ctDNA and RECIST in medical oncology

Response evaluation, liquid biopsy and clinical implementation

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ctDNA-RECIST Programme · DCCC ctDNA Research Center · ELBS

ctDNA-RECIST

from biomarker signal to treatment decision

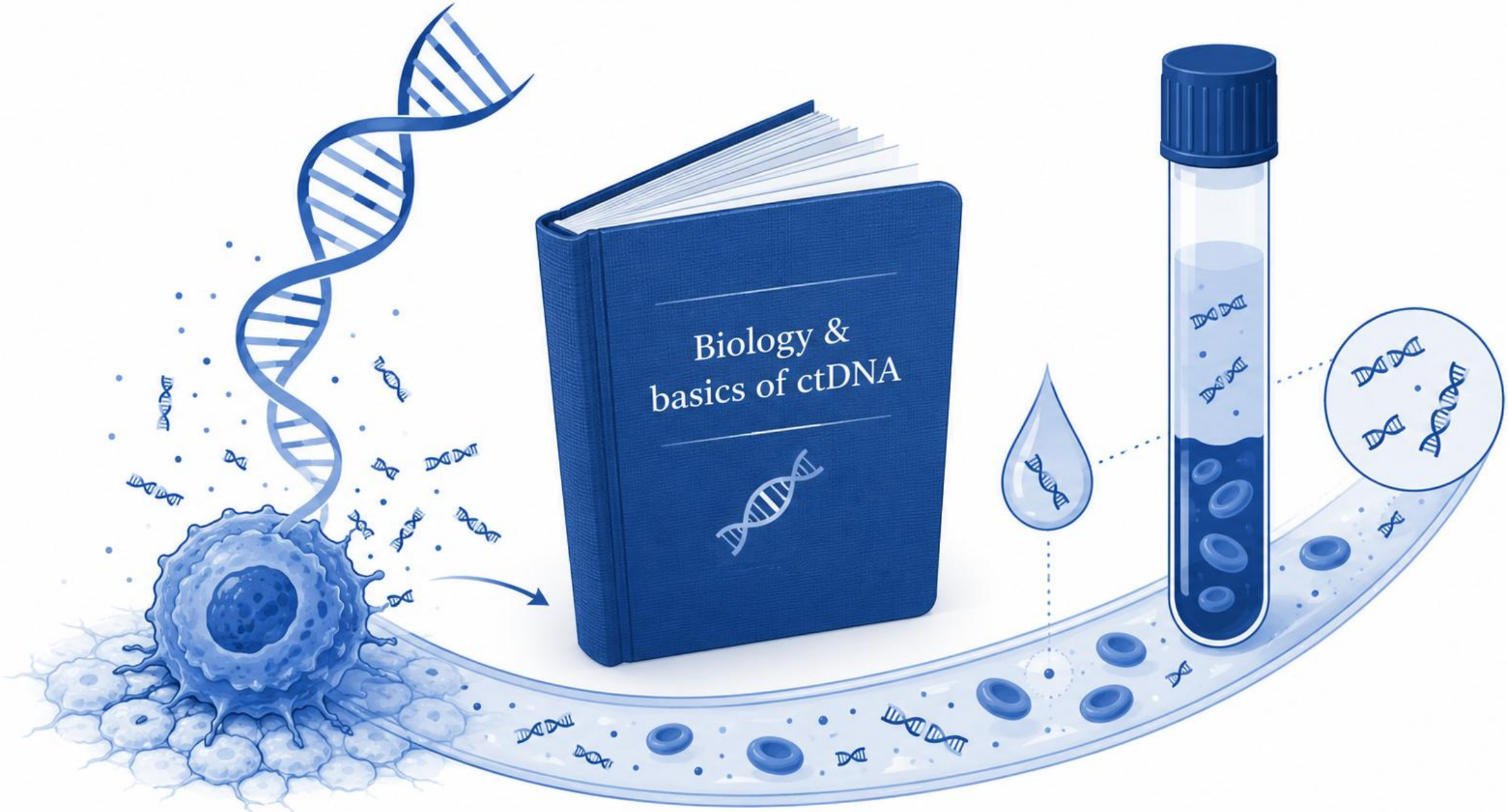
Danish Cancer Society · Kirsten and Freddy Johansen's Fond · novo nordisk foundation · midt Central Denmark Region · Danish Comprehensive Cancer Center · DCCctDNA ResearchCenter · ELBS · AARHUS UNIVERSITY HOSPITAL · ctDNA-RECIST

DISCLOSURES

Lecturing honorarium from Boston Scientific, Daiichi Sankyo Nordics ApS, Incyte Biosciences Denmark ApS, BMS Norway, MSD

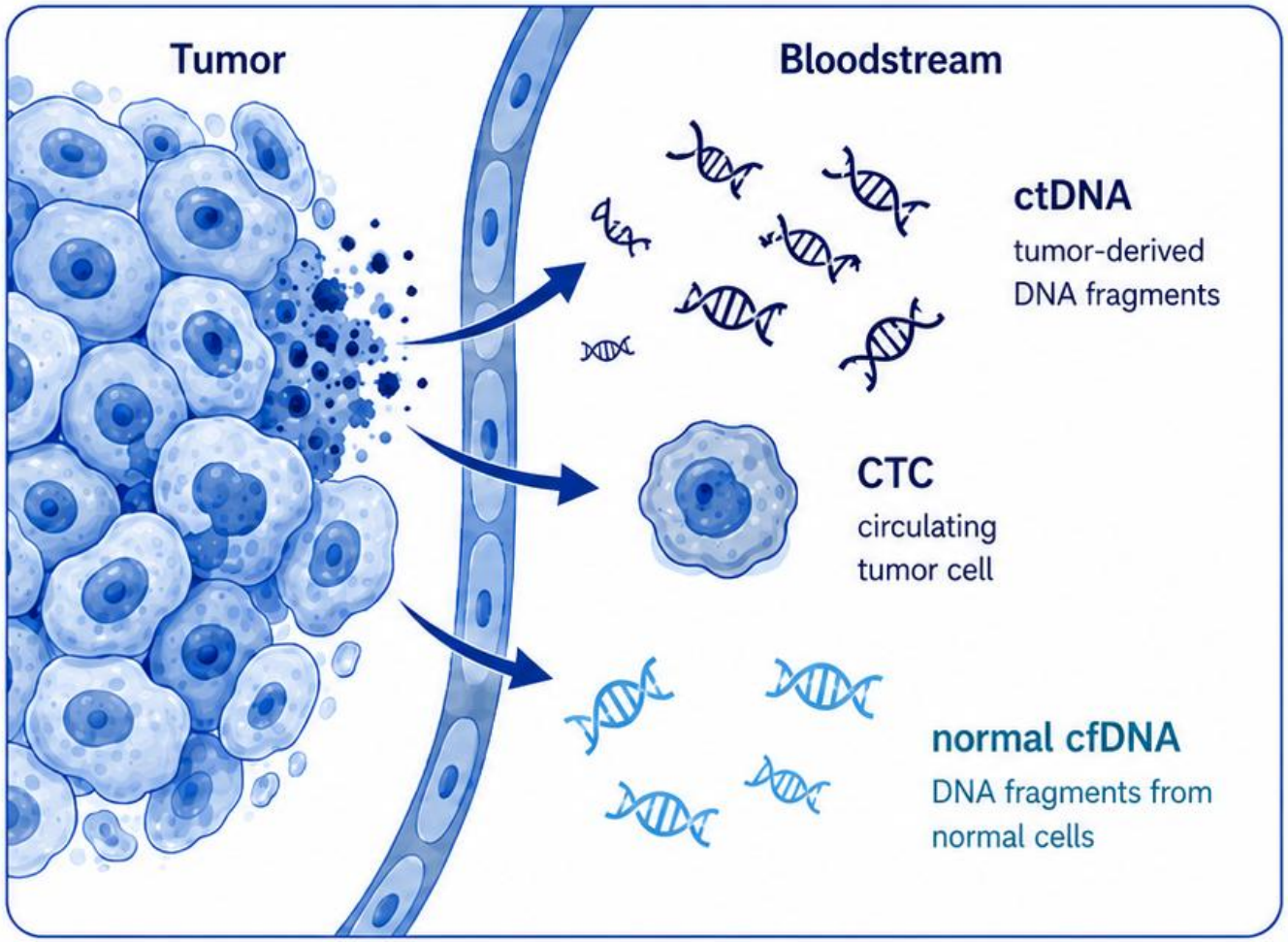
Previous meeting support from Roche, Amgen, Merck and Nordic Drugs.

I practice using AI tool for my presentations and writing -


Biology &
basics of ctDNA

What is ctDNA?

Biology

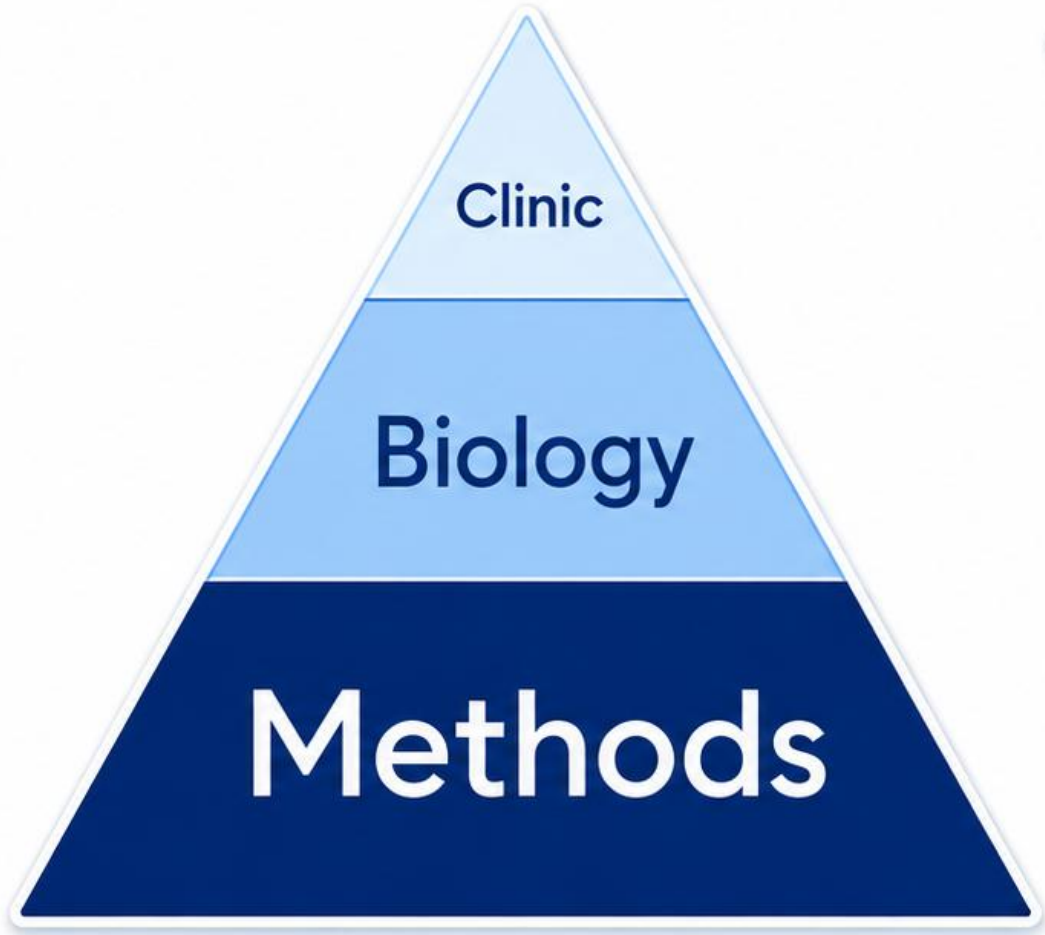


1. **ctDNA** = the tumor-derived fraction of cell-free DNA (cfDNA) in plasma
2. Released mainly through cell death (especially apoptosis/necrosis), and possibly active secretion
3. Usually only a small fraction of total cfDNA, mixed with DNA from normal cells
4. Contains tumor-specific molecular features (e.g. mutations, methylation, fragmentation) and changes rapidly over time

