ctDNA (Liquid Biopsy for MRD) in the Curative Setting

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MATOS Breast Conference

March 28, 2025

HARVARD MEDICAL SCHOOL

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Mass General Cancer Center

Objectives

- What is molecular residual disease (MRD)?
- How is MRD detected?
- What is the prognostic significance of MRD?
- Can we intervene on MRD?

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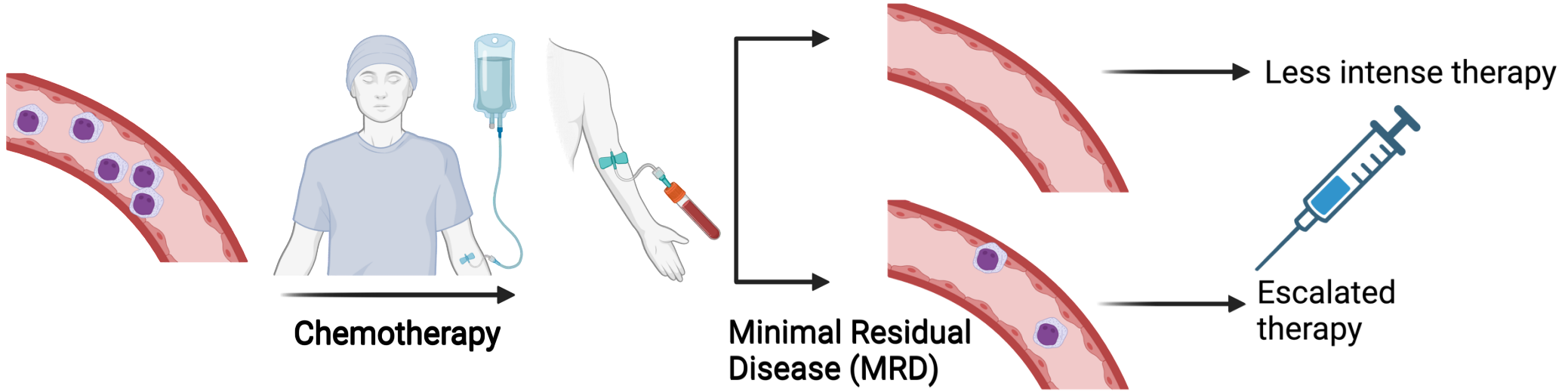
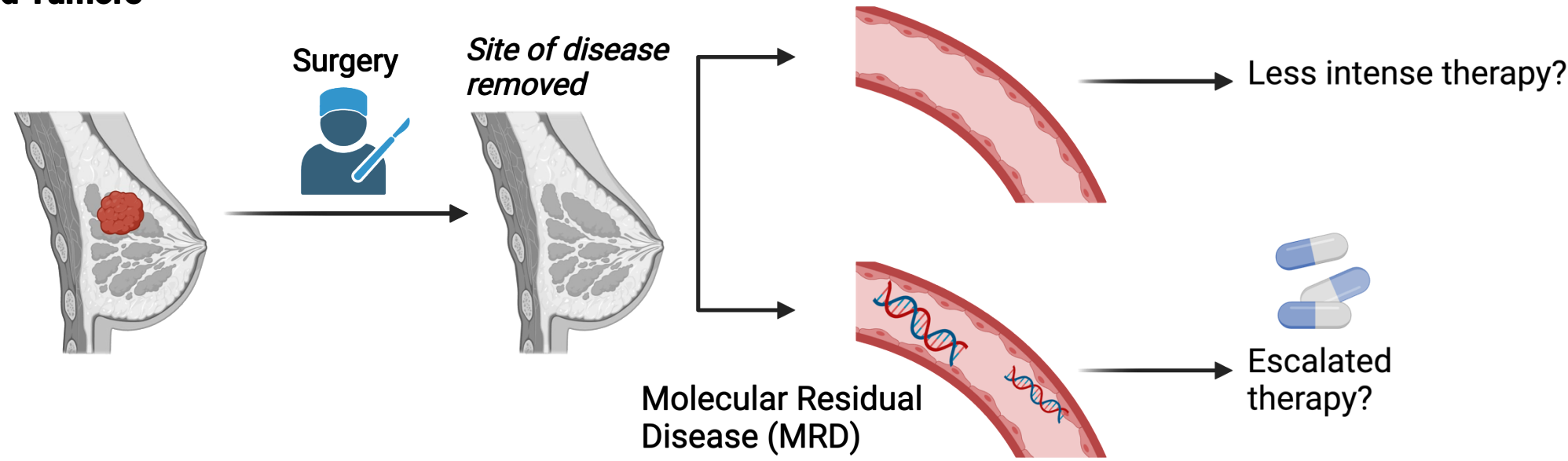
What is MRD?

