2.04.153	Tumor-Informed Circulating Tumor DNA Testing for Cancer Management		
Original Policy Date:	June 1, 2022	**Effective Date:**	June 1, 2022
Section:	2.0 Medicine	**Page:**	Page 1 of 30

Policy Statement

Tumor-informed circulating tumor DNA testing (e.g., Signatera) is considered **investigational** for all indications.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This CPT code may be used for Tumor-informed circulating tumor DNA testing:

- **81479:** Unlisted molecular pathology procedure

Description

This evidence review addresses the use of tumor-informed circulating tumor DNA (ctDNA) testing for cancer management. The purpose of tumor-informed ctDNA testing in individuals with cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following treatment.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Signatera is a laboratory developed test regulated under CLIA. Signatera has been developed and its performance characteristics determined by Natera, the CLIA-certified laboratory performing the test. The test has not been cleared or approved by the US Food and Drug Administration (FDA), but has received 3 Breakthrough Device Designations from FDA:

- In May 2019, Signatera was granted a BDD for the detection of ctDNA in localized or advanced colorectal cancer patients to optimize the use of chemotherapy alone or in combination with durvalumab.
- A March 2021 press release announced that FDA granted 2 additional Breakthrough Device Designations covering new intended uses.[1,]

Rationale

Background

The purpose of tumor-informed ctDNA testing in individuals with cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following treatment.

Signatera

Signatera is a tumor-specific ctDNA test. Tumor tissue obtained from either a diagnostic biopsy or surgically resected tissue is used to identify 16 single nucleotide variants found in the tumor but not in normal tissue and are likely to be present in all tumor cells regardless of tumor evolution. A custom assay of 16 tumor-specific clonal, somatic variants is generated for the individual and the resulting tumor signature can be monitored throughout the individual's disease course. When the test is used for detection of recurrence following curative treatment, plasma samples with 2 or more out of these 16 variants detected above a predefined confidence threshold are deemed to be tuna-positive. When the test is used to monitor treatment response, evaluation is based on whether ctDNA levels increase or decrease from a baseline measurement. The test is intended to be used in conjunction with radiological assessment.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. The first step in assessing a medical test is to formulate the clinical context and purpose of the test. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Colorectal Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals who have colorectal cancer is to inform treatment decisions and to monitor for recurrence following curative treatment.
The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA (ctDNA) testing with Signatera improve the net health outcome in individuals with colorectal cancer?

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals:

- With stage II or III colorectal cancer who have undergone surgical resection.
- Who are being monitored for relapse following treatment for stage II or III colorectal cancer.
- With metastatic (stage IV) colorectal cancer who have undergone surgical resection and are being evaluated for adjuvant chemotherapy and/or targeted therapy.

Interventions
The test being considered is ctDNA testing with Signatera:

- Following surgery, to inform decisions about adjuvant chemotherapy or targeted therapy.
- During disease surveillance after curative treatment, to identify metastatic relapse at an early timepoint, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators
For individuals with stage II colorectal cancer, the current standard of care is not to routinely administer adjuvant chemotherapy. However, current National Comprehensive Cancer Network (NCCN) guidelines are that adjuvant chemotherapy can be considered in individuals with stage II colorectal cancer, using clinicopathologic characteristics to identify individuals who might benefit.

For individuals with stage III colorectal cancer, the current standard of care is to administer adjuvant chemotherapy routinely.

For individuals who are being monitored for relapse following treatment for stage II or III colorectal cancer, guidelines suggest monitoring carcinoembryonic antigen (CEA) every 3 to 6 months for 2 years, then every 6 months for a total of 5 years, as well as imaging every 6 to 12 months for 5 years.

For individuals with metastatic colorectal cancer who have undergone surgical resection, the current standard of care is routine individual checkups, periodic computed tomography scans, and monitoring of CEA level.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, recurrence-free survival (RFS), and overall survival at follow-up.

Given that the majority of colorectal cancer recurrences occur within the first 3 years after surgical resection of the primary tumor and approximately 95% in the first 5 years, the timepoint of interest to assess recurrence is 3 to 5 years following surgical resection.

For individuals with stage II colorectal cancer who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-in* stage II individuals for adjuvant chemotherapy, the perfomance characteristics of most interest are positive predictive value and specificity.

For individuals with stage III colorectal cancer who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-out* individuals for adjuvant chemotherapy, the performance characteristics of most interest are negative predictive value and sensitivity. However, since the test would be used to select individuals who would not receive category 1 recommended treatment, direct evidence of improvement in outcomes is required. For individuals who are being monitored for relapse following treatment for colorectal cancer, recurrence at 3 to 5 years should be assessed.

Study Selection Criteria
For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trials

Four nonrandomized studies, 3 of which were noncomparative, examined the association of Signatera testing to prognosis in individuals with colorectal cancer (CRC) (Table 1). They differed in their study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Three studies evaluated the association between positive ctDNA results and prognosis in CRC (Table 2). These studies did not provide comparisons of ctDNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. One retrospective study compared Signatera testing to other surveillance strategies in individuals with resected colorectal cancer.[2,] There are no randomized controlled trials, and no studies in which Signatera testing was used to guide treatment decisions.

