Evidence Dossier
FoundationOne®CDx

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1 EXECUTIVE SUMMARY

Identifying Appropriate Treatment Options in Advanced Cancer Represents a Significant Unmet Need

The goal of treatment in advanced cancer is to provide patients with therapies that have a potential to offer the most benefit in relation to risk.[1] Biomarker-based targeted therapy and immunotherapy have improved treatment responses and survival outcomes in patients with advanced cancer with actionable alterations for which there is a biomarker-based targeted therapy available (either United States [US] Food and Drug Administration [FDA]-approved or in clinical trials) compared with standard of care chemotherapy or best supportive care.[2-18] With the continuous evolution of the treatment landscape for advanced cancers, it is projected that the number of biomarker-based targeted therapies will likely double from 2024 to 2028; as such, it is necessary for physicians and patients with advanced cancer to have access to a highly validated testing solution that comprehensively covers actionable alterations.[19]

With comprehensive genomic profiling (CGP), a single test can analyze a broad panel of genes to detect the 4 main classes of genomic alterations known to drive cancer growth (base substitutions, insertions and deletions, copy number alterations [CNAs], and rearrangements or fusions), as well as complex genomic biomarkers. As such, CGP is an increasingly valuable and important part of the molecular characterization of tumors and subsequent selection of the most relevant treatment options for patients with advanced cancer.[20] Guidelines have now incorporated recommendations pertaining to CGP or broad molecular testing for certain patients with advanced cancer, including 30 solid tumor NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[21-50] The American Society for Clinical Oncology (ASCO) Provisional Clinical Opinion has specifically endorsed genomic testing using multigene panel-based sequencing (defined as including at least 50 genes) whenever patients with metastatic or advanced solid tumors are eligible for a genomic biomarker-based therapy that a regulatory agency has approved.[51] Additionally, both the National Comprehensive Cancer Network® (NCCN®) and ASCO have incorporated recommendations for repeat molecular testing for certain patients with advanced cancer who have progressed on systemic therapy.[22,25,26,28,32,33,51]

Summary of Clinical Utility and Validity Data Supporting Foundation One CDx

FoundationOne CDx is a next-generation sequencing (NGS)-based CGP *in vitro* diagnostic device that is FDA-approved to examine 324 cancer genes in solid tumors.[20,52] FoundationOne CDx reports known and likely pathogenic short variants (base substitutions, insertions/deletions), CNAs, and select rearrangements. FoundationOne CDx also reports clinically validated, pan-tumor, proprietary biomarkers, including tumor mutational burden (TMB), microsatellite instability (MSI), and homologous recombination deficiency signature (HRDsig)[a].[53] The assessment of complex biomarkers, such as TMB, requires assessment of several hundred genes (equivalent to 1.1 megabases [Mb] for TMB) in order to cover sufficient genomic space to accurately assess the whole exome mutational burden.[54] For this reason, CGP provides coverage of actionable complex genomic biomarkers that hotspot panels (gene panels assessing ≤50 genes) cannot provide. FoundationOne CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid tumors.[52]

The clinical utility of the CGP approach of FoundationOne CDx to match advanced cancer patients to appropriate biomarker-based targeted therapy has been reported in an analysis of >191,000 US patients with solid tumors.[20] Across the 4 most common solid tumor types in the US, breast cancer, prostate cancer, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC), FoundationOne CDx provided clinical

[a] **Note:** HRDsig is reported as laboratory professional service which has not been reviewed or approved by the FDA.

decision insights for in-tumor therapy options for 77%, 24%, 71%, and 44% of patients, respectively. Further, within these 4 tumor types, matching clinical trials were reported in >80% of patients.

Additionally, FoundationOne CDx is FDA-approved for >35 companion diagnostic indications, including therapies from 3 group indications (covering therapeutic products with similar mechanisms of action [eg, BRAF inhibitors for melanoma]) to identify patients who may benefit from treatment in accordance with the approved therapeutic product labeling (Table 1-1).[52] Foundation Medicine has >50% of all approved US companion diagnostic (CDx) indications for NGS testing. Please refer to **Clinical Validity and Utility of FoundationOne CDx for Companion Diagnostic Claims** for detailed data supporting the companion diagnostic indications.

Table 1-1. FoundationOne CDx Companion Diagnostic Indications and Group Indications

Tumor type	Biomarker(s) detected	Therapy / group
Solid tumors	*NTRK1/2/3* fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)
	RET fusions	Retevmo® (selpercatinib)
	TMB ≥10 mutations per megabase	Keytruda® (pembrolizumab)
	MSI-high	Keytruda® (pembrolizumab)
NSCLC	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	EGFR TKI approved by FDA[a]
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Alunbrig® (brigatinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET SNVs and indels that lead to *MET* exon 14 skipping	Tabrecta® (capmatinib)
	ROS1 fusions	Rozlytrek® (entrectinib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D (1635G>T only), E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (alpelisib)
	AKT1 E17K; *PIK3CA* R88Q, N345K, C420R, E542K, E545A, E545D, E545Q, E545K, E545G, Q546E, Q546K, Q546R, Q546P, M1043V, M1043I, H1047Y, H1047R, H1047L, and G1049R; and *PTEN* alterations	Truqap™ (capivasertib) in combination with fulvestrant
CRC	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib)
Prostate cancer	HRR gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2,*	Lynparza® (olaparib)

Tumor type	Biomarker(s) detected	Therapy / group
	RAD51B, RAD51C, RAD51D, and *RAD54L*) alterations	
	BRCA1/2 alterations	Akeega® (niraparib and abiraterone acetate dual action tablet)
		Lynparza® (olaparib) in combination with abiraterone
Melanoma	*BRAF* V600E	BRAF inhibitors approved by FDA[a]
	BRAF V600E and V600K	Mekinist® (trametinib) or BRAF/MEK inhibitor combinations approved by FDA[a]
	BRAF V600 mutation-positive	Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre® (pemigatinib)
Glioma	*BRAF* V600 mutation-positive and *BRAF* fusions	Ojemda™ (tovorafenib)

Note: The orange text denotes links to additional information supporting each companion diagnostic or group indication.

Given the complexity and rapid growth of biomarkers and biomarker-based targeted therapies and immunotherapies, please refer to the FDA's list of cleared or approved companion diagnostic devices for the most recent list of companion diagnostic indications for FoundationOne CDx (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnosticdevices-in-vitro-and-imaging-tools).

[a] For the most current information about the therapeutic products in this group, go to https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnosticdevices-in-vitro-and-imaging-tools.

ALK, anaplastic lymphoma kinase; BRCA, breast cancer gene; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; KRAS, V-Ki-ras2 Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; SNV, single nucleotide variant; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden.

Source: FoundationOne CDx Technical Information[52]; FoundationOne CDx SSED *RET* fusions Data on File[55].

Economic Value of FoundationOne CDx

There are several published economic value analyses of FoundationOne CDx. In patients with advanced NSCLC, budget impact studies reported that FoundationOne CDx had a modest budget impact, mostly attributable to increased use of more effective treatments and prolonged survival.[56,57] Additionally, economic impact analyses in patients with NSCLC demonstrated the potential for FoundationOne CDx to be cost-saving as a CGP test when compared to single-gene or hotspot testing, with cost benefit gains having been associated with screening of both common and less common alterations and avoidance of ineffective treatments.[58,59] Additionally, studies have concluded that CGP testing can accelerate the start of first-line targeted therapy and may represent a cost-effective approach, while avoiding futile, costly immune checkpoint inhibitors (ICIs).[58-60] A retrospective observational study of patients who received a FoundationOne CDx test in a community oncology setting, established that clinical trial enrollment was facilitated by CGP use in the community setting and may have contributed to cost diversion from the payer to study sponsors.[61,62]

Conclusion

With the growing number of biomarker-based targeted therapies and immunotherapies that are efficacious in certain patients with advanced cancer, it is increasingly important to define these populations using an accurate, efficient, and broad molecular testing method, such as CGP, which is an approach recommended by clinical practice guidelines in oncology.[22-24,26-30,32,34,35,39-41,43-48,51,63-70] Foundation Medicine has >50% of all approved US CDx indications for NGS testing, and FoundationOne CDx specifically is an FDA-approved CGP technology that has >35 companion diagnostic indications alone.[20] As such, FoundationOne CDx provides clinically actionable results that allow the patient and provider to make informed treatment

decisions based on evidence-based interventions that improve health outcomes.[20,71]

2 UNMET NEED AND RATIONALE FOR MOLECULAR TESTING

Epidemiology of Advanced Cancer

In the US, approximately 2.04 million people will be diagnosed with cancer in 2025, of which approximately 1.8 million people will be diagnosed with a solid tumor.[72] Of the patients diagnosed with a solid tumor, approximately one-third will have advanced cancer (defined as stage III or IV cancer).[72-74] Based on this estimation, approximately 594,000 people in the US will be diagnosed with advanced solid tumor cancer in 2025. Prognosis remains poor for most types of advanced cancer, especially those diagnosed as metastatic, with 5-year survival rates ranging from 38% down to only 3% depending on the cancer site.[72]

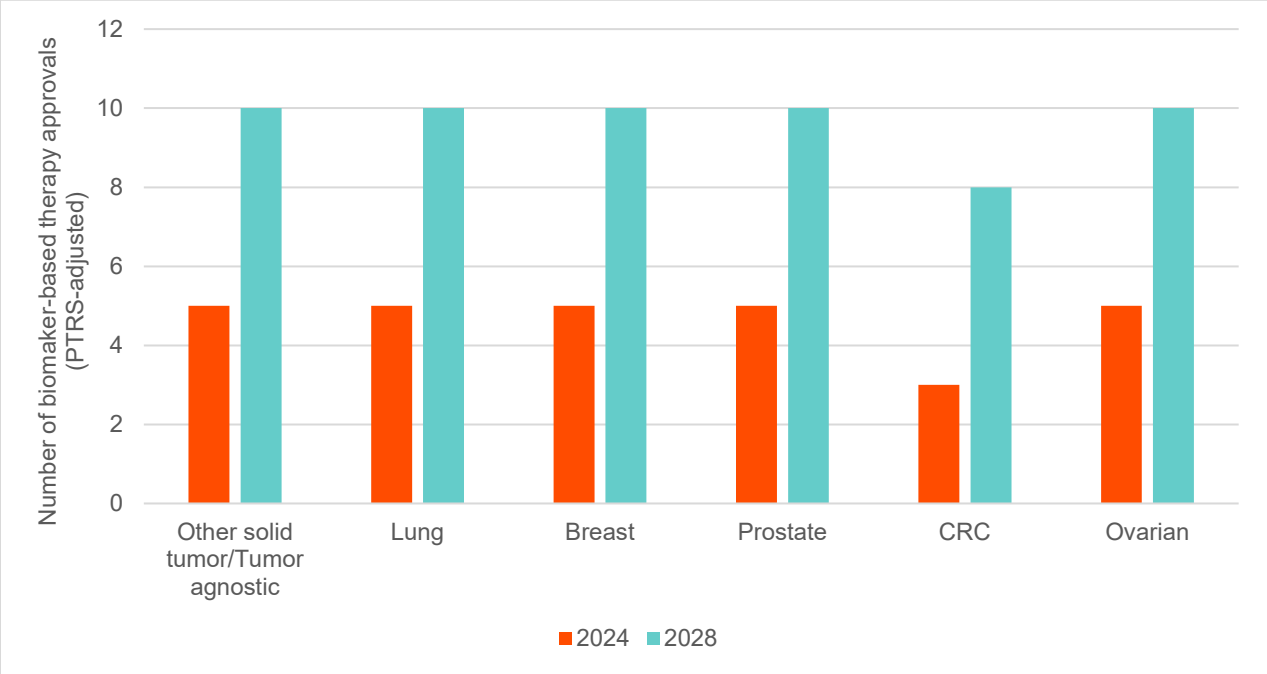
Biomarker-Based Targeted Treatment of Advanced Cancer

An increasing number of biomarker-based targeted therapies and immunotherapies have been approved by the FDA for a broad range of solid tumors; examples include tyrosine kinase inhibitors, monoclonal antibodies directed against tumor antigens, and immune checkpoint inhibitors (ICIs).[75] Biomarker-based targeted therapy and immunotherapy options have changed the treatment paradigm for certain patients with advanced cancer due to the improvement of outcomes with these therapies.[2-18]

- The use of biomarker-based targeted therapy has significantly improved treatment responses and survival outcomes in patients with actionable alterations for which there is targeted therapy available (either FDA approved or in clinical trials) compared with standard of care therapy chemotherapy or best supportive care.[2-12,18]
- Immunotherapies have also demonstrated significant improvements in outcomes such as response and survival rates in patients with advanced cancer. Although not all trials were biomarker-driven, patients having high TMB or microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) have improved outcomes with immunotherapy vs those without these biomarkers.[13-18]

The treatment landscape of advanced cancers continues to evolve, with more biomarkers being investigated as potential targets and additional biomarker-based targeted therapies in clinical development.[19] It is projected that the number of biomarker-based targeted therapies will likely double from 2024 to 2028 (Figure 2-1).

Figure 2-1. Novel Biomarker-based Targeted Therapy Projected Approvals in Solid Tumor Indications by 2028



Note: The number of novel biomarker-based targeted therapy approvals based on adjusted PTRS.
CRC, colorectal cancer; PTRS, probability of technical and regulatory success.
Source: Foundation Medicine Data on File, 2025.[19]

Public Health Implications of CGP

The US has rapidly progressed in cancer treatment through advances in understanding of cancer biology, including molecular drivers of disease; however, large segments of the population have not benefited from these advances and continue to have a disproportionate cancer burden.[76] It is well-documented that survival rates vary by race, with cancer survival after diagnosis being lower among Black people than among White people for almost every common cancer.[72] Although the reasons for this are likely multifactorial, one reason may be early access to new and potentially more effective therapies, as enrollment in clinical trials is highest in patients who are White, of younger age, have access to private insurance, and are treated at an academic center.[77] Further, the shift to personalized medicine, both in standard of care treatment and for clinical trial enrollment, may further contribute as CGP is often required to identify biomarkers for clinical trial enrollment.

- In a real-world database that included 23,488 patients diagnosed with advanced/metastatic NSCLC, metastatic CRC, or metastatic breast cancer, NGS-based testing rates were observed to be significantly lower for Black race vs White race in NSCLC and CRC ($P<0.0001$).[77] Further, in this analysis a statistically significant relationship between biomarker/NGS testing and clinical trial enrollment was observed in all cohorts ($P<0.003$) after adjusting for covariates.

As modern oncology care relies on the results of tumor genomic profiling, especially for patients with advanced cancer, it is necessary that all patients have equitable access to CGP. A recent analysis of Foundation Medicine CGP testing underscores that there has been progress in expanding access to CGP to historically marginalized groups.