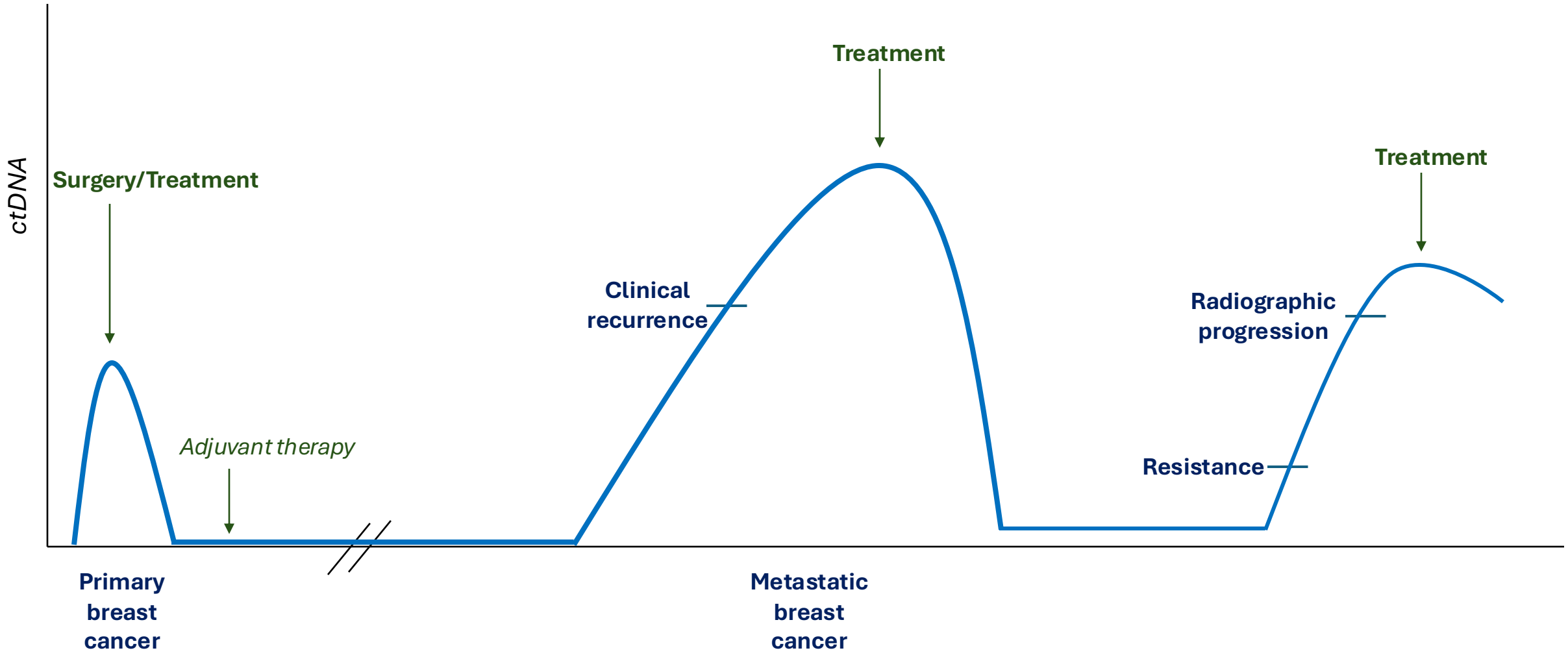
Hematologic Malignancies

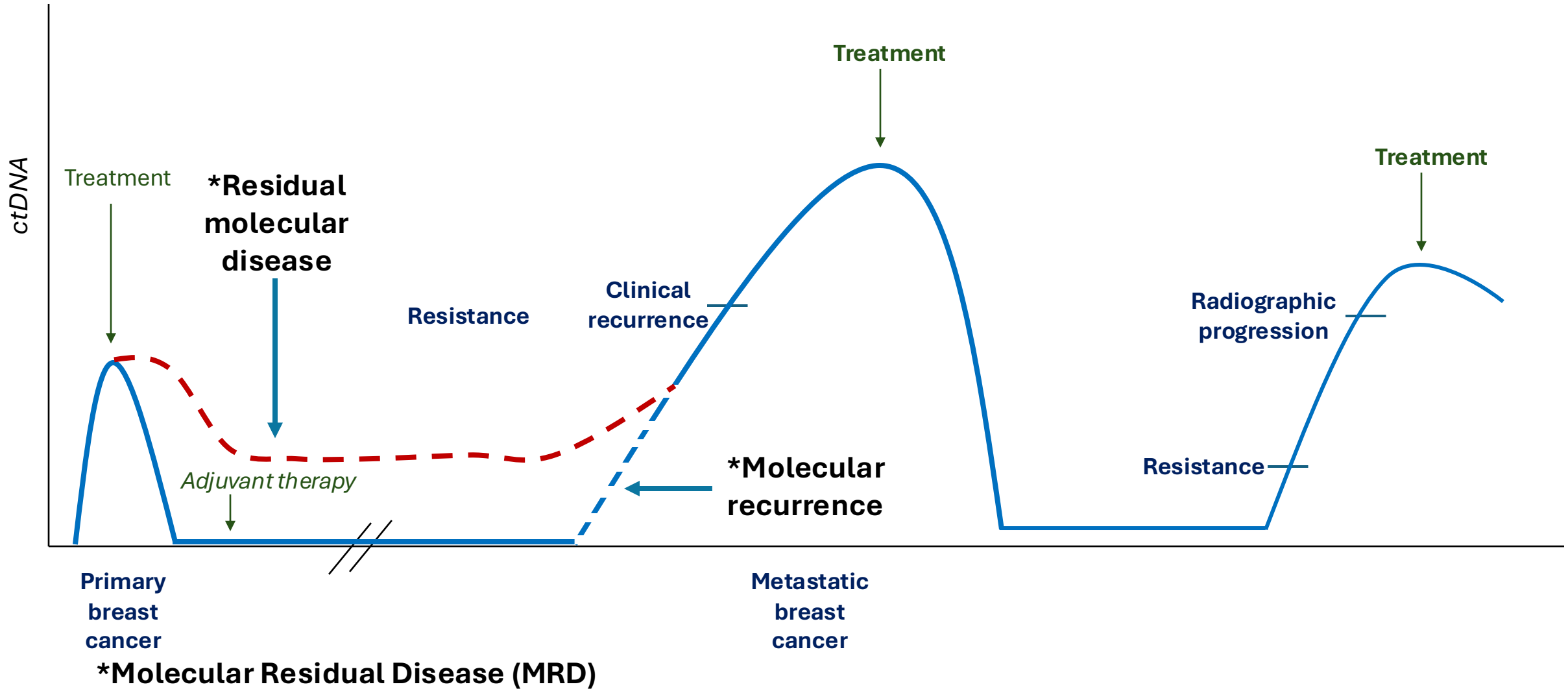


Solid Tumors



Circulating tumor DNA (ctDNA)





