

# DANSKE KRÆFTFORSKNINGS DAGE 2023

## Hurtigere kræftdiagnoser gennem cirkulerende tumor DNA drevet opsporing

Claus Lindbjerg Andersen, professor

Aarhus Universitetshospital, Aarhus Universitet

DCCC - Dansk Nationalt forskningscenter for cirkulerende tumor DNA guidet kræftbehandling

#DKD2023

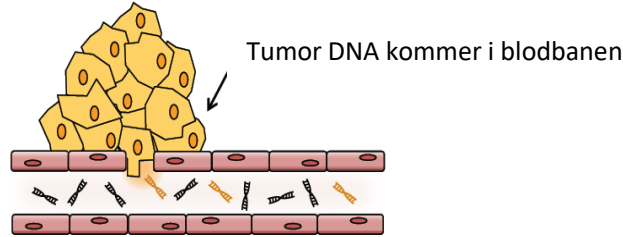
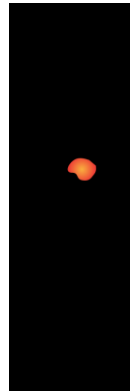
#SamarbejdeOmKræft

Sli.do

#131525

# Cirkulerende tumor DNA analyser

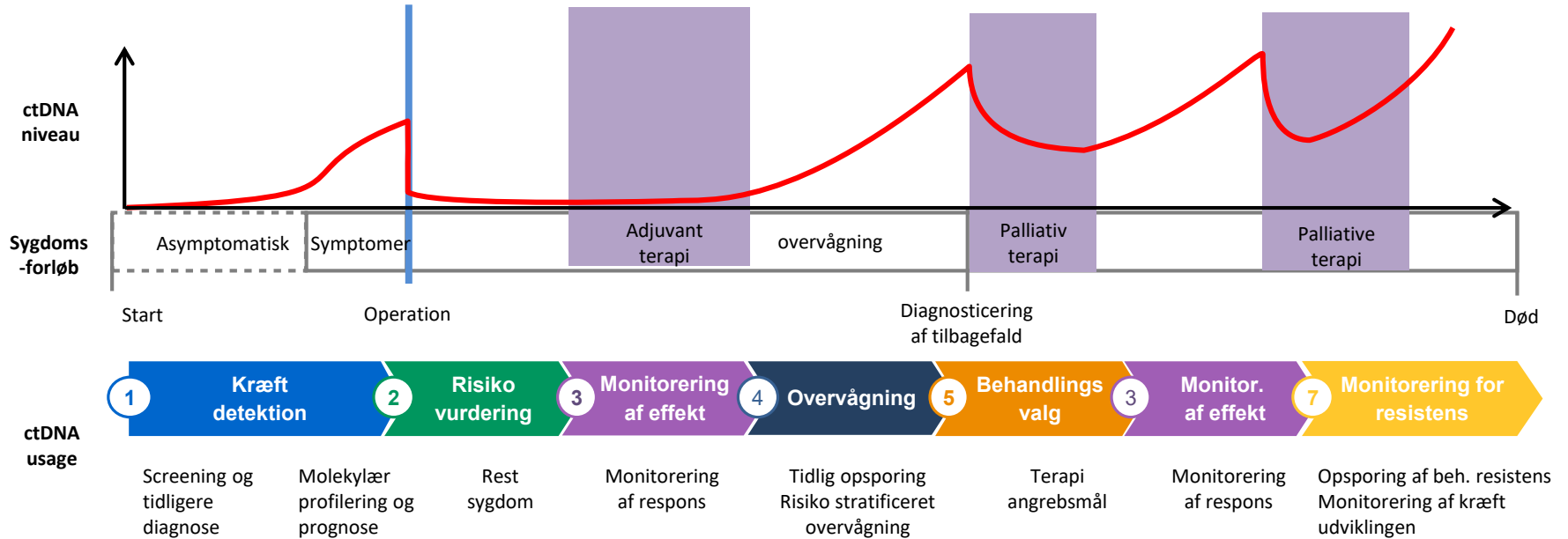
- en vigtig brik i fremtidens kræftbehandling -



Cellefrit DNA isoleret  
fra plasma

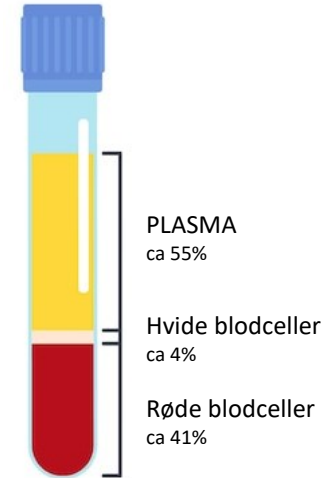
halveringstid på under 2 timer

# ctDNA har potentiale til at blive anvendt igennem hele sygdomsforløbet



# Historisk overblik: ctDNA feltet

- 1948 Opdagede DNA i blod plasma (den ikke-celleholdige del af blodet)<sup>1</sup>
- 1977 Opdagede forhøjede niveauer af celle-frit DNA i blod fra kræftpatienter<sup>2</sup>
- 1989 Opdagede tumor DNA i blodet fra kræftpatienter<sup>3</sup>
- 2008 ***Proof of principle***: kemoterapi inducerede ændringer i **ctDNA niveau afspejler tumor byrde** ændringer<sup>4</sup>
- 2010-13 Mange højt profilerede ***proof of principle artikler*** med ***retrospektive analyser*** illustrerer det store og brede **kliniske potentiale af ctDNA**<sup>5-10</sup>
- 2013- Undersøge og bekræfte det kliniske potentiale af ctDNA, i veldesignede ***prospektive observations studier*** med tilstrækkelig statistisk styrke
- 2017- ***Prospektive randomiserede kliniske interventions studier*** mhp at dokumentere fordelene (klinisk, livskvalitet, sundhedsøkonomisk) af ***ctDNA guidet klinisk beslutningstagning***



1 Mandel and Metais, C R Seances Soc Biol Fil, 1948

2 Leon et al., Cancer Research, 1977

3 Stroun et al., Oncology, 1989

4 Diehl et al., Nature Medicine, 2008

5 McBride et al., Genes Chromosomes Cancer, 2010

6 Forshew et al., Science Translational Medicine, 2012

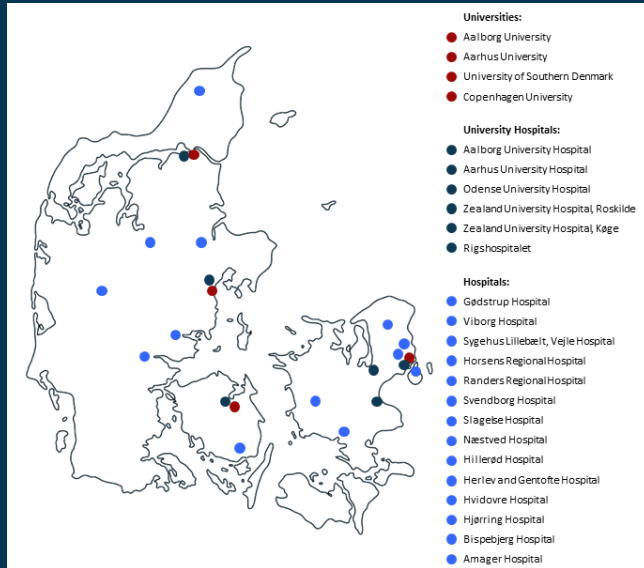
7 Dawson et al., New England Journal of Medicine 2013

8 Leary et al., Science Translational Medicine, 2013

9 Murtaza et al, Nature, 2013

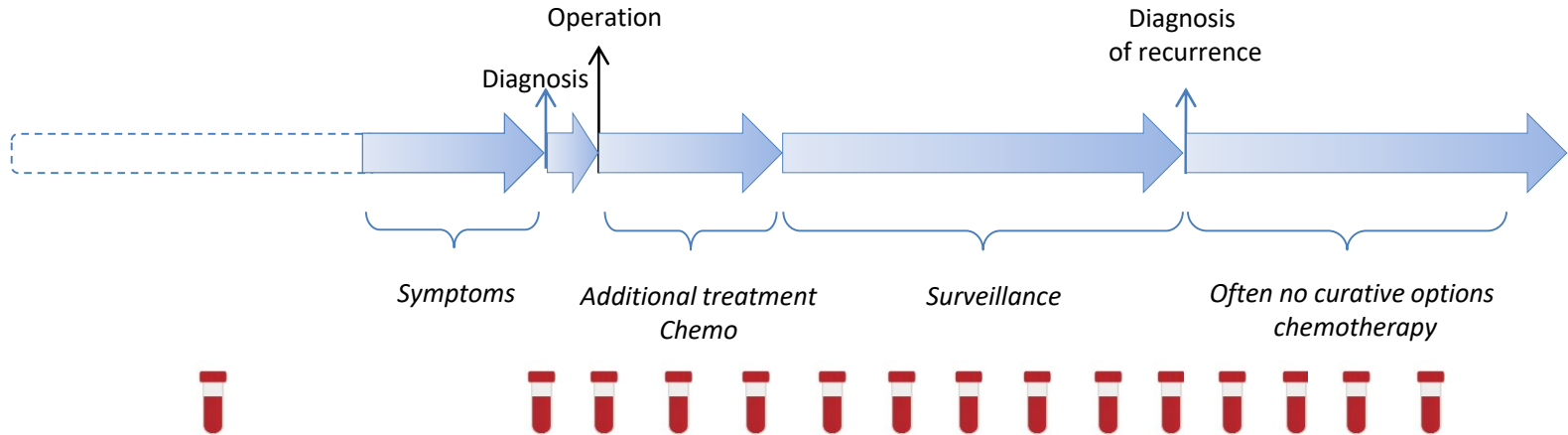
10 Spindler et al, Acta oncologica, 2013

