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次世代シークエンサー等を用いた遺伝子パネル検査に基づく
がん診療ガイダンスの改訂のための研究

（資料 5）

英訳版クリニカルクエスチョン

（全 21 ページ）

II. Clinical Questions

CQ1　Is cancer genomic profiling recommended for accurate diagnosis in patients with solid tumors?

Recommendation: Although whether cancer genomic profiling contributes to an accurate diagnosis is not clear, it has been reported to be useful in some diseases.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 2, R: 3, ECO: 17, NR: 1, A: 4]

The main purpose of approved cancer genomic profiling tests is to assist in selecting a treatment. They are not intended for the purpose of diagnosis. However, an overseas study of soft tissue sarcomas examined 5,749 patients and reported that the genomic profiling led to a change of diagnosis by detecting characteristic fusion genes in 132 patients (2%) and a more detailed diagnosis of the histological type in 99 patients (2%). In the TOP-GEAR project in Japan, which used the NCC Oncopanel test, MDM2 amplification was seen in 2 of 187 cases, and the profiling results were found to be useful in diagnosing dedifferentiated liposarcomas.[18] Although the results can be expected to vary depending on the disease and the panel test used, genomic profiling may contribute to an accurate diagnosis in some diseases and will be the topic of future investigation.

CQ2　Is genomic profiling recommended to improve the prognosis of patients with solid tumors?

Recommendation: Whether cancer genomic profiling improves prognosis is not clear. However, selecting the patients and the timing of the testing may enable improvement of prognosis.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 5, ECO: 16, NR: 1, A: 4]

In the SHIVA study, a randomized controlled trial, 195 patients with solid tumors who had completed standard treatment were randomized to a group that received the study treatment (99 patients) or a control group (96 patients). Patients in the study treatment group were administered a molecularly targeted agent to which they were matched based on test results. Those in the control group were administered a drug therapy selected by the investigator[55] (Table II-1). However, no improvement in prognosis was obtained in the study treatment group. On the other hand, in retrospective cohort or case series studies, comparisons with matched control groups or within cohorts suggested improvements in prognosis, although treatment histories and the timing of the testing varied between the studies (Table II-2). There have been no reports of randomized controlled studies that have shown an improvement in prognosis with cancer genomic profiling in patients who have not yet completed standard treatment.

The results can be expected to vary greatly depending on factors such as subject selection, timing of the testing, the genomic profiling panel used, and access to the subsequent drug therapy. Consequently, it is currently difficult to specify the types of patients who should undergo cancer genomic profiling from the perspective of prognosis improvement, and this is a topic for future investigation.

Table II-1 Molecularly targeted agents in the SHIVA study

Targets	Molecular alterations	Molecularly targeted agents
KIT, ABL 1/2, RET	Activating mutation† or amplification*	Imatinib 400 mg qd PO
PI3KCA, AKT1 AKT2, 3, mTOR, RAPTOR, RICTOR PTEN STK11 INPP4B	Activating mutation or amplification Amplification Amplification Homozygous deletion or heterozygous deletion + inactivating mutation or heterozygous deletion + IHC confirmation Homozygous deletion or heterozygous deletion + inactivating mutation Homozygous deletion	Everolimus 10 mg qd PO
BRAF	Activating mutation or amplification Abirterone 1000 mg qd PO	Vemurafenib 960 mg bid PO
PDGFRA/B, FLT3	Activating mutation or amplification	Sorafenib 400 mg bid PO
EGFR	Activating mutation or amplification	Erlotinib 150 mg qd PO
ERBB2/HER2	Activating mutation or amplification	Lapatinib 1000 mg qd PO + Trastuzumab 8 mg/kg IV followed by 6 mg/kg IV q3w
SRC EPHA2, LCK, YES1	Activating mutation or amplification Amplification	Dasatinib 70 mg bid PO
ER, PR	Protein expression > 10%	Tamoxifen 20 mg qd PO (or letrozole 2-5 mg qd PO if contraindicated)
AR	Protein expression > 10%	Abiraterone 1000 mg qd PO

