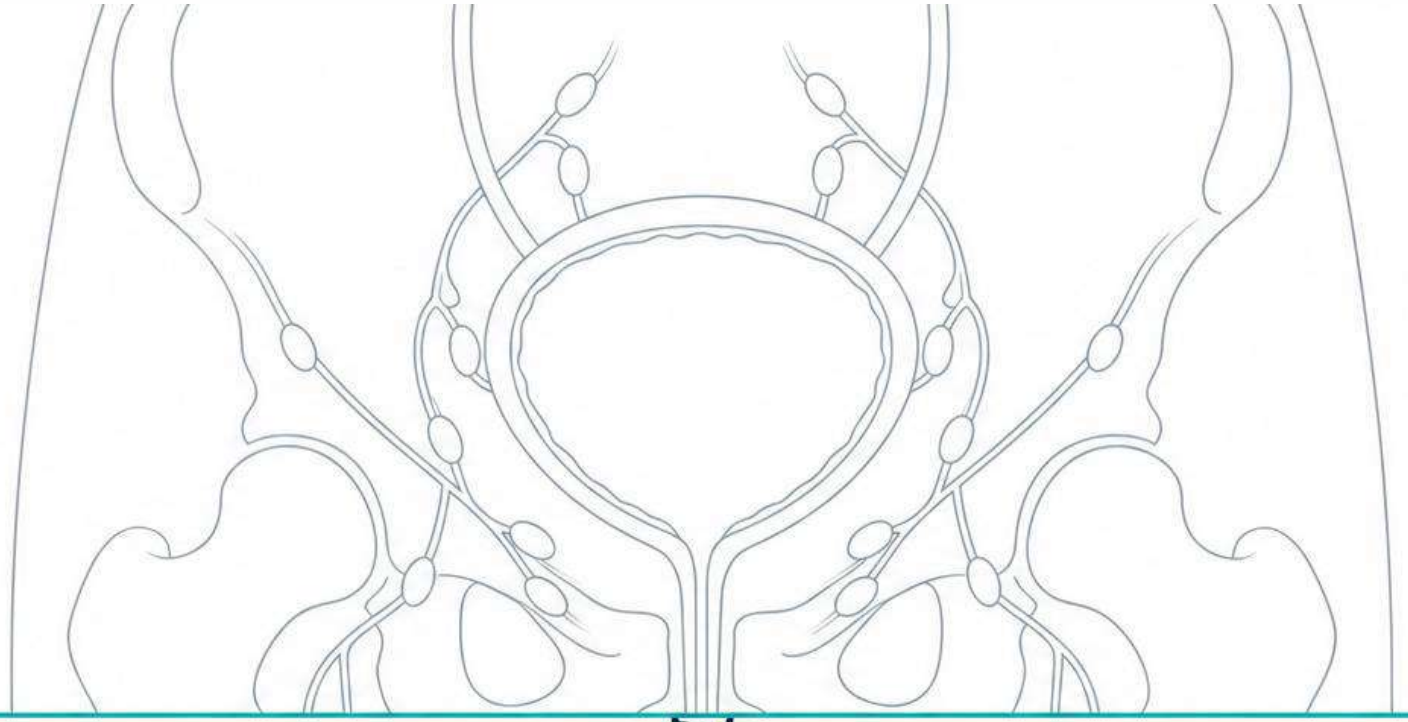
Liquid biopsy in bladder cancer

What blood and urine tests can tell us about cancer and its treatment

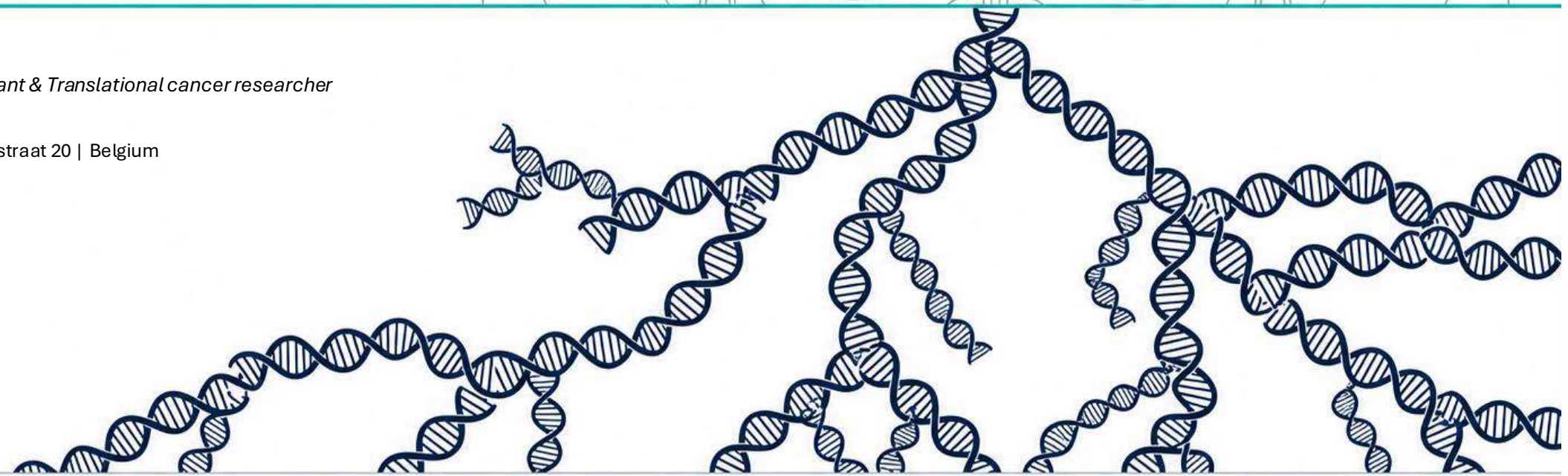


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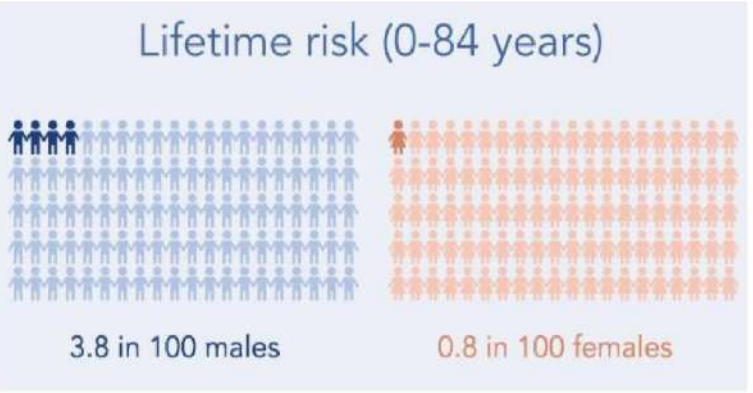
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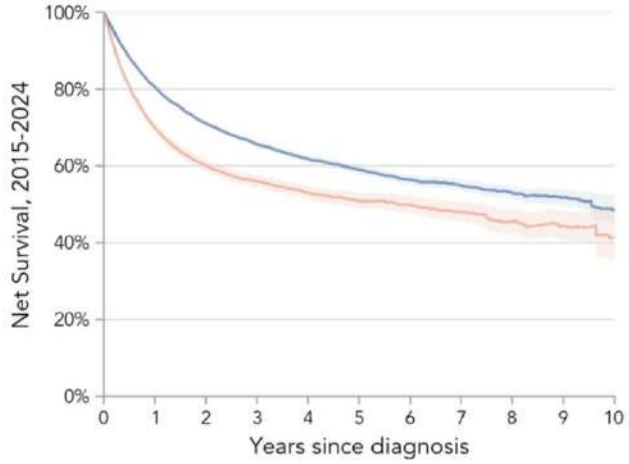


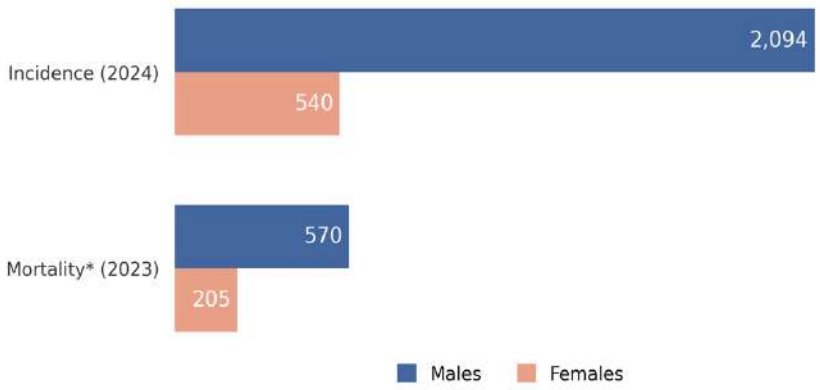
Bladder Cancer Epidemiology – Cancer Fact Sheet 2024

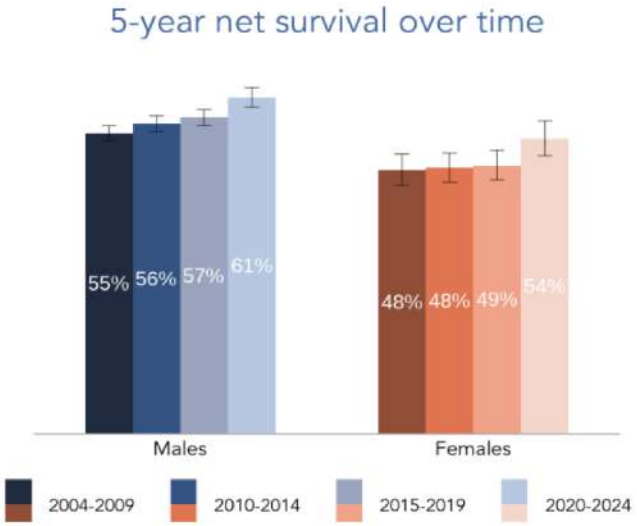
Key facts

- **4th** most common cancer in males
- **15th** most common cancer in females
- **2,634** new diagnoses in 2024
- **775** deaths due to bladder cancer in 2023
- 5-year net survival of **59.4%**





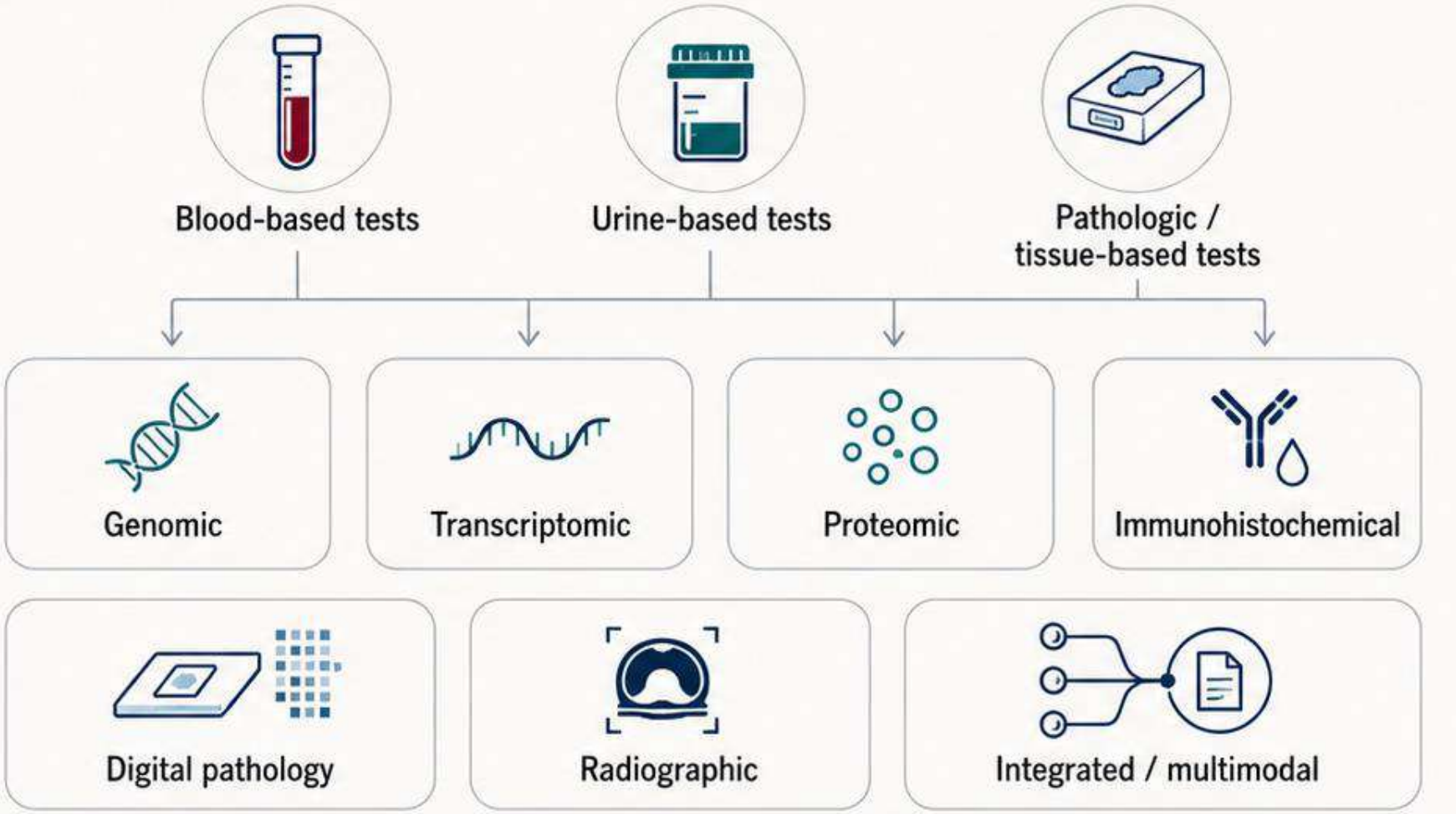




- **5-year net survival has been improving** for males and females in the last 21 years
- Diagnosis in **an early stage** is associated with a **better prognosis**
- More than **16,000 people** are living with the consequences of bladder cancer

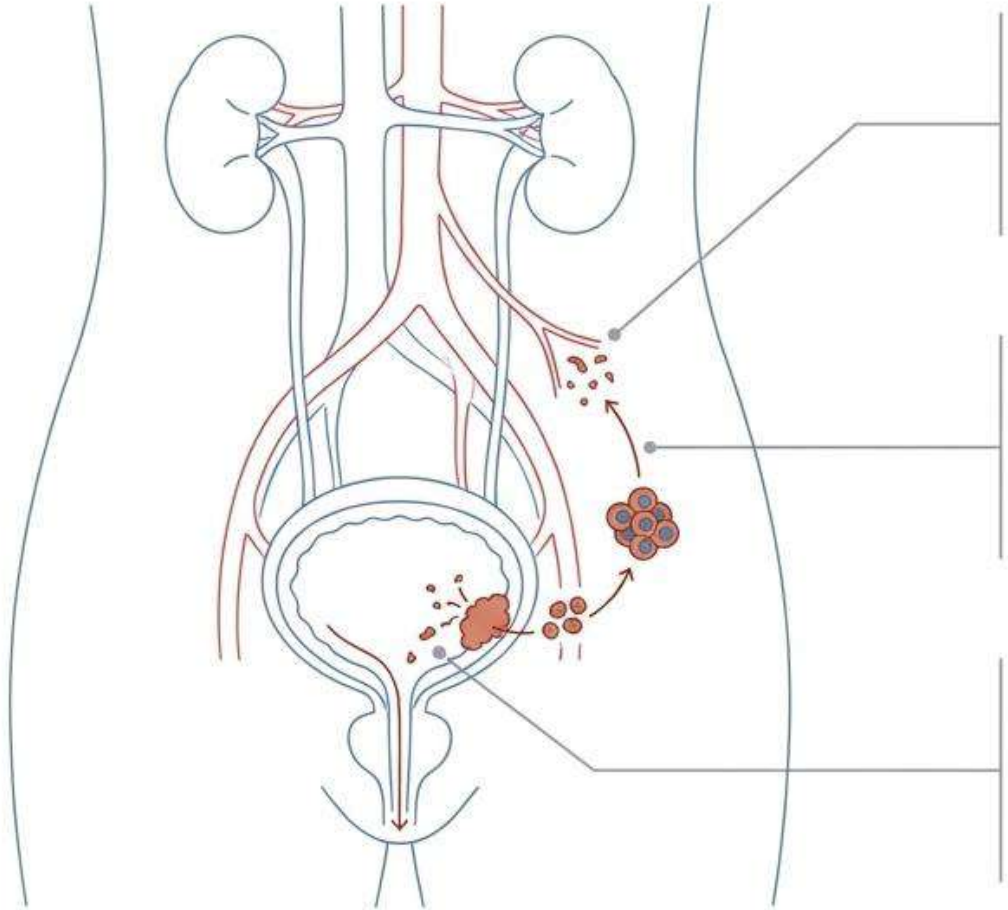
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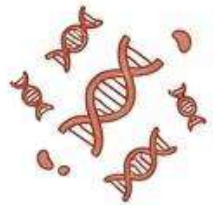
Different tests and different analytes



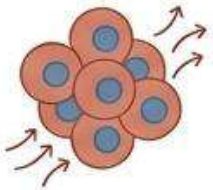
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How bladder tumors leave traces in the body fluids

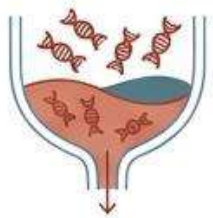




Circulating Tumour DNA (ctDNA) — Dead or dying cancer cells release tiny fragments of their genetic code directly into the bloodstream.



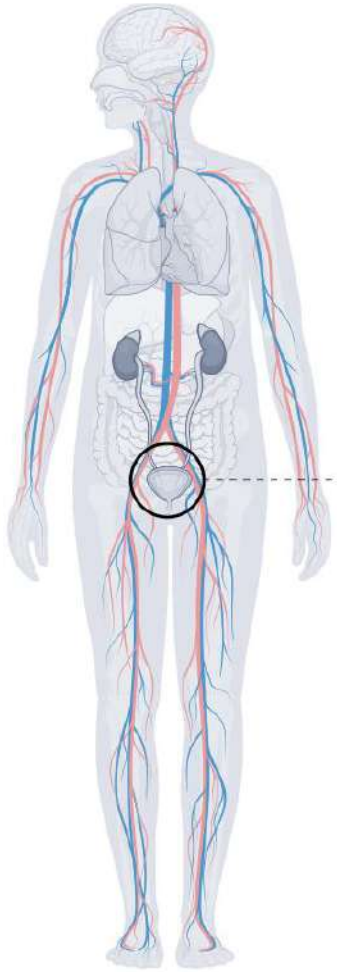
Circulating Tumour Cells (CTCs) — Whole, living cancer cells detach from the main tumor and travel through the blood, looking for new places to grow.



