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Private Payer and Medicare Coverage Policies for Use of Circulating Tumor DNA Tests in Cancer Diagnostics and Treatment

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ABSTRACT

Background: Circulating tumor DNA (ctDNA) is used to select initial targeted therapy, identify mechanisms of therapeutic resistance, and measure minimal residual disease (MRD) after treatment. Our objective was to review private and Medicare coverage policies for ctDNA testing. **Methods:** Policy Reporter was used to identify coverage policies (as of February 2022) from private payers and Medicare Local Coverage Determinations (LCDs) for ctDNA tests. We abstracted data regarding policy existence, ctDNA test coverage, cancer types covered, and clinical indications. Descriptive analyses were performed by payer, clinical indication, and cancer type. **Results:** A total of 71 of 1,066 total policies met study inclusion criteria, of which 57 were private policies and 14 were Medicare LCDs; 70% of private policies and 100% of Medicare LCDs covered at least one indication. Among 57 private policies, 89% specified a policy for at least 1 clinical indication, with coverage for ctDNA for initial treatment selection most common (69%). Of 40 policies addressing progression, coverage was provided 28% of the time, and of 20 policies addressing MRD, coverage was provided 65% of the time. Non–small cell lung cancer (NSCLC) was the cancer type most frequently covered for initial treatment (47%) and progression (60%). Among policies with ctDNA coverage, coverage was restricted to patients without available tissue or in whom biopsy was contraindicated in 91% of policies. MRD was commonly covered for hematologic malignancies (30%) and NSCLC (25%). Of the 14 Medicare LCD policies, 64% provided coverage for initial treatment selection and progression, and 36% for MRD. **Conclusions:** Some private payers and Medicare LCDs provide coverage for ctDNA testing. Private payers frequently cover testing for initial treatment, especially for NSCLC, when tissue is insufficient or biopsy is contraindicated. Coverage remains variable across payers, clinical indications, and cancer types despite inclusion in clinical guidelines, which could impact delivery of effective cancer care.

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Background

There is increased adoption of blood-based circulating tumor DNA (ctDNA) testing in cancer care.[1] These tests are used to detect gene variants that shed from solid tumor cells or arise from hematologic malignancies circulating in the blood. There are multiple reasons to perform ctDNA tests, including to identify whether a patient is a candidate for initial targeted therapy, characterize mechanisms of therapeutic resistance at time of progression, and measure minimal residual disease (MRD) after completion of treatment.[2–8] Most initial molecular testing is performed on biopsy or surgical specimens, considered the gold standard and currently the only way to detect certain types of biomarkers (eg, PD-L1). Blood-based ctDNA testing provides an alternative or complementary test to tissue-based testing, and is a valuable tool when results are needed rapidly and tissue is not available or contraindicated due to comorbidities. The turnaround time for ctDNA is significantly faster (average 10 vs 27 days) than a tissue sample.[9] ctDNA may also spare patients from the risks associated with biopsies, such as organ damage, bleeding, or infection.[10] For example, pneumothorax was recorded in 10.2% of percutaneous biopsies of the lung.[11] There are limitations to ctDNA testing, such as the fact that not all cancer cells shed DNA, and therefore ctDNA testing will not be successful in all patients.[12] Accurate detection of ctDNA is

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variable and can depend on a number of factors, including tumor burden and location, and thus may not always detect a targetable mutation even when one is found via tissue biopsy.[13,14] However, in other scenarios, such as when there may be tumor heterogeneity or necrosis in a tissue biopsy sample that limits accurate detection of a targetable mutation, ctDNA may be more accurate because in theory it is sampling DNA from all metastatic sites.

It is important to study payer coverage of ctDNA testing because policies for molecular tests evolve rapidly[15–22] and can impact clinician decision-making for cancer management.[23] Our objective was to update and expand our previous review of coverage policies with a new review of current (as of February 2022) private payer and Medicare coverage for ctDNA testing for the management of advanced solid tumor and hematologic malignancies.[15] We examined 3 clinical indications: (1) select initial targeted therapy, (2) identify mechanisms of therapeutic resistance in nonresponders or at the time of progression, and (3) measure MRD after completion of treatment (eg, surgery). Our study did not evaluate ctDNA testing coverage in conjunction with tissue-based testing in order to examine the existence and inclusion of these emerging tests in coverage policies. This study is timely given the increasing advancement in technology and recent FDA approvals for ctDNA tests. In 2020, the FDA approved 2 comprehensive ctDNA tests: Guardant360 CDx, which can detect variants in >60 different genes, for all solid tumor types and as a companion diagnostic in NSCLC, and FoundationOne Liquid CDx, which can identify variants in >300 genes, for metastatic castration-resistant prostate cancer and NSCLC.[24]

Methods

We analyzed private, publicly available coverage policies, Medicare national coverage determinations (NCDs), and Medicare Administrative Contractor (MAC) local coverage determinations (LCDs) for ctDNA testing indications of initial treatment selection, progression, and minimal residual disease (MRD) as of February 2022. For definitions of additional terms see supplemental eAppendix 1 (available with this article at JNCCN.org).

