# FDA Cleared or Approved Companion Diagnostic Testing (for Ohio Only)

**Policy Number**: CS373OH.F
**Effective Date**: March 1, 2026

➲ Instructions for Use

**Table of Contents** **Page**



**Related Policies**

- Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Ohio Only)
- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for Ohio Only)

## Application

This Medical Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

## Coverage Rationale

**Note**: This policy applies to tests that have been granted approval as FDA Cleared or Approved Companion Diagnostic (CDx) tests.

For medical necessity clinical coverage criteria for Companion Diagnostic Tests Using Comprehensive Genomic Profiling (CGP), refer to the InterQual® CP: Molecular Diagnostics:

- Comprehensive Genomic Profiling for Solid Tumor, Liquid Biopsy
- Comprehensive Genomic Profiling, Tumor Tissue

Click here to view the InterQual® criteria.

**Subsequent use of an FDA cleared or approved CDx test on a new specimen for the purpose of assisting with therapy selection is considered proven and medically necessary when both of the following criteria are met:**

- The criteria above for the CDx test are met; and
- One of the following:
  - The individual is experiencing disease recurrence; or
  - The individual's cancer has progressed or did not respond to the most recent systemic therapy

**Concurrent Testing using an FDA Cleared or Approved tissue-based CDx test and a Liquid Biopsy-based CDx test is considered proven and medically necessary for the following cancer types when the criteria above for the CDx test are met:**

- Advanced or metastatic (stage IV) breast cancer
- Advanced or metastatic (stage IV) NSCLC

**Due to insufficient evidence of efficacy, all other uses of the above FDA cleared or approved CDx tests are unproven and not medically necessary.**

**Note**: For molecular oncology tests that have not been cleared or approved by the FDA as CDx tests, refer to the Medical Policy titled Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for Ohio Only) or Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis and Treatment Decisions (for Ohio Only).

# Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the services requested.

The patient's medical record must contain documentation that fully supports the medical necessity for the requested services. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request.

# Definitions

**Advanced Cancer**: Cancer that is unlikely to be cured, but in some cases can be controlled with treatment (National Cancer Institute, 2025).

**Companion Diagnostic**: A tool that provides information that is essential for the safe and effective use of a corresponding therapeutic drug [U.S. Food and Drug Administration (FDA), 2025a]. As used in this policy, a Companion Diagnostic test means a test that is FDA cleared or approved for use with a specific drug or group of drugs and is eligible to be listed in the U.S. FDA List of Cleared or Approved Companion Diagnostic Devices table.

**Concurrent Testing**: Tissue-based testing and Liquid Biopsy ordered for the same clinical indication within a 30-day period (Iams et al., 2024).

**Liquid Biopsy**: Testing performed on a sample of bodily fluid to identify cancer cells from a tumor or pieces of DNA, RNA, or other molecules that have been released from tumor cells and are circulating in an individual's body fluids (National Cancer Institute, 2024).

# Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| CPT Code | Description |
|---|---|
| 0022U | Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider |
| 0037U | Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| 0211U | Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association |
| 0239U | Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations |

| CPT Code | Description |
|---|---|
| 0242U | Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements |
| 0473U | Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden |
| 0523U | Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single-nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change |
| 0543U | Oncology (solid tumor), next-generation sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for single-nucleotide variants, multi-nucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden |
| 81479 | Unlisted molecular pathology procedure |



# Description of Services

A Companion Diagnostic (CDx) test provides information that is essential for the safe and effective use of a specific therapeutic product, such as a drug. The use of each U.S. Food and Drug Administration (FDA) cleared or approved CDx test is stipulated in the labeling of both the test and the therapeutic product, as well as in the labeling of any generic or biosimilar equivalents of the therapeutic product.

This policy applies only to FDA cleared or approved molecular oncology CDx tests that detect alterations in five or more genes in tumor tissue or Liquid Biopsy and are listed in the U.S. Food and Drug Administration (FDA) List of Cleared or Approved Companion Diagnostic Devices and/or in the FDA Premarket Approval Database (U.S. FDA, 2025) for use with a specific therapeutic product or group of products.

# Clinical Evidence

## FoundationOne® CDx (Foundation Medicine, Inc.)

FoundationOne CDx is a qualitative next generation sequencing (NGS) based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens (Foundation Medicine, Inc., 2025).

Hayes addressed the use of FoundationOne CDx as a broad molecular profiling tool in a 2022 Molecular Test Assessment. The evidence base for this indication consisted of three clinical utility studies which reported no difference in outcomes between treatment directed by FoundationOne CDx results and treatment not directed by use of FoundationOne CDx. As such, the evidence was determined to be insufficient for this indication. The Hayes report did not assess the use of FoundationOne CDx for the primary purpose of evaluating predetermined biomarkers that are associated with at least one FDA-approved therapy for the individual's specific cancer type, nor did it address clinical or analytical validity, which would require focused review of individual biomarkers (Hayes, Inc., 2022, updated 2025).

