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REPORT

Japanese Society of Medical Oncology clinical guidelines: Molecular testing for colorectal cancer treatment, 5th edition

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Abstract

Molecular testing to determine optimal therapies is essential for managing patients with colorectal cancer (CRC). In October 2022, the Japanese Society of Medical Oncology published the 5th edition of the Molecular Testing Guideline for Colorectal Cancer Treatment. In this guideline, in patients with unresectable CRC, *RAS/BRAF* V600E mutational and mismatch repair tests are strongly recommended prior to first-line chemotherapy to select optimal first- and second-line therapies. In addition, *HER2* testing is strongly recommended because the pertuzumab plus trastuzumab combination is insured after fluoropyrimidine, oxaliplatin, and irinotecan in Japan. Circulating tumor DNA (ctDNA)-based *RAS* testing is also strongly recommended to assess the indications for the readministration of anti-EGFR antibodies. Both tissue- and ctDNA-based comprehensive genomic profiling tests are strongly recommended to assess the indications for targeted molecular drugs, although they are currently insured in patients with disease progression after receiving standard chemotherapy (or in whom disease progression is expected in the near future). Mutational and mismatch

Abbreviations: CGP, comprehensive genomic profiling; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DFS, disease-free survival; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; FOLFIRI, irinotecan, 5-FU, leucovorin; FOLFOX, oxaliplatin, 5-FU, leucovorin; FOLFOXIRI, oxaliplain, irinoteca, 5-FU, leucovorin; FFPE, formalin-fixed paraffin-embedded; JSMO, Japanese Society of Medical Oncology; IHC, immunohistochemistry; mCRC, metastatic CRC; MMR, mismatch repair; mFOLFOX6, modified FOLFOX6; MRD, minimal residual disease; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair-proficient.

This report is a digest of the *Japanese Society of Medical Oncology Clinical Guidelines: Molecular Testing for Colorectal Cancer Treatment*, 5th Edition. The English-translated full text is available at https://www.jsmo.or.jp/about/doc/guideline_20231121.pdf.

repair testing is strongly recommended for patients with resectable CRC, and *RAS/BRAF* V600E mutation testing is recommended to estimate the risk of recurrence. Mutational and mismatch repair and *BRAF* testing are also strongly recommended for screening for Lynch syndrome. Circulating tumor DNA-based minimal residual disease (MRD) testing is strongly recommended for estimating the risk of recurrence based on clinical evidence, although MRD testing was not approved in Japan at the time of the publication of this guideline.

KEYWORDS
circulating tumor DNA, colorectal cancer, comprehensive genomic profiling, guideline, microsatellite instability

1 | INTRODUCTION

The JSMO has been dedicated to providing guidance regarding the proper use of genomic testing for the management of CRC through publications.[1] In March 2023, the JSMO published the revised version Japanese version of guidelines for *Molecular Testing for Colorectal Cancer Treatment* (5th edition). The degree of recommendation for each requirement was determined through votes by working group members, based on the evidence for each test and the expected balance between the advantages and disadvantages for patients when testing was performed (Table 1).

2 | BASIC REQUIREMENTS OF MOLECULAR TESTING FOR CRC TREATMENT

2.1 | *RAS* mutation testing

> *RAS* mutation testing is strongly recommended prior to first-line therapy to assess the indications for anti-EGFR antibody in patients with unresectable CRC.
>
> [Strong recommendation]

Mutations in *KRAS* exons 2, 3, and 4 and *NRAS* exons 2, 3, and 4 ranged from 45% to 55%. Anti-EGFR antibodies were reproducibly ineffective in patients with *KRAS/NRAS* mutations, regardless of the type of anti-EGFR antibody (cetuximab or panitumumab), treatment line, or type of backbone chemotherapy (Table 2 and Figure 1). While the addition of anti-EGFR antibody significantly improved the OS and PFS in patients with *RAS* wild-type left-sided CRC, anti-EGFR antibody therapy was not beneficial in patients with right-sided colon cancer according to a meta-analysis.[2] Additionally, the Japanese PARADIGM study prospectively confirmed the significant improvement in OS in patients with *RAS* wild-type left-sided tumor treated with mFOLFOX6 + panitumumab versus mFOLFOX6 + bevacizumab.[3]