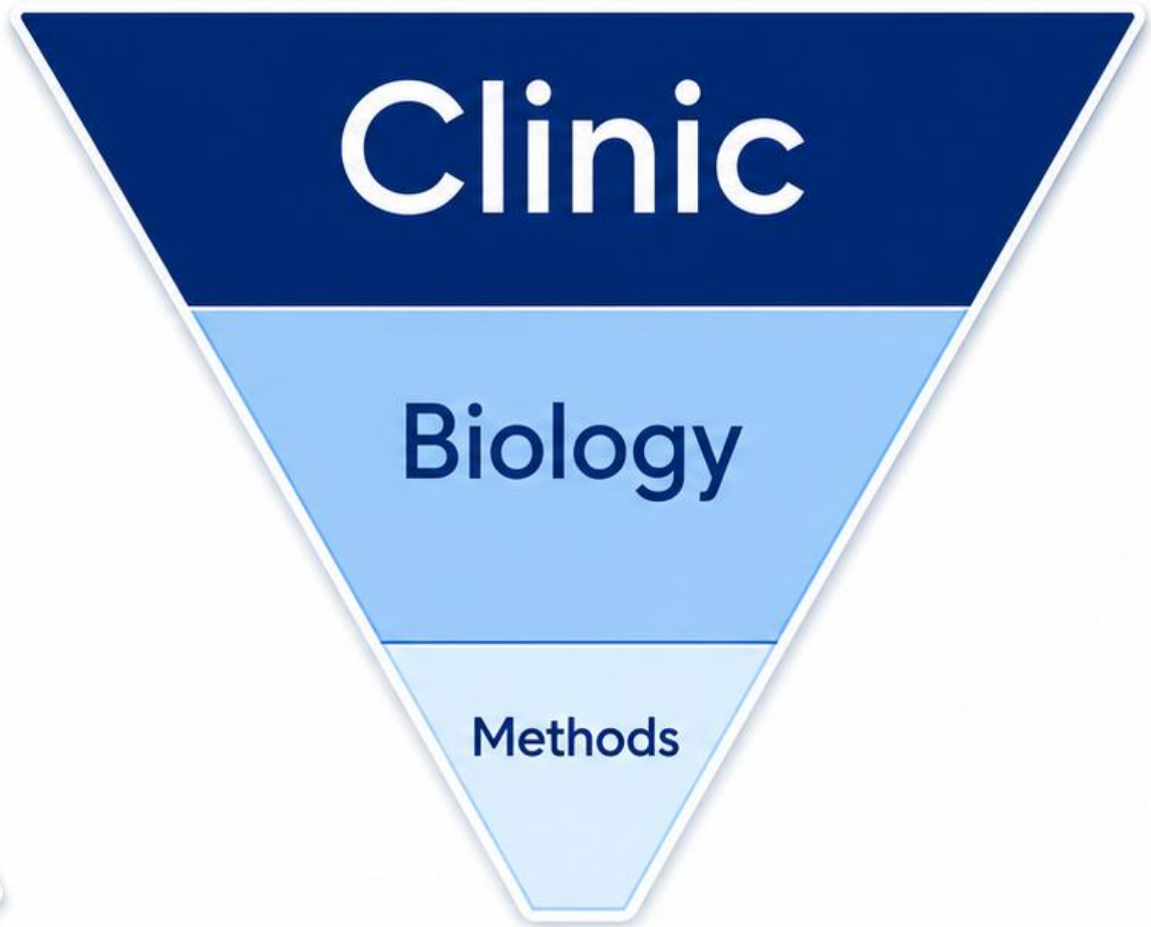
Half-life: less than 2 hours

Malki et al. Med 2026; Thierry et al. Cancer Metastasis Rev 2016; Jahr et al. Cancer Res 2001; Benesova et al. Anal Biochem 2012; Garcia-Olmo et al. Histol Histopathol 2004; Diehl et al. PNAS 2005; Spindler et al. Acta Oncol 2017.
Half-life: less than 2 hours.[1,2]

FROM VALIDITY TO CLINICAL UTILITY



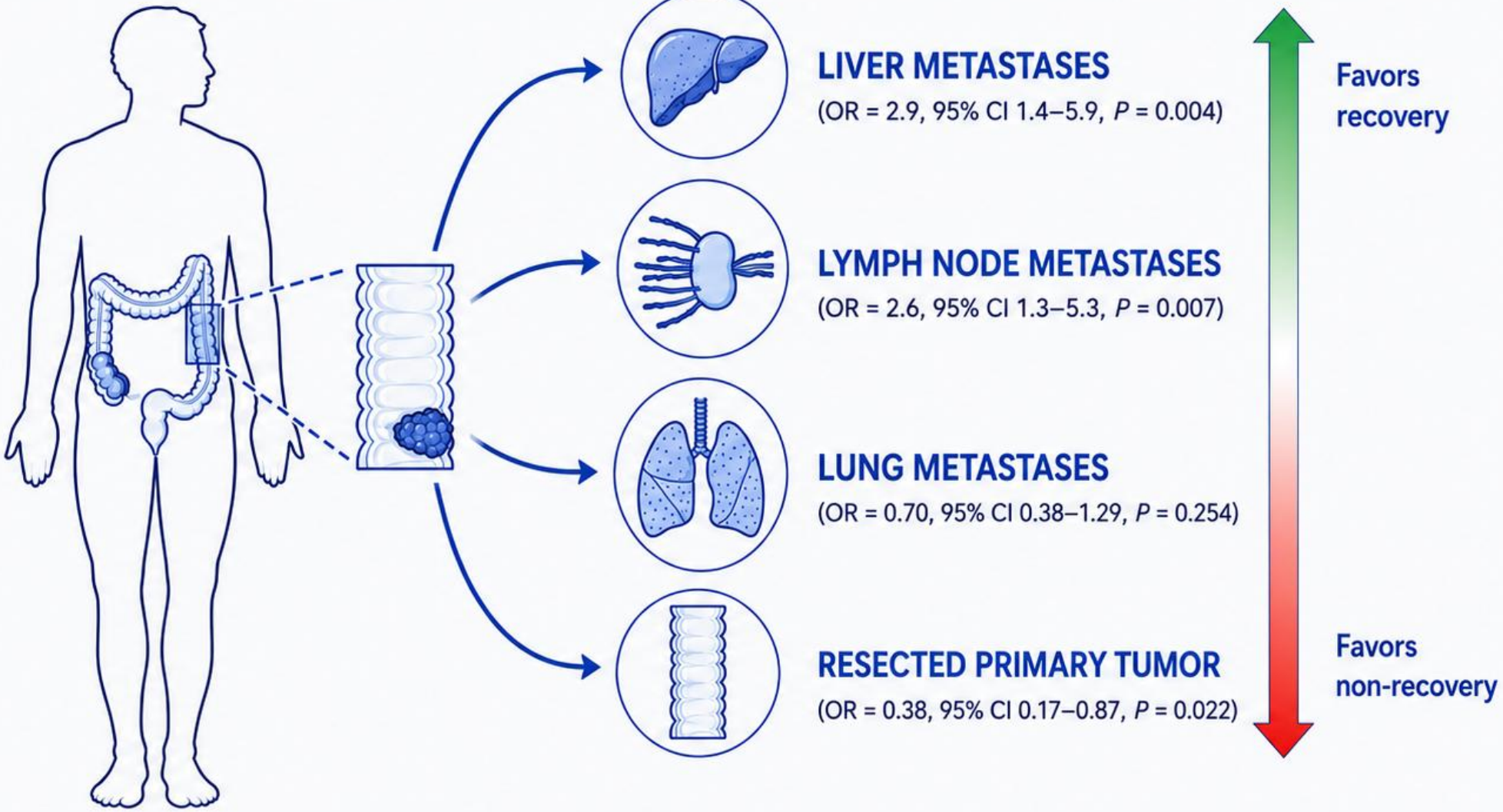
2016



2026

Figure by Garm Spindler

SHEDDING



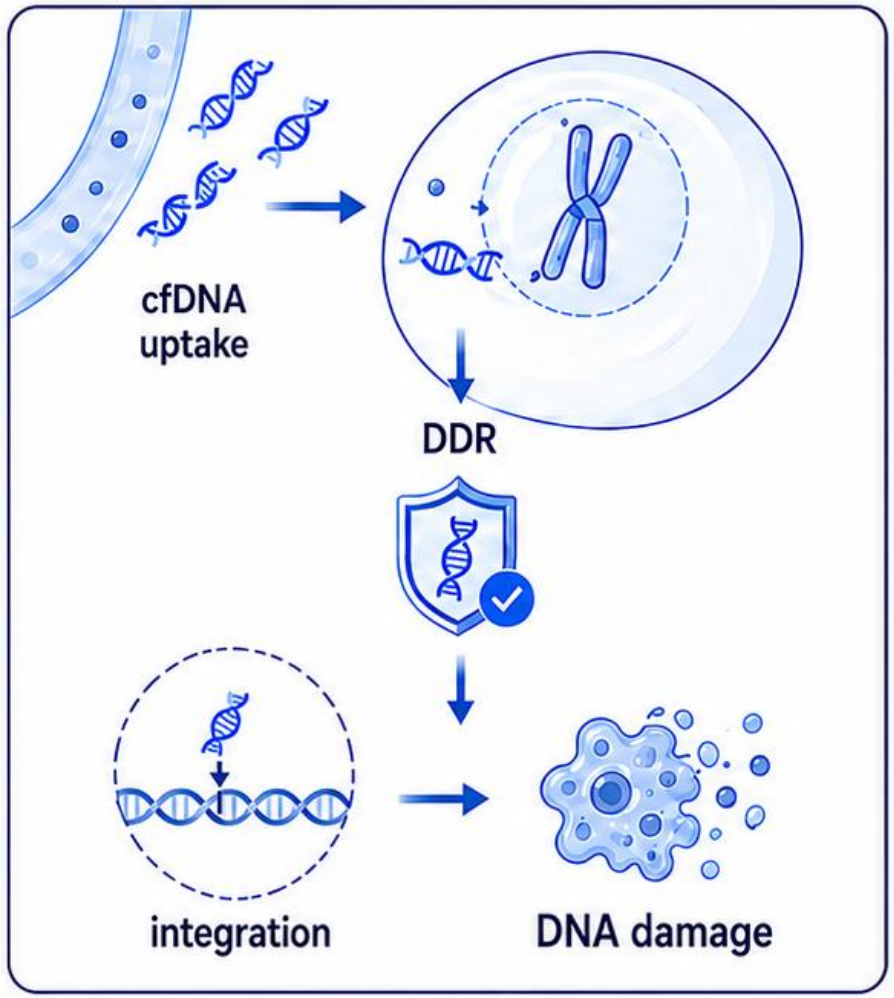
Modified from Hamfjord et al., Ann Oncol 2019

THE DARK SIDE OF CIRCULATING DNA

1. Circulating cell-free nucleic acids (cfNAs) are **taken up** by healthy cells.

2. The uptaken cfDNA activate DDR and **integrate** into host cell genomes.

3. Leads to **DNA breaks** and apoptosis.



Consequently, cfNAs act as ubiquitous, physiological, endogenous **mutagenic agents**.

Progressive cfNAs-induced mutagenesis may be implicated in **ageing and cancer**.

Gravina et al. *Aging Cell* 2016; Basak et al. *Mutation Research* 2016.

