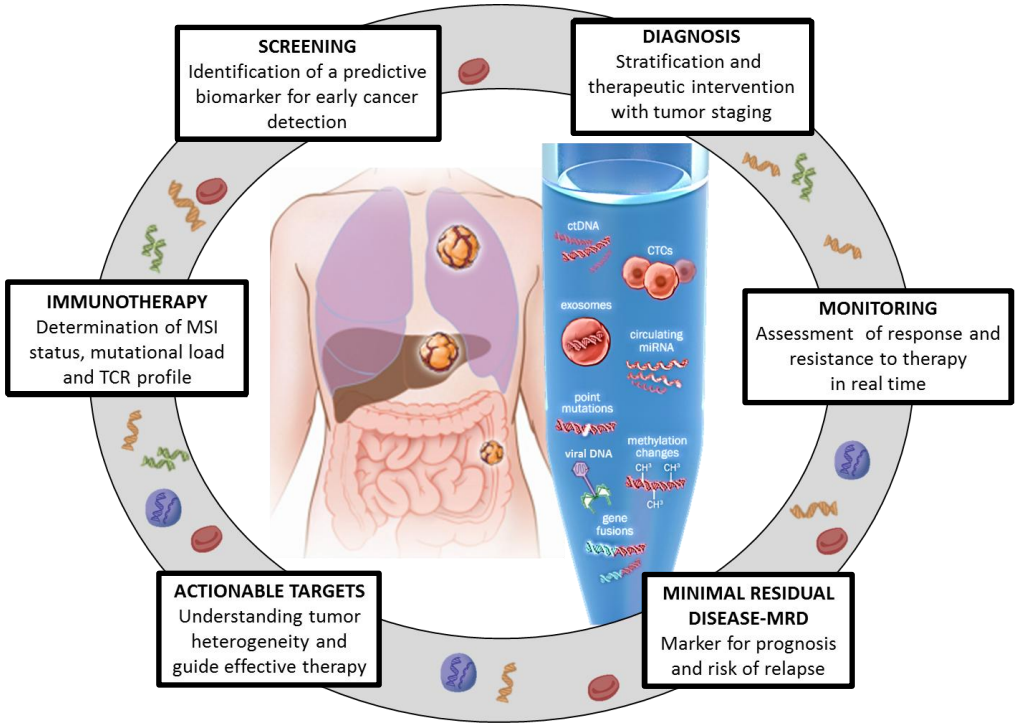


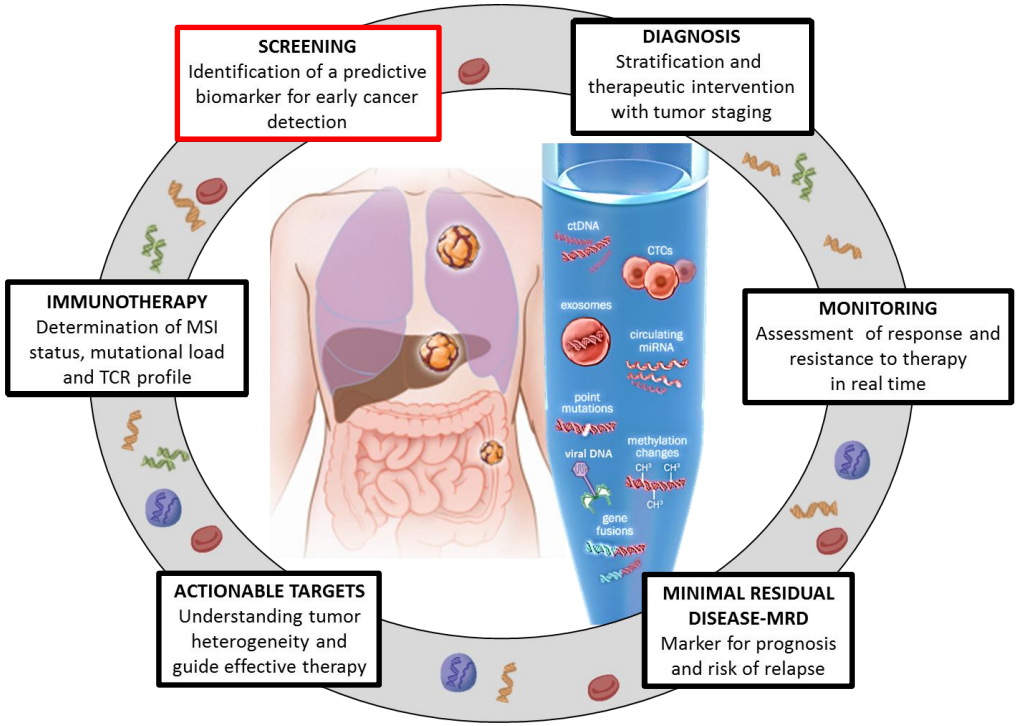
- The term Liquid Biopsy (LB) defines the collection of tumor-derived biomarkers from the blood or other body fluids.
- The main LB advantage over solid-tissue biopsy is the minimal invasiveness, which make it a safe and timely to be exploited for clinical decision-making.
- Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs) are the most deeply characterized biomarker.
- Circulating Tumor Cells (CTCs) are few in some tumor types (CRC for example)

Modified from Siravegna et al. Nat Rev Clin Oncol, 2017



What could we do?