Marcus et al. (2021) summarized the FDA approval of pembrolizumab for treatment of adults and children with unresectable or metastatic TMB-high (defined as ≥ 10 mut/Mb) solid tumors. The approval specified that TMB must be determined by an FDA-approved test and individuals must have progressed following prior treatment and have no satisfactory alternative treatment options available. The approval was based on findings from the KEYNOTE-158 multi-center single-arm trial, which showed a response rate of 29% (95% CI, 21% to 39%). 57% of those responses lasted ≥ 12 months in individuals with TMB-high solid tumors (n = 102). Nine different tumor types were included. KEYNOTE-158 pre-specified ≥ 10 and ≥ 13 mut/Mb using the FoundationOne CDx assay as cut-points to define the TMB-H population. TMB testing was blinded to clinical outcomes. At the same time as the approval of pembrolizumab for TMB-high indications, premarket approval was given for FoundationOne CDx to include a CDx indication for TMB-high solid tumors using a cut-

point of 10 mut/Mb. Whole exome sequencing was used to analyze TMB in additional individuals enrolled in several different pembrolizumab clinical trials, which also supported efficacy of pembrolizumab along with comprehensive understanding of the impact of PD-1 inhibition. Adverse events were similar to those in prior trials that supported pembrolizumab approval for other indications.

In a prospective cohort study evaluating the role of comprehensive genomic profiling (CGP) with FoundationOne CDx, Takeda et al. (2021) performed genomic testing on 181 tumor tissue samples from individuals with cytologically or histologically confirmed advanced or recurrent solid tumor cancers. Data was successfully obtained for 175 samples. Known and likely pathogenic actionable variants were found in 174 individuals (99%) and 24 of those (14%) received matched targeted therapy. *TP53* (n = 113), *PIK3CA* (n = 33), *APC* (n = 32), and *KRAS* mutations (n = 29) were the most common known/likely pathogenic variants found. Of 153 individuals evaluated for TMB, median TMB was four mutations/Mb. Tumors with high TMB (defined as ≥ 10 mutations/Mb) were more likely to be lung cancer (11/32) than other solid tumor types (9/121). The authors concluded that FoundationOne CDx testing had an overall success rate of > 95% and may assist with matching individual tumors with targeted therapy.

Marabelle et al. (2020) published results from the KEYNOTE-158 study (discussed in the above FDA summary by Marcus et al., 2021). KEYNOTE-158 evaluated anti-PD1 monoclonal antibody pembrolizumab therapy in individuals with histologically or cytologically confirmed advanced and incurable solid tumor types including anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar. Participants must have either progressed on or been intolerant to one or more standard therapies, shown measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had adequate organ function, available tumor sample and life expectancy of at least three months. TMB was assessed using FoundationOne CDx with prespecified definition of TMB-high of at least 10 mut/Mb. Participants received pembrolizumab 200 mg intravenously every three weeks for a maximum of 35 cycles. The primary outcome was the proportion of participants with a complete or partial response per RECIST v1.1. Objective responses were recorded in 29% (95% CI, 21% to 39%) of 102 participants in the TMB-high group and six percent of 688 participants in the non TMB-high group. The researchers concluded that TMB-high status can help identify individuals who may have a strong response to treatment with pembrolizumab as monotherapy and TMB may thus be a helpful predictive biomarker for response in individuals with previously treated recurrent or metastatic advanced solid tumors.

## FoundationOne® Liquid CDx (Foundation Medicine, Inc.)

FoundationOne Liquid CDx is a qualitative NGS-based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report genomic alterations in 311 genes. These include substitutions, insertions, and deletions (indels) in 311 genes, rearrangements in 8 genes, and copy number alterations in three genes. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit (Foundation Medicine, Inc., 2023).

Bhave et al. (2024) investigated the clinical utility of CGP using tumor tissue and liquid biopsy in HR+, HER2- metastatic breast cancer in a retrospective study using records from a deidentified database containing clinical and genomic testing results of affected individuals who had received tissue or liquid biopsy at Foundation Medicine. The prevalence of several genomic alterations [*ESR1*mut, *PIK3CA*mut, *AKT1*mut, *PTEN*mut, and *PTEN* homozygous copy loss (*PTEN*loss)] was calculated for both tissue and liquid biopsies. Approximately 60% of HR+, HER2- metastatic breast cancer cases demonstrated one or more genetic alterations identified by tissue or liquid biopsy with circulating tumor DNA (ctDNA) tumor fraction (TF) of at least 1% in the first line setting, whereas in liquid biopsy with ctDNA TF less than 1%, the prevalence dropped to 26.5%. *ESR1*mut frequency increased with each treatment line, especially when liquid biopsy was used; it demonstrated 59% prevalence when ctDNA TF was at least 1% in third line treatment. *PTEN*loss was found at significantly higher rates in tissue biopsy than liquid biopsy, which is consistent with the previously identified limitations of ctDNA testing. According to the authors, the study results supported the procurement of a tissue biopsy for CGP at the time of recurrent/de novo diagnosis, followed by liquid biopsy to potentially identify acquired genetic alterations in second or greater lines of treatment. Also advised was the performance of reflex tissue biopsy if ctDNA TF is lower than 1%. Funding for this study was provided by manufacturers of CGP tests, and employees of the manufacturers were involved in the design and interpretation of the study and its results, which creates potential for bias. In addition, the study was limited by its retrospective design and included no participants with serial CGP.

