

Real-World ctDNA Test Utilization and Associated Costs in US Patients With Bladder Cancer Who Underwent Radical Cystectomy

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Plain language summary

- First real-world study on uses and costs of ctDNA test in bladder cancer (BC)
- US Medicare coverage for ctDNA testing in BC began in April 2022
- Since 2022, more US surgically treated BC patients have received ctDNA tests
- Overall use of ctDNA testing is low (~17%; a median of 2 tests among those tested)
- Patients paid little out of pocket for ctDNA testing

Introduction

- Muscle-invasive bladder cancer (MIBC) is an aggressive disease that is typically treated with radical cystectomy (RC), with or without neoadjuvant therapy
- Disease recurrence after RC is common
- Adjuvant therapy is recommended for high-risk patients after RC
- In recent years, circulating tumor DNA (ctDNA)–based detection of molecular residual disease (MRD) has been increasingly used to guide adjuvant treatment decisions
- In April 2022, Medicare approved Natera's Signatera™ MRD ctDNA test for MIBC, reflecting a shift toward personalized, biomarker-driven care
- Real-world use of ctDNA testing in US MIBC patients remains poorly characterized
- This study aims to evaluate ctDNA testing prevalence, testing patterns, and associated costs among patients with bladder cancer treated with RC

Methods

Data source

- Claims data from spanning 01/19/2022–06/30/2025
- Includes members from large commercial and Medicare Advantage health plans
- The study period was selected to reflect real-world practice following Medicare coverage of Natera's Signatera™ MRD ctDNA test for MIBC (April 2022)

Study population and study design

- Study population: Adult (≥18 years) bladder cancer (BC) patients who underwent radical cystectomy
- Inclusion criteria:
 - ≥2 claims with BC (ICD-10 codes: C67.x) diagnosis codes on separate dates within a 6-month time span between April 19, 2022, and December 31, 2024
 - Received RC identified using CPT, HCPCS, or ICD-10-PCS codes, including bladder removal with urinary diversion (per validated algorithm¹)
 - Continuous enrollment ≥3 months pre-index (baseline period) and ≥6 months post-index, unless death occurred
- Index date is defined as the date of RC procedure
- Natera's Signatera™ MRD ctDNA test (CPT codes 0340U or 81479) was identified during observation period (baseline and throughout the entire post-index period)
- Patients were categorized into tested or untested cohorts

Baseline characteristics

- Patient demographics and clinical characteristics were evaluated during the baseline period or at RC
- Comorbidities were identified using the NCI Comorbidity Index during the baseline period

Treatment assessment

- Neoadjuvant therapy was identified within 3 months before RC
- Adjuvant therapy was identified within 6 months after RC

Outcomes

- Number of patients with ≥1, ≥2, and ≥3 ctDNA test(s) was reported during the baseline (within 3 months before RC), post-index (after RC), and throughout the observation period
- Among the tested cohort, median number of ctDNA tests, the interval between BC diagnosis and RC, the interval between BC diagnosis and the first pre-index ctDNA test, the interval between RC and the first post-index ctDNA test, and the interval between the first ctDNA test and the second ctDNA test were reported
- Among the overall cohort, ctDNA testing rates were reported per 1,000 patient-months
- Total and patient out-of-pocket ctDNA-associated costs were reported

Statistical analysis

- Continuous variables were reported using mean and median
- Binary and categorical variables were reported as counts and percentages
- Baseline characteristics and treatment assessments were compared between tested vs untested cohorts using Chi-square and z-tests
- Time from RC to receiving the first ctDNA test and time from first ctDNA test to receiving the second ctDNA test were estimated using the Kaplan-Meier methods

Results

- A total of 1,995 bladder cancer patients who underwent RC were identified
- Overall, 341 (17.1%) patients received at least one ctDNA test during the observation period
- Median [IQR] follow-up was 15.3 [8.6, 23.9] months (Table 2)
- Among patients tested for ctDNA, the median number of tests per patient was 2 (Table 2)
- Demographics were generally similar between the tested and untested cohorts (Table 1)
- ctDNA-tested patients more frequently received neoadjuvant chemotherapy (46.0% vs 35.8%) and adjuvant therapy (24.0% vs 10.1%) compared with patients who did not receive ctDNA testing ($P < 0.001$) (Table 1)