Modified from Siravegna et al.i, Genome Biology 2014

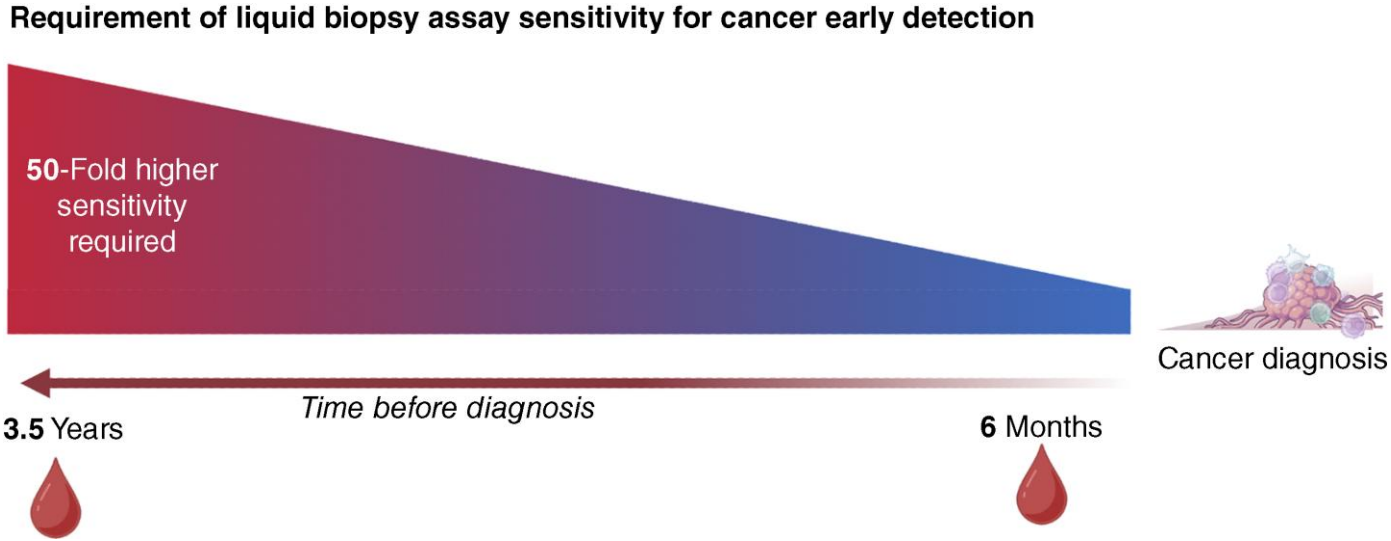


What could we do?

SCREENING

Modified from Siravegna et al.i, Genome Biology 2014

Detecting Cancer Early with Ultrasensitive Multimodal Liquid Biopsy



-) 26 patients and 26 healthy controls,

-) strategies based on amplicon panels, hybrid capture, and whole-genome sequencing (WGS).

-) tumor-derived genetic information can be detected in plasma up to 3.5 years before diagnosis,

-) highlighting the transformative potential of liquid biopsy, as previously demonstrated in pan-cancer screening foundational studies

-) LOD approximately 50-fold lower than that needed for detection 6 months before diagnosis

Crisafulli et al., Cancer Discovery 2025
Wang et al., Cancer Discovery 2025

L'INTRODUZIONE della BIOPSIA LIQUIDA nella DIAGNOSTICA ONCOLOGICA

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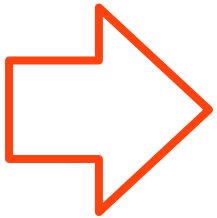
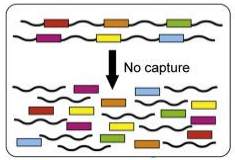
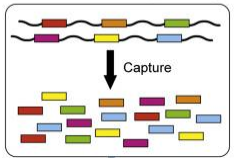
90%

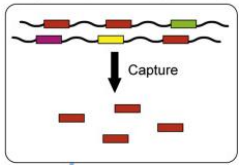
Tumor Content

0,001%









LOD

20%

1-5%

< 1*%

*** associated with sequencing error control methods (i.e. barcoding system)**

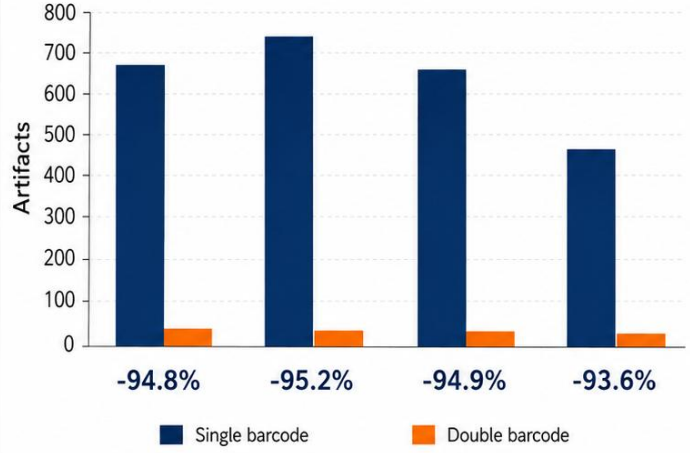
Artefact reduction in liquid biopsy workflows