Data Sources and Payer Cohorts

We obtained private payer coverage policies and Medicare NCDs and LCDs from Policy Reporter,[25] a TrialCard company (www.policyreporter.com) that obtains policies and curates a database from 1,066 payers covering 325 million individuals, including 220 individual private and 411 public payers, to track coverage of medical procedures, laboratory tests, and pharmaceuticals representative of the insured US population in real time.[25] (For additional details see supplemental eAppendix 2; the total does not equal 1,066 because other types of policies exist in the database). Policy Reporter has been used previously in several studies,[26–28] including a study on comprehensive genomic profiling in hematologic malignancies.[29]

For our study, the private payer cohort included all payers with ≥1 million enrollees and with a coverage policy for at least 1 of the 3 clinical indications (previously described). The Medicare cohort included all 7 MACs (12 jurisdictions) that issue LCDs, and the Centers for Medicaid & Medicare Services (CMS), which issues NCDs. Medicare coverage is administered by 7 MACs that each cover ≥1 of the 12 jurisdictions or regions of the United States. This study included private coverage policies for 268 million enrollees (80% of the total US population) for initial treatment and progression, and 202 million enrollees for MRD (75% of the total US population). Additionally, Medicare policies covered approximately 64 million enrollees (100% of all enrollees, 20% of US population).

In our study, we included private payers that cover two-thirds of the insured US population,[30] and limited inclusion to those with >1 million enrollees. The top 5 largest (>1 million) private payers control nearly 46% of the health insurance market (Aetna, Anthem, Cigna, Humana, and UnitedHealth).[31] We did not include Medicaid, because coverage policies are not consistently available from state Medicaid agencies.

Search Strategy and Policy Selection

We contracted with Policy Reporter to search their database by using the following search terms: "ctDNA," "circulating tumor DNA," "Liquid Biopsy," "Minimal Residual Disease," and "MRD." We reviewed titles and document types and excluded documents that were not relevant (eg, Liquid Biopsy for Transplants) and documents that were not coverage policies (eg, news/announcements or responses to LCD draft policies). Based on these criteria, we excluded 435 documents from a total of 506 documents from payers with >1 million enrollees (supplemental eFigure 1). Our study did not explicitly evaluate concordant ctDNA and tissue-based testing policies.

Variables Included, Data Abstraction, and Analysis

We abstracted data for the following variables: structure of the policy, whether it was written and administered by a Laboratory Benefit Manager (LBM; these are third-party intermediaries that manage laboratory testing for payers, including drafting coverage policies for payers),[32] which of the 3 ctDNA test indications were addressed, language used for coverage or noncoverage, covered and noncovered cancers, genes included, and specific test requirements. A complete list of variables is provided in supplemental eTable 1.

Data were coded by 2 individuals: primary coding (M.P. Douglas) and secondary coding (M.V. Ragavan, C. Chen, A. Kumar), with discrepancies resolved by