*Molecular Residual Disease (MRD)

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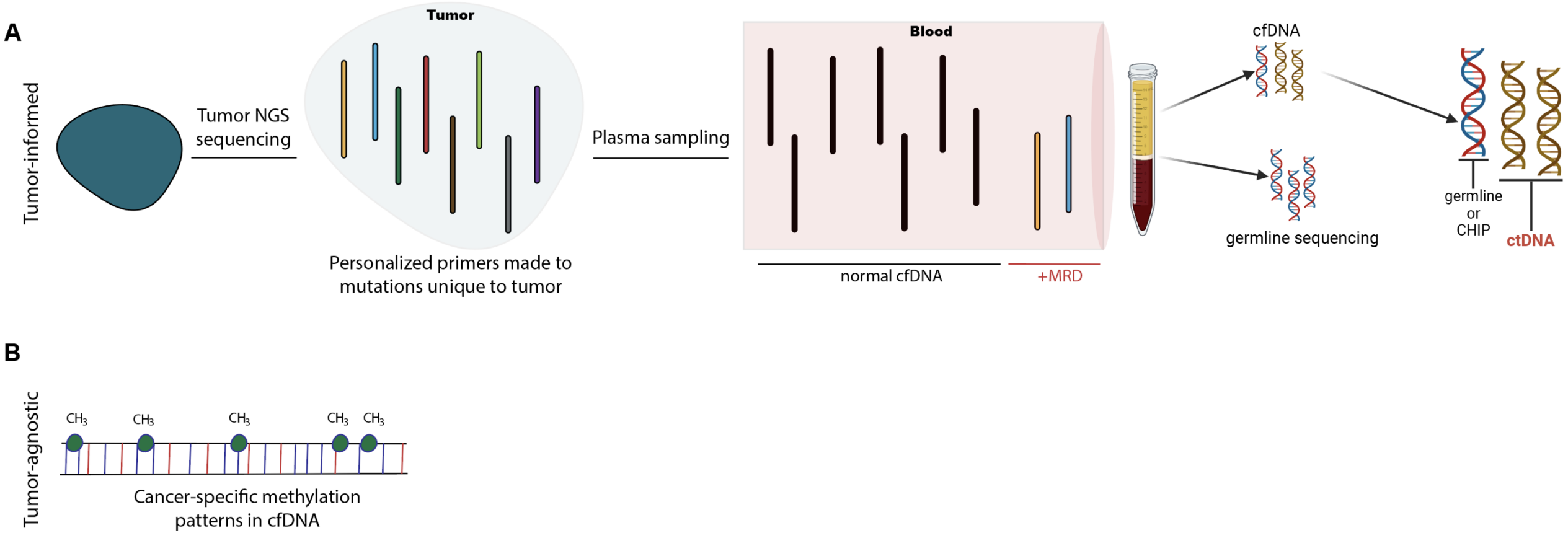
Types of MRD Assays