Reinert et al (2019) enrolled 125 individuals with stage I to III colorectal cancer in a validation study of the Signatera assay.[3,] Plasma samples were collected before surgery, at 30 days following surgery, and every 3 months for up to 3 years. The recurrence rate at 3 years was 70% in individuals with a positive ctDNA test (7 of 10) compared to 11.9% (10 of 84) of those with a negative ctDNA test. In multivariate analyses, ctDNA status was associated with recurrence after adjusting for clinicopathological risk factors including stage, lymphovascular invasion, and microradical resection status.

Henriksen et al (2022) assessed the added benefit of serial ctDNA analysis; with samples taken at diagnosis, following surgery, during adjuvant therapy, and at follow up.[4,]

Loupakis et al (2021) evaluated the association of ctDNA with Signatera on survival outcomes in 112 individuals who had undergone resection for metastatic (stage IV) CRC.[5,] The study included an analysis of the sensitivity of Signatera testing to digital droplet PCR testing but not to standard methods to identify recurrence, such as CEA and imaging.

Fakih et al (2022) directly compared Signatera testing to other surveillance strategies in individuals with resected CRC in a retrospective observational study (Table 3).[2,] This study was unique in that it used NCCN recommended guidelines for surveillance and ctDNA testing was performed at the same interval as standard surveillance with CEA and imaging. Test characteristics for Signatera were not significantly different from standard imaging techniques. Estimates were imprecise, with wide confidence intervals.

Study limitations are shown in Tables 4 and 5. Major limitations include a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations.

Table 1. Nonrandomized Studies of Signatera Testing in Colorectal Cancer - Study Characteristics

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Reinert et al (2019)[3,]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection	130 individuals with stages I to III CRC; treated from May 1, 2014 to January 31, 2017	Multicenter, Denmark	CEA and CT imaging	2 or more variants detected out of 16	Before and after surgery, during and after adjuvant chemotherapy, and during surveillance Sample at Day 30 following	Yes

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
						surgery; individuals were followed up for a median of 12.5 months	
Henriksen et al (2022)[4,]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection Assessed added benefit of serial measurements	168 individuals with stage III CRC treated with curative intent between 2014 and 2019	Multicenter, Spain and Denmark	CEA analysis-thresholds set according to national guidelines and CT imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Median sampling 2 weeks after surgery (IQR, 2 to 4 weeks); postoperative plasma samples (within 2-4 weeks) prior. Plasma samples were also collected during and after adjuvant therapy; individuals were followed up for a median of 35 months.	Yes
Loupakis et al (2021)[5,]	1. Risk stratification following surgery	112 individuals with stage IV CRC who had undergone resection with curative intent as part of the PREDATOR clinical trial	Italy	Radiological imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Plasma samples collected at the first time point and at the time of radiologic evidence of progressive disease or at the last follow-up; individuals were followed for a median of 10.7 months	Yes
Fakih et al (2022)[2,]		48 individuals with stage II to IV CRC who underwent surveillance with Signatera	US, single center, retrospective	Confirmed recurrence, defined as a positive ctDNA finding or a finding on imaging confirmed	Any positive assay finding more than 4 weeks after definitive surgery	Standard surveillance strategy included ctDNA every 3 months for 2 years and then every 6 months for 3 years. CEA at	No

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
		and underwent curative resections between 2019 and 2021		by biopsy, CEA level elevation, or subsequent tumor radiographic dynamics		the same interval as the ctDNA assay. Imaging studies performed within NCCN guidelines and included yearly CT scans for 5 years for low-risk stage II disease and every 6 months for 2 years and then every year for 3 years for high-risk stage II and III disease. Imaging studies were performed every 3 months for 2 years and then every 6 months for 3 years for resected stage IV disease.	

CEA: carcinoembryonic antigen; CRC: colorectal cancer; CT: computerized tomography; IQR: interquartile range; NCCN: National Comprehensive Cancer Network.

Table 2. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Colorectal Cancer

Study	Mean Recurrence Rate (95% CI)	
	ctDNA Positive	**ctDNA Negative**
Reinert et al (2019)[3,]	7/10; 70% (34.2% to 93.1%)	10/84; 11.9% (6.3% to 20.1%)
Hazard ratio for recurrence following surgery (95% CI)	7.2 (2.7 to 19.0); p<.001	
Hazard ratio for recurrence following adjuvant chemotherapy (95% CI)	17.5 (5.4 to 56.5); p<.001	
Henriksen et al (2022)[4,]	16/20 (80%)	22/120 (18%)
Hazard ratio for RFS (95% CI)	7.0 (3.7 to 13.5); p<.001	
Loupakis et al (2021)[5,]	59/61 (96.7%)	NR/51 Number with recurrences not reported; 49 of 51 were alive at data cutoff
Hazard ratio for RFS (95% CI)	5.8 (3.5 to 9.7); p<.001	
Hazard ratio for OS (95% CI)	16.0 (3.9 to 68.0); p<.001	

CI: confidence interval; ctDNA: circulating tumor DNA; NR: not reported; RFS: recurrence-free survival.