Table 1. Baseline demographics and clinical characteristics among bladder cancer patients who underwent RC (overall cohort), the ctDNA-tested cohort, and the untested cohort

| Patient characteristics | Overall cohort (N=1,995) | Tested cohort* (n=341) | Untested cohort (n=1,654) | P-value ^b |
|---|--------------------------|------------------------|---------------------------|----------------------|
| Age at RC, years | | | | |
| Mean ± SD | 72.6 ± 8.1 | 71.8 ± 8.5 | 72.8 ± 8.0 | 0.045 |
| Median [Q1, Q3] | 73.0 [68.0, 78.0] | 72.0 [68.0, 77.0] | 73.0 [68.0, 78.0] | |
| Follow-up duration^c after RC, months | | | | |
| Mean ± SD | 16.7 ± 9.8 | 17.3 ± 9.0 | 16.5 ± 9.9 | 0.159 |
| Median [Q1, Q3] | 15.3 [8.6, 23.9] | 16.1 [9.8, 23.6] | 15.0 [8.3, 24.0] | |
| Sex (registered at birth), n (%) | | | | |
| Female | 471 (23.6%) | 89 (26.1%) | 382 (23.1%) | 0.263 |
| Male | 1,524 (76.4%) | 252 (73.9%) | 1,272 (76.9%) | |
| Ethnicity, n (% of patients with available data^a) | | | | |
| Hispanic | 111 (6.5%) | 29 (9.8%) | 82 (5.8%) | 0.016 |
| Not Hispanic | 1,606 (93.5%) | 268 (90.2%) | 1,338 (94.2%) | |
| Unknown/missing | 278 | 44 | 234 | |
| Race, n (% of patients with available data^a) | | | | |
| White | 1,510 (89.1%) | 252 (87.8%) | 1,258 (89.3%) | 0.663 |
| Black or African American | 153 (9.0%) | 28 (9.8%) | 125 (8.9%) | |
| Asian | 32 (1.9%) | 7 (2.4%) | 25 (1.8%) | |
| Unknown/missing | 300 | 54 | 246 | |
| Census region, n (% of patients with available data^a) | | | | |
| South | 732 (36.9%) | 146 (43.1%) | 586 (35.6%) | <0.001 |
| Midwest | 571 (28.8%) | 95 (28.0%) | 476 (28.9%) | |
| West | 365 (18.4%) | 67 (19.8%) | 298 (18.1%) | |
| Northeast | 318 (16.0%) | 31 (9.1%) | 287 (17.4%) | |
| Unknown/missing | 9 | 2 | 7 | |
| Payer type, n (%) | | | | |
| Medicare | 1,722 (86.3%) | 285 (83.6%) | 1,437 (86.9%) | 0.057 |
| Commercial | 273 (13.7%) | 56 (16.4%) | 217 (13.1%) | |
| NCI Comorbidity Index | | | | |
| Mean ± SD | 0.7 ± 0.6 | 0.6 ± 0.6 | 0.7 ± 0.6 | 0.103 |
| Median [Q1, Q3] | 0.5 [0.3, 1.0] | 0.5 [0.1, 1.0] | 0.5 [0.3, 1.0] | |
| Received neoadjuvant therapy within 3 months before RC | | | | |
| n (%) | 749 (37.5%) | 157 (46.0%) | 592 (35.8%) | <0.001 |
| Received adjuvant therapy within 6 months after RC | | | | |
| n (%) | 249 (12.5%) | 82 (24.0%) | 167 (10.1%) | <0.001 |

ctDNA, circulating tumor DNA; NCI, National Cancer Institute; Q1, first quartile; Q3, third quartile; RC, radical cystectomy; SD, standard deviation.