Impact of wet-lab barcode design and custom bioinformatic processing

Wet workflow optimization

Double barcode system vs single barcode system

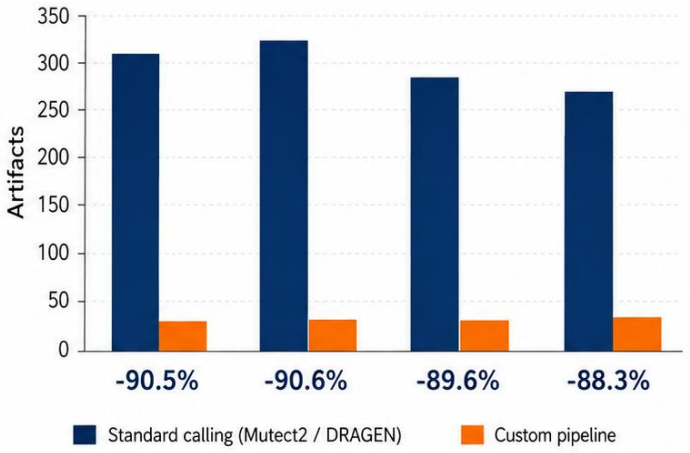
≈95% artefact reduction

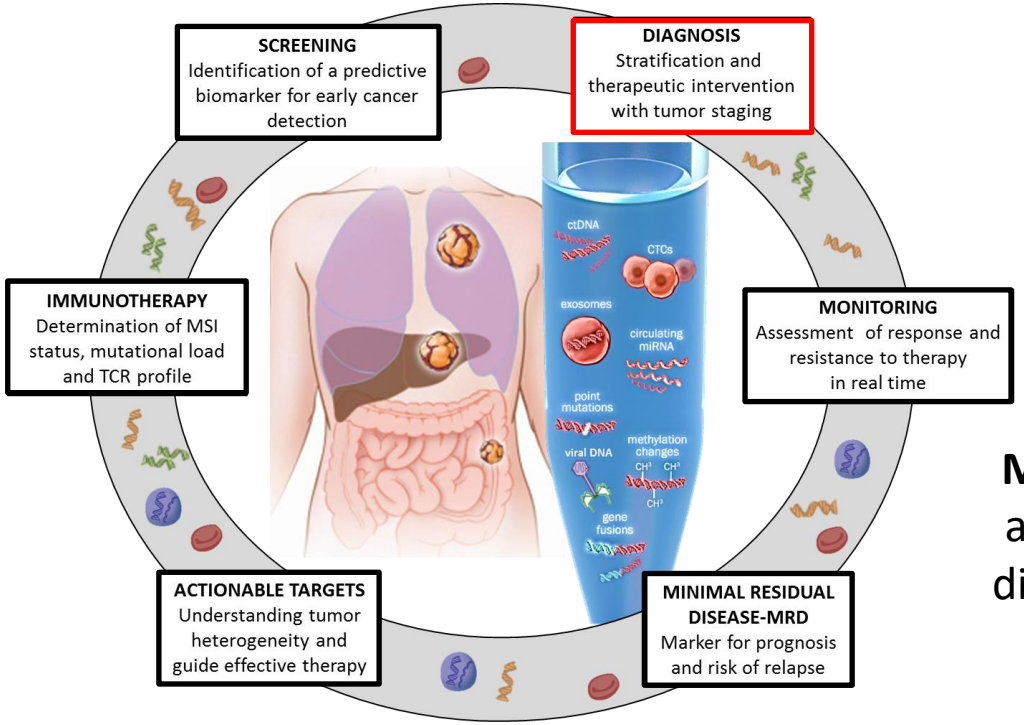


Bioinformatic workflow optimization

Custom liquid-biopsy pipeline vs standard calling (Mutect2 / DRAGEN)

≈90% artefact reduction





What could we do?

Molecular typing: Detection of genomic alterations (MSI, HER2, NTRK) useful for directing specific treatments when tissue sampling is not feasible.

Modified from Siravegna et al.i, Genome Biology 2014

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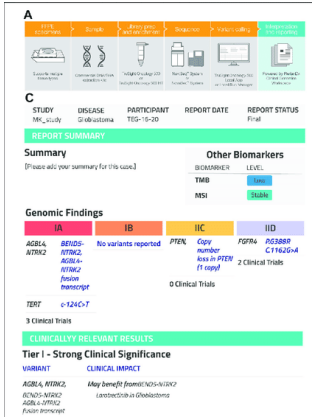
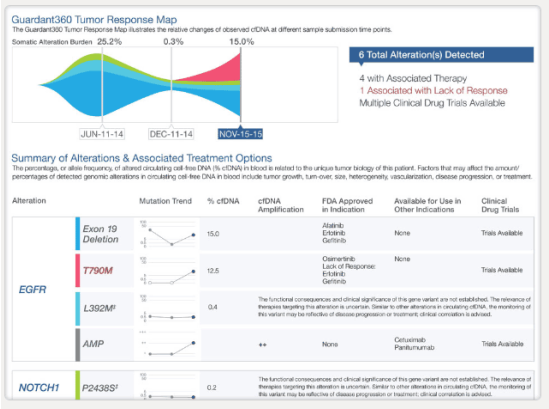
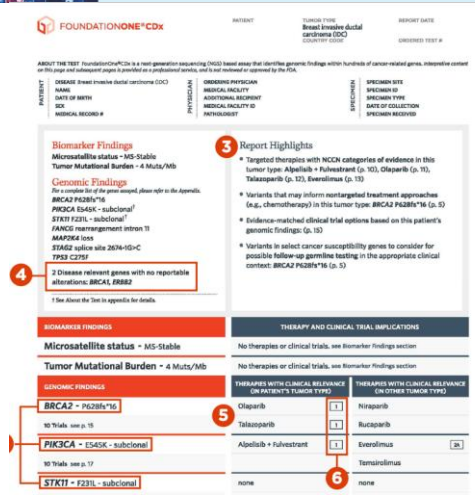
-) Gene Panel (50-700 genes)
-) Fusions (i. e. NTRK) – Amplification (i. e. ERBB2) – SNV (i.e. KRAS G12C)
-) BE CAREFULL (LOD/Performance/Pan-Cancer-Specific Panel)