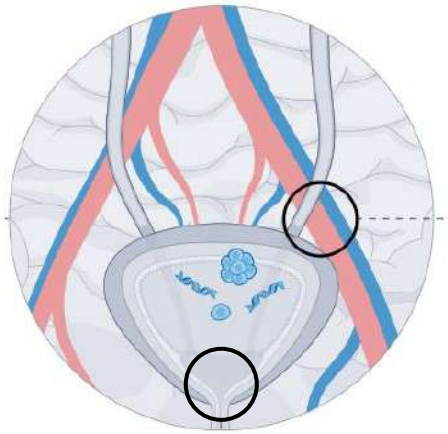
Urinary Tumour DNA (utDNA) — Because bladder tumors are constantly bathed in urine, they shed significant amounts of their DNA directly into the bladder.

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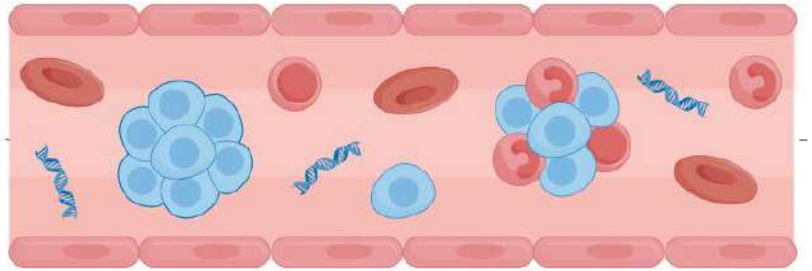
What is a liquid biopsy?



Cancer cells can release tiny fragments of DNA into blood or urine.



Circulating tumour DNA = ctDNA

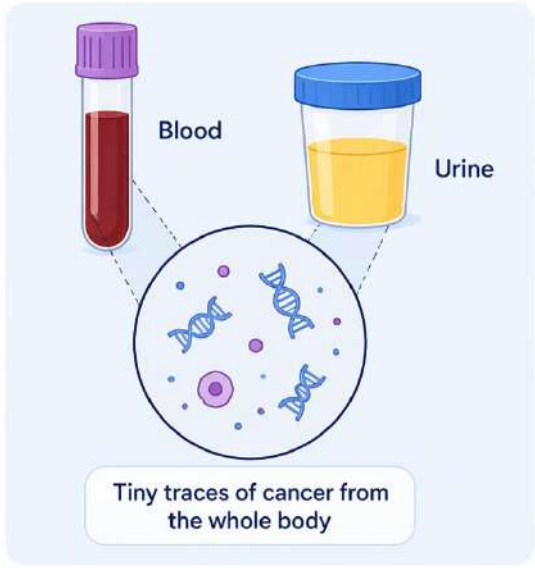


Circulating Tumour Cell = CTC



Urinary tumour DNA = utDNA

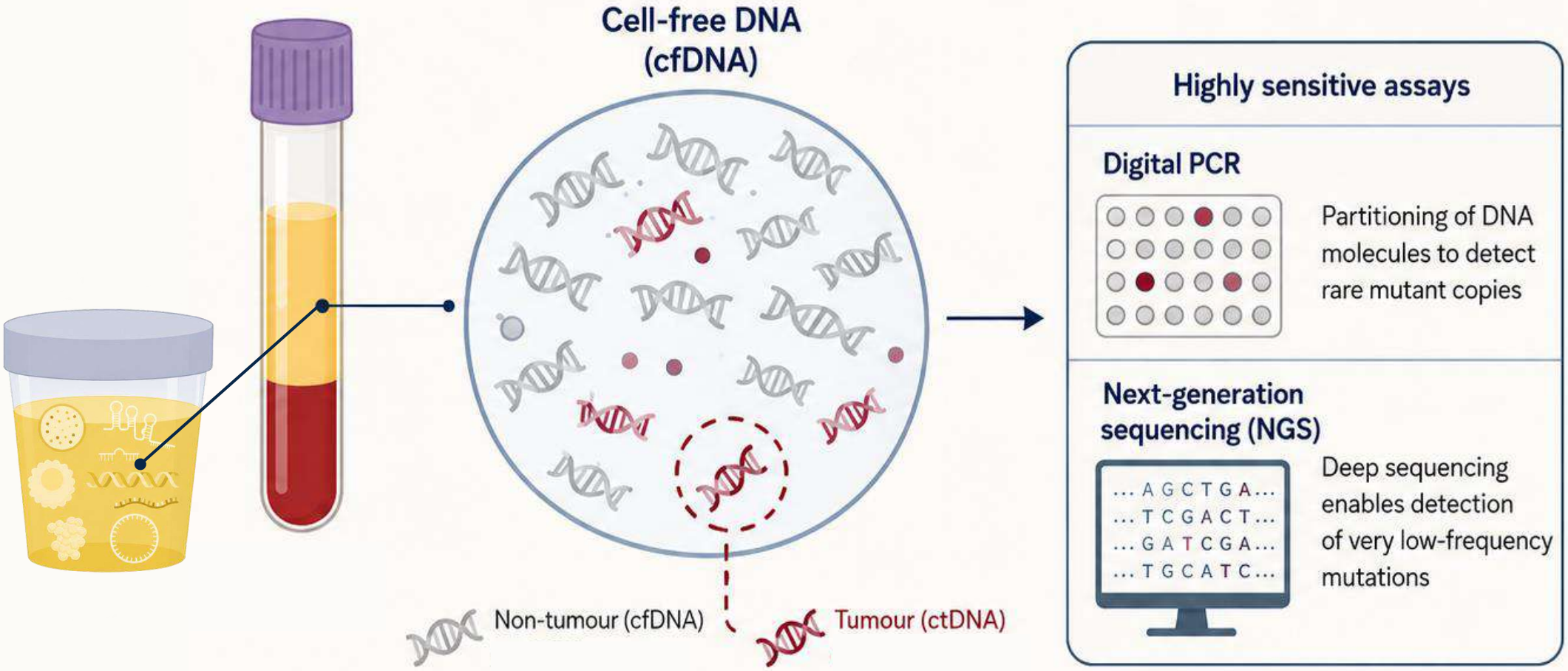
A laboratory test that looks for cancer-related material in a body fluid.



Lindskrog et al.; Nat Rev Urol 2025; Maas et al.; Nat Rev Urol 2023

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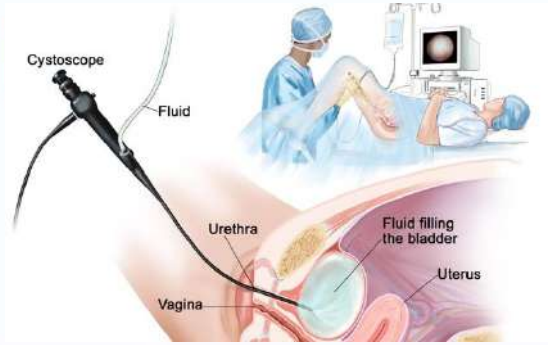
What is a liquid biopsy?



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How do they differ from traditional biopsies?

Traditional Biopsy

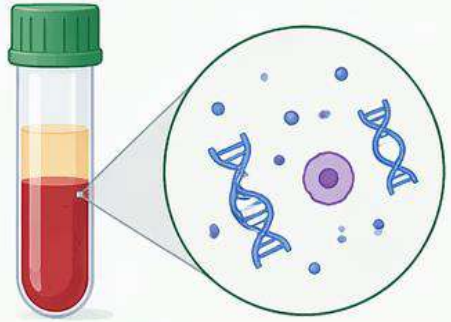


A small piece of tumor tissue is removed from the bladder using a scope or needle.

- **Invasive:** Requires a procedure, sometimes anesthesia.
- **One-time snapshot:** Shows cancer information from one specific spot and time.
- **Not easily repeatable:** Harder and less comfortable to do often.
- **Risks and discomfort:** Possible pain, bleeding, infection, or other complications.

VS.

Liquid Biopsy



A simple blood or urine sample is taken and analyzed for cancer signals.

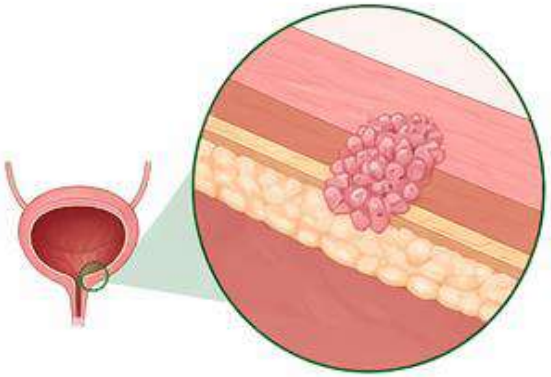
- **Minimally invasive:** Just a blood or urine draw.
- **Real-time insight:** Captures signals from many places and reflects the whole body.
- **Highly repeatable:** Easy to repeat often, enabling close monitoring.
- **Low risk and convenient:** Generally safe with quick recovery.

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The stage of cancer defines the role of the liquid biopsy

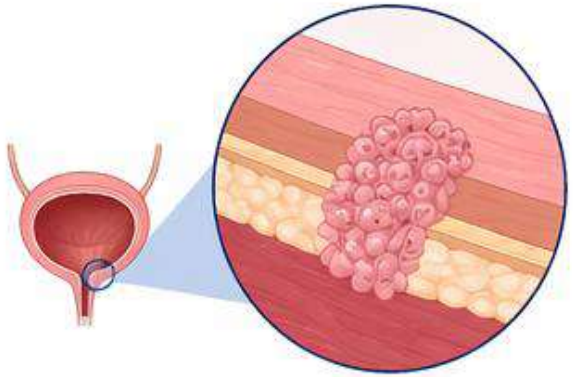
1. Non–muscle invasive (Early stage) → **2. Muscle–invasive (Locally advanced)** → **3. Metastatic (Advanced stage)**

Cancer has not reached the bladder muscle



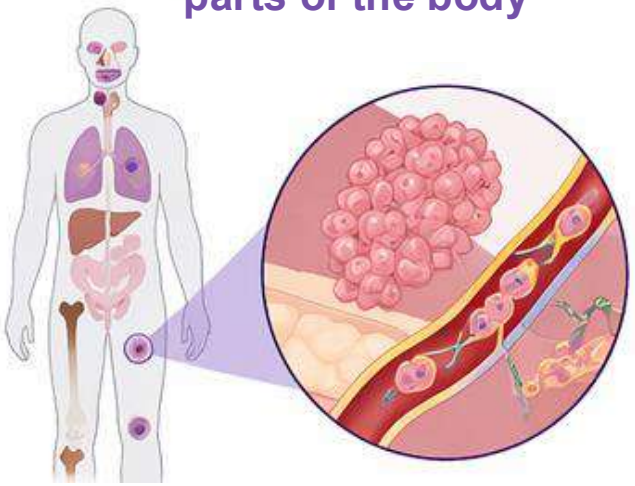
Urine tests may help detect a tumour or a recurrence inside the bladder.

Cancer has grown into the muscle



Blood tests may help assess response and cancer remaining after surgery.

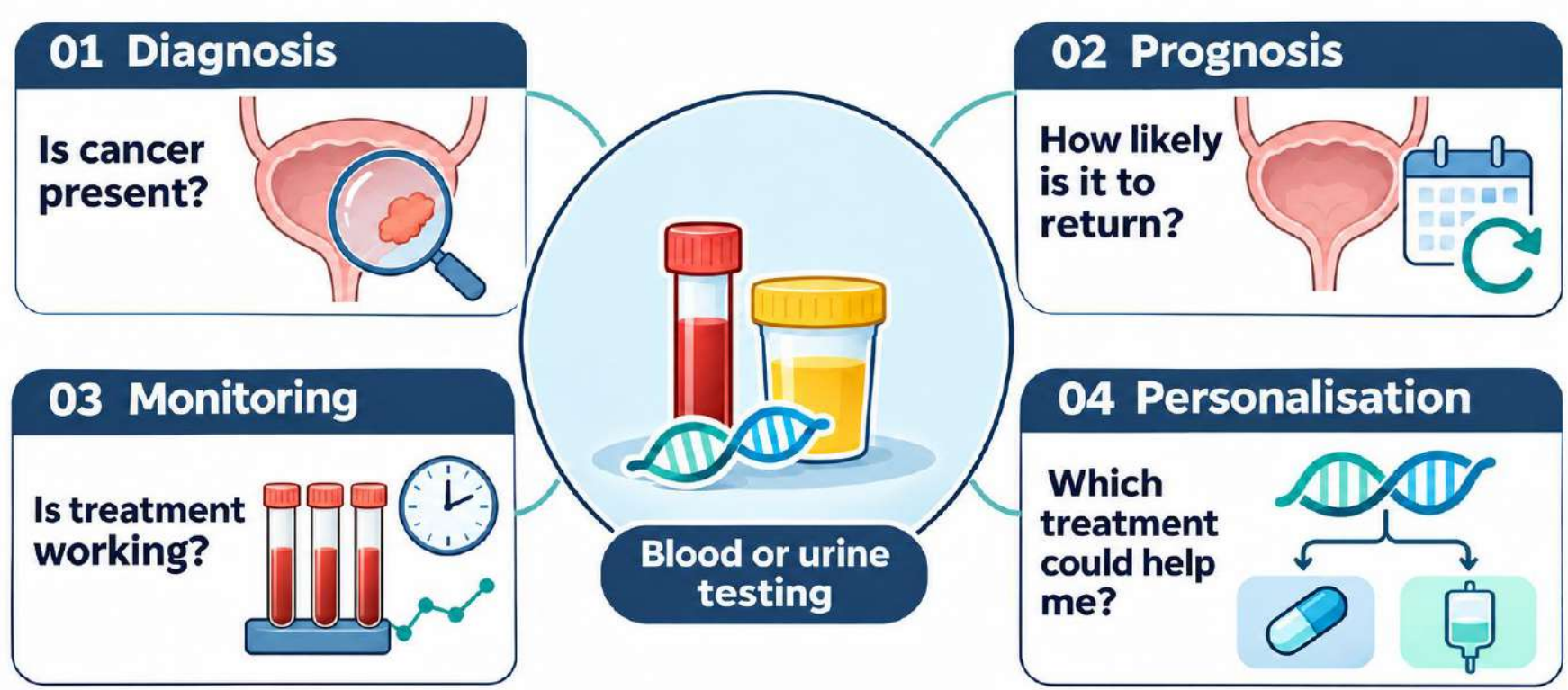
Cancer has spread to other parts of the body



Blood tests may help identify treatment targets and follow change.

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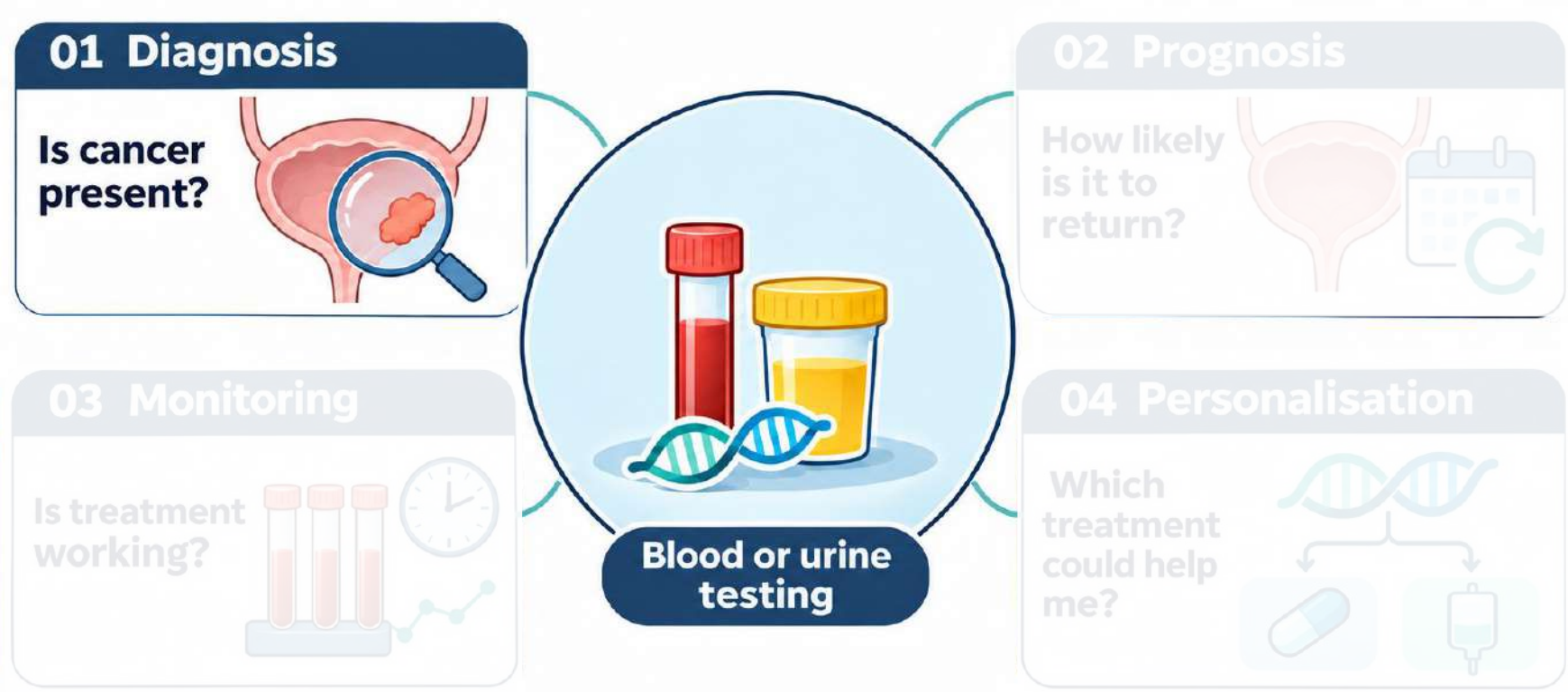
The questions that matter to patients



A liquid biopsy test should help answer a question that affects care

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The questions that matter to patients



A liquid biopsy test should help answer a question that affects care

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Bladder cancer diagnosis requires an established test

Cystoscopy

A small camera lets the specialist look inside the bladder.

Tissue examination (TUR-B)

A sample confirms the cancer type and helps establish its stage and grade.