Table 3. Retrospective Comparison of Signatera to Other Surveillance Strategies in Resected Colorectal Cancer

Study	Sensitivity	Specificity	PPV	NPV	Median Time to Recurrence, months
Fakih et al (2022)[2,]					
Signatera Testing	53.3 (27.4 to 77.7)	100 (87.0 to 100)	100 (59.8 to 100)	82.5 (66.6 to 92.1)	14.3
Imaging	60.0 (32.9 to 82.5)	96.9 (82.5 to 99.8)	90.0 (54.1 to 99.5)	84.2 (68.1 to 93.4)	15.0
CEA	20.0 (5.3 to 48.6)	90.9 (74.5 to 97.6)	50.0 (13.9 to 86.1)	71.4 (55.2 to 83.8)	Not assessed
CEA plus imaging	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	15.0
P-value **Signatera vs. imaging** **Signatera vs. imaging plus CEA** **Signatera vs. CEA**	>.99 .55 .13	>.99 .13 .25	not assessed	not assessed	.45 .79 not assessed

CEA: carcinoembryonic antigen; CI: confidence interval; ctDNA: circulating tumor DNA; NPV: negative predictive value; PPV: positive predictive value; RFS: recurrence-free survival.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Reinert et al (2019)[3,]	1. Included individuals with stage I through III colorectal cancer		3. No comparator	1. Overall survival not assessed	1. Follow up for recurrence was under 3 years (median 12.5 months)
Henriksen et al (2022)[4,]			3. No comparator		1. Follow up for recurrence was under 3 years (median 35 months)
Loupakis et al (2021)[5,]			3. No comparator		1. Follow up for recurrence was under 3 years (median 10.7 months)
Fakih et al (2022)[2,]				1. Survival outcomes not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 5. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Reinert et al (2019)[3],	1. individual selection not described					Multiple subgroup analyses, small numbers of individuals with positive ctDNA tests.
Henriksen et al (2022)[4],			2. Standard-of-care imaging frequency differed between the Spanish (every 6 months) and Danish (at month 12 and 36) cohort.			Small numbers of individuals with positive ctDNA tests.
Loupakis et al (2021)[5],						Small numbers of individuals with positive ctDNA tests.
Fakih et al (2022)[2],						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ctDNA: circulating tumor DNA.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Colorectal Cancer

For individuals with colorectal cancer (CRC) who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 3 noncomparative studies (N = 410) and 1 retrospective comparative study (N = 48).

Nonrandomized studies have reported an association between ctDNA results measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after curative treatment and prognosis, but these studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. A retrospective observational study found no advantage to surveillance with Signatera compared to standard surveillance conducted according to NCCN guidelines (p>.99 for sensitivity and specificity compared to imaging). There is no direct evidence that the use of the

test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Breast Cancer
Clinical Context and Test Purpose
The purpose of Signatera testing in individuals with breast cancer is to predict disease course (e.g., aggressiveness, risk of recurrence, death) and inform treatment decisions, and to monitor for recurrence following curative treatment.

The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA testing with Signatera improve the net health outcome in individuals with breast cancer?
The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with breast cancer, or those who have been treated for breast cancer and are being monitored for recurrence.

Interventions
The test being considered is circulating tumor DNA testing with Signatera:
- At diagnosis to inform decisions about neoadjuvant chemotherapy.
- After surgery to inform decisions about adjuvant treatment.
- Following curative treatment, to monitor for recurrence.

Comparators
- Decisions about neoadjuvant and adjuvant chemotherapy are based on clinicopathological risk factors.
- Guidelines for disease surveillance following breast cancer treatment recommend regular imaging and physical examinations, and additional testing upon presentation of symptoms.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.
The specific outcomes of interest depend on the proposed purpose of testing in individuals with breast cancer.
- If used for risk stratification to *rule-out* individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are negative predictive value and sensitivity.
- If used for risk stratification to to *rule-in* individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are positive predictive value and specificity.

If used for disease surveillance following primary treatment, beneficial outcomes of a true positive test would be earlier detection of metastasis and initiation of treatment. Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment, and experiencing adverse effects of such treatment. See also Evidence review 2.04.36 for additional discussion of outcomes in breast cancer risk assessment studies.

Study Selection Criteria
For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trials

Two noncomparative studies reported the association of Signatera testing with survival outcomes in breast cancer (Table 6). There are no randomized controlled trials (RCTs), and no studies in which Signatera testing was used to guide treatment decisions.

Coombes et al (2019) evaluated Signatera for disease surveillance in 49 individuals who had received surgery and adjuvant therapy for stage I to III breast cancer of various subtypes.[6] Signatera detected ctDNA in 16 of 18 individuals who subsequently relapsed, and the presence of ctDNA test was associated with poorer prognosis (Table 7).

Magbanua et al (2021) evaluated ctDNA clearance as a predictor of response to neoadjuvant chemotherapy (NAC) in 84 individuals with nonmetastatic breast cancer who were enrolled in the I-SPY2 trial.[7] In the population as a whole, ctDNA positivity decreased during the course of NAC, from 73% before treatment (T0), to 35% at 3 weeks (T1), to 14% at the inter-regimen time point (T2), and down to 9% after NAC (T3). Hazard ratios for recurrence at each of these timepoints are shown in Table 7 and indicate that positive predictive value increased over time. Study limitations are shown in Tables 8 and 9. Major limitations of both studies include a lack of comparison to standard methods of monitoring, and heterogeneity in the study populations.

