November 2022

Health and Global Policy Institute

Policy Recommendations: Furthering the Development of Precision Cancer Medicine

—Proposals for Effective Policy Changes Based on Key Characteristics of Precision Medicine in Cancer Treatment—

Summary

While remarkable progress has been made in cancer medicine in recent years, there are particularly high expectations for precision medicine to play a critical role in cancer treatment in the future. This field, sometimes referred to as precision cancer medicine, is a form of treatment tailored to individuals based on the genetic mutations and other characteristics of their cancer.

To further develop precision cancer medicine, it will be necessary to overcome policy issues in various areas including: (i) access to medical care, (ii) human resource development, (iii) research and development, (iv) regulatory approval and health insurance coverage, and (v) patient support. Although many of these issues are shared among various forms of cancer medicine, precision cancer medicine has the following three key characteristics which further complicate efforts to address them, namely: (a) the number of medical indications for its use are still quite limited; (b) it involves the use of genetic information; and (c) the costs of testing and treatment are often expensive. As such, attempts to address the policy issues mentioned above will be more effective if they have a firm basis in these key characteristics. Based on a recognition of this issue, Health and Global Policy Institute (HGPI) offers the following recommendations to promote the development of precision cancer medicine:

Recommendation I: To effectively allocate human resources and aggregate knowledge, a "hub-and-spokes" network should be developed across all areas, including (i) healthcare delivery systems, (ii) human resources, (iii) research and clinical trials, and (iv) patient support measures. When doing so, proactive steps to adopt information and communication technology (ICT), including the use of online services, should be taken to streamline the aggregation of information and medical resources.

Recommendation II: While establishing data repositories for genetic information, legislation prohibiting discrimination based on genetic information should be enacted and public awareness activities should be conducted.

Recommendation III: Regulatory approval, health insurance coverage, and other conditions governing the use of precision cancer medicine should be revised to be made more scientific and rational in a manner that complements the key characteristics of precision cancer medicine and practical needs in clinical settings.

HGPI strongly hopes these recommendations will be utilized in future cancer control measures to further develop patient-centered healthcare.

Introduction

Remarkable progress has been made in cancer therapies in recent years, particularly in precision cancer medicine, in which treatment is tailored to individuals based on the genetic mutations and other characteristics of their cancer.

While the devoted efforts of related parties have resulted in a steady increase in successful treatments and other accomplishments for precision cancer medicine, like other areas of cancer medicine, it faces various issues related to policy. Moving forward, it will be crucial to steadily overcome these issues with particular attention on the voices of people who serve in healthcare settings as well as those of patients. When doing so, adequate attention must be paid to the key characteristics of precision cancer medicine, namely: **(a) the number of medical indications for its use are still quite limited**; **(b) it involves the use of genetic information**; and **(c) the costs of testing and treatment are often expensive**. It is desirable that proactive steps are taken to effectively address policy issues while keeping these characteristics in mind.

In recognition of these issues, Health and Global Policy Institute (HGPI) kicked off an initiative called the "Project for Considering the Future of Precision Medicine with Industry, Government, Academia, and Civil Society" in FY2021. The recommendations offered in this document are based on repeated discussions we have held with various experts in this area as part of that initiative.

In this proposal, after (i) providing a simple explanation and overview of precision cancer medicine, including genomic cancer medicine, and their characteristics, we will (ii) arrange current policy issues by key area and (iii) provide recommendations based on those issues and, under three pillars, outline the policy actions we believe are most important to take now.

The fourth-term Basic Plan to Promote Cancer Control Programs will come into effect in 2023. HGPI strongly hopes these recommendations will be utilized in future cancer control measures to further develop patient-centered healthcare.

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1 An overview of precision cancer medicine

1.1 What are precision cancer medicine and genomic cancer medicine?

Precision cancer medicine refers to cancer treatment that is tailored to individuals. More specifically, it is the administration of drug therapies that target the mutated sections of genes of each individual's cancer cells.[1] (For more information, please refer to "Reference 1 – The Definition of Precision Cancer Medicine.")

Another term that is often used alongside precision cancer medicine is genomic cancer medicine. This document defines genomic cancer medicine as a field of precision cancer medicine, in which tests focusing on the genome (all genetic information starting with genes) are conducted, and treatment decisions are made according to test results (in which drug therapy is based on genomic information).[2]

In conventional cancer drug therapy, cancers are usually perceived in terms of the affected organ, and drugs are administered with the expectation they will be effective for that type of cancer. In precision cancer medicine, the cancer cells of the individual patient receiving treatment are identified as the section of the gene where mutations are occurring, and drugs that are particularly effective on those mutated genes and molecules called molecularly targeted drugs[3] are selected and administered. In this manner, compared to conventional cancer drug therapy, more targeted therapies are administered in precision cancer medicine, and this can reduce burdens on patients, increase response rates, and achieve better outcomes.

Recently, applications of precision cancer medicine have been gradually expanding. For example, in clinical settings, when considering optimal treatments for certain forms of cancer, like lung or breast cancer, it has become common practice to first conduct cancer gene tests to detect genetic mutations that can be targeted by molecularly targeted drugs.

In general terms, however, precision cancer medicine is (1) a form of therapy that targets specific genetic mutations for which the number of indications is still limited.[4] Additionally, (2) conducting the

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[1] Cancer cells are known to develop due to genetic mutations that generally occur because of factors like lifestyle and aging. However, certain cancers (called "familial" or "hereditary" tumors) occur due to strong influence from the genes in normal cells throughout the entire body (which cause "inborn" or "congenital" mutations).

[2] The third-term Basic Plan to Promote Cancer Control Programs (which was enacted by Cabinet Decision on March 9, 2018) defines genomic medicine as "providing medical treatment according an individual's physical characteristics or symptoms based on information, particularly individual genetic information, obtained using any form of omics-based testing." (Page 16 footnote, https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000196975.pdf)

[3] Even for two different types of cancer, one molecularly targeted drug may be effective for both if the mutated sections of the gene are the same.

[4] If all pathogenic mutations that may be targeted through precision cancer medicine are taken together, the number of patients is by no means small. However, the highly individualized nature of mutations means there is only a limited number of patients with each pathogenic mutation. Furthermore, even if certain genetic mutations are detected, there are many cases in which drugs that are likely to effectively target that mutation have not yet been developed.
Because it is likely that the number of drugs and other therapies will increase as research advances, it is safe to say that the

genetic testing required before precision cancer therapy can be provided requires advanced technology and highly-trained specialists. Furthermore, because (3) certain tests and molecularly targeted drugs are expensive, national health insurance coverage is limited.