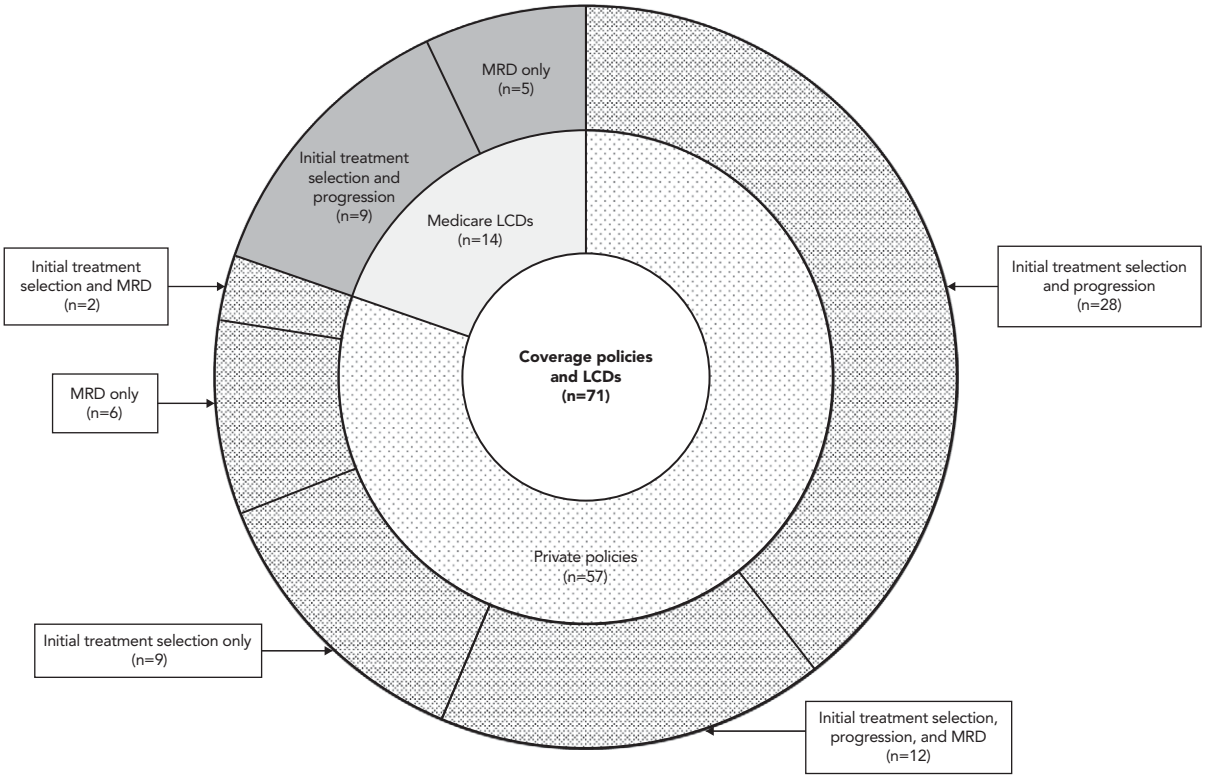

Figure 1. Coverage for ctDNA in private payer policies and Medicare LCDs. Outer ring represents clinical indications evaluated within individual policies. Middle ring represents number of policies by private payers (pattern) and Medicare LCDs (no pattern); pattern continues to outer ring as relevant. Inner circle represents total number of policies. Note: 1,066 total payers in Policy Reporter; 220 private payers; 411 public payers covering 325 million individuals.
Abbreviations: ctDNA, circulating tumor DNA; LCD, Local Coverage Determination.

discussion. We described our findings using descriptive statistics but did not statistically assess differences.

Results

We identified 57 private payer policies and 14 Medicare LCDs addressing at least 1 of the 3 clinical indications. There were no Medicare NCDs addressing any of the clinical indications. In the case of a "noncoverage" policy, payers typically do not provide any further details other than a statement similar to "ctDNA testing is not a covered benefit due to lack of clinical utility." The lack of a payer policy does not imply that the payer will or will not reimburse for ctDNA testing.

Private payers and Medicare LCDs structure their policies differently (Figure 1). Specifically, private payers structure their policies to address any of the clinical indications or combination of clinical indications, whereas Medicare LCDs address the combined clinical indication of initial treatment and progression, separate from MRD. Furthermore, private payers structure their policies to focus on the general technology (eg, genetic testing, molecular testing), specific cancers (eg, NSCLC), ctDNA testing for ≥1 indication, or a combination of several of these. Medicare used either 1 of 2 different structures: (1) focus on a specific named test (eg, Guardant360 or InVisionFirst) or (2) focus on MRD testing (eg, any test for any cancer type).

Coverage was provided in 70% (40/57) of private policies for ≥1 of the 3 clinical indications (Table 1). Among private policies (n=57), the most commonly addressed (89%) and covered (69%) clinical indication was for initial treatment only. Progression (n=40) was slightly less frequently addressed (70%), and the coverage rate was

Table 1. Private Policy Coverage of ctDNA for Initial Treatment, Progression, or MRD

Type of Coverage	Policies With Coverage % (n/N)
Any indication (n=57)	70% (40/57)
ctDNA for initial treatment (n=51)	69% (35/51)
ctDNA for progression (n=40)	28% (11/40)
MRD (n=20)	65% (13/20)

Denominators vary based on the number of policies that addressed specific clinical indications.
Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease.