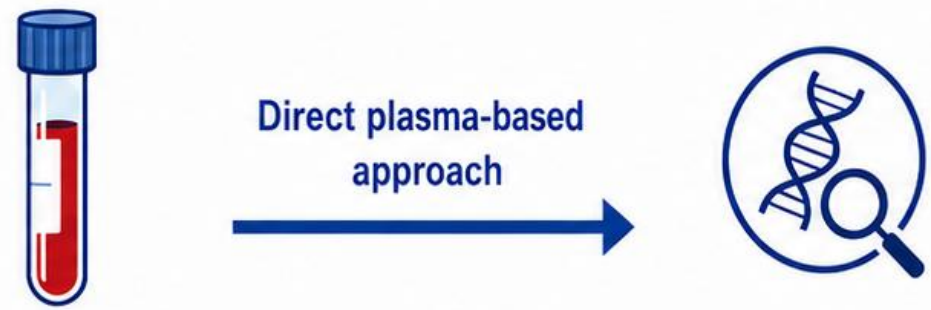
ctDNA testing strategies

A Tumor-informed

Uses tumor tissue first

Personalized approach

B Tumor-agnostic



No tumor tissue required

Direct blood-based approach

ctDNA Testing

Blood sample

Plasma

DNA purification

SOP

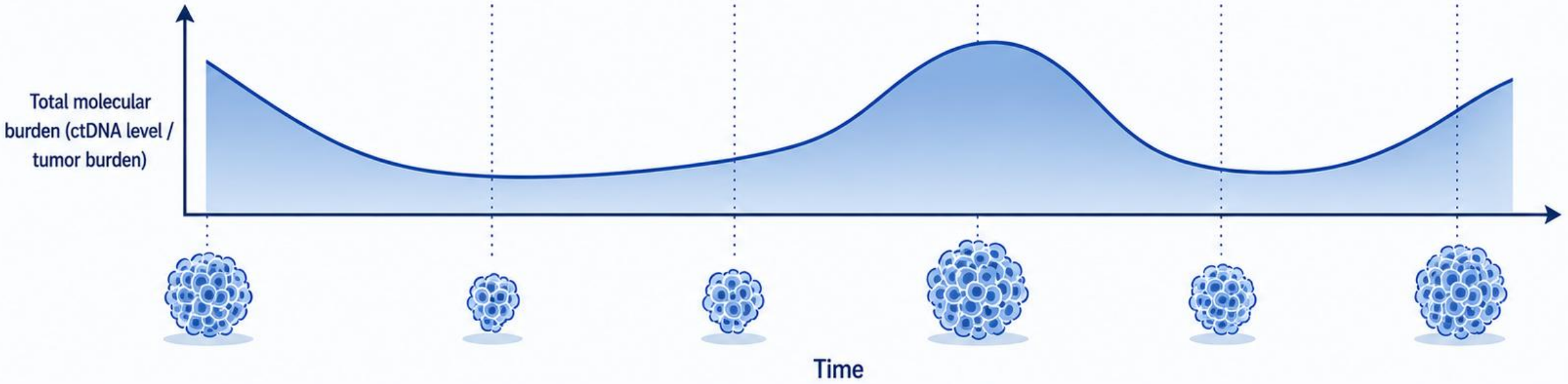
- Simple plasma sample
- in EDTA or DNA preserving tubes
- Approx 40 ml is adequate for relevant studies
- 4 ml plasma for one ctDNA analysis
- Double spin centrifugation
- Store at -80

Quantify the **Total free DNA** cfDNA

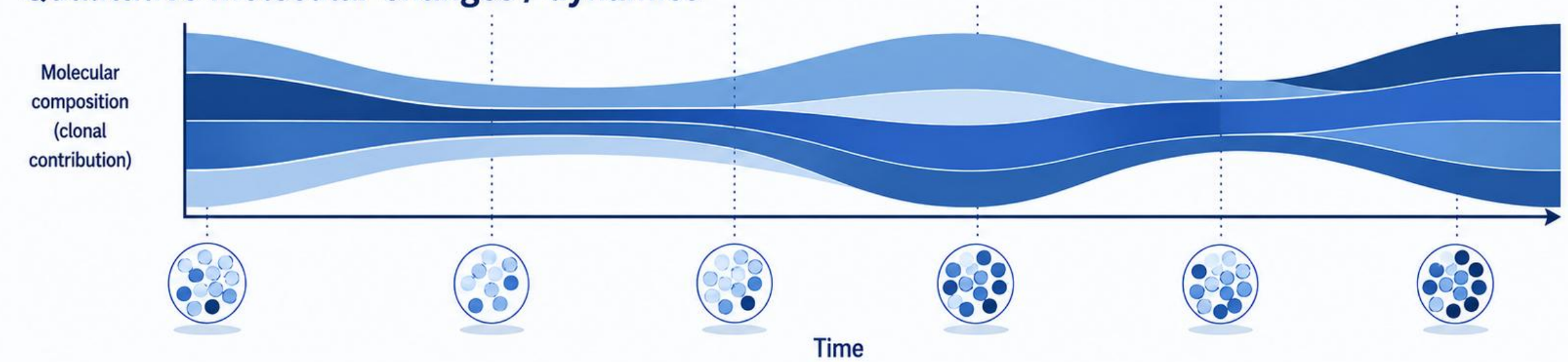
Detect and characterize the circulating tumor DNA

Quantify the circulating tumor DNA **ctDNA**

Quantitative kinetics



Qualitative molecular changes / dynamics



Possible applications of ctDNA

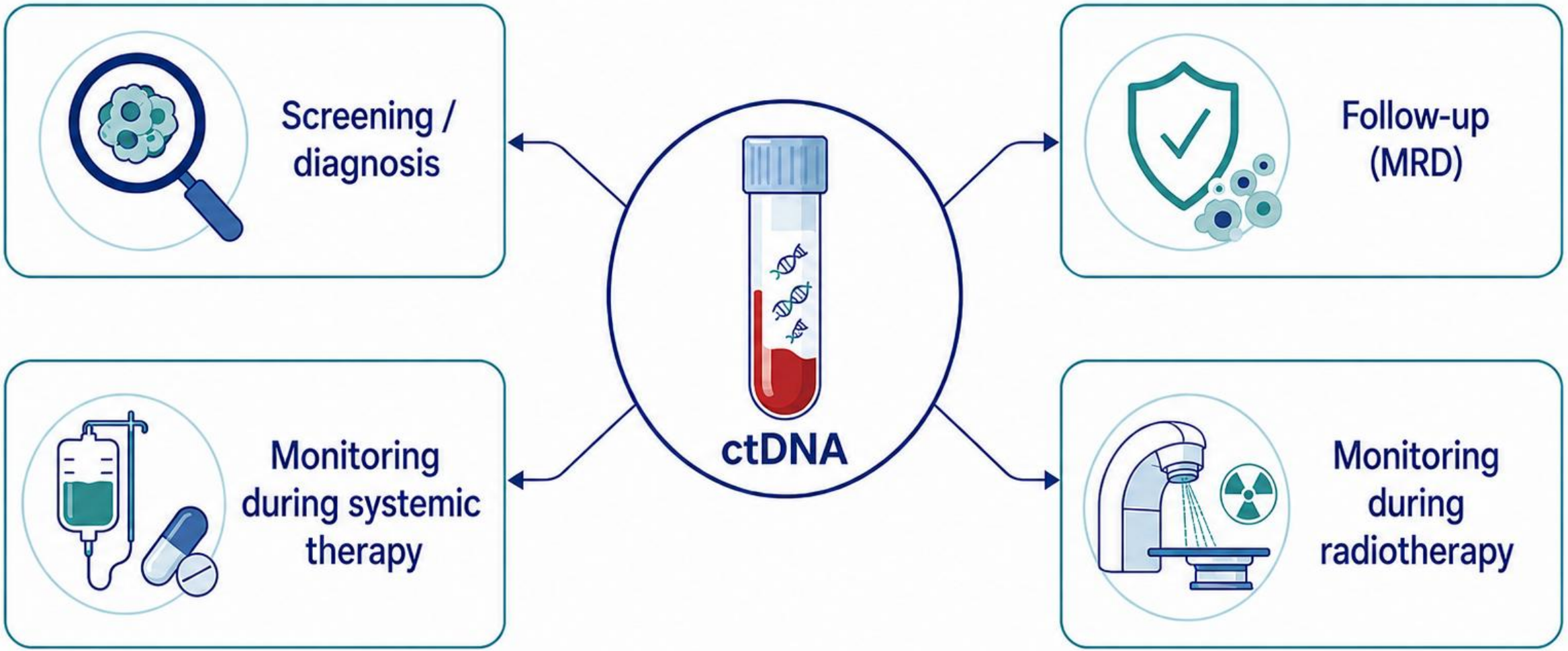
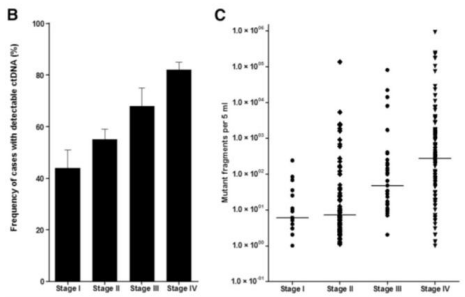


Figure by Garm Spindler

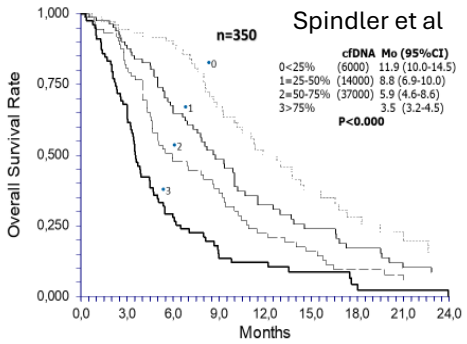
Possible applications of ctDNA

BEFORE

Chetan Bettegowda, et al. Sci Transl Med. 2015

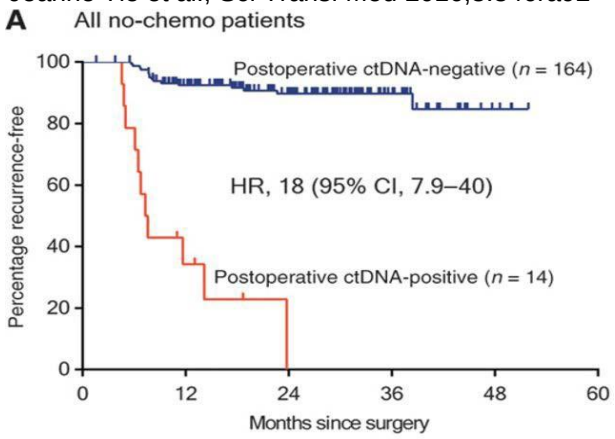


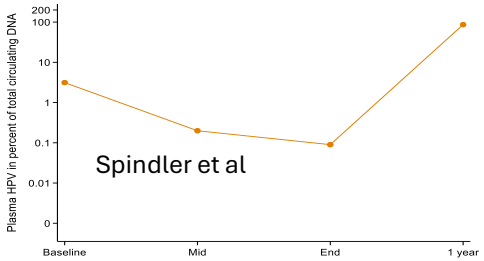
BEAMing + NGS



AFTER

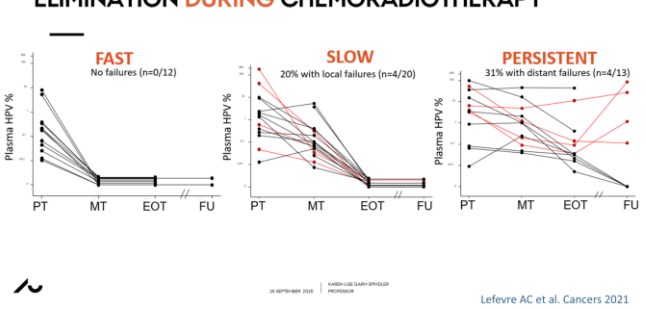
Jeanne Tie et al., Sci Transl Med 2016;8:346ra92





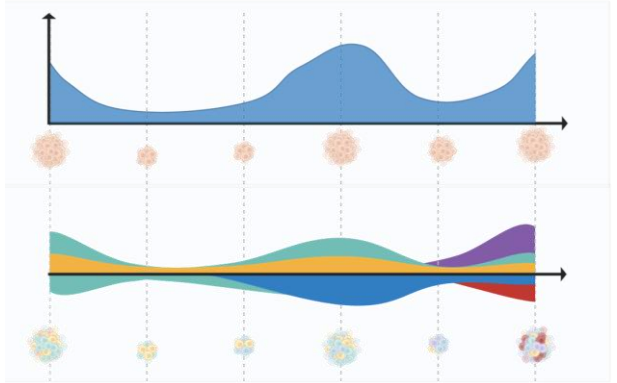
CR
Distant failure
Lead time: 2 years

DURING



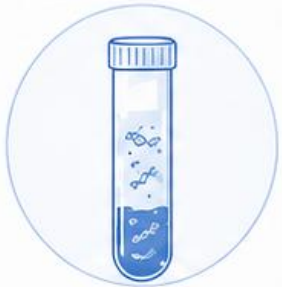
Lefevre AC et al. Cancers 2021

MONITORING – treatment effect



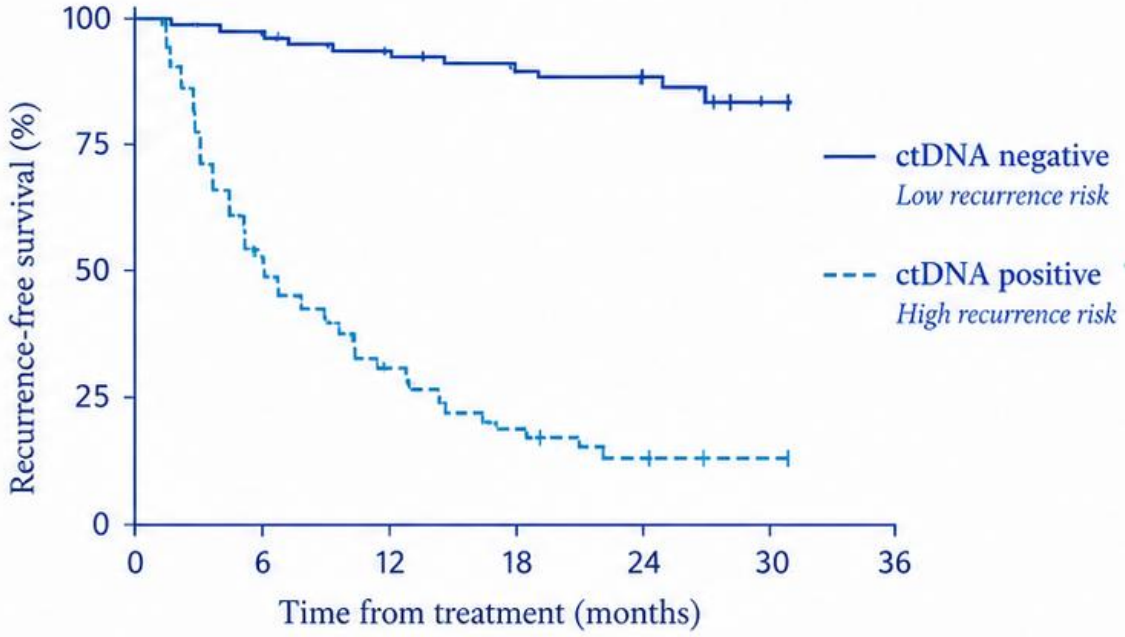
Clinical consequences of ctDNA MRD

ctDNA positive



Escalate
Treatment escalation

Recurrence-free survival
(schematic)