> *RAS* mutation testing is recommended prior to adjuvant chemotherapy to access the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.
>
> [Recommendation]

According to a meta-analysis, patients with *KRAS* mutations have significantly shorter DFS and OS than those without *KRAS* mutations.[4] Furthermore, among patients with resected metastatic lesions such as liver metastases, patients with *RAS* mutations had shorter recurrence-free survival and OS than those with *RAS* wild-type.[5]

> Circulating tumor DNA-based *RAS* mutation testing is strongly recommended to assess the indication for re-administration of anti-EGFR antibody in patients with unresectable CRC.
>
> [Strong recommendation]

According to longitudinal plasma ctDNA analyses, newly emerged *RAS* mutations were observed in some cases after resistance to

TABLE 1 Degrees of recommendation and decision criteria

Degree of recommendation	Decision criteria
Strong recommendation	Sufficient evidence and the benefits of testing outweigh the losses
Recommendation	Evidence considering the balance between benefits and losses
Expert consensus opinion	Consensus obtained although not enough evidence and information
No recommendation	Not recommended owing to the lack of evidence

Note: Sufficient evidence: consistent evidence from randomized control trials (RCTs) without important limitations or exceptionally strong evidence from observational studies; evidence: evidence from RCTs with important limitations or strong evidence from observational studies; consensus: evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws, or indirect evidence.

TABLE 2 Summary of basic requirements

	Recommendation
RAS mutation testing	
1. *RAS* mutation testing is strongly recommended prior to first-line therapy to assess the indications for anti-EGFR antibody in patients with unresectable CRC.	Strong recommendation
2. *RAS* mutation testing is recommended prior to adjuvant chemotherapy to access the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.	Recommendation
3. Circulating tumor DNA-based *RAS* mutation testing is strongly recommended to assess the indication for readministration of anti-EGFR antibody in patients with unresectable CRC.	Strong recommendation
BRAF mutation testing	
1. *BRAF* V600E mutation testing is strongly recommended prior to first-line therapy to predict the prognosis and assess the indication for the combination of BRAF inhibitor and anti-EGFR antibody, with or without MEK inhibitor in patients with unresectable CRC.	Strong recommendation
2. *BRAF* V600E mutation testing is recommended prior to adjuvant chemotherapy to access the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.	Recommendation
3. *BRAF* V600E mutation testing is strongly recommended to help diagnose Lynch syndrome.	Strong recommendation
HER2 testing	
1. *HER2* testing is strongly recommended prior to anti-*HER2* therapy to assess the indication of anti-*HER2* therapy in patients with unresectable CRC.	Strong recommendation
2. In *HER2* testing for unresectable advanced CRC, IHC testing is strongly recommended first. ISH testing is added in case of IHC 2+.	Strong recommendation
Testing for MMR deficiency	
1. MMR deficiency testing is strongly recommended prior to first-line therapy to assess the indications for immune checkpoint inhibitors in patients with unresectable CRC.	Strong recommendation
2. MMR deficiency testing is strongly recommended to assess the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.	Strong recommendation
3. MMR deficiency testing is strongly recommended to screen for Lynch syndrome	Strong recommendation
4. The following methods are strongly recommended when assessing for MMR deficiency:	
MSI testing	Strong recommendation
IHC testing	Strong recommendation
NGS-based testing	Strong recommendation
Tissue-based CGP tests	
Tissue-based CGP testing is strongly recommended to assess the indications for molecular targeted drugs in patients with unresectable CRC.	Strong recommendation
Liquid biopsy	
1. Circulating tumor DNA-based CGP testing is strongly recommended to assess the indications for molecular targeted drugs in patients with unresectable CRC.	Strong recommendation
2. Gene panel test detecting minimal residual disease is strongly recommended to assess the optimal adjuvant chemotherapy in patients with CRC having received curative resection.	Strong recommendation
Specimen handling for molecular testing	
1. FFPE tissue is suitable for genetic testing of somatic mutations in cancers. It is able to assess whether samples have sufficient amount of tumor cells by examining histologic findings using matched hematoxylin and eosin-stained slides. Selection of FFPE samples, decision on the need for macrodissection, and assessment of tumor cellularity should be performed by a pathologist.	Strong recommendation
2. In performing circulating tumor DNA testing, the manufacturer's instructions concerning the use of a collection tube and plasma preparation procedure should be followed.	Strong recommendation
Quality assurance requirements for testing	
Genetic testing for CRC treatment should be carried out under a quality assurance system.	Strong recommendation