(Reference 1) The definition of precision cancer medicine

While the definition of precision cancer medicine can vary depending on the source, in this document, we use it to refer to all tests and treatments that (1) focus on the mutated sections of genes to (2) provide the optimal drugs for those mutations (Table 1).

In practice, definitive cancer diagnoses are usually reached by using a combination of multiple testing methods, such as those listed in Table 1. For example, imaging studies may be combined with pathological examinations.

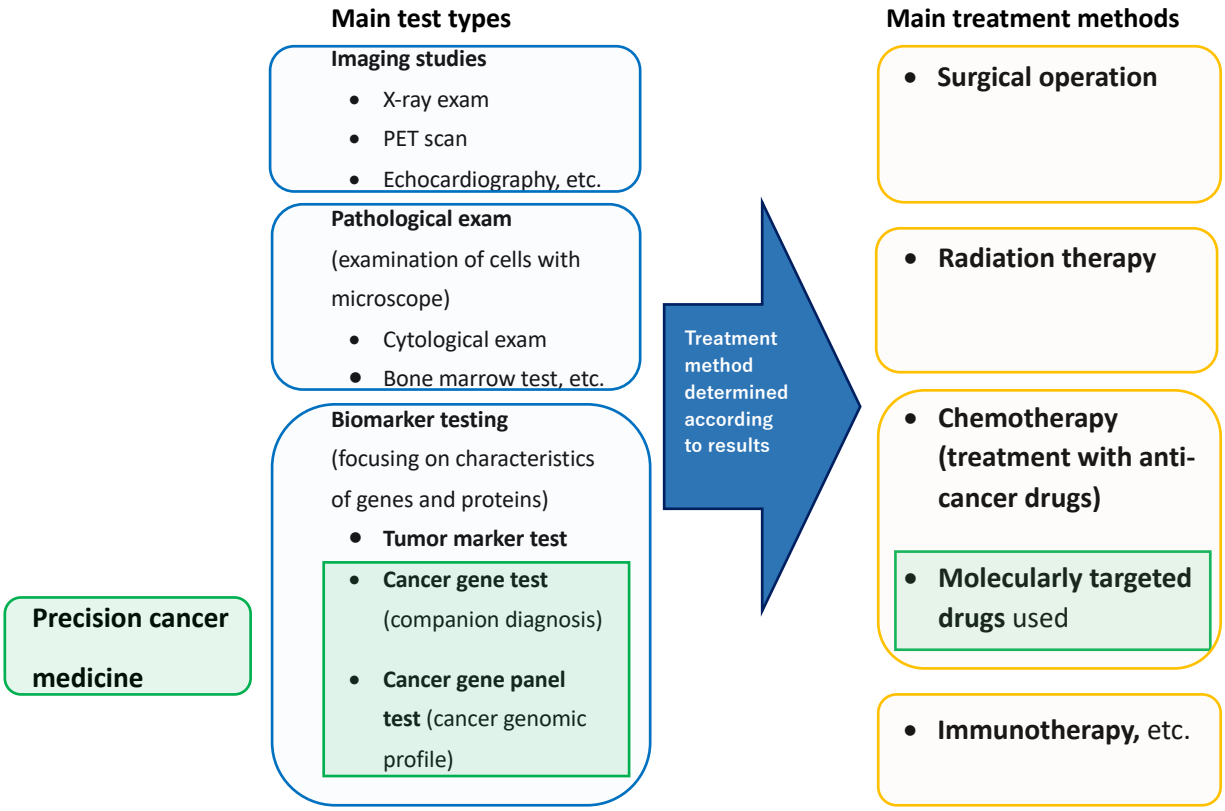
There are cases in which cancer gene tests or other such tests are conducted but molecularly targeted drugs or similar treatments are not selected.[5] We include such cases within the scope of "precision cancer medicine," since the testing phase focuses on genetic mutations.[6]

number of diseases for which precision therapy is indicated is still limited at this time.

[5] When (1) drugs that can be expected to effectively target a genetic mutation have not yet been developed, or (2) genomic cancer testing does not reveal specific genetic mutations that are targeted by existing molecularly targeted drugs, then it is assumed that existing molecularly targeted drugs will not be effective even if administered, and other treatment methods are pursued.

[6] There are also cases in which testing reveals the presence of inherited genetic mutations that are likely to result in hereditary tumors.

Table 1: Defining precision cancer medicine



(Reference 2) Methods of conducting genetic testing for cancer

The two methods of genetic testing for cancer are (1) cancer gene testing (companion diagnostic testing) and (2) cancer gene panel testing (genomic cancer testing or profiling). Summaries of testing methods and their characteristics are provided below.

a. Cancer gene testing (companion diagnostic testing)

To determine if a certain drug (namely, a molecularly targeted drug) will be effective for the cancer of the patient in question, a single test is conducted to detect mutations in one or multiple genes. As a general rule, these tests involve the use of diagnostic agents called companion diagnostics, or CDx.[7]

For certain types of cancer, such as lung cancer or breast cancer, these genetic tests are covered by insurance and are currently used in clinical settings to provide precision cancer therapy.

b. Gene panel testing (genomic cancer testing or profiling)

These procedures use a single test to detect the presence or absence of mutations in many genes, usually over 100. As the results of these tests can make it possible to more accurately grasp the

[7] The name "companion diagnostic" is derived from the fact that these diagnostic agents are administered before specific molecularly targeted drugs as sets (companions), matched on a one-to-one basis.

characteristics of the cancer that is to be treated (namely, the types of mutations), expectations are high that they will contribute to therapies using advanced treatments. However, they are even more expensive than option (1) above because they use specialized equipment to read vast amounts of genetic information at high speeds.

Due to the high cost of cancer gene panel testing (and subsequent genome information-based drug therapy), the use of these treatments – known as genomic cancer therapy – is, in most cases, subject to strict conditions. These include situations when no standard treatments are available or when standard treatments have already been completed. As a result, their use is often limited to advanced medical treatments and clinical trials.[8]

Furthermore, the genetic mutations detected by cancer gene panel tests are subject to review by committees that include multiple specialists called expert panels. This is another reason that precision cancer therapy is considered an advanced medical treatment.

[8] Certain tests are covered by insurance.