Table II-2 Investigations of cancer genomic profiling and prognosis

Clinical Study	Design	Sample Size	Cancer Type	Intervention	Results (vs control)
SHIVA[48]	Randomized phase II study	195	Metastatic solid tumors After completion of standard treatment	Molecularly targeted agents	PFS 2.3 vs 2.0 months, HR 0.88, *P*=0.41
I-PREDICT[57]	Cohort or case series	83	Solid tumors Treated	Molecularly targeted agents, immune checkpoint inhibitors	PFS 6.5 vs 3.1 months (matched >50% vs ≤50%), HR 0.40, *P*=0.001
LCMC[58]	Cohort or case series	578	Lung cancer	Molecularly targeted agents	OS 3.5 vs 2.4 years, HR 0.69, *P*=0.006
LCMCII[59]	Cohort or case series	875	Lung cancer	Molecularly targeted agents	OS 2.7 vs 1.5 years
MD Anderson Cancer Center Initiative[60]	Cohort or case series	291	Solid tumors	Molecularly targeted agents	Response 27% vs. 5%; *P*<0.0001, TTF 5.2 vs 2.2 months, *P*<0.0001, OS 13.4 vs. 9.0 months, *P*=0.017
Radovich M, et al[61]	Cohort or case series	101	Solid tumors Treatment history of at least 1 regimen	Molecularly targeted agents, chemotherapy, immune checkpoint inhibitors	PFS 86 vs 49 days, HR 0.55, *P*=0.005
UC San Diego Moores Cancer Center PREDICT[62]	Cohort or case series	180	Solid tumors	Molecularly targeted agents, endocrine therapy	PFS 4.0 vs 3.0 months, *P*=0.039, OS 15.7 vs 10.7 months, *P*=0.04
WINTHER trial[63]	Cohort or case series	107	Solid tumors Subsequent to the standard therapy	Molecularly targeted agents, chemotherapy, immune checkpoint inhibitors	HR 0.482 (ARM A), 0.561 (ARM B)
Princess Margaret IMPACT/COMPACT[64]	Cohort or case series	245	Solid tumors	Molecularly targeted agents, chemotherapy, immune checkpoint	Response 19% vs 9%, *P*<0.026

				inhibitors	
Von Hoff DD, et al[65]	Cohort or case series	86	Solid tumors Refractory to 2 or more regimens	Molecularly targeted agents, chemotherapy	PFS ratio ≥ 1.3, *P*=0.007
Schwaederle M, et al[66]	Metaanalysis (phase I studies)	13,203	Solid tumors, hematologic al neoplasm	Molecularly targeted agents, chemotherapy	Response 30.6% vs 4.9%, *P*<0.001, PFS 5.7 vs 2.95 months *P*<0.001
Schwaederle M, et al[67]	(phase II studies)	32,149	Solid tumors, hematologic al neoplasm	Molecularly targeted agents, chemotherapy	Response 31% vs 10.5%, *P*<0.001, PFS 5.9 vs 2.7 months, *P*<0.001, OS 13.7 vs 8.9 months, *P*<0.001

PFS: progression-free survival

HR: hazard ratio

OS: overall survival

TTF: time to treatment failure

CQ3 What are the facility requirements for implementing cancer genomic profiling?

Recommendation: It is recommended that the requirements set forth in the "Guidelines for Establishing Core Hospitals, etc. for Cancer Genomic Medicine" issued by the Ministry of Health, Labour and Welfare be complied with.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 3, R: 8, ECO: 13, NR: 0, A: 3]

Because a variety of capabilities are required to implement the clinical use of gene panel tests with cancer genomic profiling functions, the Ministry of Health, Labour and Welfare (MHLW) established the "Guidelines for Establishing Core Hospitals, etc. for Cancer Genomic Medicine" (referred to as the "establishment guidelines" below). In accordance with the requirements specified in the establishment guidelines, the following medical institutions were established (the numbers of facilities shown are as of September 2019).