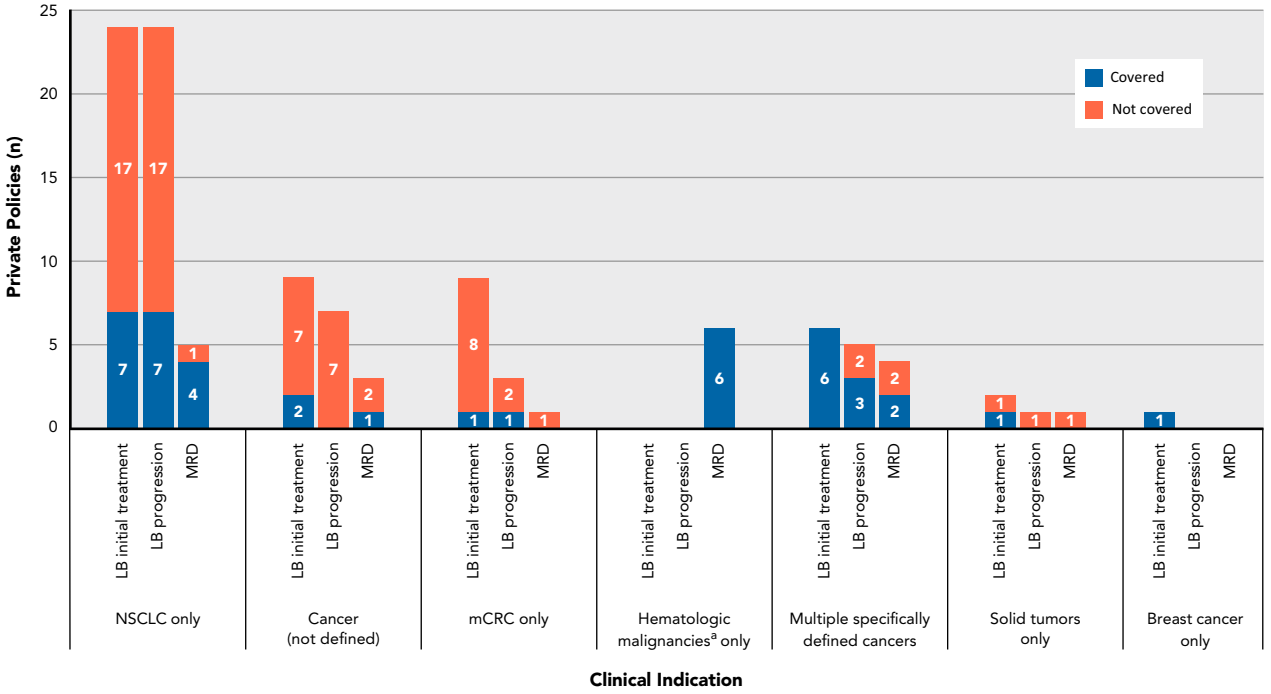

Figure 2. Three categories of private policies organized by cancer type.
Abbreviations: LB, liquid biopsy; mCRC, metastatic colorectal cancer; MRD, minimal residual disease; NSCLC, non–small cell lung cancer.
[a]Acute myeloid leukemia and acute lymphocytic leukemia.

much lower (28%). MRD (n=20) was less frequently addressed (35%) although more often (65%) covered. Of the private payer policies providing coverage for treatment selection (n=35), most (91%) policies limit coverage to when tissue was unavailable or when tissue biopsy was contraindicated.

There were 38 policies that were issued by Blue Cross Blue Shield (BCBS) Association payers, accounting for 67% of all policies examined. Of the 57 policies from private payers, 75% were issued directly by private payers, and 25% were cobranded policies (n=14) between private payers and LBM. Of the cobranded LBM/private payer policies, all but 2 were issued from BCBS payers.

Private payer policies addressed a variety of cancers, with some policies explicitly written for certain cancer types and others written for any cancer type (Figure 2). For initial treatment selection (n=51), the most commonly addressed cancer was NSCLC, which was addressed in 47% of private payer policies, and 29% of those provided coverage. For progression (n=40), more than half (60%) of private payer policies addressed NSCLC only and 29% of those provided coverage. For MRD (n=20), the most commonly addressed cancers were hematologic malignancies (30%) and NSCLC (25%). When addressed, hematologic malignancies were the only cancer type with coverage in all MRD policies.