A. Medford et al, Clinical Cancer Research, 2023

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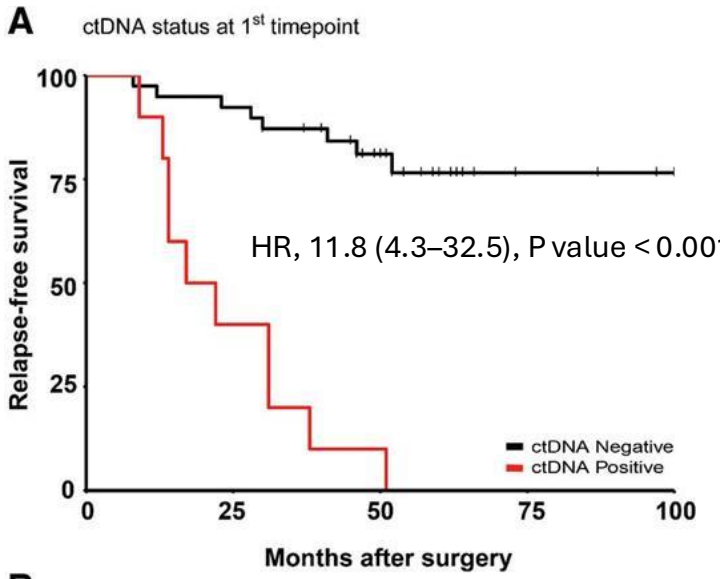
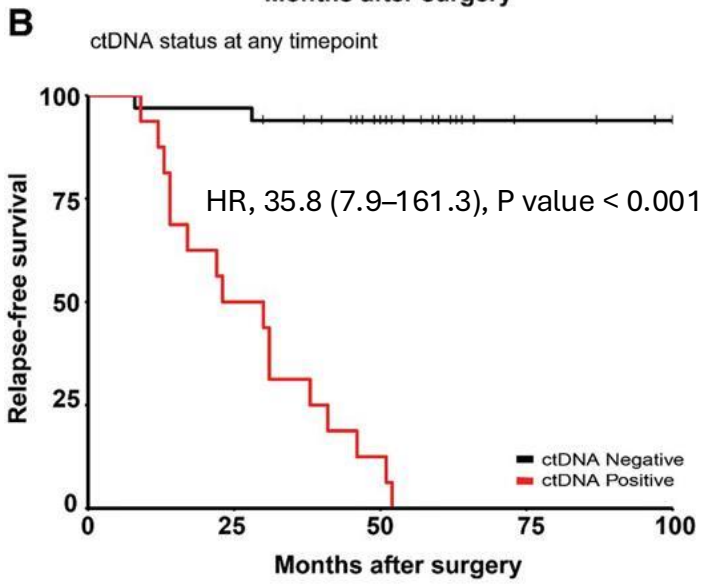
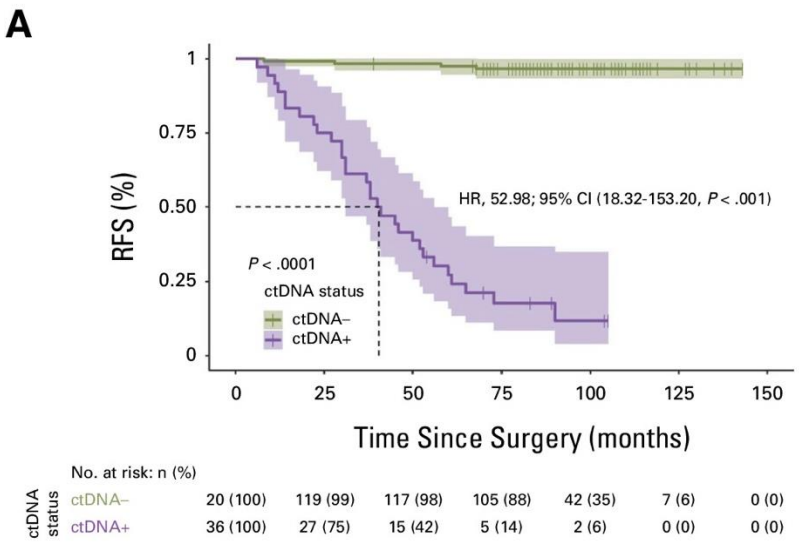
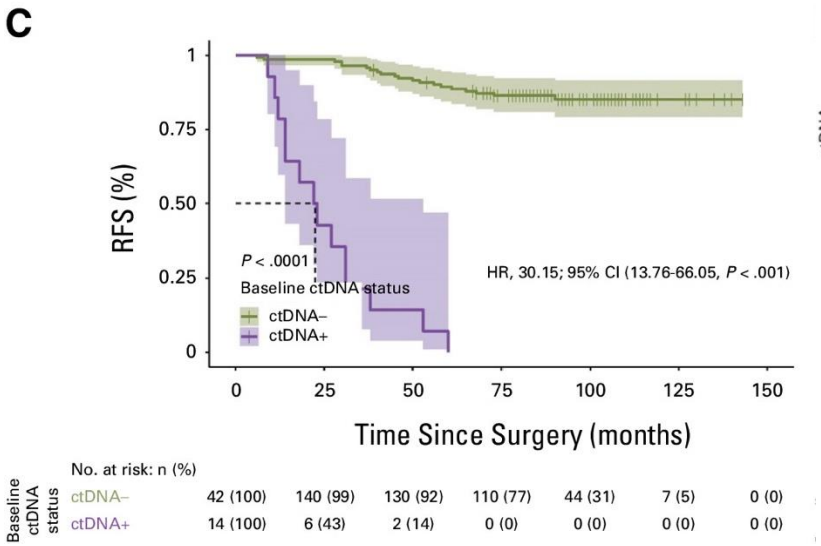
MRD means a very poor prognosis – hazard ratio up to 50+, lead time to clinical recurrence 9-18 months