• Core hospitals for cancer genomic medicine (11 facilities: designated by the MHLW; referred to as "core hospitals" below)

• Cooperative hospitals for cancer genomic medicine (156 facilities: designated by the MHLW; 34 of these facilities were designated as hub hospitals for cancer genomic medicine in September 2019; referred to as "cooperative hospitals" below)

• Hub hospitals for cancer genomic medicine (34 facilities: designated by the MHLW; referred to as "hub hospitals" below)

The establishment guidelines include the items needed to perform cancer genomic profiling, and adhering to these requirements is recommended.

The period of designation as a core hospital or hub hospital extends through March 2022. The subsequent designation period requires further deliberation and has not yet been determined. To add or eliminate medical institutions as cooperative hospitals, the collaborating core hospital or hub hospital must submit requests to the MHLW annually.

For the 2 gene panel tests with cancer genomic profiling functions that were listed in the national health insurance (NHI) reimbursement price list in June 2019, it was required to undergo these tests at medical institutions indicated in the establishment guidelines. Therefore, currently an individual can undergo gene panel tests covered by insurance at core hospitals, hub hospitals, and cooperative hospitals (referred to below as "core hospitals, etc. for cancer genomic medicine") only.

The establishment guidelines and medical institutions can be seen by clicking on the link to the MHLW website below.

Core hospitals, etc. for cancer care

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/gan/gan_byoin.html

Details regarding the requirements for core hospitals, etc. for cancer genomic medicine and the application procedure can be seen by referring to the establishment guidelines. An overview of the capabilities required of such facilities is provided below.

Table II-3 Capabilities core hospitals, etc. for cancer genomic medicine

		Core Hospitals	Hub Hospitals	Cooperative Hospitals
Capability of providing care based on gene panel testing	Explanation to patients (tests)	Required	Required	Required
	Specimen preparation	Required	Required	Required
	Sequencing	Can be outsourced	Can be outsourced	Can be outsourced
	Holding expert panels	Required	Required	To be requested of a core hospital or hub hospital (participation of attending physician required)
	Report preparation	Required	Required	
	Explanation to patients (results)*1	Required	Required	Required
	Treatment*2	Required	Required	Required
Capability of advancing cancer genomic medicine	Registration with C-CAT*3	Required	Required	Required
	Biobank system	Required	Required	Required
	Clinical research and development	Required	Provide cooperation	Provide cooperation
	Personnel development	Required	Provide cooperation	Provide cooperation

*1: Along with explaining the results of gene panel tests, provide and cooperate in genetic counseling as needed.

*2: Cooperates with other institutions as needed.

*3: Only patients who consent to providing information to C-CAT

In the established system, it is assumed that all of the core hospitals, etc. for cancer genomic medicine have the capability to provide care based on gene panel tests (as for an expert panel, which requires specialists, a cooperative hospital requests the core hospital or hub hospital, with which the cooperative hospital collaborates, to hold an expert panel), and the patients examined undergo the entire process from testing to receiving an explanation of the results without changing the locations. Core hospitals also play a role in advancing cancer genomic medicine. Therefore, they are expected

to take the initiative in areas such as training personnel involved in genomic medicine, developing new genomic tests, and developing drug therapies linked to genes discovered through testing, by collaborating with other medical institutions.

In the 3rd Term Basic Plan to Promote Cancer Control Programs, the Japanese government established the goal of building a system that will enable cancer patients to receive genomic medicine anywhere in the country. Although the establishment of this system will likely continue to progress in stages, the requirements for medical institutions and the system for providing genomic medicine are expected to change flexibly, reflecting the development of new technologies and the associated systemic changes.