A Hayes Molecular Test Assessment (2023a, updated 2024) assessed the clinical validity and utility of the FoundationOne Liquid CDx test when used as a CDx for specific cancer treatments or for tumor mutational profiling for individuals with solid tumor cancer. A total of seven studies met inclusion criteria and were evaluated for the report. All studies were determined to have very poor-quality. These studies suggest that FoundationOne Liquid CDx may help with determination of the eligibility of impacted individuals for various treatments, which can be especially helpful for individuals with

advanced cancer diagnoses. However, the studies did not determine conclusively whether comprehensive testing can lead to better clinical outcomes when compared with more limited testing, nor did they provide clarity regarding the use of cfDNA testing in place of tissue biopsy test. The Hayes report indicates that weak support is provided by existing guidelines and position statements with regard to the use of ctDNA testing but notes that the test is FDA-approved as a CDx for breast cancer, colorectal cancer (CRC), prostate cancer, non-small cell lung cancer (NSCLC), ovarian cancer and solid tumors in individuals who may benefit from treatment with targeted therapies in accordance with the approved product labeling.

Bayle et al. (2023, included in the 2023 Hayes FoundationOne Liquid CDx Molecular Test Assessment) reported results from a prospective study which explored the use of comprehensive molecular profiling of ctDNA in individuals with advanced solid tumor cancers. FoundationOne Liquid CDx was used to obtain genomic evaluation on 1,772 with metastatic solid tumors. The results of 1,658 individuals were used in the analysis. Actionable targets were identified using the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT). In 1,059 participants, at least one actionable target was identified (64%); 1,825 actionable variants, total, were found. Results were reviewed by a multidisciplinary tumor board and matched therapy was advised for 56% (n = 597) individuals. Ultimately, 122 individuals underwent treatment and data was available for 107 of those individuals. Median progression-free survival (PFS) was 4.7 months (95% CI, 2.7-6.7 months) and median overall survival (OS) was 8.3 months (95% CI, 4.7-11.9 months). The researchers concluded that ctDNA sequencing using a large comprehensive molecular profiling panel can be efficiently used to match individuals with advanced solid tumor cancers to targeted treatments.

A FoundationOne CDx test (either tissue-based or liquid biopsy) was performed on specimens from 203 individuals with cancer in a prospective, single-center study by Pinet et al. (2023, included in the 2023 Hayes FoundationOne Liquid CDx Molecular Test Assessment). The primary goal was to improve understanding of the real-world impact of standard use of FoundationOne CDx for individuals with cancer and a poor prognosis/limited treatment options or individuals whose treatment progressed after a minimum of one course of standard treatment. Secondary aims were: evaluation of the feasibility of using FoundationOne CDx in terms of rate of failure, assessment of the rate of detection of targetable and non-targetable abnormalities, assessment of the rate of targeted treatment based on results of testing, and evaluation of the OS of individuals receiving targeted therapy compared to those who did not. After application of exclusion criteria, 162 participants were included in the cohort. Successful results were obtained for 93% (n = 150) of the participants. A total of 2,419 gene variants were detected. Median number of variants per tumor was 11 (range 0-86). Common or likely pathogenic variants were detected most frequently in TP53, TERT, PI3KCA, CDKN2A/B, KRAS, CCDN1, FGF19, FGF3, and SMAD4. Of participants with TMB available, the median TMB was three/Mb (range 0-117). Thirteen participants (8.6%) received matched targeted therapy based on known or likely pathogenic variants. Of the 69 participants whose cases went to a molecular tumor board for evaluation, 60 received treatment recommendations. OS was not significantly impacted by genotype-directed treatments [13 months with genotype-directed treatment vs. 14 months without genotype-directed treatment; p = 0.95; hazard ratio = 1.04 (95% CI, 0.48–2.26)]. Based on these outcomes, the researchers indicate that a well-organized facility including a multidisciplinary molecular tumor board and availability of NGS can produce results similar to those of larger cancer centers related to appropriate enrollment in clinical trials. The primary limitations to pursuing genetically-guided therapies were the clinical condition of the affected individual and available access to drugs. Limitations included small size, lack of randomization and a mixed population of cancer types. Larger, randomized clinical trials with focus on specific cancer types are recommended.

To investigate the relationship between ctDNA TF and the identification of actionable genomic alterations across various cancer types, Husain et al. (2022, included in the Hayes 2023 FoundationOne Liquid CDx Molecular Test Assessment) evaluated a consecutive series of liquid biopsies [performed with FoundationOne Liquid CDx (F1LCDx)] conducted in the United States during routine clinical care. Specimens from a total of 23,482 individuals with 25 solid tumor types were evaluated. The primary outcome assessed was the prevalence of targeted alterations according to cancer type and detection by ctDNA. Also evaluated was the sensitivity of liquid biopsy in a group of 1,289 participants with tissue testing results available. Overall, detectable ctDNA was found in 94% (n = 22,130) of liquid biopsy samples and the median TF was 2.2%. Genetic alterations in National Comprehensive Cancer Network (NCCN) Category 1 genes were detected by liquid biopsy in 37% of individuals with lung cancer, 30% of individuals with prostate cancer, 36% of individuals with breast cancer and 51% of individuals with colon cancer. In samples with TF of at least 10%, sensitivity of liquid biopsy to detect driver alterations that had been found in tumor tissue analysis from the same individual were consistently near or at 100%. Samples with lower TF ranged in sensitivity from 58% to 86%. Based on these results, the authors assert that CGP of ctDNA is a practical approach to the detection of guideline-associated actionable genomic alterations for various cancer types, and elevated ctDNA shedding relates to both high sensitivity and high negative predictive value for the identification of actionable genetic alterations. When liquid biopsy specimens have higher TF, it is likely the results are sufficient and may lead to a reduction in reflex to confirmatory tissue testing when negative liquid biopsy results are obtained. Although the evidence supporting improvement in clinical outcomes related to use of ctDNA detected biomarkers is growing, this

study was limited by its retrospective design and did not directly evaluate whether liquid biopsy profiling improves clinical outcomes when incorporated into routine clinical care.

