April 2025

HGPI Health and Global Policy Institute

HGPI Cancer Control Project Policy Recommendations: Ensuring Equitable Access to Comprehensive Genomic Profiling and Key Considerations for Applying the Mixed Medical Services Program

Executive Summary

Background

Comprehensive genomic profiling (CGP) is a core technology in genomic cancer medicine and has seen increasing use in clinical settings since it was granted insurance coverage in 2019. However, in principle, the current medical service fee reimbursement system restricts the use of CGP to "patients with solid tumors for which no standard treatment is available or who have completed standard treatment with local progression or metastasis (including those who are expected to complete treatment)." This results in treatment lag and people are missing opportunities to be provided with optimal and more targeted and personalized treatments. In fact, one finding (from Advanced Medical Care B usage) showed that the percentage of patients linked to treatment is about three times higher when CGP is performed during first-line treatment selection compared to when it is performed after standard treatment is completed. While the FY2024 revision of the medical service fee schedule included gene panel testing performed at appropriate times, insurance coverage was not expanded. Due to concerns over the potential impact of CGP on public health finances, efforts are currently advancing to examine the Mixed Medical Services Program as an option for covering CGP performed at the start of treatment, but the use of that program carries the risk of widening access disparities based on patient economic status. In light of these circumstances, this proposal presents urgent issues and outlines a medium- to long-term approach for achieving patient-centered genomic cancer medicine.

Overview of recommendations

Perspective 1: **Eliminate the restriction limiting the use of comprehensive genomic profiling (CGP) to "patients with solid tumors who have completed (or are expected to complete) standard treatment" from the medical service fee schedule. CGP should be made available and provided to patients who require it the most in a timely manner based on chemotherapy guidelines and evidence-based research from oncology associations and experts.**

Basis:

- It is estimated that the current restrictions may be causing as many as 12,000 patients to miss treatment opportunities per year.
- Current restrictions also prevent access to CGP for companion diagnosis when needed for standard treatment selection (e.g., the capivasertib problem).
- Overseas, there are no such restrictions based on the completion of standard treatment, and early CGP is recommended in certain cases (e.g., advanced cancer).
- While early CGP can increase health expenditures to a certain degree (that is estimated to be limited and controllable), studies from Japan and overseas suggest clear clinical benefits to performing CGP early, including prolonged survival.

Perspective 2: **When considering the application of the Mixed Medical Services Program for the use of CGP from first-line treatment, discussions should be based on the intent of seeing public insurance coverage granted to CGP because it is being used to select standard treatments and because there are socioeconomic disparities in private insurance coverage rates.**

Items of note:

- CGP is already an essential part of standard treatment selection (e.g., for breast cancer or prostate cancer).
- There are socioeconomic disparities in private health insurance coverage rates (especially in terms of riders for advanced medical care, which cover less than half of all households). There are concerns that use of the Mixed Medical Care Program will widen the access gap.
- Consistency with the principles of the National Health Insurance system must be considered.
- Exit strategies (or paths to insurance coverage) for technologies that have been shown to be effective in the Advanced Medical Care B program must be clarified.

Perspective 3: **Ongoing discussions should be held on eliminating the systemic divide between CGP and drug-agnostic companion diagnostics (CDx) in the medical service fee schedule as well as on the future integration of whole-genome sequencing while promoting the development of CDx as a transitional measure to improve future patient access.**

Challenges:

- Current systems for approval and reimbursement of CDx result in restricted access to optimal drugs (which is a factor that results in drug lag).
- Various issues are preventing progress in the development of drug-agnostic CDx, such as economic rationality.
- Integrating operations for CDx, CGP, and whole-genome sequencing should be examined as a means of responding to future advances in genomic medicine.

Conclusion

To ensure that everyone can enjoy equal access to the benefits of genomic cancer medicine, **it is crucial that existing systemic barriers be eliminated, particularly restrictions on when CGP can be performed**. We must consider the use of the Mixed Medical Services Program carefully, consider how to avoid creating access disparities, and provide a clear path to insurance coverage for CGP. It will also be essential to make continuous efforts to **address structural issues related to CDx** and to design systems that take future technological advances into account.