Guidelines for Establishing Core Hospitals, etc. for Cancer Genomic Medicine:
https://www.mhlw.go.jp/content/000532262.pdf

CQ4 What are the requirements for an expert panel?
Recommendation: It is recommended that the requirements set forth in the "Guidelines for Establishing Core Hospitals, etc. for Cancer Genomic Medicine" issued by the MHLW be complied with. It is also recommended that a system be constructed that enables close cooperation with the necessary specialists in clinical genetics, genetic counseling, and bioinformatics if such personnel cannot be employed full-time.
Evidence level: Low
Recommendation level: Expert consensus opinion [SR: 2, R: 8, ECO: 13, NR: 1, A: 3]

If the number of gene panel tests increases in the future, returning results to patients could be delayed due to conference wait times if the number of facilities that can hold expert panels independently without relying on a core hospital for cancer genomic medicine does not increase, preventing the genome data obtained from being utilized for care. The MHLW's "Guidelines for Establishing Core Hospitals, etc. for Cancer Genomic Medicine" acknowledge that the specialists required to convene expert panels, particularly specialists in clinical genetics, genetic counseling, and bioinformatics, are difficult for many hospitals to employ on a full-time basis because of the limited number of such specialists in Japan. Clinical genetics specialists and genetic counselors play important roles in responding to secondary findings, but since such findings are more central to the care of the patient's relatives than to the care of the cancer patient himself or herself, there is comparatively more leeway in time to disclose such findings. Therefore, if a system that enables the assistance of a clinical genetics specialist or genetic counselor to be obtained when needed has been established, it is not essential that they be employed full-time. The role of bioinformatics specialists is mainly to validate the quality of specimens and data. However, the gene panel tests that have been approved for insurance are performed in laboratories that have precision controls in place. Therefore, there are unlikely to be many cases in which a data quality validation by a bioinformatics specialist is needed.

In summary, for facilities that do not have full-time specialists in clinical genetics, genetic counseling, or bioinformatics, a system that enables the assistance of such specialists to be quickly obtained should be established in order for these facilities to independently convene expert panels.

CQ5 What types of patients should undergo cancer genomic profiling?

Recommendation: It is not clear what types of patients should undergo cancer genomic profiling. This is a topic for future investigation. The treatments considered after cancer genome profiling are mainly expected to be experimental drug therapies like those used in clinical trials. In other cases, such as when off-label use is considered, patients should be selected whose general condition and organ function after testing indicates that they will be able to tolerate the drug therapy.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 1, ECO: 19, NR: 1, A: 5]

In the SHIVA study, a randomized controlled trial, patients with solid tumors were enrolled after completing standard treatment but showed no improvement in prognosis. On the other hand, improved prognosis as compared with a control group were suggested by the results of retrospective cohort studies. However, although some of these studies limited enrollment to patients with types of cancer such as lung cancer, many enrolled patients with solid tumors as a whole. Consequently, it is unclear what types of cancer patients see improvements in prognosis as a result of genomic profiling.

Approved cancer genomic profiling tests are covered by the national health insurance for the following patients: "of patients with solid tumors for which there is no standard treatment or patients with solid tumors in whom locally advanced disease or metastasis is seen and who have completed standard treatment (including patients expected to complete the treatment), those who are judged by the attending physician to have a strong likelihood of being suitable for chemotherapy after the test according to the chemotherapy guidelines, etc. of the relevant academic society, based on factors such as their general condition and organ function." For each patient, the national health insurance point is calculated once.

If there is a companion diagnostic method for the standard treatment for which evidence has been established, the companion diagnosis should be performed first.

The treatments considered after cancer genomic profiling are mainly expected to be experimental drug therapies like those used in clinical trials. In other cases, such as when off-label use is considered, patients should be selected whose general condition and organ function after testing indicates that they will be able to tolerate the drug therapy.

CQ6 When should cancer genomic profiling be performed?