ctDNA negative

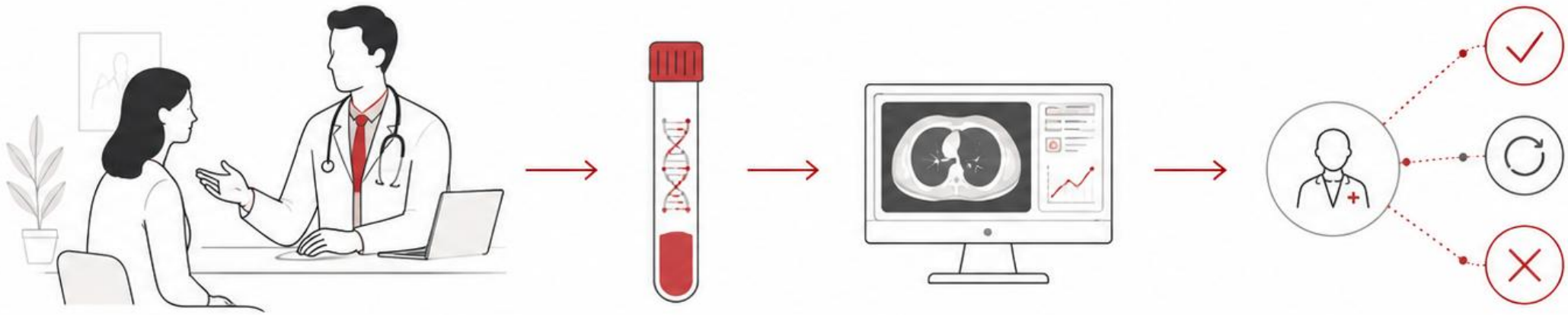
De-escalate
Treatment de-escalation

Illustrative concept: **ctDNA-positive** may need **escalation;**
ctDNA-negative may allow **de-escalation.**

The end
of the little blue
introduction book

The clinic and ctDNA potentials

Life-prolonging treatments

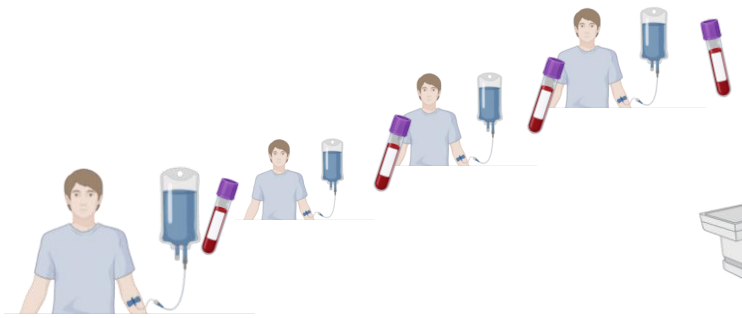


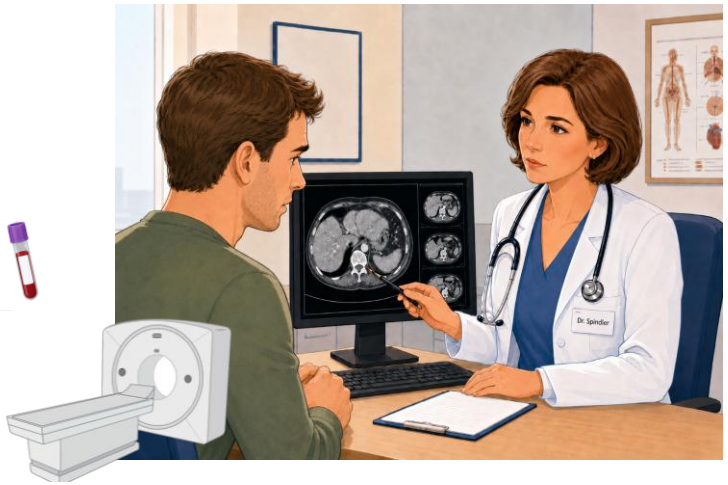
Clinical situation – life-prolonging therapy

Information about
- Disease extent
- Prognosis
- Treatment options
- Side effects
- Monitoring

If it gets smaller – does it mean that I will live longer?

Consultation on:
Does treatment work?
What are the side effects?
Is treatment tolerated?





RECIST evaluation:

Continue?
Pause?
Change?
Stop?

Inform | Monitor | Interpret | Decide

Aims of palliative systemic treatment

Treatment benefit

Prolonged life
Relieved cancer symptoms
Preserved quality of life

Created with Open AI

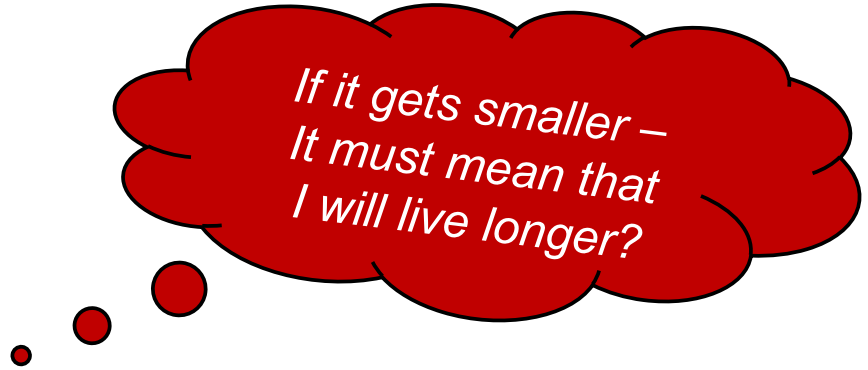
Treatment burden

Toxicity
Hospital visits
Reduced quality of life

Clinical limitations of RECIST (Imaging)

- Imaging is performed at fixed intervals
- Anatomical response may lag behind biological response
- Some diseases are difficult or impossible to measure
- Mixed response and pseudoprogression can complicate interpretation
- CT-based monitoring adds burden for patients and healthcare systems

Is imaging RECIST the optimal surrogate marker for survival?



The problem: surrogate endpoints ≠ patient benefit

Modern phase III oncology trials: primary endpoint “success” is often not matched by OS or QoL superiority

Meta-epidemiological analysis of 791 trials

Sherry et al., JAMA Oncology 2025

53%

interpreted as showing primary endpoint superiority

Most commonly based on response rate or progression-free survival.

28% **Overall survival superiority**

only 28% of trials

11% **Quality-of-life superiority**

only 11% of trials

6% **Both OS and QoL superiority**

only 6% of trials

Take-home: response tools must prove value in outcomes that matter — survival, quality of life, burden and cost.

Reference: Sherry AD et al. Overall Survival and Quality-of-Life Superiority in Modern Phase 3 Oncology Trials: A Meta-Epidemiological Analysis. JAMA Oncol. 2025;11(7):718–724. doi:10.1001/jamaoncol.2025.1002

RECIST a suboptimal surrogate endpoint

Meta-analyses show limitations of response rate as surrogate endpoint

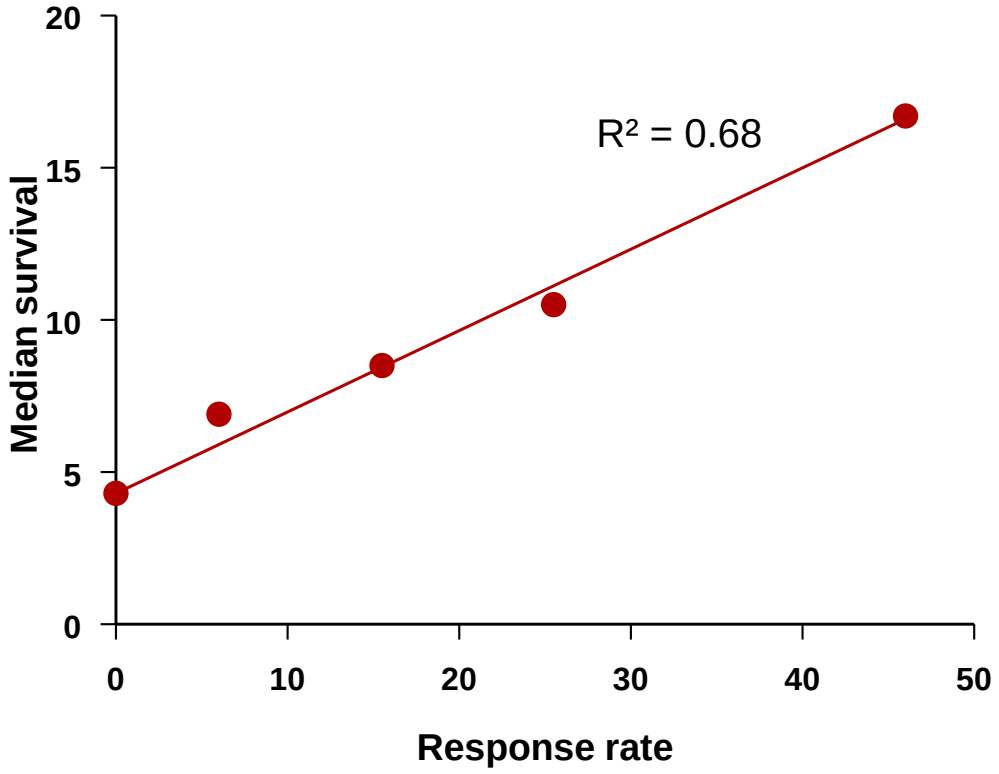
> ***For 21 years, novel cancer drugs have typically been approved based on one single, often uncontrolled, clinical trial, measuring surrogate endpoints.***
>
> ***This leaves cancer patients without solid evidence that novel drugs improve their survival or QoL — and there is no indication towards improvement.***

Response rate ≠ reliable evidence of survival benefit

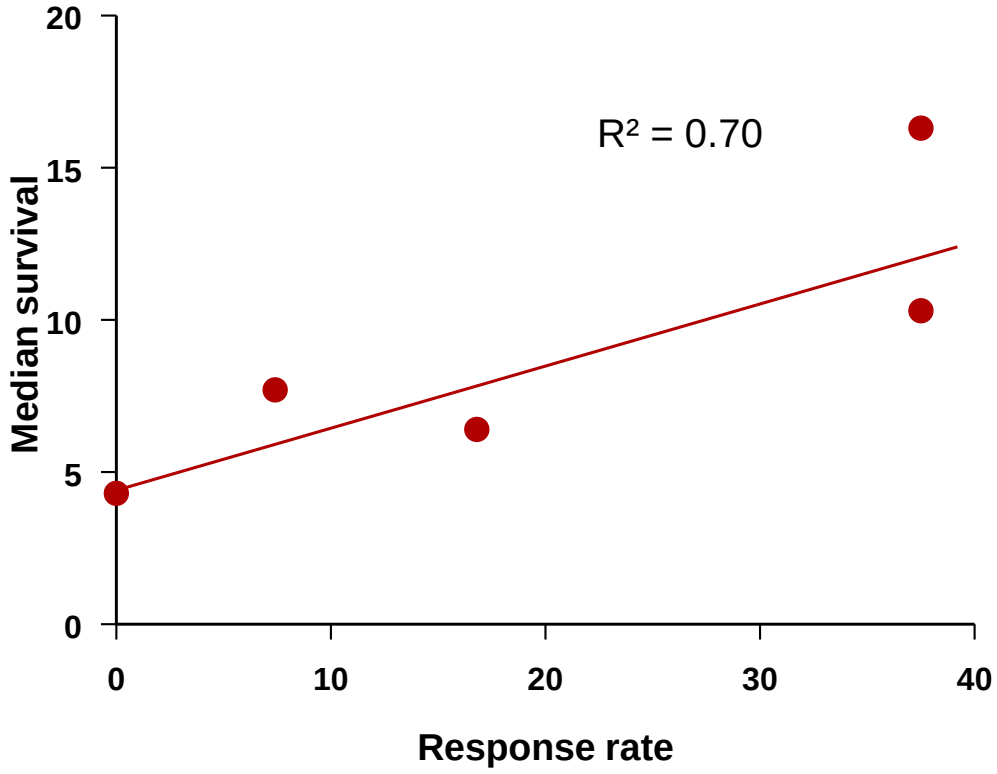
The evidence base of US Food and Drug Administration approvals of novel cancer therapies from 2000 to 2020. Gloy et al. Int J Cancer. 2023;152(12):2474–2484.