- A retrospective analysis of 620,500 solid-tumor and liquid-biopsy samples submitted to a national commercial laboratory (Foundation Medicine) in the US for broad-panel genomic profiling from April 2013 through September 2022 were reviewed to examine the genetic ancestry of patients who received CGP.[78] Over the 9-year period, a total of 75.6% of the patients had predominantly European ancestry, 10.4% had African ancestry, 9.1% had admixed American ancestry, 3.7% had East Asian ancestry, and 1.1% had South Asian ancestry. The number of patients who underwent CGP increased with time in all groups. In particular, the percentage of patients who underwent genomic testing who had predominantly African ancestry increased by half a percentage point each year, reaching 12.4% by September 2022; this percentage is similar to the 11.6% of adults 55 to 74 years of age who identified as Black or African American in 2021 US Census data.

It is imperative to continue to ensure that CGP is a reflexive step in the evaluation of patients with advanced cancer, specifically as clinical trials exploring specific molecular alterations and new targeted therapies have become standard of care.[78]

CGP for Biomarker Testing in Advanced Cancer

Given the considerable number of biomarker-based targeted therapies and immunotherapies in development with anticipated approvals in upcoming years, a highly validated CGP diagnostic, such as FoundationOne CDx, allows these advancements to be incorporated into a single assay, potentially providing physicians with the opportunity to receive more comprehensive and time-sensitive information to better inform treatment selection for their patients.[70]

3 PRODUCT DESCRIPTION

FoundationOne CDx Product Description

FoundationOne®CDx is a qualitative 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 CNAs in 324 genes and select gene rearrangements, as well as genomic signatures including MSI and TMB, using DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens (the assay employs two extraction methods [either DNAx or CoExtraction, an automated DNA/RNA co-extraction methodology] for DNA extraction from routine FFPE biopsy or surgical resection specimens).[52] In addition to the clinically validated, pan-tumor, proprietary biomarkers, MSI and TMB, FoundationOne CDx also reports HRDsig, which is reported as a laboratory professional service that has not been reviewed or approved by the FDA.[53] The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1-1 in accordance with the approved therapeutic product labeling. Additionally, FoundationOne CDx is intended to provide tumor mutation profiling to be used by qualified healthcare professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1-1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Given the complexity and rapid growth of biomarkers and biomarker-based targeted therapies and immunotherapies, please refer to the **FDA's list of cleared or approved companion diagnostic devices** for the most recent list of companion diagnostic indications specific to FoundationOne CDx.

Foundation Medicine Precision Enrichment

Prior to genomic testing, the standard practice was to determine a pre-test incipient tumor nuclei percentage (TN%) to determine if the minimal TN% required for NGS testing is met (ie, 20%).[79] Similar to TN%, a minimum computational tumor purity threshold (ie, 20% or 30%) may be required to confidently report complex biomarkers such as MSI, TMB, copy number gains and losses, and certain fusions. Samples that do not meet the minimum TN% and/or the minimum computational tumor purity threshold may result in test failure or in false-negative results. Therefore, precise, safe, efficient, and scalable methods are needed to salvage cases with low tumor purity and to confidently determine biomarker status.[80]

The Foundation Medicine-validated Precision Enrichment using needle punch enrichment (NPE) from FFPE specimens improves the detection of clinically actionable genomic alterations and biomarkers.[80] With the laboratory adoption of pathologist-directed NPE in one laboratory over a 30-month period, the FFPE enrichment rate increased from ~30% (with razor-blade macro-enrichment) to ~50% with NPE.[79] Additionally, with the use of NPE, the quantity not sufficient rate decreased from 3% to 1% and the proportion of pass/qualified reports increased from 89% to 90-91%.[79,80] Pathologist-directed NPE also improved complex biomarker determinations, such as TMB and MSI, from FFPE tumor blocks. By enhancing biomarker results, Foundation Medicine Precision Enrichment may optimize patient matching to approved therapies and/or clinical trial enrollment while maximizing tissue preservation for additional tests.

Clinically Validated Proprietary Biomarkers

The clinically validated, pan-tumor, proprietary biomarkers provide better guidance for therapy based on peer-reviewed evidence.[53] The biomarkers available through FoundationOne CDx include TMB, MSI, and HRDsig[b].

TMB

TMB is measured by counting coding short variants present at ≥5% allele frequency and filtering out potential germline variants according to published databases of known germline polymorphisms.[20,52] Additional germline alterations are assessed for potential germline status and filtered out using a somatic-germline/zygosity (SGZ) algorithm. Known and likely driver mutations are also filtered out to exclude bias. The resulting mutation number is then divided by the coding region corresponding to the number of total variants counted, or approximately 790 kilobases (kb); the resulting number is reported in units of mut/Mb.

The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mut/Mb in the KEYNOTE 158 trial (Table 3-4). Additionally, clinical validity was reported in a real-world analysis of 8,440 patients with advanced or metastatic cancer who received anti-programmed death-1/ligand-1 (PD-1/L1) monotherapy and had TMB measured by FoundationOne CDx, FoundationOne, or FoundationOne Heme (provided as laboratory professional service) from the Flatiron Health–Foundation Medicine–deidentified clinicogenomic database between January 2011 and September 2022.[81] In this analysis, increasing TMB was associated with increasing real-world overall survival (rwOS) relative to patients with TMB <5 mut/Mb: those with 5 to <10 had a hazard ratio (HR) of 0.95 (95% confidence interval [CI]: 0.89, 1.02; *P*=0.153), 10 to <20 had HR 0.79 (95% CI: 0.73, 0.85; *P*<0.001), those with ≥20 had HR 0.52 (95% CI: 0.47, 0.58; *P*<0.001). For individual cancer types with prespecified statistical power, adjusted rwOS comparing TMB ≥10 vs TMB < 10 significantly favored TMB ≥10 in 9 of 10 cancer types. Despite wide variability in the range of TMB levels among different tumor types, these real-world data support the clinical validity FoundationOne CDx measurement of TMB ≥10 mut/Mb in patients receiving anti-PD-1/L1 monotherapy across multiple tumor types.

MSI

To determine MSI status, repetitive loci (minimum of five repeat units of mono-, di-, and trinucleotides) are assessed to determine what repeat lengths are present in the sample.[20,52] FoundationOne CDx employs a fraction-based (FB) MSI algorithm to categorize a tumor specimen as MSI-H or microsatellite stable (MSS).[82] The FB-MSI algorithm calculates the fraction of microsatellite loci determined to be altered or unstable (ie, the fraction unstable loci score) based on an analysis across >2,000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the qualified microsatellite is categorized as unstable if remaining alleles differ in length from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. Two FB-MSI score thresholds are applied to classify the MSI status of a tumor specimen: MSI-H tumors have FB-MSI scores ≥0.0124; MSS tumors have FB-MSI scores ≤0.0041; MSI-equivocal tumors have FB-MSI intermediate scores >0.0041 and <0.0124 (reported result is MSI "cannot be determined").

FoundationOne CDx MSI status had high analytical concordance with both polymerase chain reaction (PCR) and mismatch repair (MMR) immunohistochemistry (IHC) (Table 3-1).[83]

[b] **Note:** HRDsig is reported as laboratory professional service which has not been reviewed or approved by the FDA.

Table 3-1. Concordance of FoundationOne CDx MSI with PCR and IHC

	Number of samples	Concordance of F1CDx FB-MSI algorithm	
		PPA, % (95% CI)	NPA, % (95% CI)
Promega PCR	N = 264	98.9 (94.1, 99.8)	97.1 (93.4, 98.8)
Orthogonal MMR IHC	N=279[a]	90.5 (79.7, 95.9)	99.5 (97.5, 99.9)

[a] Including 179 CRC, 69 endometrial cancers, and 31 other non-CRC/non-endometrial cancers.

CI, confidence interval; F1CDx, FoundationOne CDx; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; NPA, negative percent agreement; PCR, polymerase chain reaction; PPA, positive percent agreement.

Source: Lin 2024.[83]

The clinical validity of MSI status utilizing these cutoffs has been established as part of a retrospective bridging clinical study from KEYNOTE-158 Cohort K and KEYNOTE-164 (Table 3-5). [20,52] Additionally, in real-world cancer patients from a deidentified clinicogenomic database, FoundationOne CDx was at least equivalent in assessing clinical outcome following immunotherapy compared with MMR IHC.[83] In a cohort of 246 CRC patients, agreement between FoundationOne CDx FB-MSI status and MMR by IHC was strong among patients that received immunotherapy (majority received pembrolizumab) in any line of therapy, with a Cohen's kappa coefficient of 0.86. Similarly, in a cohort of 105 endometrial cancer patients, agreement between FoundationOne CDx FB-MSI status and MMR by IHC was also strong, with a Cohen's kappa statistic of 0.826.

HRDsig

Normally, cells use a method called homologous recombination to repair DNA breaks. If this is impaired, known as homologous recombination deficiency (HRD), cells end up with DNA changes, or "scars" that can contribute to the development of cancer. The Foundation Medicine HRDsig is a machine learning algorithm designed to identify the genomic scarring in all solid tumors to understand which patients may benefit from poly (ADP-ribose) polymerase (PARP) inhibitor therapy and other DNA-damaging cancer drugs, regardless of homologous recombination repair (HRR) gene mutation status.[53,84] HRDsig is a NGS scar-based genomic signature that does not rely on detecting HRR alterations in genes like *BRCA* or *PALB2* to detect HRD, but instead on identifying genome-wide copy number (CN) features, avoiding the potential for false negatives that could occur with other testing methods.[84] It was built with a diverse set of more than 100 CN features and trained using the extensive Foundation Medicine pan-tumor genomic database from over 500,000 patients. HRDsig positivity is detected in approximately 8% of pan-tumor cases in the Foundation Medicine genomic database, including over 5% of NSCLC and gastroesophageal cancers.

The clinical validity of HRDsig in predicting outcomes in response to therapy has been reported in multiple real-world studies in patients with ovarian cancer, prostate cancer, and breast cancer (Table 3-2).

Table 3-2. Clinical Validity of FoundationOne CDx HRDsig

Tumor type	Patient population	Clinical outcome
Ovarian cancer	673 patients with ovarian cancer	▪ HRDsig-positive status receiving maintenance PARPi vs no maintenance had more favorable rwPFS (HR: 0.36; 95% CI: 0.24, 0.55; $P<0.001$) and tended to have more favorable rwOS (HR: 0.46; 95% CI: 0.21, 1.02; $P=0.0561$)

		▪ Patients with HRDsig-negative status had no significant difference for rwPFS or rwOS between receiving maintenance PARPi vs no maintenance ▪ Looking specifically at BRCA-WT patients (n=543), those who were HRDsig-positive receiving maintenance PARPi vs no maintenance had favorable rwPFS (HR: 0.40; 95% CI: 0.22, 0.72; median 26.8 vs 6.2 months) and rwOS (HR: 0.58; 95% CI: 0.21, 1.61; median not reached vs 38.9 months), whereas no difference was observed for those who were HRDsig-negative
	220 patients with ovarian cancer treated with PARPi	▪ HRDsig-positivity was associated with improved TTD (multivariate HR: 0.50; 95% CI: 0.36, 0.70; *P*<0.001)
Prostate cancer	72 patients with mCRPC treated with PARPi	▪ HRDsig-positivity was significantly associated with prolonged TTD on PARPi (HR: 0.50; 95% CI: 0.26, 0.96; *P*=0.036)
Breast cancer	28,920 patients with mBC	▪ Patients with HRDsig-positive vs HRDsig-negative had longer rwPFS (HR: 0.62; 95% CI: 0.42, 0.92) and numerically longer rwOS (HR: 0.72; 95% CI: 0.46-1.14)
	497 patients with TNBC who had record of neoadjuvant treatment	▪ Platinum vs non-platinum treatment showed a trend towards moderately enriched pCR rates in the HRDsig-positive group (OR: 1.87; 95% CI: 0.97, 3.84; *P*=0.08), but not in the HRDsig-negative group (OR: 0.86; 95% CI: 0.23, 2.55; *P*=0.767)

Note: Flatiron Health and Foundation Medicine real-world CGDB was utilized in these studies for the real-world data source.

BRCA-WT, breast cancer gene-wild type; CGDB, clinicogenomic database; CI, confidence interval; HR, hazard ratio; HRDsig, homologous recombination deficiency signature; mBC, metastatic breast cancer; mCRPC, metastatic castration-resistant prostate cancer; OR, odds ratio; PARPi, poly (ADP-ribose) polymerase inhibitor; pCR, pathological complete response; rwOS, real-world overall survival; rwPFS, real-world progression-free surivival; TNBC, triple-negative breast cancer; TTD, time to treatment discontinuation; TTNT, time to next treatment.

Source: Moore 2023[85]; Richardson 2024[86]; Batalini 2023[87]; Gupta 2024[88].

FoundationOne CDx Report Results

An example **report guide**, which points out key features of the FoundationOne CDx report, is provided in the Appendix (Figure 6-1). The report, which is the output of the test, includes:

- FDA-approved therapies and other biomarkers are provided in the report:
  - A list of FDA-approved companion diagnostic claims associated with the patient's findings.
  - A summary of all other genomic and biomarker findings, including MSI and TMB including those without companion diagnostic claims.
- Professional services section provides interpretive content that supports guideline-based decision making:
  - Therapies for each associated genomic finding are listed in alphabetical order within the patient's tumor type and other tumor types.
  - Associated NCCN category that has been assigned to the therapy listed with the patient's tumor type is reported.
  - Identifies clinical trials based on the patient's unique genomic profile with page number for quick reference.

- The report also highlights key actionable findings and pertinent negatives.

Clinical Utility of the CGP Approach of FoundationOne CDx

Evidence from tissue-based CGP testing has demonstrated the additional value of using a CGP-based approach to match patients to therapy compared with standard genomic tests such as fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), single-gene tests, and hotspot testing, as CGP identified missed genomic alterations from other testing methods in 37% to 84% of previously tested patients (Table 3-3).[2,89,90] Additionally,

Table 3-3. Improved Detection of Genomic Alterations With CGP Testing

Author/year	Study description	Percent of patients with ≥1 missed genomic alteration identified with CGP	Percent of patients who received targeted therapy
Reitsma 2019[89]	Retrospective analysis of medical records including 96 patients in community oncology practice who received CGP testing using FoundationOne or FoundationOne Heme Subset of 32 patients who previously received conventional testing	84%	19%
Kopetz 2019[2]	Prospective study of 521 patients with refractory cancers comparing a 46- or 50-gene NGS assay with a 409-gene whole exome assay	41%	19%
Rozenblum 2017[90]	Retrospective study that included 101 patients with advanced lung cancer on whom hybrid capture-based NGS was performed	36.6%	19%

Note: The orange text for author/year is a link to the full text publication supporting this data.

CGP, comprehensive genomic profiling; NGS, next-generation sequencing.