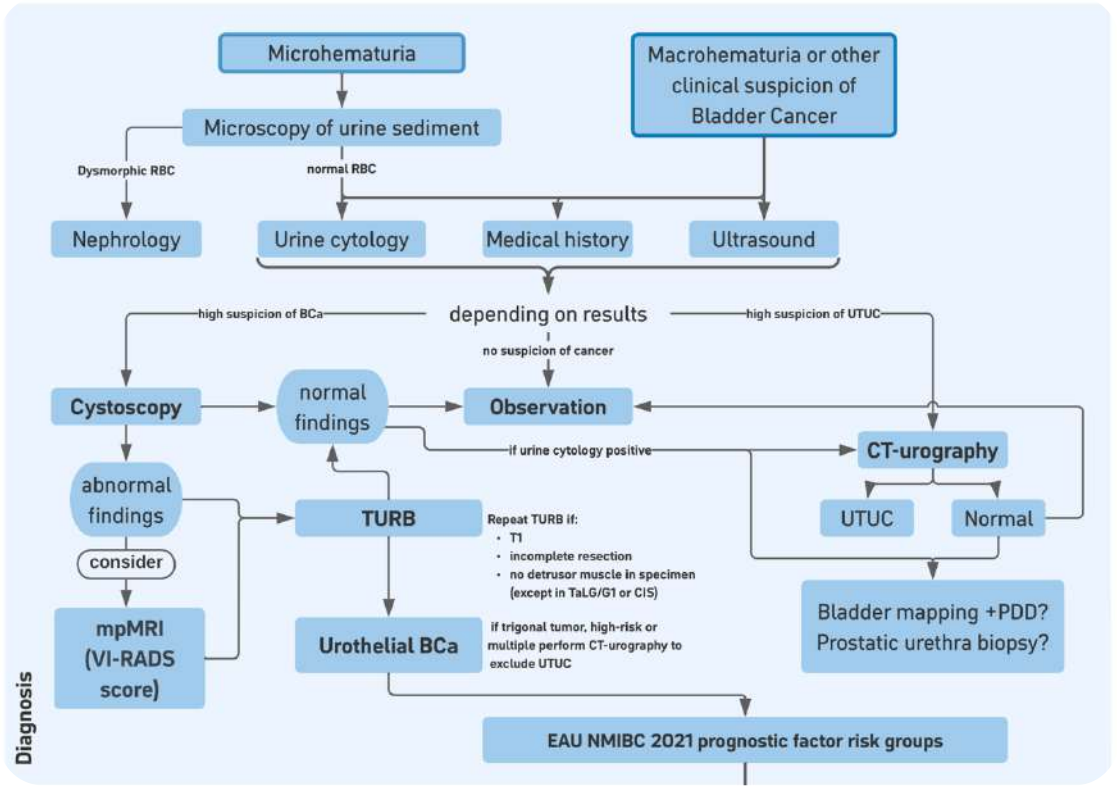
Urine markers

Selected tests may add information, but they do not establish the diagnosis alone.

Biomarker/Assay	Methodology	Sensitivity (%)	NPV (%)
Urine cytology	Cytomorphologic examination	41–44	96
AssureMDx	Multi-omics DNA-based assay	93–96	99–100
CxBladder	Multigene mRNA panel	77–95	96–99
EarlyTect BCD	PENK DNA methylation assay	81–87	98
NMP22 BladderChek	Nuclear matrix protein	41–81	95–100
UroVysion FISH	Chromosomal aneuploidy	72–89	98
Xpert BCD	mRNA expression (five-gene panel)	78–94	98

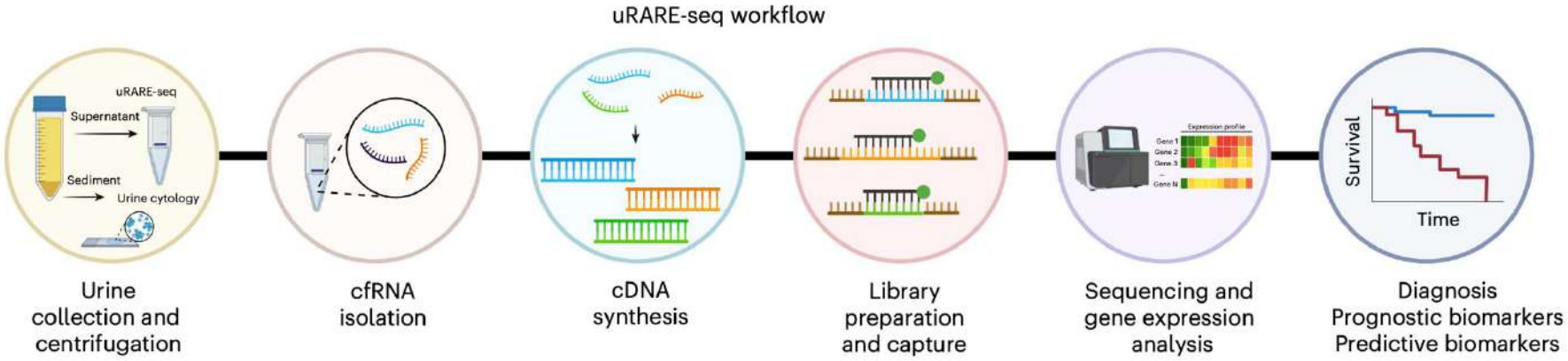
High Negative Predictive Value (NPV) in these assays largely reflects the critically low baseline prevalence of malignancy (1-3%) in AMH populations, while sensitivity remains dangerously variable.

EAU guidelines 2026



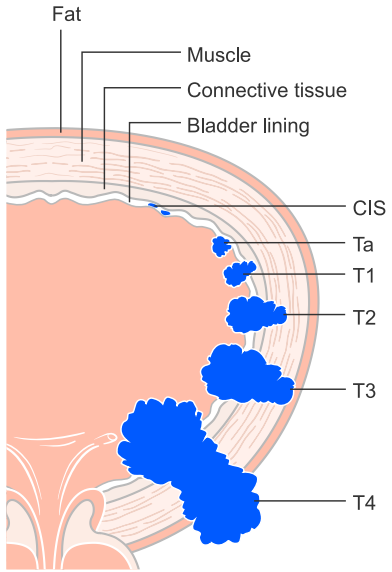
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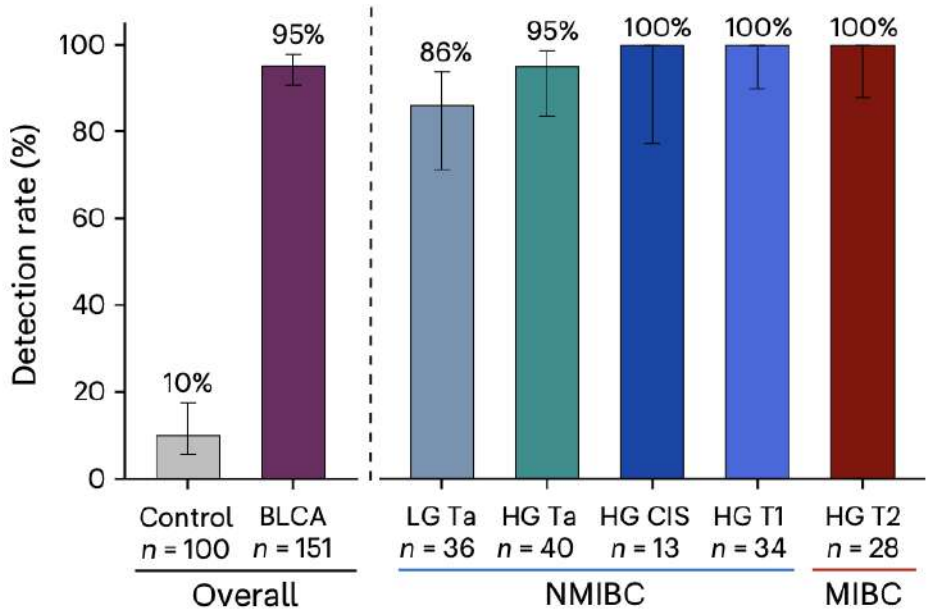
Urine cell-free RNA for localised bladder cancer detection



95 out of 100

people with cancer would test positive at 95% sensitivity.





90 out of 100

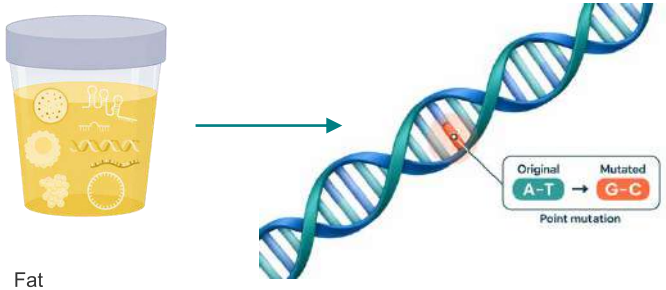
people without cancer would test negative at 90% specificity.

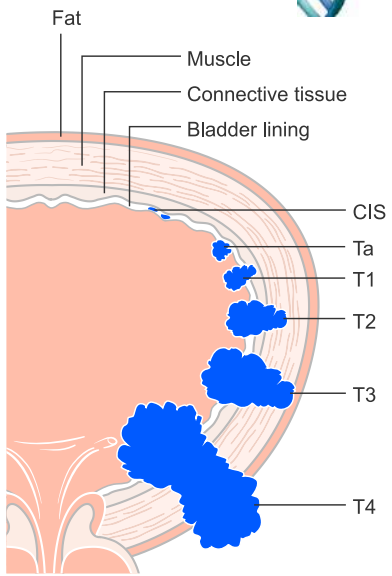
Liu et al.; Nat Med, 2026; CRUK

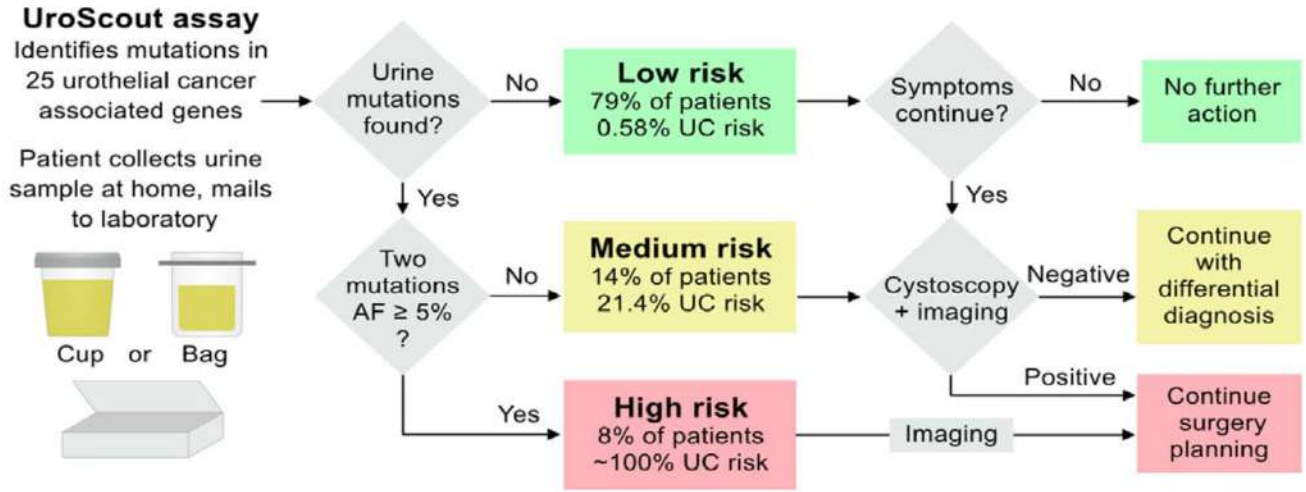
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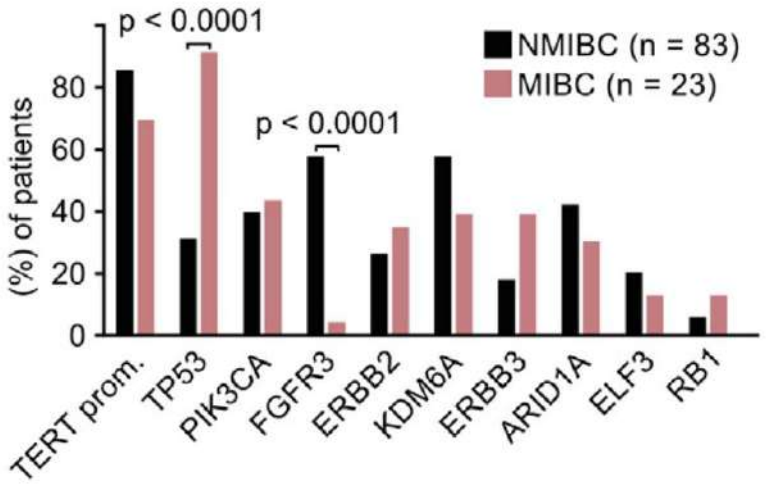
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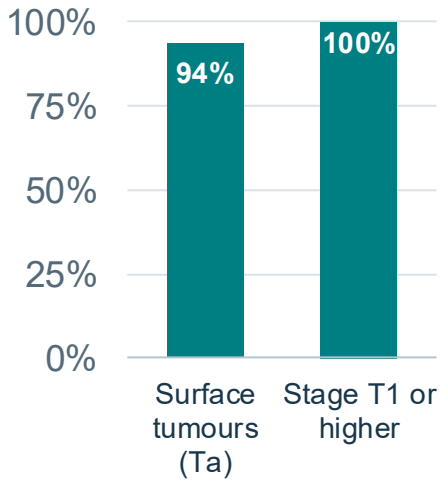
UroScout research study in 281 patients using a large urine sample.











88%

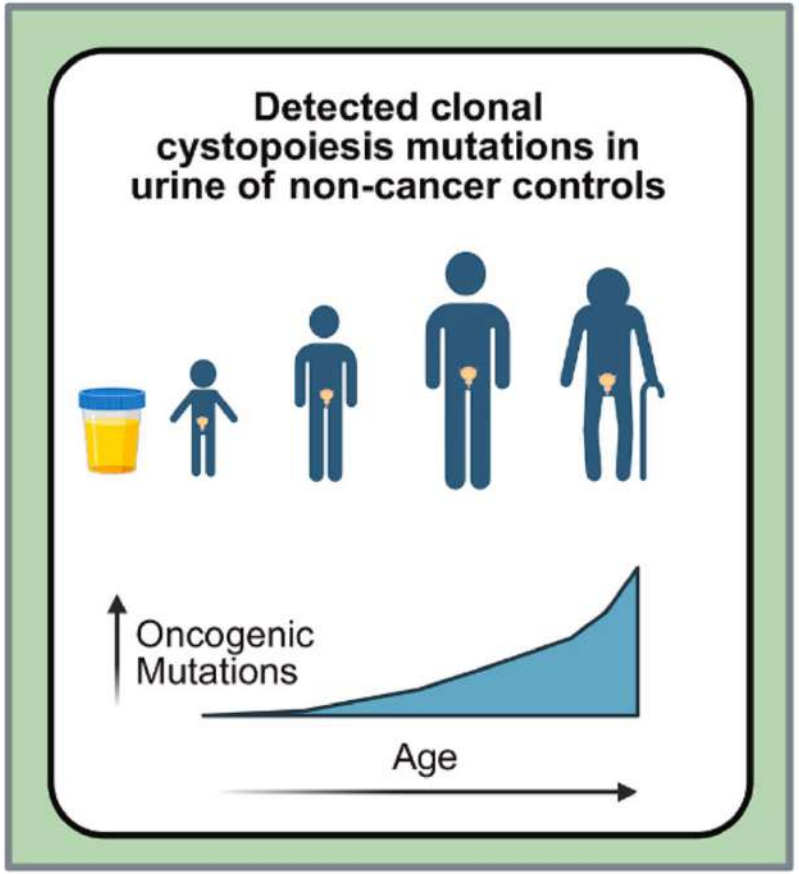
specificity among people without urothelial cancer

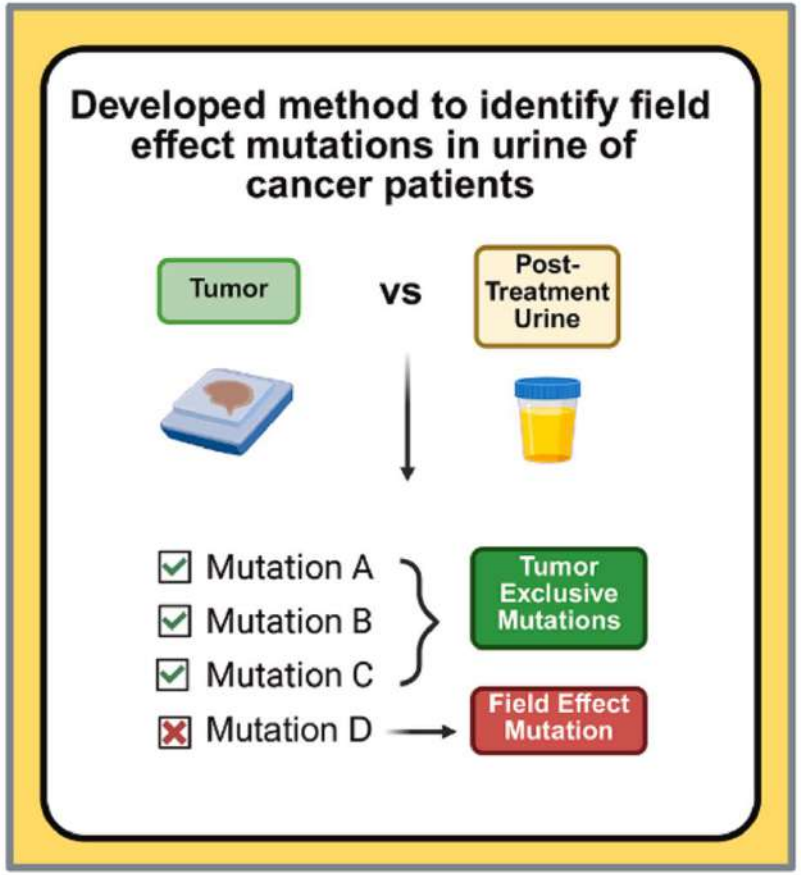
Nikkola et al.; Eur Urol, 2024

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Why a urine DNA signal can be misleading

Some DNA changes also occur in bladder cells that are not cancerous.





The “field effect”

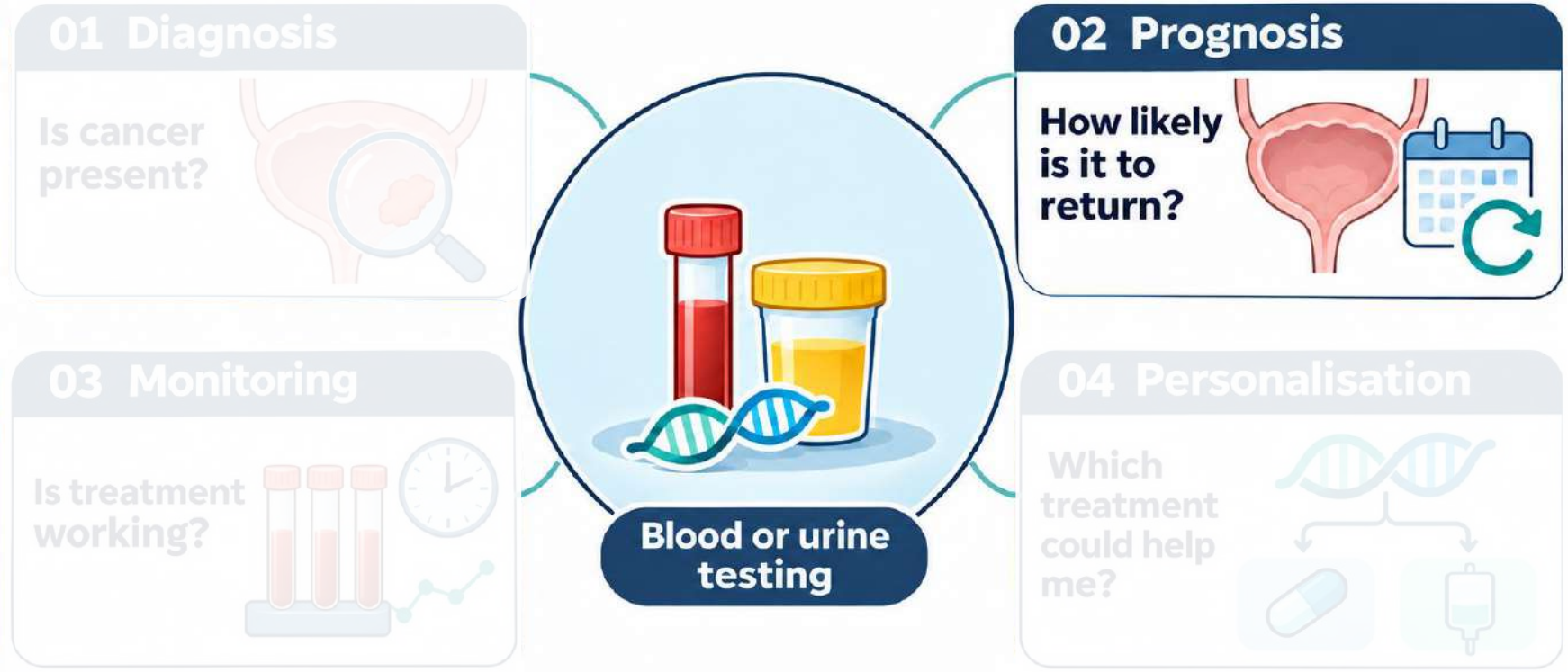
Ageing or previously exposed bladder tissue can release altered DNA.