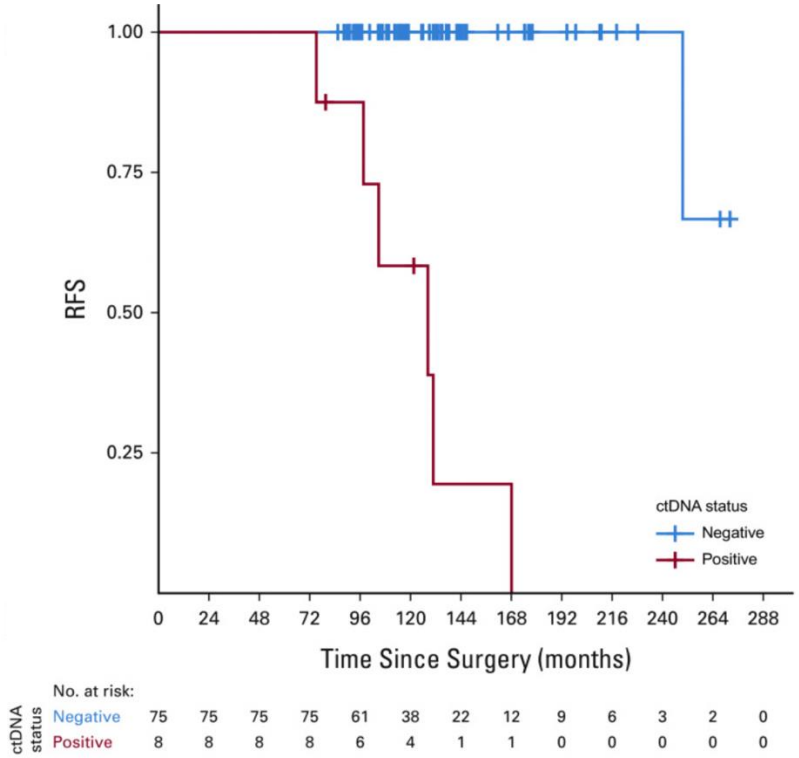


Coombes et al, CCR 2019





Shaw et al, JCO PO 2024



Lipsyc-Sharf, JCO 2022

High-risk stage II-III ER+/HER2-
≥5 years after surgery
8 (10%) with +MRD
6 distant recurrences at 2-years, all +MRD

MRD detection & lead times to BC recurrence

Study	Assay	Cancer Type	# patients	Median Lead Time	Hazard Ratio (RFS)	Median f/u	Sensitivity	Specificity
Garcia-Murillas et al (2015)	dPCR	All subtypes	55	7.9 months	Single timepoint: 25.1 (95% CI 4.08-130.5) Serial: 12.0 (95% CI 3.36-43.07)	~2 years	Post-surgery: 50% Serial: 80%	96%
Olsson et al (2015)	dPCR	All subtypes	20	11 months	N/A	9.2 years	93%	100%
Garcia-Murillas et al (2019)	dPCR	All subtypes	Primary cohort: 101 Combined cohort: 144	Primary: 38.0 months Combined: 10.7 months	Primary: 16.7 (95% CI 3.5-80.5, p < .001) Combined: 17.4 (95% CI 6.3-47.8)	Primary: 35.5 months Combined: 36.3 months	88.4%	100%
Coombes et al (2019)	Signatera	All subtypes	49	8.9	Post-surgery: 11.8 (95% CI 4.3–32.5) Serial: 35.8 (95% CI 8.0–161.3)	~2 years (study midpoint)	89%	100%
Parsons et al (2020)	Internal tumor-informed	HR+/HER2-	35	18.9 months	Post-surgery: 5.1 (95% CI 2.0–12.7] 1 year post surgery: 20.8 (95% CI 7.3–58.9)	7.1 years	Post-surgery: 23% 1-year: 19%	Post-surgery: 96% 1-year: 100%
Lipsyc-Sharf et al (2022)	RaDaR	HR+/HER2-	85	12.4 months	N/A	10.4	85.7%	97.4%