# DCCC – Dansk Nationalt forskningscenter for cirkulerende tumor DNA guidet kræftbehandling



- Opstartet i 2020
- En national ramme til at fremme ctDNA guidet beslutningstagning
- Styrke og fremme interaktion og samarbejde omkring ctDNA
- Fremme etableringen af nationale kliniske interventionsforsøg mhp at vurdere den kliniske effekt af cirkulerende kræft-DNA guidet behandling
- Effektiv og hurtig translation af ctDNA forskningsresultater ind i klinisk praksis
- Generere det nødvendige evidensgrundlag for at beslutningstagere kan vælge at implementere ctDNA guidet beslutningstagning
  - Opstarts penge
  - Reducere barriere
  - Give adgang til state-of-the-art ctDNA detektions teknologier
  - Etablere nationale standarder og ”bedste praksis” for ctDNA analyser
  - Etablere ekstern kvalitetskontrol af ctDNA undersøgelser
  - Adgang til sundhedsøkonomisk ekspertise

# Clinical Focus Areas



Clinical focus areas:

**CFA1:**  
Early detection

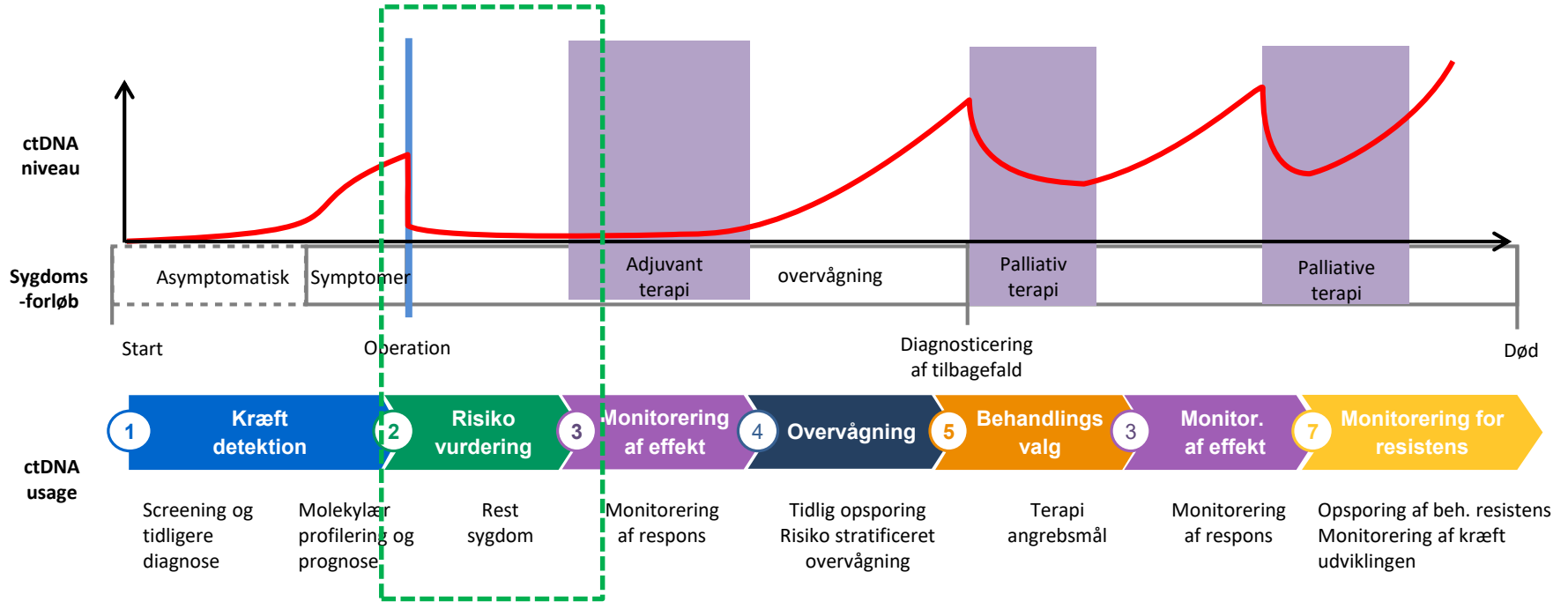
**CFA2:** Guiding adj.  
treatment

**CFA3:** Guiding  
surveillance

**CFA4:** Monitoring  
response

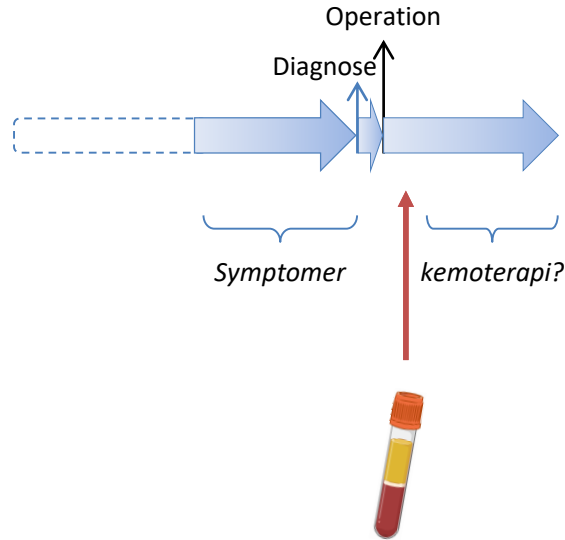
**CFA5:** Actionable targets,  
resistance, predict response

# ctDNA har potentiale til at blive anvendt igennem hele sygdomsforløbet



# Kan måling af ctDNA efter OP identificere restsygdom?

Er ctDNA en stærkere markør for restsygdom end TNM stadie ?





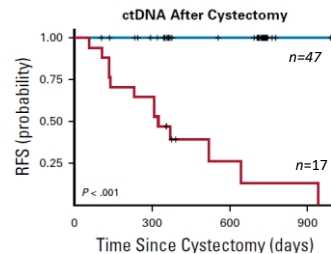
# Kan måling af ctDNA efter OP identificere restsygdom?

2019 **Journal of Clinical Oncology**  
An American Society of Clinical Oncology Journal

Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma

Emil Christensen, PhD<sup>1</sup>; Karin Birkenkamp-Demtröder, PhD<sup>1</sup>; Himanshu Sethi, MPH<sup>2</sup>; Svetlana Shchegrova, PhD<sup>2</sup>; Raheleh Salari, PhD<sup>2</sup>; Iver Nordentoft, PhD<sup>1</sup>; Hsin-Ta Wu, PhD<sup>1</sup>; Michael Knudsen, PhD<sup>1</sup>; Philippe Lamy, PhD<sup>1</sup>; Sia Viborg Lindskrog, BS<sup>1</sup>; Ann Taber, MD<sup>1</sup>; Mustafa Balcioglu, PhD<sup>1</sup>; Senen Yang, PhD<sup>1</sup>; Zoe Assaf, PhD<sup>1</sup>; Shruti Sharma, PhD<sup>1</sup>; Anthony S. Tin, PhD<sup>1</sup>; Romya Srinivasan, MS<sup>1</sup>; Dina Häfetz, PhD<sup>1</sup>; Thomas Reinert, PhD<sup>1</sup>; Samantha Navarro, BS<sup>1</sup>; Alexander Olaso, BS<sup>1</sup>; Rosalyn Ram, PhD<sup>1</sup>; Scott Dushner, BS<sup>1</sup>; Matthew Rabinowitz, PhD<sup>2</sup>; Paul Billings, MD, PhD<sup>2</sup>; Styrmyr Sigurjónsson, PhD<sup>2</sup>; Claus Lindbjerg Andersen, PhD<sup>1</sup>; Ryan Swernten, PhD<sup>1</sup>; Alesey Aleshin, MD<sup>1</sup>; Bernhard Zimmermann, PhD<sup>1</sup>; Mads Agerbæk, MD<sup>1</sup>; Cheng-Ho Jimmy Lin, MD, PhD, MHS<sup>1</sup>; Jørgen Bjerregaard Jensen, MD, DMSc<sup>1,2</sup>; and Lars Dyrskjot, PhD<sup>1,2</sup>