Illumina TruSight Oncology 500 ctDNA

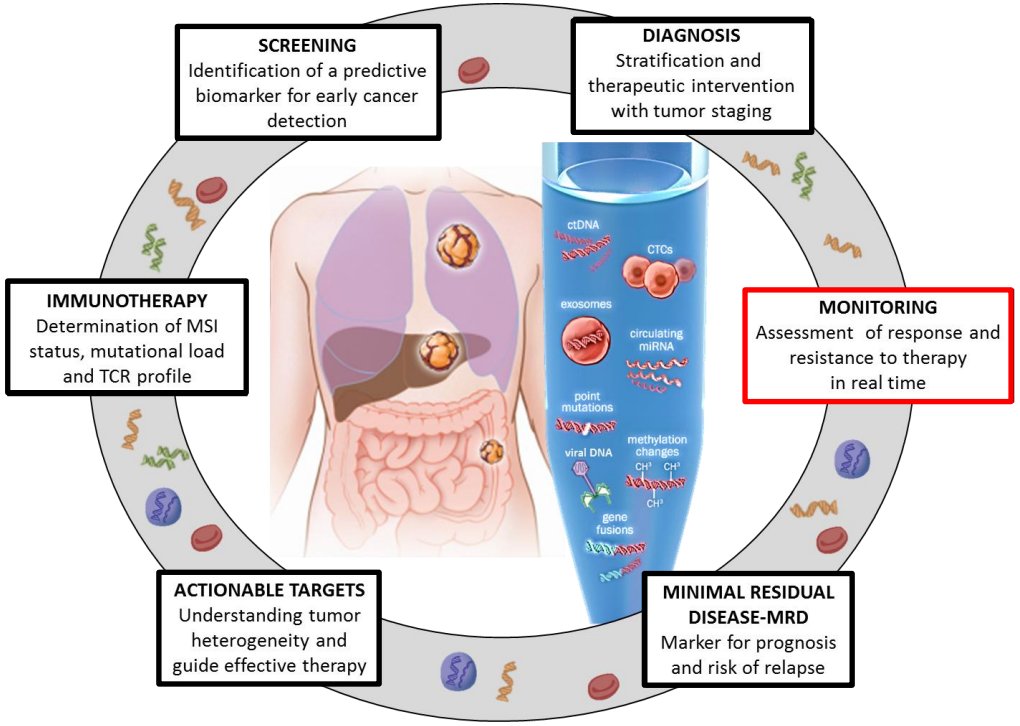
Guardant 360 liquid





FoundationOne® Liquid CDx

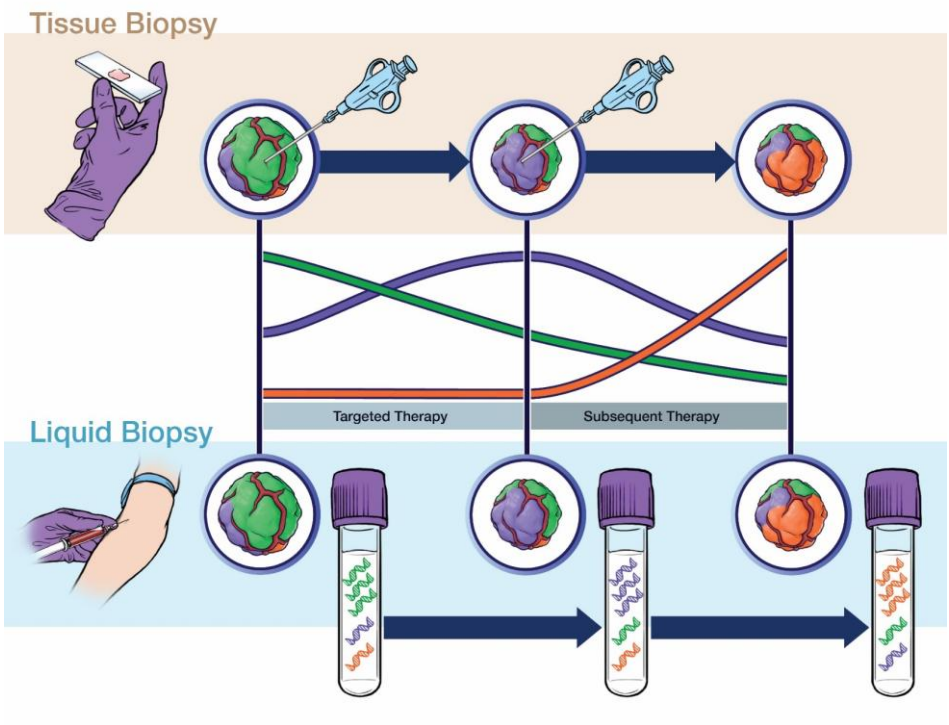
Images from Guardant/FoundationOne/Illumina websites



What could we do?

MONITORING

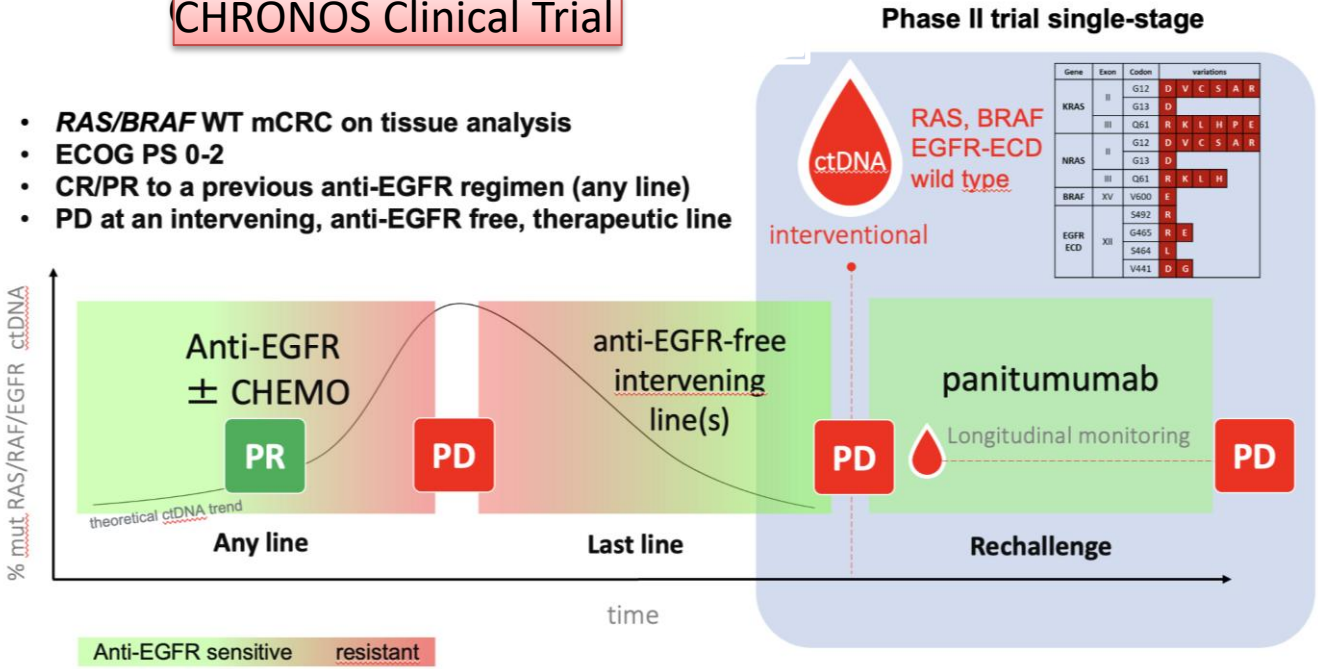
Modified from Siravegna et al.i, Genome Biology 2014