1.2 Key characteristics of precision cancer medicine

As seen above, precision cancer medicine is a promising method of treating cancer. However, it possesses three key characteristics: **(a) the number of medical indications for its use are still limited**; **(b) it involves the use of genetic information**;[9] and **(c) testing and treatment tend to be expensive** (Table 2).

Table 2: Key characteristics of precision cancer medicine

(a) The number of medical indications for its use are still quite limited
(b) It involves the use of genetic information.
(c) The costs of testing and treatment are often expensive.

In general, existing testing, examination, and treatment systems have been designed around the premise of examining cancers by organ. In contrast, in precision cancer medicine, diseases are examined with the focus on genetic mutations. Therefore, in order to fully incorporate and utilize precision medicine within cancer treatment, a paradigm shift that encompasses all cancer testing, examination, and treatment systems (as well as R&D, regulatory approval, and patient support systems) is needed. Furthermore, because it can be said that its development is still an ongoing process of this, many policy issues exist.

Given these circumstances, when addressing the various policy issues for precision cancer medicine, it is necessary that effective actions are taken in a proactive manner and are firmly based on the key characteristics of precision cancer medicine. (These actions will be described in a later section.)

[9] Not only is advanced technology required to conduct genetic testing, careful measures are also required to protect genetic information, which is highly personal. (These measures will be described later.)

2. Major policy issues facing precision cancer medicine

2.1 Summary

On one hand, while precision medicine is an emerging form of cancer treatment, the many policy issues it faces are s not uncommon within the realm of cancer treatment methods.

For example, it goes without saying that a key issue for all forms of cancer medicine is improving access by establishing health systems that allow all patients and citizens in all regions to receive treatment in an equitable manner.[10]

On the other hand, as previously discussed, precision cancer medicine **(a) is still only indicated for a limited number of diseases**, **(b) involves the use of genetic information**, and **(c) tends to involve expensive tests and treatments**. Accordingly, (i) there are a number of policy issues unique to precision cancer medicine, and (ii) even when the issues it faces are shared with other forms of cancer medicine, there are times overcoming those issues in precision cancer medicine is more difficult.

For example, regarding healthcare access there is often a lack of trained specialists or facilities that have been established to provide precision cancer medicine. This reflects the first two key characteristics, (**(a) the number of indications is still limited** and **(b) it involves the use of genetic information**). Such issues make it more difficult to achieve equitable access to care while still centering care around existing core cancer hospitals.[11]

Taking these characteristics into account, current policy issues for precision cancer medicine in each key area have been summarized in the following section.

2.2 Policy issues by key area

A) Improving healthcare access and achieving equity in the healthcare provision system

As to healthcare access, policy issues on precision cancer medicine may be categorized as follows:

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[10] For example, looking at the current number of core hospitals and other institutes providing general cancer treatments, in addition to (i) the National Cancer Center, which serves as the central medical institution for cancer and has two locations, there are also (ii) core hospitals for coordinated cancer care (including (a) 51 prefectural core hospitals for coordinated cancer care and (b) 354 regional core hospitals for coordinated cancer care, with around one in each secondary care area). Efforts to consolidate care and achieve nationwide care equity are currently underway, but disparities in progress among prefectures still exist. (Listed numbers of institutions current as of April 1, 2022.)

[11] In recent years, steady developments have been made in establishing systems for providing genomic cancer treatment. For example, (i) data from genetic tests is now being gathered at a central location, the Center for Cancer Genomics and Advanced Therapies, (ii) a system for designating healthcare institutions to provide genomic cancer care and to enable collaboration among care facilities have been established, and (iii) expert panels have been established at core hospitals for genomic cancer care and similar facilities for evaluating test results and proposing optimal approaches to treatment. As of May 2022, there are currently (a) twelve central cancer hospitals for genomic cancer treatment, (b) 33 core cancer hospitals for genomic cancer treatment, and (c) 188 core hospitals for coordinated genomic cancer treatment (which coordinate with the facilities described in (a) and (b) to conduct cancer gene panel tests).

(1) Need to establish care provision systems and similar systems centered around core hospitals

As discussed above, there are shared issues between precision cancer medicine and the field of cancer medicine as a whole with respect to establishing care provision systems and similar systems centered around core hospitals. Sufficient progress, however, has yet to be made in efforts to build said systems for precision cancer medicine, due to one of its key characteristics: (**(a) only indicated for a limited number of diseases**) (Table 3-A: A-1).[12]

(2) Shortages of specialists including physicians and nurses

Shortages of specialists, including physicians and nurses, is commonly seen in all types of cancer care (Table 3-A: A-2). However, for precision cancer medicine, **(a) the number of indications is still limited** and **(b) it involves the use of genetic information**, so educating and securing specialized human resources (including pathologists, clinical laboratory technicians, genetic counselors,[13] and expert panel members) presents a major challenge (Table 3-A: A-2 through A-4).

[12] Similar circumstances can also be seen for rare diseases which affect relatively few patients, such as Parkinson's disease and ulcerative colitis.

[13] Genetic counselors: Specialists who utilize their expertise in genetics to support patients (such as by providing them with psychological care, counseling, or appropriate medical information).

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Table 3-A: Main policy issues for precision cancer medicine (Improving access to care, etc.)

◎: Key characteristic of precision cancer medicine, etc. with a relatively strong relationship to an individual issue

○: Key characteristic of precision cancer medicine, etc. related to an individual issue

(A) Improving Access and Equal Distribution of Medical Care						
	Issue	Explanation and Supplementary Information	Common Issue in Cancer Medicine in General	Issues Related to Precision Cancer Medicine		
				(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
A– 1	**Disparities in Access to Medical Care Delivery Systems that are Centered Around Core**	Improvement from a hardware approach remains difficult due to population decline and budget issues. Use of ICT can be expected to improve access disparities from a software approach, but currently its use is limited.	○	◎	○	
A– 2	**Human Resource Shortages** (physicians, nurses, pathologists, clinical technologists)	Not all medical personnel possess knowledge and experience related to precision cancer medicine, and training opportunities are limited. Development of human resources is especially difficult in rural areas. In the development of core hospitals for precision cancer medicine, it is necessary to meet the requirements for human resource standards and medical treatment systems within each facility.	○	◎	◎	
A– 3	**Human Resource Shortages** (genetic counselors)	As genomic medicine continues to develop, the demand for genetic counselors is expected to rise. Despite this need, certification is carried out only by academic societies. Furthermore, the training of genetic counselors is also a challenge not only in terms of quantity, but in terms of quality as well.		◎	◎	
A– 4	**Expert Panel Shortages**	There is concern that widespread implementation of precision cancer medicine and the associated tests and diagnosis that go with it will cause even large hospitals to face difficulties in providing expert panels and other related services.		◎	◎	