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HGPI Policy Recommendations:
Ensuring Equitable Access to Comprehensive Genomic Profiling and Key Considerations for Applying the Mixed Medical Services Program

Background to these recommendations

Even within the context of precision cancer medicine, genomic cancer medicine was recognized as highly innovative when it was first introduced. Several years have now passed since Comprehensive Genomic Profiling (CGP) was granted insurance coverage in 2019, and people serving in clinical settings have accumulated experience with this form of testing. We are now at a stage where we must further improve patient access to genomic cancer medicine and take steps to deliver genomic cancer medicine broadly to the public based on the view that it is a technology that should benefit all. In fact, when CGP is performed during first-line treatment selection for cancer as part of the Advanced Medical Care B program (previously Notification No. 51), the percentage of patients linked to treatment is about three times higher than when CGP is performed after standard treatment is completed, which is currently a requirement for insurance coverage. Changing this system so CGP can be performed at the right time will be an important step in improving treatment access.

Health and Global Policy Institute (HGPI) has conducted surveys and interviews with a wide range of experts as part of its precision cancer medicine project launched in 2021 (titled the "Project for Considering the Future of Precision Medicine with Industry, Government, Academia, and Civil Society"). Based on our findings, we presented policy recommendations titled "Proposals for Effective Policy Changes Based on Key Characteristics of Precision Medicine in Cancer Treatment" in September 2022 and "Improving Patient Access to Genomic Cancer Medicine" in August 2023.

In addition to HGPI's independent policy advocacy activities, to advocate for better opportunities for patient access to CGP, HGPI endorsed the "Joint Statement on the Implementation of Comprehensive Genomic Profiling Test" presented in December 2023. Other signatories included the Japan Federation of Cancer Patient Groups, the European Federation of Pharmaceutical Industries and Associations (EFPIA Japan), the Pharmaceutical Research and Manufacturers of America (PhRMA), the Japanese Society of Medical Oncology, the Japanese Society of Clinical Oncology, the Japanese Cancer Association, and the Social Insurance Union of Societies Related to Internal Medicine.

While performing CGP at appropriate times was included in the Basic Policy on Economic and Fiscal Management and Reform as well as in the fourth Basic Plan to Promote Cancer Control Programs, the original recommendation that "Insurance coverage for CGP should be expanded so it can be performed at the appropriate timing from first-line treatment" was not reflected in the FY2024 revision of the medical service fee schedule due to insufficient evidence and other factors. The objective of performing CGP for cancer is to ensure patients can benefit from optimal, personalized and targeted treatments in a timely manner. Patients who need treatment for advanced cancer urgently do not have time to wait several years for this system to be changed; it must be updated and reformed at the earliest possible opportunity.

At the same time, healthcare and social security expenditures continue to increase, meaning concerns toward the financial impact of expanded use of CGP cannot be ignored. In the context of such discussions, the Basic Policy on Economic and Fiscal Management and Reform 2024 and other related policies have indicated that further consideration will be given to how to best implement the Mixed Medical Services Program that includes the use of private insurance, with the implementation of CGP at first-line treatment for cancer in mind. While utilizing the Mixed Medical Services Program is likely to improve patient access to CGP, it may also lead to greater disparities in treatment access due to the differences in patients' socioeconomic status.

Against this backdrop, these recommendations aim to outline noteworthy points when expanding patient opportunities to access CGP for cancer treatment and when considering the use of the Mixed Medical Services Program, as well as to provide a vision of how to best advance discussions from a medium- to long-term perspective and create opportunities for further and more thorough discussion in the future. We hope that these recommendations are utilized in future policy responses for genomic cancer medicine and to drive further advances in patient-centered healthcare.

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Policy recommendations

Eliminate the restriction limiting the use of comprehensive genomic profiling (CGP) to "patients with solid tumors who have completed (or are expected to complete) standard treatment" from the medical service fee schedule. CGP should be made available and provided to patients who require it the most in a timely manner based on chemotherapy guidelines and evidence-based research from oncology associations and experts.

