TruSight Oncology Comprehensive

illumina®

Physician Insert

FOR IN VITRO DIAGNOSTIC USE.

Intended Use

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

The test is intended to be used as a companion diagnostic to identify cancer patients who may benefit from treatment with the targeted therapies listed in Table 1, in accordance with the approved therapeutic product labeling.

In addition, the test is intended to provide tumor profiling information for use by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 of the intended use statement are not conclusive or prescriptive for labeled use of any specific therapeutic product.

Table 1 Companion Diagnostic Indications

Tumor Type	Biomarker(s) Detected	Therapy
Solid Tumors	*NTRK1/2/3* fusions	VITRAKVI® (larotrectinib)
Non-Small Cell Lung Cancer (NSCLC)	*RET* fusions	RETEVMO® (selpercatinib)

Interpretation of Test Results

Variant results, including companion diagnostic results, tumor profiling results, or a Tumor Mutational Burden (TMB) score, are summarized in a TSO Comprehensive results report output to the testing laboratory and interpreted by a qualified health care professional.

Any companion diagnostic variant with an associated therapy, or any clinically significant or potentially clinically significant variant from the test, should be interpreted by board-certified clinical molecular geneticists or pathologists (or equivalent). These specialists review the results and determine which variants are most impactful for the patient in the context of tumor diagnosis, histopathology, and available laboratory data. These results are meant to be incorporated into a report produced by the laboratory and provided to clinicians who make decisions on patient management.

Additional information is available from applicable professional guidelines such as CAP/IASLC/AMP NSCLC Testing Guidelines[1] or the CAP/AMP/ASCO Interpretation and Reporting Guidelines[2].

⚠ CAUTION

The assay is not intended as a primary diagnostic tool by physicians or to be used as a substitute for professional health care advice. Each laboratory is responsible for ensuring compliance with applicable international, national, and local clinical laboratory regulations and other specific accreditation requirements.

Illumina recommends that patients seek information from their oncologist and/or consult with a genetic counselor regarding their results.

What the Test Detects

TSO Comprehensive is an *in vitro* diagnostic test that uses targeted next-generation sequencing to detect variants in 517 genes using nucleic acids extracted from FFPE tumor tissue samples from previously diagnosed cancer patients with solid malignant neoplasms using the Illumina NextSeq 550Dx instrument. The test can be used to detect single nucleotide variants, multi-nucleotide variants, insertions, deletions, and a TMB score from DNA, and RNA fusions in 24 genes and splice variants in one gene from RNA (EGFR).

For complete clinical and analytical performance of the test for companion diagnostics and tumor profiling indications, example reports, and interpretation of possible results, refer to the TruSight Oncology Comprehensive documentation available on the Illumina support site. Refer to the FDA website for the Summary of Safety and Effectiveness (SSED).

Companion Diagnostics

The test is intended as a companion diagnostic to identify previously diagnosed cancer patients for treatment with targeted therapies listed in Table 1, in accordance with approved therapeutic product labeling. Companion diagnostics claims in Table 1 are supported by analytical performance of the test for each specific biomarker and results from a clinical study establishing the link between the result of the test and patient outcomes.

Tumor Profiling

In addition to a companion diagnostic, the test is intended to provide tumor profiling information in previously diagnosed cancer patients with solid malignant neoplasms, for use by qualified health care professionals, in accordance with professional guidelines. The test is not conclusive or prescriptive for labeled use of any specific therapeutic product other than those listed in Table 1.

Background

Companion Diagnostic Tests for Targeted NTRK Therapy Selection

NTRK fusions are a well-established oncogenic driver of disease across a variety of adult and pediatric cancers[3]. The tropomyosin receptor kinase (TRK) family of receptor tyrosine kinases consists of TRKA, TRKB, and TRKC encoded by the neurotrophic tyrosine receptor kinase genes NTRK1[4], NTRK2[5], and NTRK3[6], respectively. Somatic inter- and intra-chromosomal rearrangements that cause an NTRK gene to fuse with another, unrelated gene have been shown to drive oncogenesis in a variety of both pediatric and adult tumors.

NTRK gene fusions have been estimated to occur in up to 1% of all solid tumors[7], although the frequency varies considerably between tumor types[3,7,8]. Available evidence suggests that NTRK gene fusions are useful biomarkers to predict tumor response to TRK inhibitors. There is currently a selective tyrosine kinase inhibitor, larotrectinib (VITRAKVI), that is active against TRKs. Larotrectinib[7,9] is a potent inhibitor of all three TRK variant types and has been authorized by the US FDA[10] for the treatment of adult and pediatric patients with solid tumors that harbor NTRK fusions. For the most current information on the association between biomarkers and therapeutic outcomes, refer to the drug labeling information available on the FDA website[11].