B) Scope of health insurance coverage

Regarding health insurance coverage, it is not surprising to see that precision cancer medicine faces significant limitations since **(c) tests and treatments for precision cancer medicine tend to be expensive**. However, when looking at the current scope and conditions for health insurance coverage, we see that they do not sufficiently reflect the latest scientific advances and needs in clinical settings. In addition, when examining those conditions from a health economics perspective, we see that many of them have become unreasonable.[14]

Policy issues on health insurance coverage of precision cancer medicine may be categorized into the following:

(1) Limited scope of health insurance coverage for testing

First, when using companion diagnostics, even though it is not rare for measurements to fail because of factors like insufficient specimen volume or poor specimen quality, tests in which specimens have been resubmitted are not covered. This causes an unreasonable problem – namely, that retesting is virtually impossible (Table 3-B: B-1).

Second, despite the fact that it is extremely important to monitor for gene mutations that may occur over the course of treatment to enhance treatment outcomes, liquid biopsies,[15] which provide that information, are not covered by insurance (Table 3-B: B-2).

Third, despite the fact that conducting cancer gene panel tests[16] at diagnosis has the potential to result in better prognosis, at the present, these tests can only be performed after patients have completed standard treatments. Because of this, there have been very many cases in which a patient can no longer undergo a treatment by the time they get their test results, which is a serious problem (Table 3-B: B-3).

(2) Limited scope of health insurance coverage for medical services

Despite being an essential part of genetic testing, genetic counselling is not usually covered by

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[14] If, when utilizing precision cancer medicine, (1) patients with genotypes that are eligible for new treatments are identified *in advance* by screening with cancer gene panel tests and other such tests and (2) the majority of patients (those who do not possess the genetic mutations that would make them eligible for targeted therapies) are provided with standard treatments, it would not only be much more scientific, it would also be much more likely to achieve patient-centered healthcare. In fact, it is safe to say this is already happening to a degree for certain types of cancers, such as lung cancer or breast cancer.
For other types of cancer treatment, however, owing to the fact that **(c) testing and treatments tend to be expensive**, an issue rooted in health economics, testing is currently treated as something that should only be conducted in a limited capacity. Promising treatments are not being sufficiently provided nor is sufficient evidence being gathered, which results in negative effects for "D. Regulatory Approval" (described in a later section).

[15] An analysis of genes contained in bodily fluids samples ("liquid biopsy samples") such as blood, urine, sputum, cerebrospinal fluid, and stool.

[16] Health insurance currently covers three cancer gene panel tests.

insurance. This demonstrates an imbalance between what is covered and what is not (Table 3-B: B-4).

(3) Timing the start of genomic cancer therapy

Patients generally cannot begin genomic cancer therapy unless they have already completed standard treatments. This means patients with conditions where prognosis is severe, like pancreatic cancer, face absurd situations in which they cannot receive what are likely to be optimal treatments at early stages (Table 3-B: B-5).

Table 3-B: Main policy issues for precision cancer medicine (Scope of health insurance coverage)

(B)Scope of Health Insurance Coverage						
				Issues Related to Precision Cancer Medicine		
	Issue	**Explanation and Supplementary Information**	**Common Issue in Cancer Medicine in General**	**(a)Limited Medical Indications**	**(b)Use of Genetic Information**	**(c)High Cost of Testing and Treatment**
B- 1	**Limitations related to the Number of Tests** (companion diagnostics (CDx))	Re-testing due to technical failures is not covered by insurance. A significant number of such cases have been observed, creating a barrier to optimal treatment.			○	◎
B- 2	**Limitations related to the Number of Tests and Testing Period** (liquid biopsies)	Insurance does not cover the monitoring that is necessary to examine dynamic genetic changes over the course of treatment.			○	◎
B- 3	**Limitations related to the Timing of Testing** (cancer gene panel test)	If done at the time of diagnosis, cancer gene panel testing has the potential to improve treatment prognosis. However, it currently is not carried out until after standard cancer treatment has finished.			○	◎
B- 4	**Limitations related to Target Services** (genetic counseling)	Insurance does not cover much of the genetic counseling that is required in conjunction with genetic testing.			○	◎
B- 5	**Limitations related to the Timing of Treatment** (cancer genome medicine)	Genomic therapies are only available after the completion ofstandard cancer treatment (or in the absence of possible standard treatment), which prevents early access to optimal treatment.			○	◎

C) Research and development (including clinical trials, effective data utilization, etc.)

With regards to research and development (including clinical trials, effective data utilization, etc.), policy issues generally fall into one of three categories:

(1) Reinforcing collaboration among researchers and health specialists or among organizations

Collaboration among researchers and health specialists or between organizations is a shared issue for all forms of cancer medicine. Precision cancer medicine, however, faces additional issues because **(a) the number of indications is still quite limited**. In particular, (a) insufficient systems and human resources have resulted in regional disparities in access to clinical trials; (b) it is difficult to gather sufficient data for clinical trials and similar efforts because overall patient numbers are low in terms of affected organ or genetic mutation; and (c) it is difficult for hospitals to coordinate (Table 3-C: C-1 and C-2).

(2) Building databases and making effective use of data

Another issue that is common across cancer medicine is building databases and making effective use of data. Particular care must be taken for precision cancer medicine, however, because **(b) it involves the use of genetic information** (Table 3-C: C-3 and C-4).[17]

(3) Providing feedback on the results of research to the patients and general public

Another policy issue shared among all cancer treatments is returning the results of research to the patients and to general public. Once again, particular care is necessary with precision cancer medicine because it **(b) involves the use of genetic information**. Regardless, efforts to establish systems to share such information and return it to the public have been slow (Table 3-C: C-5).