All LCDs provided coverage (ie, in contrast to private policies, there were no noncoverage LCDs). We identified 14 LCDs from 4 of 7 MACs that represent 7 of 12 local jurisdictions or regions of the United States. Of the LCDs published, 64% of LCDs provided coverage of initial treatment selection and progression and 36% of LCDs provided coverage for MRD (Table 2). The LCDs were organized by

Table 2. Medicare LCD Policy ctDNA Testing Indications Addressed (N=14)

Indication Addressed	Policies
ctDNA initial treatment	64% (n=9)
ctDNA initial treatment using Guardant360 for any cancer type	36% (n=5)
ctDNA initial treatment using InVisionFirst for lung cancer only	29% (n=4)
Coverage limited by "tissue not available"	64% (n=9)
ctDNA progression	64% (n=9)
ctDNA progression using Guardant360 for any cancer type	36% (n=5)
ctDNA progression using InVisionFirst for lung cancer only	29% (n=4)
Coverage limited by "tissue not available"	64% (n=9)
MRD	36% (n=5)
Any cancer, any test	36% (n=5)

For the scenarios analyzed, all issued policies provide coverage (ie, there are no noncoverage policies). Only 4 of the 7 MACs issued LCDs.
Abbreviations: ctDNA, circulating tumor DNA; LCD, Local Coverage Determination; MACs, Medicare Administrative Contractor; MRD, minimal residual disease.

specific tests, with coverage for Guardant 360 for any type of cancer and for InVisionFirst for lung cancer, and in both cases, they state that coverage was limited to when tissue was not available or biopsy was contraindicated. LCDs for MRD provided coverage for any cancer and any test.

Discussion

Private payer policies and Medicare LCDs for ctDNA tests were often found to specify particular cancer types for coverage and specific tests to be used, or they offered example tests, and nearly all provided coverage when tumor tissue was not available or biopsy was contraindicated. Medicare LCDs commonly include a requirement for tests to be FDA-approved, and therefore named specific tests, whereas FDA approval or use of specifically named tests is less often required by private payers.

A new finding was that private payers relied on the use of LBM cobranded policies 25% of the time to develop their draft coverage policies (n=14). Most (93%) of these policies were developed by one LBM (Evicore) and 79% were on behalf of BCBS plans. The impact of LBMs on coverage policies has not been well studied and was not included in our previous study of tissue-based testing, and it is unknown whether there are benefits or harms.[32] Future studies should investigate differences within coverage when private payers are LBM cobranded or among BCBS plans that are cobranded versus those that are not.

Furthermore, we found that BCBS plans were heavily represented in our sample, constituting two-thirds (67%) of the private payer policies reviewed. In our previous study, BCBS plans constituted 64% of the private payer policies.[32] The national BCBS Association issued a technology assessment for "Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management" and an opinion on "Tumor-informed Circulating Tumor DNA Testing for Cancer Management" that has informed coverage for some BCBS plans (n=38),[33] whereas 71% of associated payers determined their own coverage policies and 29% wrote cobranded policies. For example, some payers provide detailed written policies (eg, include evidence reviewed to inform coverage decisions) and therefore have a more transparent set of criteria for coverage. However, payers, including BCBS plans, have coverage variation, which does not indicate faster adoption of the technology. Future studies should investigate differences in coverage when a payer provides more transparent evidence used in coverage criteria.

There were some distinct differences between private payer policies and Medicare LCDs. An important finding was that Medicare has not issued an NCD for any of the 3 clinical indications examined. However, only 4 of the 7 MACs have issued LCDs, which is consistent with a previous study.[15] CMS has issued an NCD on sequencing for advanced cancer that does not explicitly state coverage for ctDNA testing, because it is assumed to include such test coverage if the test was FDA-approved.[34] Additionally, Medicare LCDs defined specific brand-name tests that were covered, whereas private payers did not always list specific tests (some provided example tests) and instead described specific clinical indications. Finally, Medicare LCDs never combine initial treatment and progression with MRD indications. Furthermore, private payer coverage for MRD is primarily focused on hematologic malignancies, whereas Medicare provided MRD coverage primarily independent of cancer type even though in practice it is mainly used in hematologic malignancies.[35]

Although we did not investigate the coverage of tissue and ctDNA-based testing as a direct comparison, we understand that many times tissue and ctDNA testing are ordered concurrently. However, one private payer policy stated the ctDNA-based testing would not be covered in this scenario (data not shown).

Comparisons to our prior study show that coverage for ctDNA has increased in the past 3 to 7 years.[15] As of July 2019, private payer coverage policies for ctDNA tests to inform initial treatment were found 38% (28/73) of the time and for disease progression 11% (3/28) of the time.[15] In comparison, the current study found private payer coverage 69% and 28% of the time, respectively. In both studies, most of the policies were for NSCLC (24 policies in each) or for pan-cancers (15 policies in current study, 4 in previous study); however, the current study also found policies with coverage specific to metastatic colorectal cancer and breast cancer, which were not present in our previous study. The increase in coverage was not surprising given the recent FDA approval of the Guardant360 and FoundationOne Liquid CDx ctDNA-based tests, the increasing number of FDA approvals for targeted therapy across cancer types,[24,36] and evolving guidelines to recommend comprehensive molecular testing up-front across many cancer types.[37] BCBS plans covered ctDNA testing 89% of the time for any clinical indication, in contrast to 79% of the time in our previous study.