Blære kræft



2021 **CLINICAL CANCER RESEARCH**

ABOUT ▾ ARTICLES ▾ FOR AUTHORS ▾ ALERTS NEWS COVID-19 WEBINARS

Volume 28, Issue 3  
1 February 2022



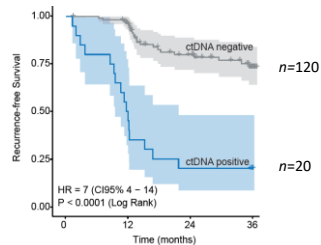
PRECISION MEDICINE AND IMAGING | FEBRUARY 01 2022

Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrences

Tanya Heisterman-Herselman, Isabela Taxonera, Amanda Frutkin, Thomas Rissari, Francisco Gimeno-Valiente, Juan Antonio Carbonell-Aurio, Shridi Sharma, Dennis Rennie, Dina Häfetz, Desamparado Rivas, Marco Russo, Susana Ribeiro, Andrei-Ionel Madalin, Lita S. Law, Per Vastgaard-Andersen, Ole Thorlacius-Ussing, Lane Harrell Iverson, Silke Anderson-Gutschalko, Himanshu Sethi, Aleksey Alekshin, Andres Cervantes, Claus Lindbjerg Andersen

Check for updates  
+ Author & Article Information  
Clin Cancer Res (2022) 28 (3): 597-617  
<https://doi.org/10.1158/1078-0432.CCR-21-2404> Article history

Tyktarms kræft  
Stage III

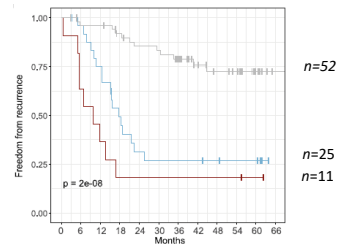


2023 **nature** | April 2023

Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA

Christopher Abbosh, Alexander M. Frankell, Thomas Harrison, Judit Kisistok, Aaron Garnett, Laura Johnson, Selvaraju Veeriah, Mike Moreau, Adrian Chesh, Tafadzwa L. Chaunzwa, Jakob Weiss, Morgan R. Schroeder, Sophia Ward, Kristiana Grigoriadis, Aamir Shahpurwalla, Kevin Litchfield, Clare Puttick, Dhruva Biswas, Takahiro Karasaki, James R. M. Black, Carlos Martínez-Ruiz, Maisee Al Bakir, Oriol Pich, Thomas R. K. Watkins, TRACERx Consortium, ... Charles Swanton

Lunge kræft  
Adenocarcinoma



# Klinisk betydning

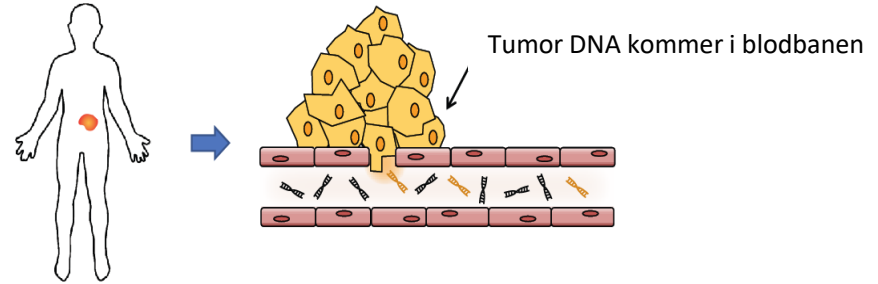
ctDNA-positiv



Mikroskopisk restsygdom



Kan mere behandling redde liv ?