Table 3-C: Main policy issues for precision cancer medicine (Research and development)

(C) Research and Development (Clinical Testing, Data Use, etc.)						
				Issues Related to Precision Cancer Medicine		
	Issue	Explanation and Supplementary Information	Common Issue in Cancer Medicine in General	(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
C- 1	Lack of Collabortaion between Core Hospitals	Although core hospitals are supposed to play a central role in promoting clinical trials, there are geographical disparities in terms of access to clinical trials. In order to increase the number of participants in clinical trials, close collaboration among core hospitals is necessary.	○	◎	○	
C- 2	Lack of Collaboration between Industry, Government, and Academia	Along with the commencement of the "Anti-Tumor Drug Development Forum", efforts have been made to promote collaboration between industry, government, and academia. However, further efforts are needed.	○	◎		
C- 3	Delay in the Construction of a Database for Genomic Information	Systems and methods for utilizing results from whole genome analyses are being investigated as a part of the Whole Genome Analysis Action Plan. However, the construction of a large-scale Japanese whole genome sequence data base has been delayed.	○	○	◎	
C- 4	Delay in the Industrial Utilization of Data for Secondary Uses, Drug Discovery, etc.	Due to the protection of personal information and maintenance of database construction, secondary uses of registry data from academic societies have not progressed.	○	○	◎	
C- 5	Insufficient Return of Research Results to Patients and the Public	The current system is not structured to provide prompt feedback to patients when new treatments are developed as a result of research. The current structure also makes it difficult for patients to understand the benefits of participating in research.	○		◎	

D) Regulatory approval and related topics

Looking at how precision cancer medicine is handled during regulatory approval and similar processes, there are certain aspects that do not line up with conditions in research and development or in clinical

[17] The "Basic Policy on Economic and Fiscal Management and Reform 2022" (approved by Cabinet Decision on June 7, 2022) reads, "To promote drug discovery related to cancer and intractable diseases, we will build information infrastructure that links and carries clinical information and such information as the results of whole genome analyses, and immediately lay down the groundwork for its utilization."
(https://www5.cao.go.jp/keizai-shimon/kaigi/cabinet/2022/2022_basicpolicies_en.pdf, page 46)

settings, and that could be considered unreasonable.

Policy issues on regulatory approvals of precision cancer medicine may be categorized into two as follows:

(1) Regulatory approval for therapeutic agents

Simultaneous approval is required for the companion a diagnosis (that **(b) involves the use of genetic information**) and the drug that is to be prescribed based on the results of the genetic test. Although, there is a certain degree of rationality to perceiving companion diagnostics and therapeutic agents as a single treatment set to be matched on a one-to-one basis, therefore requiring simultaneous approval, this means that even when a proven therapeutic agent is already available, it will not receive approval from regulatory bodies until approval is granted to the companion diagnostic to which it will be paired. This contributes to what is known as a drug lag.

Furthermore, recent development in medical science have resulted in more complex methods of detecting the presence or absence of specific genetic mutations, making it less necessary for those items to be matched as sets. As such, the time has come to review the practice of approving diagnostics and therapeutic agents as a set (Table 3-D: D-1).[18]

(2) Verifying the effectiveness of diagnostic and therapeutic agents

There are also major issues for verifying the effectiveness of diagnostic and therapeutic agents (using cost-effectiveness calculations).

For example, for cancer gene panel tests, as discussed above in "B. Scope of health insurance coverage," **(c) tests and treatments tend to be expensive**. This means they face very restrictive conditions for coverage, and despite the fact that their use at diagnosis could lead to better prognosis, tests can currently only be performed after standard treatments are completed. It is safe to say this creates unreasonable obstacles for cancer gene panel tests and genomic cancer therapy during cost-effectiveness assessment (Table 3-D: D-2).[19]

In addition, because **(a) the number of indications for precision cancer medicine is still limited**, it is difficult to make regulatory approvals or pharmaceutical prices that are based on sufficient evidence. It will be necessary to conduct a thorough review of the evidence assessment framework, while taking into account the characteristics of precision cancer medicine (Table 3-D: D-3).

[18] For example, examples of therapeutic agents being granted earlier approval with greater flexibility are starting to appear in the U.S.

[19] This could be considered an issue to address by reviewing the conditions for insurance coverage, which have been made more restrictive because testing and treatments are costly.

Table 3-D: Main policy issues for precision cancer medicine (Regulatory approval, etc.)

(D) Regulatory Approval						
	Issue	Explanation and Supplementary Information	Common Issue in Cancer Medicine in General	Issues Related to Precision Cancer Medicine		
				(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
D- 1	**Requirements for Approval of Therapeutics** (requirement that therapeutics are approved at the same time as companion diagnostics (CDx))	Approval of therapeutic drugs is delayed in comparison to other countries (one of the causes of drug lag). Flexible measures such as pre-approval of therapeutics are necessary.			○	◎
D- 2	**Cost-effectiveness Calculations** (timing of cancer gene panel testing)	Cancer gene panel testing is currently limited to after standard cancer treatment has finished. This inevitably reduces the cost-effectiveness of testing and cancer genome therapy.			○	◎
D- 3	**Cost-effectiveness Calculations** (need for evidence based on the unique characteristics of precision medicine)	At present, indications for the use of precision medcine is limited, making it difficult to gather the necessary evidence for approving and determining market-prices of therapeutic drugs.		◎	○	○

E) Ethical, Legal and Social Issues (ELSI)

Generally speaking, policy issues in the area of Ethical, Legal and Social Issues (ELSI)[20] are shared between precision cancer medicine and the field of cancer medicine as a whole, and should be addressed in a comprehensive manner.

For example, learning the results of cancer gene panel tests places extreme psychological burdens and other burdens on patients.[21] At the same time, this could be considered an issue that is shared for all forms of cancer medicine. In this case, it is likely that comprehensive measures that encompass other forms of cancer medicine will be more effective for providing patient-centered responses (Table 3-E: E-1 to E-2).

When it comes to precision cancer medicine, however, there are some areas that require additional consideration because it **(b) involves the use of genetic information**:

(1) Social discrimination

Regarding social discrimination, one issue that is unique to precision cancer medicine is that **(b) it involves the use of genetic information**. To prevent this from causing discrimination or other harm, it will be important to implement broad allowances in terms of both legislation and social awareness (Table 3-E: E-3).

(2) Securing health-related data

As to securing health-related data, it is necessary to handle personal information related to precision cancer medicine in an even more careful manner than when handling other private health and medical data, because **(b) genetic information** can be considered the most private form of personal information (Table 3-E: E-4).