Table 6. Nonrandomized Studies of Signatera Testing in Breast Cancer - Study Characteristics

Study	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Coombes et al (2019)[6]	Relapse detection following primary treatment	49 individuals with stage I to III breast cancer who had undergone surgery and adjuvant chemotherapy; 34 HR–positive/HER2-negative, 8 HER2-positive, 7 TNBC	Prospective cohort, multicenter, UK	Cancer antigen 15-3 serum testing, CT imaging	2 or more variants detected out of 16	Plasma samples every 6 months for up to 4 years	Yes
Magbanua et al (2021)[7]	Response to neoadjuvant chemotherapy	84 individuals with ≥ 2.5 cm nonmetastatic stage II/III breast cancer	Retrospective analysis of samples prospectively collected as part of the I-SPY2 TRIAL	Radiological imaging	2 or more variants detected out of 16	Plasma samples collected before, during, and after neoadjuvant chemotherapy	Yes

CT: computerized tomography; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple-negative breast cancer.

Table 7. Nonrandomized Studies of Signatera Testing in Breast Cancer - Study Results

Study	Initial N	Final N	Excluded Samples	Recurrence Rate	Median Time to Recurrence, months (range)	Clinical Validity			
						Sensitivity	***Specificity***	***PPV***	***NPV***
Coombes et al (2019)[6],	197	49	148	18/49 (36.7%)	8.9 (0.5 to 24.0)	16/18 (89%)	31/31 (100%)	NR	NR
Hazard ratio (95% CI) for RFS (first postsurgical sample)	11.8 (4.3 to 32.5), p<.001								
Hazard ratio (95% CI) for RFS (any follow up sample)	35.8 (7.9 to 161.3), p<.001								
Magbanua et al (2021)[7],	84	75	9	NA	NA	NR	NR	4/6 (67%)	50/54 (93%)
Hazard ratio (95% CI) for recurrence (T0, baseline)	4.11 (0.52 to 32.4)								
Hazard ratio (95% CI) for RFS (T1, 3 weeks after therapy initiation)	4.5 (1.2 to 17.4)								
Hazard ratio (95% CI) for RFS (T2, between regimens)	5.4 (1.3 to 22.5)								
Hazard ratio (95% CI) for RFS (T3, after neoadjuvant chemotherapy)	11.5 (2.9 to 46.1)								

CI: confidence interval; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RFS: recurrence-free survival.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Coombes et al (2019)[6],	2. Study population included a mix of individuals with stage I to III breast cancer		3. Not compared to tests used for the same purpose		
Magbanua et al (2021)[7],			3. Not compared to tests used for		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
			the same purpose		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 9. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Coombes et al (2019)[6],						1. Confidence intervals for test characteristics not reported; small number of positive ctDNA tests
Magbanua et al (2021)[7],	2. Retrospective analysis					1. Confidence intervals for test characteristics not reported; small number of positive ctDNA tests

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Breast Cancer

For individuals with breast cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 2 noncomparative studies (N = 133). One study evaluated Signatera testing for disease surveillance following primary treatment, and 1 reported the association of test results at different timepoints with response to neoadjuvant chemotherapy. Although the studies found an association of test results with prognosis, the studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study

populations. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Bladder Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with bladder cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following curative treatment.

The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA testing with Signatera improve the net health outcome in individuals with bladder cancer? The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with bladder cancer, or those who have been treated for bladder cancer and are being monitored for recurrence.

Interventions

The test being considered is circulating tumor DNA testing with Signatera:

- At diagnosis, to identify individuals at low risk of recurrence after cystectomy who may be eligible for cystectomy without neoadjuvant chemotherapy.
- After chemotherapy before cystectomy, to determine treatment response and inform treatment decisions (e.g., additional cycles of chemotherapy or other therapeutic strategies).
- During disease surveillance after cystectomy, to identify metastatic relapse after cystectomy at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment. For individuals with bladder cancer who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-in* individuals for adjuvant chemotherapy, the performance characteristics of most interest are positive predictive value and specificity.

Comparators

- Urine testing, cystoscopy, and radiographic imaging are used for disease monitoring in individuals with bladder cancer.
- Detection of relapse and monitoring of response to treatment in the metastatic setting is performed by standard computed tomography scan.

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

If used to *rule in* individuals with bladder cancer who would be likely to benefit from adjuvant chemotherapy, the performance characteristics of most interest are positive predictive value and specificity.

If used to *rule out* patients with bladder cancer who could forego adjuvant chemotherapy, the performance characteristics of most interest are negative predictive value and sensitivity. However, since the test would be used to select individuals who would not receive category 1 recommended treatment, direct evidence of improvement in outcomes is required.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard

- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trials

Two nonrandomized studies have reported an association between Signatera testing and prognosis in bladder cancer (Tables 10 and 11).

Christensen et al (2019) assessed the association of ctDNA with prognosis in 68 individuals with localized advanced bladder cancer.[8,]

Powles et al (2021) reported the association of a positive Signatera test to treatment response in 581 individuals who had undergone surgery for urothelial cancer and were enrolled in a RCT of atezolizumab versus observation.[9,] Study participants who were positive for ctDNA had improved disease-free survival and overall survival in the atezolizumab arm versus the observation arm (disease-free survival hazard ratio = 0.58 [95% CI, 0.43–0.79]; p=.0024 and overall survival hazard ratio = 0.59 [95% CI, 0.41–0.86]). No difference in disease-free survival or overall survival between treatment arms was noted for patients who were negative for ctDNA.