Caputo et al. (2022) used FoundationOne Liquid (either FoundationOne Liquid or FoundationOne Liquid CDx) to evaluate clinical impact and viability of these tests across different tumor types. In all, 398 samples were evaluated with an overall success rate of 92%, with a 97% success rate in FoundationOne Liquid CDx, specifically. The most common molecular alterations were *TP53* (n = 74), *APC* (n = 40), *DNMT3A* (n = 39), and *KRAS* (n = 23). Overall clinical impact of the FoundationOne Liquid assays use compared to standard testing was 64.7% vs. 22.1% [risk ratio (RR) = 2.94; p < 0.001] and potential clinical impact was 58.6% compared to 11.0% (RR = 5.32; p < 0.001). FoundationOne Liquid detected actionable alterations that offered unexpected therapeutic choices. The authors asserted that NGS using a FoundationOne Liquid assay was helpful in guiding treatment decisions, but commented that more study is needed in terms of selection criteria for affected individuals to avoid over-diagnosis.

The TRITON2 trial was an international open-label phase II study assessing the use of rucaparib in individuals diagnosed with metastatic castration-resistant prostate cancer (mCRPC) associated with a mutation in *BRCA* or another homologous recombination-directed DNA damage repair (DDR) gene who had progressed after treatment with next-generation androgen receptor (AR)-directed therapy and taxane-based chemotherapy. Abida et al. (2020) reported on results of this study related to mCRPC associated with a *BRCA* mutation that was treated with rucaparib twice daily. Key outcomes included ORR per RECIST as determined by blinded, independent radiology reviewers and investigators and locally assessed prostate specific antigen (PSA) response rate. The population under review was comprised of 115 individuals with a *BRCA* gene alteration that did or did not have measurable disease. Confirmed ORRs were 43.5% (95% CI, 31.0% to 56.7%; 27 of 62 participants) for those with measurable disease and 50.8% (95% CI, 38.1% to 63.4%; 33 of 65 participants) for those without measurable disease. PSA response rate was 54% (95% CI, 45.2% to 64.1%; 63 of 115 participants). Consistent ORRs were seen in individuals with germline or somatic BRCA alterations and for those individuals with a *BRCA1* or *BRCA2* alteration. A higher PSA response rate was seen, however, in those individuals with *BRCA2* alterations. The authors concluded that data from the TRITON2 study highlight the importance of use of genomics in the identification of individuals that may benefit from treatment with a PARP inhibitor and are consistent with results of other studies on PARP inhibitors and their association with mCRPC and *BRCA* alterations. Although no control arm was present in this study and OS data is limited so far, the researchers assert that the TRITON2 study results support the importance of the antitumor impact of rucaparib in individuals with mCRPC and a detrimental *BRCA* mutation while maintaining a manageable safety profile.

In a clinical and analytical validation of FoundationOne Liquid CDx, Woodhouse et al. (2020) published data to support the use of this test across multiple types of cancer. Validation studies for FoundationOne Liquid CDx included more than 7,500 tests and at least 30,000 individual variants over more than 300 genes and 30+ types of cancer. The results of this analysis showed a 95% limit of detection of 0.40% variant allele fraction for select substitutions and insertions or deletions, 0.37% variant allele fraction for select rearrangements, 21.7% TF for copy number amplifications and 30.4% TF for copy number losses. The false positive variant rate was 0.013% or 1 in 8,000. Reproducibility of variant identification was 99.59%. Overall positive percent agreement and negative percent agreement of 96.3% and over 99.9%, respectively, was observed. The authors concluded that FoundationOne Liquid CDx is accurate with reproducible results and can reliably detect the main types of genomic alterations as well as complex biomarkers (e.g., MSI, blood TMB, and TF).

## Guardant360® CDx (Guardant Health Inc.)

Guardant360® CDx is a qualitative NGS-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications in two genes, and fusions in four genes. Guardant360 CDx utilizes circulating cfDNA from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (Guardant Health, Inc., 2023).

In a retrospective study aimed to assess the feasibility and potential benefit of liquid biopsy performed simultaneously with tissue testing in a group of individuals newly diagnosed with stage IV lung adenocarcinoma, Maity et al. (2023) compared participants from a community-based academic medical institution who received tissue genotyping alone (standard biopsy) with participants who received simultaneous tissue and liquid genotyping (combined biopsy). Liquid biopsy tests were performed using Guardant360 CDx. A total of 120 participants met inclusion criteria and were evaluated in the study (78 in the standard biopsy group and 42 in the combined biopsy group). Participants were diverse in age, sex, race, and smoking status. For the standard group, the mean time to diagnosis was 33.5 days, while the combined group had a mean time to diagnosis of 20.6 days (p < .001 by two-tailed t-test). Fourteen of the participants in the combined group did not have sufficient tissue available for molecular testing, but for 79% of those (11/14), the liquid biopsy detected a genomic alteration, eliminating the need for another tissue biopsy. Importantly, in participants who completed both tests, each test found actionable alterations that had been missed by the other test. Of the 28 participants in the combined group that successfully completed both tissue and liquid testing, 39% (n = 11/28) had informative genetic alterations

detected with only one of the two tests performed. This is consistent with results of other studies performed at large academic centers. The authors concluded that simultaneous performance of liquid and standard tissue biopsy for genotyping could result in positive outcomes including shorter time to definitive molecular diagnosis, reduction in repeat tissue biopsies, and better detection of actionable genomic alterations. They also suggest that a sequential strategy that begins with liquid biopsy may be more cost-effective. Although the study results are promising, this study was small, retrospective, and observational, with no randomization, limiting the quality of the results. Additional study is recommended to determine the best genotyping strategy for individuals with stage IV lung adenocarcinoma.