[20] ELSI is a concept that refers to all non-technical challenges that may arise during research, development, and the implementation of new science and technology in society. In the area of precision cancer medicine, it encompasses multi-faceted issues such as: (1) methods of managing genetic information, an extremely personal form of information; (2) methods of communicating and providing psychological care to patients and their families when genetic diseases are detected in test results; and (3) preventing or addressing discrimination or social disadvantages that may occur as a result of genetic diagnoses.

[21] Because the results of genetic information analysis can detect a potential disease not only for the patient but also their blood relatives, special consideration should be paid when providing said results.

Table 3-E: Main policy issues for precision cancer medicine (Ethical, Legal and Social Issues (ELSI))

(E) Ethical, Legal, and Social Implications (ELSIs)						
	Issue	Explanation and Supplementary Information	Common Issue in Cancer Medicine in General	Issues Related to Precision Cancer Medicine		
				(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
E- 1	**Reducing the Psychological Burden on Patients** (in the case that precision cancer medicine is not an option)	It is anticipated that there will be cases in which the results of genetic analysis show that effective methods using precision cancer medicine may not be an option. Sufficient communication with the patient and the family is required beforehand regarding this possibility.	◎		○	
E- 2	**Reducing the Psychological Burden on Patients** (in the case that a patient is found to have a genetic mutation that is associated with hereditary cancer)	In cases where it is revealed that a patient has a genetic mutation associated with hereditary cancer, it is possible that related family members carry the same mutation. Sufficient communication with the patient and the family is required beforehand regarding this possibility.	◎		○	
E- 3	**Remediating Social Discrimination** (in the case of certain genetic mutations)	In addition to legislating the prohibition of genetic discrimination, it is necessary to raise awareness, including in school education, for a wide range of generations.	○		◎	
E- 4	**Protection of Personal Data related to Medical Care and Genetic Information**	The development of guidelines for the handling of genetic information is in progress. As a prerequisite for the use of this data, it is necessary to establish a system for the protection of personal information.	○		◎	

F) Patient and Public Involvement (PPI)

On the topic of policy issues related to Patient and Public Involvement (PPI),[22] just as with the Ethical, Legal and Social Issues (ELSI) described above, we believe that there are many items that should be addressed as shared issues for both precision cancer medicine and other forms of cancer medicine (Table 3-F: F-1).[23]

In general, it is difficult to establish and foster patient advocacy organizations for diseases where **(a) the number of indications is limited** However, we may, consider educating and supporting patient

[22] Patient and Public Involvement (PPI): The act of researchers utilizing the knowledge possessed by patients and citizens (including the family members of patients, former patients, and future patients) as reference throughout the processes of medical research and clinical trials (AMED: Japan Agency for Medical Research and Development, AMED; https://www.amed.go.jp/ppi/teiginado.html). In recent years, the concept of PPI has evolved, and it is now considered necessary to not only involve patients and citizens in research, but in all aspects of health, including in health policy and in decision-making forums (Office of Pharmaceutical Industry Research, https://www.jpma.or.jp/opir/news/065/02.html).

[23] For example, patient advocacy groups are currently participating in formulating guidelines for certain types of cancer. As these sorts of activities expand to include other types of cancer, it will be necessary to establish a framework that enables patient participation from the earliest stages of all policy discussions, including during asset development.

advocacy organizations as a critical first step for promoting PPI in precision cancer medicine (Table 3-F: F-2).[24] [25]

Table 3-F: Main policy issues for precision cancer medicine (Patient and Public Involvement)

(F) Patient and Public Involvement（PPI）						
				Issues Related to Precision Cancer Medicine		
	Issue	Explanation and Supplementary Information	Common Issue in Cancer Medicine in General	(a)Limited Medical Indications	(b)Use of Genetic Information	(c)High Cost of Testing and Treatment
F- 1	**Involvement of Patient Groups** (development of guidelines, process of regulatory approval, etc.)	Although PPI initiatives are underway, they are not sufficiently developed in the field of precision cancer medicine.	◎			
F- 2	**Supporting and Fostering Patient Groups**	In particular, it would be desierable to foster cultivate patient groups that can be involved in policy making and other advocacy activities. The formation of patient groups is considered to be difficult when the number of cases is small. Precision cancer medicine is considered to fall within this category.	○	◎		

[24] "Rare cancers," for example, are defined as tumors with fewer than 6 cases per 100,000 people, making them extremely uncommon. This makes it difficult for affected parties to readily form connections with people with similar diseases who live nearby to share problems and concerns.

[25] Overseas, there are movements to establish patient advocacy groups that match people by "driver genes" which are closely linked to the growth and spread of cancer cells.

3. Recommendations

3.1 Key points of our three recommendations

As discussed in the previous section (Section Two), precision cancer medicine faces various policy issues across a wide range of areas, many of which are closely linked to its key characteristics: **(a) the number of indications is limited**, **(b) it involves the use of genetic information**, and **(c) the costs of testing and treatment are often expensive**.

Given these circumstances, we believe that thorough consideration of these characteristics will contribute to more effective policy approaches. Specifically, it is desirable that multi-faceted policy responses are taken under the pillars of the three recommendations described below (Table 4).

Table 4: Responding to policy issues of precision cancer medicine (key points)

Key characteristic of precision cancer medicine		Three recommendations
(a) The number of indications is still quite limited	→	**Rec. I: To effectively allocate human resources and aggregate knowledge, a "hub-and-spokes" network should be developed across all areas, including (i) healthcare delivery systems, (ii) human resources, (iii) research and clinical trials, and (iv) patient support measures. When doing so, proactive steps to adopt information and communication technology (ICT) including the use of online services, should be taken to streamline the aggregation of information and medical resources.**
(b) It involves the use of genetic information	→	**Rec. II: While establishing data repositories for genetic information, legislation prohibiting discrimination based on genetic information should be enacted and public awareness activities should be conducted.**
(c) The costs of testing and treatment are often expensive	→	**Rec. III: Regulatory approval, health insurance coverage, and other conditions governing the use of precision cancer medicine should be revised to be made more scientific and rational in a manner that complements the key characteristics of precision cancer medicine and practical needs in clinical settings.**

It is our strong hope that urgent policy responses are taken with cooperation from related parties along the three pillars described above.

3.2 Explanation of Recommendation I

1. Basic concept

Because **(a) the number of indications is still quite limited**, precision cancer medicine faces difficult issues not only in providing patients with access to care, but in various fields including securing specialized human resources, gathering research and development-related information (clinical trial data), and patient support.