The current system and present issues

The current medical service fee reimbursement system schedule places restrictions on CGP under item D006-19, Cancer Genome Profiling Test, which reads "(2) This premium is restricted to patients with solid tumors for whom no standard treatment is available or who have completed standard treatment with local progression or metastasis (including those who are expected to complete standard treatment) and in cases which the attending physician determines there is high potential for the application of chemotherapy following testing based on chemotherapy guidelines from related academic societies or equivalent resources and the patient's general status and organ function." However, in the real-world clinical setting, the understanding of how to interpret "standard treatment" is vague, which adversely affects patients who lose their eligibility for testing or additional treatment because their general condition worsened while waiting to complete standard treatment.[i]

There are also cases in which patients who visit hospitals other than a designated core hospital for genomic cancer medicine or other designated hospitals do not receive timely referrals to designated hospitals, or in which they go without an explanation from their primary physician and remain unaware of their eligibility for genomic therapy. It is no exaggeration to say this is a factor that contributes to treatment lag and is preventing patients from accessing appropriate treatment.

Overview of people adversely affected by the CGP restriction in Japan

This restriction may be preventing approximately 12,480 cancer patients from reaching treatment each year

In the "Prospective clinical study of comprehensive genomic profiling for patients with chemotherapy-naive advanced cancer" conducted by Kyoto University[ii], a total of 180 eligible patients underwent CGP prior to standard treatment, among whom 105 patients (61%) were provided with a recommended treatment from the expert panel and 34 patients (19.8%) were actually provided with that treatment.[1] Of those 34 cases, 22 (64.7%) of the treatments were covered by insurance at Evidence Level A, 1 was covered at Evidence Level B, and 11 were undergoing clinical trial.[iii] As of June 30, 2022, 9.4% of patients registered in C-CAT had been linked to treatment. The report from Kyoto University not only found that 19.4% of patients had been linked to treatment (including clinical trials), but that multiple patients had been linked to treatment in the follow-up survey, as well.[iv] While it may not be appropriate to apply these figures directly to the total number of patients in Japan, using them as reference values, we can estimate that if CGP had been performed on 30,822 patients at the time of chemotherapy failure, it may have been possible to link an additional 10.4% or 3,205 patients (10.4% of the total 30,822 of cases in the expert panel) to further treatment[v].

In Japan, there are approx. 1 million new cancer cases per year, and the ratio of CGP tests is 58:1 (in other words, 1 person in 58 undergoes a panel test). In South Korea, where there were approx. 250,000 new cancer cases and about 25,000 CGP tests in 2023, this ratio is 10 to 1. This ratio is also 10 to 1 in Australia, where there are approx. 150,000 new cancer cases and approx. 15,000 CGP tests per year. In Germany, this ratio is 13 to 1. As these reports show, CGP tests are being performed four to five times more frequently overseas than in Japan.[vi] About 2,000 CGP tests are currently being performed in Japan every month, but if this ratio were similar to other countries, Japan would be performing 10,000 CGP tests per month or 120,000 per year. Maintaining existing restrictions to genomic medicine access, namely, the need to complete standard treatment and the strict facility requirements for holding expert panels may negatively impact 12,480 people per year (or 10.4% of 120,000 CGP tests per year).

[1] As reported at the March 8, 2025 meeting of the Japanese Society of Medical Oncology, the interim report for one-year follow-up (with data through March 2023) found that 39 cases (22.7%) had arrived at the expert panel's recommended treatment. Based on this outcome, we can estimate that a total of 4,100 patients (13.3% of 30,822 cases) may have arrived at treatment.

Removing the need to complete standard treatment will expand access to different drug options within standard treatment as well as to non-standard treatments, such as clinical trials, thus facilitating the selection of optimal treatments

As previously discussed, among the total of 30,826 eligible patients registered in C-CAT from June 1, 2019 to June 30, 2022, 2,888 patients or 9.4% had been administered therapeutics recommended by expert panels. Of that figure, 1,857 patients (64.3%) were administered therapeutics registered as health insurance treatments; 477 patients (16.5%) were enrolled in private sector clinical trials; 154 patients (5.3%) were enrolled in investigator-led clinical trials; 2 patients (0.1%) were receiving advanced medical care; 63 patients (9.1%) were receiving "Patient-Proposed Healthcare Services 2," and 35 patients (4.7%) were "Other 1."