The major limitation of these studies was lack of comparison to other tests used for the same purpose (Tables 12 and 13).

Table 10. Nonrandomized Studies of Signatera Testing in Bladder Cancer - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Christensen et al (2019) [8,]	68 individuals with muscle-invasive bladder cancer who were receiving neoadjuvant chemotherapy before cystectomy between 2013 and 2017	Prospective, one University Hospital, Denmark	Radiological imaging	greater or equal to 2 variants detected out of 16	Surveillance according to European Guidelines. Blood samples collected at uniformly scheduled clinical visits and before each chemotherapy cycle. Median follow-up of 21 months after cystectomy.	Yes
Powles et al (2021)[9,]	581 individuals with urothelial cancer from a randomized Phase III trial of adjuvant atezolizumab vs. observation who had undergone surgery and were evaluable for ctDNA	Retrospective	Radiological imaging	greater or equal to 2 variants detected out of 16	Post-surgical plasma samples were collected and tested at baseline and 6 weeks after randomization and individuals were followed up for a median of 23 months	No

Table 11. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Bladder Cancer

Study	Mean Recurrence Rate (95% CI)	
	ctDNA Positive	ctDNA Negative
Christensen et al (2019) [8],		
At diagnosis before chemotherapy	11/24 (46%)	1/35 (3%)
Adjusted hazard ratio (95% CI) for recurrence	29.1; p=.001	
After chemotherapy before cystectomy	6/8 (75%)	6/55 (11%)
Adjusted hazard ratio (95% CI) for recurrence	12.0; p<.001	
During disease surveillance after cystectomy	13/17 (76%)	0/47 (0%)
Adjusted hazard ratio for recurrence	129.6; p<.001	
Powles et al (2021)[9],		
Following surgery (cycle 1 day 1)		
Hazard ratio (95% CI) for DFS	6.3 (4.45 to 8.92); p<.0001	
6 weeks after randomization (cycle 3 day 1)		
Hazard ratio (95% CI) for DFS	8.65 (5.67 to 13.18); p<.0001	

CI: confidence interval; ctDNA: circulating tumor DNA; DFS: disease-free survival.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Christensen et al (2019) [8],			3. Not compared to tests used for the same purpose		
Powles et al (2021)[9],	.		3. Not compared to tests used for the same purpose		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 13. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Christensen et al (2019) [8],						1. Confidence intervals for hazard ratios not reported.
Powles et al (2021)[9],						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Bladder Cancer
For individuals with bladder cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 uncontrolled prospective cohort study (N = 68) and 1 retrospective subgroup analysis from a RCT (N = 581). The prospective study reported an association between Signatera test results at diagnosis, during chemotherapy treatment, and during surveillance following cystectomy to prognosis. The retrospective analysis reported an association between test results and response to atezolizumab treatment. Study limitations, including a lack of comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Non-Small Cell Lung Cancer
Clinical Context and Test Purpose
The purpose of Signatera testing in individuals with non-small cell lung cancer (NSCLC) is to predict disease course to inform treatment decisions and to monitor for recurrence following surgical resection.

The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA testing with Signatera improve the net health outcome in individuals with NSCLC?
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with NSCLC, or those who have been treated for NSCLC and are being monitored for recurrence.

Interventions
The test being considered is circulating tumor DNA testing with Signatera following surgical resection, to identify metastatic relapse at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Adjuvant platinum-based chemotherapy is not the standard of care following surgery for NSCLC; treatment improves cure rates after surgery in only 5% of patients, and 20% of patients receiving chemotherapy experience acute toxicities. Signatera testing is proposed to select patients who are very likely to relapse post-operatively and who might benefit from adjuvant treatment.

Comparators
Radiographic imaging is used for disease monitoring in individuals with NSCLC. Detection of relapse and monitoring of response to treatment in the metastatic setting is performed by

standard computed tomography scan, with frequency and type of imaging depending on primary treatment and stage. For patients with stage I-II NSCLC following completion of definitive therapy, NCCN guidelines recommend history and physical and chest CT every 6 months for 2 to 3 years, then annually. For patients with primary treatment that included radiotherapy, surveillance is recommended every 3 to 6 months for 3 years, and every 6 months for 2 years, then annually. Treatment options following recurrence include resection and/or systemic therapy.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

Beneficial outcomes of a true positive test would be an individual undergoing potentially beneficial additional treatment such as chemotherapy at an earlier time point than if a relapse were identified clinically.

Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment, and experiencing adverse effects of such treatment.

Nonrandomized Trial
The evidence for the use of Signatera to detect relapse in NSCLC following surgery is limited to a subgroup analysis of 24 individuals enrolled in TRACERx, a longitudinal cohort study of tumor sampling and genetic analysis in individuals with NSCLC.[10,] Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least 2 single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%).

Study limitations are shown in Tables 15 and 16. Major limitations include no comparison to standard surveillance methods and imprecise estimates due to the small sample size. Additionally, the commercially available Signatera has been updated since this publication.