The clinical utility of the CGP approach of FoundationOne CDx to match patients to appropriate biomarker-based targeted therapy have been reported within large analyses of US patients with solid tumors.[20,91]

- A study analyzed the impact of clinical decision insights provided from 191,575 unique US patients with solid tumors who received FoundationOne CDx testing between January 14, 2018 to March 31, 2021.[20] The FoundationOne CDx reports provided clinical decision insights overall and by disease group rank-ordered by therapy options: in-tumor type, other tumor type, matching clinical trials, and companion/complementary diagnostics. For the 4 most common tumor types in the US, breast cancer, prostate cancer, NSCLC, and CRC, FoundationOne CDx provided clinical decision insights for in-tumor therapy options in 24%-77%, other tumor type therapy options in 43%-79%, matching clinical trials in 81%-95%, and companion/complementary diagnostic therapy options in 28%-60%. Additional information for FoundationOne CDx across 46 solid tumors can be found in **Clinical Decision Insights Provided by the CGP Approach of FoundationOne CDx** in the Appendix.
- An observational study analyzed the impact of clinical decision insights from 109,695 clinical reports generated based on FoundationOne CDx tumor profiles between April 1, 2020, and March

31, 2021.[91] In the predefined cancer types[c], clinically significant predictive markers were observed in 47.6% (range: 3.5-79.7), prognostic markers in 13.2% (range: 0-76.1), and diagnostic markers in 4.5% (range: 0-92.3) of tumor samples. Pan-cancer predictive markers of TMB (≥10 mutations per megabase [mut/Mb]), MSI-H, or *NTRK1/2/3* fusions were observed in 15.6%, 2.0%, and 0.1% of solid tumors, respectively. In the total population, 89.2% of patients had tumor profile results that could inform decisions on the selection of immunotherapy and targeted therapy clinical trials.

Additionally, an analysis from the Prospective Clinicogenomic Program clinical trial (NCT04180176) reported that tissue CGP can meaningfully add to the detection of biomarkers and should be considered as a follow-up when an actionable alteration is not identified by liquid biopsy.[92]

- An analysis of the Prospective Clinicogenomic Program clinical trial, an observational study, included 515 patients with advanced nonsquamous NSCLC to assess the value of liquid biopsy for detecting driver alterations.[92] Of the 131 patients who completed tissue CGP with FoundationOne CDx, an additional 30 patients (23% of the subcohort) who were liquid biopsy-negative were detected to harbor an NCCN biomarker[d] with tissue CGP. This outlines the need for sequential reflex to tissue CGP after liquid biopsy when there are no actionable alterations detected.

As evidenced above, FoundationOne CDx reports support clinical decision making by interpreting predictive, prognostic, and diagnostic biomarkers according to professional guidelines as well as investigational markers for the enrollment in clinical trials.

Clinical Validity and Utility of FoundationOne CDx for Companion Diagnostic Claims

For FoundationOne CDx, each of the companion diagnostic claims were FDA-approved based upon the clinical validity and/or clinical utility as determined in 1 of 3 ways (described in more detail below): (1) by use of FoundationOne CDx as the clinical trial assay (CTA) through prospective or retrospective or analyses of tumor samples; (2) clinical bridging studies; or (3) non-inferiority concordance testing against FDA-approved companion diagnostics for that indication.[20,52]

FoundationOne CDx as the CTA

The clinical utility of FoundationOne CDx was demonstrated as the CTA, through either retrospective or prospective analysis of tumor samples, for TMB-H (≥10 mut/Mb) in solid tumors, *PIK3CA*, *AKT1*, and *PTEN* alterations in breast cancer, somatic *BRCA1/2* alterations in ovarian cancer, and for deleterious alterations within a panel of homologous recombination repair (HRR) genes or for *BRCA1/2* alterations in patients with castration-resistant prostate cancer (Table 3-4).[20,52]

- The FoundationOne CDx CTA was used to identify TMB-H (≥10 mut/Mb) in patients with select advanced cancer in the KEYNOTE-158 trial for pembrolizumab FDA approval in solid tumors.[52] TMB-H (≥10 mut/Mb) was associated with a clinically meaningful improvement in median duration of response (DOR) (not reached in the TMB-H (≥10 mut/Mb) group vs 33.1 months in the non-TMB-H group).[93-96]
- The FoundationOne CDx CTA was used to identify *PIK3CA*, *AKT1*, and *PTEN* alterations in patients with HR-positive and HER2-negative breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor for treatment with capivasertib in combination with fulvestrant in the CAPItello-291

[c] **Note:** 14 predefined cancer types included: NSCLC, colorectal cancer, breast cancer, ovarian cancer, prostate cancer, pancreatic adenocarcinoma, gastroesophageal adenocarcinoma, unknown primary carcinoma, urothelial carcinoma, cholangiocarcinoma, melanoma, glioma, head and neck squamous cell carcinoma, and uveal melanoma.

[d] **Note:** NCCN biomarkers included 9 oncogenes: *EGFR, KRAS, ALK, ROS1, RET, BRAF, MET, NTRK*, and *ERBB2.*

trial.[52] In the primary analysis of the overall population, the median progression-free survival (PFS) was 7.2 months in the capivasertib + fulvestrant group and 3.6 months in the placebo + fulvestrant group (hazard ratio [HR] for progression or death: 0.60; 95% CI: 0.51, 0.71; *P*<0.001).[97]

- The FoundationOne CDx CTA was used to identify somatic *BRCA1/2* alterations on prospectively collected tumor samples for patients enrolled in the SOLO-1 trial for olaparib in ovarian cancer based on local (germline or somatic) or central (germline) testing. At the 7-year follow-up of the SOLO-1 trial, the median overall survival (OS) was not reached vs 75.2 months for patients treated with olaparib vs placebo, respectively (HR: 0.55; 95% CI: 0.40, 0.76; *P*=0.0004).[52,98-101]
- The FoundationOne CDx CTA was also used as the registrational assay in the PROfound trial for patients to prospectively select metastatic castration resistant prostate cancer patients with HRR alterations for treatment with olaparib.[52,101-105] In the PROfound trial, olaparib showed improved clinical outcomes in those patients with HRR mutations as determined by FoundationOne CDx compared to those patients who received placebo, with the median OS for olaparib being 19.1 months vs 14.7 months for placebo (HR: 0.69; 95% CI: 0.50, 0.97, *P*=0.0175).[101]
- FoundationOne CDx CTA was used as the registrational assay in the MAGNITUDE trial (PCR3001) to prospectively identify patients with *BRCA1/2* alterations for patients with metastatic castration resistant prostate cancer for treatment with niraparib and abiraterone acetate.[52,106] In the *BRCA1/2* subgroup of this trial, median rPFS by central review was significantly longer in the niraparib + abiraterone acetate group than in the placebo + abiraterone acetate group (16.6 months vs 10.9 months; HR: 0.53; 95% CI: 0.36, 0.79; *P*=0.001).[106]
- FoundationOne CDx CTA was used to prospectively detect *BRCA1/2* alterations in patients with mCRPC for first-line treatment with olaparib in combination with abiraterone in the PROpel trial.[52] The primary endpoint of the PROpel trial, median rPFS by investigator assessment, was significantly longer in the abiraterone + olaparib group vs the placebo + abiraterone group (24.8 months vs 16.6 months, respectively; HR: 0.66; 95% CI: 0.54, 0.81; *P*<0.001).[107]

Table 3-4. Clinical Utility of FoundationOne CDx as the CTA

Tumor type	Biomarker	Therapy	Trial	Clinical endpoint	F1CDx results[a]	Full analysis set results[b]
Solid tumors	TMB-H (≥ 10 mut/Mb)	Pembrolizumab	KEYNOTE-158	ORR[c], % (n/N) (95% CI)	33 (30/91) (24, 44) N=91	29 (30/102) (21, 39) N=102
Breast cancer	*PIK3CA, AKT1, PTEN*	Capivasertib + fulvestrant	CAPItello-291	PFS[d], months HR (95% CI)	7.3 0.49 (0.38, 0.64) N=153	7.3 0.50 (0.38, 0.65) N=155
Ovarian cancer	*BRCA1/2*	Olaparib	SOLO-1	PFS[d], months HR[e] (95% CI)	Not reached 0.28 (0.20, 0.38) N=206	Not reached 0.30 (0.23, 0.41) N=260
Prostate cancer	HRR (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B,*	Olaparib	PROfound	rPFS[f], months HR[g] (95% CI)	6.2 0.49 (0.38, 0.63) N=248	5.8 0.49 (0.38, 0.63) N=256

Tumor type	Biomarker	Therapy	Trial	Clinical endpoint	F1CDx results[a]	Full analysis set results[b]
	RAD51C, RAD51D, and *RAD54L*)					
	BRCA1/2	Niraparib + abiraterone acetate	MAGNITUDE	rPFS, months HR[h] (95% CI)	18.43[i] 0.45 (0.28, 0.71)	
		Olaparib + abiraterone	PROpel	rPFS[j], months HR (95% CI)	Not reached 0.31 (0.13, 0.68) N=50	Not reached 0.24 (0.12, 0.45) N=85

[a] For pembrolizumab, this column represents the device validation population.

[b] For pembrolizumab, this column represents the therapeutic efficacy population.

[c] ORR was assessed per central radiology using RECIST v1.1.

[d] Investigator-assessed median PFS evaluated according to RECIST v1.1.

[e] HR for both FoundationOne CDx and full analysis set compares olaparib to placebo for risk of disease progression or death.

[f] rPFS based on BICR using RECIST v1.1 and/or PCWG3, or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression.

[g] HR for both FoundationOne CDx and full analysis set compares olaparib to investigator's choice of therapy (either enzalutamide 160 mg orally once daily or abiraterone acetate 1000 mg orally once daily with prednisone 5 mg orally twice daily [prednisolone was permitted for use instead of prednisone, if necessary]) for radiological disease progression or death.

[h] HR by stratified Cox regression.

[i] The median rPFS for placebo + abiraterone acetate was 10.87 months. The HR suggested a 55% reduction in the risk of radiographic progression when using niraparib + abiraterone acetate compared with placebo + abiraterone acetate.

[j] rPFS was based on investigator assessments per RECIST v1.1.

BICR, blinded independent central review; CI, confidence interval; CTA, clinical trial assay; HR, hazard ratio; HRR, homologous recombination repair; Mb, megabase; mut, mutation; ORR, overall response rate; PCWG3, Prostate Cancer Working Group 3; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiological progression-free survival; TMB-H, tumor mutational burden-high.

Source: FoundationOne CDx Label.[52]

Clinical Bridging of FoundationOne CDx to the CTA

The FoundationOne CDx assay was further clinically validated through clinical bridging analyses to establish clinical utility.[20,52] In each scenario, concordance with CTAs was assessed, and the clinical efficacy as demonstrated by the local CTAs was compared to the clinical efficacy as demonstrated by the FoundationOne CDx assay. The clinical bridging validation for companion diagnostic indications is summarized in Table 3-5.

Table 3-5. Clinical Validity and Utility of FoundationOne CDx via Clinical Bridging Data

Biomarker detected	Therapy (references)	Clinical trial(s)	Concordance to local CTAs		Clinical efficacy		
			PPA, % (95% CI)	NPA, % (95% CI)	Clinical endpoints	F1CDx results	CTA results
Solid tumors							
***NTRK1/2/3* fusions**	Larotrectinib[a,b,c]	LOXO-TRK-14001; LOXO-TRK-15002; LOXO-TRK-15003[108-110]	84.1 (69.9, 93.4)	100.0 (98.4, 100.0)	ORR, % (n/N) (95% CI)	77 (20/26) (56, 91) N=26	75 (41/55) (61, 85) N=55
					DOR, range (months)	1.6, 20.3	1.6, 33.2
					% with duration ≥6 months	80.0	73.2
					% with duration ≥9 months	65.0	63.4
					% with duration ≥12 months	25.0	39.0
	Entrectinib	ALKA; STARTRK-1; STARTRK-2[111,112]	63.6 (46.6, 77.8)	100.0 (98.4, 100.0)	ORR, % (n/N) (95% CI)	81.0 (17/21) (58.1, 94.6) N=21	62.2 (46/74) (50.1, 73.2) N=74
					DOR, median, months	9.2	7.4
					% with duration ≥6 months	52.9	54.3
					% with duration ≥9 months	52.9	43.5
					% with duration ≥12 months	35.3	30.4
***RET* fusions**	Selpercatinib	LIBRETTO-001[113,114]	90.1 (81.0, 95.1)	100.0 (97.3, 100.0)	ORR[b], % (n/N) (95% CI)	75.0 (48/64) (63.2, 84.0)	66.5 (141/212) (59.9, 72.5)
MSI-H	Pembrolizumab	KEYNOTE-158 (Cohort K); KEYNOTE-164[93,115]	69.8 (63.0, 75.8)	99.3 (98.5, 99.7)	ORR[b],% (n/N) (95% CI)	43.0 (46/107) (33.5, 52.9)	31.8 (141/444) (27.4, 36.3)
NSCLC							
***MET* SNVs and indels that lead to exon 14 skipping**	Capmatinib[d,e]	GEOMETRY-mono 1 trial[116-119]	98.6[f] (92.6, 100.0)	100.0[f] (97.1, 100.0)	Cohort 4: ORR[g], % (n/N) (95% CI)	44.2 (23/52) (30.5, 58.7) N=52	40.6 (28/69) (28.9, 53.1) N=69
					Cohort 5b: ORR[g], % (n/N) (95% CI)	70.0 (14/20) (45.7, 88.1) N=20	67.9 (19/28) (47.6, 84.1) N=28

Biomarker detected	Therapy (references)	Clinical trial(s)	Concordance to local CTAs		Clinical efficacy		
			PPA, % (95% CI)	NPA, % (95% CI)	Clinical endpoints	F1CDx results	CTA results
					Cohort 4: Median DOR[g], months (95% CI)	9.72 (4.27, 12.98)	9.7 (5.5, 13.0)
					% with DOR >12 months	34.8	32
					Cohort 5b: Median DOR[g], months (95% CI)	12.58 (5.55, 25.33)	12.6 (5.5, 25.3)
					% with DOR >12 months	50.0	47
***ROS1* fusions**	Entrectinib	ALKA; STARTRK-1; STARTRK-2[112,120]	73.9 (59.7, 84.4)	99.2 (97.1, 99.8)	ORR, % (n/N) (95% CI)	64.7 (22/34) (46.5, 80.3) N=34	67.3 (107/159) (59.4, 74.5) N=159
					DOR, median, months	10.1	9.5
					% with duration ≥6 months	72.7	61.7
					% with duration ≥9 months	36.4	41.1
					% with duration ≥18 months	4.5	19.6
***BRAF* V600E alterations**	Encorafenib + binimetinib	PHAROS (ARRAY-818-202)[121,122]	93.15 (84.95, 97.04)	100.00 (96.30, 100.00)	Treatment-naïve[h]		
					ORR, % (n/N) (95% CI)	82.9 (34/41) (67.9, 92.8) N=41	74.6 (44/59) (61.6, 85.0) N=59
					DOR, median, months	NA[i]	NA[i]
					% with duration ≥6 months	79.4	75.0
					% with duration ≥12 months	61.8	59.1
					Previously treated[j]		
					ORR, % (n/N) (95% CI)	51.9 (14/27) (31.9, 71.3) N=27	46.2 (18/39) (30.1, 62.8) N=39
					DOR, median, months	NA[i]	16.7
					% with duration ≥6 months	64.3	66.7
					% with duration ≥12 months	28.6	33.3
Breast cancer							
***PIK3CA* C420R, E542K, E545A,**	Alpelisib + fulvestrant	SOLAR-1[123-125]	93.8 (87.7, 97.5)[k]	98.8 (95.6, 99.8)[k]	PFS[l], months, HR (95% CI) CTA1	11.2 0.52 (0.29, 0.93)	11.0[m]

Biomarker detected	Therapy (references)	Clinical trial(s)	Concordance to local CTAs		Clinical efficacy		
			PPA, % (95% CI)	NPA, % (95% CI)	Clinical endpoints	F1CDx results	CTA results
E545D (1635G>T only), E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y						N=56	0.65 (0.50, 0.85) N=169
					PFS[l], months, HR (95% CI) CTA2	10.9 0.35 (0.16, 0.77) N=42	
Cholangiocarcinoma							
***FGFR2* fusions and select rearrangements**	Pemigatinib	FIGHT-202[126,127]	87.08 (61.4, 98.3)[n]	99.59 (92.87, 100.0)[n]	ORR[o], % (95% CI)	37.50 (26.92, 49.04) N=80	35.51 (26.50, 45.35) N=107
Glioma							
***BRAF* V600 mutations and *BRAF* fusions**	Tovorafenib	FIREFLY-1[128,129]	77.08 (63.46, 86.69)	98.32 (94.08, 99.54)	ORR[p], % (95% CI)	51.22 (36.48, 65.75) N=41	52.00 (40.87, 62.93) N=75

[a] PPA and NPA results exclude the F1CDx invalid results. Including the F1CDx invalid results, the PPA was 82.2% (95% CI: 67.9, 92.0) and the NPA was 98.3% (95% CI: 95.6, 99.5).