A system that facilitates the aggregation of necessary health resources (including human resources, supplies, data, and know-how) should be established as soon as possible. When doing so, it may be useful for precision cancer medicine to adopt an approach that is similar to that of rare diseases treatment, where nationwide "hub-and-spokes" networks have been established to make the best possible use of human resources, equipment, data, and know-how. When implementing ICT, while advancing efforts to standardize data and to share knowledge, it is desirable that steps are taken to help specialists respond to all patients, including those who are in remote areas, such as by providing remote medical examinations using the internet.

2. Content of recommendation

Rec. I: To effectively allocate human resources and aggregate knowledge, a "hub-and-spokes" network should be developed across all areas, including (i) healthcare delivery systems, (ii) human resources, (iii) research and clinical trials, and (iv) patient support measures.
When doing so, proactive steps to adopt information and communication technology (ICT) including the use of online services should be taken to streamline the aggregation of information and medical resources.

Specific items to which **Recommendation I** apply are described below (Table 5-1).

1) The healthcare provision system: Build and reinforce a "hub-and-spokes" network centered around central cancer hospitals for genomic cancer treatment to further enhance the healthcare system (related to Table 3-A: A-1).[26]
2) Human resources: Utilizing the network described in (1) above to make it easier to aggregate the clinical knowledge and skills possessed by each specialist. Furthermore, address human resource shortages and enhance human resource quality through the proactive adoption of ICT including effective use of online technologies (related to Table 3-A: A-2 to A-4).
3) Clinical trials: Building and reinforcing a "hub-and-spokes" network in research will also promote decentralized clinical trials (DCTs) (related to Table 3-C: C-1).[27]
4) Establishing data repositories: Establish the data necessary for (1) and (3) above in a centralized manner (related to Table 3-C: C2 to C-4). (For C-3 to C-4, please refer to (1) under "Section 2 – Content of recommendation" under 3. Explanation of **Recommendation II** below)
5) Patient support: When establishing the systems for (1) and (3) above, create an environment that enables information sharing and facilitates cooperation among patients (related to Table 3-F: F-2).

[26] The current system of genomic cancer treatment (see footnote 11) provides a collaborative network of healthcare institutions, and discussions on conditions for designating each hospital based on their operational issues are being held at the working group. However, those discussions are centered around the perspective of what human resources, equipment, and systems will be needed to designate individual institutions, and satisfying those criteria presents high hurdles for healthcare institutions.

[27] Decentralized clinical trials (DCTs): A method of conducting clinical trials that does not require meeting in person by utilizing smartphones, wearable devices, and other digital technologies. In traditional clinical trials, patients visit healthcare institutions where all procedures are performed, including medical examinations, tests, and the administration of pharmaceuticals. This requires them to visit healthcare institutions frequently. With DCT, however, test kits are sent to the patients' homes and physicians provide explanations on pharmaceuticals over the internet. This eliminates the need to commute and lightens the burden on patients.

Table 5-I: Responding to policy issues facing precision cancer medicine (Recommendation I)

	Issue	Recommendation		Issues Related to Precision Cancer Medicine		
			Common Issue in Cancer Medicine in General	(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
A- 1	**Disparities in Access to Medical Care Delivery Systems that are Centered Around Core hospitals**	Further develop the medical system, centered around core hospitals for precision cancer medicine. (1)A network of medical institutions should be established following the "hub and spokes" model. (2)Additionally, ICT should be actively used to promote online medical care and share medical information (PHR).	○	◎	○	
A- 2	**Human Resource Shortages** (physicians, nurses, pathologists, clinical technologists)	(1)Utilize ICT based methods such as online medical care and tele-nursing in order to accumulate knowledge and utilize human resources. (2)Share expert human resources within the network of core hopsitals, rather than within each facility.	○	◎	◎	
A- 3	**Human Resource Shortages** (genetic counselors)	(1)Utilize ICT based methods such as online counseling in order to accumulate knowledge and utilize human resources across regions. (2)Share expert human resources within the network of core hopsitals, rather than within each facility. (3)Promote human resource recruitment and education, including the consideration of national qualifications.		◎	◎	
A- 4	**Expert Panel Shortages**	In the case that an expert panel is required, consider relaxing requirements (e.g. introducing AI or other software algorithms)		◎	◎	
C- 1	**Lack of Collabortaion between Core Hospitals**	(1)A platform centered around the core hospitals for precision cancer medicin will have a collaborative function between researchers in industry, government, and academia. (2)Use the platform to promote "Decentralized Clinical Trials" (DCT).	○	◎	○	
C- 2	**Lack of Collaboration between Industry, Government, and Academia**	A detailed R&D consultation scheme between domestic and foreign companies and regulatory authorities should be established to ensure competitive advantage in the Japanese market.	○	◎		
D- 3	**Cost-effectiveness Calculations** (need for evidence based on the unique characteristics of precision medicine)	Fundamentally re-examine methods of evidence evaluation using real world evidence following the launch of a product.		◎	○	○
F- 2	**Supporting and Fostering Patient Groups**	While utilizing a network of medical institutions, support the activities of patient groups on a national scale.	○	◎		

6) Regulatory approval: Thoroughly reexamine which evidence assessment methods are best, such as conducting ex-post value assessment using post-market evidence in clinical settings (related to Table 3-D: D-3).

For items related to regulatory approval, because **(a) the number of indications for precision cancer medicine is still limited**, it will not be sufficient to only establish a "hub-and-spokes" network and facilitate the collection of clinical trial data and other information. Instead, it will be necessary to be very flexible when thinking of topics such as how to make use of information obtained post-market as evidence.

3.3 Explanation of Recommendation II

1. Basic concept

Because precision cancer medicine **(b) involves the use of genetic information**, which can be considered the most personal form of information, it requires more careful information management and handling compared to other forms of health and medical information.

In addition, to ensure that individual patients and citizens do not face social discrimination due to their genetic information, laws and regulations that prohibit discrimination based on said genetic information must be established and efforts to raise awareness among all citizens must be taken.

2. Content of recommendation

Rec. II: While establishing data repositories for genetic information, legislation prohibiting discrimination based on genetic information should be enacted and public awareness activities should be conducted.

Specific items to which Recommendation II applies are described below (Table 5-II).