Modified from Siravegna et al.i, Genome Biology 2014

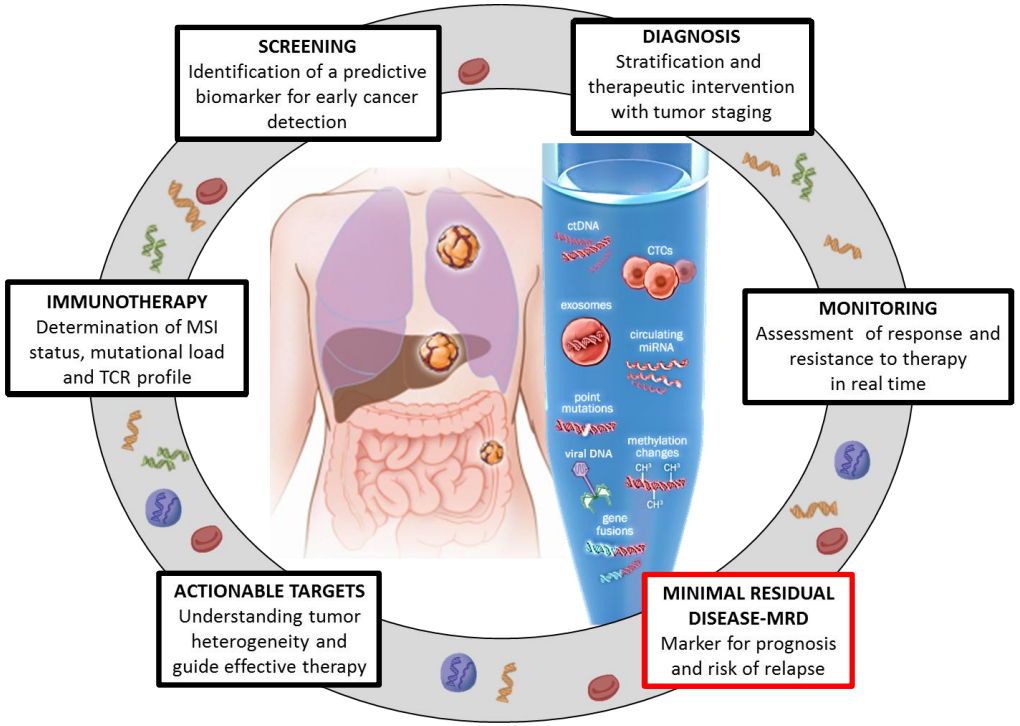
CHRONOS Clinical Trial

- ***RAS/BRAF*** **WT mCRC on tissue analysis**
- **ECOG PS 0-2**
- **CR/PR to a previous anti-EGFR regimen (any line)**
- **PD at an intervening, anti-EGFR free, therapeutic line**



Treatment with anti-EGFR if no mutations in EGFR pathway was found.

Modified from Sartore-Bianchi et al. Nature Medicine 2022



What could we do?

Minimal Residual Disease

Modified from Siravegna et al.i, Genome Biology 2014

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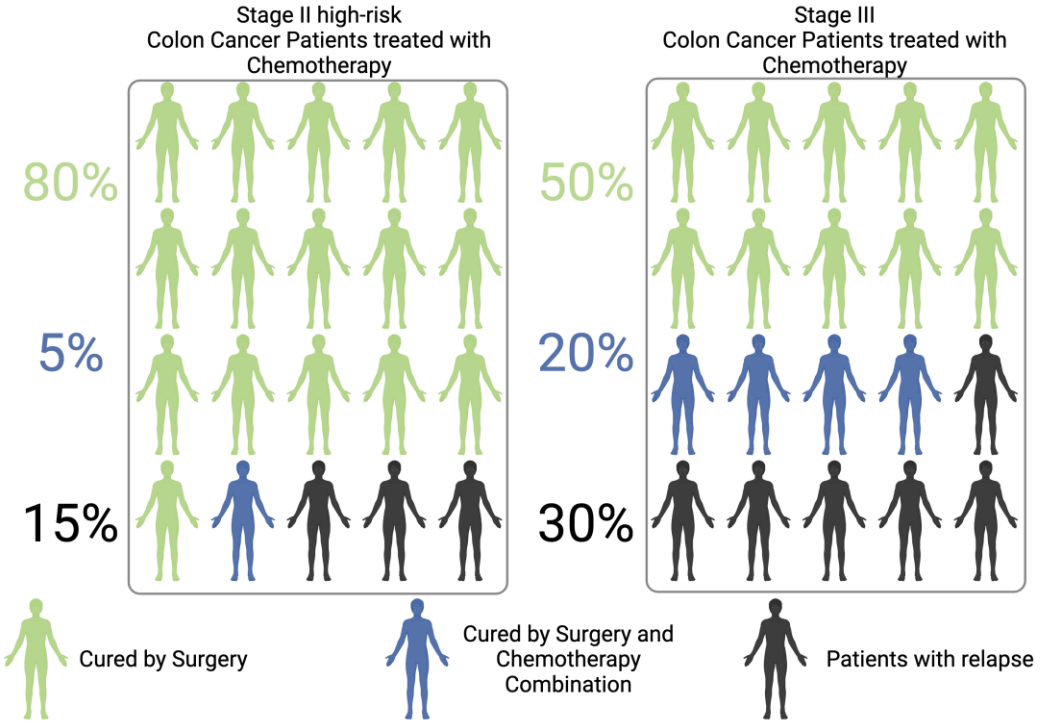
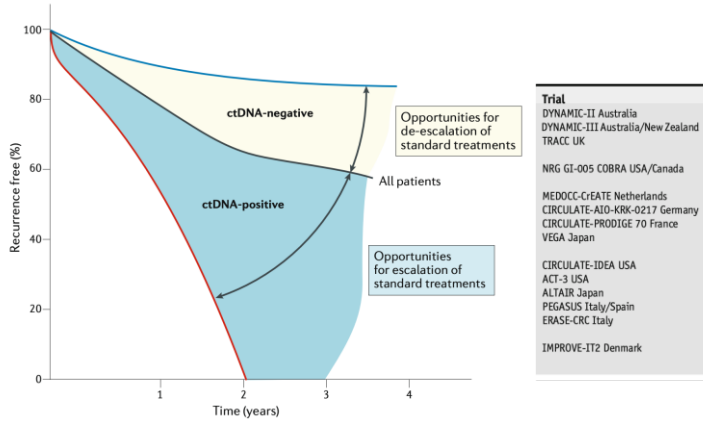