[b] ORR was assessed by an independent review committee using RECIST v1.1.

[c] Local CTAs included DNA NGS, RNA NGS, FISH, and RT-PCR methods, with the majority (92%) of the clinical trial patients with known *NTRK* fusion status enrolled with NGS methods.

[d] Using an RT-PCR CTA, Cohort 4 enrolled 69 patients with *MET* exon 14 skipping alterations and 1 or 2 prior lines of therapy, while Cohort 5b enrolled 28 patients with *MET* exon 14 skipping alterations who were treatment-naïve. F1CDx was used to analyze samples retrospectively from patients enrolled in the GEOMETRY-mono 1 trial.

[e] The results exclude the F1CDx invalid results. Including the F1CDx invalid results, the PPA was 92.3% (95% CI: 84.0, 97.1) and the NPA was 99.2% (95% CI: 95.7, 100.0).

[f] The concordance reported is for the combined cohorts (Cohort 4 and Cohort 5b).

[g] Cohort 4: Previously treated patients. Cohort 5b: Treatment-naïve patients. ORR as assessed by BICR according to RECIST v1.1. DOR is based on data reported in the capmatinib prescribing information.

[h] For the CTA results, 59 enrolled trial patients include 57 patients enrolled by CTA and 2 patients enrolled by F1CDx.

[i] Median DOR could not be calculated as the response rate had not yet fallen to 50%.

[j] For the CTA results, 39 enrolled trial patients include 35 patients enrolled by CTA and 4 patients enrolled by F1CDx.

[k] CTA1 = PCR-based PIK3CA hot-spot test; CTA2 = PCR-based *PIK3CA* hot-spot test. The results shown exclude the F1CDx invalid results. Including the F1CDx invalid results, the CTA1 PPA was 93.0% (95% CI: 86.6%, 96.9%) and the CTA1 NPA was 95.8% (95% CI: 91.5%, 98.3%). Including the F1CDx invalid results, the CTA2 PPA was 90.4% (95% CI: 85.7%, 93.9%) and the CTA2 NPA was 97.0% (95% CI: 93.2%, 99.0%).

[l] PFS by investigator assessment in patients with *PIK3CA* alteration-positive tumors. The HR shown here for both the F1CDx results and the CTA results is for alpelisib + fulvestrant for risk of disease progression or death compared to placebo in the *PIK3CA* alteration-positive population.

[m] The CTA results report the combined efficacy of both CTA1- and CTA2-enrolled patients.

[n] Due to the low prevalence of *FGFR2*-rearrangements, samples were selected by the F1CDx assay, and therefore prevalence-adjusted PPA, adjusted NPA, PPV, and NPV statistics with corresponding 95% 2-sided score CIs were calculated. The adjusted PPA and NPA were calculated based on PPV and NPV values using the prevalence of *FGFR2* rearrangements in the cholangiocarcinoma population from the Foundation Medicine clinical database (ie, 9.60%).

[o] ORR per central review per RECIST v1.1. Note that ORR is objective response rate for pemigatinib.

[p] ORR as determined by IRC using the RAPNO-LGG Criteria.

BICR, blinded independent central review; CI, confidence interval; CTA, clinical trial assay; DOR, duration or response; F1CDx, FoundationOne CDx; FISH, fluorescence *in situ* hybridization; HR, hazard ratio; indel, indel insertion and deletion; IRC, independent review committee; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NPA, negative percent agreement; NPV, negative predictive value; NR, not reported; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PCR, polymerase chain reaction; PPA, positive percent agreement; PPV, positive predictive value; RAPNO-LGG, Response Assessment in Pediatric Neuro-Oncology-low-grade gliomas; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcriptase-polymerase chain reaction; SNV, single nucleotide variant.

Source: FoundationOne CDx Technical Information[52]; FoundationOne CDx SSED *RET* fusions Data on File[55]; FoundationOne CDx SSED P170019S011[130]; FoundationOne CDx SSED P170019S013[131].

Non-Inferiority Concordance of FoundationOne CDx Against FDA-Approved Diagnostics

For companion diagnostic indications for which an FDA-approved companion diagnostic previously existed for that indication, non-inferiority concordance testing of FoundationOne CDx against that FDA-approved diagnostic was used for the FDA approval.[20,52] For more information regarding the non-inferiority testing methodology and results of this testing, please refer to **Clinical Validity of FoundationOne CDx via Non-Inferiority** in the Appendix.

Analytical Validity of FoundationOne CDx

The analytical validation of FoundationOne CDx included several in-depth evaluations of the assay performance including limit of detection, limit of blank, precision, and orthogonal concordance for short variants (including base substitutions and insertions/deletions), CNAs (including amplifications and homozygous deletions), genomic rearrangements, and select complex biomarkers.[20,52] The performance characteristics of FoundationOne CDx were established using DNA from a wide range of FFPE tumor tissue types. The assay validation of >30,000 test results comprise a considerable and increasing body of evidence that supports the clinical utility of FoundationOne CDx to match patients with solid tumors to targeted therapies or immunotherapies based on their tumor's genomic alterations and biomarkers. For detailed information concerning the analytical validity of FoundationOne CDx, please refer to the **FoundationOne CDx Technical Information**.

Medical Policy Coverage of FoundationOne CDx

The Centers for Medicare & Medicaid Services outlined coverage criteria for FDA-approved NGS-based *in vitro* companion diagnostic assays, like FoundationOne CDx, through a national coverage determination (NCD).[71] FoundationOne CDx is covered under the NCD when the patient has:

a. Either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and

b. not been previously tested with CGP for the same cancer genetic content; and

c. decided to seek further cancer treatment.

Over 300 million lives already have coverage for Foundation Medicine tests across all major insurers.[132] Coverage of Foundation Medicine testing continues to expand with more than 100 commercial health plans currently in-network and covering 1 or more Foundation Medicine CGP test across multiple tumor types.[133] Additionally, all national payers – Aetna, Elevance Health (Anthem), Humana, Tricare and UnitedHealthcare – cover both FoundationOne CDx and FoundationOne Liquid CDx.[133] Many regional Blue Cross Blue Shield plans also cover Foundation Medicine's CGP tests, and the Veterans Affairs National Precision Oncology Program contract provides access to Foundation Medicine's FoundationOne CDx CGP test. Further, Foundation Medicine's CGP tests are currently listed as covered tests on the laboratory fee schedules of a growing number State Medicaid programs.[133]

In addition to initial CGP testing in advanced cancer, national and regional payers are increasingly determining that repeat CGP testing (pan-tumor) at disease progression and concurrent tissue-based and plasma-based testing[e] are medically necessary for certain tumor types, such as advanced/metastatic NSCLC and breast cancer.

- Repeat CGP testing at disease progression or recurrence aids in making the best possible informed next-line therapy decision, as it allows identification of new actionable alterations and/or acquired

[e] **Note:** Concurrent testing is defined as tissue-based CGP testing and plasma-based (ie, liquid) CGP testing that are pending at the same time.

resistance alterations (eg, T790M mutation in patients with *EGFR*-mutated NSCLC and the *ESR1* gene mutation in patients with hormone receptor-positive breast cancer who have received prior endocrine-based therapy) (Table 3-6).[134-139] Several recent publications and presented data demonstrate the clinical utility of repeat expanded molecular testing at disease progression across advanced solid tumor types. Further, multiple oncology treatment guidelines support repeat expanded molecular panel testing at disease progression (refer to **Additional Supporting Evidence** for guideline recommendations regarding repeat molecular testing).[51,140-142]

Table 3-6. Repeat CGP Testing at Disease Progression: Detection of New Mutations and Acquired Resistance Mutations in Advanced Solid Tumors

Source	Patient population	Detection rates of new mutations and acquired resistance mutations
Park 2024	Prostate Cancer Precision Medicine Multi-Institutional Collaborative Effort registry of men with metastatic prostate cancer, of which 144 underwent serial NGS	▪ New actionable data were found on 11.1% (16 of 144) of second NGS tests, with 3.5% (5 of 144) of tests detecting a new *BRCA2* alteration or MSI-H ▪ A targeted therapy (PARP inhibitor or immunotherapy) was given after an actionable result on the second NGS test in 31.3% (5 of 16) of patients
Bhave 2024	CGP was used to characterize the prevalence of *ESR1*mut and alterations in the PI3K/AKT pathway at the start of successive lines of therapy in 7,450 patients with HR+/HER2- metastatic breast cancer	▪ The prevalence of *ESR1*mut clearly increased across the lines of therapy, most likely due to exposure to ET, with up to 33% harboring an *ESR1*mut detected by tissue biopsy and 39% detected by liquid biopsy at time of 3rd-line therapy (59% in liquid biopsy with TF ≥1% and 17.2% in liquid biopsy with TF <1%) ▪ Patients receiving 1st-line aromatase inhibitor + CDK4/6 inhibitor with *ESR1*mut had less favorable rwPFS and rwOS vs *ESR1* wild-type; no differences were observed for fulvestrant + CDK4/6 inhibitor
Husain 2022	23,842 liquid biopsy samples of 25 solid tumor types underwent CGP testing and for acquired resistance mutation analysis were compared with tissue biopsy specimens from patients with NSCLC, CRC, prostate, or breast cancer taken from the local or metastatic site (N = 92,932: local site, n = 55,944; metastatic site, n = 36,988)	▪ Certain genes showed enrichment of polyclonal variants only in specific cancer types with established targeted therapy paradigms, suggesting that the multiple mutations could be caused by different treatment resistance mutations arising in separate tumor subclones ▪ Polyclonality was identified in genes with well-established roles in resistance: *ALK* in NSCLC, *AR* in prostate cancer, *ESR1* in breast cancer, *BRCA2* reversions in prostate and breast cancer, and *EGFR* and *KRAS* in CRC ▪ Disease-specific analysis also identified polyclonality in more emergent resistance genes including *RB1* and *NF1* in breast cancer ▪ For some genes, enrichment of polyclonality in liquid biopsy was apparent across cancer types, presumably because of CH (*DNMT3A, TET2*, and *ASXL1*)

AKT, protein kinase B; BRCA, BReast CAncer gene; CDK4/6, cyclin dependent kinase 4/6; CGP, comprehensive genomic profiling; EGFR, epidermal growth factor receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; HR, hormone receptor; MAPK, mitogen-activated protein kinases; MSI-H, microsatellite instability-high; mut, mutated; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; TF, tumor fraction.

Source: Hussian 2022[139]; Park 2024[137]; Bhave 2024[138].

- Concurrent testing using tissue-based and liquid biopsy CGP can improve time to test results and first-line treatment and should be considered in the appropriate clinical situation.[143,144] A

retrospective review of 3,005 patients with advanced NSCLC who underwent tissue-based and/or liquid biopsy demonstrated that concurrent testing provided a significant increase in the rate of driver alteration (defined as a genomic alteration with available biomarker-based targeted therapy) detection and overall first-line targeted therapy receipt as compared to sequential, tissue-only, and liquid-only testing. Furthermore, concurrent testing also led to a statistically significant improvement in the time to first-line treatment after CGP testing as compared to sequential and tissue-only testing (Table 3-7).[144] These results indicate that tissue-based and liquid biopsy testing should be completed concurrently in order to fully capture the full spectrum of targetable driver alterations in NSCLC.

Table 3-7. Concurrent Tissue-based and Liquid Biopsy: Detection and First-line Treatment Rates by Testing Type

	Concurrent testing[a]	Sequential testing[b]	Tissue-only testing[c]	Liquid-only testing[c]
Rate of driver alteration detection	65%	59%	53%	48%
***P*-value[d]**	N/A	*P*<0.01	*P*<0.01	*P*<0.01
First-line targeted therapy receipt	24%		16-21%[e]	
***P*-value[d]**	N/A		*P*<0.01	
Time from first CGP test order to first-line treatment	24 days	28 days	30 days	23 days
***P*-value[d]**	N/A	*P*<0.01	*P*<0.01	*P*=0.20

[a] Tissue and liquid tests were classified as concurrent when both were ordered before the report date of either test.

[b] Tissue and liquid tests were classified as sequential if the first test was ordered before first-line therapy and the second was ordered 1-60 days after the first report.

[c] Tissue and liquid tests were classified as single testing if one test result reported before first-line therapy and no second test was ordered within 60 days.

[d] *P*-value is for the comparison of current testing vs sequential, tissue-only, and liquid-only testing.

[e] The range provided is for sequential testing, tissue-only testing, and liquid-only testing and the *P*-value was significant for all 3 comparisons.

CGP, comprehensive genomic profiling; N/A, not applicable.