# Klinisk betydning

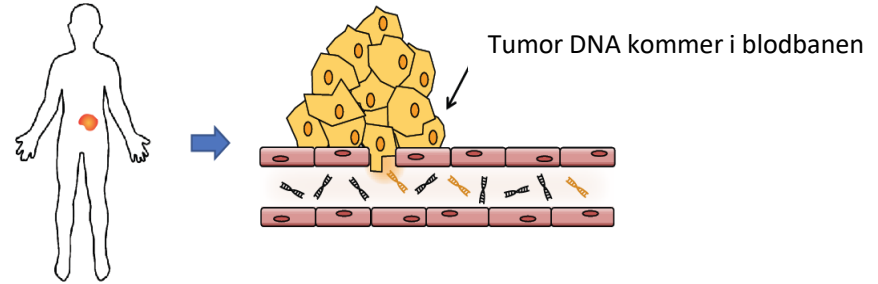
**ctDNA-negativ**



**Intet tegn på mikroskopisk  
restsygdom**

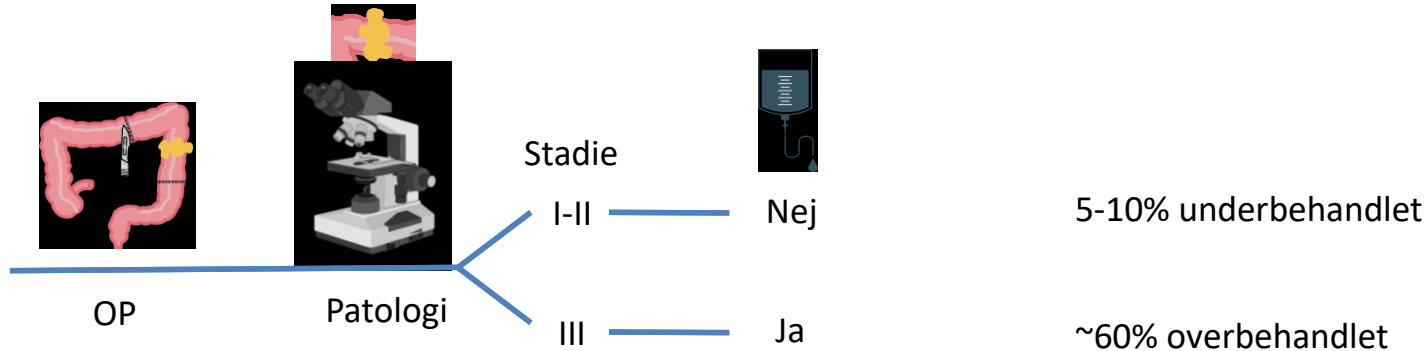


**Kan vi behandle mindre og undgå  
bivirkninger?**

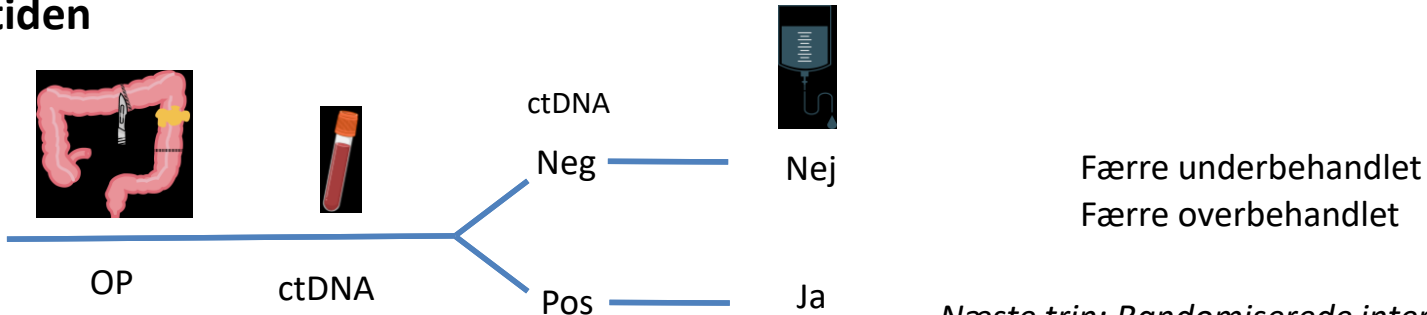


# Klinisk betydning

Idag



Fremtiden



Næste trin: Randomiserede interventionsstudier

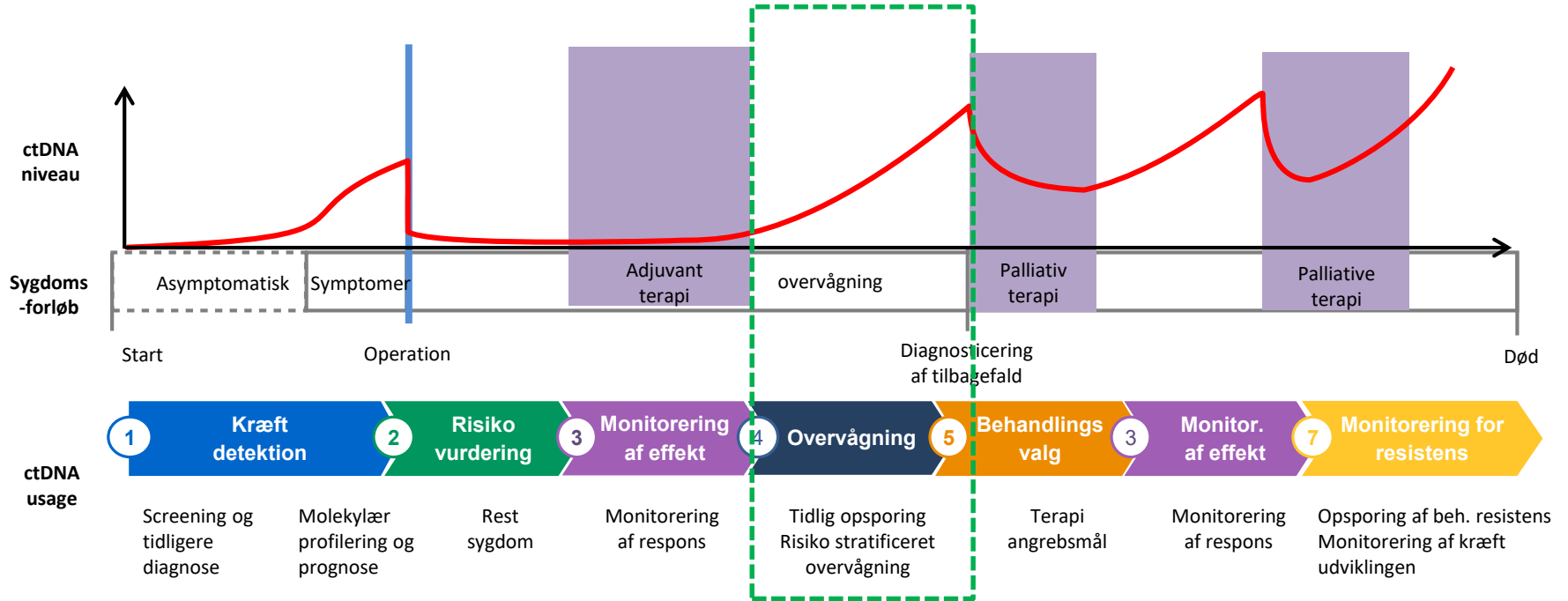
# Stadie II: randomiserede eskaleringsstudier

Trial Name/Country	Patient Population	Sample Size	ctDNA Assay	Timing of ctDNA Testing	Trial Intervention	Primary Objective
DYNAMIC (ACTRN-12615000381583) Australia	Stage II colon cancer	450	Safe-SeqS	Week 4 and 7 post-op	<b>Standard of care:</b> clinician determined management (surveillance or adjuvant chemotherapy) based on standard clinicopathological features <b>ctDNA-guided:</b> ctDNA-positive → adjuvant chemotherapy; ctDNA-negative → surveillance	To demonstrate that an adjuvant therapy strategy based on post-op ctDNA results will reduce the number of patients receiving adjuvant chemotherapy without compromising recurrence-free survival
MEDOCC-CrEATE (NL6281/NTR6455) [80] Netherlands	Stage II colon cancer	1320	PGDx elio™	4–21 days post-op	<b>Standard of care:</b> surveillance <b>ctDNA-guided:</b> ctDNA-positive → 6 months of CAPOX; ctDNA-negative → surveillance	To investigate the willingness of patients to receive adjuvant chemotherapy after detection of ctDNA post-surgery <ul style="list-style-type: none"> <li>To compare the clearance of ctDNA between arms for the baseline ctDNA-positive patient at 6 months (phase II)</li> <li>To compare median RFS between arms for the baseline ctDNA-positive patients at 6 months (phase III)</li> </ul>
NRG GI-005 (COBRA) NCT04068103 [81] United States/Canada	Stage IIA colon cancer	1408	Guardant LUNAR-1™	Post-op	<b>Standard of care:</b> Surveillance <b>ctDNA-guided:</b> ctDNA-positive → adjuvant FOLFOX/CAPOX; ctDNA-negative → surveillance	
IMPROVE-IT Denmark	Stage I and II ctDNA positives	36	Tumor informed ddPCR	Post-op	ctDNA-positive patients randomized to: <b>Standard of care:</b> surveillance <b>Experimental:</b> adjuvant FOLFOX/CAPOX	To demonstrate that adjuvant therapy improves 3-year DFS and TTR for ctDNA positive patients
CIRCULATE AIO-KRK-0217 (NCT04089631) [82] Germany	Stage II colon cancer (MSS tumours)	4812	Not reported	Post-op	ctDNA-positive patients randomised to: <b>Standard of care:</b> surveillance <b>Experimental:</b> adjuvant chemotherapy (capecitabine or CAPOX)	To compare the disease-free survival in patients who are positive for postoperative ctDNA treated with or without adjuvant chemotherapy
CIRCULATE PRODIGE 70 (NCT04120701) [83] France	Stage II colon cancer	1980	ddPCR (2 methylated markers WIF1 and NPY)	Week 2–8 post-op	198 ctDNA-positive patients randomised to: <b>Standard of care:</b> surveillance <b>Experimental:</b> adjuvant FOLFOX	To demonstrate a 17.5% gain in 3-year DFS in post-op ctDNA-positive patients treated with adjuvant FOLFOX compared to observation alone

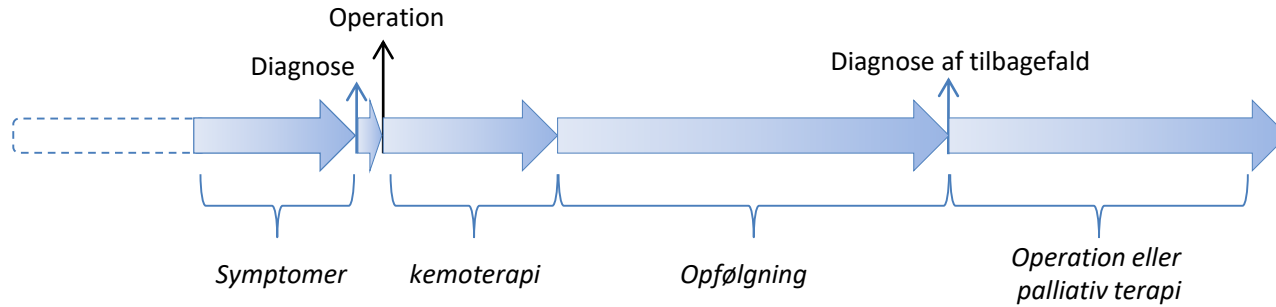
# Stadie III: randomiserede de-eskaleringsstudier

Trial Name/Country	Patient Population	Sample Size	ctDNA Assay	Timing of ctDNA Testing	Trial Intervention	Primary Objective
DYNAMIC-III (ACTRN-12617001566325) Australia/New Zealand	Stage III colon cancer	1000	Safe-SeqS	Week 5–6 post-op	<p><b>Standard of care:</b> clinician determined standard of care adjuvant chemotherapy based on clinical risk</p> <p><b>ctDNA-guided:</b> ctDNA-positive → escalated chemotherapy regimen from pre-planned treatment (increase duration or number of agents); ctDNA-negative → de-escalated chemotherapy regimen from pre-planned treatment (reduction in duration or number of agents)</p>	<p>To evaluate the impact of de-escalation/escalation treatment strategies as informed by post-op ctDNA-informed management</p> <ul style="list-style-type: none"> <li>Achieve an acceptable rate of de-escalation in the ctDNA-informed negative cohort (phase II)</li> <li>Demonstrate non-inferiority of ctDNA-guided management with respect to recurrence in the de-escalation (ctDNA-informed negative) cohort (phase III)</li> <li>Investigate superiority of a ctDNA-informed management with respect to recurrence in the escalation (ctDNA-informed positive) cohort (Phase III)</li> </ul>
VEGA (UMIN000039205) [84] Japan	High-risk stage II, low-risk stage III colon cancer— ctDNA-negative	1240	Signatera™	1-month post-op	<p>Post-op ctDNA-negative patients randomised to:</p> <p><b>Standard of care:</b> 3 months of CAPOX</p> <p><b>Experimental:</b> Surveillance</p> <ul style="list-style-type: none"> <li>Patients enroll in ALTAIR study if ctDNA becomes positive at 3 months</li> </ul>	<p>To demonstrate the non-inferiority of observation vs. adjuvant CAPOX with absence of ctDNA at 1 month post-surgery</p>
TRACC (NCT04050345) [79] United Kingdom	High risk stage II, stage III colorectal cancer	1621	NGS-based 22-gene colorectal panel	<8 weeks post-op, 3 months post-op	<p><b>Standard of care:</b> 6 months of capecitabine or 3 months of CAPOX</p> <p><b>ctDNA-guided:</b> ctDNA-positive → standard adjuvant chemotherapy; ctDNA-negative → de-escalate treatment but re-escalate if ctDNA becomes positive at 3 months</p>	<ul style="list-style-type: none"> <li>To demonstrate non-inferiority in 3-year DFS between standard of care arm and ctDNA-guided adjuvant chemotherapy arm</li> </ul>