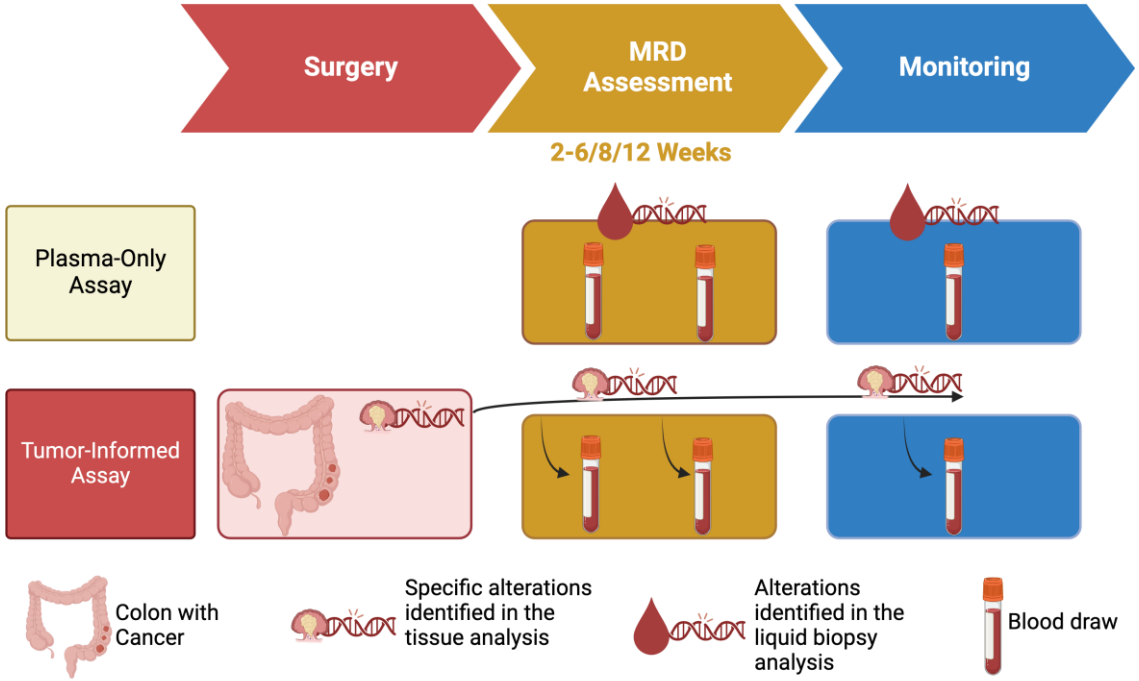
Paradigm in stage II-III colon cancer: 80%-50% patients cured and treated with chemotherapy



PEGASUS Clinical Trial

Modified from
Crisafulli Genes 2025
O'Connell JB et al, J Natl Cancer Inst 2004
Collienne M and Arnold D, Cancers 2020
Taieb J et al, Cancer Treat Rev 2019
Lonardi S et al, ESMO Congress. 2023

Differences in MRD assays

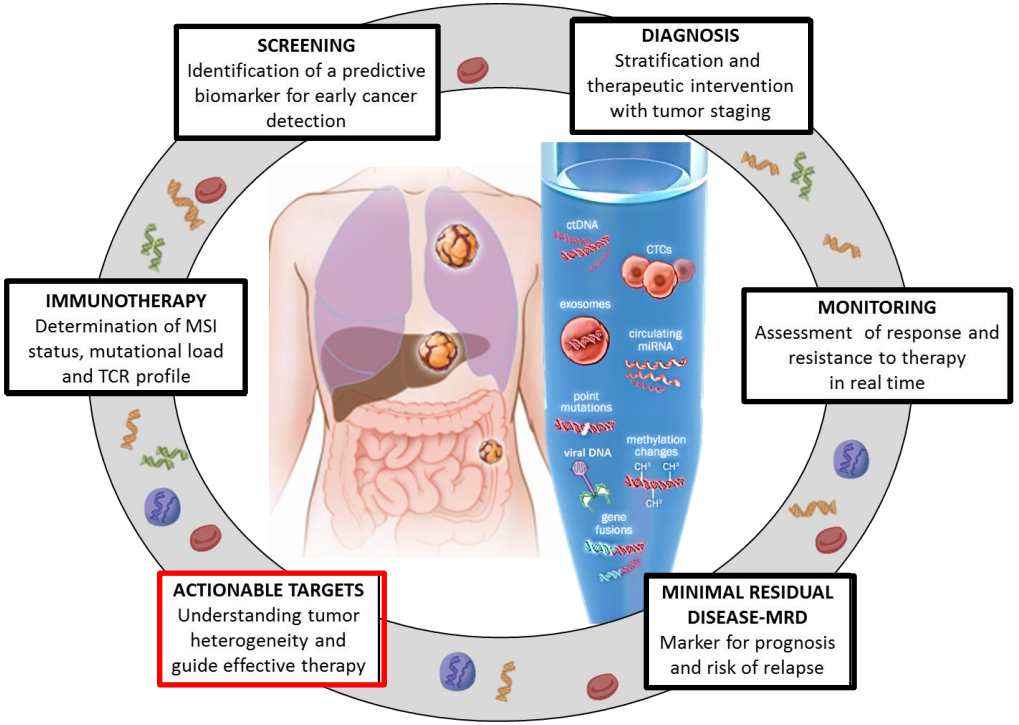


Limitations

(A) metastases located in specific organs are known to release low levels of ctDNA.
(B) smaller genetic targets may fail to capture the specific genetic alterations of each type of tumor.

(A) metastases located in specific organs are known to release low levels of ctDNA.
(B) clonal mutations in the sequenced tissue could not accurately reflect the entire tumor's genetic makeup.
(C) there are disappearances of specific mutations that were originally used to define the tumor signature.
(D) tumor tissue could be unavailable for the analysis.