Recommendation: It is recommended that the optimal timing for cancer genomic profiling be examined without limiting it only by the treatment line and taking into account the subsequent treatment plan.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 8, ECO: 12, NR: 2, A: 4]

In the SHIVA study, a randomized controlled trial, which examined whether administration of a drug to which the patient was matched based on a comprehensive cancer genomic profiling improved the prognosis of patients who had completed standard treatment, no improvement in prognosis was seen. On the other hand, improvements in prognosis were seen as compared with control groups in retrospective cohort studies, many of which did not include only patients who had completed standard treatment. There have been no controlled studies that have examined the timing of cancer genomic profiling with which improvements in prognosis can be expected, and this is a topic for future investigation. However, although it should be noted that there were differences with respect to the subjects and endpoints in these studies, a randomized controlled trial limited to patients who had completed standard treatment did not indicate the efficacy of cancer genomic profiling, while a study not limited to patients who had completed standard treatment suggested efficacy. Thus, there is little scientific basis for restricting cancer genomic profiling to patients have completed standard treatment.

In patients with solid tumors for which a standard treatment has not been established, such as rare cancers and cancers of unknown primary, it is recommended that testing be performed before the start of treatment to assist in selecting a treatment.

It is recommended that the optimal timing for cancer genomic profiling be examined without limiting it only to the treatment line but rather taking into account the plan for subsequent treatment. This is based on the fact that some clinical studies of novel drugs examine the initial treatment, even in types of cancer for which there are multiple standard treatments; the fact that the test results may affect the determination of the treatment plan; and the fact that factors such as the patient's general condition and organ function may worsen while waiting for the standard treatment to be completed, eliminating the opportunity for treatment.

CQ7 What types of specimens should be used for cancer genomic profiling?

Recommendation: It is recommended that the testing be performed according to the relevant rules, such as the guidelines on the handling of pathological tissue samples for genomic medicine.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 4, R: 10, ECO: 9, NR: 0, A: 4]

Formalin-fixed paraffin embedded (FFPE) tissue used for routine pathological diagnosis is used in the gene panel test for cancer genome profiling. However, to obtain high-quality DNA, attention should be paid to tissue collection, fixation, storage, and the percentage tumor cell content and tumor cell content in specimens provided for testing.

The percentage tumor cell content is the proportion of tumor cell nuclei among nucleated cells in the tissue to be analyzed. Since this is sometimes confused with tumor cell occupancy (proportion in terms of area), caution is needed in this regard.

CQ8 What types of gene panels are recommended for cancer genomic profiling?

Recommendations:

1. Selection of a gene panel test performed under the quality assurance requirements for laboratory testing is recommended.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 8, R: 4, ECO: 11, NR: 0, A: 4]

2. It is preferable to first consider using a gene panel test covered by insurance, in view of the financial burden on the patient and the fact that information on clinical trials in Japan is provided by the Center for Cancer Genomics and Advanced Therapeutics (C-CAT).

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 8, ECO: 14, NR: 0, A: 4]

3. There have been no evidence obtained from direct comparisons of the usefulness of different gene panel tests. Therefore, a gene panel test is selected depending on factors such as the purpose of the test and the specimens that can be provided.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 6, ECO: 15, NR: 0, A: 5]

Explanation:

1. Most genetic analysis performed using next-generation sequencers has been implemented for research. However, quality assurance of laboratory testing is required in order to perform gene panel tests in the course of clinical care and to use the results in the care of patients, and in October 2018, the Japanese Promotion Council for Laboratory Testing issued the "Basic Concepts for Ensuring the Quality and Precision of Cancer Gene Panel Tests" (version 2.0, May 31, 2019).[19]
   In the United States, analyses must be performed in clinical laboratories certified according to the provisions of the Clinical Laboratory Improvement Amendments (CLIA), which are laws that establish quality standards for clinical laboratories. In Japan, ISO 15189 and the Laboratory Accreditation Program of the College of American Pathologists (CAP) are used as the clinical laboratory evaluation standards. In a Q & A document issued by the Medical Economics Division, Health Insurance Bureau, MHLW on June 4, 2019, the following question and answer are presented: "Regarding the FoundationOne® CDx Cancer Profile and OncoGuide™ NCC Oncopanel System, which were covered by insurance as of June 1, 2019, the amended Points to Consider Notification dated May 31, 2019 states the following: 'To perform the testing, the measures required to ensure the quality and precision of tests performed using sequencer systems must be established, and the testing must be performed at an insurance medical institution that has been accredited by an appropriate third party involved in testing using sequencer systems. If the testing is subcontracted to a clinical laboratory, the laboratory should also have a similar third-party accreditation.' In this instruction, what does 'an appropriate third-party accreditation' refer to?" To this question, the answer provided states: "Currently, the CAP's Laboratory Accreditation Program corresponds to such a third-party accreditation. If an appropriate new accreditation system is identified, it will be publicly announced."