*The tested cohort included bladder cancer patients who received at least one ctDNA test during the study period.

^aPatients with unknown/missing data were omitted from calculation of percentages and from statistical testing to generate P-values.

^cDuration of follow-up was defined as the interval from the index date (ie, RC) to the earliest of end of continuous enrollment, end of study period, or death.

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Data availability: Data for this analysis was made available to the authors through a third-party license from Optum's Clinformatics® Data Mart Database, a commercial data provider in the United States. As such, the authors cannot make these data publicly available due to data use agreement. Other researchers can access the data by purchasing a license through Optum's Clinformatics® Data Mart Database.

Ethics committee approval: This study was determined to be exempt from institutional review board (IRB) review by the Western Institutional Review Board-Copernicus Group (WICG) IRB (#1-1822047-1) in accordance with federal regulation 45 CFR 46 and associated guidance.

References

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- A small number of the study population received ≥1 test before RC (4.7%; 94/1,995) (Table 2)
- The median interval from BC diagnosis to first pre-RC ctDNA test was 2.6 months (Table 2)
- A larger proportion received ≥1 test after RC (14.7%; 293/1,995) (Table 2)

Table 2. ctDNA testing prevalence and patterns among bladder cancer patients who underwent RC

| | During the observation period | | |
|---|-------------------------------|-----------------|-------------------|
| | Surrounding RC ^a | Before RC | After RC |
| Overall cohort (N=1,995) | | | |
| Received ≥1 ctDNA test(s), n (%) | 341 (17.1%) | 94 (4.7%) | 293 (14.7%) |
| Received ≥2 ctDNA test(s), n (%) | 184 (9.2%) | 22 (1.1%) | 169 (8.5%) |
| Received ≥3 ctDNA test(s), n (%) | 143 (7.2%) | 10 (0.5%) | 132 (6.6%) |
| Tested cohort, n | | | |
| Median number of tests per patient [Q1, Q3] | 2.0 [1.0, 5.0] | 1.0 [1.0, 1.0] | 2.0 [1.0, 4.0] |
| Interval (months) from BC diagnosis to RC [Q1, Q3] | 4.7 [2.3, 7.2] | 6.0 [4.6, 10.4] | -- |
| Interval (months) from BC diagnosis to first pre-RC test [Q1, Q3] | -- | 2.6 [1.3, 4.9] | -- |
| Duration (months) of follow-up after RC [Q1, Q3] | 15.3 [8.6, 23.9] | -- | 16.4 [10.3, 24.2] |
| Interval (months) from RC to first post-RC test [Q1, Q3] | -- | -- | 3.1 [1.4, 7.7] |