An excerpt from an evaluation of a general report from the 146th meeting of the Advanced Medical Technology Review Committee on March 9, 2023 states, "These findings suggest that compared to the past, there are a certain number of cases in which patients can access non-standard treatments that may be considered optimal before initiating standard treatment." While the report mentions that eliminating the need to complete standard treatment may improve access to non-standard treatments, examining the actual situation surrounding treatment access, we can conclude that CGP not only improves access to non-standard treatments, such as clinical trials, but also expands access to different drug options within standard treatment. By removing the need to complete standard treatment, patients can benefit from a broader range of therapeutic options at the most appropriate timing for their clinical situation.

Regarding access to standard treatments, the May 2024 launch of the AKT inhibitor capivasertib (brand name: TRUQAP) highlights the difficulty of accessing medicines that may emerge when companion diagnosis is only possible with CGP.[vii] Under the medical service fee schedule, CGP can only be performed after someone completes (or is expected to complete) standard treatment, so when a hospital uses FoundationOne® CDx as the companion diagnostic and then decides to administer capivasertib, they can only be reimbursed for 12,000 points, or up to a maximum of 16,000 points. Because hospitals incur greater financial losses as the number of these tests they perform increases, this has led to a situation in which CDx are going mostly unused and medicines are not reaching patients. Given these circumstances, to provide support from a humanitarian perspective, capivasertib developer AstraZeneca launched the "TRUQAP® (capivasertib) Tablets Companion Diagnosis Results Support Program" which provides the FoundationOne® CDx free of charge outside of the scope of treatments covered by health insurance, as well as information on all three genes related to capivasertib. This is a temporary program that will provide support until diagnostics other than FoundationOne® CDx are approved or the restrictions on its reimbursement are removed.

The Designated Core Hospitals for Genomic Cancer Medicine Liaison Conference of the Medical Care Working Group presented an opinion statement regarding AstraZeneca's companion diagnosis results support program in February 2025. After expressing that the Group does not renounce the implementation of the support program itself, it points out that there are health institutions using FoundationOne®CDx in companion diagnosis for capivasertib while continuing to comply with medical service fee schedule requirements, and includes an explanation that providing appropriate access to the drug is possible by following the Group's "Approach to the Appropriate Use of Cancer CGP Tests that Include Companion Diagnosis." In that method, FoundationOne®CDx would be used as a CDx in initial testing and reimbursed under "D004-2 Malignant tumor histology," which provides points for the companion diagnosis. Then, when explaining the results of the expert panel or profiling test, the points applied during the companion diagnosis would be subtracted from the 44,000 points provided by "D006-19 Cancer genome profiling test," and the test provider would be able to apply for "B011-5 Cancer genome profiling evaluation."

There are seven other drugs for which CGP is the only method of providing companion diagnosis, and this number is likely to increase in the future.[2] Although reimbursements can be obtained through the medical service fee schedule if some ingenuity is applied, there is no doubt this system itself is restricting access to drugs. To prevent a repeat of the situation that occurred with capivasertib, efforts to modify and reform this system is warranted.

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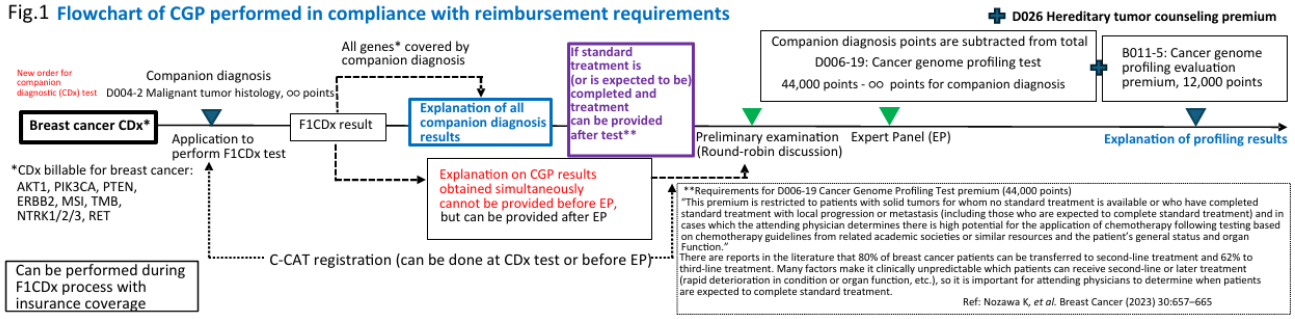
[2] As of March 2025, they are: TRK inhibitor Rozlytrek, TRK inhibitor Vitrakvi, FGFR inhibitor Pemazyre, PD-1 inhibitor Keytruda, FGFR inhibitor Lytgobi, PARP inhibitor Talzenna, and RET inhibitor Retevmo.