Researchers are developing filters to separate this background from tumour signals.

Shi et al.; Cell, 2026

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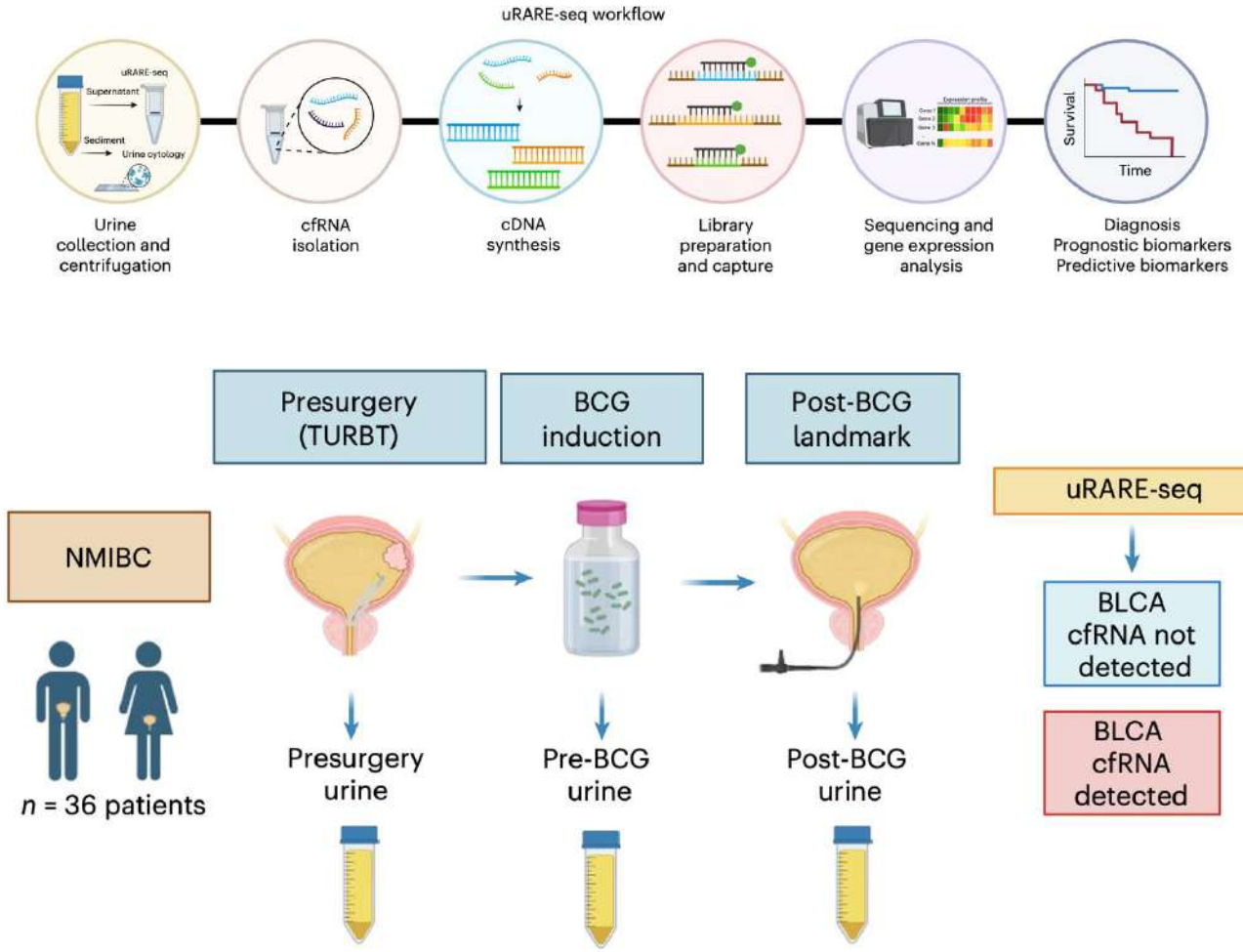
The questions that matter to patients



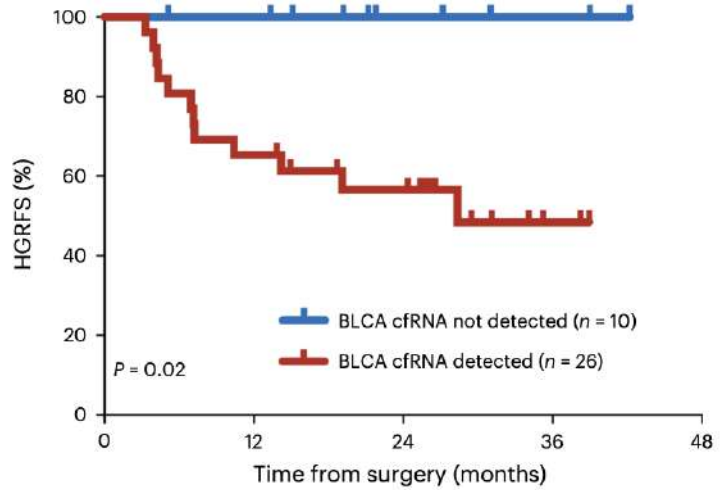
A liquid biopsy test should help answer a question that affects care

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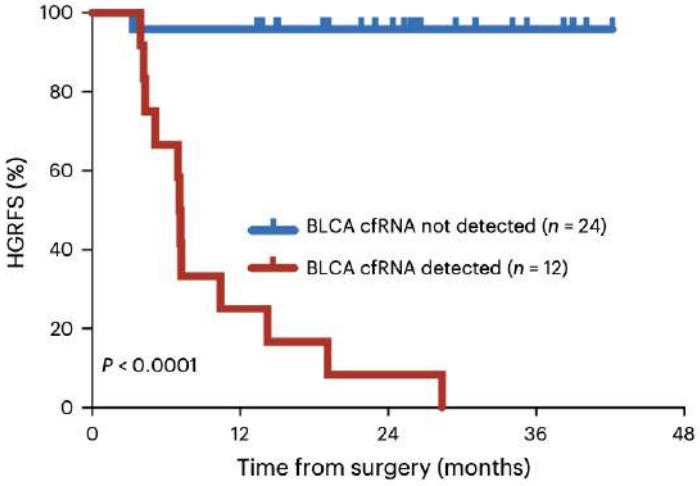
Prognostic value of urine cell-free RNA in NMIBC



Pre BCG urine



Post BCG urine

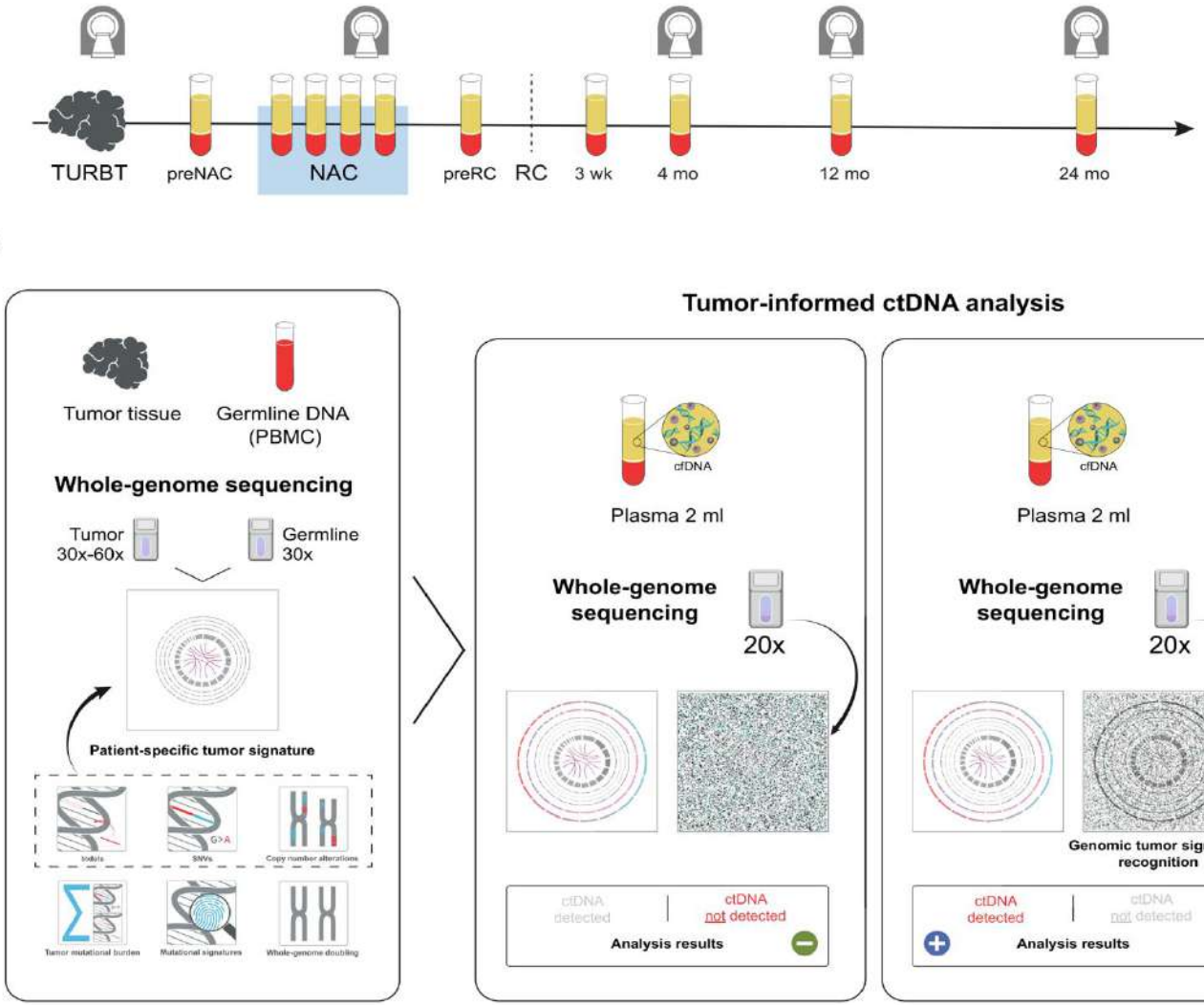


Liu et al.; Nat Med, 2026

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Prognostic value of ctDNA in de perioperative setting of MIBC

- Early observational data show that **ctDNA positivity** is associated with **worse outcomes**. [4]
- This association is seen when ctDNA is measured **before chemotherapy, before cystectomy,** and **after cystectomy**.
- Across these time points, ctDNA-positive patients show **poorer** recurrence-free survival (RFS) and overall survival (OS).



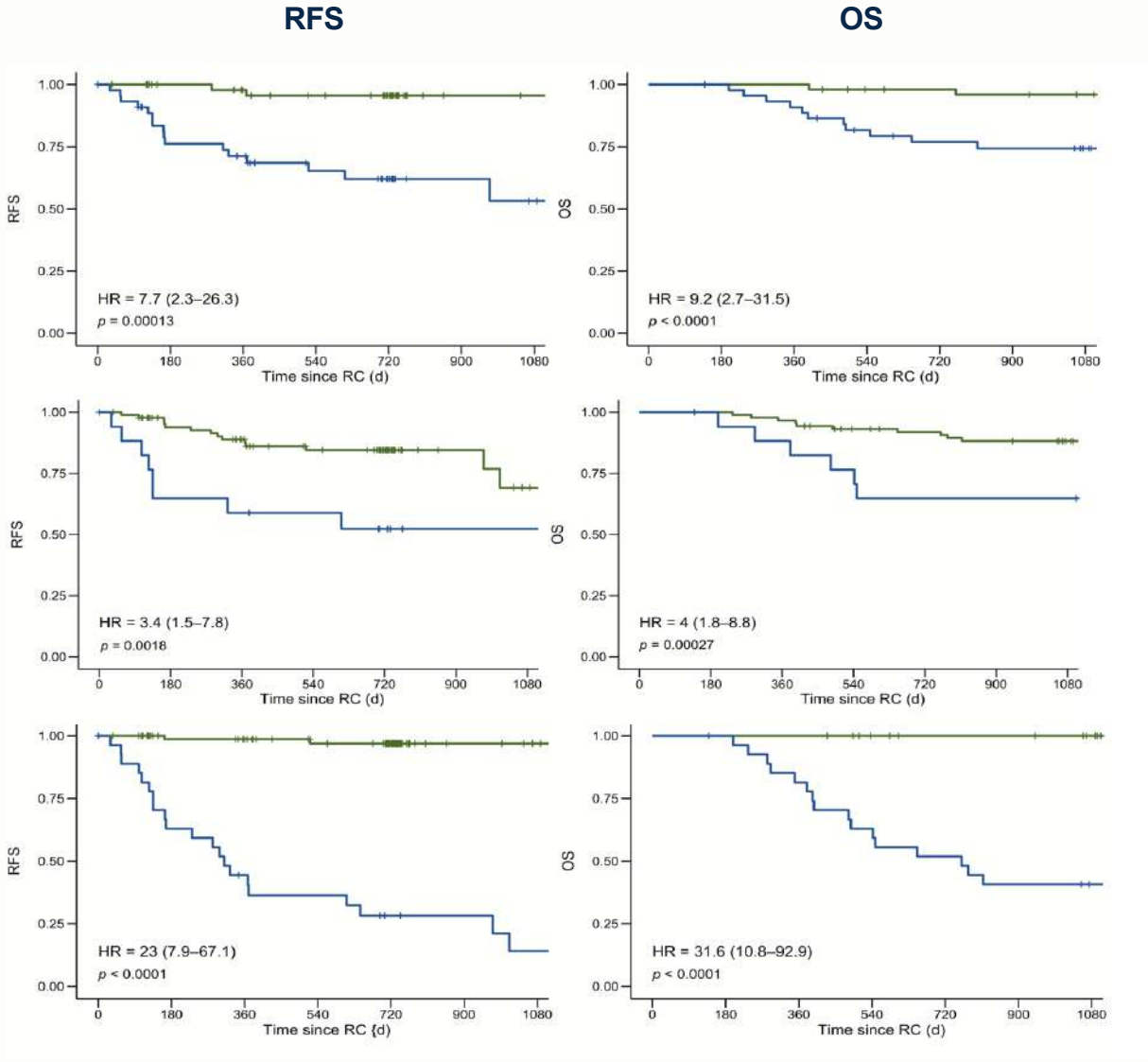
Nordentoft et al.; Eur Urol 2024

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ctDNA status Negative Positive

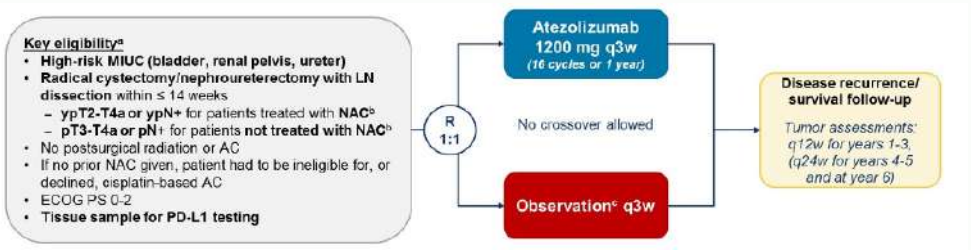


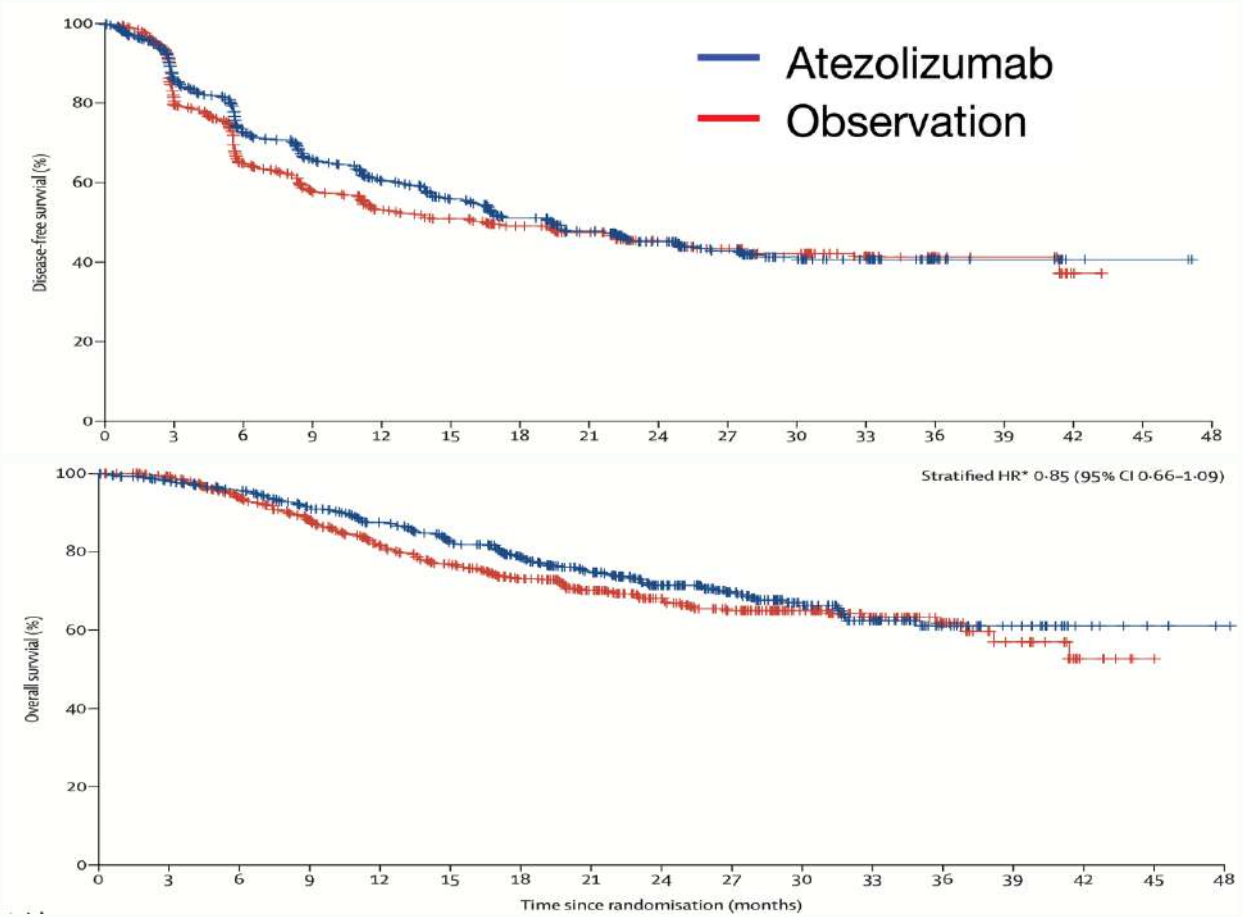
Nordentoft et al.; Eur Urol 2024

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Predictive value of ctDNA in the adjuvant setting of MIBC

- Phase III **IMvigor010** randomized high-risk MIBC patients after surgery to **adjuvant atezolizumab** versus **observation**.
- In the overall intention-to-treat population, the trial **did not meet** its primary **disease-free survival (DFS)** endpoint.
- Overall survival (OS) curves also showed **no clear benefit** in the unselected population.