We found wide variation and complex language specifying coverage in private payer policies and Medicare LCDs. Additionally, as shown in Figure 1, both payer types include different clinical indications within each of their policies, issue policies specific to different cancers (Figure 2), and may have multiple policies to address each of the clinical indications. Specifically, private payers issued 5 different types of policies to address the clinical indications and Medicare LCDs issued 2 types of policies (Figure 1).

Clinical Implications

Payer policies may not reflect standard clinical practice or evidence found in systematic reviews or clinical guidelines, where ctDNA testing is increasingly being used for all of the clinical indications evaluated in this study. The

lack of a payer policy or a noncoverage policy does not imply the patient will not obtain testing, but it increases the uncertainty to access and procedure to access testing. Specifically, the lack of a policy may have a number of downstream consequences for patients and providers, such as the need for prior authorization or for appeals following denial from a payer, which can be burdensome and onerous for patients and providers. Furthermore, patients may need to seek alternative means to access the test, such as paying out of pocket or applying for patient assistance programs.

Although national guidelines are still evolving on the utility of ctDNA tests both as complementary to tumor testing and as an independent test, there are a number of organizations supporting the use of ctDNA tests. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC indicate that ctDNA testing can be considered when a patient is medically unfit for invasive tissue sampling or if, after pathologic confirmation of an NSCLC diagnosis, there is insufficient material for molecular analysis.[38] In addition, the International Association for the Study of Lung Cancer (IASLC) developed a consensus statement on ctDNA testing and concluded that it is an acceptable alternative to tissue biopsy for biomarker testing, both in the initial workup of a patient with newly diagnosed cancer and for identifying mechanisms of acquired resistance to targeted therapies in oncogene-driven lung cancers.[2] An increasing number of studies are demonstrating the feasibility of utilizing peripheral blood for routine MRD monitoring in hematologic malignancies where it is indicated, including acute lymphoblastic leukemia and multiple myeloma.[39]

The clinical indications for which ctDNA tests may be used are expanding rapidly, and thus adoption of changing guidelines and practices into payer coverage will be of paramount importance to ensure appropriate evidence-based cancer management. Although the use of MRD is currently only approved for hematologic malignancies, it is currently being extensively studied in solid tumors and incorporated into landmark clinical trials in the form of ctDNA. For example, in a multicenter cohort study of patients with stage III colorectal cancer who underwent surgical resection followed by adjuvant therapy, the presence of ctDNA was shown to be associated with lower disease-free survival rates.[40] Similar prospective studies have been conducted across solid tumor types, such as melanoma.[41] The FDA recently granted breakthrough designation for a novel ctDNA test, Signatera, for detection of MRD in multiple solid tumors.[42] Accordingly, clinical trials are beginning to incorporate ctDNA into secondary endpoints (vs no ctDNA), such as the recently published CheckMate 816 trial.[43]

Although there has been an increase in coverage for the use of ctDNA testing at initial diagnosis, coverage at thr time of disease progression remains limited. Although in some cases there is sufficient tissue for traditional tissue testing to determine initial treatment selection, any testing at the time of disease progression would require a subsequent biopsy or biopsies to obtain tissue. Additional invasive biopsies may be associated with higher complication rates, can be logistically challenging (eg, bone-only metastases) or contraindicated due to comorbidities. Awaiting results from a tissue biopsy can also significantly delay the start of the next line of therapy or enrollment on a clinical trial.[9] Tumor heterogeneity is an important concern in NSCLC, and a biopsy of a single site of metastasis may miss clinically relevant mechanisms of treatment resistance present at other sites of disease that ctDNA testing might detect.[44] In these cases, use of ctDNA testing at the time of progression would be ideal if the test has proven analytic and clinical validity. However, there are concerns about the ability of ctDNA to substitute for tissue samples to detect clinically relevant variants, given that concordance ranged from 53% to 64%.[45] However, a significant limitation of ctDNA-based testing is the inability to detect PD-L1, which can only be detected via tissue sample.