Source: Foundation Medicine Data on File, 2025.[144]

Addition of FoundationOne RNA to FoundationOne CDx Enhances Fusion Detection

FoundationOne CDx is the only tissue CGP test FDA-approved to detect fusions with DNA alone.[145] FoundationOne RNA[f] is a laboratory-developed test that builds on the proven DNA fusion detection of FoundationOne CDx by adding a layer of fusion detection across 318 cancer-associated genes, including all gene fusions recommended in professional guidelines for therapy selection in solid tumors. An example of fusion detection in solid tumors using FoundationOne RNA is for zenocutuzumab-zbco for patients with advanced, unresectable or metastatic NSCLC or pancreatic adenocarcinoma harboring an *NRG1* gene fusion.[146,147] The large intronic regions of *NRG1* make it difficult to sequence using DNA.[148] As such, *NRG1*

[f] FoundationOne®RNA is a laboratory-developed test that was developed and its performance characteristics determined by Foundation Medicine. FoundationOne RNA has not been cleared or approved by the US FDA. FoundationOne RNA is a test for solid tumors, which utilizes RNA sequencing to interrogate 318 cancer-related genes to capture gene fusions and rearrangements. A negative result does not rule out the presence of an alteration. Genomic findings are not prescriptive or conclusive for labeled use of any specific therapeutic product.

fusion detection may be uniquely suited for RNA testing with FoundationOne RNA to more accurately detect these cancer-causing fusions and inform potential treatments.[147,148] Additionally, since sarcomas harbor a high rate of rearrangement and fusion alterations, RNA-based sequencing should be considered in addition to DNA-based sequencing.[149] Importantly, FoundationOne RNA is an easy add-on to the FoundationOne CDx order and does not require an additional sample – the same sample for FoundationOne CDx is used.[145] The results for FoundationOne CDx and FoundationOne RNA are reported in a single report for ease of healthcare provider review.

4 ECONOMIC VALUE OF FOUNDATIONONE CDX

Economic Benefits Associated With FoundationOne CDx in Advanced Cancer

The use of a biomarker-based targeted therapy approach may lead to an increase in total medical costs primarily because it achieves the ultimate goal in oncology of prolonging life and delaying disease progression.[150,151] However some recent studies have also provided evidence that CGP has clear potential to be both clinically efficient and provide cost savings in comparison to sequential single-gene or hotspot testing.[152-156] In cost-effectiveness analyses, CGP was shown to be a cost-effective strategy for molecular testing for patients with gastrointestinal stromal tumor (GIST; to match treatment of *KIT* alterations to imatinib) and also in patients with advanced/metastatic NSCLC for the selection of first-line therapy.[153,154,156,157] However, it should be noted that the value of CGP-directed therapy varies by the willingness-to-pay threshold of the decision-maker (payer). Further, a recent genomic testing cost calculator reported the cost to correctly identify clinically actionable genomic alterations was lower for NGS than sequential single-gene testing in most cancer types, and that CGP testing may lead to lower overall costs to identify clinically actionable genomic alterations compared with sequential single-gene testing in most solid tumor cancer types.[152] Although further research is needed to determine whether the main drivers of patient costs are shifting, current evidence shows that CGP can be cost-effective, and patients treated with biomarker-based targeted therapy may live longer and have fewer treatment-related complications, with a manageable increase in overall budgets.[152-156] The rapid expansion of targeted therapies and accompanying biomarkers are anticipated to further support NGS as a preferred diagnostic standard for precision oncology.[152] In addition to the opportunity to improve outcomes among these patients, enrollment into clinical trials that require biomarker-based testing may also lead to economic benefits arising from the diversion of anticancer drug costs to the study sponsor.[61,62] An analysis of the impact of CGP on clinical trial enrollment rates in patients with advanced-stage NSCLC, colorectal, breast, and prostate cancer reported clinical trial enrollment in line of therapy immediately after CGP report receipt was significantly higher compared to preceding lines of therapy ($P<0.001$).[158] This analysis supports a significant association between CGP report availability and increased clinical trial enrollment.

There are few published economic analyses of FoundationOne CDx and other CGPs that evaluate their cost-effectiveness and impact on health plans.

- In 2 identified budget impact studies analyzing the impact of increased testing using Foundation Medicine-based CGP in patients with advanced NSCLC, the budget impact to a US payer was modest (ranging from $0.005-$0.02 per member per month dependent upon the frequency of increased CGP use [8%-10% increase]), with increased duration of treatment and longer survival noted as the primary drivers of the cost increase.[56,57]
- Further, 3 additional studies assessed the economic impact of Foundation Medicine-based CGP in patients with NSCLC. In the first analysis by Pennell et al, NGS was associated with cost savings for both CMS ($1,393,678; $1,530,869; and $2,140,795 less than exclusionary, sequential testing, and hotspot panels, respectively) and commercial payers ($3,809; $127,402; and $250,842 less than exclusionary, sequential testing, and hotspot panels, respectively) using a decision analytic model.[58] Additionally, in a study by Muthusamy and colleagues that quantified the value of multigene testing in resected early-stage adenocarcinoma NSCLC patients found that the CGP can identify driver alterations and accelerate the start of first-line therapy at recurrence and was expected to reduce costs by $1,597.23 per patient relative to *EGFR* single-gene testing.[59] In a study by Yorio et al, timely initiation of CGP prior to first-line therapy was associated with increased targeted therapy use, decreased spending on ICIs among *ALK/EGFR/RET/ROS1* driver-positive patients, and longer time to therapy discontinuation.[60] CGP has clear potential to be clinically efficient and provides

cost savings in comparison to sequential single-gene testing or hotspot testing.

5 ADDITIONAL SUPPORTING EVIDENCE

Summary of Guideline Recommendations for CGP, Broad Molecular Profiling, Multigene Panels, and FDA-approved Assays

The need for biomarker-based testing has continued to increase with the evolving role of biomarker-based targeted therapies and immunotherapies. As such, various clinical practice guidelines now provide recommendations for CGP and/or broad molecular testing.

The NCCN Guidelines® have made recommendations for CGP, broad molecular profiling, multigene panels, FDA-approved assays, or language supporting relevant biomarkers in CGP tests for certain patients in the following 30 solid tumor NCCN Guidelines: ampullary adenocarcinoma, biliary tract cancers, bone cancer, breast cancer, central nervous system cancer, cervical cancer, colon cancer, esophageal and esophagogastric junction cancers, gastric cancer, gastrointestinal stromal tumors, head and neck cancers, cutaneous melanoma, neuroendocrine and adrenal tumors, NSCLC, occult primary cancer, ovarian cancer, pancreatic adenocarcinoma, peritoneal mesothelioma, pleural mesothelioma, penile cancer, prostate cancer, rectal cancer, small bowel adenocarcinoma, small cell lung cancer, soft tissue sarcoma, testicular cancer, thyroid carcinoma, uterine cancer, vaginal cancer, and vulvar cancer (Table 6-2).[21-50] Additionally, the NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.[21-50] Trials should be designed to maximize inclusiveness and broad representative enrollment. Importantly, approximately 40% of clinical trials utilize the presence of tumor genomic alterations or biomarkers for eligibility and/or stratification.[159] Please note the NCCN Guidelines update regularly; please refer to NCCN.org for the most recent version of the NCCN Guidelines.

In addition to NCCN Guidelines, other organizations have made recommendations for CGP and/or broad molecular testing.[51,63-69] For example, the American Society for Clinical Oncology (ASCO) Provisional Clinical Opinion has specifically endorsed genomic testing using multigene panel-based sequencing (defined as including at least 50 genes) whenever patients with metastatic or advanced solid tumors are eligible for a genomic biomarker-based therapy that a regulatory agency has approved.[51] Additionally, multigene panel-based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy.

Furthermore, both the NCCN and ASCO have incorporated recommendations for repeat molecular testing for certain patients with advanced cancer who have progressed on systemic therapy. The NCCN Guidelines have made recommendations regarding repeat molecular testing for certain patients with advanced cancer who have progressed on systemic therapy in the following 6 solid tumor NCCN Guidelines: colon cancer, esophageal and esophagogastric junction cancers, gastric cancer, NSCLC, prostate cancer, and rectal cancer.[22,25,26,28,32,33] The ASCO provisional clinical opinion for somatic genetic testing in patients with metastatic or advanced cancer states that repeat genomic testing may be justified in patients: 1) initially sequenced with limited NGS panels; 2) with acquired resistance on targeted therapies, especially when known acquired resistance mechanisms may affect the choice of next-line therapy; or 3) for whom identifying new targets with tumors after progression or after prolonged stable disease on targeted therapies.[51]

The NCCN Guidelines for NSCLC recommend complete genotyping for *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, ERBB2* (HER2), and *NRG1* via biopsy and/or plasma testing.[26] Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Please note the NCCN Guidelines update regularly; please refer to NCCN.org for the most recent version of the NCCN Guidelines.

Please refer to the Appendix (Table 6-2) for a comprehensive overview of guideline recommendations for CGP, broad molecular testing, multigene panels, and FDA-approved assays.

6 APPENDICES

Tables

Figures

List of Abbreviations

AKT	protein kinase B
ALK	anaplastic lymphoma kinase
AMP	Association for Molecular Pathology
ASCO	American Society for Clinical Oncology
ATM	ataxia telangiectasia mutated
AUA	American Urological Association
BICR	blinded independent central review
BRCA	breast cancer gene
BRCA-WT	breast cancer gene-wild type
CAP	College of American Pathologists
CDK	cyclin-dependent kinase
CGP	comprehensive genomic profiling
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CN	copy number
CNA	copy number alteration
CRC	colorectal cancer
CTA	clinical trial assay
ctDNA	circulating tumor DNA
CTNNB1	beta-catenin
DDR	DNA damage repair
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
EGFR	epidermal growth factor receptor
ESR1	estrogen receptor 1
F1	FoundationOne
F1CDx	FoundationOne CDx
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence *in situ* hybridization
FLT1	FMS-related tyrosine kinase 1
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRD	homologous recombination deficiency
HRDsig	homologous recombination deficiency signature
HRR	homologous recombination repair
IASLC	International Association for the Study of Lung Cancer
ICI	immune checkpoint inhibitor
IDH	isocitrate dehydrogenase
IHC	immunohistochemistry
indel	insertion and deletion
KRAS	V-Ki-ras2 Kirsten rat sarcoma
Mb	megabase
mCRPC	metastatic castration-resistant prostate cancer
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
mut	mutation
NCCN	National Comprehensive Cancer Network® (NCCN®)
NCD	national coverage determination
NGS	next-generation sequencing
NPA	negative percent agreement
NPV	negative predictive value
NR	not reported
NRAS	neuroblastoma RAS viral [v-ras] oncogene
NRG1	neuregulin 1 gene
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PCR	polymerase chain reaction
PD-1/L1	programmed death-1/ligand-1
PFS	progression-free survival
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PPA	positive percent agreement
PPV	positive predictive value
PTEN	phosphatase and tensin homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
rPFS	radiographic progression-free survival
RT-PCR	real-time polymerase chain reaction
rwOS	real-world overall survival
SNV	single nucleotide variant
SUO	Society of Urologic Oncology
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
TP53	tumor protein P53
US	United States
WT	wild-type

FoundationOne CDx Report Guide

Figure 6-1. FoundationOne CDx Report Guide

FOUNDATIONONE®CDx FOUNDATIONONE®LIQUID CDx

Guide to FoundationOne®CDx and FoundationOne®Liquid CDx Reports

Professional Services Summary Page

The Professional Services summary at the beginning of the report provides information for all of the reported biomarker and genomic findings upfront. It serves as the overview for clinicians to help ensure no findings are missed.
This section is not reviewed or approved by the FDA.

1 Report Highlights

This feature distills important genomic insights in one easy-to-find place, helping you focus on the key actionable results to inform your patient's treatment plan.

Such key findings may include targeted therapies with **potential resistance, germline implications, non-targeted therapy implications and more** depending on each patient case.

2 Therapy and Clinical Trial Implications

Therapies for each associated genomic finding are listed in the therapy table. On the left are therapies within your patient's tumor type, and on the right are those with proven clinical benefit in other tumor types. Therapy resistance based on your patient's genomic profile will also be indicated. If there are matched clinical trials, the number of trials and the corresponding report page are listed for each biomarker or genomic finding.

3 Incidental Findings Banners

Identifies potential germline or clonal hematopoiesis alterations that may warrant follow-up testing. The appearance of the germline banner indicates that an alteration has been previously reported in literature or genomic databases as a germline alteration, not that it is a germline alteration in the patient's sample.

4 Genomic Findings with no Reportable Therapeutic or Clinical Trial Options

Identifies number of trials based on your patient's unique genomic profile with page number for quick reference.

Continued ⟶

FDA-Approved Claims Page

Any FDA-approved claims for companion diagnostic (CDx) findings will appear on the FDA-approved claims page, which comes directly after the Professional Services Summary page(s).

1 FDA-Approved CDx Claims

List of FDA-approved companion diagnostics associated with your patient's findings.

A companion diagnostic provides essential information for the safe and effective use of a corresponding drug or biological product.

Professional Services Continued

You can find the remainder of the professional services section after the FDA-approved claims page. FoundationOne Liquid CDx reports also include a Variant Allele Frequency (VAF) Percentage Graph and Table with historical results for up to 5 previous tests shown. This feature is not present in FoundationOne CDx reports, where VAF values are displayed in the Biomarker and Genomic Findings section.

1 Biomarker and Genomic Findings

Following the initial pages of the report, the professional services section goes into more detail about your patient's findings, as well as the context of those findings in the patient's tumor type.

2 Therapeutic Options

Clinical evidence associated with therapeutic sensitivity or resistance for identified genomic alterations or biomarkers in the context of the patient's tumor type are discussed in this section.

Continued ⟶

Professional Services Continued

3 Clinical Trial Information

Detailed information about the clinical trials your patient has been matched to, ranked for the patient based on location and trial phase.

Report Interpretation Assistance

For additional help with report interpretation, please submit a question to our Medical team at https://foundationmedicine.com/contact Alternatively, questions can be submitted through "Ask An Expert" feature on your provider portal or by contacting Client Services at (888) 988-3639 or client.services@foundationmedicine.com.

To learn more about our FDA-approved portfolio, go to *foundationmedicine.com/portfolio*

FoundationOne®CDx and FoundationOne®Liquid CDx are for prescription use only and are FDA-approved qualitative next-generation sequencing based in vitro diagnostic tests for advanced cancer patients with solid tumors. FoundationOne CDx utilizes FFPE tissue and analyzes 324 genes as well as genomic signatures. FoundationOne Liquid CDx analyzes 324 genes utilizing circulating cell-free DNA and is FDA-approved to report short variants in 311 genes, rearrangements in 8 genes and copy number alterations in 3 genes. The tests are companion diagnostics to identify patients who may benefit from treatment with specific therapies in accordance with the approved therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the tests does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Some patients may require a biopsy which may pose a risk. When considering eligibility for ROZLYTREK® based on the detection of NTRK1/2/3 and ROS1 fusions, or for TEPMETKO® based on the detection of MET SNVs and indels that lead to MET exon 14 skipping, testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing. Patients who are tested with FoundationOne Liquid CDx and are negative for companion diagnostic mutations should be reflexed to tumor tissue testing and mutation status confirmed using an FDA-approved tumor tissue test, if feasible. For the complete labels, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com and www.F1LCDxLabel.com.