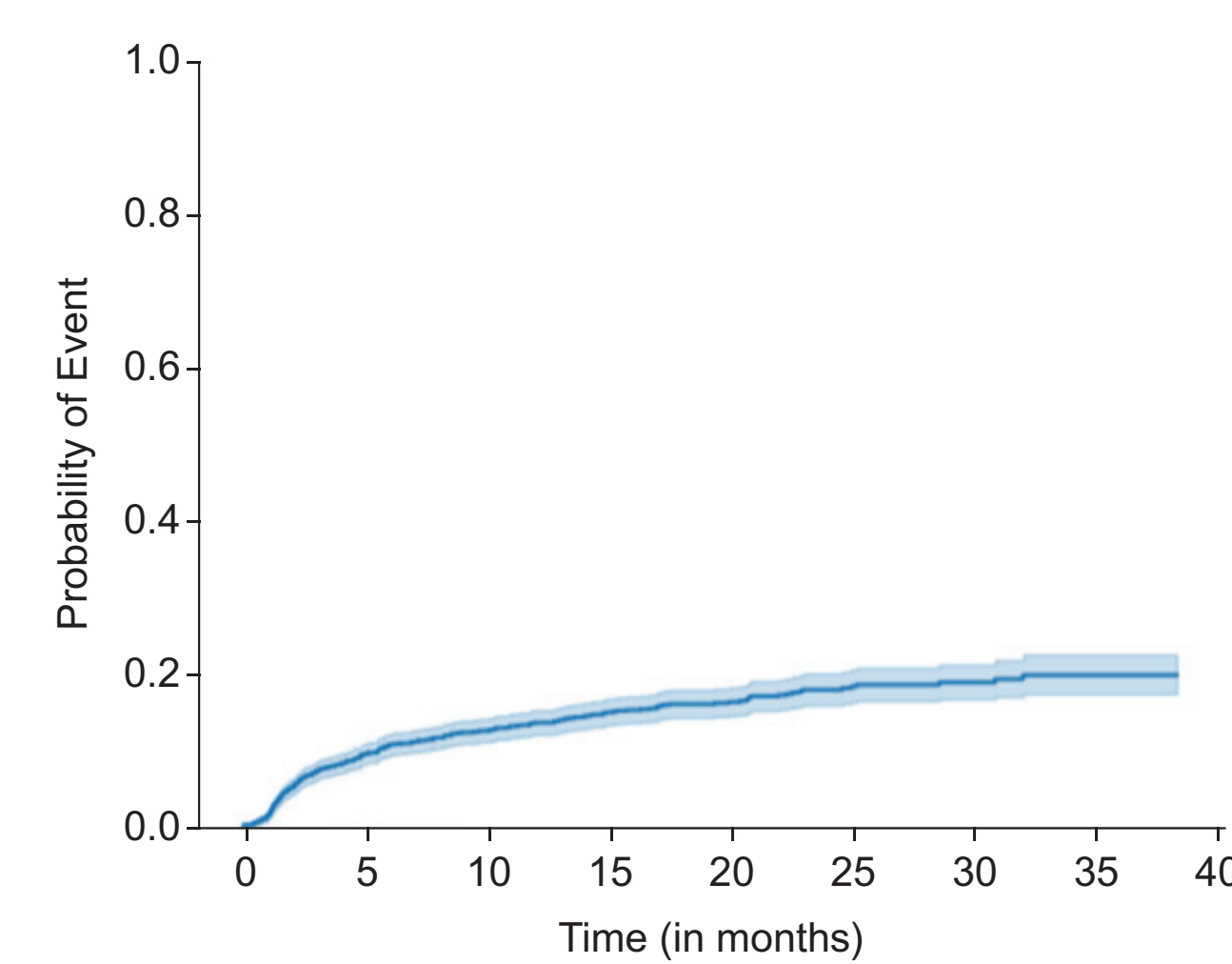
ctDNA, circulating tumor DNA; RC, radical cystectomy; Q1, first quartile; Q3, third quartile.

^actDNA testing was assessed during the observation period, from ≥3 months prior to RC (baseline) and for ≥6 months after RC (until end of continuous enrollment, end of study period, or death).