Medford et al, Clinical Cancer Research, 2023

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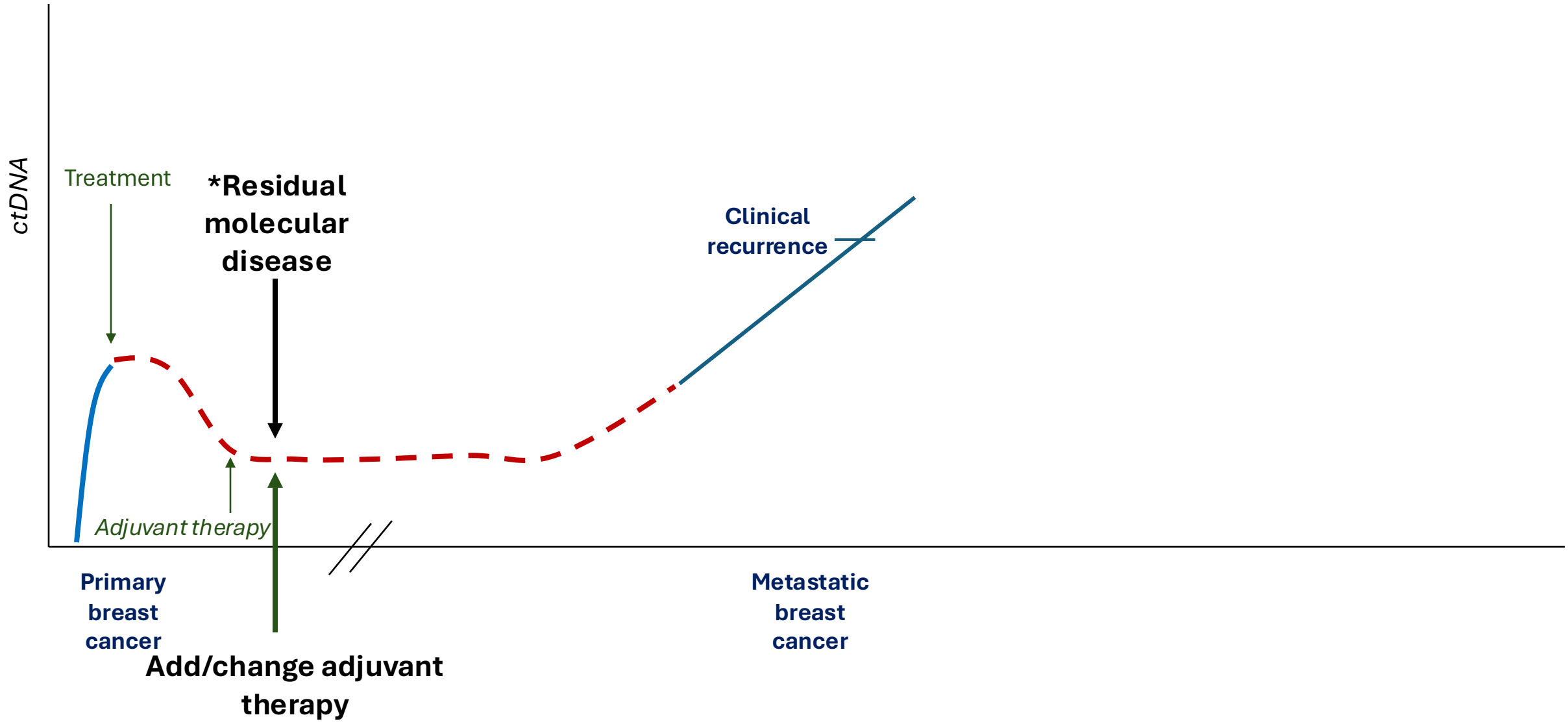
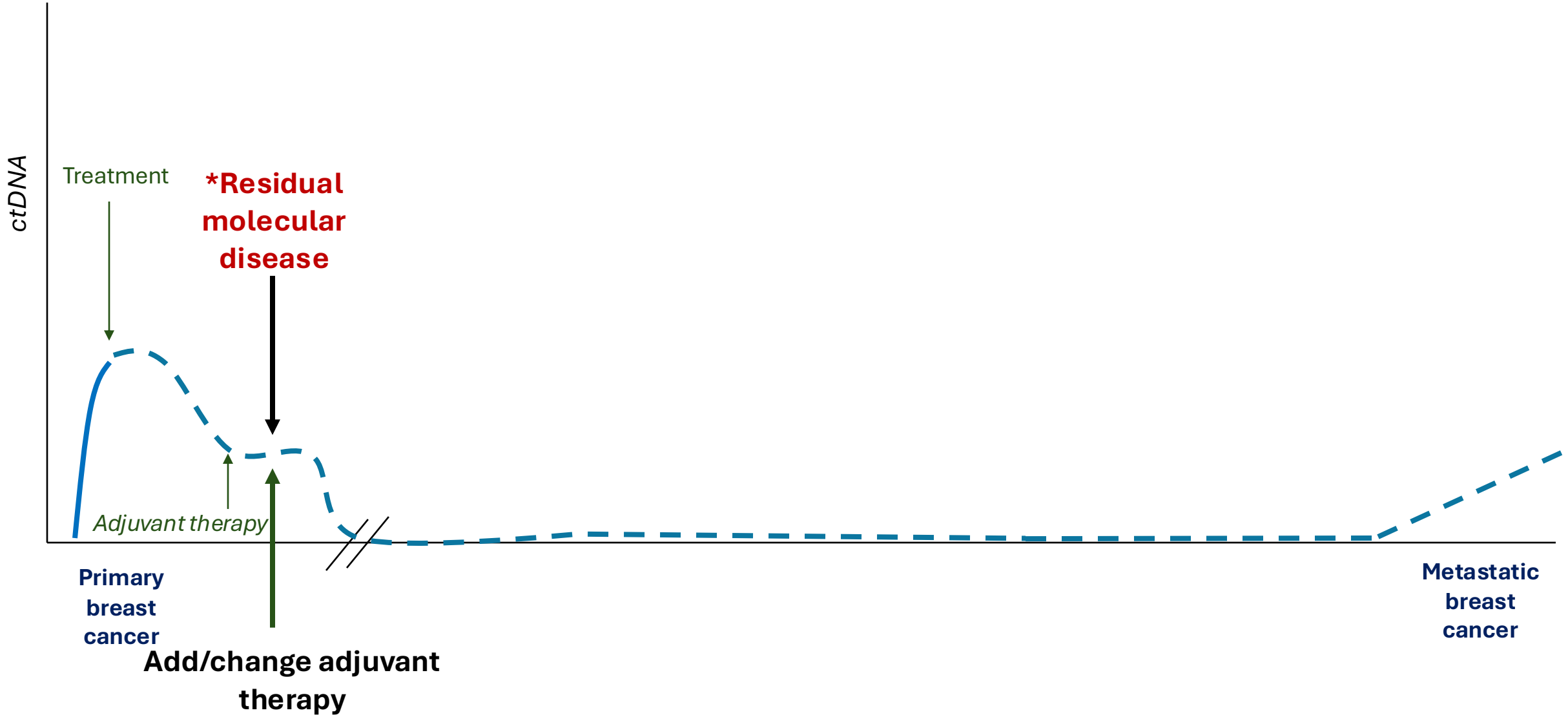