Table 14. Nonrandomized Study of Signatera Testing in Non-Small Cell Lung Cancer

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Main Results
Abbosh et al (2017)[10,]	24 individuals with early-stage NSCLC	Prospective, subgroup of patients enrolled in the TRACERx Study	Clinical assessment and chest radiograph	Greater or equal to 2 variants detected out of 16	Every 3 months for 2 years, then every 6 months thereafter; individuals were followed up for a median of 775 days	Yes	Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test Of 10 individuals with no relapse after a median followup of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%).

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Main Results
							Median interval between ctDNA detection and NSCLC relapse confirmed by CT imaging indicated by clinical and chest radiograph follow-up (lead time) was 70 days (range, 10 to 346 days).

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Abbosh et al (2017)[10],			3. No comparison to standard methods of monitoring for relapse	1. Health outcomes not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 16. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Abbosh et al (2017)[10],	2. Subgroup analysis, subset of the first 100 participants enrolled in the study; unclear if selection was consecutive		2. Timing of ctDNA testing unclear			1. No comparison to imaging, no confidence intervals

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Non-Small Cell Lung Cancer
For individuals with NSCLC who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 subgroup analysis of participants enrolled in a prospective observational study (N = 24). Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least 2 single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%). This study's small sample size and lack of a comparator preclude drawing conclusions about clinical validity. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Esophageal Cancer
Clinical Context and Test Purpose
The purpose of Signatera testing in individuals with esophageal cancer is to detect minimal residual disease following surgical resection and to monitor for disease recurrence.

The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA testing with Signatera improve the net health outcome in individuals with esophageal cancer? The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with esophageal cancer who have undergone surgical resection.

Interventions
The test being considered is circulating tumor DNA testing with Signatera:
- Following surgical resection, to detect minimal residual disease and aid in the selection of individuals who may benefit from early/adjuvant treatment.
- For disease monitoring after curative treatment, to identify metastatic relapse at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators
Recommendations on surveillance and monitoring following esophageal cancer treatment include periodic upper endoscopy, laboratory tests, and imaging as indicated. Specific recommendations depend on tumor classification.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

Beneficial outcomes of a true positive test would be an individual undergoing potentially beneficial additional treatment at an earlier time point than if a relapse were identified clinically. Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment and experiencing adverse effects of such treatment.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trial

One noncomparative retrospective study reported the association of Signatera testing measured before and after surgery with relapse and recurrence in 17 individuals with esophageal adenocarcinoma (Tables 17 and 18). Patients who were ctDNA-positive before surgery had significantly poorer disease-free survival (DFS) (p<.042), with a median DFS of 32.0 months vs. 63.0 months in ctDNA-negative preoperative patients. This study was limited by the very small number sample size, and its retrospective design (Tables 19 and 20).

Table 17. Nonrandomized Study of Signatera Testing to Predict Relapse in Esophageal Cancer - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Ococks et al (2021)[11],	17 individuals with esophageal adenocarcinoma who had undergone surgery	Retrospective	Radiological imaging	2 or more variants detected out of 16	Blood samples were collected before and after surgical treatment and patients were followed up for a median of 43.4 months.	Yes

Table 18. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Resected Esophageal Cancer

Study	Median Disease-Free Survival		
	ctDNA Positive	ctDNA Negative	p for comparison
Ococks et al (2021)[11],			
ctDNA status before surgery			
Recurrence rate	5/11	0/6	
Median disease-free survival	32.0 months	63.0 months	.042
ctDNA status following surgery			
Recurrence rate	4/4	1/13	NR
Median disease-free survival	14.2 months	51.2 months	NR

ctDNA: circulating tumor DNA; NR: not reported; RFS: recurrence-free survival.

Table 19. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Ococks et al (2021)[11],		2. Unclear if the test used was the commercially available version	3. No comparison to tests used for the same purpose		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 20. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Ococks et al (2021)[11],					Excluded individuals who did not undergo surgery	Imprecise estimates due to small sample size

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Esophageal Cancer

For individuals with esophageal cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 noncomparative, retrospective study (N = 17). Patients who were ctDNA-positive before surgery had significantly poorer disease-free survival (DFS) (p<.042), with a median DFS of 32.0 months versus 63.0 months in ctDNA-negative preoperative patients. This study was limited by its small number sample size and retrospective design. There is no direct evidence that the use of the test improves health outcomes. Due to the study's limitations and lack of additional supporting studies, the evidence is not sufficient to draw conclusions on clinical validity. Additionally, the management pathway for Signatera testing in esophageal cancer has not been clearly defined.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Solid Tumors Receiving Immunotherapy

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with solid tumors who have received immunotherapy is to monitor treatment response and inform subsequent treatment decisions. Signatera is proposed as a method to stratify patients according to their likelihood of response to immunotherapy, to guide treatment decisions.

The question addressed in this evidence review is: Does tumor-informed circulating tumor DNA testing with Signatera improve the net health outcome in individuals with solid tumors who have received immunotherapy?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with solid tumors who have received immune checkpoint therapy.

Interventions

The test being considered is circulating tumor DNA testing with Signatera.

Comparators

For individuals with solid tumors receiving immunotherapy, treatment response is monitored by repeated radiographic evaluation of the tumor.

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

If the test is used to *rule-in* individuals with solid tumors who are likely to respond to immunotherapy, the performance characteristics of most interest are positive predictive value and specificity.