So how can ctDNA change oncology ?

ctDNA / blood based assessment



Radiologic imaging



Better – Earlier – Easier measurement of effect

Jakobsen A, Andersen RF, Hansen TF, et al. Early ctDNA response to chemotherapy. A potential surrogate marker for overall survival.
Eur J Cancer 2021;149:128–133.

Patient perspective

“The benefits for patients are obvious:

Earlier detection of progression or resistance

No useless treatment with pointless toxicity

Option to change treatment early and potentially improve survival

Reduced travel burden when blood samples can be handled locally

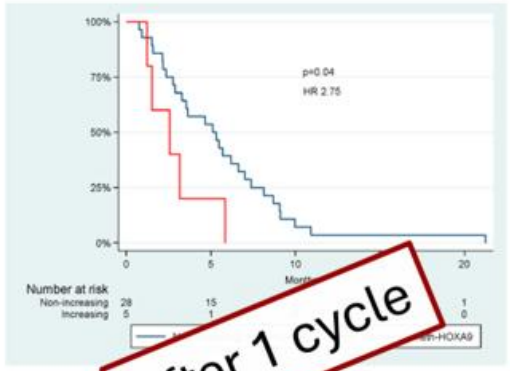
ctDNA utilization may improve QoL!”

Former patient quote, adapted for presentation.

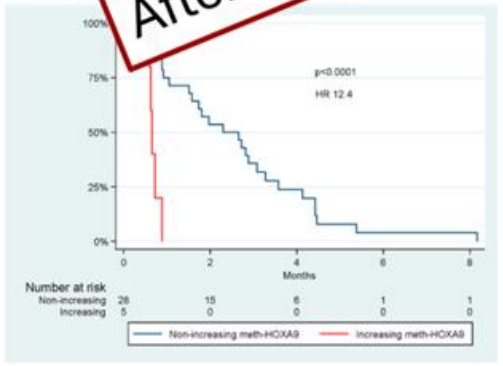
Evidence base

Biliary tract cancer

OS



PFS

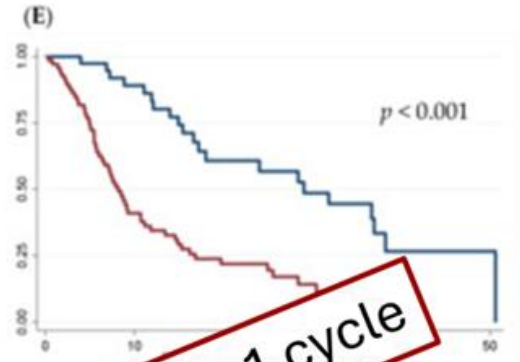


After 1 cycle

Andersen LB et al. *Cancers.* 2022

Ovarian cancer

OS



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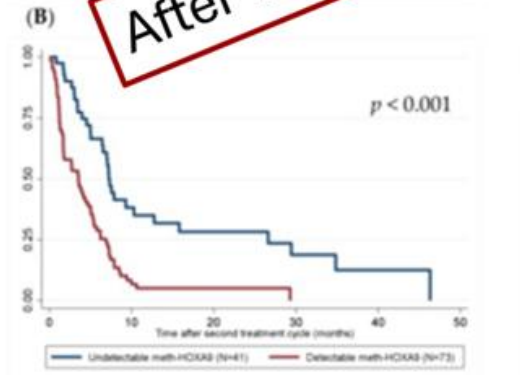
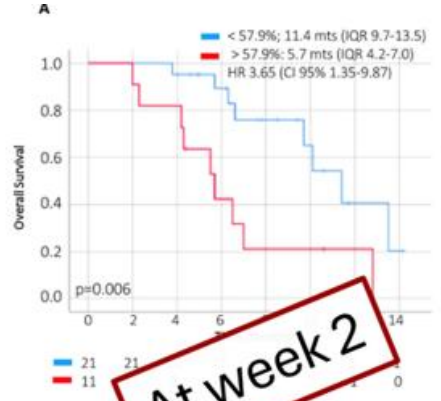


After 1 cycle

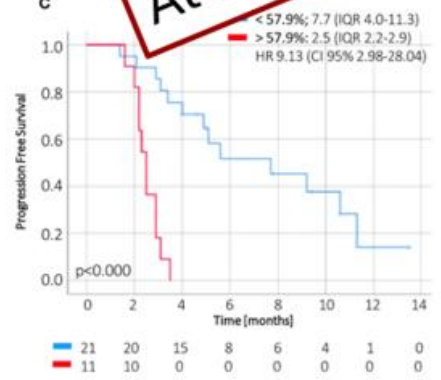
Faaborg L et al. *Cancers.* 2022

Pancreatic cancer

OS



PFS



At week 2

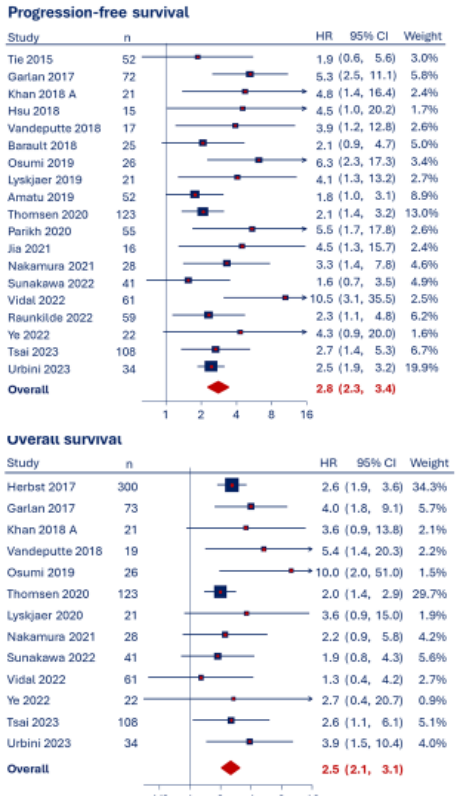
Kirchweger P et al. *Front Oncol.* 2022

Early ctDNA dynamics show prognostic signal across tumor types

Evidence base

DACY
Danish Group of Young ctDNA researchers
– working towards implementing ctDNA in the clinical setting

Colorectal cancer



Non small celle lung cancer

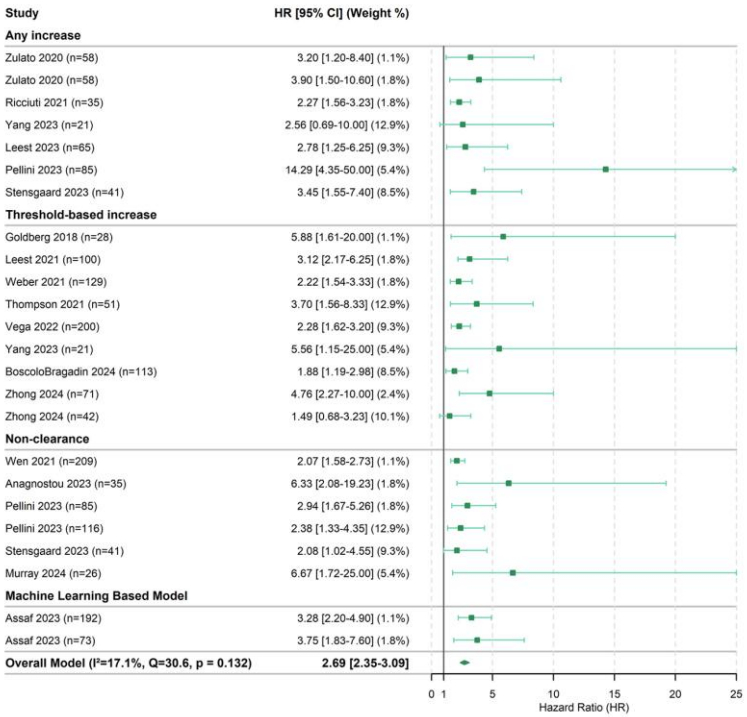
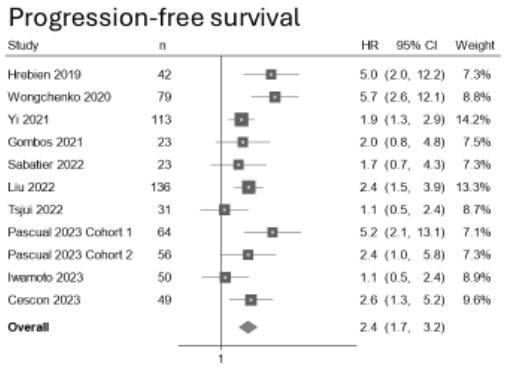
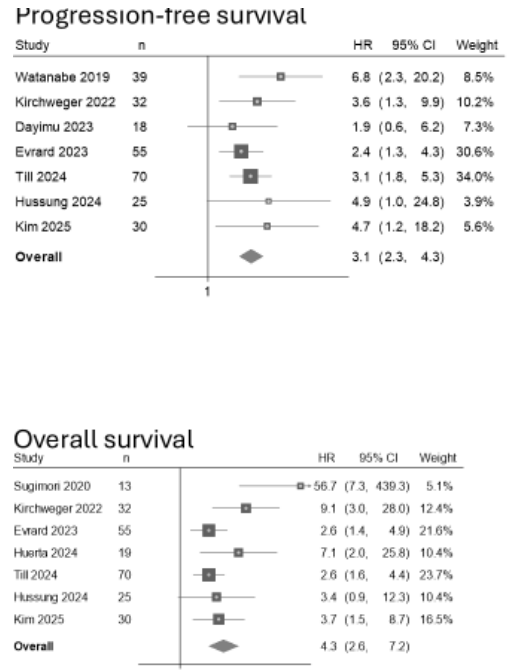


Fig. 5. Meta-analysis of ctDNA Dynamics and OS

Breast cancer



Pancreatic cancer



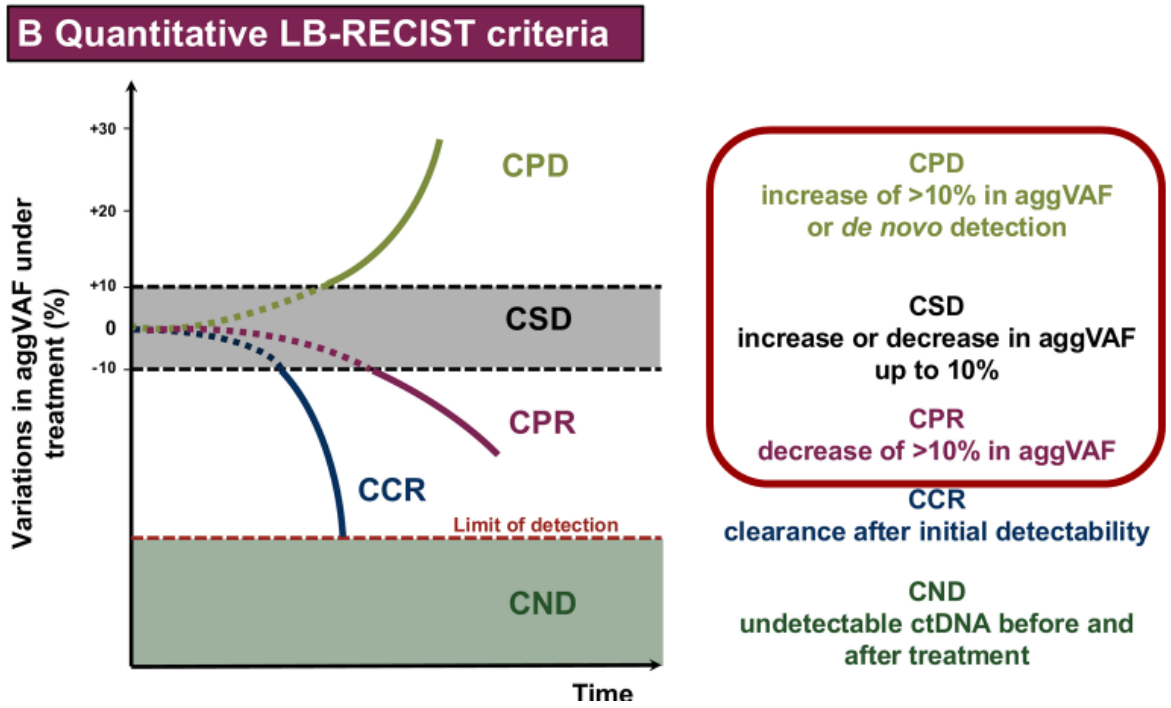
Early ctDNA dynamics show prognostic value across tumour types

References: Callesen et al. 2026; Steiniche et al. 2026; Andersen et.al.2026, and selected analyses which are confidential / unpublished data (DACY).