# ctDNA har potentiale til at blive anvendt igennem hele sygdomsforløbet

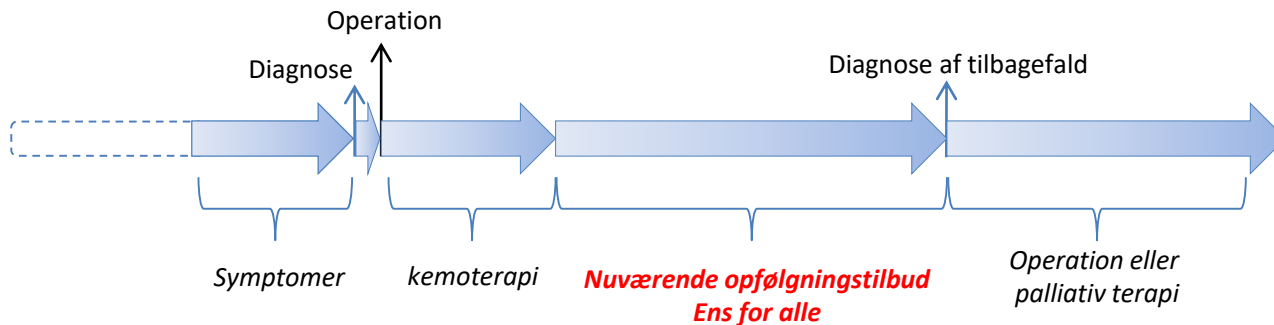


# Opfølgning – opsporing af tilbagefald

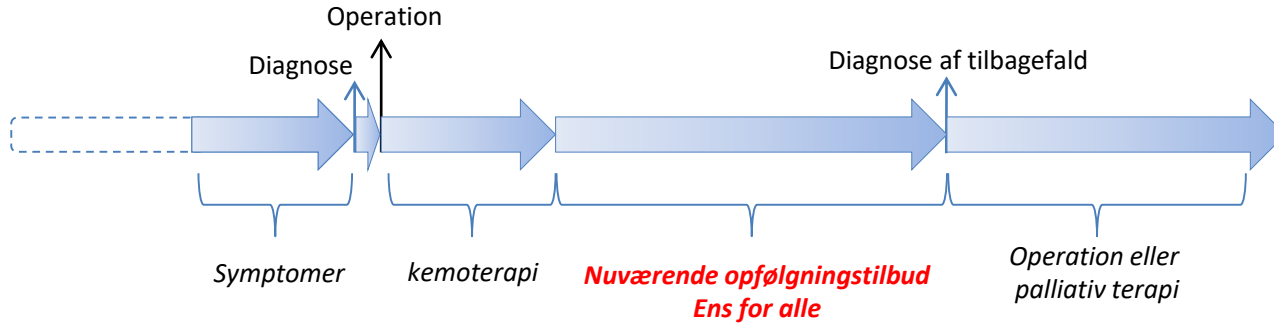




# Opfølgning – opsporing af tilbagefald

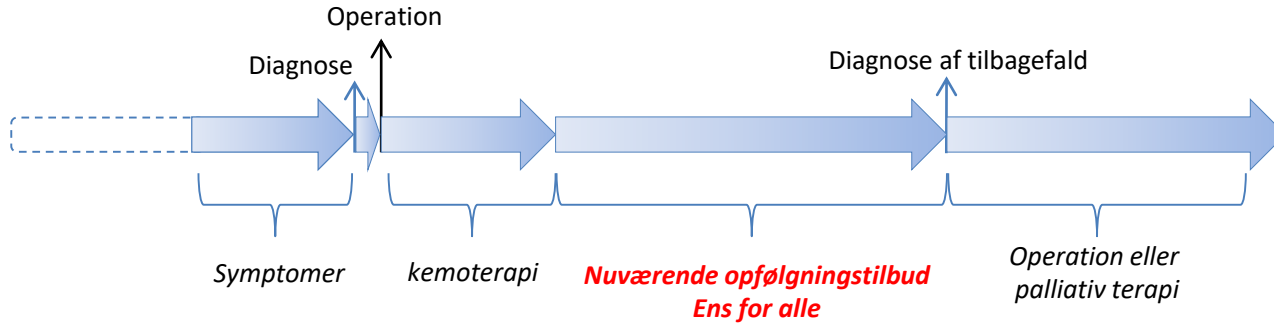


# Opfølgning – opsporing af tilbagefald



- 1) **Kun for ~15% af tilbagefaldspatienterne opdages tilbagefaldet tilstrækkeligt tidligt til at de kan tilbydes kurativt intenderet behandling**
  - 5-års overlevelsesraten for patienter der får konstateret metastaser under opfølgningen er kun 9,3%
- 2) **70-80% af patienter har ikke brug for overvågning**, de var allerede helbredt af operationen (udfordringen er at vi IKKE ved hvem de er)

# Opfølgning – opsporing af tilbagefald

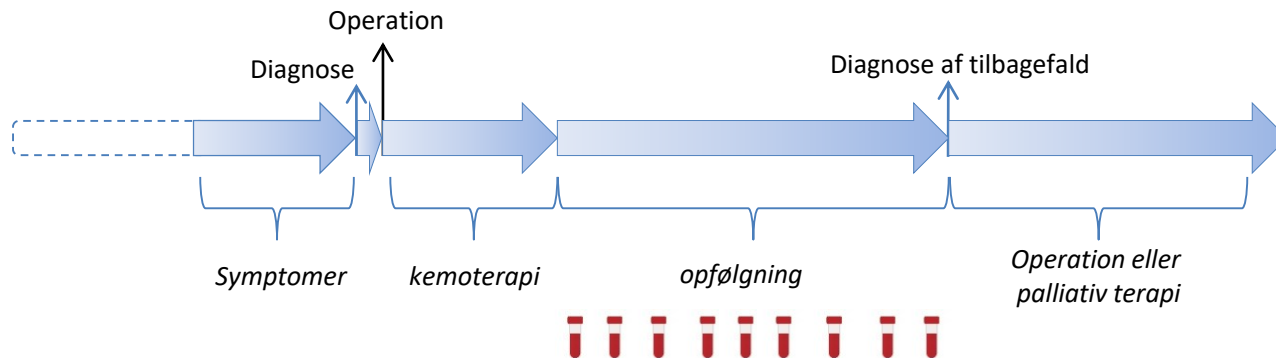


- 1) Kun for ~15% af tilbagefaldspatienterne opdages tilbagefaldet tilstrækkeligt tidligt til at de kan tilbydes kurativt intenderet behandling
  - 5-års overlevelsesraten for patienter der får konstateret metastaser under opfølgningen er kun 9,3%

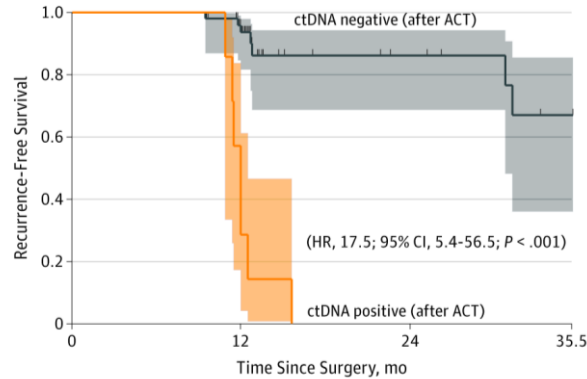
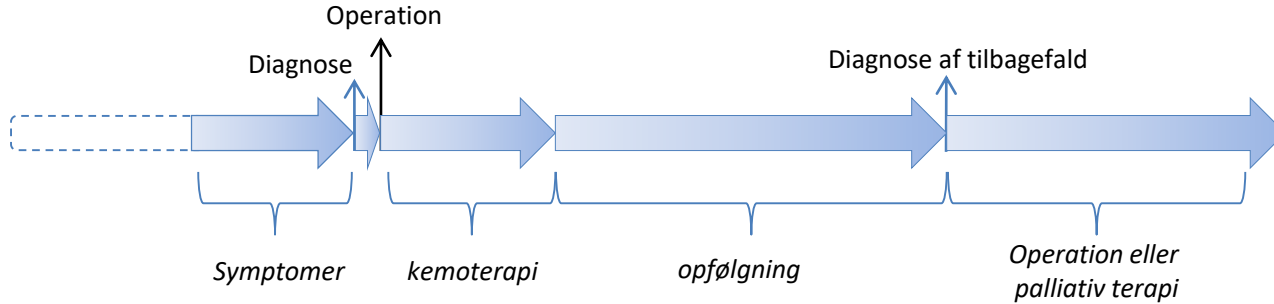
2)