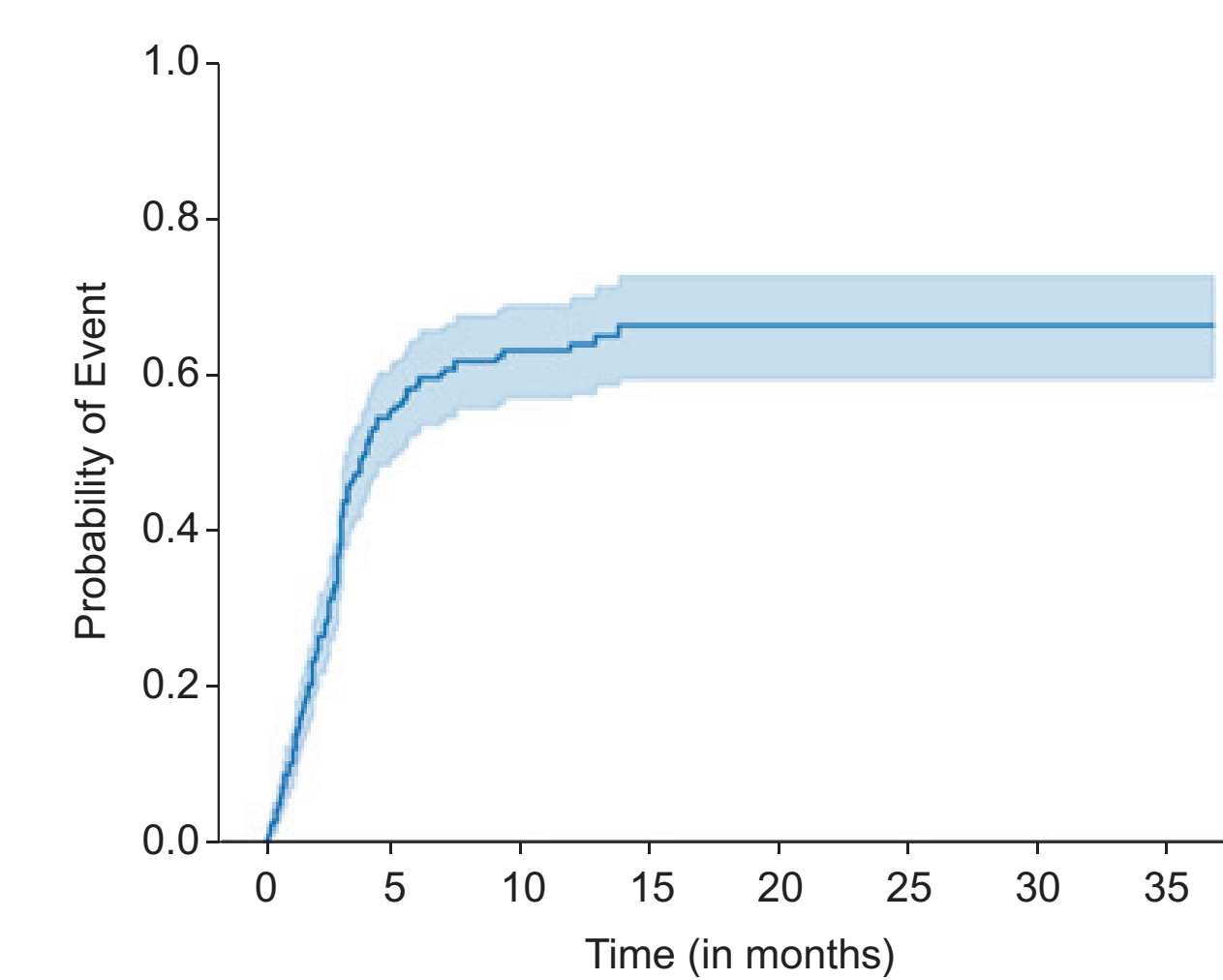
- Among the overall cohort, the Kaplan-Meier estimated probability of receiving a test after RC was 7.5% by 3 months and 10.9% by 6 months after RC, respectively (Figure 1A)
- Among patients with ≥1 test after RC, the median time to receive a second test was 3.8 months, with an estimated probability of 59.3% by 6 months after the first test (Figure 1B)

Figure 1. Kaplan-Meier estimates for receiving post-RC ctDNA test among bladder cancer patients

A. Probability of receiving the first post-RC ctDNA test among the overall cohort (N=1,995)



B. Probability of receiving a second ctDNA test after the first post-RC test, among patients with ≥1 test after RC* (N=293)



| Time from RC to receiving first post-RC ctDNA test | Probability (95% CI) |
|--|----------------------|
| 3 months | 7.5% (6.3%, 8.6%) |
| 6 months | 10.9% (9.5%, 12.3%) |
| 12 months | 13.8% (12.2%, 15.4%) |
| 18 months | 16.2% (14.4%, 18.1%) |
| 24 months | 18.1% (16.0%, 20.2%) |
| 36 months | 20.0% (17.4%, 22.6%) |
| Median [Q1, Q3], months | Not reached |