If the test is used to *rule-out* individuals with solid tumors who are unlikely to respond to immunotherapy, the performance characteristics of most interest are negative predictive value and sensitivity.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trial

Bratman et al (2020) evaluated Signatera to predict treatment response in 106 individuals receiving pembrolizumab for solid tumors, including squamous cell cancer of head and neck, triple negative breast cancer, high-grade serous ovarian cancer, malignant melanoma, and mixed solid tumors (Tables 21 and 22).[12,]

Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted hazard ratio [HR] 0.49, 95% CI 0.29 to 0.83) and progression free survival (adjusted HR 0.54, 95% CI 0.34 to 0.85). Among participants with at least 2 ctDNA measurements, any rise in ctDNA levels during surveillance above baseline was associated with rapid disease progression

and poor survival (median overall survival 13.7 months), whereas among 12 patients whose ctDNA cleared during treatment, overall survival was 100% at a median follow up of 25.4 months (range 10.8 to 29.5 months) following the first clearance.

Study limitations are shown in Tables 23 and 24. This single-center study is limited by its small sample size and variability in results across different tumor types. The study did not include a comparison of monitoring with ctDNA to standard methods of monitoring response such as repeat imaging.

Table 21. Nonrandomized Study of Signatera Testing to Predict Response to Immunotherapy in Individuals with Solid Tumors - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Bratman et al (2020)[12,]	106 individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab (NCT02644369)	Prospective, single center	TMB, PD-L1 testing, radiological imaging	Greater or equal to 2 variants detected out of 16	Baseline sample obtained and after every 3 cycles; individuals were followed up for a median of 25 months	Yes

PD-L1: programmed death ligand-1; TMB: tumor mutational burden.

Table 22. Overall Survival by Risk Category in a Nonrandomized Study of Signatera to Monitor Response to Immunotherapy

	Overall Survival
Bratman et al (2020)[12,]	
Lower than median ctDNA at baseline	adjusted HR 0.49 (95% CI 0.29–0.83)
ctDNA increased (n = 45)	13.7 months
ctDNA decreased but still detectable (n = 16)	23.8 months
ctDNA cleared (n = 12)	25.4 months (range 10.8 to 29.5 months)

CI: confidence interval; ctDNA: circulating tumor DNA; RFS: HR: hazard ratio.

Table 23. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Bratman et al (2020)[12,]	1, 2. Unclear what management changes would be implemented based on test results.		No comparison to standard surveillance methods	3. Clinical validity outcomes not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 24. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Bratman et al (2020)[12,]						2. Comparison to other tests not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Solid Tumors Receiving Immunotherapy

For individuals with solid tumors who receive tumor-informed ctDNA testing with Signatera to monitor response to immunotherapy, the evidence includes a subgroup analysis of individuals enrolled in a nonrandomized trial of pembrolizumab (N = 106). The subgroup analysis evaluated Signatera testing to monitor response to immunotherapy in individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab. Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted HR 0.49, 95% CI 0.29 to 0.83) and progression free survival (adjusted HR 0.54, 95% CI 0.34 to 0.85). The study was limited by a small sample size, variability in results across different tumor types, and lack of a comparison to standard methods of monitoring response to treatment. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. Additionally, the management pathway for Signatera testing for monitoring response to immunotherapy has not been clearly defined.

Summary of Evidence

For individuals with CRC who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 3 noncomparative studies (N = 410) and 1 retrospective comparative study (N = 48). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Nonrandomized studies have reported an association between ctDNA results measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after curative treatment and prognosis, but these studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. A retrospective observational study found no advantage to surveillance with Signatera compared to standard surveillance conducted according to NCCN guidelines (p>.99 for sensitivity and specificity compared to imaging). There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not

sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 2 noncomparative studies (N = 133). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. One study evaluated Signatera testing for disease surveillance following primary treatment, and 1 reported the association of test results at different timepoints with response to neoadjuvant chemotherapy. Although the studies found an association of test results with prognosis, the studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bladder cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 uncontrolled prospective cohort study (N = 68) and 1 retrospective subgroup analysis from a RCT (N = 581). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The prospective study reported an association between Signatera test results at diagnosis, during chemotherapy treatment, and during surveillance following cystectomy to prognosis. The retrospective analysis reported an association between test results and response to atezolizumab treatment. Study limitations, including a lack of comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 subgroup analysis of participants enrolled in a prospective observational study (N = 24). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least 2 single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%). This study's small sample size and lack of a comparator preclude drawing conclusions about clinical validity. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with esophageal cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 noncomparative, retrospective study (N = 17). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Patients who were ctDNA-positive before surgery had significantly poorer disease-free survival (DFS) (p<.042), with a median DFS of 32.0 months versus 63.0 months in ctDNA-negative preoperative patients. This study was limited by its small number sample size and retrospective

design. There is no direct evidence that the use of the test improves health outcomes. Due to the study's limitations and lack of additional supporting studies, the evidence is not sufficient to draw conclusions on clinical validity. Additionally, the management pathway for Signatera testing in esophageal cancer has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with solid tumors who receive tumor-informed ctDNA testing with Signatera to monitor response to immunotherapy, the evidence includes a subgroup analysis of individuals enrolled in a nonrandomized trial of pembrolizumab (N = 106). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The subgroup analysis evaluated Signatera testing to monitor response to immunotherapy in individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab. Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted [HR 0.49, 95% CI 0.29 to 0.83) and progression free survival (adjusted HR 0.54, 95% CI 0.34 to 0.85). The study was limited by a small sample size, variability in results across different tumor types, and lack of a comparison to standard methods of monitoring response to treatment. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. Additionally, the management pathway for Signatera testing for monitoring response to immunotherapy has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
National Comprehensive Cancer Network guidelines do not specifically address tumor-informed ctDNA testing for any of the cancer types included in this review. The guidelines on colon cancer state: "The panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy."[13,]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 25.