Modified from Crisafulli Genes 2025

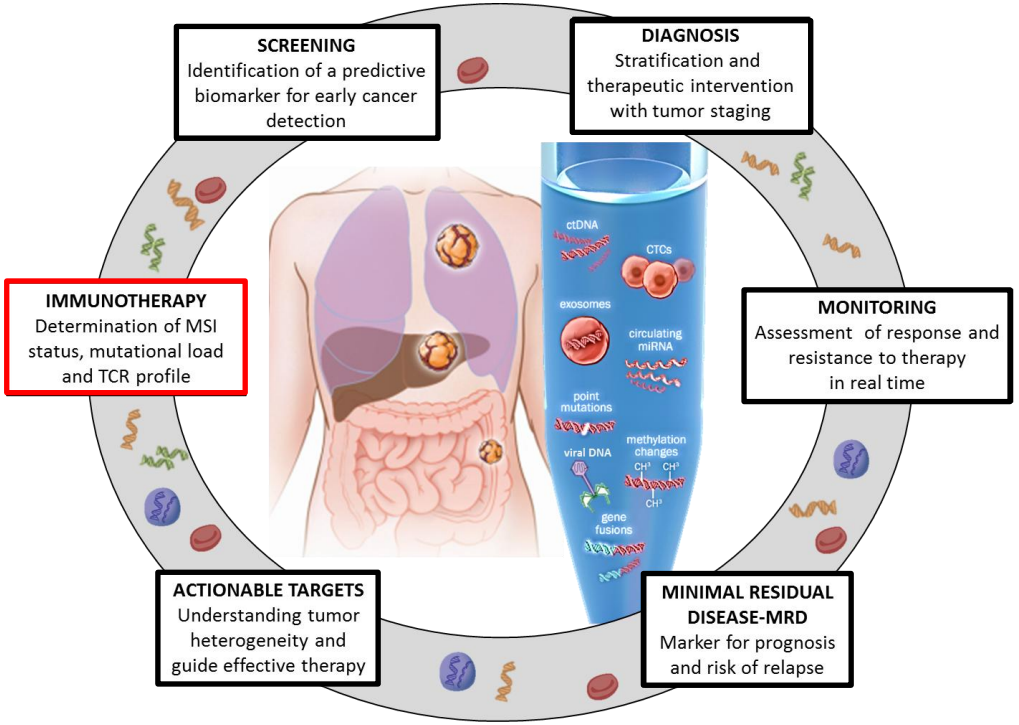


What could we do?

HOTSPOTS

- *KRAS* G12C
- *NTRK* fusion
- *ERBB2* Amplification
- *EGFR*

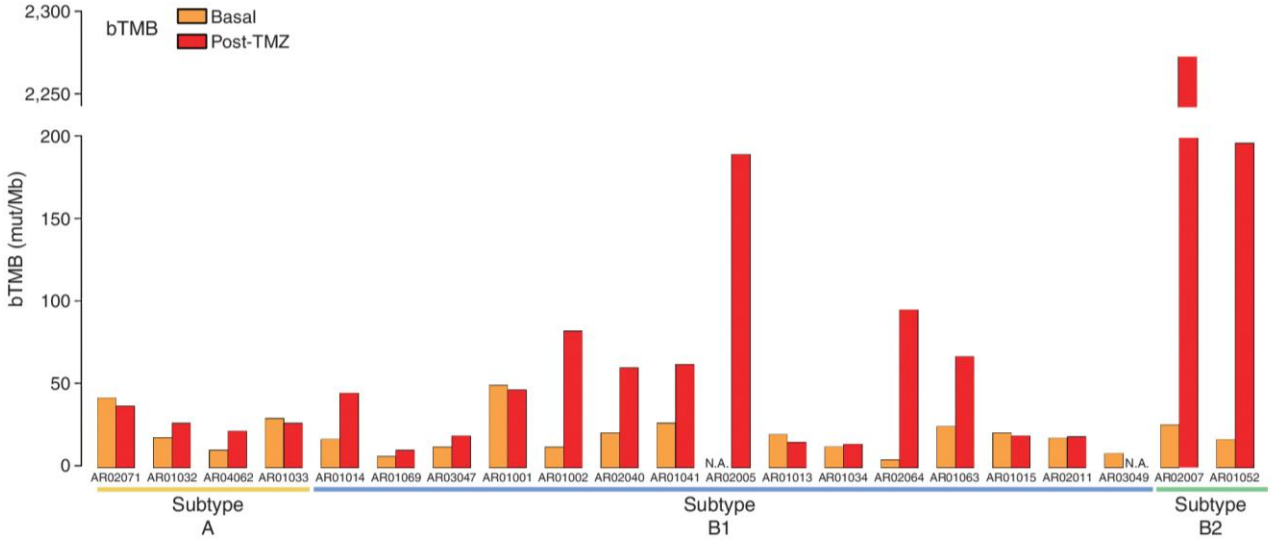
Modified from Siravegna et al.i, Genome Biology 2014

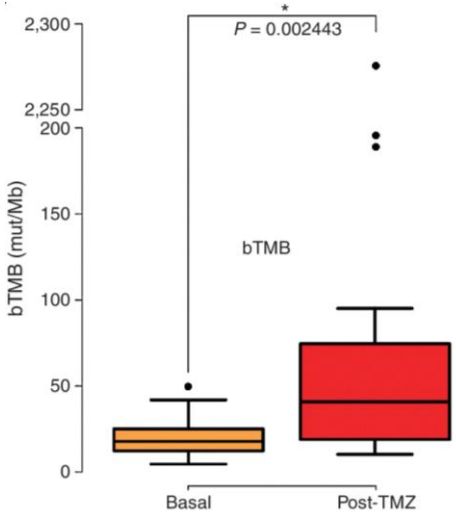


What could we do?