2. In Japan, a large number of gene panel tests are implemented, including those not

covered by insurance. With such uncovered tests, the cost to the patient may be 500,000 yen or more, which is not insignificant. In 2018, C-CAT was founded for the purpose of collecting, managing, and utilizing genome data from testing performed under insurance-covered medical care. For patients who consent to registration in C-CAT, Japanese clinical trial information corresponding to obtained gene alterations is extracted from the "integrated knowledge base for genomic medicine" created by C-CAT and provided to expert panels as C-CAT survey results. Because this is useful information for the patient, it is preferable to first consider gene panel tests that are covered by insurance.

3. There have been no evidence obtained from direct comparisons of the usefulness of gene panel tests that are covered by insurance or used in the advanced medical care. On the other hand, the amount of specimen required, the eligibility requirements for specimens, and the capabilities of the test differ in part by the gene panel test (see Table I-2). Therefore, a gene panel test should be selected according to the status of the specimens that can be provided and the purpose of the test, based on a thorough understanding of the characteristics of each test.

CQ9 What should be explained to the patient before cancer genomic profiling is performed?

Recommendation: It is recommended that the following be explained: the purpose of the test, who is tested, the method used, the cost, the expected results and limitations, foreseeable drawbacks, pathological germline mutations and suspicion of such, etc.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 4, R: 7, ECO: 13, NR: 0, A: 3]

There have been no controlled studies that have examined the information provided to patients about cancer genomic profiling, how well the patient and their family members understand the information, and their reaction to the information.

The information that should be provided to patients is elaborated on below.

1. The purpose of the cancer genomic profiling

Explain why the test will be performed. The cancer genomic profiling tests that have been approved are those used to explore appropriate drug therapies and therapeutic methods by comprehensively examining large number of cancer-related genes.

2. Patients who undergo cancer genomic profiling

Explain who will undergo cancer genomic profiling. The indication of currently approved cancer genomic profiling tests is "of patients with solid tumors for which there is no standard treatment or patients with solid tumors in whom locally advanced disease or metastasis is seen and who have completed standard treatment (including patients expected to complete the treatment), those who are judged to have a strong likelihood of being suitable for chemotherapy after the test according to the chemotherapy guidelines of the relevant academic society, based on factors such as their general condition and organ function."

3. Method used to perform cancer genomic profiling

The information provided to the patient should also include the following: the types of specimens used (e.g., tissue, blood), the method of collection (whether new specimens will be collected or existing specimens used, etc.), the type of gene panel used (if testing can be performed, what can and cannot be detected, etc.), the risks and cost associated with the test, the possibility that the test may ultimately be unsuccessful, and the fact that core hospitals, hub hospitals, and cooperative hospitals for cancer genomic medicine will share information to enable a detailed examination of the analysis results.

4. Results obtained from cancer genomic profiling

For each test objective, explain what types of results can be expected. If the genomic profiling would be performed to explore appropriate drug therapies and therapeutic methods, explain how likely it is that a drug therapy will be identified. At the same time, also explain beforehand that there is strong possibility that a drug therapy cannot be identified and that the patient should therefore consider whether they wish to undergo the test. It is also necessary to explain beforehand that even if an appropriate drug is identified as a result of the test, it may not be a treatment option in cases such as the following.

- The drug has not received marketing approval in Japan.
- The drug has not received an indication for the type of cancer the patient has.
- The drug has been used only in clinical studies and trials whose eligibility criteria the patient does not meet.