Table 25. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05212779	Predicting the Risk of Ovarian Cancer Recurrence Using Circulating Tumor DNA to Assess Residual Disease	45	Dec 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04761783[a]	BESPOKE Study of ctDNA Guided Immunotherapy	1539	May 2025
NCT04264702[a]	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	2000	Jan 2025
NCT04786600[a]	A Phase II Randomized Therapeutic Optimization Trial for Subjects With Refractory Metastatic Colorectal Cancer Using ctDNA: Rapid 1 Trial	78	May 2025
NCT05178576[a]	A Single Arm Phase II Study to Evaluate Treatment With Gevokizumab in individuals With Stage II/III Colon Cancer Who Are ctDNA-positive After Curative Surgery and Adjuvant Chemotherapy	31	Nov 2025
NCT04920032[a]	Proof of Concept Study of ctDNA Guided Change in Treatment for Refractory Minimal Residual Disease in Colon Adenocarcinomas	22	Jun 2024
NCT05060003[a]	A Phase II Randomized Study of Tiragolumab Plus Atezolizumab Versus Atezolizumab in the Treatment of Stage II Melanoma individuals Who Are ctDNA-positive Following Resection	244	Feb 2028
NCT05081024[a]	Establishing a ctDNA Biomarker to Improve Organ Preserving Strategies in individuals With Rectal Cancer	50	Sep 2024
NCT05067842	A Pilot Observational Study to Assess Feasibility of Tumor Response Assessment by Circulating Tumor DNA (ctDNA) in individuals With Locally Advanced Esophageal and GE Junction Adenocarcinoma Undergoing Treatment With Total Upfront Chemotherapy and Chemoradiation	30	Jan 2028
NCT04670588	A Prospective Observational Study to Determine the Feasibility of Tumor Response Assessment by Circulating Tumor DNA in individuals With Locally Advanced Rectal Cancer Undergoing Total Neoadjuvant Therapy	30	Dec 2025
NCT04929015	Peritoneal Carcinomatosis Leveraging ctDNA Guided Treatment in GI Cancer Study (PERICLES Study)	30	Nov 2024
NCT05058183[a]	Safe De-escalation of Chemotherapy for Stage 1 Breast Cancer	400	Nov 2027
NCT05174169[a]	Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease	1912	Jan 2030

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Natera. FDA Grants Two New Breakthrough Device Designations for Nateras Signatera MRD Test. March 24, 2021. https://www.natera.com/company/news/fda-grants-two-new-breakthrough-device-designations-for-nateras-signatera-mrd-test/. Accessed April 5, 2022
2. Fakih M, Sandhu J, Wang C, et al. Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer. JAMA Netw Open. Mar 01 2022; 5(3): e221093. PMID 35258578
3. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. JAMA Oncol. Aug 01 2019; 5(8): 1124-1131. PMID 31070691
4. Henriksen TV, Tarazona N, Frydendahl A, et al. Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrences. Clin Cancer Res. Feb 01 2022; 28(3): 507-517. PMID 34625408
5. Loupakis F, Sharma S, Derouazi M, et al. Detection of Molecular Residual Disease Using Personalized Circulating Tumor DNA Assay in Patients With Colorectal Cancer Undergoing Resection of Metastases. JCO Precis Oncol. Jul 2021; 5. PMID 34327297

6. Coombes RC, Page K, Salari R, et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. Clin Cancer Res. Jul 15 2019; 25(14): 4255-4263. PMID 30992300
7. Magbanua MJM, Swigart LB, Wu HT, et al. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. Ann Oncol. Feb 2021; 32(2): 229-239. PMID 33232761
8. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al. 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. J Clin Oncol. Jun 20 2019; 37(18): 1547-1557. PMID 31059311
9. Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature. Jul 2021; 595(7867): 432-437. PMID 34135506
10. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. Apr 26 2017; 545(7655): 446-451. PMID 28445469
11. Ococks E, Sharma S, Ng AWT, et al. Serial Circulating Tumor DNA Detection Using a Personalized, Tumor-Informed Assay in Esophageal Adenocarcinoma Patients Following Resection. Gastroenterology. Nov 2021; 161(5): 1705-1708.e2. PMID 34284036
12. Bratman SV, Yang SYC, Iafolla MAJ, et al. Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. Nat Cancer. Sep 2020; 1(9): 873-881. PMID 35121950
13. National Comprehensive Cancer Network. Guidelines on Colon Cancer. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed April 5, 2022.

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2022	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Tumor-Informed Circulating Tumor DNA Testing for Cancer Management 2.04.153** **Policy Statement:** Tumor-informed circulating tumor DNA testing (e.g., Signatera) is considered **investigational** for all indications.