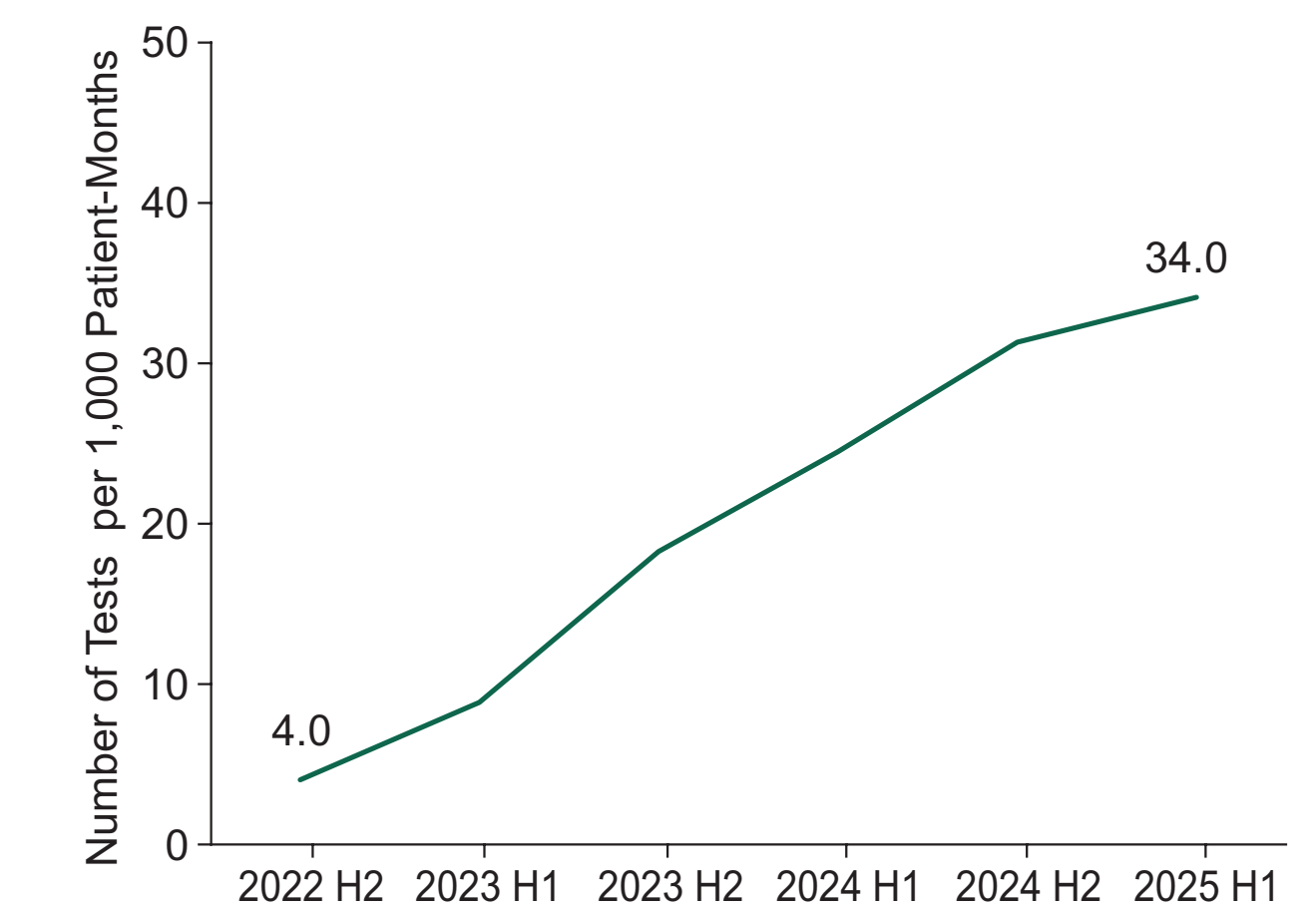
| Time from first post-RC ctDNA test to second test | Probability (95% CI) |
|---|----------------------|
| 3 months | 41.9% (36.1%, 47.8%) |
| 6 months | 59.3% (53.3%, 65.4%) |
| 12 months | 64.1% (57.9%, 70.4%) |
| 18 months | 66.4% (59.9%, 73.0%) |
| 24 months | 66.4% (59.9%, 73.0%) |
| 36 months | 66.4% (59.9%, 73.0%) |
| Median [Q1, Q3], months | 3.84 [2.06, NR] |

CI, confidence interval; ctDNA, circulating tumor DNA; RC, radical cystectomy; NR, not reached.