ctDNA
Treatment
*Residual molecular disease
Clinical recurrence
Adjuvant therapy
Primary breast cancer
Metastatic breast cancer
Add/change adjuvant therapy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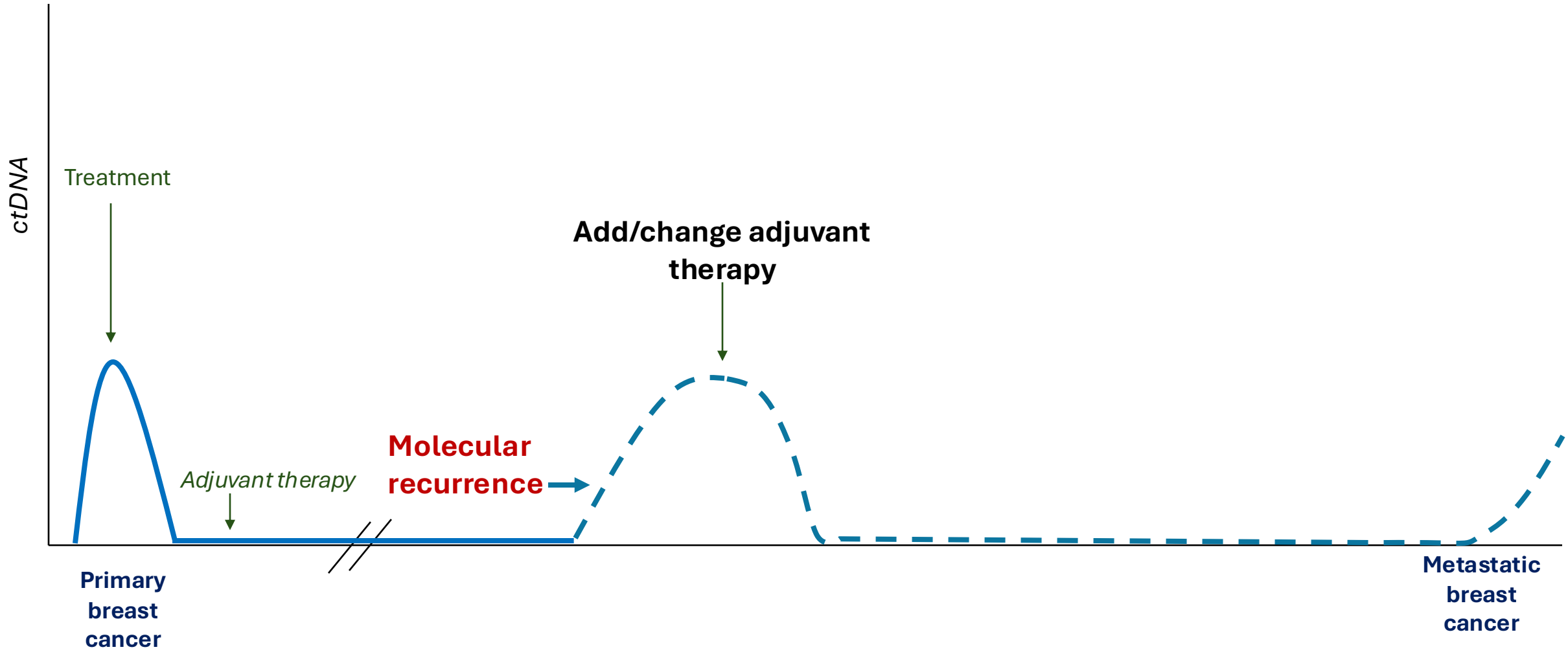
ctDNA
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Add/change adjuvant therapy
Adjuvant therapy
Molecular recurrence
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Metastatic breast cancer

Prospective interventional clinical trials in MRD and Breast Cancer

Trial ID/name/ disease/phase	Drug treatment	Primary end point	Trial eligibility: MED[a]	Trial eligibility: scan required[a]	Sample size: ctDNA$^+$ patients in intervention arm[b]	Trial status	Biopharma sponsored	Geography
Breast cancer								
DARE NCT04567420 (ref. 73) Stage II–III ER$^+$/HER2$^-$ breast Phase II	Palbociclib + endocrine therapy	ctDNA positivity during surveillance Relapse-free survival	Landmark or surveillance	Yes, scan required	100 (target)	Recruiting	No	USA (13 states; 15 sites)
LEADER NCT03285412 (ref. 74) Localized ER$^+$/HER2$^-$ breast Phase II	Ribociclib + endocrine therapy	ctDNA clearance	Landmark or surveillance	No	30 (target)[c]	Recruiting	No	Massachusetts (3 sites)
TRAK-ER NCT04985266 (ref. 75) Early stage ER$^+$/HER2$^-$ breast Phase II	Palbociclib + fulvestrant	ctDNA positivity during surveillance Relapse-free survival	Landmark or surveillance	Yes, scan required after MED	1,100 (surveillance target)[d]	Recruiting	No	UK and France (36 sites)
TREAT ctDNA NCT05512364 (ref. 76) Early stage ER$^+$/HER2$^-$ breast Phase III	Elacestrant	Distant metastasis-free survival	Landmark or surveillance	Yes, scan required after MED	220 (target)	Recruiting	No	Global (>10 countries, 120 sites)
ZEST NCT04915755 (ref. 77) Stage I–III triple-negative breast or HR$^+$/HER2$^-$ breast with BRCA mutation Phase III	Niraparib	Treatment emergent adverse events Change in ECOG Performance Status	Post-op or landmark	No	43 (actual)	Discontinued	Yes	Global (>10 countries, 200 sites)
c-TRAK-TN NCT03145961 (ref. 78) Early stage triple-negative breast Phase II	Pembrolizumab	ctDNA positivity during surveillance ctDNA clearance	Landmark or surveillance	Yes, scan required	45 (actual)[79]	Complete	No	UK (17 sites)
ASPRIA NCT04434040 (ref. 80) Early stage triple-negative breast Phase II	Atezolizumab + sacituzumab govitecan	ctDNA clearance	Landmark	No	40 (actual)	Active, not recruiting	No	USA (5 states, 9 sites)

