News Release

February 15, 2021
Sysmex Corporation

Sysmex Receives Approval for a Partial Change to the OncoGuide™ NCC Oncopanel System for Use in Cancer Genome Profiling

- Detection of 10 New Gene Mutations Including MSH6 and PMS2, NTRK3 Gene Fusion and Microsatellite Instability -

Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu) announced today that on February 1, 2021, it received approval for a partial change to the manufacturing and marketing approval for the OncoGuide NCC Oncopanel System,[1] a gene mutation analysis set for use in cancer genome profiling (the "System"), which was made as a result of an enhancement of the System's functions, including an expanded scope of detectable gene mutations.
With this change, it has become possible to detect mutations and copy number alterations of 124 genes, fusions[2] of 13 genes, and microsatellite instability[3] (MSI), up from the mutations and copy number alterations of 114 genes before. These enhancements allow for more detailed gene information that aids in cancer diagnosis and treatment and selection of anti-cancer drugs. The System also detects germline variants[4] of all 124 genes for reference purposes and provides them as part of the results.

Since receiving manufacturing and marketing approval in December 2018, the System has been introduced into clinical settings to perform tests that provide information useful in determining treatment methods, including diagnosis and the selection of anti-cancer drugs. Capable of obtaining comprehensive cancer genome profiles by measuring 114 cancer-related genes in tumor tissues for analysis of all solid tumors, the System has been instrumental in analyzing mutations of cancer-specific genes.
Meanwhile, there is a pressing need for a technique that more accurately monitors gene mutations associated with existing cancers and expands the number of detectable genes in pursuit of more comprehensive cancer genome profiling. This would allow for greater diagnostic accuracy and the selection of anti-cancer drugs with higher efficacy.

On February 1, 2021, Sysmex received approval for a partial change to the manufacturing and marketing approval of the System, regarding the enhancement of its functions, including greater scope of detectable gene mutations. With this enhancement, it has become possible to detect the fusions of 13 genes, including the NTRK3 gene,[5] which is detected in a tumor-agnostic manner, as well as mutations of 124 genes, regardless of fusion partners. Detection of MSI has also been made possible, as it appears to be related to abnormalities in the ability to repair DNA and thus serves as evidence that cancer is likely to occur.
The System also detects germline variants of all 124 genes for reference purposes and provides them as part of the results of the matched-pairs test[6] that the System performs using tumor and non-tumor tissues (blood).
It is expected that these additional functions will make it easier to select drugs targeting patient-specific mutations and improve treatment outcomes.

RIKEN Genesis Co., Ltd., a subsidiary of Sysmex that provides cancer genome profiling lab-assay services, aims to promptly commence genetic testing using the System with the additional functions included in this approval.

Sysmex remains committed to contributing to the development and advancement of personalized healthcare by working to increase testing opportunities for patients and creating high-value-added testing and diagnosis technologies.

List of Genes to be Detected

Mutations / Amplifications of 124 genes					Fusions of 13 genes
ABL1	*CDK12*	*HRAS*	*MTAP*	*POLE*	*AKT2*
ACTN4	*CDKN2A*	*IDH1*	*MTOR*	*PRKCI*	*ALK*
AKT1	*CHEK2*	*IDH2*	*MYC*	*PTCH1*	*BRAF*
AKT2	*CREBBP*	*IGF1R*	*MYCN*	*PTEN*	*ERBB4*
AKT3	*CRKL*	*IGF2*	*NF1*	*RAC1*	*FGFR2*
ALK	*CTNNB1*	*IL7R*	*NF2*	*RAC2*	*FGFR3*
APC	*CUL3*	*JAK1*	*NFE2L2/Nrf2*	*RAD51C*	*NRG1*
ARAF	*DDR2*	*JAK2*	*NOTCH1*	*RAF1/CRAF*	*NTRK1*
ARID1A	*EGFR*	*JAK3*	*NOTCH2*	*RB1*	*NTRK2*
ARID2	*ENO1*	*KDM6A/UTX*	*NOTCH3*	*RET*	*NTRK3*
ATM	*EP300*	*KEAP1*	*NRAS*	*RHOA*	*PDGFRA*
AXIN1	*ERBB2/HER2*	*KIT*	*NRG1*	*ROS1*	*RET*
AXL	*ERBB3*	*KRAS*	*NT5C2*	*SETBP1*	*ROS1*
B2M	*ERBB4*	*MAP2K1/MEK1*	*NTRK1*	*SETD2*	
BAP1	*ESR1/ER*	*MAP2K2/MEK2*	*NTRK2*	*SMAD4*	
BARD1	*EZH2*	*MAP2K4*	*NTRK3*	*SMARCA4/BRG1*	
BCL2L11/BIM	*FBXW7*	*MAP3K1*	*PALB2*	*SMARCB1*	
BRAF	*FGFR1*	*MAP3K4*	*PBRM1*	*SMO*	
BRCA1	*FGFR2*	*MDM2*	*PDGFRA*	*STAT3*	
BRCA2	*FGFR3*	*MDM4*	*PDGFRB*	*STK11/LKB1*	
CCND1	*FGFR4*	*MEN1*	*PIK3CA*	*TP53*	
CCNE1	*FLT3*	*MET*	*PIK3R1*	*TSC1*	
CD274/PD-L1	*GNA11*	*MLH1*	*PIK3R2*	*TSC2*	
CDK4	*GNAQ*	*MSH2*	*PMS2*	*VHL*	
CDK6	*GNAS*	*MSH6*	*POLD1*		