*Assessment of the post-RC period included the index day.

- Testing rate in the overall population increased from 4.0 (second half of 2022) to 34.0 (first half of 2025) tests per 1,000 patient-months (Figure 2)

Figure 2. ctDNA testing rates following Medicare approval among patients with bladder cancer who underwent RC^{a,b}



ctDNA, circulating tumor DNA; H1, first half; H2, second half; RC, radical cystectomy.

^aTesting rate was defined as the total number of ctDNA tests performed, divided by the cumulative person time among all patients (counting from MIBC diagnosis) with continuous enrollment in each time period.

^bTesting rate: P for trend <0.001.

- The mean total cost related to each ctDNA test was \$3,409 (SD: \$2,958), and the median cost per ctDNA test was \$4,178 [Q1, Q3: \$1,756, \$4,178] (Table 3)
- The median out-of-pocket expense (ie, sum of copay, coinsurance, and deductible) for patients per test was \$0 (Q1, Q3: \$0, \$0).

Table 3. Costs associated with ctDNA testing among bladder cancer patients who underwent RC^a

| | Total costs related to ctDNA testing (in \$USD) | Out-of-pocket cost ^b – ctDNA testing claims only (in \$USD) |
|-------------------------------------|---|--|
| Number of valid claims ^c | 1,144 | 1,144 |
| Mean ± SD | \$3,409 ± \$2,958 | \$6 ± \$59 |
| Median [Q1, Q3] | \$4,178 [\$1,756, \$4,178] | \$0 [\$0, \$0] |

ctDNA, circulating tumor DNA; RC, radical cystectomy; Q1, first quartile; Q3, third quartile; SD, standard deviation; USD, United States dollar.

^aCosts were adjusted to September 2025 USD using the Consumer Price Index medical service component.

^bPatient cost was defined as the sum of the copay, coinsurance, and deductible.

^cA valid claim was defined as one that had a paid status of paid and a cost >\$0.00.

Discussion

- First real-world US study evaluating ctDNA testing patterns and costs among bladder cancer patients undergoing radical cystectomy (RC)
- Following Medicare coverage approval (2022), ctDNA use increased over time, but overall uptake remained modest (≈17% of RC patients tested)
- Testing intensity was low to moderate (median of 2 tests per tested patient), suggesting selective use for surveillance or decision support rather than routine monitoring
- Patient out-of-pocket costs were minimal, reflecting effective third-party coverage, despite variability in total costs across payers and settings
- Clinical, technical, and logistical barriers (eg, low ctDNA shedding, lack of assay standardization, long turnaround times) likely contributed to limited adoption; prospective evidence is still needed to demonstrate survival benefit
- Limitations: Claims-based design with limited clinical detail and no staging information; potential ctDNA misclassification due to CPT code use; and restricted perioperative windows that may not capture all therapies

Conclusions

- While ctDNA is a promising biomarker, this real-world analysis demonstrates a modest uptake of ctDNA testing in the US among bladder cancer patients undergoing RC, following Medicare coverage approval of ctDNA testing
- Only ~17% of RC-treated patients received at least one ctDNA assay, with a median of 2 tests per tested patient in the perioperative period
- Total costs varied by payer and setting, but patient out-of-pocket expenses were minimal
- These findings suggest that reimbursement facilitates adoption but has not driven routine use
- Future research is essential to standardize assay sensitivity and validate ctDNA-guided interventions through large-scale clinical trials

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