Abbreviations: CGP, comprehensive genomic profiling; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; ISH, in situ hybridization; MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing.

anti-EGFR antibodies. Because the variant allele frequency of acquired alterations was generally subclonal and attenuated exponentially,[6] *RAS* mutation is expected to be undetected after 4–6 months of treatment withdrawal, and it can be a predictive marker of the efficacy of anti-EGFR rechallenge. The OncoBEAM RAS CRC kit (SYSMEX), which detects *RAS* mutations in ctDNA, has been

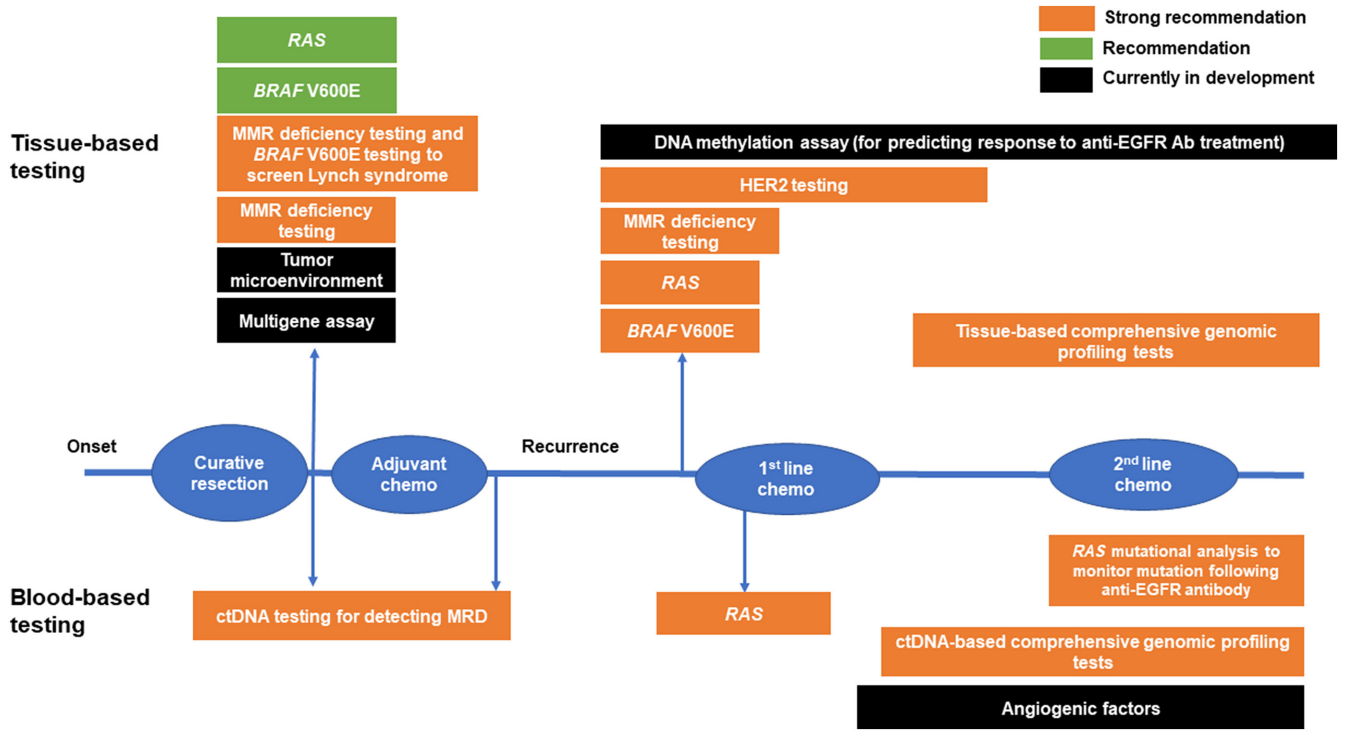

FIGURE 1 Timing for each genetic test in patients with colorectal cancer. Timing (surgically resectable stage, before first-line therapy, or after first-line therapy) and recommendation (Strong recommendation, Recommendation, or Currently in development) of each genetic test are visualized. Tissue-based and blood-based testing are also separately described. ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; MMR, mismatch repair; MRD, minimal residual disease.

approved for the selection of optimal therapies for patients with metastatic CRC, especially in cases without tissue samples. Repeat testing is also possible when considering the readministration of anti-EGFR antibodies.