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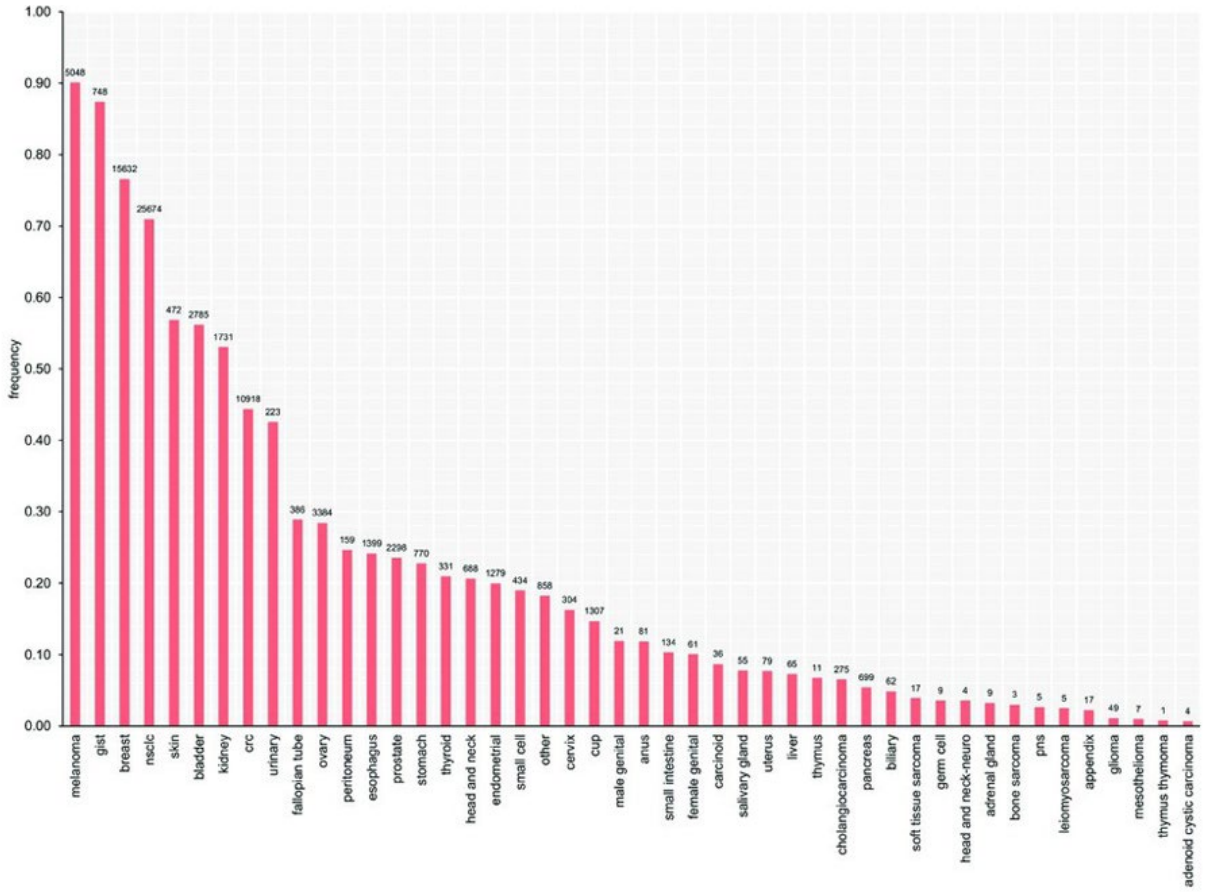
Clinical Decision Insights Provided by the CGP Approach of FoundationOne CDx

The frequency of FoundationOne CDx reports with potential therapeutic implications by disease group and definition of actionability is shown below: therapy options available within the tumor type indicated (Figure 6-2); therapy options available in tumor types other than the assigned indication (Figure 6-3); disease groups with clinical trial options (Figure 6-4); and disease groups with FDA-approved companion/complementary diagnostics within the tumor type indicated (Figure 6-5).[20] Note that all disease groups contained at least 100 specimens.

Figure 6-2. Frequency of FoundationOne CDx Reports with Therapy Options Available Within the Tumor Type

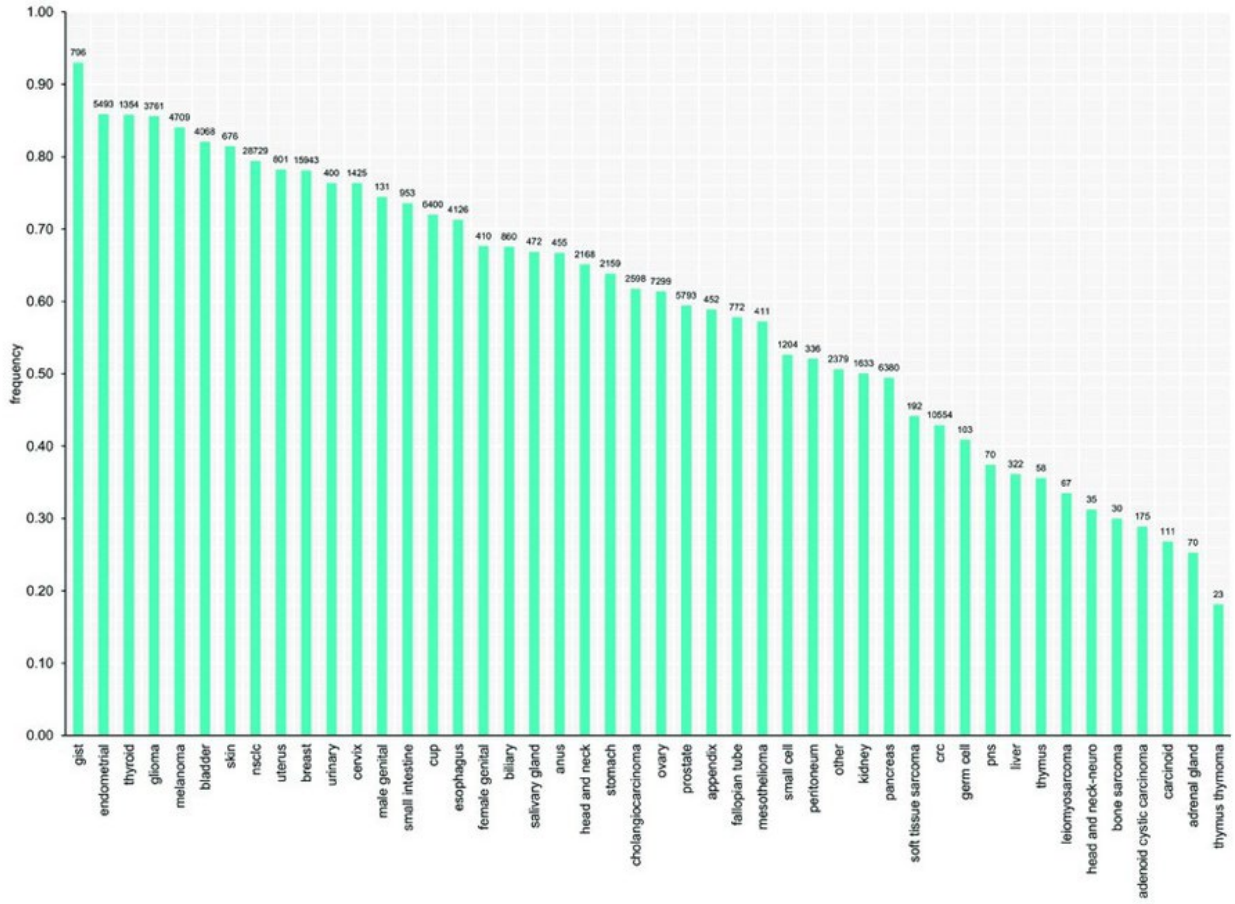


Values indicate counts per disease group.

CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; PNS, peripheral nervous system.

Source: Milbury 2022.[20]

Figure 6-3. Frequency of FoundationOne CDx Reports with Therapy Options Available in Tumor Types Other Than the Assigned Indication

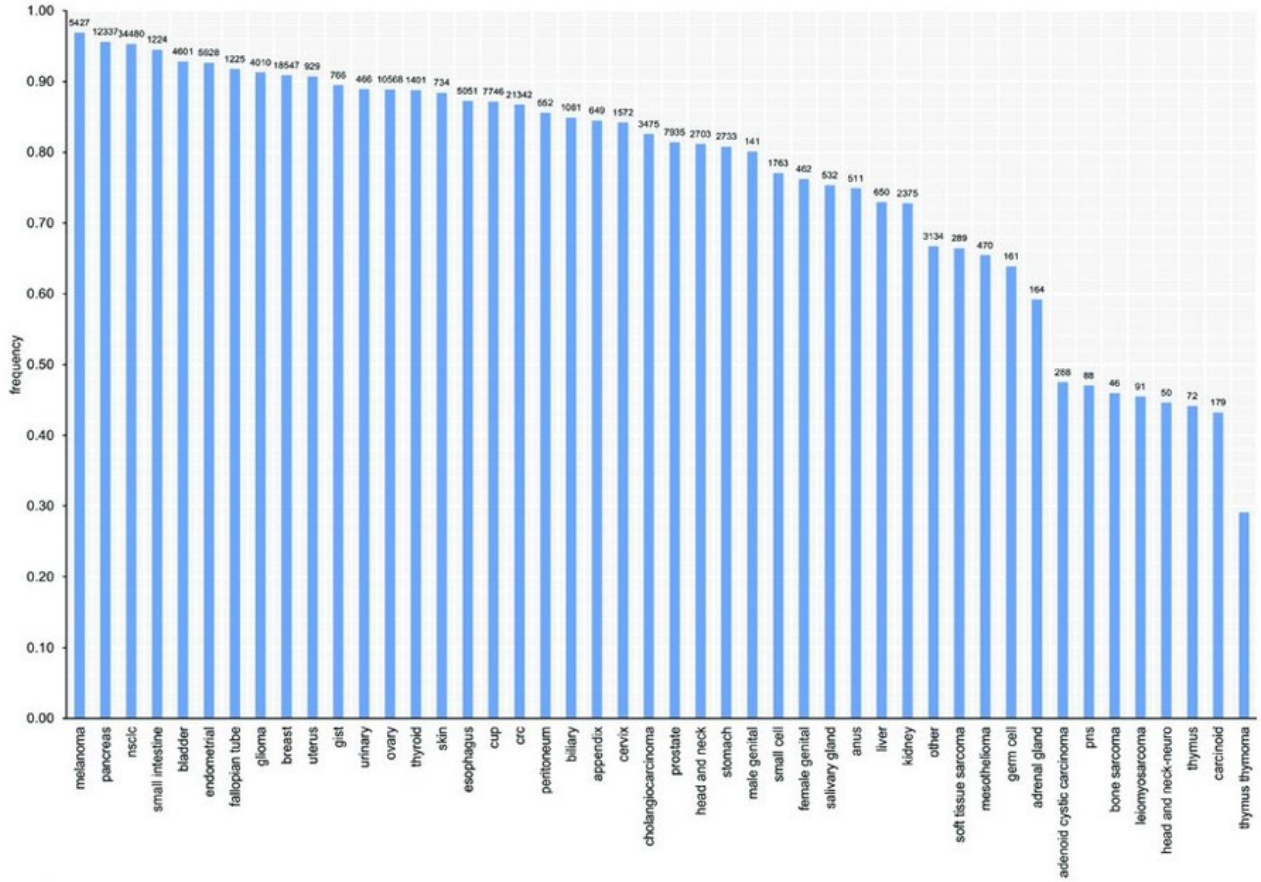


Values indicate counts per disease group.

CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; PNS, peripheral nervous system.

Source: Milbury 2022.[20]

Figure 6-4. Frequency of FoundationOne CDx Reports with Therapy Options Available in Disease Groups With Clinical Trial Options

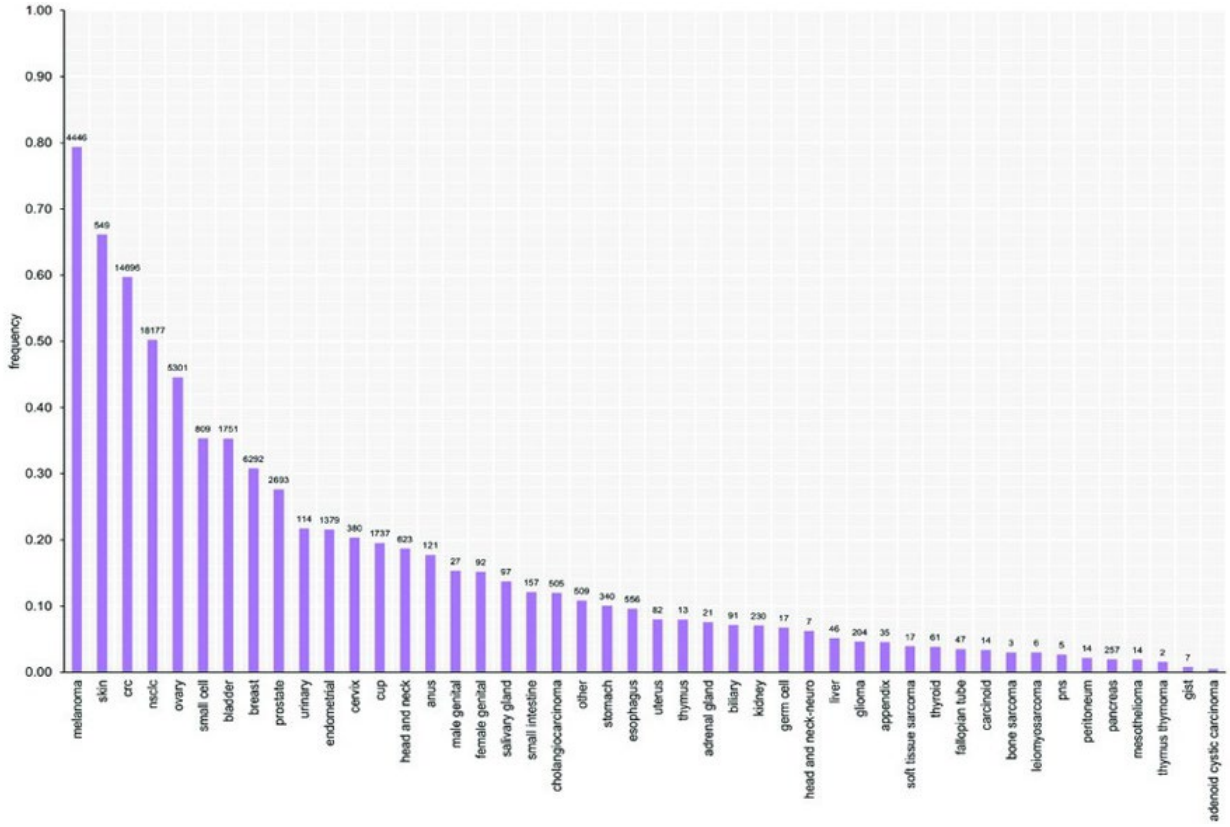


Values indicate counts per disease group.

CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; PNS, peripheral nervous system.

Source: Milbury 2022.[20]

Figure 6-5. Frequency of FoundationOne CDx Reports with Therapy Options Available in Disease Groups with FDA-Approved Companion/Complementary Diagnostics Within the Tumor Type Indicated



Values indicate counts per disease group.

CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; PNS, peripheral nervous system.

Source: Milbury 2022.[20]

Clinical Validity of FoundationOne CDx via Non-Inferiority

Using non-inferiority, the clinical validity of the FoundationOne CDx assay as a companion diagnostic was evaluated for identifying patients with specific cancer indications for eligibility of treatment with targeted therapies for defined biomarkers.[20,52] Concordance between FoundationOne CDx and a validated orthogonal comparator assay were assessed through the evaluation of negative percent agreement (NPA) and positive percent agreement (PPA). The orthogonal concordance assay was considered the gold standard within each non-inferiority analysis. The clinical validation performed via the demonstration of non-inferiority for companion diagnostic indications are summarized in Table 6-1.

Table 6-1. Clinical Validity of FoundationOne CDx via Non-Inferiority for Companion Diagnostic Claims

Disease Indication	Biomarker	Therapy	PPA, % (95% CI)	NPA, % (95% CI)	Comparator Assay
NSCLC	*EGFR* exon 19 deletions and exon 21 L858R	EGFR TKI approved by FDA[160-162]	98.1 (93.5, 99.8)	99.4 (96.4, 100.0)	cobas® EGFR Mutation Test v2 (Roche Molecular Systems)

NSCLC	*EGFR* T790M	Osimertinib[161]	98.9 (93.8, 100.0)	86.1 (78.1, 92.0)	cobas® *EGFR* mutation Test v2 (Roche Molecular Systems)
NSCLC	*ALK* rearrangements[a]	Alectinib[163], crizotinib[164], ceritinib[165], brigatinib[166]	92.9 (85.1, 97.3)	100 (95.2, 100.0)	Ventana ALK (D5F3) CDx Assay Vysis *ALK* Break Apart FISH Probe Kit
Breast cancer	*ERBB2* (HER2) amplification	Trastuzumab[167], ado-trastuzumab emtansine[168], pertuzumab[169]	89.4 (82.2, 94.4)	98.4 (95.3, 99.7)	HER2 FISH PharmDx® Kit (Dako Denmark, A/S)
CRC	*KRAS* wild-type[b]	Cetuximab[170]	100 (97.9, 100.0)	100 (97.6, 100.0)	therascreen® KRAS RGQ PCR Kit (QIAGEN)
	KRAS and *NRAS*-wild type[c]	Panitumumab[171]	100 (96.26, 100)	98.96 (96.88, 100)	Praxis Extended RAS Panel
Melanoma	*BRAF* V600	Trametinib[172] or BRAF/MEK inhibitor combinations approved by FDA (*BRAF* V600E and V600K)[173]	99.4 (166/167)	89.6 (121/135)[d]	cobas® 4800 BRAF V600 mutation test (Roche Molecular Systems, Inc)
	BRAF V600E[e]	BRAF inhibitors approved by FDA[173-176]	99.3 (149/150)	99.2 (121/122)	
Melanoma	*BRAF* V600 dinucleotide	Atezolizumab[177] + cobimetinib[178] + vemurafenib[176] (*BRAF* V600 mutation-positive)[173]	96.3 (26/27)	100 (24/24)	THxID® BRAF Kit (bioMérieux)

[a] Samples evaluated were from a phase 3, multicenter, open-label study (NCT02075840) that evaluated the efficacy and safety of alectinib compared with crizotinib in treatment-naïve cancer patients with *ALK* rearrangements.

[b] F1CDx is an approved companion diagnostic for *KRAS* WT (absence of mutations in codon 12 and 13) for cetuximab

[c] F1CDx is an approved companion diagnostic for *KRAS* WT (absence of mutations in exons 2, 3, and 4) and *NRAS* WT (absence of mutations in exons 2, 3, and 4) for panitumumab.

[d] The reported difference in NPA values for *BRAF* V600 and *BRAF* V600E is likely attributed to known sensitivity differences in the cobas *BRAF* mutation test, which has lower sensitivity for detection of dinucleotide V600 alterations than for the single nucleotide V600E c.1799T>A alteration, especially for samples in which F1CDx detected the nucleotides to be of lower than 40% mutational allele frequency, leading to low NPA values.

[e] *BRAF* V600E is also a companion diagnostic biomarker approved for dabrafenib in combination with trametinib for NSCLC.

CI, confidence interval; CRC, colorectal cancer; F1CDx, FoundationOne CDx; FDA, Food and Drug Administration; FISH, fluorescence *in situ* hybridization; NPA, negative percent agreement; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PPA, positive percent agreement; TKI, tyrosine kinase inhibitor; WT, wild type.

Source: FoundationOne CDx Technical Information.[52]

Details of Guideline Recommendations for CGP, Broad Molecular Profiling, Multigene Panels, and FDA-approved Assays

Table 6-2 provides a comprehensive overview of guideline recommendations for CGP, broad molecular testing, multigene panels, and FDA-approved assays. Please note the NCCN Guidelines update regularly; please refer to NCCN.org for the most recent version of the NCCN Guidelines.

Table 6-2. Guideline Recommendations for CGP (Including Language Supporting Relevant Biomarkers in CGP Tests), Broad Molecular Profiling, Multigene Panels, and FDA-Approved Assays

Guideline	Description of recommendation
NCCN Guidelines[a]	
Ampullary adenocarcinoma V.2.2025[42]	▪ Tumor/somatic molecular profiling is recommended for patients with locally advanced/ metastatic disease who are candidates for anticancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to, fusions (*ALK, NRG1, NTRK, ROS1, FGFR2*, and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), MSI, dMMR, or TMB via an FDA-approved and/or validated NGS-based assay (AMP-3, 6, 7, footnote h)
Biliary tract cancers V.1.2025[41]	▪ Comprehensive molecular profiling is recommended for patients with unresectable or metastatic biliary tract cancers (gallbladder cancer, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma) who are candidates for systemic therapy (BIL-B, 1 of 8)
Bone cancer V.2.2025[43]	▪ Consider CGP with a validated and/or FDA-approved assay to determine targeted therapy opportunities for patients with metastatic chondrosarcoma, recurrent chordoma, metastatic Ewing sarcoma, and metastatic osteosarcoma (CHON-4, footnote k, CHOR-3, footnote f, EW-3, footnote o, OSTEO-3, footnote l) ▪ Consider CGP or other fusion panel for Ewing sarcoma to identify translocations if pathologic workup of targeted polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or cytogenetics is negative (EW-1, footnote d) ▪ Consider CGP with a validated and/or FDA-approved assay to determine targeted therapy opportunities. TMB-high (TMB-H) for patients with unresectable or metastatic tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options. Not for Giant Cell Tumor of Bone. (BONE-B, 1 of 6, footnote b)
Breast cancer V.4.2025[24]	▪ Stage IV (M1) or recurrent: Comprehensive germline and somatic profiling to identify candidates for targeted therapies (BINV-18) ▪ NGS is a testing option for *PIK3CA* activating mutations, *AKT1* activating mutations, or *PTEN* alterations; *ESR1* mutation; *NTRK* fusion; MSI-H/dMMR; TMB-H (≥10 mut/Mb); *RET*-fusion. Tissue biopsy is more sensitive than ctDNA (liquid biopsy) at detecting homozygous copy loss of *PTEN* or TMB-H (BINV-Q, 6 of 15, BINV-Q, 7 of 15, footnote dd)
Central nervous system cancers V.1.2025[31]	▪ NGS is now the preferred approach for pathologic workup of CNS tumors, as it screens for multiple diagnostic and prognostic mutations in one test. NGS results from tumor tissue cannot prove the existence of a heritable cancer predisposition syndrome (eg, Lynch syndrome, Li-Fraumeni syndrome). If such a syndrome is suspected based on clinical and family history, genetic counseling and testing of "germline" DNA from the bloodstream is required (BRAIN-E, 2 of 9)
Cervical cancer V.4.2025[39]	▪ Persistent or recurrent disease: Consider comprehensive molecular profiling as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory (CERV-10) ▪ Patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma: In the setting of metastatic or recurrent disease, consider comprehensive molecular profiling as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory including at least HER2, MMR/MSI, TMB testing, *NTRK*, and *RET* for predicting rare pan-tumor targeted therapy opportunities (CERV-A, 1 of 7)
Colon cancer V.3.2025[22]	▪ Suspected or proven metastatic adenocarcinoma: Molecular testing including *RAS* and *BRAF* mutations, HER2 amplifications, MMR or MSI status (if not previously done). Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*. Tissue- or blood-based NGS panels have the ability to pick up rare and actionable mutations and fusions (COL-2, footnote k) ▪ Repeat molecular testing should not be performed after standard cytotoxic chemotherapy as significant molecular changes are rarely observed. Changes in the molecular profile can more commonly be seen after targeted therapies and repeat testing may be considered to

Guideline	Description of recommendation
	guide future targeted therapy decisions (COL-B, 4 of 10) ▪ NGS is a testing option for *KRAS*, *NRAS*, *BRAF*, MSI, HER2, *NTRK* fusions, *POLE/POLD1*, *RET* fusions, Testing for MSI may be accomplished by PCR or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF* (COL-B, 4-6 of 10)
Esophageal and esophagogastric junction cancers V.3.2025[32]	▪ NGS should be considered in the workup of patients with esophageal and esophagogastric junction cancers (ESOPH-1) ▪ Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients (ESOPH-1) ▪ At present, several targeted therapeutic agents have been approved by the FDA for use in esophageal and esophagogastric junction cancers. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing. The list of targeted biomarkers includes: HER2 overexpression/amplification, PD-L1 expression, MSI, CLDN18.2, TMB, *NTRK* gene fusion, *RET* gene fusion, *BRAF* V600E mutation Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic esophageal and esophagogastric junction adenocarcinoma (ESOPH-B, 3, 6 of 7)
Gastric cancer V.2.2025[33]	▪ NGS should be considered in the workup of patients with gastric cancer (GAST-1) ▪ Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients (GAST-1) ▪ At present, several targeted therapeutic agents have been approved by the FDA for use in gastric cancer. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing. The list of targeted biomarkers includes: HER2 overexpression/amplification, PD-L1 expression, MSI, CLDN18.2, TMB, *NTRK* gene fusion, *RET* gene fusion, *BRAF* V600E mutation Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic gastric cancer (GAST-B, 3, 6 of 7)
Gastrointestinal stromal tumors V.1.2025[21]	▪ Patients with resectable GIST with significant morbidity or unresectable primary disease: Mutational testing (NGS) + SDHB IHC at primary presentation. Mutational analysis may predict response to therapy with TKIs. Tumors with SDH deficiency or *NF1* mutations that lack mutations in *KIT/PDGFRA* may be considered for observation as most, but not all, have more indolent behavior (GIST-2, footnote e) ▪ All GIST lacking a *KIT* or *PDGFRA* mutation should be tested for SDH deficiency and alternative driver mutations using NGS. Alternative driver mutations (eg, *BRAF, NF1, NTRK*, and *FGFR* fusions) may be detected by NGS to identify potential targeted therapies (GIST-B)
Head and neck cancers V.4.2025[37]	▪ For recurrent or persistent very advanced head and neck cancer: Consider NGS genomic profiling for biomarker identification (ADV-3, 4, footnote f) ▪ Systemic therapy for non-nasopharyngeal cancers: NGS genomic profiling, including testing for at least combined positive score (CPS), MSI, dMMR, TMB, HER2, and *FGFR* may be considered to guide patient treatment options, including clinical trials (SYST-A, 1 of 5). Systemic therapy for nasopharyngeal cancers: Use NGS profiling and other appropriate biomarker testing to test for at least CPS and TMB prior to treatment (category 2B) (NASO-B, 1 of 3) ▪ Use NGS profiling and other appropriate biomarker testing to check status of at least the following: androgen receptor (AR), HER2, *NTRK, FGFR, BRAF, RET*, microsatellite instability (MSI), mismatch repair deficiency (dMMR), tumor mutational burden (TMB), and programmed death ligand 1 (PD-L1) prior to treatment (category 2B) (SALI-4, footnote p)
Melanoma: Cutaneous V.2.2025[23]	▪ Stage III melanoma: *BRAF* mutation testing is recommended for patients with stage III melanoma for whom future BRAF-directed therapy may be an option. Consider broader genomic profiling if the test results might guide further treatment decisions or eligibility for

Guideline	Description of recommendation
	participation in a clinical trial (ME-5, ME-6, ME-7, footnote jj) ▪ For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, *KIT*, *BRAF* non-V600) (ME-C, 4 of 8)
Mesothelioma: Peritoneal V.2.2025[29]	▪ Broad molecular tumor profiling is recommended with the goal of identifying rare driver alterations (eg, *NTRK* or *ALK*) for which effective drugs may be available or to appropriately counsel patients regarding the availability of clinical trials (PEM-D, 1 of 3, footnote b)
Mesothelioma: Pleural V.2.2025[30]	▪ Broad molecular tumor profiling is recommended with the goal of identifying rare driver alterations (eg, *NTRK* or *ALK*) for which effective drugs may be available or to appropriately counsel patients regarding the availability of clinical trials (PM-C, 1 of 3)
Neuroendocrine and adrenal tumors V.2.2025[49]	▪ Consider molecular profiling of tumor tissue for well-differentiated grade 3 neuroendocrine tumors. Tumor/somatic molecular profiling should be considered for patients with locoregional unresectable/metastatic disease who are candidates for anticancer therapy to identify actionable alterations (WDG3-1, footnote f) ▪ Consider molecular profiling of tumor tissue for extrapulmonary poorly differentiated: neuroendocrine carcinoma, large or small cell carcinoma, and mixed neuroendocrine-non-neuroendocrine neoplasm. Tumor/somatic molecular profiling should be considered for patients with locoregional unresectable/metastatic disease who are candidates for anticancer therapy to identify actionable alterations. Consider specifically testing for potentially actionable somatic findings including, but not limited to, *NTRK* fusions, *RET* fusions, *BRAF* V600E mutations, MSI-H, MMR deficiency, and TMB-H (PDNEC-1A, footnote g)
Non-small cell lung cancer V.5.2025[26]	▪ The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in the NCCN Guidelines for NSCLC in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers. Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC (NSCL-19, footnote pp) ▪ At progression, the panel recommends considering plasma and/or tissue-based testing using broad molecular profiling for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral (NSCL-23, 28, 29, 31, footnote fff) ▪ Advanced or metastatic NSCLC: Complete genotyping for *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET*, *ERBB2* (HER2), and *NRG1* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NSCL-19, 20, footnote mm)
Occult primary V.2.2025[36]	▪ Suspected metastatic malignancy: TMB determination by a validated and/or FDA-approved assay (category 2B), MSI/MMR testing. Molecular profiling of tumor tissue using NGS (or other technique to identify gene fusions) can be considered after an initial determination of histology has been made. Consider tumor/somatic molecular profiling for patients who are candidates for anti-cancer therapy to identify uncommon mutations (ie, *RET* fusions) (OCC-1, OCC-1A, footnote h)

