Physician Insert: Guardant360® CDx

For *In Vitro* Diagnostic Use

Genetic Companion Diagnostic Testing for Therapy Selection in Cancer Patients

For the most current information on the association of the biomarker and therapeutic outcomes, refer to the therapeutic labels available at Drugs@FDA on the FDA website.

Guardant360 CDx Intended Use

Guardant360® CDx is a qualitative next generation sequencing-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes. Guardant360 CDx utilizes circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs). The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the therapies listed in **Table 1** in accordance with the approved therapeutic product labeling.

Table 1. Companion Diagnostic Indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions, L858R, and T790M*	TAGRISSO® (osimertinib)
	EGFR exon 20 insertions	RYBREVANT® (amivantamab-vmjw)
	ERBB2/*HER2* activating mutations (SNVs and exon 20 insertions)	ENHERTU® (fam-trastuzumab deruxtecan-nxki)
	KRAS G12C	LUMAKRAS™ (sotorasib)
Breast cancer	*ESR1* missense mutations between codons 310 and 547	ORSERDU™ (elacestrant)

A negative result from a plasma specimen does not assure that the patient's tumor is negative for genomic findings. Patients who are negative for the biomarkers listed in **Table 1** should be reflexed to tissue biopsy testing for **Table 1** biomarkers using an FDA-approved tumor tissue test, if feasible.

*The efficacy of TAGRISSO (osimertinib) has not been established in the *EGFR* T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore, testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.

Additionally, the test is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasm. The test is for use with patients previously diagnosed with cancer and in conjunction with other laboratory and clinical findings.

Genomic findings other than those listed in **Table 1** are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Guardant360 CDx is a single-site assay performed at Guardant Health, Inc.

Warnings and Precautions

- Alterations reported may include somatic (not inherited) or germline (inherited) alterations. The assay filters germline variants from reporting except for pathogenic *BRCA1, BRCA2, ATM,* and *CDK12* alterations. However, if a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
- The test is not intended to replace germline testing or to provide information about cancer predisposition.
- Somatic alterations in *ATM* and *CDK12* are not reported by the test as they are excluded from the test's reportable range.
- Genomic findings from cfDNA may originate from circulating tumor DNA (ctDNA) fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP).
- Allow the tube to fill completely until blood stops flowing into the tube. Underfilling of tubes with less than 5 mL of blood (bottom of the label indicates 5 mL fill when tube is held vertically) may lead to incorrect analytical results or poor product performance. This tube has been designed to fill with 10 mL of blood.

Limitations

- For *in vitro* diagnostic use.
- For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
- The efficacy of TAGRISSO (osimertinib) has not been established in the *EGFR* T790M plasma-positive, tissue-negative or unknown population, and clinical data for T790M plasma-positive patients are limited; therefore, testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.
- TAGRISSO efficacy has not been established in patients with *EGFR* exon 19 deletions < 0.08% MAF, in patients with *EGFR* L858R < 0.09% MAF, and in patients with *EGFR* T790M < 0.03% MAF.
- RYBREVANT efficacy has not been established in patients with *EGFR* exon 20 insertions < 0.02% MAF.
- LUMAKRAS efficacy has not been established in patients with *KRAS* G12C biomarkers < 0.11% MAF.
- ENHERTU efficacy has not been established in patients with *ERBB2* exon 20 insertions < 0.03% MAF and in patients with *ERBB2* SNVs < 0.23% MAF.
- ORSERDU efficacy has not been established in patients with *ESR1* missense mutations < 0.03% MAF.
- The test is not intended to be used for standalone diagnostic purposes.
- The test is intended to be performed on specific serial number-controlled instruments by Guardant Health, Inc.
- A negative result for any given variant does not preclude the presence of this variant in tumor tissue.
- Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care.
- ctDNA shedding rate may be lower in patients with primary central nervous system (CNS) tumors.

Explanation of the Tiered Reporting

Genomic findings other than those listed in **Table 1** are not prescriptive or conclusive for labeled use of any specific therapeutic product. Test results should be interpreted in the context of pathological evaluation of tumors, treatment history, clinical findings, and other laboratory data.

The test report includes genomic findings reported in the following categories (**Table 2**).

Table 2. Category Definitions

Category	Guardant360 CDx			Comments
	Prescriptive Use for a Therapeutic Product	**Clinical Performance**	**Analytical Performance**	
Category 1: Companion Diagnostic (CDx)	**Yes**	**Yes**	**Yes**	ctDNA biomarkers linked to the safe and effective use of the corresponding therapeutic product, for which Guardant360 CDx has demonstrated clinical performance shown to support therapeutic efficacy and strong analytical performance for the biomarker.
Category 2: ctDNA Biomarkers with Strong Evidence of Clinical Significance in ctDNA	No	No	**Yes**	ctDNA biomarkers with strong evidence of clinical significance presented by other FDA-approved liquid biopsy companion diagnostics for which Guardant360 CDx has demonstrated analytical reliability but not clinical performance.

Category	Guardant360 CDx			Comments
	Prescriptive Use for a Therapeutic Product	Clinical Performance	Analytical Performance	
Category 3A: Biomarkers with Evidence of Clinical Significance in tissue supported by: strong analytical validation using ctDNA	No	No	**Yes**	ctDNA biomarkers with evidence of clinical significance presented by tissue-based FDA-approved companion diagnostics or professional guidelines for which Guardant360 CDx has demonstrated analytical performance including analytical accuracy, and concordance of blood-based testing to tissue-based testing for the biomarker.
Category 3B: Biomarkers with Evidence of Clinical Significance in tissue supported by: analytical validation using ctDNA	No	No	**Yes**	ctDNA biomarkers with evidence of clinical significance presented by tissue-based FDA-approved companion diagnostics or professional guidelines for which Guardant360 CDx has demonstrated minimum analytical performance including analytical accuracy.
Category 4: Other Biomarkers with Potential Clinical Significance	No	No	**Yes**	ctDNA biomarkers with emergent evidence based on peer-reviewed publications for genes/variants in tissue, variant information from well-curated public databases, or *in-vitro* pre-clinical models, for which Guardant360 CDx has demonstrated minimum analytical performance.