Medford, Carmeli, Ritchie et al, Nature Reviews Cancer, 2024

A new approach to MRD-based clinical trials

Cancer Centers

MRD-based clinical trials

Biopharma Companies

Patient tumor information and serial ctDNA test results

ctDNA test results to advance ctDNA research

Eligibility criteria for MRD-based trials

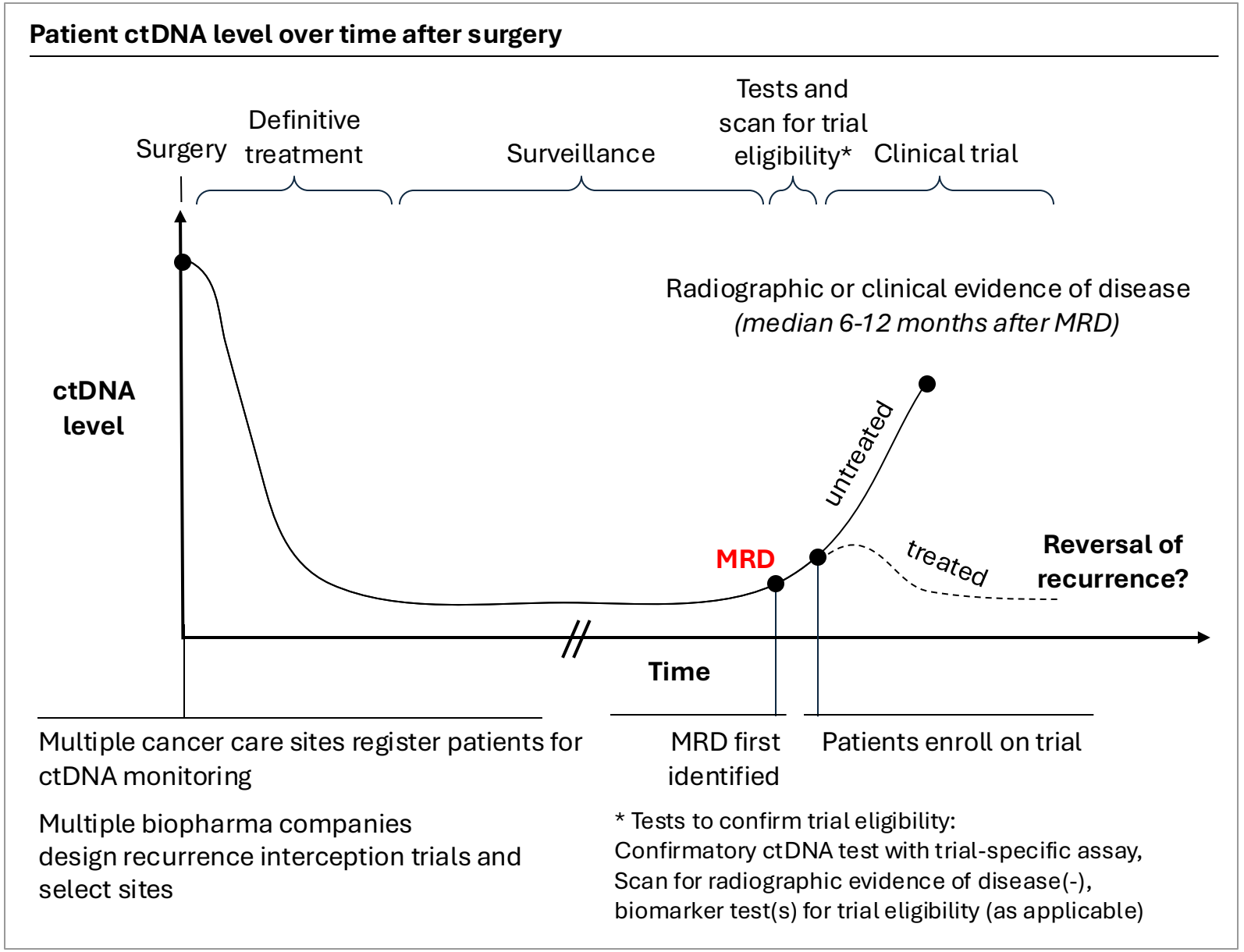
Assist center with management of rapid screening assessments upon ctDNA(+) to find trial opportunities

Non-profit Hub

Trial feasibility solution with patient characteristics (e.g., ctDNA, tumor info) summarized across participating cancer centers

Medford, Carmeli, Ritchie et al, Nature Reviews Cancer, 2024

A standing platform for MRD-based clinical trials



Medford, Carmeli, Ritchie et al, Nature Reviews Cancer, 2024

Summary

- MRD indicates breast cancer is going to recur.
- Patients are able to access MRD tests today, but no therapies are approved to intervene. **This is a key area of unmet clinical need**.
- Innovative translational research is required to understand mechanisms of therapy resistance and optimal MRD interventional clinical trials.
- An overhaul of the MRD-based clinical trial infrastructure is needed (and underway) to improve patient access and study opportunities.

Thank you!

Mentorship
Dejan Juric
Gaddy Getz
Aditya Bardia

Science for America/Reversing Early Recurrence
Aparna Parikh
Eric Lander
Ariel Carmeli
Alex Ritchie
Kaitlin Browman
Sarah Neely

Haber/Maheswaran Lab
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Shyamala Maheswaran
Lecia Sequist
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Michelle Trodella
Lauren Scarpetti

LEADER Study Team
Zanta Ephrem
Zack Smolar

Getz Lab
Team thanks!