For the most current list of FDA-approved companion diagnostic devices for detection of NTRK fusions to select patients who may benefit from treatment with targeted therapies, refer to the FDA website[12].

Companion Diagnostic Tests for Targeted RET Therapy Selection

Lung cancer remains the leading cause of cancer death worldwide, accounted for 2.2 million new cases (11.4% of all cancers) diagnosed in 2020 and claimed over 1.8 million lives[13]. It is estimated that in the US, there will be 234,580 new cases of lung cancer with 125,070 deaths in 2024, accounting for 20.4% of cancer deaths in the US[14]. Genomic variants in the RET gene have been estimated to occur in approximately 0.5%–2% of all solid tumors[15,16], however, frequencies vary considerably between the type of RET abnormality and specific tumor types. In lung cancer, RET fusions are most prevalent in non-smokers and younger individuals[17]. A number of fusion partner genes have been identified[18], with the most common fusions varying between tumor types. In NSCLC, a common fusion partner is KIF5B[17,18]. Selpercatinib (RETEVMO) is a tyrosine kinase inhibitor that has significant activity against RET fusions. Selpercatinib[19] is a potent inhibitor of RET fusions and has been authorized by the US FDA[20] for the treatment of adult patients with NSCLC that harbor RET fusions. For the most current information on the association between biomarkers and therapeutic outcomes, refer to the drug labeling information available on the FDA website[11].

For the most current list of FDA-approved companion diagnostic devices for detection of RET fusions to select patients who may benefit from treatment with targeted therapies, refer to the FDA website[12].

Limitations of the Procedure

For *in vitro* diagnostic use only.

- For prescription use only. The test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
- Genomic findings listed in the TSO Comprehensive results report under Cancer Mutations with Evidence of Clinical Significance (Level 2) and Cancer Mutations with Potential Clinical Significance (Level 3) are not prescriptive or conclusive for labeled use of any specific therapeutic product, and clinical validation has not been performed.
- 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 in a given community.
- Performance of TSO Comprehensive in samples obtained from patients that have had organ or tissue transplantation has not been evaluated.
- Accuracy of small DNA tumor profiling variants below 5% variant allele frequency has not been established.
- Accuracy for the EGFRvIII splice variant from RNA has only been established in brain tissue. Accuracy for EGFRvIII in other tissue types has not been established.
- TSO Comprehensive performance has been demonstrated for insertions and deletions up to 24 bp.
- A negative result does not rule out the presence of a mutation below the limits of detection (LoD) of the assay. Alterations at allele frequencies below the established LoD may not be detected consistently.
- The overall negative percent agreement for NTRK fusions between drug trial enrollment assays and TSO Comprehensive was 96.3% (95%CI: 93.1%, 98.3%). False positive results for gene fusions such as NTRK may be due to non-specific detection.
- The clinical significance of Tumor Mutational Burden (TMB) measurement has not been established. TMB is reported as mutations per megabase (Muts/Mb). TMB is a function of characteristics of a patient's specimen and testing parameters; therefore, TMB may differ across specimens (eg, primary vs metastatic, tumor content) and targeted panels.
- Annotation or Knowledge Base errors can cause a false positive or false negative result, including listing a variant in the wrong cancer mutation level (between Level 2 and 3), or the annotation information in the report could be incorrect. Annotation or Knowledge Base errors do not impact variants reported in the CDx Results. The possibility of error exists from the following three sources:
  - TSO Comprehensive variant annotation. There is an error rate of approximately 0.0027% based on an analysis of 2,448,350 variants from COSMIC v92, therefore there is a low possibility for error.
  - Knowledge Base error due to the curation or leveling process.
  - The report reflects the knowledge at the time when the Knowledge Base version was curated.

- TSO Comprehensive is designed to report somatic variants and is not intended to report germline variants. When reporting variants with evidence of clinical significance or variants with potential clinical significance, as a tumor-only test, germline (inherited) variants may be inadvertently reported since TSO Comprehensive uses a Knowledge Base to report somatic variants without explicitly annotating germline or somatic origin.
- The Knowledge Base only includes therapeutic, diagnostic, and prognostic associations that are relevant for variants present within an established solid malignant neoplasm. Susceptibility or cancer risk associations are not included in the Knowledge Base.

Refer to the package insert for additional assay related limitations.

References

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Revision History

Document	Date	Description of Change
Document # 200061833 v00	October 2024	Initial release

Patents and Trademarks

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IVD

Product Labeling

For a complete reference of symbols that appear on product packaging and labeling, refer to the symbol key at support.illumina.com on the *Documentation* tab for your kit.