Strengths and Limitations

We conducted a comprehensive review of policies across cancer types for 3 clinical indications most relevant to precision oncology applications in cancer treatment using private payer and Medicare NCDs/LCDs identified using Policy Reporter, an established source of payer policy data. We further analyzed these policies using rigorous established methods developed and used by UCSF Center for Translational and Policy Research on Precision Medicine (TRANSPERS) in many previous publications.[46] This study had several limitations. First, we did not include Medicaid policies, representing approximately 83 million enrollees,[47] and Policy Reporter may not include all policies from all US private payers. However, the Policy Reporter database includes >1,000 payers, and we limited our analysis to payers with >1 million enrollees. Even with these limitations, our analysis reflected private coverage policies for 268 million enrollees for initial treatment and progression, and 202 million enrollees for MRD. Additionally, we included all Medicare policies, and Medicare enrollees account for approximately 64 million persons.[47] Second, we are limited to the information in the published coverage policies, which is highly variable and may not reflect the actual decision-making process or claims payment by individual payers.

Conclusions

Although ctDNA testing coverage has increased over the past several years, inconsistent coverage policies across payers could influence its implementation and may lead to unwanted treatment variation and barriers to access

to targeted therapies and appropriate personalized cancer management. As applications in precision oncology continue to evolve rapidly, payers' policies need to keep pace with the ever-increasing scientific evidence and advances in clinical care. Future research should continue to track payer coverage and test utilization to understand how payer policies influence access to precision oncology services.

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Supplemental online content for:

Private Payer and Medicare Coverage Policies for Use of Circulating Tumor DNA Tests in Cancer Diagnostics and Treatment

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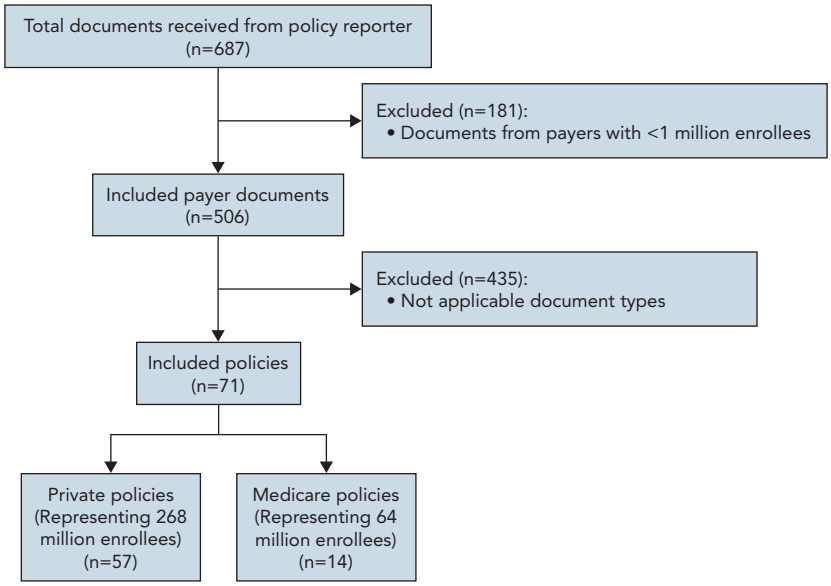

eFigure 1. PRISMA diagram.

eTable 1. Variables Coded for Private and Medicare Policies

Variable Name	Variable Definition	Variable Details/Coding[a]
Policy unique ID	Automatic unique number	Fill down sequentially
Payer name	Payer full name	(eg, Aetna)
Payer type	Private or public	Private or public
Policy title	Official name of policy	(copy from Policy Source Information table)
Policy from third party?	Was this policy adapted by the payer from a third party (eg, eviCore)?	Yes (note third party)/No
Policy date (effective date)	Date of policy	(MM/DD/YYYY)
Policy exists (screening variable, additional variables are not coded if no policy exists; lack of policy does not equate to a negative policy)	Yes/No	Yes/No
Coverage	Yes/No	Yes/No
Noncoverage	Reason stated for noncoverage, if provided/applicable	Copy/Paste from policy
Covered clinical scenario	For which clinical indications is ctDNA considered medically necessary (eg, for all solid tumors, for advanced lung cancer)?	Copy/Paste from policy
Prior authorization	Yes/No	Yes/No
Prior authorization details	Specific details of prior authorization requirements	Copy/Paste from policy
Evidence cited and study type	Evidence cited that support or refute the coverage or lack of coverage, and the study type	Copy/Paste from policy
Cancers included	Covered cancers (eg, lung cancer, pan-cancer, solid tumors)	Copy/Paste from policy
How ctDNA testing is covered	Policy covers any liquid biopsy testing or specific named tests	Copy/Paste from policy
How monitoring is covered	Policy covers any liquid biopsy testing for monitoring	Copy/Paste from policy
How MRD testing is covered	Policy covers any liquid biopsy testing for MRD	Copy/Paste from policy

Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease.
[a]For variables that were copy/paste, we subsequently coded these into discrete categories for counting purposes.

eAppendix 1. Definitions

Initial treatment selection: Sequencing of circulating tumor DNA (ctDNA) to inform and select targeted therapy.