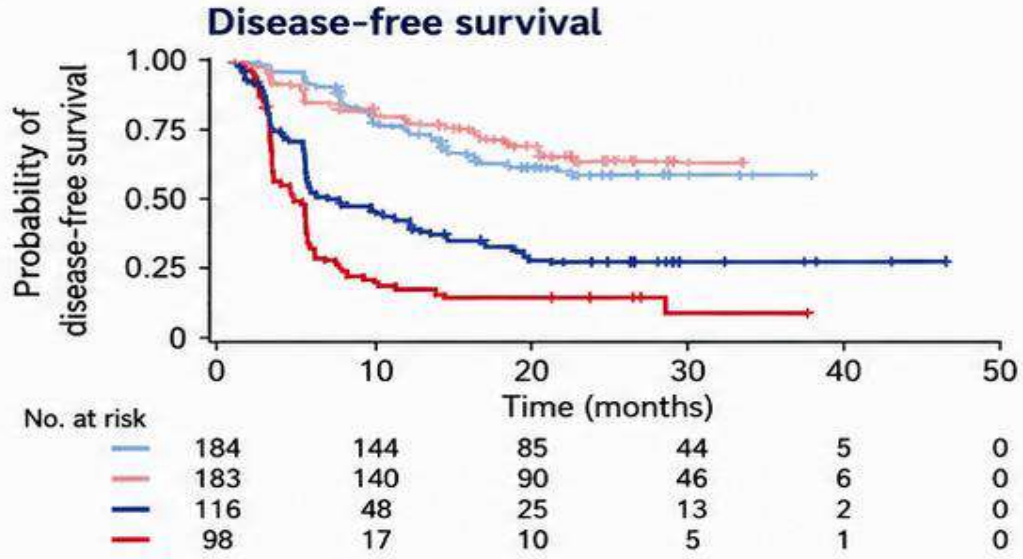




Bellmunt et al.; Lancet Onc, 2021

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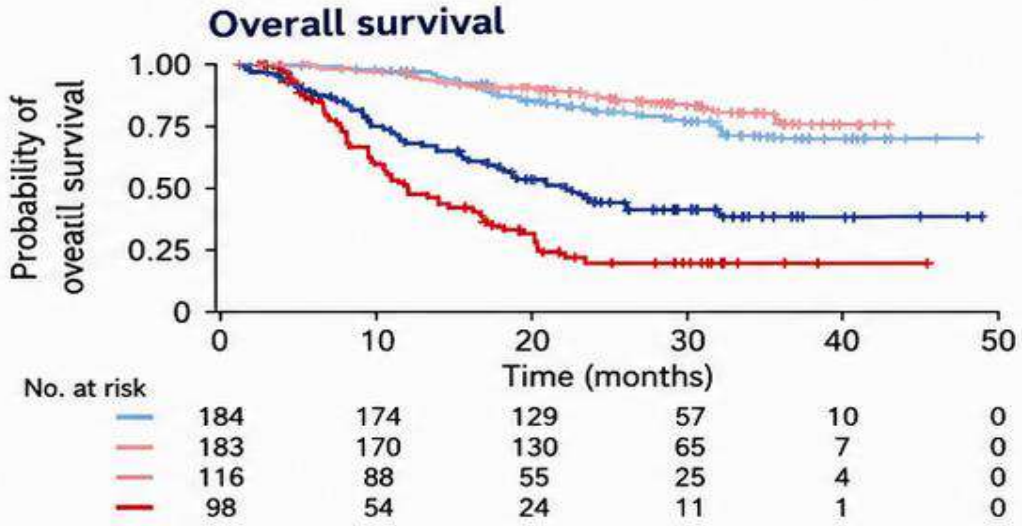


Post RC

ctDNA⁻:
HR 1.14 (95% CI 0.81–1.62)

ctDNA⁺:
HR 0.58 (95% CI 0.43–0.79)

Atezolizumab ctDNA⁻
Observation ctDNA⁻
Atezolizumab ctDNA⁺
Observation ctDNA⁺



Post RC

ctDNA⁻:
HR 1.31 (95% CI 0.77–2.23)

ctDNA⁺:
HR 0.59 (95% CI 0.41–0.86)

Atezolizumab ctDNA⁻
Observation ctDNA⁻
Atezolizumab ctDNA⁺
Observation ctDNA⁺

Powels et al, Nat Med, 2021

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Prognostic value of ctDNA prior/post surgery for MIBC

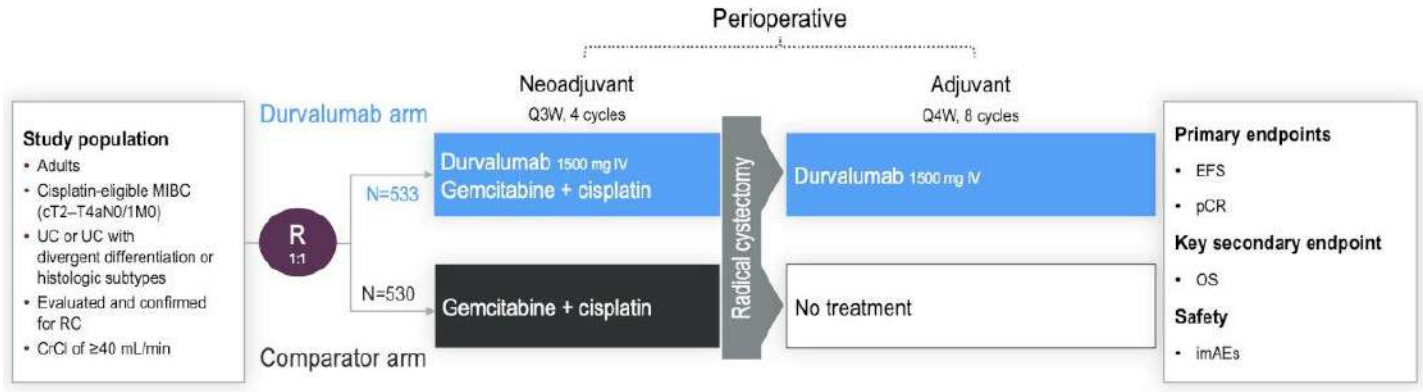
NIAGARA

Perioperative durvalumab with NAC provides EFS benefit to MIBC patients with or without detectable ctDNA at baseline

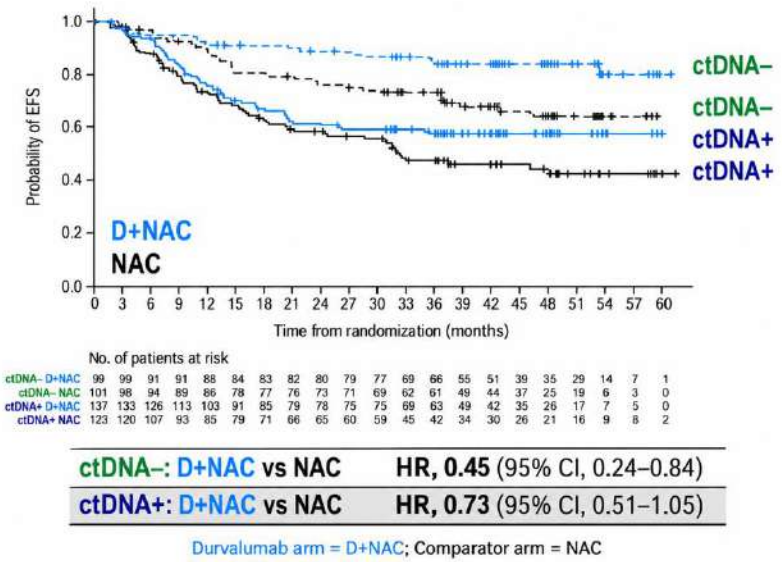
➔ ctDNA detection is prognostic

Post radical cystectomy D+NAC provides DFS benefit to patients with ctDNA-negative status

➔ ctDNA detection is prognostic



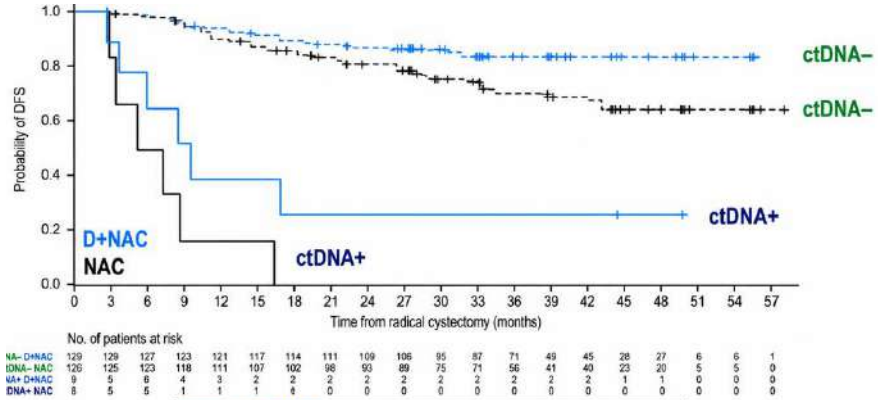
EFS (baseline ctDNA)



ctDNA–: D+NAC vs NAC	HR, 0.45 (95% CI, 0.24–0.84)
ctDNA+: D+NAC vs NAC	HR, 0.73 (95% CI, 0.51–1.05)

Durvalumab arm = D+NAC; Comparator arm = NAC

DFS (post RC)

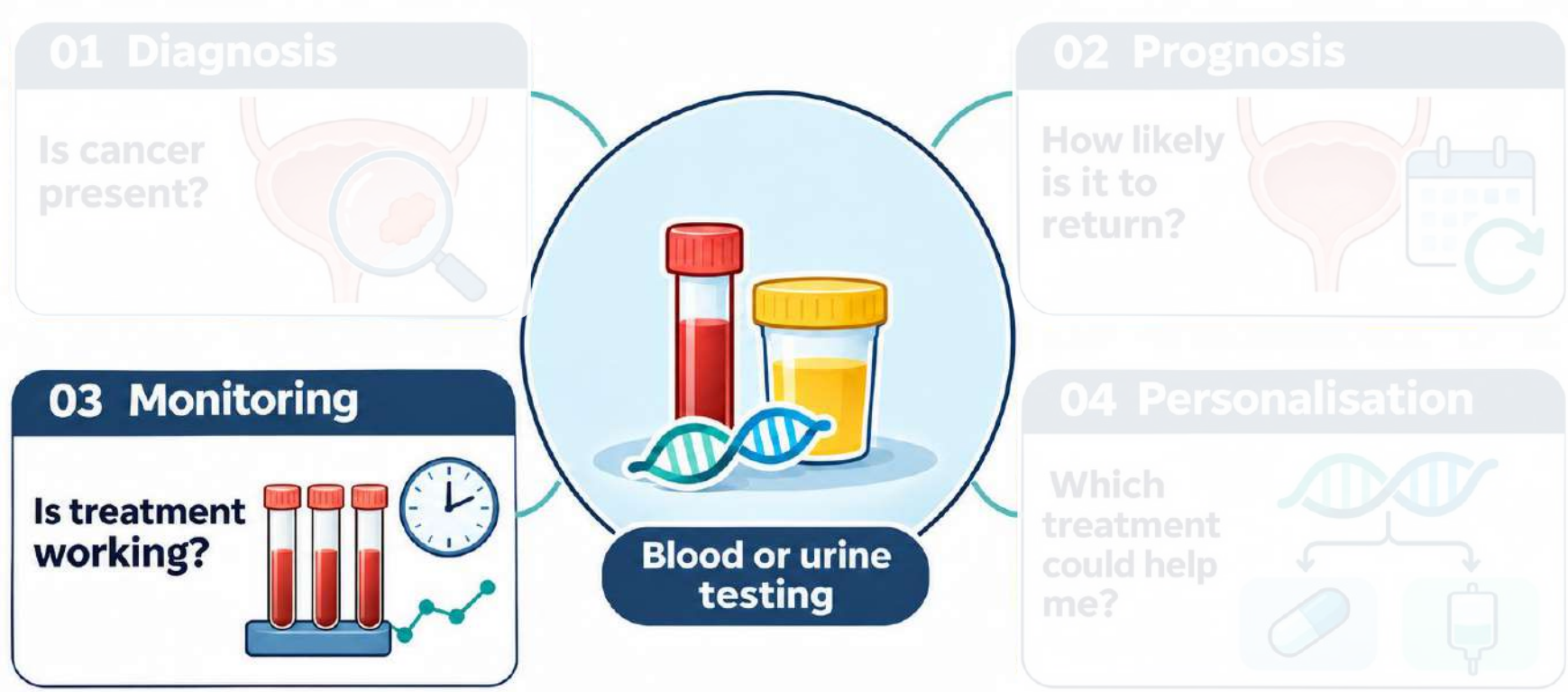


ctDNA–: D+NAC vs NAC	HR, 0.49 (95% CI, 0.28–0.84)
ctDNA+: D+NAC vs NAC	HR not calculated[a]

Durvalumab arm = D+NAC; Comparator arm = NAC

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The questions that matter to patients

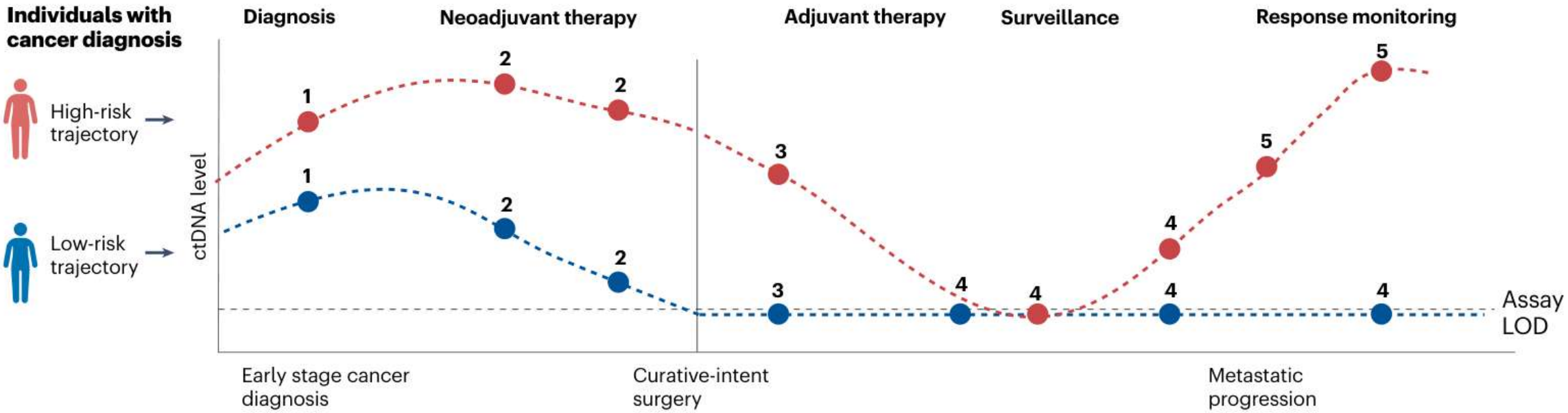


A liquid biopsy test should help answer a question that affects care

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ctDNA liquid biopsy Monitoring – Why?

Molecular residual disease (MRD) means a cancer signal that may remain after treatment.



1 • **Baseline systemic tumor burden assessment**
- Risk classification
- Therapy stratificaton

2 • **Neoadjuvant therapy response monitoring**
- Prediction of recurrence
- Neoadjuvant therapy optimization

3 • **Landmark MRD assessment**
- Prediction of recurrence
- Adjuvant therapy optimization

4 • **Longitudinal disease surveillance**
- Early prediction of recurrence
- Adjuvant therapy duration and de-escalation

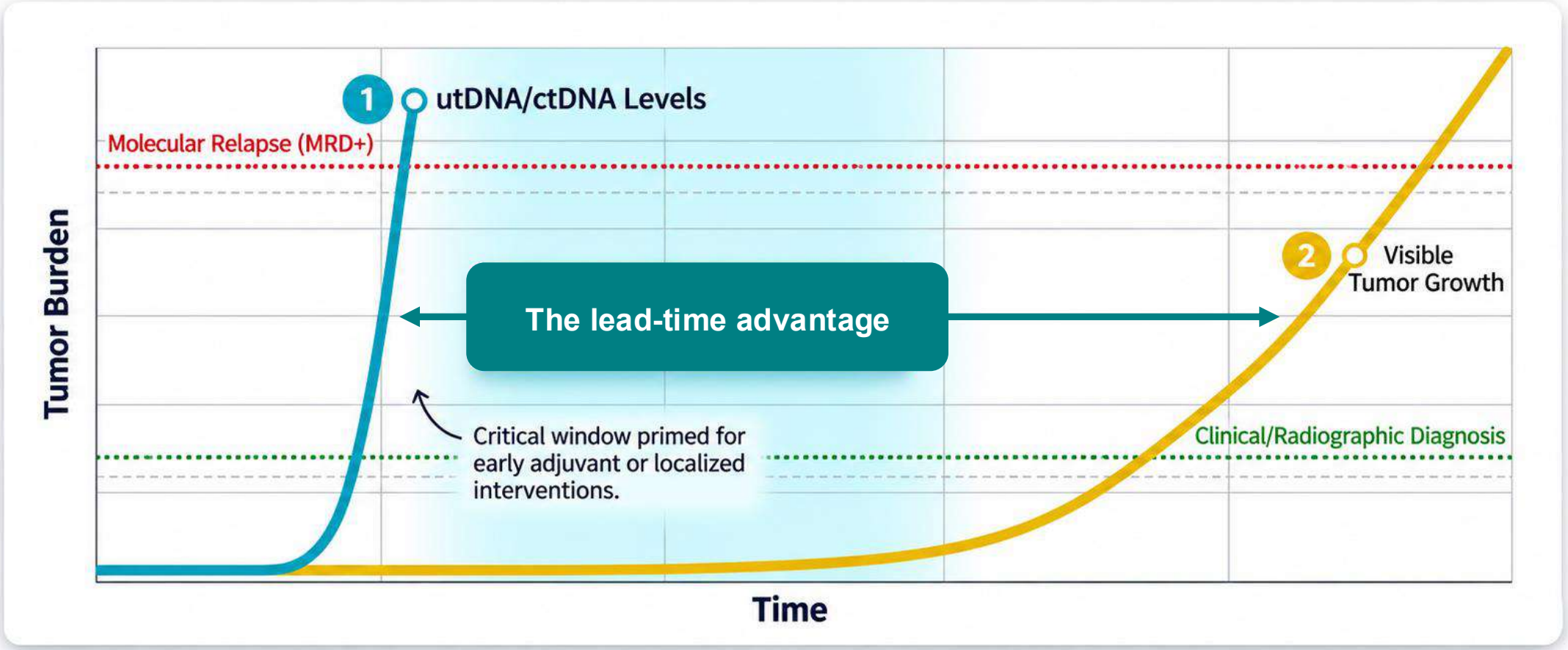
5 • **Early detection of metastatic progression**
- Therapy response monitoring
- Therapy escalation

Landon et al, Nat Med, 2025

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A liquid biopsy may have a lead time advantage

Liquid biopsies detect molecular recurrence long before a physical tumor manifests on imaging or cystoscopy, creating a critical, actionable therapeutic window.