2.2 | *BRAF* mutation testing

> *BRAF* V600E mutation testing is strongly recommended prior to first-line therapy to predict the prognosis and assess the indication for the combination of BRAF inhibitor and anti-EGFR antibody, with or without MEK inhibitor in patients with unresectable CRC.
>
> [Strong recommendation]

The prevalence of *BRAF* V600E mutation is 5%–10% in metastatic CRC. Patients with *BRAF* V600E mCRC have a poor prognosis. A meta-analysis showed that anti-EGFR antibody monotherapy or in combination with cytotoxic agents was not effective in mCRC patients with *BRAF* V600E,[7] and a bevacizumab-based first-line regimen was considered a favorable therapy. Because the overall survival benefit of FOLFOXIRI combined with bevacizumab is comparable to that of FOLFOX or FOLFIRI combined with bevacizumab,[8] both FOLFOXIRI and FOLFOX/FOLFIRI were selected as backbone chemotherapies. The BEACON CRC phase III trial combining BRAF and anti-EGFR antibodies with or without MEK inhibitors significantly improved the OS and ORR compared to FOLFIRI or irinotecan + cetuximab as second- or third-line therapy in patients with *BRAF* V600E mutant metastatic CRC.[9,10]

> BRAF V600E mutation testing is recommended prior to adjuvant chemotherapy to access the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.
>
> [Recommendation]

BRAF V600E mutation is associated with poor prognosis, especially in patients with MSS resectable CRC. Accordingly, *BRAF* V600E mutation has been shown to be a risk factor for recurrence in a meta-analysis of phase III trials of adjuvant chemotherapy in patients with stage II/III colon cancer.[4] In relation with MSI status, patients with MSS and *BRAF* mutations were associated with poor prognosis, while favorable prognosis was observed in patients with MSI-H and *BRAF* wild-type compared with those with MSS and *BRAF* wild-type. Microsatellite instability-high and *BRAF* mutations resulted in a moderate prognosis.[11]

> *BRAF* V600E mutation testing is strongly recommended to help diagnose Lynch syndrome.
>
> [Strong recommendation]

BRAF V600E mutations are predominantly observed in patients with sporadic dMMR CRCs. Lynch syndrome harbors germline mutations in MMR genes, whereas most sporadic dMMR CRCs, such as those in

the *MLH1* gene, are caused by promoter methylation. Among dMMR tumors, Lynch syndrome can be excluded with high probability when the *BRAF* V600E mutation is present, especially with concomitant loss of MLH1 expression.

2.3 | *HER2* testing

> *HER2* testing is strongly recommended prior to anti-*HER2* therapy to assess the indication of anti-*HER2* therapy in patients with unresectable CRC.
>
> [Strong recommendation]

HER2 overexpression accounts for only 3% of all colorectal cancers (5%–7% in *RAS/BRAF* wild-type cancers). Although *HER2* overexpression is associated with primary and acquired resistance to anti-EGFR therapies, its prognostic relevance remains controversial. The combination of pertuzumab with trastuzumab has been insured after standard therapy including fluoropyrimidine, oxaliplatin, and irinotecan in Japan based on the phase II TRIUMPH study. In this study, *HER2* overexpression was determined using tumor tissue and/or ctDNA analysis.[12]

> Immunohistochemical testing is strongly recommended first for *HER2* testing in advanced unresectable CRC. In situ hybridization testing is added in case of IHC 2+.
>
> [Strong recommendation]

An international study harmonizing provisional diagnostic criteria for ERBB2-positive mCRC[13] and The Japanese Society of Pathology defined *HER2*-positive colorectal cancer as IHC 3+ or IHC 2+ plus an *ERBB2/CEP17* ratio by fluorescence in situ hybridization of ≥2.0. In surgically resected specimens, complete lateral or circumferential membrane staining in >10% of tumor cells is required for the diagnosis of IHC 3+. In biopsy specimens, there is no definition of the stained tumor cell ratio.[13] Based on the above definitions and our internal discussions, IHC testing is strongly recommended. In situ hybridization testing was performed in patients diagnosed as 2+.