In a Molecular Test Assessment, Hayes explored the evidence on Guardant360 CDx and evaluated its utility in directing clinical decision-making in individuals with advanced solid tumor cancers. Overall, Hayes identified a low-quality body of evidence for use of Guardant360 CDx for the identification of targeted therapy in individuals with advanced NSCLC and a very low-quality body of evidence for individuals with metastatic breast cancer and other types of advanced solid tumors. The report notes, however, that there are factors which complicate evidence-based decision making related to the use of Guardant360 and Guardant360 CDx. Though there is a lack of direct evidence demonstrating survival benefit associated with this test, there is implied clinical utility in certain circumstances, such as seeking specific genetic variants in solid tumors to facilitate use of FDA-approved targeted treatments, testing for TMB or MSI in individuals who may be eligible for immune checkpoint inhibitor therapy, and the use of liquid-based tests in individuals with insufficient tumor biopsy samples or for whom a biopsy is not feasible. (Hayes, Inc., 2023b, updated 2024).

To investigate whether immediate testing of plasma ctDNA along with standard tissue testing could potentially shorten the time to implementation of treatment and improve clinical outcomes compared to tissue testing alone in individuals affected with suspected advanced NSCLC, Yang et al. (2023, included in the Hayes Guardant360 CDx Molecular Test Assessment) conducted a prospective, randomized trial. A total of 180 participants were enrolled and randomized into two groups. After clinical tumor workup, individuals who were found to have benign disease, small cell lung cancer, early-stage NSCLC, or any other type of cancer were excluded. Group A, comprising of 63 participants and Group B, comprising of 59 participants were included in the trial analysis. All were suspected to have advanced NSCLC and underwent liquid biopsy with NGS testing (using Guardant360 CDx) at their first visit, then went on to undergo standard histological diagnosis along with tissue genotyping. Group A received their NGS results after tissue genotyping and Group B received NGS results as soon as possible after histological diagnosis of advanced NSCLC was confirmed. Time to start of systemic treatment was the primary outcome and secondary outcomes were biomarker discovery, ORR, and PFS. Most participants had adenocarcinoma (77.8% in Group A and 79.7% in Group B). The rate of *EGFR* variants was similar in Group A and Group B (57.1% vs. 56.6%, respectively), and other driver mutations were uncommon. The researchers determined that median time to treatment was shorter for Group B (20 days) than Group A (28 days). The ORR and PFS did not differ significantly between the two groups. Concordance between liquid NGS and tissue NGS was high. Notably, liquid NGS identified driver mutations in 20/47 (42.6%) cases where tissue testing was negative. Although this study was small and lacked the power to detect differences in survival outcomes, the researchers suggest that their results support the use of liquid NGS at the initial clinic visit for suspected advanced NSCLC to provide complete genotyping quickly to identify individuals who may benefit from targeted treatment and shorten the time to treatment initiation.

In 2022, Bauml assessed the clinical validity of Guardant360 CDx as a blood-based CDx for sotorasib to detect *KRAS*p.G12C (an oncogenic NSCLC driver mutation). The primary aim was to evaluate the clinical validity of Guardant360 CDx via data and samples from the CodeBreaK100 (NCT03600883) study. The secondary purposes were to evaluate the concordance among *KRAS* p.G12C mutation status decided by the therascreen® *KRAS* RGQ PCR kit and Guardant360 CDx in individuals with NSCLC, to assess the representativeness of the Guardant360 CDx-positive cohort related to the entire analysis group, and to consider duration of response (DOR), disease control rate, and time to response in individuals with *KRAS*p.G12C-mutant NSCLC as detected by Guardant360 CDx comparative to the whole analysis group. The ORR (95% CI; individuals with objective response/all individuals in the dataset) for all individuals was 37.1% (28.6%, 46.2%; n = 46/124) in the full analysis set, 36.4% (25.7%, 48.1%; n = 28/77) in the Guardant360 positive cohort, and 46.7% (28.3%, 65.7%; n = 14/30) in the Guardant360 CDx-negative cohort. Rates of progressive disease, stable disease, and partial response were similar among the cohorts, with stable disease being the most common outcome [full analysis set, n = 54/124 (43.5%); Guardant360 CDx-evaluable, n = 46/107 (43.0%); Guardant360 CDx-positive, n = 32/77 (41.6%); Guardant360 CDx-negative, n = 14/30 (46.7%)]. Disease control rate (95% CI; individuals with disease control/all those in the dataset) was 80.6% (72.6%, 87.2%; n = 100/124) in the full analysis set and 77.9% (67.0%, 86.6%; n = 60/77) in the Guardant360 CDx-positive cohort. Among responders, DOR was ≥ 3 months in 38/46 (82.6%) of those in the full analysis set and 24/28 (85.7%) in the Guardant360 CDx-positive cohort; DOR was ≥ 6 months in 28/46 (60.9%) and 15/28 (53.6%) of those in the full analysis set and Guardant360 CDx-positive cohort, respectively. Of the four cohorts, DOR ≥ three months among responders was numerically highest in the Guardant360 CDx-positive cohort [n = 4/28 (85.7%)], while DOR ≥ 6 months was mathematically highest in the Guardant360 CDx-negative [n = 9/14 (64.3%)] cohort. The average time to objective response was comparable among all cohorts. The authors concluded that