**BEHOV: en markør som muliggør tidlig identifikation af patienter med restsygdom**

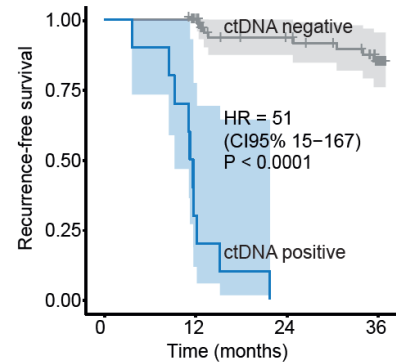
# Opfølgning – opsporing af tilbagefald



# Opfølgning – opsporing af tilbagefald



No. at risk	0	12	24	35.5
Negative	51	40	11	5
Positive	7	2	0	0



	0	12	24	36
-ctDNA	83	74	49	25
+ctDNA	10	3	0	0

Reinert et al  
JAMA Oncology  
2019

Henriksen et al  
Clinical Cancer Research  
2021

# Lead-time analysis: ctDNA vs SoC-surveillance

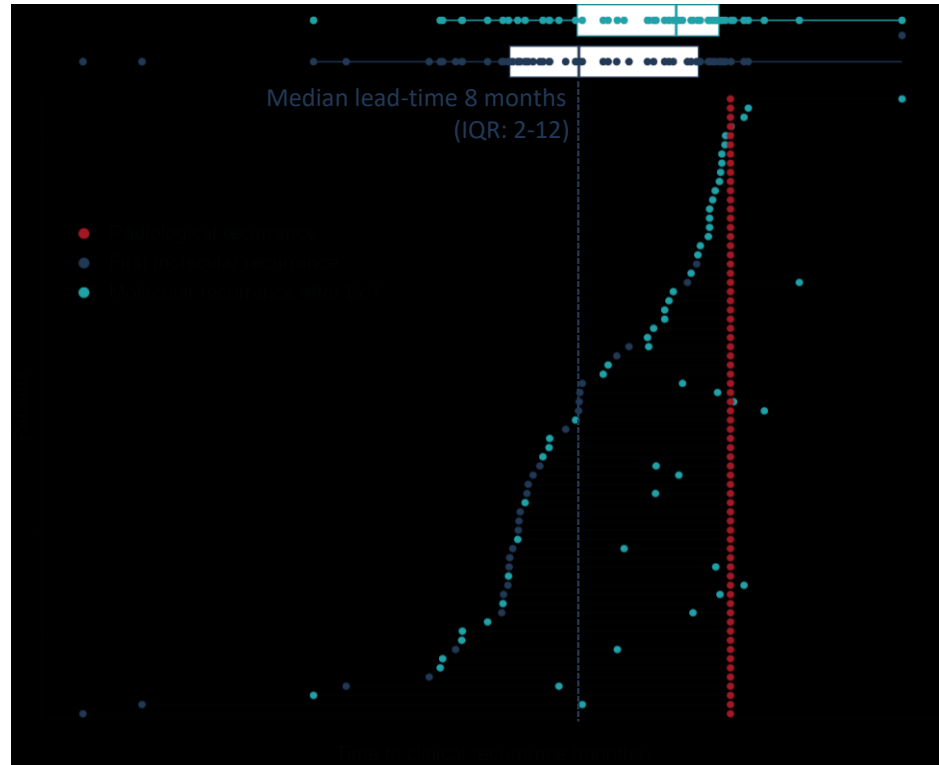
N= 68 recurrence patients

Schøler et, al., Clin Cancer Res. 2017

Reinert et al JAMA Oncology 2019

Henriksen et al Clin Can Res 2021

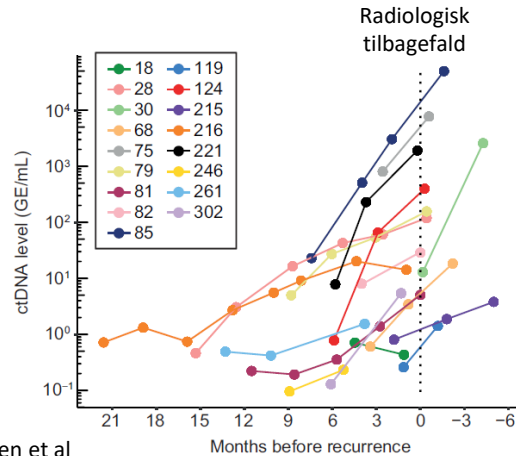
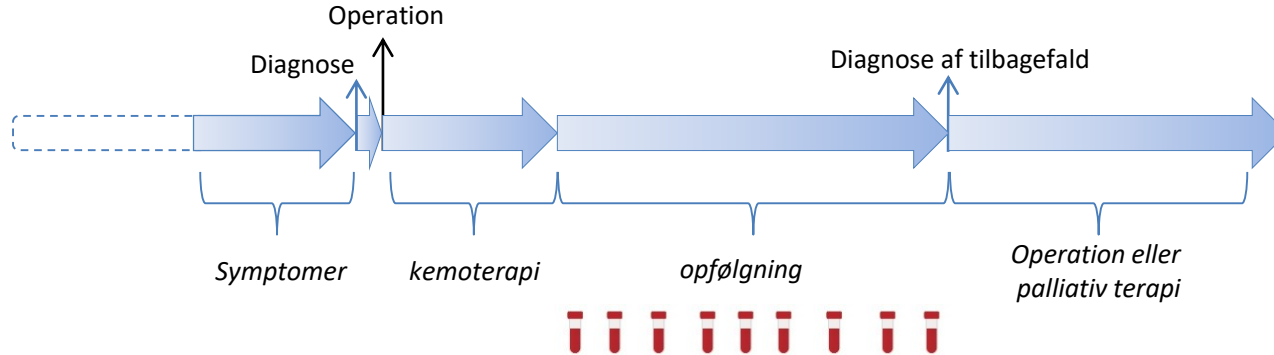
Øgaard et al. Eur J Can 2022