“ We need reliable ctDNA response criteria to inform clinical decisions „

Liquid Biopsy Criteria - example

LB-RECIST response categories



CPD
increase of >10% in aggVAF
or *de novo* detection

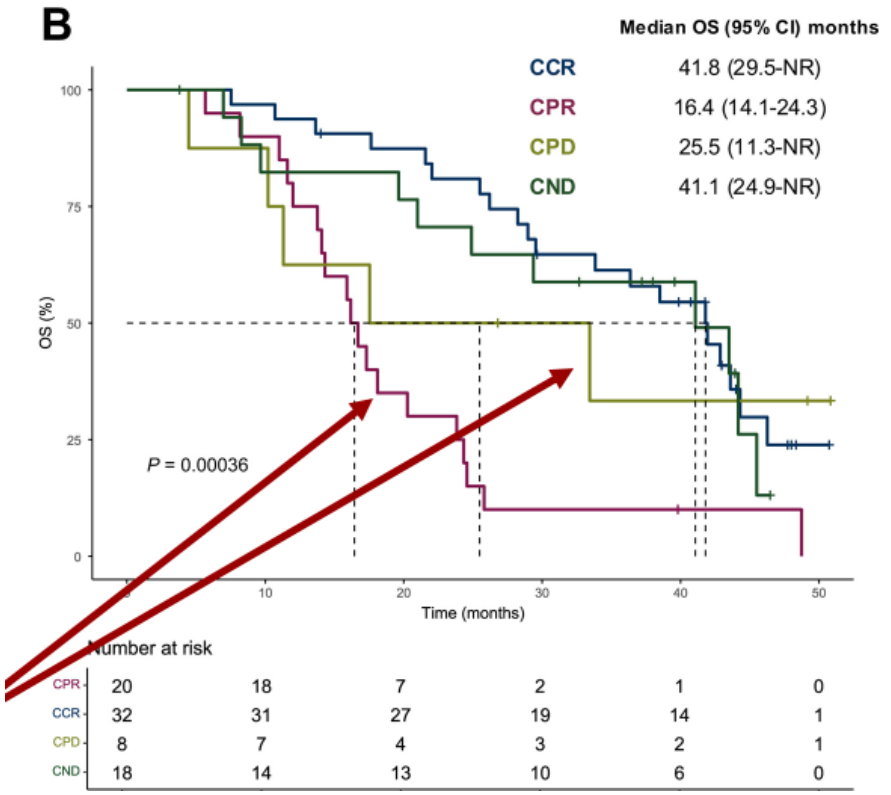
CSD
increase or decrease in aggVAF
up to 10%

CPR
decrease of >10% in aggVAF

CCR
clearance after initial detectability

CND
undetectable ctDNA before and
after treatment

Association with overall survival

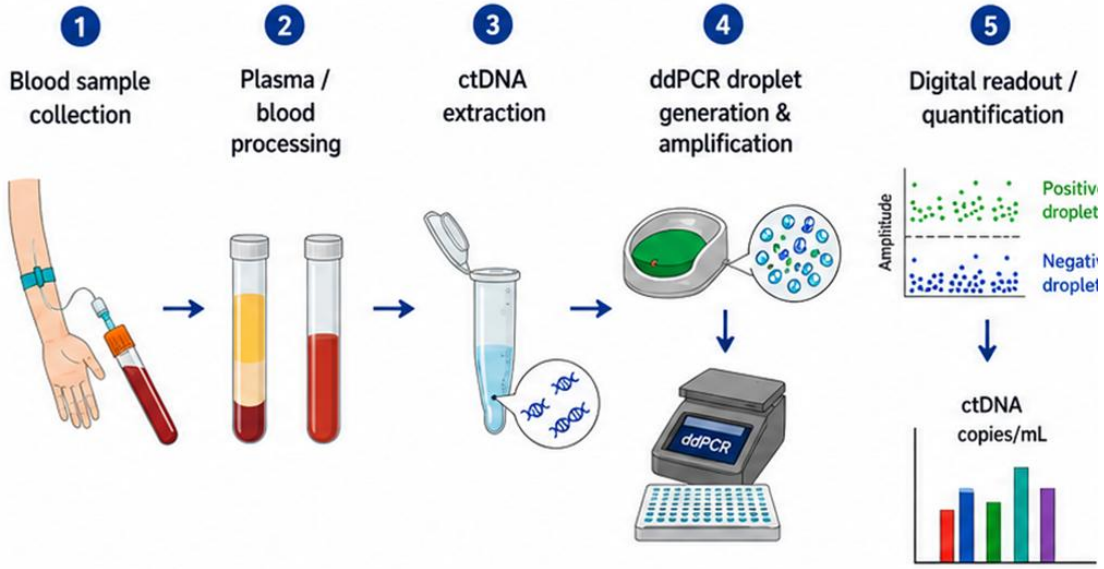


Response categories are simple to apply — but based on relative ctDNA/VAF changes

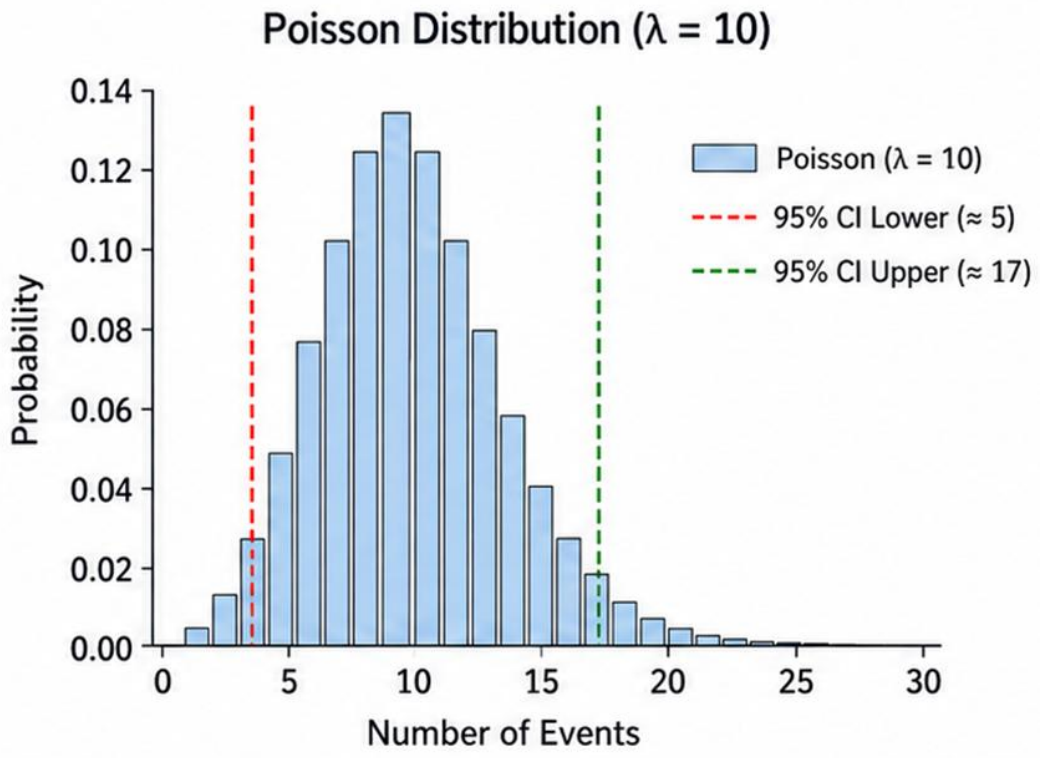
Martelli V et al. ESMO Open. 2025;10(9):105760.

Can we find (better) independent criteria?

ddPCR workflow



Sample-specific Poisson uncertainty



ddPCR provides sample-specific quantification with 95% CIs for the individual sample

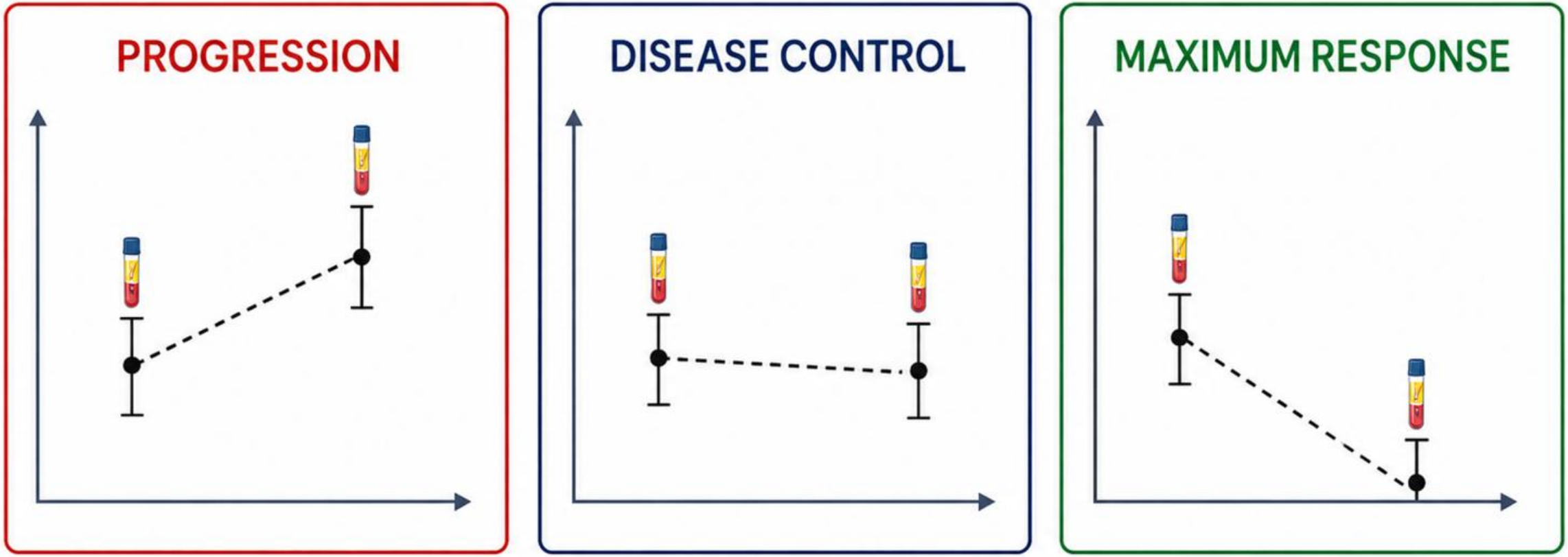
Modified from Jacobsen CM et al. *Clin Colorectal Cancer* 2025. Concept of ddPCR quantification based on Poisson statistics.