liquid biopsy using Guardant360 CDx has clinical validity for the identification of individuals with *KRAS*p.G12C-mutant NSCLC and, amplified by tissue testing methodologies, will identify individuals for treatment with sotorasib.

## MI Cancer Seek™ (Caris Life Sciences)

MI Cancer Seek is a NGS-based *in vitro* diagnostic device using total nucleic acid isolated from FFPE tumor tissue specimens for the detection of SNVs and insertions and deletions in 228 genes, MSI, TMB in patients with previously diagnosed solid tumors, and copy number amplification in one gene in patients with breast cancer (Caris Life Sciences, 2024).

## Oncomine™ Dx Express Test (Life Technologies Corporation)

The Oncomine Dx Express Test is a qualitative *in vitro* diagnostic test that uses targeted NGS technology to detect substitutions, insertions, and deletions in 42 genes, copy number variants in 10 genes from DNA, and fusions or splice variants in 18 genes from RNA isolated from FFPE tumor samples using the Genexus™ Dx Integrated Sequence (Life Technologies Corporation, 2025).

## Oncomine™ Dx Target Test (Life Technologies Corporation)

The Oncomine Dx Target Test is a qualitative *in vitro* diagnostic test that uses targeted high-throughput, parallel-sequencing technology to detect SNVs, deletions, and insertions in 23 genes from DNA and fusions in *ROS1* and *RET* from RNA isolated from FFPE tumor tissue samples from patients with NSCLC, *IDH1* SNVs from FFPE tumor tissue samples from patients with cholangiocarcinoma, *BRAF* V600E mutations from FFPE tumor tissue samples from patients with anaplastic thyroid cancer, *IDH1* and *IDH2* SNVs from FFPE tumor tissue samples from patients with astrocytoma or oligodendroglioma, *RET* SNVs, multi-nucleotide variants , and deletions from DNA isolated from FFPE tumor tissue samples from patients with medullary thyroid cancer, and *RET* fusions from RNA isolated from FFPE tumor tissue samples from patients with thyroid cancer using the Ion PGM™ Dx System (Life Technologies Corporation, 2024).

## oncoReveal™ CDx (Pillar Biosciences, Inc.)

The oncoReveal CDx is a qualitative NGS-based *in vitro* diagnostic test that uses amplicon-based target enrichment technology for detection of SNVs, insertions and deletions in 22 genes using DNA isolated from FFPE tumor tissue specimens and using the Illumina MiSeqDx® (Pillar Biosciences, 2024).

## TruSight™ Oncology Comprehensive (Illumina, Inc.)

TruSight Oncology Comprehensive is a qualitative *in vitro* diagnostic test that uses targeted NGS to detect variants in 517 genes using nucleic acids extracted from FFPE tumor tissue samples from cancer patients with solid malignant neoplasms using the Illumina® NextSeq™ 550Dx instrument. The test can be used to detect SNVs, multi-nucleotide variants, insertions, and deletions from DNA, and fusions in 24 genes and splice variants in one gene from RNA. The test also reports a TMB score (Illumina, Inc., 2024).

## xT CDx (Tempus Labs, Inc.)

xT CDx is a qualitative NGS-based *in vitro* diagnostic device intended for use in the detection of substitutions (SNVs and multi-nucleotide variants) and insertion and deletion alterations in 648 genes, as well as MSI status, using DNA isolated from FFPE tumor tissue specimens, and DNA isolated from matched normal blood or saliva specimens, from previously diagnosed cancer patients with solid malignant neoplasms (Tempus Labs, Inc., 2023).

Iams et al. (2024) conducted an observational cohort analysis using the Tempus multimodal database. The study included 3209 participants with stage IV NSCLC (n = 1302), breast cancer (n = 660), CRC (n = 923), or prostate cancer (n = 324) who underwent concurrent tissue-based (Tempus xT CDx) and ctDNA NGS between May 2020 and December 2022. The primary objective was to compare detection rates of NCCN guideline-based actionable variants using concurrent testing and tissue-only testing. Among the 3209 participants, 1448 (45.1%) had at least one actionable variant. Of these, 9.3% (135/1448) had variants uniquely detected by ctDNA, while 24.2% (351/1448) had variants uniquely detected by tissue. Concordance between assays was 66.4% overall, highest in CRC (75.0%) and lowest in prostate cancer (51.2%). Breast cancer showed the greatest incremental benefit from ctDNA: 20.2% (71/352) of participants with actionable variants had findings unique to ctDNA, most commonly *ESR1* mutations (55.0% of ctDNA-unique variants), resulting in a 24.7% increase (23/93) in *ESR1* detection compared with tissue alone. In NSCLC, 5.3% of actionable variants were ctDNA-unique, with *KRAS* most frequent (29.6%), whereas tissue-unique variants were often *EGFR* (40.3%). Higher ctDNA burden strongly correlated with ctDNA-unique detection (median 16.8% vs 10.3% for concordant; $p = 4.8\times10^{-3}$), while tissue-unique variants were associated with very low ctDNA burden (median 0.5%; $p = 5.6\times10^{-110}$). The authors noted limitations including retrospective design, lack of treatment outcome data, and potential confounding from clonal hematopoiesis. Clinically, the findings suggest that concurrent tissue and ctDNA profiling improves identification of

actionable mutations beyond tissue testing alone, particularly in breast cancer where *ESR1* detection can guide endocrine therapy decisions. These results support integrating dual-modality genomic testing into routine care for advanced solid tumors to optimize targeted therapy selection.