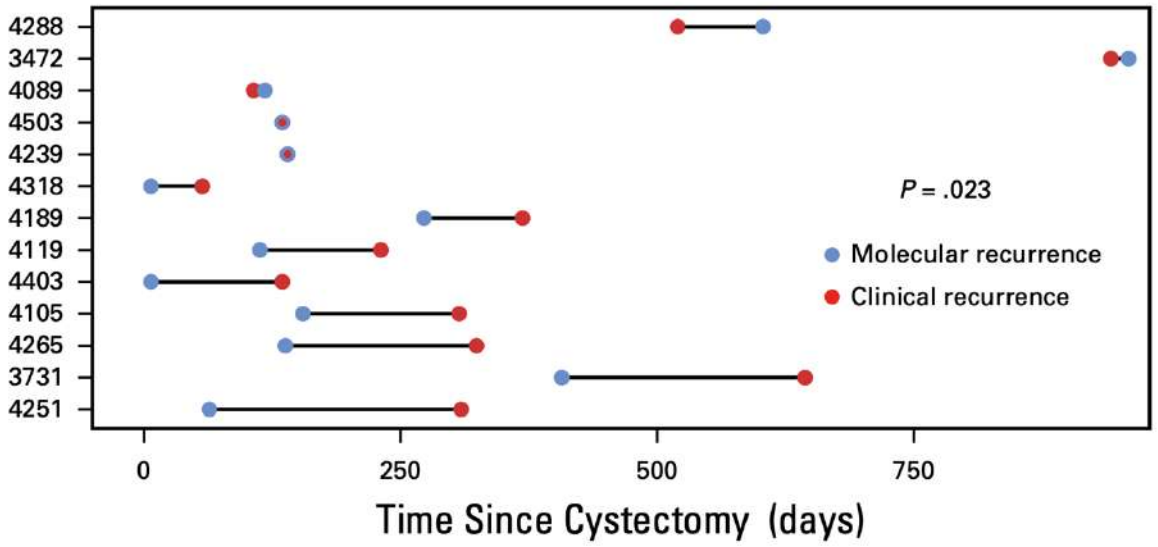


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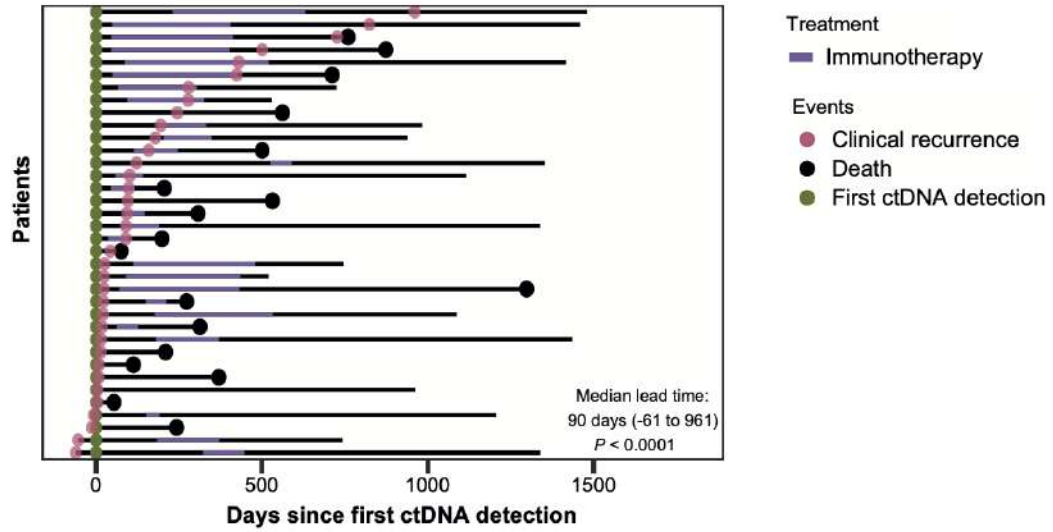
A liquid biopsy can detect relapse before scans

Lead time from first post-RC ctDNA detection to clinical recurrence.

Study 2019



Study 2026



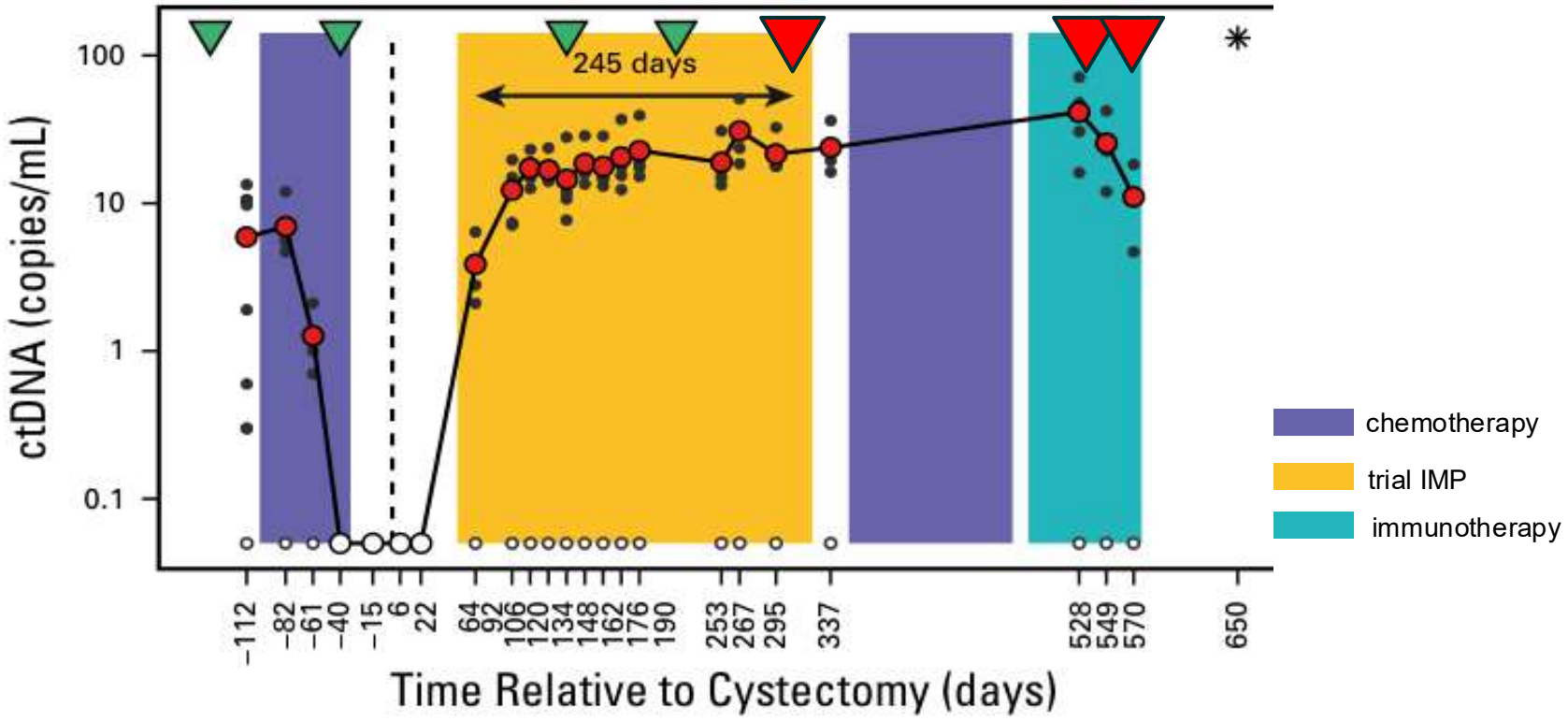
90-96 days median earlier detection than imaging

Christensen et al, JCO, 2019; Dyrskjøy et al., Ann of Onc, 2026

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Repeated ctDNA measurements can show change

Falling or rising circulating tumour DNA may add information about response or resistance.



A falling signal

Can be consistent with a response to treatment.

A rising signal

May trigger closer assessment or further tests.

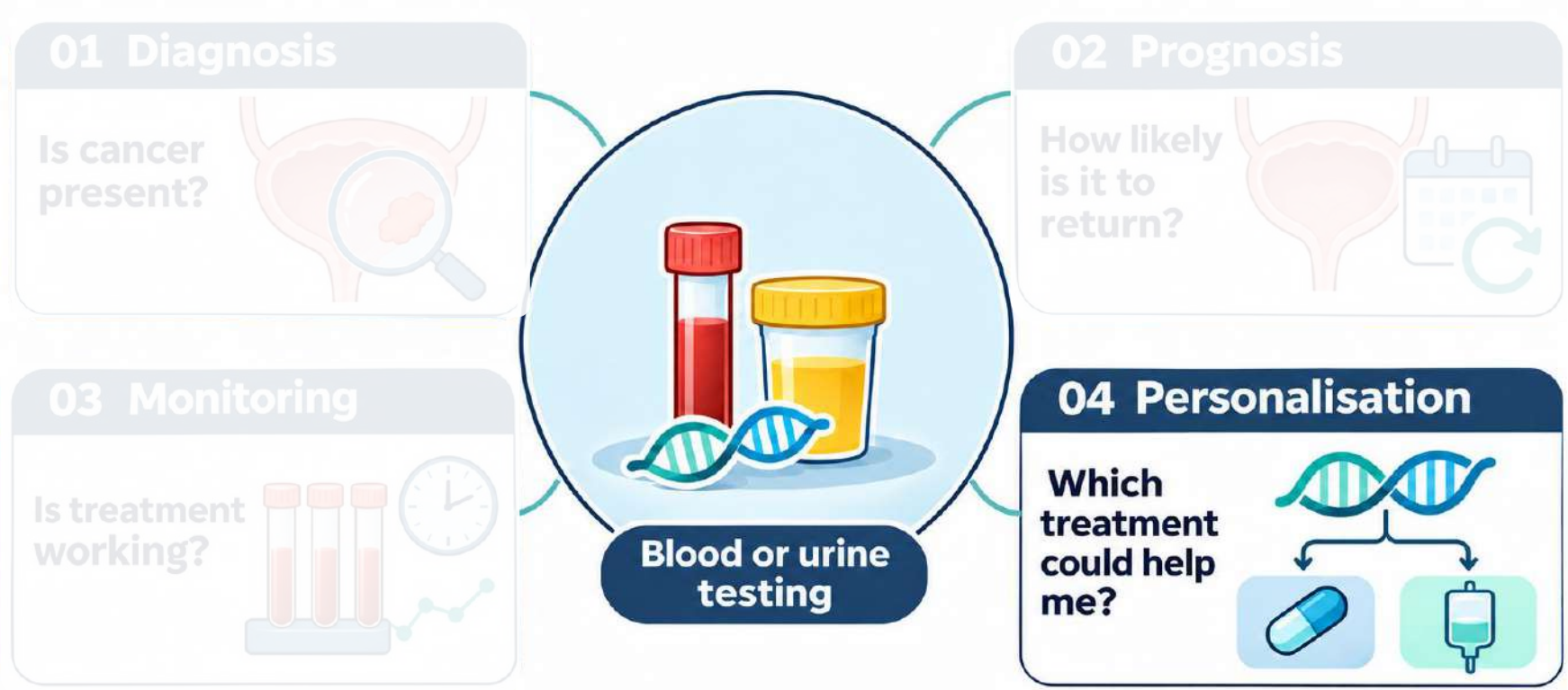
The decision still needs context

Scans, symptoms and the treatment plan remain important.

Christensen et al, JCO, 2019

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The questions that matter to patients

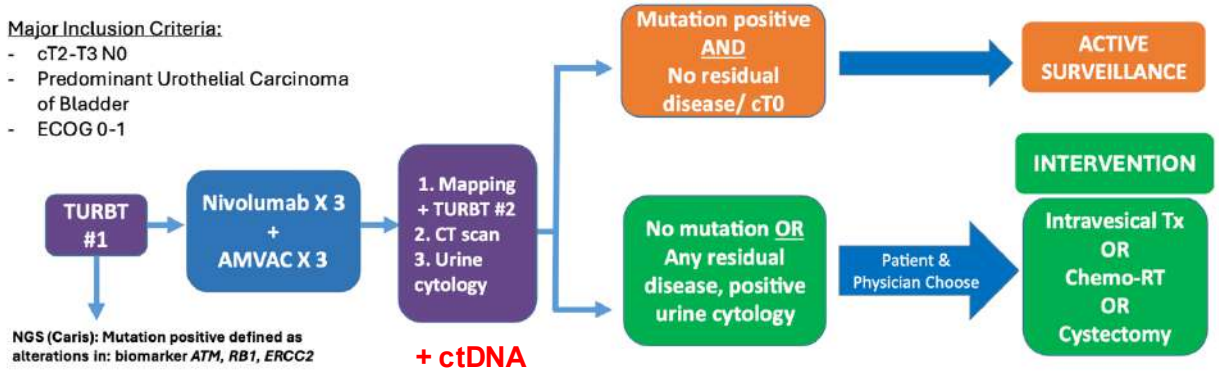


A liquid biopsy test should help answer a question that affects care

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A ctDNA-guided strategy for bladder-sparing therapy

RETAIN
(non-randomised Ph2)

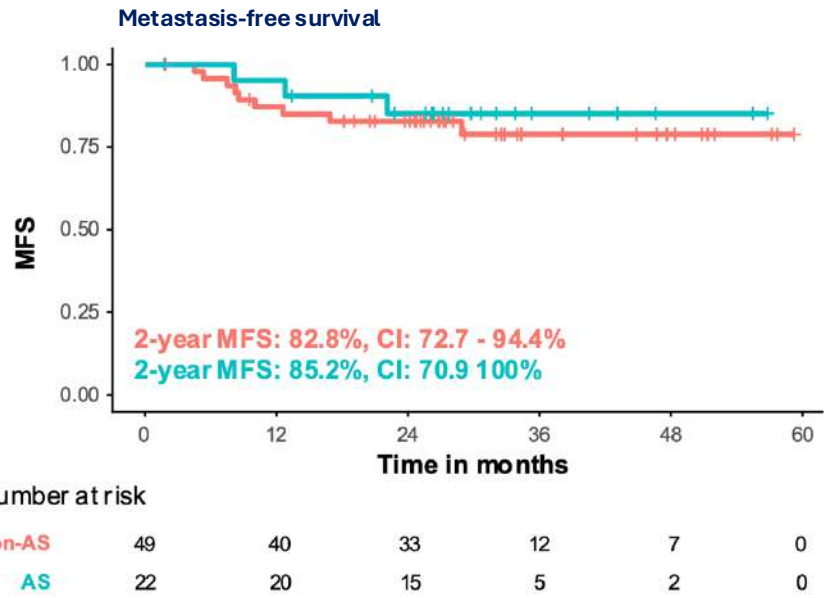


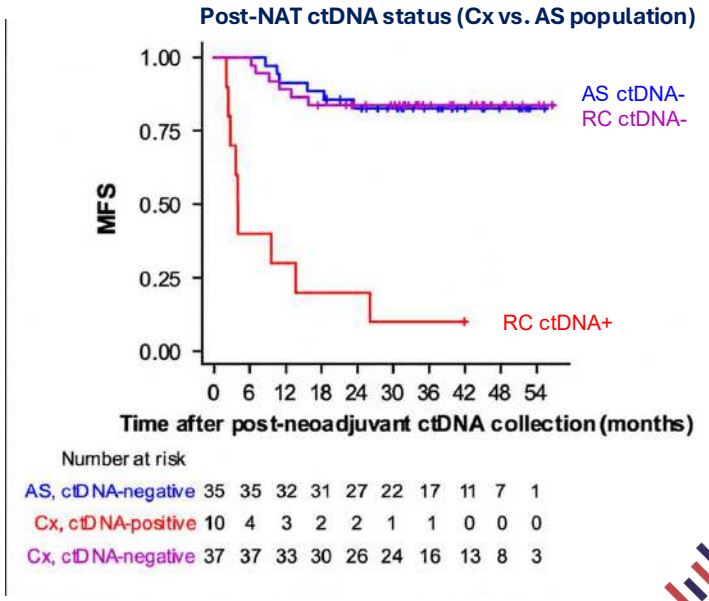
LOWER RISK OF SPREAD

85%

Free of cancer spread at 2 years (estimate)