> Mismatch repair deficiency testing is strongly recommended prior to first-line therapy to assess the indications for immune checkpoint inhibitors in patients with unresectable CRC.
>
> [Strong recommendation]

The dMMR ranged from 3.5% to 5% in patients with unresectable CRC. A randomized phase III trial, KEYNOTE-177, found that pembrolizumab had superior PFS and confirmed ORR compared with the standard FOLFOX/FOLFIRI + cetuximab/bevacizumab,[14] although the OS of patients treated with pembrolizumab was not statistically superior to that of patients treated with chemotherapy because of the 60% effective cross-over to immuno-oncology therapy.[14,15] Based on the results of KEYNOTE-177, pembrolizumab is the first-line treatment for patients with MSI-H and/or dMMR mCRC.

> Mismatch repair deficiency testing is strongly recommended to assess the optimal chemotherapy based on the risk of recurrence in patients with resectable CRC.
>
> [Strong recommendation]

Although dMMR had better survival than pMMR in patients with curatively resected stage II and III colon cancer, fluoropyrimidine-based adjuvant chemotherapy could increase the risk of recurrence in patients with dMMR stage II colon cancer.[16] On the contrary, adding oxaliplatin to fluoropyrimidine improves both DFS and OS in patients with stage III dMMR colon cancer.[17] Oxaliplatin-based regimen should be selected when adjuvant chemotherapy is considered in patients with stage II/III dMMR colon cancer. Furthermore, the presence of *BRAF* V600E mutations is significantly associated with the risk of recurrence and poor prognosis in pMMR stage III colorectal cancer, suggesting the application of intensive chemotherapy. Additionally, *BRAF* V600E mutations are observed more frequently in patients with dMMR than in those with pMMR.

In patients with stage II/III dMMR locally advanced rectal cancer, immune checkpoint inhibitors indicated higher clinical complete response rate, suggesting potentially curability without CRT and surgical resection. Mismatch repair deficiency testing before neoadjuvant therapy can be the optimal timing.

> Mismatch repair deficiency testing is strongly recommended to screen for Lynch syndrome.
>
> [Strong recommendation]

Lynch syndrome is an autosomal dominant inherited disorder caused by germline mutations in one of the MMR genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Lynch syndrome is a rare disease occurring in 2%–4% of Caucasians and 0.7% of Japanese patients with CRC. However, patients and their families are at an increased risk of many types of malignancies. Notably, dMMR has also been observed in a subset of sporadic CRC, such as in tumors with hypermethylation of the *MLH1* promoter.

The following methods are strongly recommended when assessing for MMR deficiency:

> *Microsatellite instability testing* [Strong recommendation].
> *Immunohistochemistry testing* [Strong recommendation].
> *Next-generation sequencing-based testing* [Strong Recommendation].

In MSI testing, mononucleotide markers are more sensitive and specific than dinucleotide markers, such as those of the Bethesda panel, for the detection of MSI and are also less influenced by polymorphisms. The MSI test kit (FALCO) determines the MSI status based on five mononucleotide markers.

In IHC testing, tumors without MMR deficiency express all four proteins (MLH1, MSH2, MSH6, and PMS2), whereas proteins corresponding to inactivated MMR genes are not expressed in patients

with dMMR tumors. The IHC and MSI tests show high concordance rates. Currently, IHC is approved as a companion diagnostic assay for pembrolizumab, an assessment of the choice of chemotherapy, and screening for Lynch syndrome.

FoundationOne CDx (Foundation Medicine) detects MSI status by evaluating 95 intronic microsatellite markers, showing more than 95% of concordance rate with MSI testing and IHC. There are other algorithms to analyze MSI status, such as the MSI sensor algorithm in MSK-IMPACT (Memorial Sloan Kettering Cancer Center) and the MOSAIC and MANTIS algorithms with whole exome sequencing. Each of these methods uses different microsatellite markers and algorithms.