## Clinical Practice Guidelines

### *American Society of Clinical Oncology (ASCO)*

A 2024 ASCO Rapid Recommendation Update (Burstein et al., 2024) addressed emerging evidence regarding endocrine and targeted treatments for HR+, HER- metastatic breast cancer. This update focused on the CAPItello-291 phase III, double-blind, randomized controlled trial, which analyzed fulvestrant with the AKT pathway inhibitor capivasertib and led to the U.S. FDA's approval of capivasertib and FoundationOne CDx. A similar study, FAKTION, which was a randomized phase II comparison of fulvestrant with either capivasertib or a placebo, resulted in outcomes similar to CAPItello-291, showing benefit in tumors with only *PIK3CA/AKT1/PTEN* variants. In this update, the expert panel recommended multiple lines of endocrine treatment, often paired with targeted agents identified by prior treatments as well as routine testing for activating mutations in *PIK3CA, AKT1*, or *PTEN* (evidence quality: high, strength of recommendation: strong).

### *International Association for the Study of Lung Cancer (IASLC)*

In a 2021 consensus statement from the IASLC, Rolfo et al. acknowledged the dramatic advances in precision medicine on the clinical management of NSCLC and advanced stage cancers overall. The authors noted that while the data are most robust for NSCLC, there may be benefit for other cancer types as well, impacting selection of targeted therapies as research progresses. Recommendations included using a clinically validated NGS platform rather than single gene, PCR-based approaches, considering plasma ctDNA to be a valid tool for genotyping advanced NSCLC in newly diagnosed patients, and using liquid biopsy either as complementary to tissue-based analysis or as the initial approach to biomarker evaluation in oncogene-addicted NSCLC and for monitoring efficacy of therapies.

### *National Comprehensive Cancer Network® (NCCN®)*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) address the use of FDA cleared or approved Companion Diagnostic testing in certain cancer types.

### Ampullary Adenocarcinoma

Testing for potentially actionable somatic findings including, but not limited to, fusions (i.e., *ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations (i.e., *BRAF, BRCA1/2, KRAS, PALB2*), amplifications (*HER2*), MSI, mismatch repair (MMR) deficiency, or TMB via an FDA-approved and/or validated NGS-based assay is recommended by NCCN as an option for those individuals with locally advanced/metastatic ampullary adenocarcinoma who are candidates for treatment with anti-cancer therapy (NCCN, 2025a).

### Bone Cancer

- Consideration of CGP with a validated and/or FDA-approved assay is recommended by NCCN as an option for individuals with metastatic chondrosarcoma, recurrent chordoma, metastatic Ewing sarcoma, or metastatic osteosarcoma to identify potential targeted therapy opportunities.
- Consideration of testing for TMB and MMR/MSI as determined by a validated and/or FDA-approved assay is recommended by NCCN as an option for select patients with metastatic chondrosarcoma, recurrent chordoma, metastatic Ewing sarcoma, or unresectable metastatic osteosarcoma (NCCN, 2025b).

### Cervical Cancer

- TMB testing by an FDA-approved assay is recommended by NCCN as an option for tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (second-line or subsequent therapy).
- Consideration of CGP via a validated plasma ctDNA assay is recommended by NCCN as an option to guide appropriate biomarker-directed second line therapy if tissue biopsy of the metastatic site is not feasible or tissue is not available.
- Consideration of CGP as determined by FDA-approved assay is recommended by NCCN as an option for better selection of systemic therapy in individuals who develop distant metastases, either at initial presentation or at relapse (NCCN, 2025c).

### Cutaneous Melanoma

Testing *BRAF* mutational status using an FDA-approved test is recommended by NCCN as an option for selection of individuals for treatment with dabrafenib and trametinib (NCCN, 2025d).

### Neuroendocrine and Adrenal Tumors

Consideration of MSI, MMR, and TMB testing by an FDA-approved test is recommended by NCCN as an option for individuals with adrenocortical carcinoma (NCCN, 2025e).

### Non-Small Cell Lung Cancer (NSCLC)

NCCN has provided recommendations for individual biomarkers that should be tested and recommend testing techniques, accompanied by a statement of non-endorsement of any specific commercially available biomarker assays or commercial laboratories (NCCN, 2025f).

### Occult Primary

Determination of TMB by a validated and/or FDA-approved assay is recommended by NCCN as a Category 2B option for individuals with cancer of unknown primary (NCCN, 2025g).

### Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer

An FDA-approved CDx test is recommended by NCCN as an option for the selection of patients for niraparib, olaparib, or rucaparib therapy (NCCN, 2025h).