Selected patients with negative ctDNA managed with active surveillance



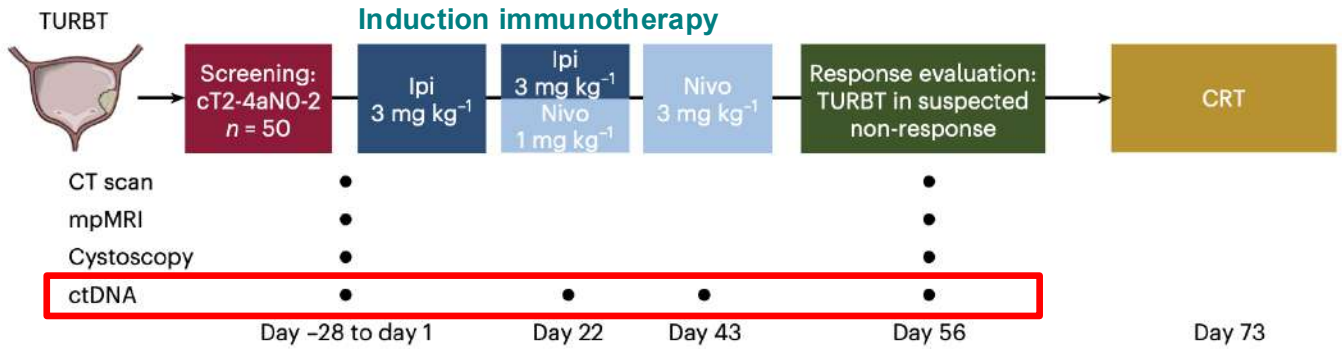


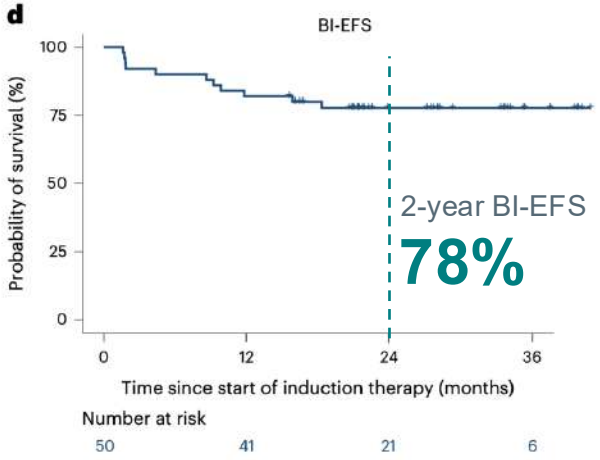
Geynisman et al, JCO, 2025; Ross et al; ASCO GU26

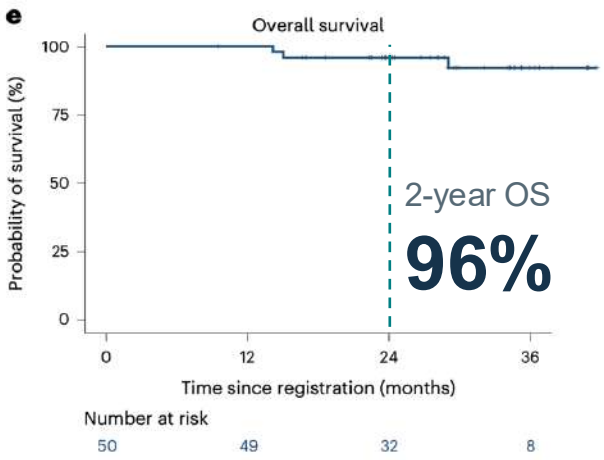
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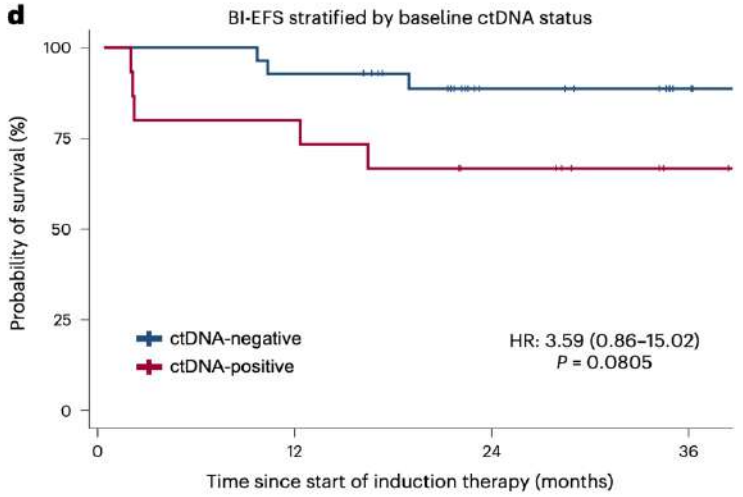
A ctDNA-guided strategy for bladder-sparing therapy

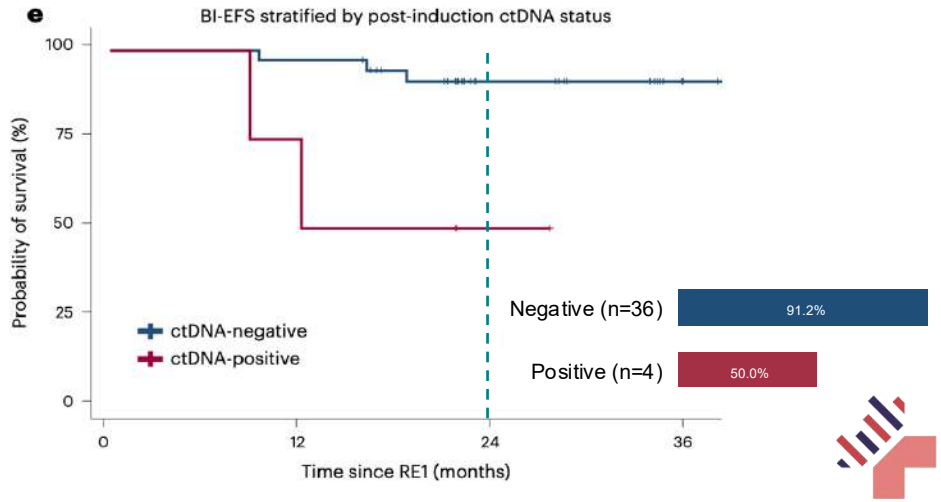
INDI-BLADE









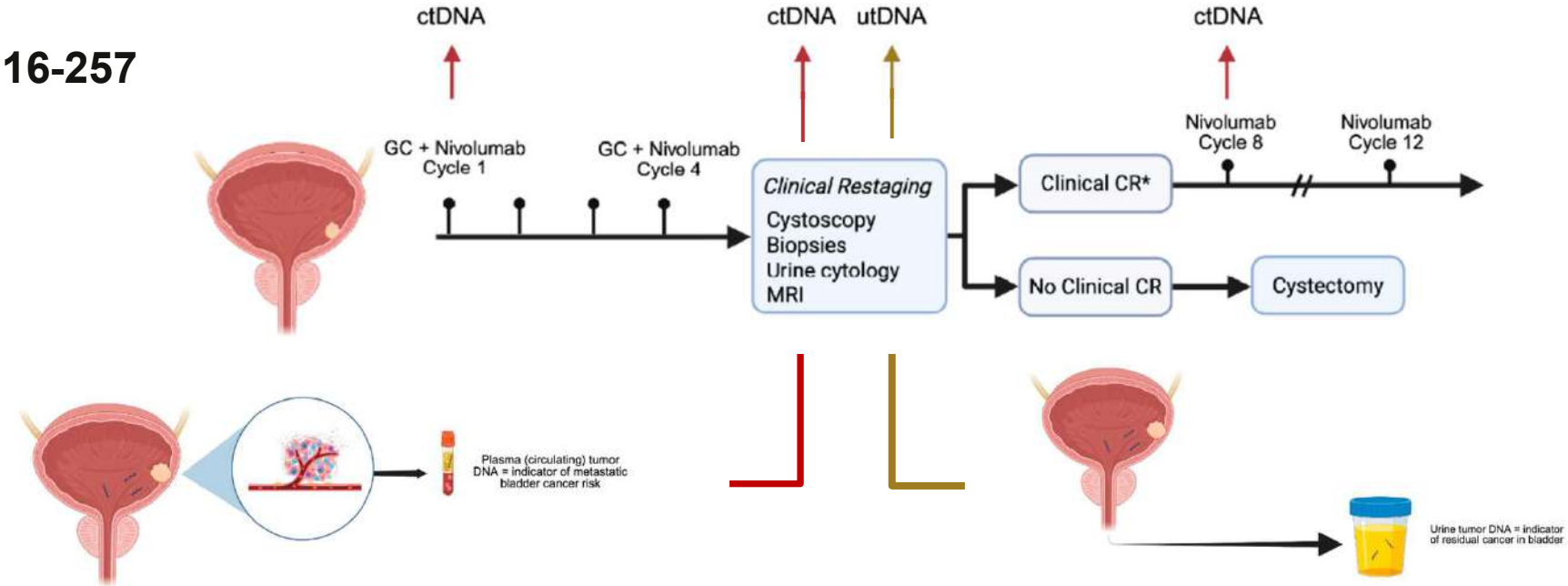


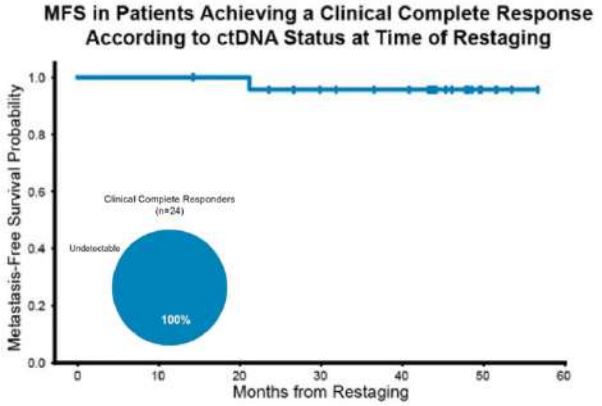
Mellema et al, Nat Med, 2026

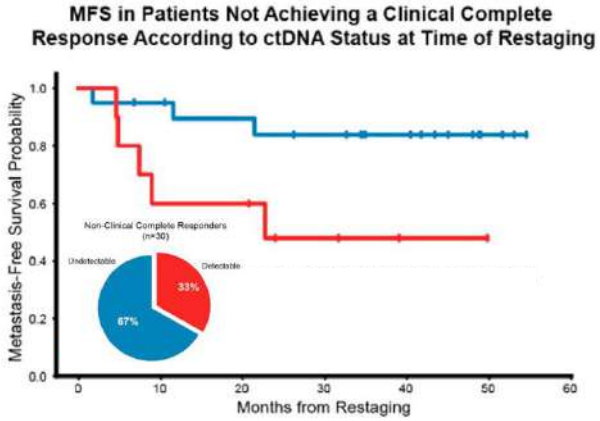
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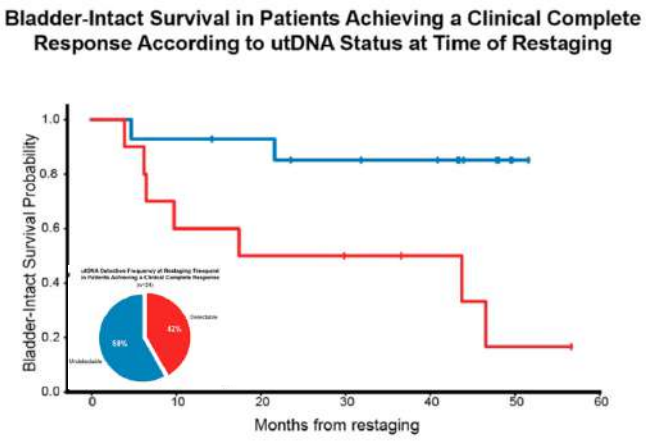
A ctDNA-guided strategy for bladders-sparing therapy

HCRN GU16-257









Galsky et al, PNAS, 2026

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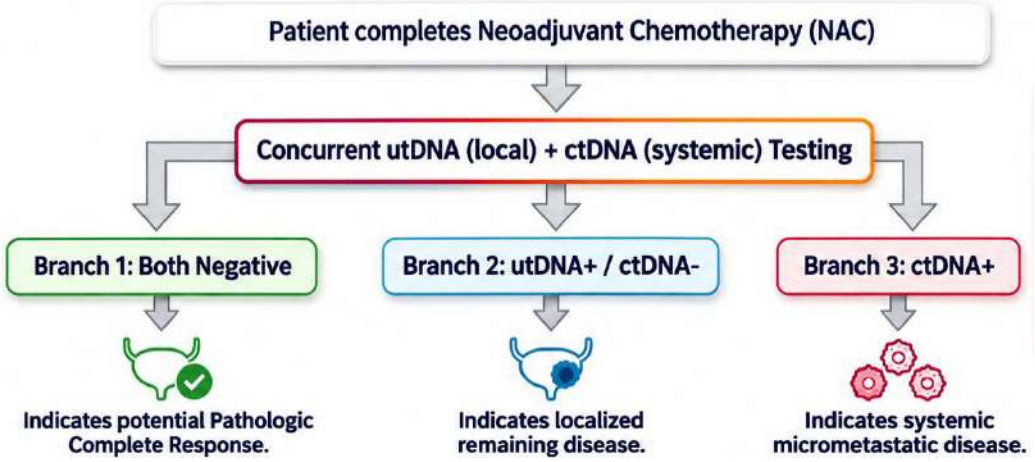
A ctDNA-guided strategy for bladders-sparing therapy

Editorial – Platinum Opinion

Combining ctDNA and utDNA as a Dual Biomarker-driven Strategy for Bladder-sparing Therapy in Muscle-invasive Bladder Cancer: Neither Alone Is Sufficient

A synthesized comparison of biomarker performance across recent bladder-sparing trials (HCRN GU16-257, DFCI-MGH TMT, INDIBLADE, SunRISe-4).

Metric	Plasma ctDNA	Urine utDNA
Baseline Positivity	32% - 64%	82%
Clearance Rates	73% - 91%	46% - 80%
Detects Local Recurrence	**NO**	YES
Detects Systemic Disease	YES	**NO**

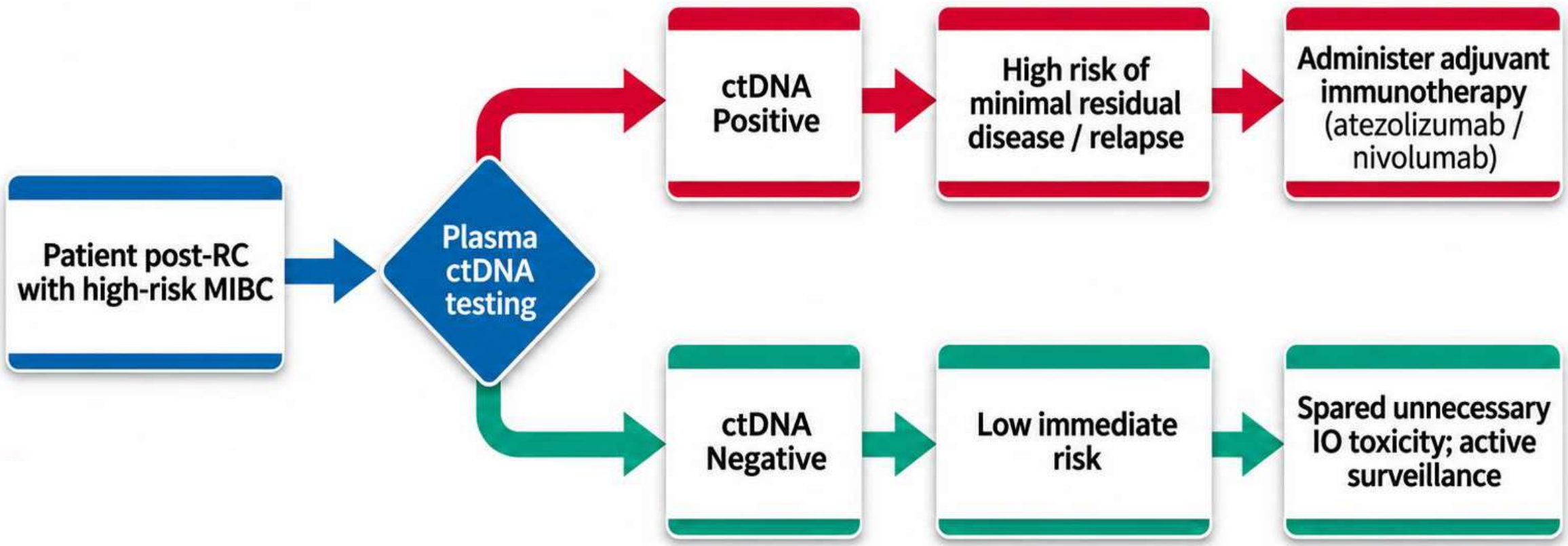


AS? RC? RC +systemic therapy?

Subiela et al, Eur Urol, 2026

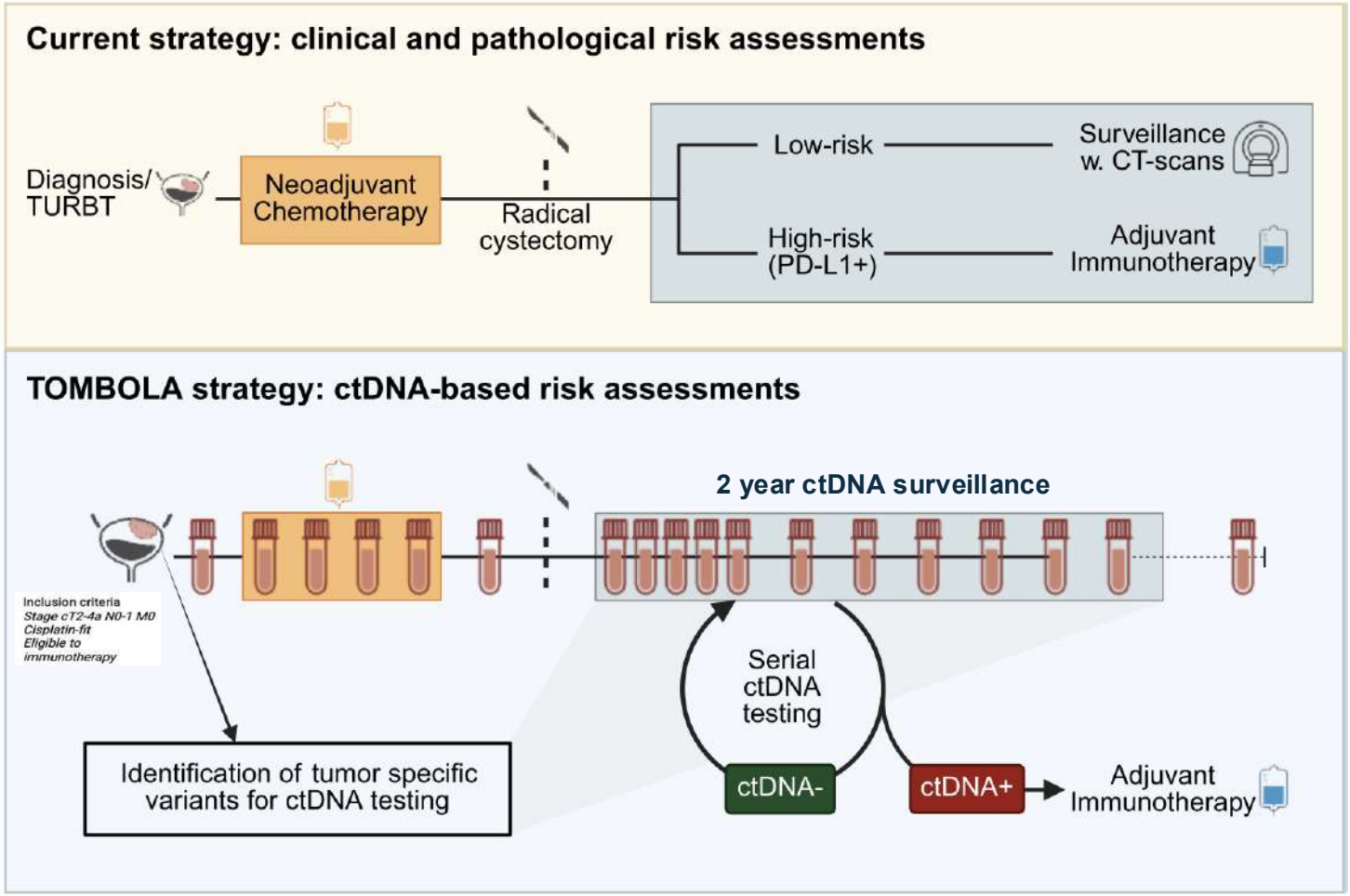
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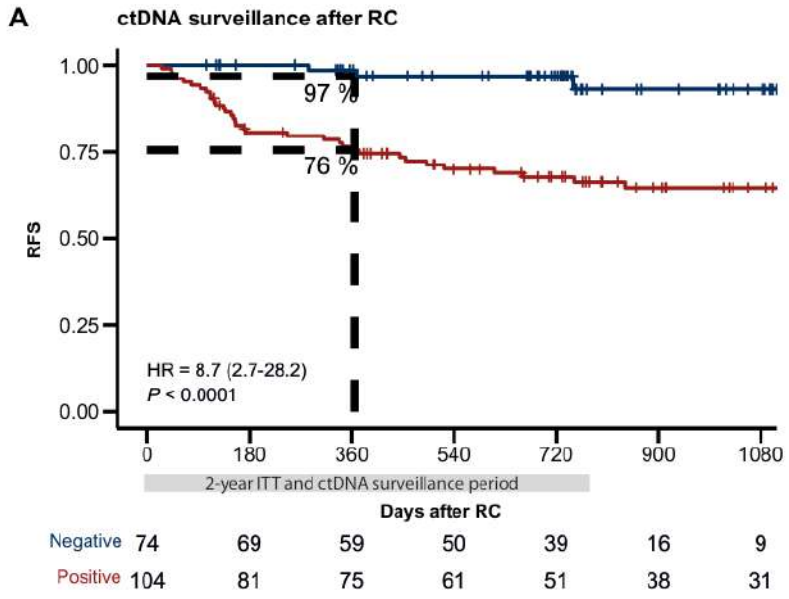
ctDNA-guided adjuvant therapy