Modified from Siravegna et al.i, Genome Biology 2014

Liquid biopsy can check the MSI status (dMMR pharmacologically induced)



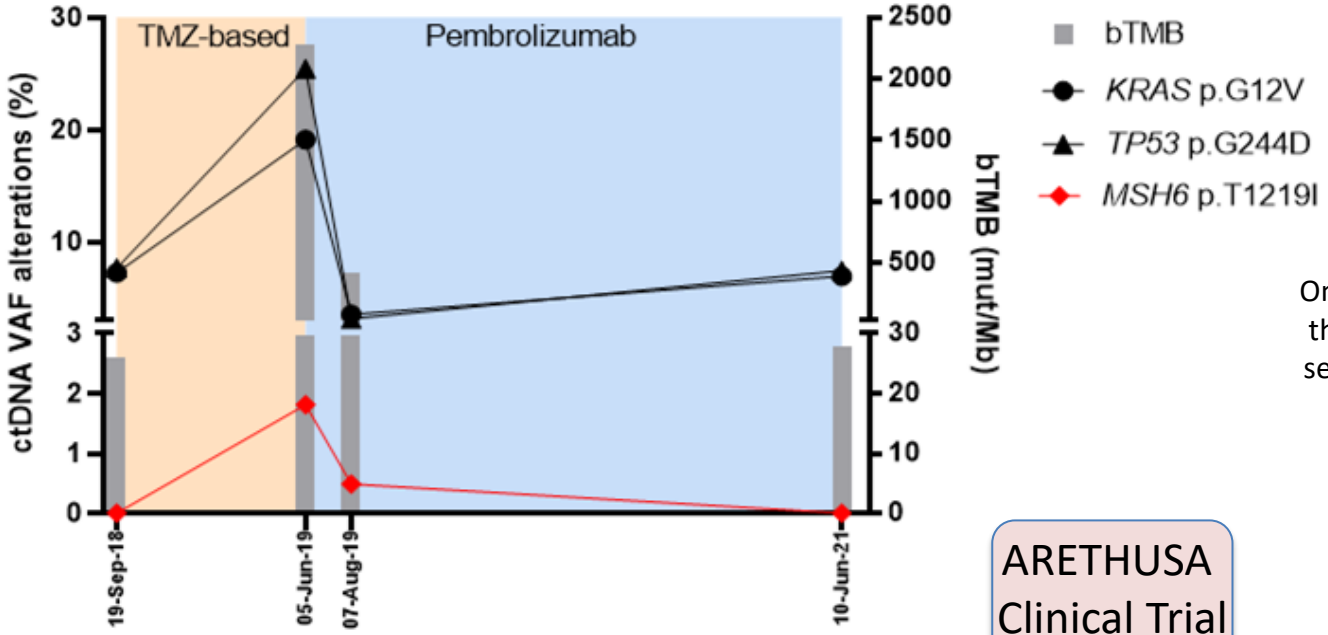


ARETHUSA Clinical Trial

Overcoming the tissue heterogeneity: the blood-based TMB analysis confirms the TMB increase after priming

Modified from Crisafulli et al. Cancer Discovery 2022

Longitudinal monitoring of the *MSH6* mutation during immunotherapy: *MSH6* mutation emerged after TMZ-priming and disappeared at pembro progression



Only 7.1% of tumor load was MMRd but the subclonal MMRd part of the tumor seems to guide the disease stabilization during pembro treatment

ARETHUSA Clinical Trial

Modified from Crisafulli et al. Cancer Discovery 2022

Thank you

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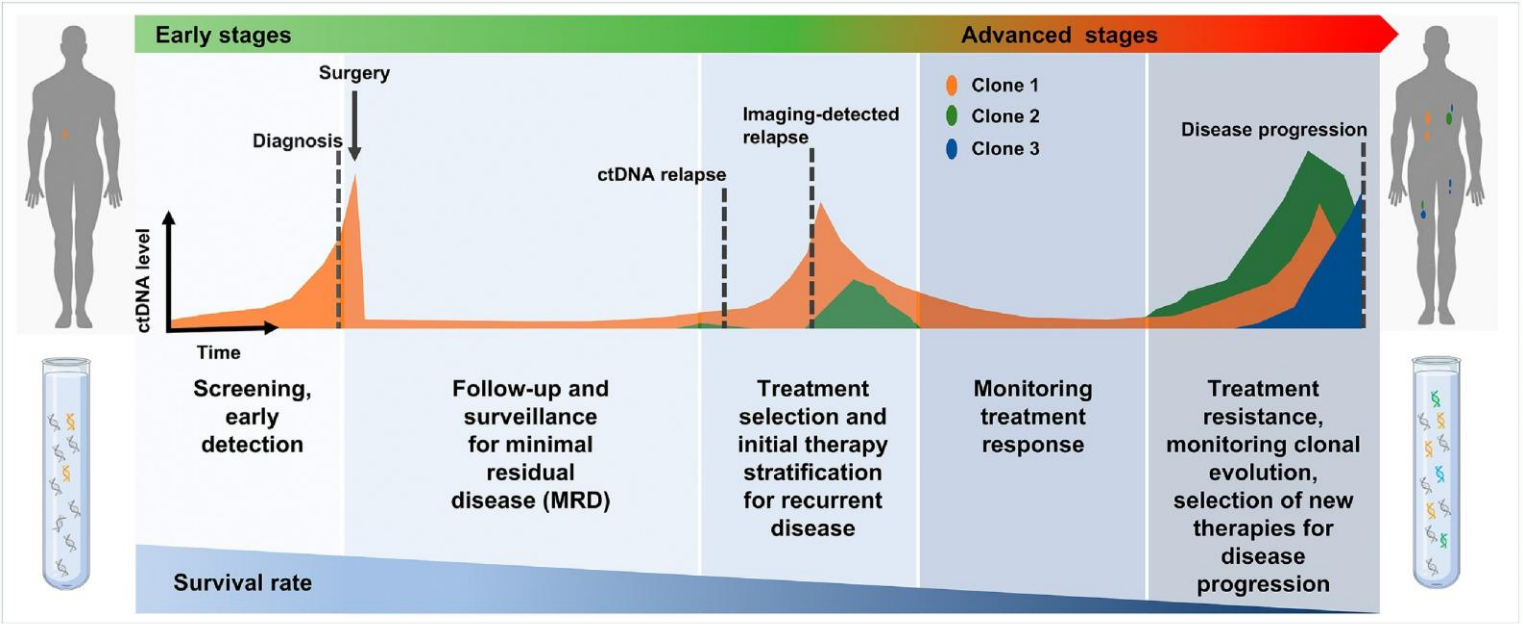

Trends in Molecular Medicine

Modified from Siravegna and Bardelli, Genome Biology 2014