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Sysmex Corporation

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## Insurance Coverage Received for Liquid Biopsy *RAS* Gene Mutation Testing for Colorectal Cancer Using High-Sensitivity Digital PCR

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Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu) announced today that it has received approval for insurance coverage for blood-based *RAS* gene<sup>1</sup> mutation testing for colorectal cancer using the OncoBEAM™ *RAS* CRC Kit.<sup>2</sup> The coverage went into effect on August 1, 2020.

With this regulatory approval, even when it is difficult to obtain *in vivo* diagnostics (biopsy) on a sample taken from tumor tissue, *RAS* gene mutation testing using the kit may be performed with a minimal physical and mental burden on patients when it is necessary, owing to the fact that it uses the patient's blood as a sample. This will have the effect of optimizing decisions on the administration of anti-EGFR<sup>3</sup> monoclonal antibody drugs. Receipt of insurance coverage will also make it possible for us to provide more patients with testing to allow physicians to select an appropriate treatment method.

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Currently, at the beginning of therapy, colorectal cancer patients treated with medication undergo *RAS* gene mutation testing using tumor tissue, the results of which inform a decision on whether or not to administer anti-EGFR monoclonal antibody drugs. Several studies have reported that re-challenge of anti-EGFR monoclonal antibody drugs is an effective treatment method for patients with recurrent colorectal cancer after treatment by anti-EGFR monoclonal antibody drugs, and that the *RAS* gene mutation status may change by the time of re-challenge from what it was in initial therapy. The relevant guidance published by the Japanese Society of Medical Oncology<sup>4</sup> indicates that it is desirable to assess the gene mutation status several times over time to make appropriate re-challenge decisions based on the state at the time of relapse. As such, much has been expected from a practical application of liquid biopsy, which checks the *RAS* gene mutation status using the patient's blood samples when biopsy may not be performed easily.

The OncoBEAM™ *RAS* CRC Kit is used to test samples of tumor-derived DNA (circulating tumor DNA, or ctDNA) suspended in the blood of colorectal cancer patients. Using BEAMing technology, the kit detects *RAS* gene mutations with a high degree of sensitivity (mutant allele frequency of no more than 1% in approximately 30% of mutation cases thus detected).<sup>5</sup> As the first colorectal cancer liquid biopsy testing in Japan that provides auxiliary test data to determine the appropriateness of anti-EGFR monoclonal antibody drugs - Cetuximab and Panitumumab (gene recombination) - for patients with colorectal cancer, this product was approved as an *in vitro* diagnostic reagent in July 2019 and was covered under health insurance from August 1, 2020. Please note that an insurance-covered assay service for colorectal cancer using this product is also due to start in August 2020.

Performance of *RAS* gene mutation testing when it is necessary and with a minimal physical and mental burden on patients for whom biopsy is challenging to perform is expected to optimize the administration of anti-EGFR monoclonal antibody drugs. On the other hand, there is a possibility that this testing may deem patients whose ctDNA is not sufficiently leaked into the blood to have wild-type *RAS*, even though *RAS* gene mutation exists in tumor tissue. For patients with lung metastasis

only, it is particularly necessary to prioritize testing using tumor tissue. Sysmex will remain committed to the provision of scientific information so that medical institutions may perform testing properly.

Going forward, Sysmex will continue to contribute to the advancement of personalized medicine by working on expanding testing opportunities for patients and providing testing and diagnostic technologies with high diagnostic value.

### Details of Insurance Coverage

Classification: E3  
Item of measurement: RAS gene mutation (plasma)  
Measurement method: High-sensitivity digital PCR method and flow cytometry method  
NHI points: 7,500

### Product Overview

Name: OncoBEAM™ RAS CRC Kit  
*In vitro* diagnostics manufacturing and marketing approval number: 30100EZX00010000  
Obtained on July 19, 2019  
Manufacture and sale: Sysmex Corporation

Use: To detect RAS (KRAS and NRAS) gene mutations in genomic DNA extracted from plasma  
(Auxiliary use to determine the appropriateness of Cetuximab or Panitumumab (gene recombination) for patients with colorectal cancer)

Target market: Japan  
Target institutions: Healthcare institutions and clinical testing centers in Japan, other

### References

“Sysmex Obtains First Manufacturing and Marketing Approval in Japan for Blood-Based RAS Gene Mutation Testing for Colorectal Cancer,” released on August 2, 2019  
<https://www.sysmex.co.jp/en/news/2019/190802.html>

“Sysmex Presents Academic Report Related to the Clinical Utility of RAS Gene Mutation Testing for Colorectal Cancer Using Liquid Biopsy - Details of Report on Clinical Utility of OncoBEAM™ RAS CRC Kit presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2020 (ASCO-GI 2020),” released on March 5, 2020  
[https://www.sysmex.co.jp/en/news/2020/pdf/200305\\_02\\_e.pdf](https://www.sysmex.co.jp/en/news/2020/pdf/200305_02_e.pdf)

### Terminology

1. RAS gene:  
As the likelihood is high that patients with RAS gene (KRAS/NRAS gene) mutations will not benefit (prolongation of life, tumor reduction) from the administration of anti-EGFR drugs, companion diagnostics may be performed to treat the gene mutation first.

2. OncoBEAM™:  
The name of Sysmex's technology to detect minute gene mutations circulating in the blood with a high degree of sensitivity using BEAMing technology. "BEAM" is an acronym for "bead, emulsion, amplification and magnetics", a gene analysis method developed at Johns Hopkins University combining digital PCR and flow cytometry technologies for highly sensitive analysis of genetic mutations.
3. EGFR:  
Epidermal growth factor receptors (EGFRs), which exist in large numbers on the surface of colorectal cancer cells, are known to stimulate the proliferation of cancer cells.
4. The Guidance on Genetic Testing in the Treatment of Colorectal Cancer:  
The Guidance on Genetic Testing in the Treatment of Colorectal Cancer Vol. 4 (December 2019) published by the Japanese Society of Medical Oncology, indicates the necessity of using liquid biopsy for colorectal cancer and the clinical utility of ctDNA testing.
5. Results of multi-facility evaluation in Japan:  
The results indicate that this new testing method provides detection results on par with conventional *RAS* gene mutation testing using tumor tissue. Source: *British Journal of Cancer* volume 120, 982-986 (2019)