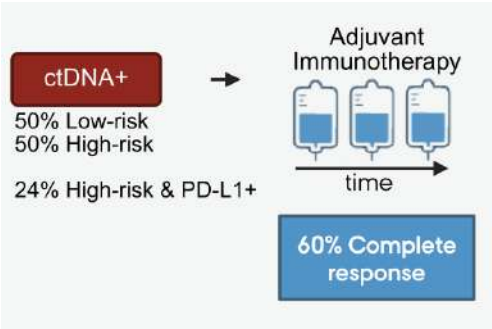


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ctDNA-guided adjuvant therapy – TOMBOLA







50 of 84 (60%)

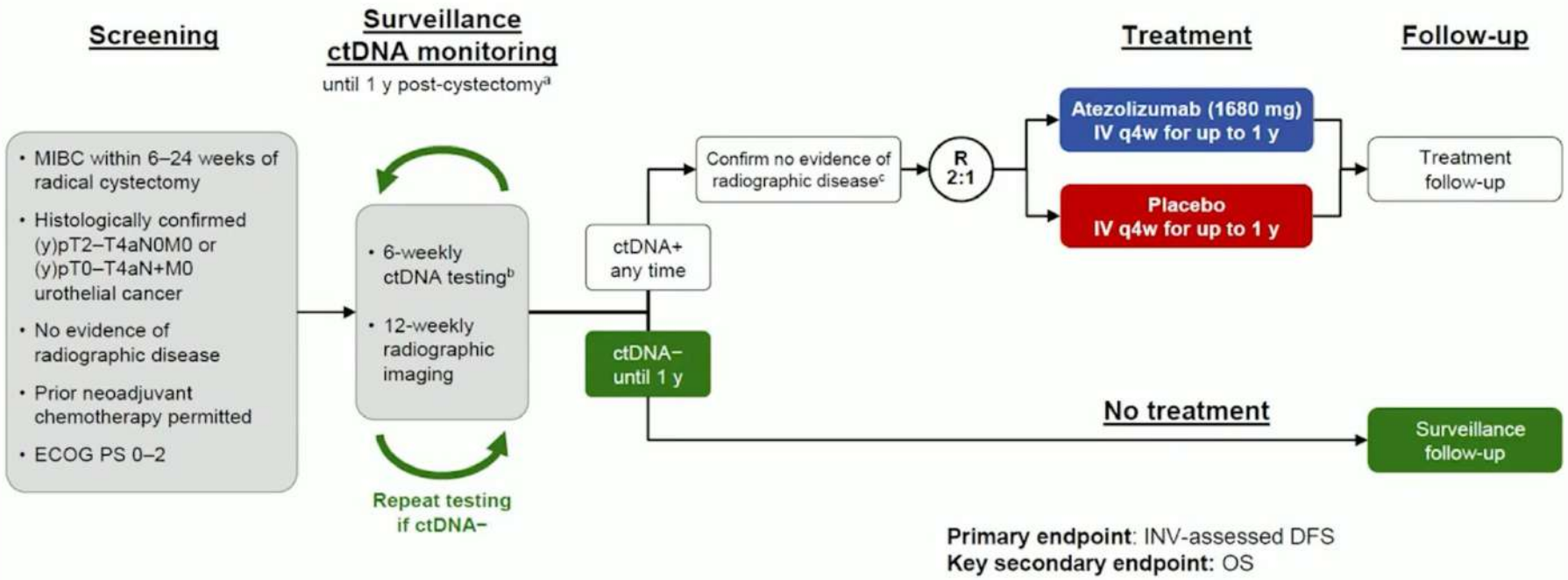
assessable treated patients achieved a complete response on both blood testing and scans.

Dyrskjøt et al, Ann of Onc, 2026

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ctDNA-guided adjuvant therapy – IMvigor011

- IMvigor011 is a randomized, double-blind phase III trial evaluating ctDNA-guided adjuvant atezolizumab versus placebo in high-risk MIBC after cystectomy.
- Patients enter surveillance after radical cystectomy if they have no radiographic evidence of disease; prior neoadjuvant chemotherapy is permitted.
- Signatera ctDNA testing is performed serially during the first year after cystectomy (approximately every 6 weeks, up to seven tests), with imaging performed approximately every 12 weeks.
- Only patients who become Signatera-positive are randomized 2:1 to atezolizumab or placebo; patients remaining ctDNA-negative continue surveillance without treatment.



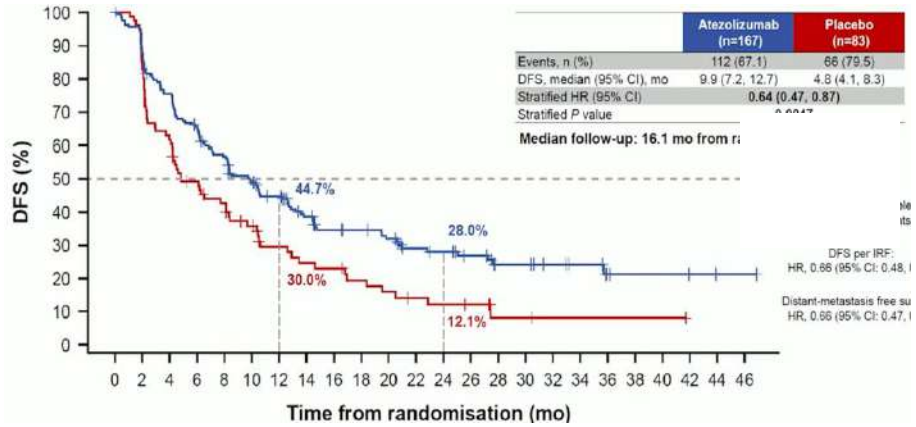
IMvigor011 tested whether acting on the ctDNA signal helps in high-risk MIBC

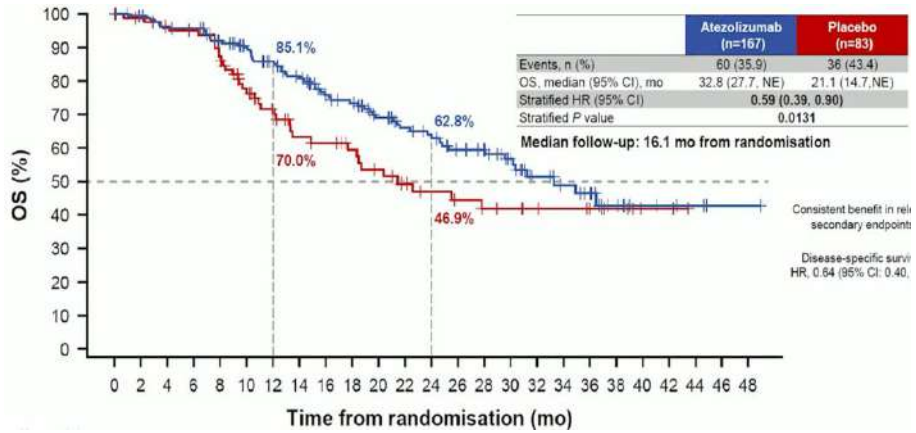
Powels et al, NEJM, 2025

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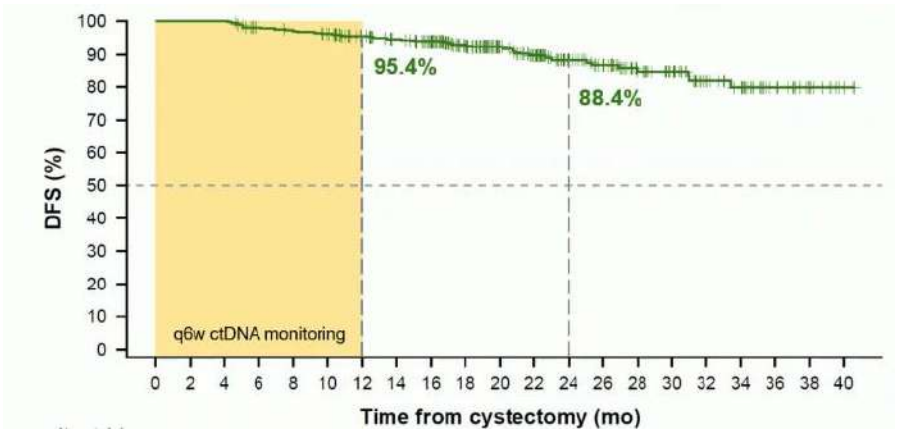
ctDNA-guided adjuvant therapy – IMvigor011

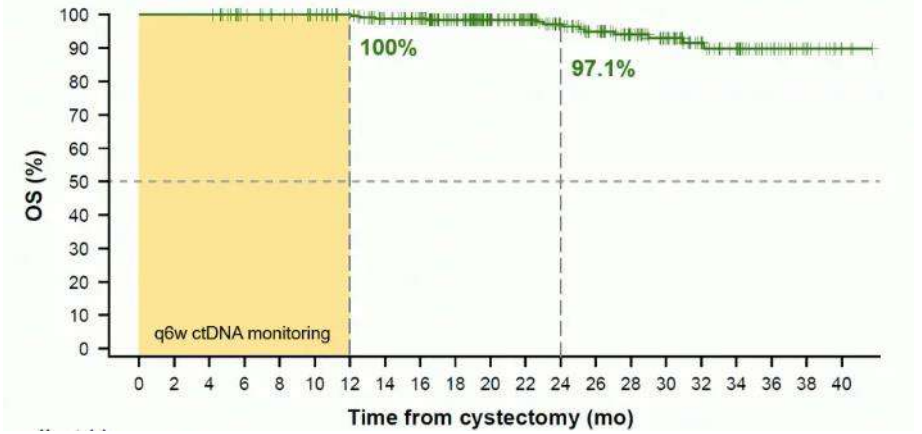
Adjuvant IO in ctDNA-positive patients improves survival





Surveillance in ctDNA-negative avoids IO toxicity without compromising survival





Powels et al, NEJM, 2025

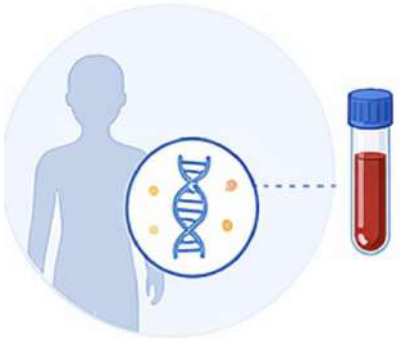
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Liquid biopsy targeted therapy when cancer has spread



Different patients.
Different molecular changes.

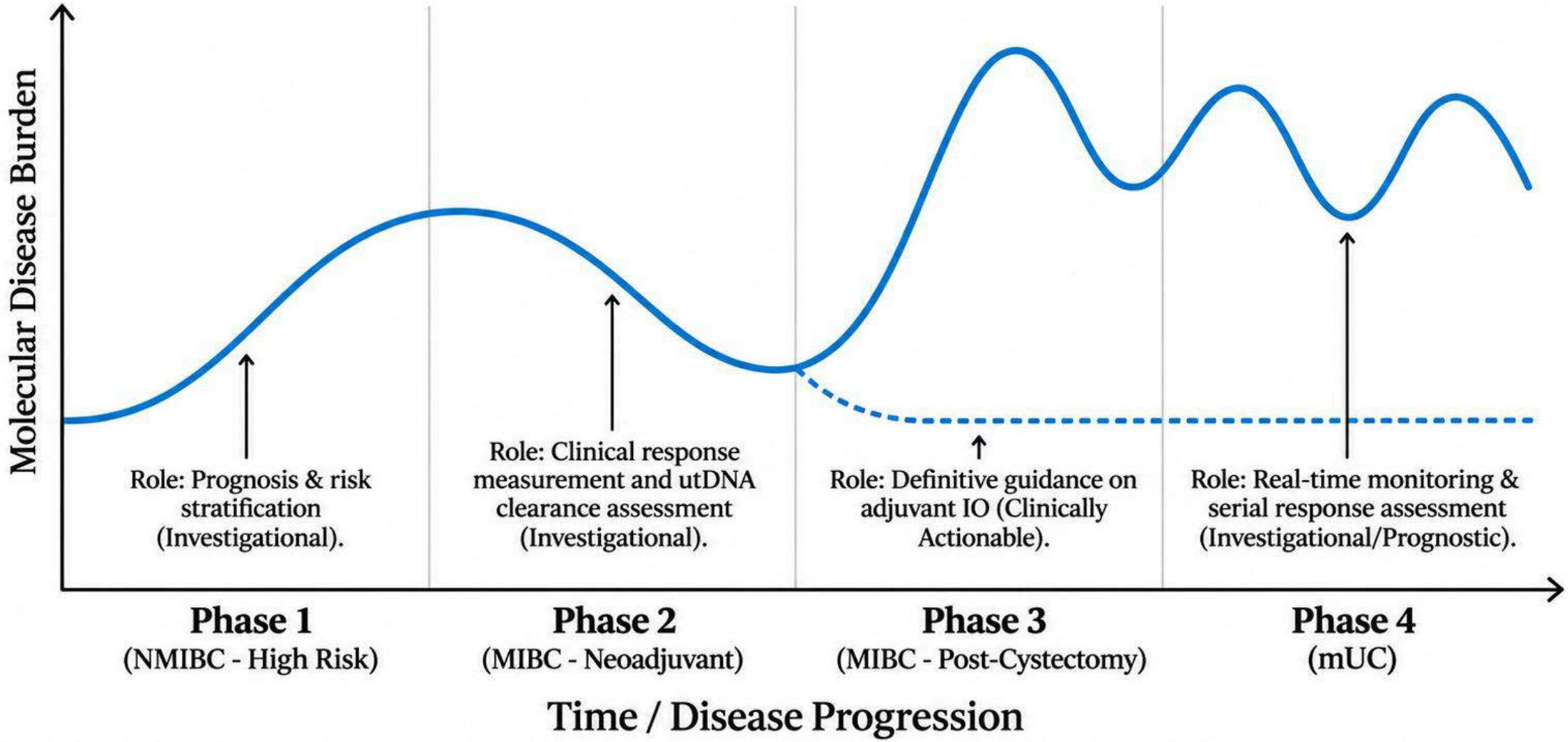
Liquid biopsies reveal unique alterations that guide targeted therapy.



Patient	Molecular alteration (via liquid biopsy)	Therapeutic option (example)	Treatment approach
Patient A	FGFR3 alteration	FGFR inhibitor (e.g., erdafitinib)	Targeted therapy
Patient B	DDR gene alteration (e.g., BRCA1/2)	PARP inhibitor (e.g., olaparib)	Targeted therapy
Patient C	High TMB / Immune markers (e.g., PD-L1+)	Immunotherapy (e.g., anti–PD-1/PD-L1)	Immunotherapy
Patient D	PI3K / AKT / mTOR alteration	Pathway inhibitor (e.g., PI3K inhibitor)	Targeted therapy

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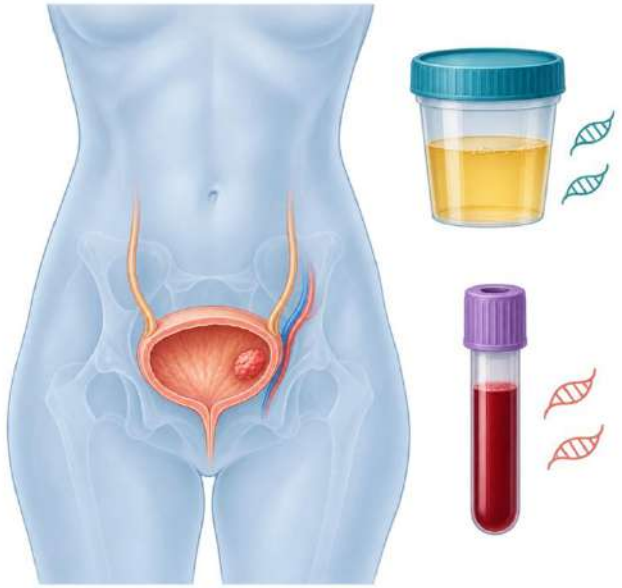
Synthese: Positioning ctDNA vs utDNA



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Liquid Biopsy in Bladder Cancer

Blood and urine provide complementary clues about a patient's cancer



Urine: clues inside the bladder

May help detect a tumour or its return inside the bladder.

Blood: clues about cancer in the body

Help detect cancer left after treatment, assess recurrence risk, track response and identify treatment targets.

ctDNA = tumour DNA circulating in blood

Treatment after bladder removal

IMvigor011: immunotherapy improved survival in patients with a positive blood ctDNA test. [1]

Preserving the bladder

Promising results, but test-guided decisions still need validation. [2]

These tests complement cystoscopy, scans and tissue testing.
A negative result does not rule out cancer.

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