1) Building genomic information databases: Build a (1) whole genome sequence database and a (2) registry database containing prospective data gathered with use in regulatory approval and similar processes in mind, and develop systems and laws that aim to facilitate the effective use of these databases among industry, Government, and academia (related to Table 3-C: C-3 and C-4; Table 3-E: E-4).
2) Returning research results to patients and the public: Establish a feedback system for returning research results to patients and the general public (related to Table 3-C: C-5).
3) Addressing social discrimination: Enact legislation prohibiting discrimination based on genetic information and take steps to build awareness among all ages, including during school education (related to Table 3-E: E-3).

Table 5-II: Responding to policy issues facing precision cancer medicine (Recommendation II)

	Issue	Recommendation		Issues Related to Precision Cancer Medicine		
			Common Issue in Cancer Medicine in General	(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
C- 3	**Delay in the Construction of a Database for Genomic Information**	Promptly establish a "whole genome sequence database" that can be easily utilized by industry, government, and academia.	○	○	◎	
C- 4	**Delay in the Industrial Utilization of Data for Secondary Uses, Drug Discovery, etc.**	Establish systems and legislation for the construction and utilization of a database that can be publicly integrated with registry data currently owned by academic societies for the purpose of regulatory approval of pharmaceuticals.	○	○	◎	
C- 5	**Insufficient Return of Research Results to Patients and the Public**	Establish a feedback system for the return and dissemination of research results to patients and the public.	○		◎	
E- 3	**Remediating Social Discrimination** (in the case of certain genetic mutations)	(1)Promote the development of laws against societal disadvantages caused by genetic and genomic information along with self-regulation by related companies. Furthermore, in order to design a system that addresses current issues, promote open discussions with such companies. 2)Raise awareness among a wide range of generations (e.g. through school education).	○		◎	
E- 4	**Protection of Personal Data related to Medical Care and Genetic Information**	(1)Promote the development of laws and guidelines for data sharing. (2)In particular, promote the development of laws based on the premise of genomic medicine following the US "Genetic Information Nondiscrimination Act."	○		◎	

3.4 Explanation of Recommendation III

1. Basic concept

Because **(c) the costs of testing and treatment are often expensive** in precision cancer medicine, it faces extremely tight limitations regarding health insurance coverage and regulatory approval. It is likely those limitations were reasonable from a health economics perspective when they were first introduced.

However, given advances in science and technology, the accumulation of clinical examples, and other such developments that have taken place since then mean that those limitations are currently preventing people from enjoying better outcomes. In addition, many of these limitations are no longer reasonable from a health economics perspective, which was the reason they were established in the first place.

Moving forward, while listening to the voices of researchers and those who serve in clinical settings and referring to recent responses taken abroad, urgent steps should be taken to revise these systems to make them more reasonable from both treatment and health economics perspectives.

2. Content of recommendation

Rec III: Regulatory approval, health insurance coverage, and other conditions governing the use of precision cancer medicine should be revised to be made more scientific and rational in a manner that complements the key characteristics of precision cancer medicine and practical needs in clinical settings.

Specific items to which **Recommendation III** applies are described below (Table 5-II).

Conditions for health insurance coverage and related items

Each of the following items should be granted health insurance coverage.

1) Companion diagnostics: Tests in which specimens have been resubmitted (related to Table 3-B: B-1)
2) Liquid biopsies: Tests taken for monitoring (related to Table 3-B: B-2)
3) Cancer gene panel tests: Certain tests taken during examinations (related to Table 3-B: B-3)
4) Genetic counseling: Some of the counseling (related to Table 3-B: B-4)
5) Genomic cancer therapy: Certain treatments, when provided before standard treatments begin (related to Table 3-B: B-5 and Table 3-D: D-2)

Regulatory approval

1) Therapeutics: Certain regulations surrounding simultaneous approval requirements for companion diagnostics and therapeutic agents should be relaxed (related to Table 3-D: D-1)

Table 5-III: Responding to policy issues facing precision cancer medicine (Recommendation III)

	Issue	Recommendation		Issues Related to Precision Cancer Medicine		
			Common Issue in Cancer Medicine in General	(a) Limited Medical Indications	(b) Use of Genetic Information	(c) High Cost of Testing and Treatment
B- 1	**Limitations related to the Number of Tests** (companion diagnostics (CDx))	Regarding tests that use companion diagnostics (CDx), review the limitations on the number of re-tests covered by insurance.			○	◎
B- 2	**Limitations related to the Number of Tests and Testing Period** (liquid biopsies)	Regarding liquid biopsies, review the limitations on the number of tests covered by insurance for monitoring purposes.			○	◎
B- 3	**Limitations related to the Timing of Testing** (cancer gene panel test)	Review the limitations on insurance coverage so that gene panel tests can be performed prior to the completion of standard cancer treatment.			○	◎
B- 4	**Limitations related to Target Services** (genetic counseling)	Genetic counseling and related online medical services, which should be combined with genetic testing, should be covered by insurance.			○	◎
B- 5	**Limitations related to the Timing of Treatment** (cancer genome medicine)	Review the limitations on insurance coverage so that gene panel tests can be performed prior to the completion of standard cancer treatment.			○	◎
D- 1	**Requirements for Approval of Therapeutics** (requirement that therapeutics are approved at the same time as companion diagnostics (CDx))	For therapeutics with proven efficacy, approval processes should be flexible to allow for certain exceptions such as prior approval under the termporary provision of alternate tests for CDx (e.g. tests in clinical trials).			○	◎
D- 2	**Cost-effectiveness Calculations** (timing of cancer gene panel testing)	Review the limitations on insurance coverage so that gene panel tests can be performed prior to the completion of standard cancer treatment.			○	◎

Conclusion

The people involved in precision cancer medicine are extremely diverse, and even if we narrow our focus on key areas, we see that this field faces a wide range of policy challenges.

Therefore, even if those involved have the shared central goal of “actively promoting precision cancer medicine,” the issues that each person considers to be most important can vary greatly depending on, for example, the field in which they are involved. Many of the discussions are complicated and efforts to mount policy responses tend to scatter.

Given these circumstances, these recommendations attempt to provide a foundation and general framework to enable shared understanding among related parties with various opinions as described above. We hope these recommendations can assist efforts to build shared recognition among related parties and encourage cooperation and collaboration among them to advance precision cancer medicine.

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These recommendations were compiled by the author, HGPI, in its capacity as an independent health policy think-tank based on the hearings mentioned above. They should not be taken to represent the opinions of any advisory board member or related party, or of any organization to which they belong.

"The Project for Considering the Future of Precision Medicine with Industry, Government, Academia, and Civil Society"

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