2.4 | Tissue-based CGP tests

> Tissue-based CGP testing is strongly recommended to assess the indications for targeted molecular drugs in patients with unresectable CRC.
>
> [Strong recommendation]

Currently, the FoundationOne CDx and OncoGuide NCC Oncopanel (SYSMEX) are insured to screen for indications of targeted molecular drugs for metastatic CRC patients with disease progression after standard chemotherapy (or in whom disease progression is expected in the near future) in Japan. However, the CGP test ideally should be performed before the first-line therapy. Patients with driver mutations who received a matched targeted agent showed better PFS and OS than those with tumors that did not harbor druggable driver mutations.

2.5 | Liquid biopsy

> Circulating tumor DNA-based CGP testing is strongly recommended to assess the indications for molecular targeted drugs in patients with unresectable CRC.
>
> [Strong recommendation]

Currently, FoundationOne Liquid CDx and Guardant360 CDx (Guardant Health) have been approved for the screening of molecular targeted drugs in patients with metastatic CRC with disease progression after standard chemotherapy (or in whom disease progression is expected in the near future). Compared to tissue-based CGP testing, ctDNA-based CGP testing makes it easier to collect specimens, achieves a short turnaround time, and allows for repeat evaluations. However, if the tumor volume is insufficient, genetic alterations may not be detected. False positives are also expected because of clonal hematopoiesis with indeterminate potential in older patients.[18] In addition, copy-number changes and gene fusions may be difficult to detect. Evaluations of tumor mutational burden in FoundationOne Liquid CDx (Foundation Medicine) is not validated and not insured for the use of pembrolizumab. For those reasons, CGP testing using ctDNA has mainly been used in Japanese clinical practice for cases lacking appropriate tissue samples.

> Gene panel test detecting minimal residual disease is strongly recommended to assess the optimal adjuvant chemotherapy in patients with CRC having received curative resection.
>
> [Strong recommendation]

Circulating tumor DNA has an extremely short half-life in the plasma, that is, 2 h. Next-generation sequencing-based ctDNA analysis has been developed for the evaluation of MRD and detection of cancer recurrence, and its clinical utility has been intensively studied. The Australian DYNAMIC trial reported that a ctDNA-guided approach reduced the use of adjuvant chemotherapy without compromising recurrence-free survival in stage II colon cancer.[19] Although MRD testing has not been approved in Japan, a nationwide project named CIRCULE-Japan has prospectively enrolled up to 6300 patients with clinical stage II/III CRC and resectable oligometastatic disease (GALAXY trial).[20] Clinical utilities of ctDNA testing using large-scale data were also reported in the GALAXY trial.[21]

2.6 | Specimen handling for molecular testing

> Formalin-fixed paraffin-embedded tissue is suitable for genetic testing of somatic mutations in cancers. It is able to assess whether samples have sufficient amount of tumor cells by examining histologic findings using matched hematoxylin and eosin-stained slides. Selection of FFPE samples, decision on the need for macrodissection, and assessment of tumor cellularity should be performed by a pathologist.
>
> [Strong recommendation]

> In performing ctDNA testing, the manufacturer's instructions concerning the use of a collection tube and plasma preparation procedure should be followed.
>
> [Strong recommendation]

2.7 | Quality assurance requirements for testing

> Genetic testing for CRC treatment should be carried out under a quality assurance system.
>
> [Strong recommendation]

AUTHOR CONTRIBUTIONS

Hideaki Bando: Conceptualization; funding acquisition; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Kyoko Yamaguchi:** Writing – review

and editing. **Seiichiro Mitani:** Writing – review and editing. **Kentaro Sawada:** Writing – review and editing. **Saori Mishima:** Writing – review and editing. **Keigo Komine:** Writing – review and editing. **Yoshinaga Okugawa:** Writing – review and editing. **Waki Hosoda:** Writing – review and editing. **Hiromichi Ebi:** Conceptualization; funding acquisition; methodology; project administration; visualization; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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