5. Pathological germline mutations that may be identified by performing cancer genomic profiling and the suspicion of such

Depending on the test performed, pathological germline mutations and the suspicion of such should be examined. The following should be explained prior to the test: what a pathological germline mutation is, what can be expected, whether the patient wishes for a pathological germline mutation or the suspicion of such to be disclosed, matters concerning the individual to whom such information would be disclosed, and genetic counseling and additional genetic tests.

CQ10 What information should be included in a cancer genomic profiling report?
Recommendation: It is recommended that a cancer genomic profiling report include information on the scope and limitations of the test with regard to specimen quality, the clinical significance of gene alterations, and pathological germline mutations or the suspicion of such.
Evidence level: Low
Recommendation level: Expert consensus opinion [SR: 3, R: 8, ECO: 13, NR: 0, A: 3]

There has been little reported on the content of cancer genomic profiling reports.

As the consensus of the Clinical Genome Resource (ClinGen) working group in the United States, the minimum variant level data (MVLD) were proposed as the minimum information to be provided when evaluating the clinical significance of genetic alterations. The MVLD include the following: the version of the reference genome, gene name (HUGO gene nomenclature), gene position (HGVS nomenclature), somatic cell/germline distinction and whether determined, alterations of genes and amino acids (HGVS nomenclature), type of anomaly (e.g., SNV, missense), information on clinical significance (e.g., type of markers for response prediction/prognosis prediction/diagnosis, evidence level), and the PMIDs of articles serving as evidence. Although the MVLD constitute the standard for registering clinical evidence related to genetic alterations in the knowledge base, it can also be referenced for cancer genomic profiling reports.[56]

All tests have limitations, and it is difficult to expect cancer genomic profiling to be perfectly accurate or comprehensive. Even if a test is considered the best at the time it is implemented, scientific and technical advances may enable more extensive anomalies to be detected and more appropriate evaluations to be performed in the future. Because the test results can be expected to be reviewed again later, it is best to indicate the scope and limitations of the test in the report so that this information is available for review.

In preparing this guidance, the following items were listed as desirable to indicate in reports by testing facilities and reports by expert panels.

<u>○ Reports by testing facilities (including C-CAT reports)</u>

- Genes targeted, scope of sequencing,[1)] types of anomalies[2)]
- Whether the report should include the results on germline anomalies (if it should includes partially, indicate to that effect)
- Disease name, organ from which specimen collected, date specimen collected, tumor cell percentage[3)]
- Test start date, quality of specimens such as DNAs

- Details on gene alteration detected,[4] specimen in which detected[5]
- Biological significance of gene alteration detected[6]
- Specific candidate drug(s) for gene alteration and evidence level
- Indication(s) of candidate drug(s) and availability rank based on clinical trial information[7]
- Presence/absence and significance of pathological germline mutations or suspicion of such
- Types of databases used to determine significance[8] and dates accessed
- Points to consider that the evaluations of detected gene alterations and their clinical significance, etc. depend on the test method used, programming, and the databases referenced and may change in the future

1) the entire coding region of the gene or a specific region; 2) whether any of fusion, amplification, TMB, MSI, etc., is included; for amplification, its definition; 3) if part of a specimen has been selectively resected (dissection), indicate to that effect; 4) including type of anomaly and variant allele frequency; 5) whether derived from somatic cell or germline; 6) pathological mutations, etc.; 7) ease of accessing treatments; and 8) genetic polymorphism database, knowledge base that compiles evidence for candidate drugs, and other

○ Reports by expert panels

- Whether there is a recommended treatment and a description of any such treatment
- Treatment options other than the recommended treatment
- Whether there are germline mutations for which an explanation to the patient is recommended and descriptions of any such anomalies
- Revisions and additions to reports prepared by testing facilities, etc.
- Sources used as evidence
- That although the review of the expert panel is based on the patient's treatment history, treatments reviewed are other than the standard treatment, and that it is the attending physician's responsibility to judge the implementation of standard treatment
- That the conclusions of the expert panels are based on the scientific knowledge and clinical study information currently available and may change as new information is obtained in the future.