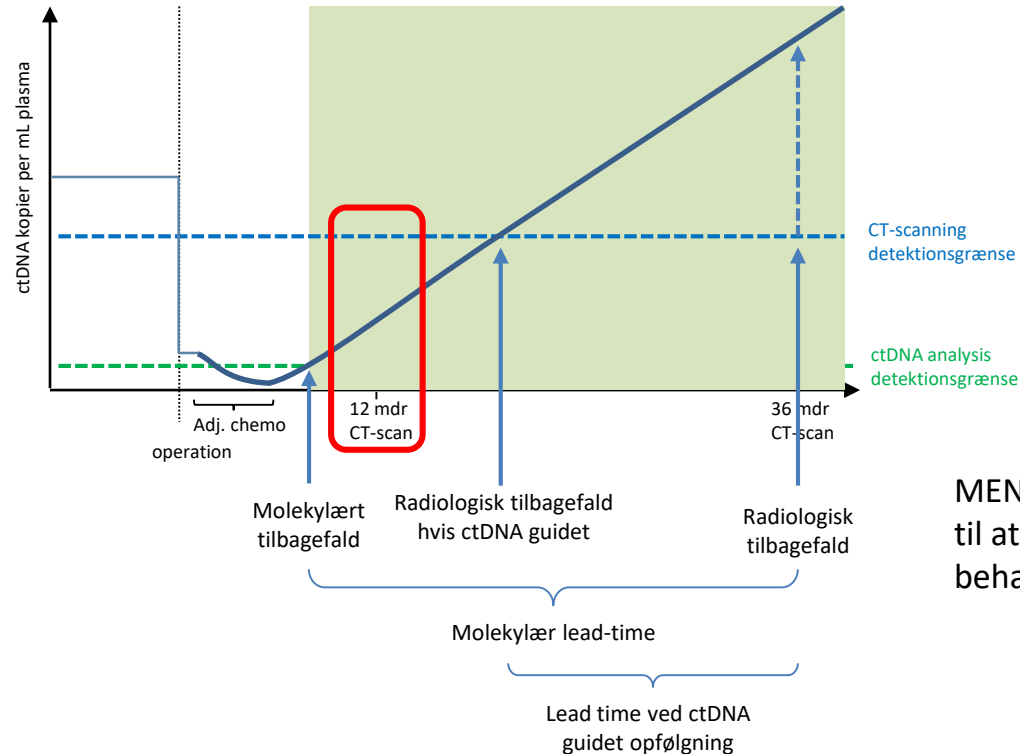
published  
Henriksen, MOMA

**DO NOT POST**

# ctDNA en markør for tumor tilvækst



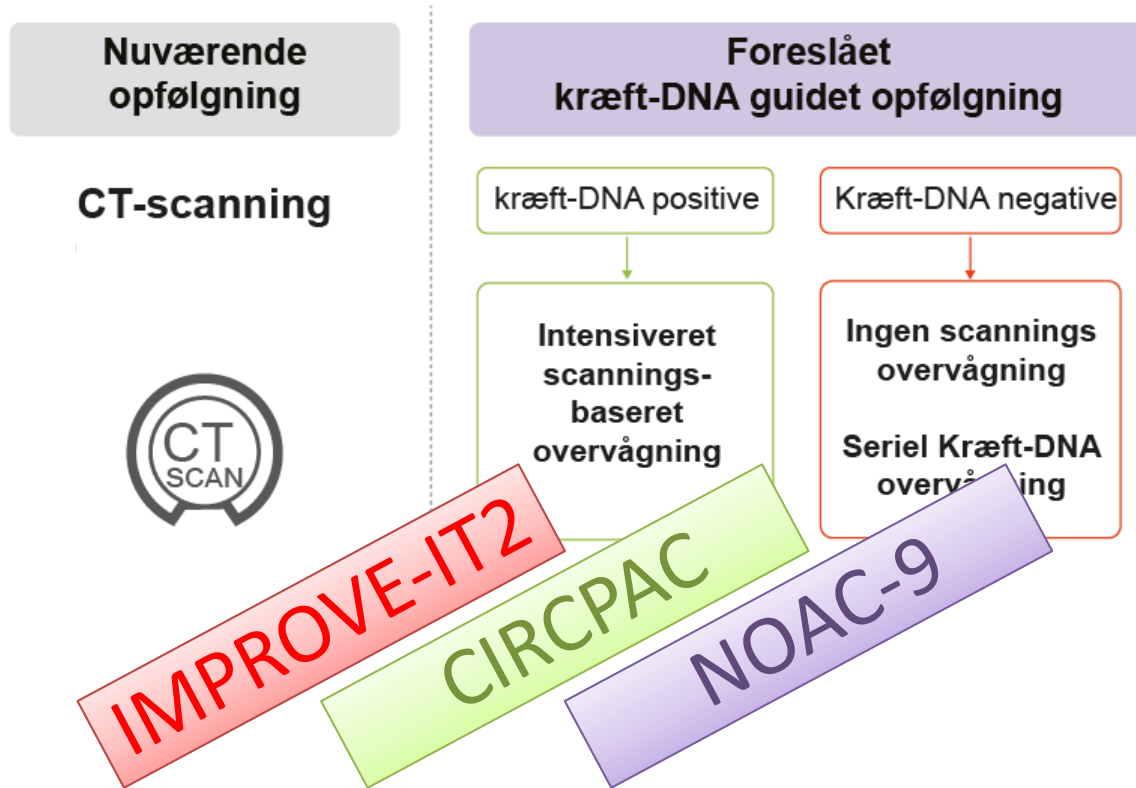
# Perspektivet: ctDNA guidet opfølgning



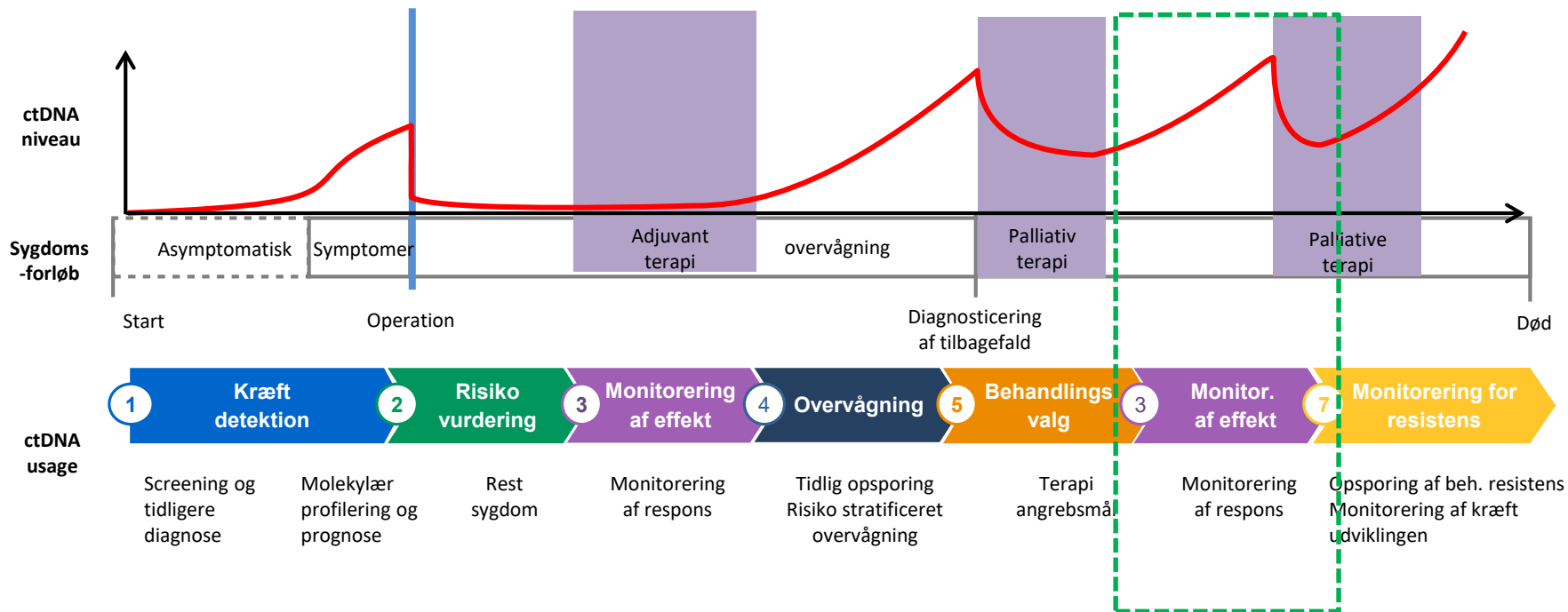
MEN, er det tilstrækkeligt til at ændre behandlingen?



# Randomiserede studier



# ctDNA har potentiale til at blive anvendt igennem hele sygdomsforløbet



# Behandlingsmonitorering

**Overlevelse** er det GYLDNE endepunkt i klinisk onkologi

I praksis anvendes surrogat endepunkter



- Objektiv respons (vurdering af ændring i læsionernes størrelse)
- Tid til progression (progressions fri overlevelse)

Response Evaluation Criteria In Solid Tumors (RECIST v1.1), Eisenhauer et al EJC 2009

**Objektiv respons** er **IKKE** et optimalt surrogat endepunkt for **Overlevelse**



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)



Current Perspective

ctDNA-Response evaluation criteria in solid tumors – a new measure in medical oncology



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<sup>a</sup> Institute of Regional Health Services, University of Southern Denmark, Department of Oncology, Vejle University Hospital, 7100, Vejle, Denmark

<sup>b</sup> Department of Oncology, Aarhus University Hospital, Denmark

<sup>c</sup> Department of Clinical Medicine, Aarhus University, Denmark

Received 21 November 2022; accepted 24 November 2022

Available online 17 December 2022

THERAPEUTIC ADVANCES in  
*Medical Oncology*

Review

# Circulating tumor DNA: Response Evaluation Criteria in Solid Tumors – can we RECIST? Focus on colorectal cancer

Karen-Lise Garm Spindler and Anders Jakobsen 

*Ther Adv Med Oncol*

2023, Vol. 15: 1–11

DOI: 10.1177/  
17588359231171580

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Circulating tumour DNA –  
**ctDNA-RECIST**