Guideline	Description of recommendation
Ovarian cancer/fallopian tube cancer/primary peritoneal cancer V.2.2025[27]	▪ Recurrent disease: Tumor molecular testing if not previously done. Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF,* FRα (*FOLR1*), *RET*, and *NTRK* if prior testing did not include these markers. More comprehensive testing may be particularly important in less common ovarian cancers with limited approved therapeutic options (OV-6-8, footnote dd, LCOC-7, footnote o, OV-B, 1 of 3)
Pancreatic adenocarcinoma V.2.2025[34]	▪ Locally advanced or metastatic disease at diagnosis, recurrence after resection, or disease progression: Molecular profiling of tumor tissue is recommended. Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anticancer therapy to identify actionable and/or emerging alterations. These alterations include, but are not limited to, fusions (*ALK, NRG1, NTRK, ROS1, FGFR2*, and *RET*), mutations (*BRAF, BRCA1/2, KRAS*, and *PALB2*), amplifications (*HER2*), MSI, dMMR, or TMB using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS (PANC-1A, 5, 6A, 9A-11, footnote j)
Penile cancer V.2.2025[47]	▪ Metastatic penile cancer: Consider molecular/genomic testing in a CLIA-approved laboratory to include broad molecular profiling, which would identify rare and actionable mutations and fusions (PN-10)
Prostate cancer V.2.2025[25]	▪ At present, tumor molecular and biomarker analysis is recommended for patients with metastatic disease for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility (PROS-C, 2 of 2) ▪ Multigene tumor testing for alterations in HRR genes, including but not limited to *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12* is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer (PROS-C, 2 of 2) ▪ Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at the time of cancer progression for treatment decision-making (PROS-C, 2 of 2)
Rectal cancer V.2.2025[28]	▪ Rectal cancer with suspected or proven distant metastases: Determination of tumor gene status for *RAS* and *BRAF* mutations; HER2 amplifications; MMR or MSI status (if not previously done). Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*. Tissue- or blood-based NGS panels have the ability to pick up rare and actionable mutations and fusions (REC-2, footnote l) ▪ NGS is a testing option for *KRAS*, *NRAS*, *BRAF*, MSI, HER2, *NTRK* fusions, *POLE/POLD1*, *RET* fusions, Testing for MSI may be accomplished by PCR or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF* (REC-B, 5-7 of 10) ▪ Repeat molecular testing should not be performed after standard cytotoxic chemotherapy as significant molecular changes are rarely observed. Changes in the molecular profile can more commonly be seen after targeted therapies and repeat testing may be considered to guide future targeted therapy decisions (REC-B, 5 of 10)
Small bowel adenocarcinoma V.3.2025[48]	▪ Metastatic adenocarcinoma: Molecular testing, including *KRAS* mutations and *BRAF* V600E mutations; HER2 amplifications; MMR or MSI status (if not previously done). Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/ POLD1*, *RET*, *NTRK*, and TMB (SBA-5)

Guideline	Description of recommendation
Small cell lung cancer V.4.2025[44]	▪ Diagnosis of SCLC or combined SCLC/NSCLC on biopsy or cytology of primary or metastatic site: Consider molecular profiling. Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management (SCL-1, footnote g)
Soft tissue sarcoma V.1.2025[50]	▪ Molecular genetic testing has emerged as an ancillary testing approach since many sarcoma types harbor characteristic genetic aberrations, including single base pair substitutions, deletions and amplifications, and translocations. Molecular testing utilizes multiple techniques such as FISH, PCR-based methods, or NGS-based methods (including DNA and RNA sequencing). The selection of the "best" technique depends on the individual tumor and clinical needs. NGS may be beneficial; the timing of when to perform NGS and for which patients must be evaluated individually. NGS findings can: determine patient eligibility for clinical trials, identify actionable mutations that may not have been targeted previously, and select patients who may benefit from immunotherapy. Thus, NGS may be appropriate for patients who may qualify for and who are interested in enrolling in a clinical trial or for patients with disease that is refractory or has progressed on standard therapies. NGS also may be helpful in certain histologies where NGS is likely to provide clinically actionable information. NGS should not replace expert pathology review, as NGS only rarely results in a diagnosis change following expert review. Technically successful NGS on bone biopsies requires use of decalcification agents, such as ethylenediaminetetraacetic acid (EDTA), that do not interfere with genomic testing. Each type of molecular testing is associated with test limitations and sources of false-negative results; if negative results are received when a molecular aberration clinically was expected, discussion with the testing lab is highly recommended as testing by another technique may be indicated (SARC-C, 1 of 4)
Testicular cancer V.2.2025[40]	▪ TMB-H (≥10 mut/Mb) tumors, as determined by a validated and/or FDA-approved CGP assay to determine third-line therapy for metastatic germ cell tumors (TEST-G, 1 of 3, footnote c)
Thyroid carcinoma V.1.2025[38]	▪ For advanced, progressive, or threatening disease (papillary, follicular, oncocytic carcinoma), somatic testing to identify actionable mutations (including *ALK, NTRK, BRAF*, and *RET* gene fusions), dMMR, MSI, and TMB (PAP-10, FOLL-9, ONC-9) ▪ Recurrent or persistent locoregional disease, asymptomatic distant metastatic disease, symptomatic distant metastatic disease, or at progression medullary carcinoma: Somatic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown (MEDU-6-7, footnote x) ▪ Anaplastic thyroid carcinoma: Molecular testing should include *BRAF, NTRK, ALK, RET,* MSI, dMMR, and tumor mutational burden. *BRAF* IHC testing is recommended due to faster turnaround compared to genetic testing (ANAP-1, footnote b)
Uterine neoplasms V.3.2025[35]	▪ Endometrial carcinoma: Comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, in the initial evaluation of uterine neoplasms (ENDO-A, 2 of 4) ▪ Uterine sarcoma: CGP in setting of metastatic disease as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, is informative for predicting rare pan-tumor targeted therapy opportunities and should include at least *NTRK*, MSI, *RET*-fusion, and TMB (UTSARC-A, 1 of 8)
Vaginal cancer V.5.2025[46]	▪ Consider comprehensive molecular profiling by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory including at least MSI, TMB testing, *NTRK*, and *RET* for predicting rare pan-tumor targeted therapy opportunities (VAG-A, 2 of 2)
Vulvar cancer V.1.2025[45]	▪ Consider comprehensive molecular profiling by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory including at least MMR/MSI, TMB, and *NTRK* testing for predicting rare pan-tumor targeted therapy opportunities (VULVA-A, 2 of 4)
ASCO guidelines	

Guideline	Description of recommendation
Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion[51]	▪ For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker-linked therapy that a regulatory agency has approved (strength of recommendation: moderate) ▪ Multigene panel-based genomic testing (defined as an NGS test that sequences a defined list of genes with at least 50 genes in total) should be used whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy (strength of recommendation: strong) ▪ dMMR status should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess MSI. Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong) ▪ When TMB may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong) ▪ Repeat genomic testing may be justified for patients initially sequenced with limited NGS panels[b] ▪ Repeat genomic testing may be performed for patients with acquired resistance on targeted therapies, especially when known acquired resistance mechanisms may affect the choice of next-line therapy[b] ▪ Repeat testing may also assist in identifying new targets in tumors after progression or after prolonged stable disease on targeted therapies[b]
MMR and MSI testing for immune checkpoint inhibitor therapy: ASCO endorsement of CAP Guideline[66]	▪ The ASCO Endorsement Panel endorses Recommendations 1, 2, and 3 as written as the questions asked by the guideline. However, other potentially important information can be gained via NGS testing beyond MSI detection (eg, detection of HER2 amplification [particularly in gastrointestinal tract carcinomas], TMB-H because of non-MSI mechanisms, fusion detection, and, in some laboratories, paired germline-somatic analysis). These potential uses should be considered in decision-making. This can be important when the amount of available tissue limits the ability to perform multiple sequential tests. IHC and NGS are likely to prove most effective when used as complementary tools, particularly when one or the other generates equivocal results, and one should not necessarily be used to the exclusion of another. Importantly, this testing should not be perceived as duplicative or unnecessary (eg, by payers) when a reasonable need for both types of testing exists
Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update[64,140,141]	▪ Patients with locally recurrent unresectable or metastatic hormone receptor-positive and HER2-negative breast cancer who are candidates for a treatment regimen that includes a PI3K inhibitor and a hormonal therapy should undergo testing for PIK3CA mutations using NGS of tumor tissue or ctDNA in plasma to determine their eligibility for treatment with the PI3K inhibitor alpelisib plus fulvestrant ▪ For patients with hormone receptor-positive, HER2-negative metastatic breast cancer, the Expert Panel recommends multiple lines of endocrine treatment (ET), frequently paired with targeted agents, with choices informed by prior treatments and by routine testing for activating mutations in *ESR1, PIK3CA,* or *AKT1* or inactivation of *PTEN*. Panelists recommend inclusion of CDK4/6 inhibitor therapy with ET in the first line. Second and third-line therapies reflect targeted options based on tumor genomics (Evidence quality: High; Strength of recommendation: Strong) ▪ For patients with hormone receptor-positive, HER2-negative metastatic breast cancer, tumor genomic testing includes sequencing for targetable mutations, accomplished through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. In addition to selecting patients whose tumors have increased PIK3CA or AKT1 activity because of the presence of activating mutations, it is also important to identify those whose tumors have inactivation of PTEN protein. *PTEN* inactivation can be identified based on the presence of premature stop codons, frameshift alterations, splice site mutations, *PTEN* homozygous deletion, PTEN rearrangements that disrupt protein function, or specific missense mutations (C124R,

Guideline	Description of recommendation
	C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R, and R173C) on next-generation sequencing ▪ For patients with hormone receptor-positive, HER2-negative metastatic breast cancer, the Expert Panel recommends routine testing for emergence of *ESR1* mutations at recurrence or progression on ET (given with or without CDK4/6 inhibitor). Testing with a CLIA–certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor. Blood-based ctDNA is preferred owing to greater sensitivity. If not performed earlier, testing for *PIK3CA* mutations should also be performed to guide further therapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)
Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted TKIs: ASCO endorsement of the CAP/IASLC/AMP clinical practice guideline update[68]	▪ Multiplexed genetic sequencing panels are preferred, where available, over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK, BRAF, and ROS*1[c]
Management of stage III NSCLC: ASCO rapid recommendation update[179]	▪ Molecular testing by appropriately sensitive methods (including but not mandatorily NGS) for detection of oncogenic driver alterations such as sensitizing *EGFR* mutations wherein the preferred adjuvant (for surgically resected stage IB-III NSCLC) and consolidation (for unresectable stage III NSCLC) treatment is now an EGFR-targeted drug (osimertinib) rather than a PD-(L)1 immune check point inhibitor for which the most commonly tested biomarker is PD-L1 expression by immunochemistry
Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline summary[69]	▪ All women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1, BRCA2*, and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be performed in women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong) ▪ Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for dMMR (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate) ▪ Women with epithelial ovarian cancer who have not had germline testing at the time of diagnosis should be offered germline genetic testing as soon as feasibly possible, as outlined above. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be offered. Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for time of recurrence for women who have completed upfront therapy and are currently in observation, as the presence of these mutations qualifies the patient for FDA-approved treatments (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)
Germline and somatic genomic testing for metastatic prostate cancer: ASCO guideline[142]	▪ All patients with metastatic prostate cancer should undergo germline genetic testing with next-generation sequencing technologies. (Evidence quality: High; Strength of recommendation: Strong) ▪ The panel recommends that sequential somatic testing may be offered when there has been a meaningful change in the patient's status or treatment plan, especially in cases where prior tests were negative or uninformative (eg, insufficient or low tumor content). (Evidence quality: Moderate; Strength of recommendation: Weak) ▪ Archival tissue samples are preferred in initial testing. ctDNA is preferred when there is no accessible metastatic site to biopsy or for sequential testing. In the setting of minimal disease burden associated with low ctDNA fraction, metastatic biopsy is preferred. (Evidence quality: Low; Strength of recommendation: Weak)
AUA/SUO guidelines	

Guideline	Description of recommendation
Advanced prostate cancer[65]	▪ In patients with mHSPC, clinicians should offer germline testing and consider somatic testing and genetic counseling (Clinical Principle) ▪ In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, MSI status, TMB, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct potential targeted therapies (Clinical Principle)
CAP/IASLC/AMP guidelines	
Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted TKIs[67]	▪ Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK*, and *ROS1*
CAP/AMP guidelines	
MMR and MSI testing for immune checkpoint inhibitor therapy[63]	▪ For patients with CRC being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR for the detection of DNA MMR defects. Although MMR-IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA MMR defects (Strong Recommendation). Note: MSI by NGS assay must be validated against MMR-IHC or MSI by PCR and must show equivalency ▪ For patients with gastroesophageal and small bowel cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR over MSI by NGS for the detection of DNA MMR defects (Strong Recommendation). Note: This recommendation does not include esophageal squamous cell carcinoma ▪ For patients with endometrial cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA MMR defects (Strong Recommendation) ▪ For patients with cancer types other than CRC, GEA, small bowel, and endometrial being considered for immune checkpoint inhibitor therapy, pathologists should test for DNA MMR, although the optimal approach for the detection of MMR defects has not been established (Conditional Recommendation). Note: Assays must be adequately validated for the specific cancer type being tested with careful consideration of performance characteristics of MMR-IHC and MSI by NGS or PCR for the detection of DNA MMR defects

[a] The NCCN Guidelines recommendations are updated frequently and without notice. NCCN Guidelines content in this dossier is current as of 6/20/2025. To access the most recent version of the NCCN Guidelines, please refer to nccn.org.

[b] The ASCO Provisional Clinical Opinion for somatic genomic testing in patients with advanced or metastatic cancer provides insight into repeat testing for patients with advanced or metastatic cancer; these are not recommendations and therefore do not have strength of recommendations provided.

[c] ASCO Endorsed Recommendation with modifications or qualifications in ***bold italics***.

ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; AUA, American Urological Association; BRCA, breast cancer gene; CAP, College of American Pathologists; CGP, comprehensive genomic profiling; CLIA, Clinical Laboratory Improvement Amendments; CRC, colorectal cancer; ctDNA, circulating tumor DNA: dMMR, mismatch repair-deficient; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; KRAS, V-Ki-ras2 Kirsten rat sarcoma; Mb, megabase; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MMR, mismatch repair; mut, mutation; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NRG1, neuregulin 1 gene; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PCR, polymerase chain reaction; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; SUO, Society of Urologic Oncology; TMB, tumor mutational burden; TMB-H, tumor mutational burden-high.

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