### Pancreatic Adenocarcinoma

Testing for actionable somatic mutations including, but not limited to, fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1*/2, *HER2*, *KRAS*, and *PALB2*), amplifications (*HER2*), MSI, MMR deficiency, or TMB via an FDA-approved and/or validated NGS-based assay is recommended by NCCN as an option for patients with locally advanced or metastatic disease who are candidates for anticancer therapy (NCCN, 2025i).

### Uterine Neoplasms

- Comprehensive molecular profiling via a validated and/or FDA-approved assay is recommended by NCCN as an option in the initial evaluation of uterine neoplasms to help facilitate cancer diagnosis.
- Testing of at least *NTRK*, MSI, *RET*-fusion, and TMB proteins in the setting of metastatic disease with a validated and/or FDA-approved assay is recommended by NCCN as an informative option for predicting rare pan-tumor-targeted therapy opportunities in uterine sarcoma.
- Consideration of *NTRK* gene fusion testing and TMB testing through a validated and/or FDA-approved assay is recommended by NCCN as an option for metastatic or recurrent endometrial carcinoma.
- TMB-H testing by a validated and/or FDA-approved test is recommended by NCCN as an option for individuals with endometrial carcinoma who have progressed following prior treatment and who have no satisfactory alternative treatment options (NCCN, 2025j).

### Vaginal Cancer

- TMB testing by an FDA-approved assay is recommended by NCCN as an option for individuals with tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Consideration of comprehensive molecular profiling by an FDA-approved assay including at least MSI, TMB testing, *NTRK*, and *RET* is recommended by NCCN as an option for predicting rare pan-tumor targeted therapy.
- Consideration of comprehensive molecular profiling as determined by FDA-approved assay is recommended by NCCN as an option for better selection of systemic therapy in disseminated disease (NCCN, 2025k).

### Vulvar Cancer

Consideration of comprehensive molecular profiling by an FDA-approved assay including at least MMR/MSI, TMB, and *NTRK* testing is recommended by NCCN as an option for predicting rare pan-tumor targeted therapy opportunities in vulvar squamous cell carcinoma (NCCN, 2025l).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The list of FDA-approved or cleared Companion Diagnostic tests is available at: List of Cleared or Approved Companion Diagnostic Devices | FDA. (Accessed August 12, 2025)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed August 12, 2025)

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National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine neoplasms. Version 3.2025.

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 03/01/2026 | **Coverage Rationale**<br>• Revised language to indicate:<br>  ○ This policy applies to tests that have been granted approval as FDA cleared or approved Companion Diagnostic (CDx) tests<br>  ○ For medical necessity clinical coverage criteria for Companion Diagnostic Tests Using Comprehensive Genomic Profiling (CGP), refer to the InterQual® CP: Molecular Diagnostics:<br>  ▪ Comprehensive Genomic Profiling for Solid Tumor, Liquid Biopsy<br>  ▪ Comprehensive Genomic Profiling, Tumor Tissue<br>  ○ Subsequent use of an FDA cleared or approved CDx test on a new specimen for the purpose of assisting with therapy selection is considered proven and medically necessary when both of the following criteria are met:<br>  ▪ The criteria above for the CDx test are met, and<br>  ▪ One of the following:<br>  – The individual is experiencing disease recurrence<br>  – The individual's cancer has progressed or did not respond to the most recent systemic therapy<br>  ○ Concurrent Testing using an FDA cleared or approved tissue-based CDx test and a Liquid Biopsy-based CDx test is considered proven and medically necessary for the following cancer types when the criteria above for the CDx test are met:<br>  ▪ Advanced or metastatic (stage IV) breast cancer<br>  ▪ Advanced or metastatic (stage IV) NSCLC<br>  ○ Due to insufficient evidence of efficacy, all other uses of the above FDA cleared or approved CDx tests are unproven and not medically necessary<br>  ○ For molecular oncology tests that have not been cleared or approved by the FDA as CDx tests, refer to the Medical Policy titled:<br>  ▪ *Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for Ohio Only)*<br>  ▪ *Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis and Treatment Decisions (for Ohio Only)*<br>**Medical Records Documentation Used for Reviews**<br>• Added language to indicate:<br>  ○ Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service<br>  ○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested<br>  ○ The patient's medical record must contain documentation that fully supports the medical necessity for the requested services<br>  ○ This documentation includes but is not limited to relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures<br>  ○ Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request<br>**Definitions** |

| Date | Summary of Changes |
|---|---|
| | • Added definition of “Concurrent Testing”<br>• Removed definition of:<br>  ○ Comprehensive Genomic Profiling (CGP)<br>  ○ Next Generation Sequencing (NGS)<br>• Updated definition of:<br>  ○ Advanced Cancer<br>  ○ Companion Diagnostic<br>  ○ Liquid Biopsy<br>**Applicable Codes**<br>• Added CPT codes 0211U and 0523U<br>• Removed CPT codes 0179U, 81445, 81449, 81450, 81451, 81455, 81456, and 81599<br>**Supporting Information**<br>• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information<br>• Archived previous policy version CS373OH.E |

# Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]) or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC) or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC) or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC) or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare uses InterQual® for the primary medical/surgical criteria, and the American Society of Addiction Medicine (ASAM) for substance use, in administering health benefits. If InterQual® does not have applicable criteria, UnitedHealthcare may also use UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and/or Utilization Review Guidelines that have been approved by the Ohio Department for Medicaid Services. The UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and Utilization Review Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.