Progression: Identify mechanisms of therapeutic resistance in nonresponders or at time of progression.

Minimal residual disease (MRD): Measure presence of ctDNA as an indicator for tumors that may not be detected using conventional methods (eg, imaging) after completion of treatment (eg, surgery). This may also be called molecular residual disease.

Medicare policies are consistently recorded and available to the public on the Centers for Medicare & Medicaid Services (CMS) website. The website has both draft and final versions, along with public comments.

Medicare National Coverage Determinations (NCDs) are developed and issued by CMS and coverage decisions apply to all 50 states and Puerto Rico. When it comes to molecular testing, Medicare will commonly not issue a NCD but defer to the individual Local Coverage Determinations (LCDs).

Medicare LCDs are developed and issued by ≥1 of 7 Medicare Administrative Contractors (MACs). These LCDs apply only to the states in which the test or service was performed. Of the 7 MACs, 4 routinely issue LCDs for molecular tests. These LCDs have previously been written to address individual tests (eg, Guardant360) but also need to be written to address a category of testing (eg, minimal residual disease).

MAC jurisdictions—represented with policies in this study (28 states)

Noridian covers California, Nevada, Hawaii, Washington, Oregon, Idaho, Montana, Wyoming, North Dakota, South Dakota, Utah, Arizona, Alaska.

Palmetto covers Georgia, Alabama, Tennessee, South Carolina, North Carolina, Virginia, West Virginia.

WPS covers Michigan, Indiana, Nebraska, Iowa, Missouri, Kansas.

CGS covers Ohio, Kentucky.

MAC jurisdictions—not represented with policies in this study (22 states and Puerto Rico)

Novitas covers Pennsylvania, New Jersey, Maryland, Delaware, Colorado, New Mexico, Texas, Oklahoma, Arkansas, Louisiana, Mississippi.

NGS covers New York, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, Maine, Wisconsin, Minnesota, Illinois.

FCSO covers Florida, Puerto Rico.

Cell-free DNA (cfDNA) are degraded DNA fragments released to the blood plasma. cfDNA can be used to describe various forms of DNA freely circulating the bloodstream, including circulating tumor DNA (ctDNA) and cell-free fetal DNA (cffDNA). Elevated levels of cfDNA are observed in cancer, especially in advanced disease.

Circulating tumor DNA (ctDNA) is tumor-derived fragmented DNA in the bloodstream that is not associated with cells. ctDNA should not be confused with cell-free DNA (cfDNA), a broader term that describes DNA that is freely circulating in the bloodstream but is not necessarily of tumor origin. ctDNA originates directly from the tumor or from circulating tumor cells (CTCs). Because ctDNA may reflect the entire tumor genome, it has gained traction for its potential clinical utility; "liquid biopsies" in the form of blood draws may be taken at various time points to monitor tumor progression throughout the treatment regimen.

Circulating tumor cells (CTCs) are whole tumor cells shed into the vasculature from a primary tumor and are carried around the body in the blood. CTCs may constitute seeds for subsequent growth of additional tumors (metastasis) in distant organs, a mechanism that is responsible for most cancer-related deaths. We do not examine coverage policies for CTC testing in this study.

eAppendix 2. Policy Reporter

Policy Reporter, a TrialCard company, provides innovative healthcare software solutions to track payer policies in near real time and enhances market access for the therapies patients need most. The company's patented software-driven solutions include a suite of billing and reimbursement tools for providers and laboratories, market intelligence tools for payers, and a suite of market access solutions for life science companies.

Policy Reporter includes policies from 1,066 payers offering government, commercial, public, public employees, international, and undefined types of products. Some payers offer multiple types of products (eg, government [Managed Medicare, Medicaid], and commercial).

Policy Reporter Covered Lives data are calculated using a proprietary methodology utilizing multiple sources of information from a plan's self-reported data. This includes annual/quarterly reports, press releases, US Securities and Exchange Commission (SEC) filings, National Association of Insurance Commissioners (NAIC) reported data, and Centers for Medicare & Medicaid Services (CMS) data with permissions/licenses. Figures have been validated using multiple sources when available. Any conclusions or analyses are not endorsed by entities of original or commingled data sources. Specifically, but not exclusively, CMS, the NAIC, the SEC, or any other third party is not liable whatsoever for the data contained within this file or your use of the data. The third parties have not endorsed the data and they are not responsible for its contents in any way.