Response Evaluation Criteria in Solid Tumours

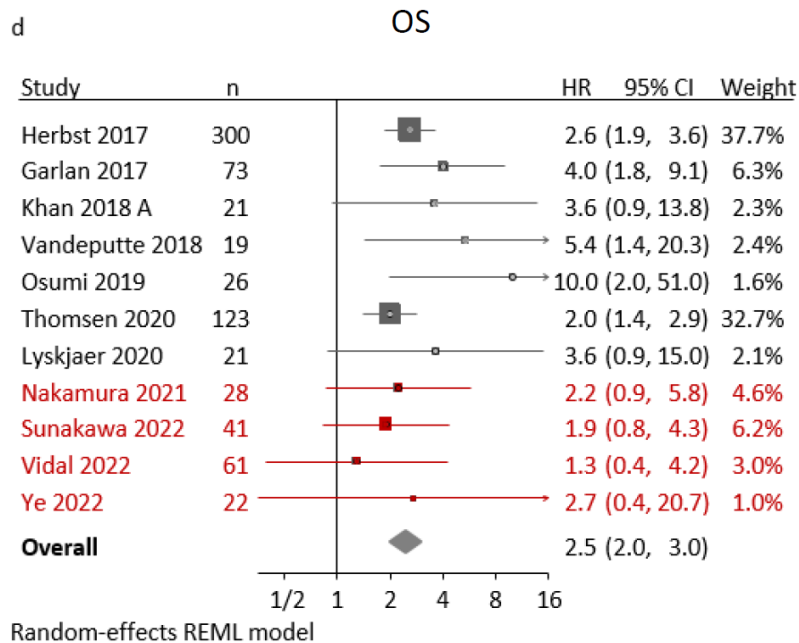
## ctDNA RECIST – Videnskabelige spørgsmål ?

Er en **ændring i ctDNA niveau** forbundet med en **tilsvarende ændring i overlevelse** ?

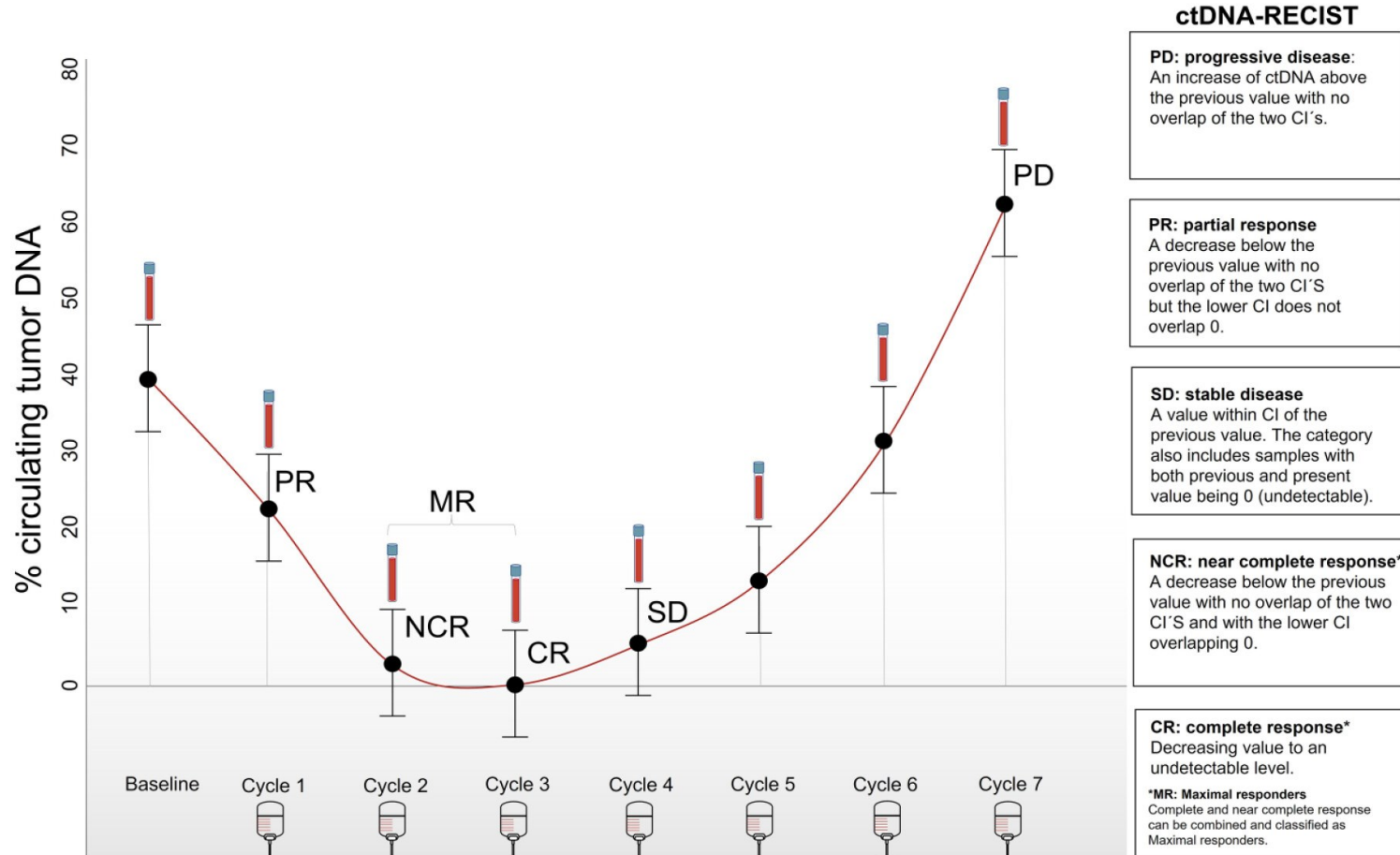
Er ctDNA guidet beslutningstagning **gennemførlig** ?

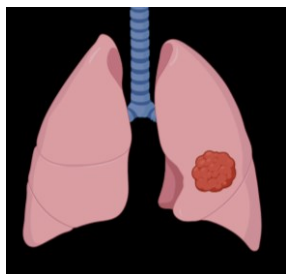
Kan ctDNA RECIST **supplere eller erstatte** konventionel billede-baseret RECIST?

# Quantitative ctDNA DYNAMICS IN mCRC



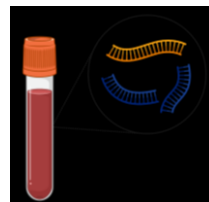
# ctDNA response criteria according to ctDNA-RECIST





# PRELUCA

ctDNA guidet



VS

scannings guidet



Respons monitorering

- **Prospektivt nationalt randomiseret interventionsstudie**
- **N= 350 patienter med avanceret ikke-småcellet lungekræft i beh med 1. line immunterapi**
- **Non-inferiority studie design**
  - Primære endepunkt: Overall Survival
  - Sekundære endepunkter: cost-utility and cost-effectiveness, QoL
- **Region Sjælland (Næstved/Roskilde), Region Syddanmark (Vejle) og Region Nord (Aalborg)**



# DCCC – Dansk National forskningscenter for cirkulerende tumor DNA guidet kræftbehandling

- > 150 klinikere og forskere
- > 40 kliniske protokoller (> 15 kræftformer)
  - Inkl. 9 ctDNA guidede interventionsstudier
- Publikationer: 58 peer-reviewede artikler



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# ctDNA guided intervention studies in the Danish ctDNA research center

## Randomized studies

<b>OPTIMISE</b>	Oligo metastatic CRC	Investigating use of ctDNA-guided therapy compared to SOC after local treatment for metastatic CRC
<b>IMPROVE-IT</b>	ctDNA pos CRC stage I-II	Adjuvant chemo versus Observation
<b>IMPROVE-IT2</b>	CRC stage III	ctDNA guided versus Standard-of care follow-up
<b>CIRCPAC</b>	Pancreas cancer	ctDNA guided versus Standard-of care follow-up
<b>NOAC-9</b>	Anal cancer	ctDNA guided versus Standard-of care follow-up
<b>CAHOXA</b>	Recurrent ovarian cancer	meth-ctDNA versus CA125 as treatment response assessment tools
<b>PRELUCA</b>	ICI treated advanced NSCLC	ctDNA based response assessment (ctDNA-RECIST) versus iRECIST

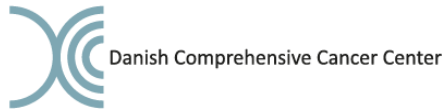
## Non-randomized studies

<b>RESET-R</b>	ICI to dMMR rectal cancer	Watch full waiting guided by ctDNA, endoscopy, and imaging
<b>TOMBOLA</b>	Bladder cancer	Serial ctDNA analysis post radical cystectomy is used to select patients to immunotherapy



Stor tak til ALLE deltagere i  
"DCCC – Dansk National forskningscenter for cirkulerende  
tumor DNA guidet kræftbehandling"

**Stor TAK til alle patienterne for deres deltagelse !**



 Kraftens Bekæmpelse