RECIST v1.1 versus ctDNA-RECIST

Response category	RECIST v1.1	ctDNA-RECIST
Progression	At least a 20% increase in the sum of diameters of target lesions	An increase of ctDNA above the previous value with no overlap of the two CI's
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression	Overlap of the current and previous CI's, indicating no significant change
Partial response	At least a 30% decrease in the sum of diameters of target lesions	A decrease below the previous value with no overlap of the two CI's, but the lower CI does not overlap 0
Complete / near complete response	Complete response: disappearance of all target lesions. No specific near-complete RECIST category	Near complete response: a decrease below the previous value with no overlap of the two CI's and with the lower CI overlapping 0. Complete response: undetectable ctDNA

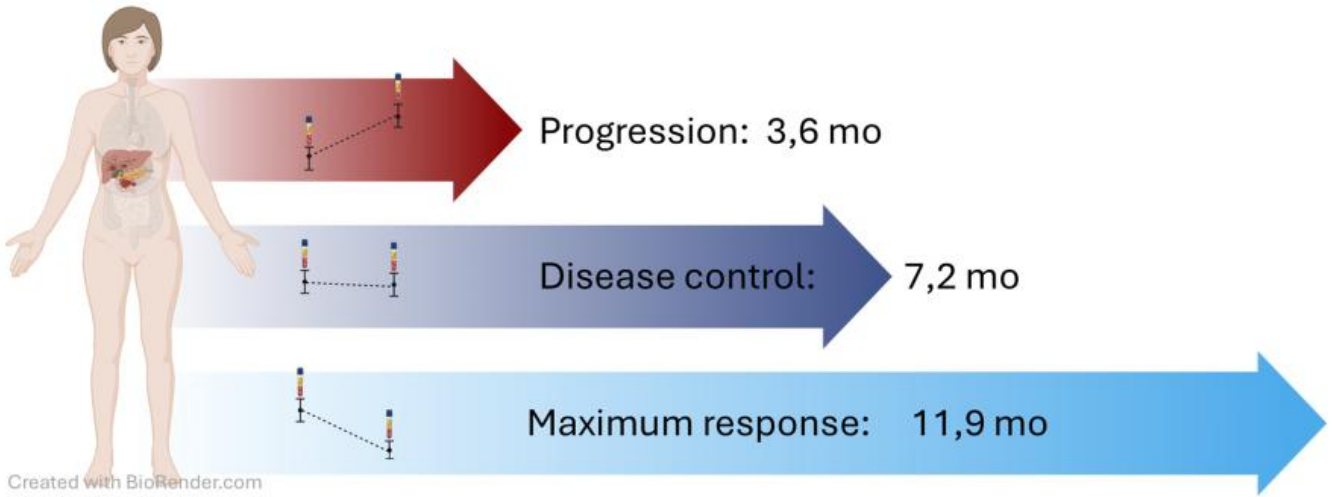
1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–247.
2. Jakobsen AKM, Spindler KLG. ctDNA-Response evaluation criteria in solid tumors – a new measure in medical oncology. Eur J Cancer. 2023;180:180–183.
3. Spindler KLG, Jakobsen A. Circulating Tumor DNA: Response Evaluation Criteria in Solid Tumors – can we RECIST? Focus on colorectal cancer. Ther Adv Med Oncol. 2023;15:17588359231171580.

Clinical ctDNA-RECIST response groups

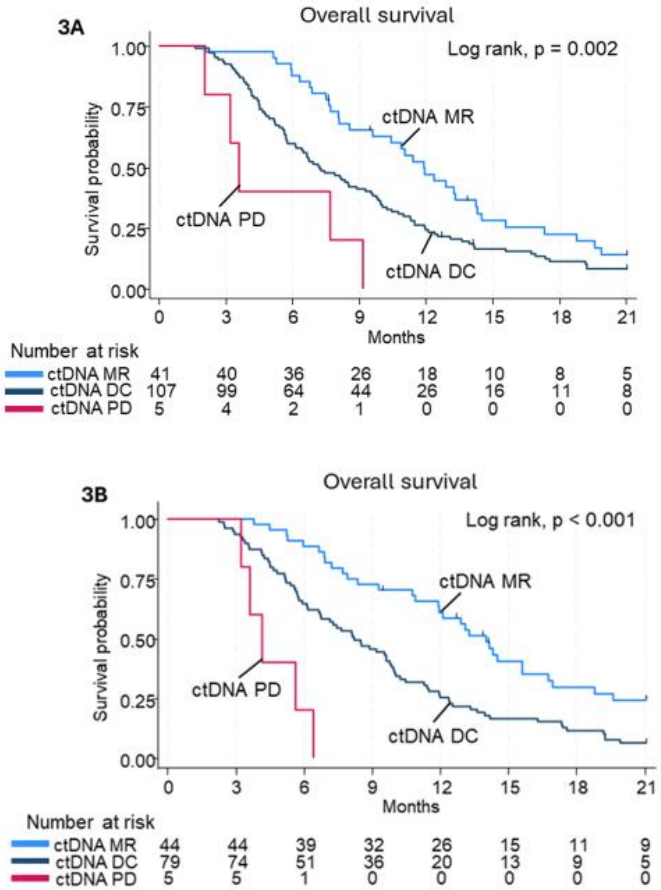


ctDNA-RECIST validation in pancreas cancer

ctDNA-RECIST response groups



Overall survival



Steiniche MM et al. *Clin Cancer Res* 2025 – The Danish BIOPAC collaboration.

ctDNA
Better – Earlier – Easier ?

for response evaluation

Blood-based assessment as a clinical decision tool

How can we use ctDNA for monitoring?

RECIST v2.0

Integrating the value of liquid biopsy into monitoring with imaging

—

ctDNA-RECIST

Validating our specific ddPCR criteria for supplementing or replacing imaging

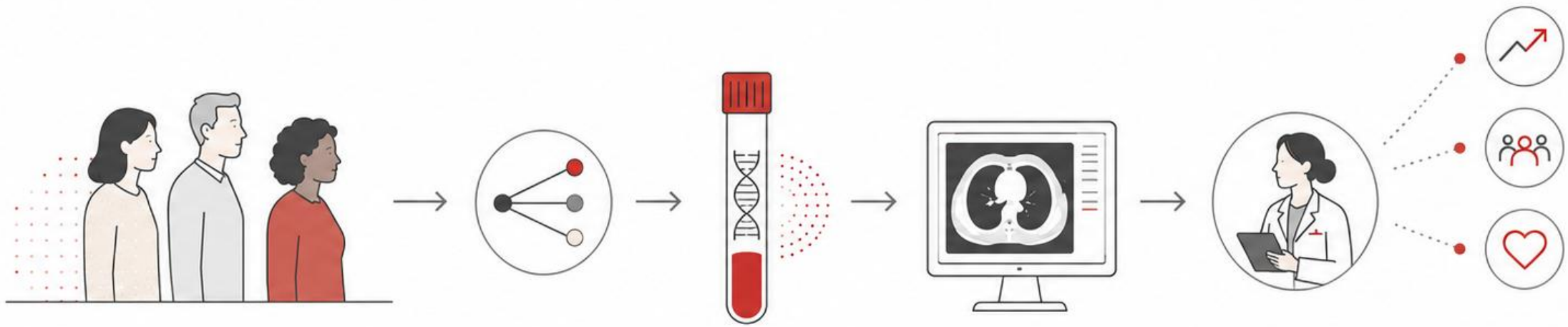
Unmet questions I would like to discuss

- Which challenges cannot be overcome with imaging alone?
- Which tumor types are ready for use of ctDNA testing?
- Which tumor types can be candidates for sparing of routine imaging ?
- Which procedures are best options?
- Which clinical situations should not be considered for use of ctDNA-RECIST?
- How do we handle ctDNA negative situations?
- What is the cost-effectiveness of ctDNA use compared to SOC?
- How do we best design the clinical trials for validation?

Collaboration across imaging, pathology and liquid biopsy is needed to solve these questions.

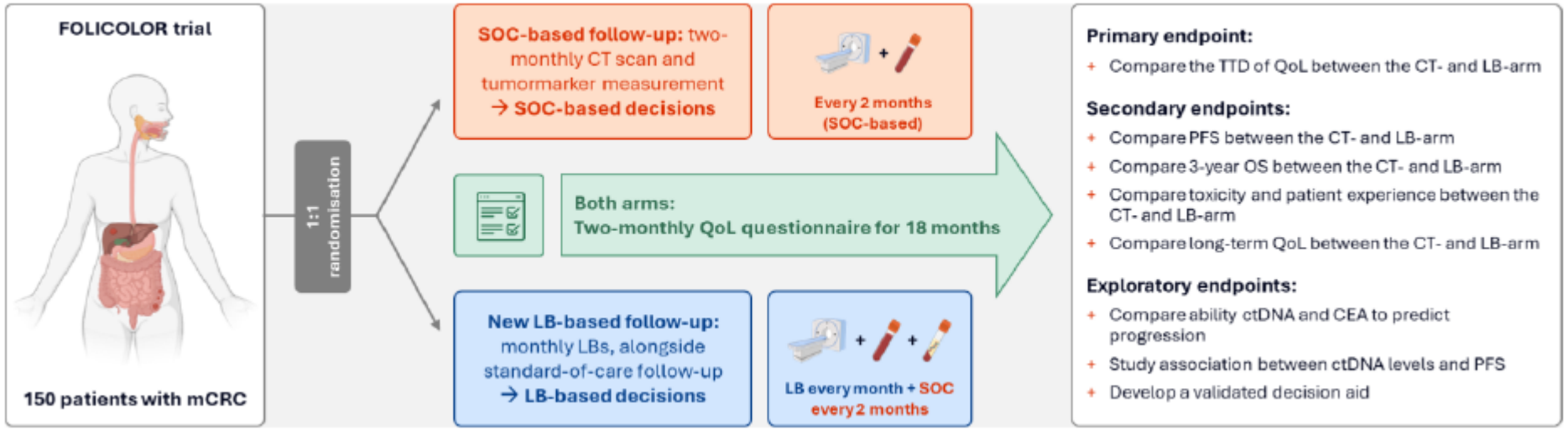
Ongoing Clinical Trials

Testing ctDNA in clinical practice



FOLICOLOR: Following therapy response through liquid biopsies in metastatic colorectal cancer patients

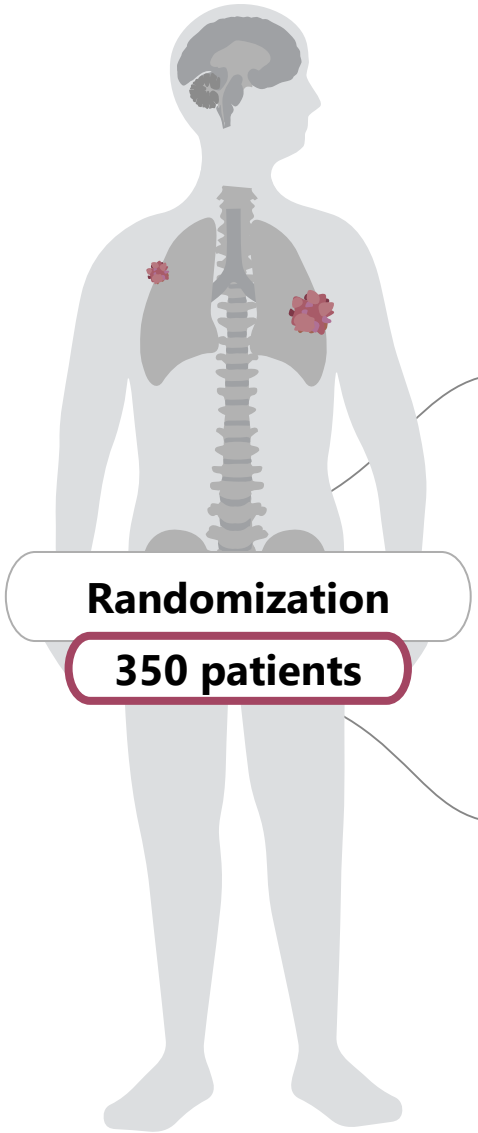
- **Phase III, open-label, prospective, randomized, multicentric study (NCT07558083) in 9 sites in Belgium**
- **Patients with non-resectable mCRC receiving first line chemotherapy**
- **113 patients included and still open for recruitment**
- **Primary endpoint: time to deterioration of quality of life (TTD) – Secondary endpoints: OS, PFS, patient experience,…**
- **Study design:**
  - Arm A (experimental): ctDNA guided disease monitoring based on NPY methylation. Switch to second line therapy upon progression in LB
  - Arm B (control): Standard of care monitoring with imaging techniques.