CQ11 What are points to note when explaining the results of cancer genomic profiling?

Recommendation: It is recommended that the following be explained, with adequate consideration given to the emotional state and privacy of the patient and their family members: whether there is an appropriate treatment based on the test results, and the feasibility of implementing any such treatment; and whether pathological germline mutations are found with the cancer gene panel test, and methods of treating them.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 3, R: 7, ECO: 14, NR: 0, A: 3]

There have been no controlled studies that have examined the important points to note when explaining cancer genomic profiling results and the reactions of patients and their family members to the explanation.

When explaining the results, set aside adequate time for the explanation and arrange an environment that takes privacy into account.

In disclosing the results, explain their significance and the treatments and approaches recommended based on the results of the expert panel's review of the test results obtained, and in line with the information explained before the test (see CQ9). Explain that although an appropriate drug is often not found, even if one is found, it often may not be a treatment option for the reasons raised under CQ9.

Before explaining a pathological germline mutation or the suspicion of such, first confirm whether the patient wishes to have the information disclosed and whether they have family members with whom they wish to share the test results. In addition, it is recommended that the patient be told whether there were secondary findings and, as necessary, that information be provided on genetic counseling or the need for supplemental genetic testing.

If the patient is a child, adolescent, or young adult (see "*3: Confirmation of willingness in child, adolescent, or young adult patients" in Section 2.7 "Genetic counseling"), effort will be made to obtain the informed assent of the subject himself or herself, in addition to the informed consent of the patient's parent or legal guardian.

Because the test results may not necessarily lead to an effective response such as a treatment, it is recommended that the emotional state of the patient also be considered.

CQ12 When should an examination by an expert panel be conducted?

Recommendations:

1. If cancer genomic profiling is performed for the following patients, the results should be reviewed by an expert panel and explained to the patient as soon as possible: "of patients with solid tumors for which there is no standard treatment or patients with solid tumors in whom locally advanced disease or metastasis is seen and who have completed standard treatment (including patients expected to complete the treatment), those who are judged by the attending physician to have a strong likelihood of being suitable for chemotherapy after the test according to the chemotherapy guidelines of the relevant academic society, based on factors such as their general condition and organ function."

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 9, ECO: 14, NR: 0, A: 3]

2. An expert panel should also review the results as soon as possible when cancer genomic profiling results are obtained for patients other than those described above. It is recommended that the timing of the results explanation be determined on an individual basis after the review by the expert panel.

Evidence level: Low

Recommendation level: Expert consensus opinion [SR: 1, R: 9, ECO: 13, NR: 1, A: 3]

1. It is expected that cancer genomic profiling will be performed to assist in selecting treatments for patients with solid tumors for which there is no standard treatment or for which the standard treatment has been completed. In order not to miss the opportunity for treatment, and to enable the results to be quickly provided to the patient, the expert panel should review the test results and they should be explained to the patient as soon as possible.

2. Currently (as of September 2019), the following rule is specified: "The national health insurance point can also be calculated when the results for a comprehensive genome profile obtained in conjunction with an assessment of a specific gene mutation, which was performed to select an anticancer drug treatment, are provided to the patient after being reviewed by an expert panel following the completion of standard treatment and a written explanation of the treatment strategy, etc., is provided to the patient."

If, for any reason, the results of cancer genomic profiling have already been received

for a patient, delaying the expert panel review until after the completion of standard treatment and waiting to provide the results to the patient are not permitted from scientific and ethical perspectives, because such actions could limit the patient's treatment options, delay a response to information that ought to be addressed, such as secondary findings, or result in delayed or insufficient information provision. It is preferable for the expert panel to review the test results as soon as possible. With regard to when to provide the results to the patient, it is preferable to respond on an individual basis following the review by the expert panel and after deciding what results to provide quickly and what results require further appropriate discussion.