*Genes added are in red.

Product Overview

Generic name:	Gene mutation analysis set (for use in cancer genome profiling)
Name:	OncoGuide™ NCC Oncopanel System (*In vitro* diagnostic medical device registration number: 23000BZX00398000 / Obtained on: December 25, 2018)
Manufacturer and seller:	Sysmex Corporation
Target market:	Japan
Target institutions:	Medical institutions that have in place diagnostic systems appropriate for cancer genome profiling

Overview of the application for approval of partial change

- Addition of a gene panel for analysis (from 114 genes to 124 genes)
- Addition of a function to detect microsatellite instability (MSI)
- Version upgrade of software as a result of the improvement to the OncoGuide NCC Oncopanel Analysis Program
- Partial change to the composition of the OncoGuide NCC Oncopanel Kit
- Extension of expiry dates of the OncoGuide NCC Oncopanel Kit (from nine months to 12 months)

Approval obtained: February 1, 2021.

Reference

Press release dated December 25, 2018: “Sysmex Receives Manufacturing and Marketing Approval to Use the OncoGuide™ NCC Oncopanel System in Cancer Genome Profiling”
https://www.sysmex.co.jp/en/news/2018/181225.html

Press release dated February 21, 2019: “Commencement of Assay Service Using the OncoGuide™ NCC Oncopanel System in Cancer Genome Profiling”
https://www.sysmex.co.jp/en/corporate/news/2019/190221.html

Press release dated May 31, 2019: “The OncoGuide™ NCC Oncopanel System Receives Insurance Coverage for Use in Cancer Genome Profiling”
https://www.sysmex.co.jp/en/news/2019/190531.html

Press release dated April 1, 2020: “Advanced Medical Care Approval for Cancer Gene Panel Testing at the Time of Initial Treatment”
https://www.sysmex.co.jp/en/news/2020/pdf/200401.pdf

Terminology

1 OncoGuide NCC Oncopanel System:
On December 25, 2018, Sysmex received manufacturing and marketing approval for the System as Japan's first medical device for cancer genome profiling under the Ministry of Health, Labour and Welfare's *Sakigake* Designation system. This combination medical device was subsequently covered under the NHI as of June 1, 2019. NHI coverage for D006-

19 cancer genome profiling using the System includes patients with solid tumors for which no standard treatment exists and patients with solid tumors confirmed to have spread locally or metastasized (including patients for whom treatment is expected to conclude). Coverage is limited to cases in which the attending physician determines the potential for applying chemotherapy following this testing is high, based on chemotherapy guidelines from related societies and the patient's general status and organ function. Its utility at the time of initial treatment was assessed in the study which was applied as Advanced Medical Care as described in the press release dated April 1, 2020.

2 Gene fusion:
A type of mutation where one gene (Gene A) fuses with another to behave as a single gene. Gene A fuses with various genes, but the System can detect the fusion of Gene A, regardless of the types of genes that fuse with Gene A.

3 Microsatellite instability (MSI):
A phenomenon where repeated sequences called "microsatellites", short nucleotide repeats (from one to several bases per unit) in genomic DNA display a different number of repetitions in tumor tissues than in non-tumor (normal) tissues, due to malfunctions of the mismatch repair system that may occur during DNA replication.

4 Germline variants:
Natural genetic variants involved in cancer risk or hereditary disorders.

5 NTRK3 gene:
A gene that produces the protein involved in the differentiation and maintenance of neurons. It is believed that cancer is likely to occur when unnecessary cells multiply as abnormal proteins are produced by the NTRK fusion gene (the NTRK gene fusing with various other genes).

6 Matched-pairs test:
A test that simultaneously sequences DNA from tumor tissues of a patient with solid cancer and non-tumor tissues (blood) of the same patient. Performed to confirm (for secondary findings) genetic mutations (variants) that may be determined as pathological, and unrelated to the primary purpose for testing.