Courtsy Dr. Timmo Vandamme; Antwerpen, BE

PRELUCA study

Prediction in Lung Cancer

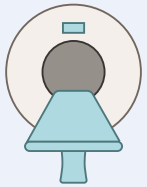


Diagnosis

Randomization

350 patients

CT scan evaluation



CT scan
/12 weeks

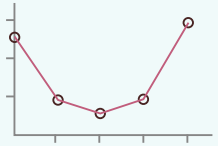
Evaluation by
iRECIST

Immunotherapy

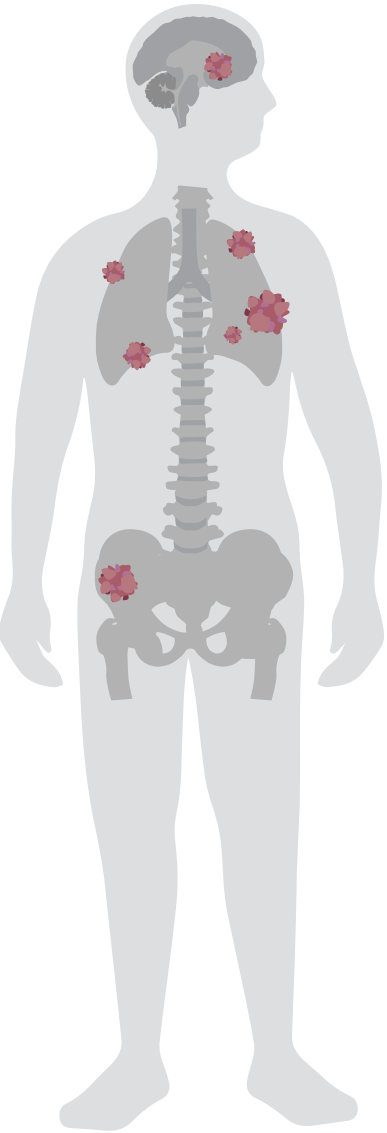
Observation

ctDNA evaluation

Liquid biopsy
/3-4 weeks



Evaluation by
ctDNA RECIST

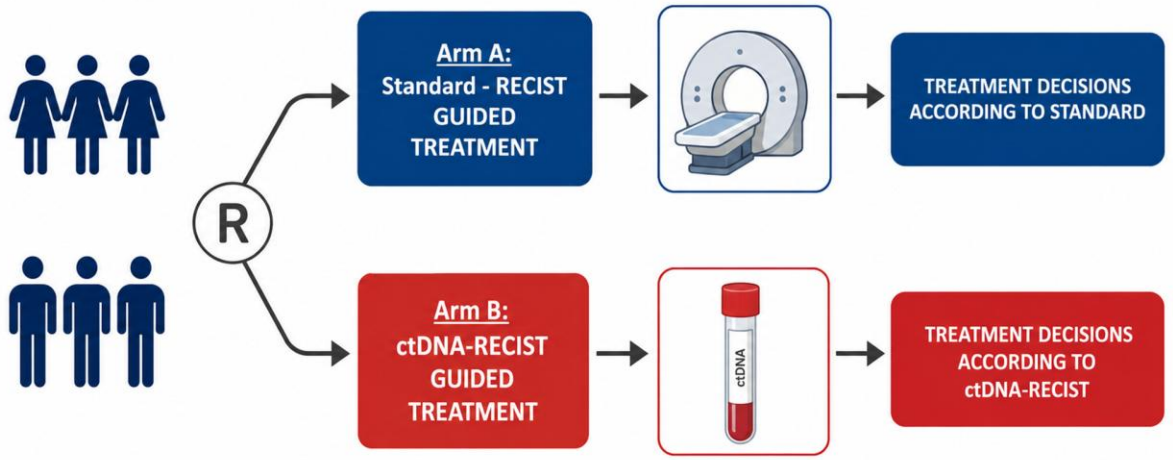


Progression

Malene Støchkel Frank
Consultant, Clinical Research Associate Professor
Department of Clinical Oncology, Zealand University Hospital, Denmark
malf@regionsjaelland.dk

ctDNA-RECIST Trial - NCT06562348 - including

Criteria
Non-curable GI cancer
Measurable disease
Systemic treatment
Not immunotherapy
All lines



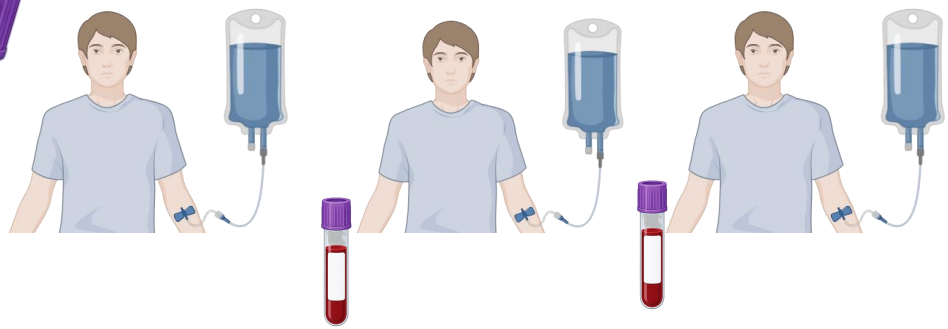
Endpoints
Feasibility N=167
Non-inferiority N=368
QoL
Biology
Methods
Cost-effectiveness

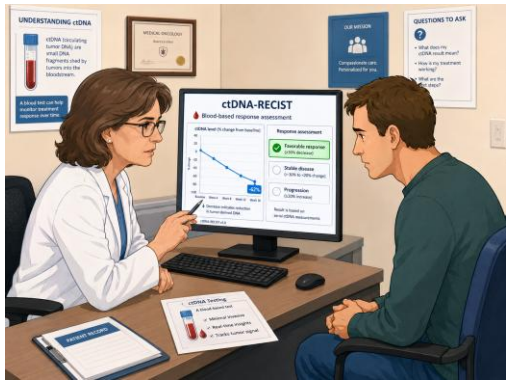
AIM: To investigate ctDNA-RECIST guided treatment of metastatic cancer in a randomized trial.

Sponsor, Principal Investigator, Initiator: Karen-Lise Garm Spindler, MD, PhD, DMSc, Professor, Dept. of Oncology, Aarhus University Hospital, DK
Site Investigator: Torben Frøstrup Hansen, MD, PhD, DMSc, Professor, Vejle Hospital, Denmark
Laboratory lead: Rikke Fredslund Andersen, PhD, Vejle Hospital, Denmark
Statistician feasibility study: Signe Timm, PhD, Vejle Hospital, Vejle, Denmark
Scientific advisor: Anders Jakobsen, Advisor, MD, DMSc, Professor Emeritus, Vejle Hospital, Denmark
Scientific study coordinator: Mette Møller Steiniche, MD, Aarhus University Hospital,, Denmark

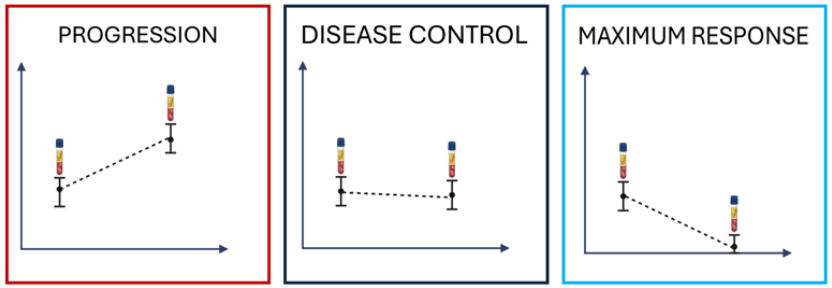
ctDNA-TEST : Pragmatic tumor-agnostic droplet digital PCR test for NPY (CRC)/HOXA9 (PDAC) Aberrant methylations

Early ctDNA response evaluation in the ctDNA-RECIST trial

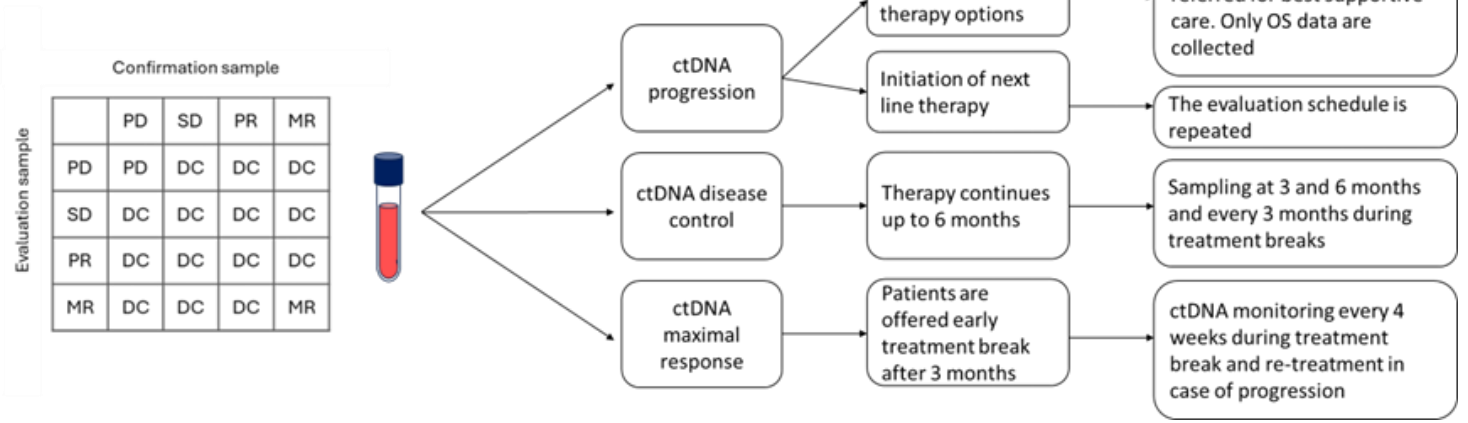




ctDNA-RECIST classification



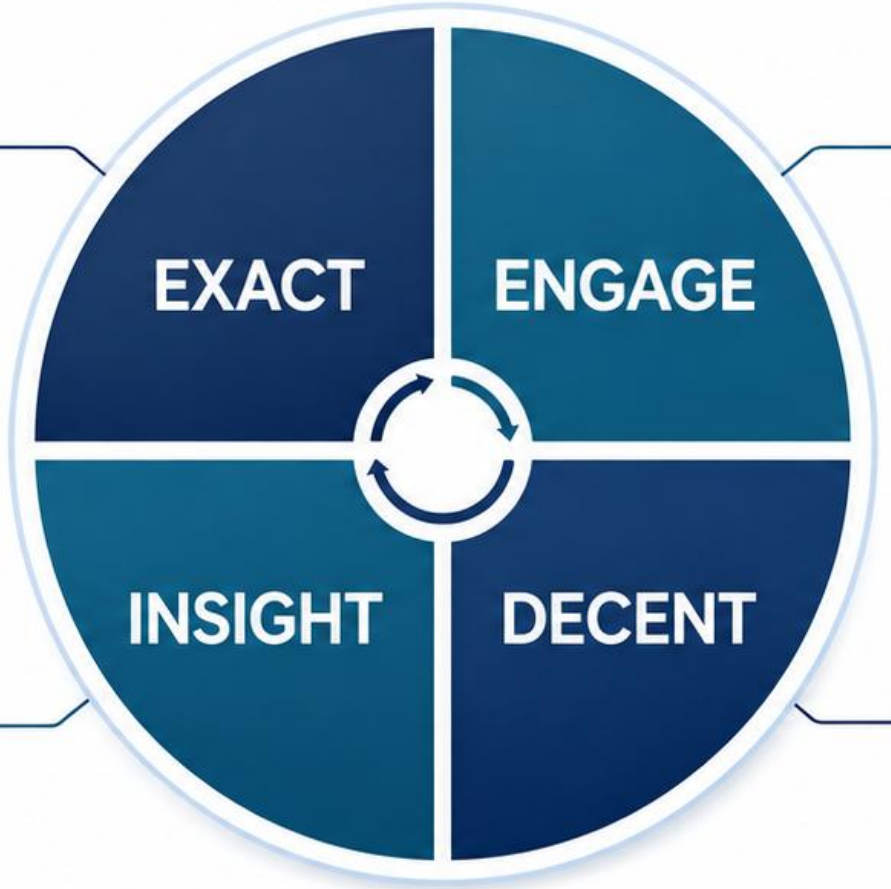
ctDNA decision making



Better – earlier – easier - measurement of effect ?

The ctDNA-RECIST Program

External Validation of ctDNA-RECIST Across Cancer Types



Empowering ctDNA-Guided Oncology through Awareness, Guidance and Engagement

AI optimized ctDNA guided treatment

Decentralization of ctDNA testing

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Thank you!

ctDNA – Can we RECIST?

ACKNOWLEDGEMENTS

- Patients and families
- Colleagues and collaborators

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- Regionernes Medicin Pulje
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