Fig.1 **Flowchart of CGP performed in compliance with reimbursement requirements**



Circumstances accompanying the current use of CGP overseas

While CGP is performed selectively based on factors like progression, recurrence, and family history, there are no restrictions that limit its use to after the completion of standard treatment

Every year, the NHS Genomic Medicine Service in the U.K. performs approx. 650,000 genomic tests (including whole-genome sequencing) and is the first system in the world that provides companion diagnosis, CGP, and whole-genome sequencing in an integrated manner. This approach has been highly successful, with the Cancer Research UK Cambridge Innovation Centre reporting that approx. 40% of patients saw a significant change in management of their cancer as a result of genomic testing.

Other countries are also making progress on the use of genetic testing in cancer care.[viii] In the US, the National Comprehensive Cancer Network (NCN) Clinical Practice Guidelines in Oncology recommends CGP for each type of cancer and a clinical opinion of the American Society of Clinical Oncology (ASCO) recommends it for patients with metastatic or advanced solid tumors.[ix] In the US, Medicare covers genetic testing for patients with recurrent, relapsed, refractory, metastatic, and/or advanced stages III or IV cancer for all senior citizens age 65 years and older and with no restriction limiting its use to after the completion of standard treatment. In principle, patients have no out-of-pocket expenses for Medicare-covered laboratory tests.[xxi] Furthermore, it has been reported that 12.8% of people enrolled in Medicare who underwent CGP underwent two or more genetic tests. France is also gradually moving toward a precision medicine approach, where patients with non-hereditary[3] somatic mutations[4] are eligible to be considered for CGP at multidisciplinary committee meetings.[5] Testing is provided as needed, and the number of tests has more than doubled from 2015 to 2020. There are also challenges such as delays in reimbursement for facilities that perform testing, limited human and material resources in certain regions, and long turnaround times (TATs) for test results.[xii] In Germany, health insurance companies provide full coverage for non-small cell lung cancer testing (including some CGP tests) approved by the European Medicines Agency (EMA) for all patients, and a total of 82 million people covered by public or private insurance (approx. 73 million people for public insurance and approx. 9 million for private insurance) are eligible.[xiii] In Canada, in addition to publicly-funded CGP tests, free CGP tests sponsored by pharmaceutical and biotechnology companies are also available. While this has certain advantages such as lower out-of-pocket costs for patients and shorter waiting times, a number of clinical and ethical issues have also been pointed out regarding test quality or the use of private personal information. Furthermore, publicly-funded CGP is impacted by geographic and socioeconomic disparities that are causing differences in testing rates.[xiv] In South Korea, CGP can only be performed at 67 accredited facilities (as of September 2022), and from 2017 to 2021, the number of CGP tests performed increased 5.4-fold, from 5,436 tests to 29,557 tests. Gene panel tests can be performed two or more times in cases of somatic mutations that either relapse or demonstrate a lack of response to first-line treatment, and 10.6% of patients who have been tested have received multiple tests.[xv] In a report on the clinical use of CGP at Seoul National University, 53.3% of gene panel tests were performed during first-line treatment, which is the highest percentage reported to date.[xvi]

[3] Germline mutation: Genetic changes that occur in germ cells (eggs or sperm) and are passed onto offspring in the DNA of all cells. A factor in the development of hereditary tumors.

[4] Somatic mutation: Somatic cells are cells other than germ cells (eggs or sperm). A somatic mutation is an acquired mutation of a normal somatic cell. Somatic mutations are not passed onto offspring.

[5] Multi-disciplinary meetings that are held in most parts of Europe, North America, Australia, and other regions. Generally attended by the surgeons, oncologists, radiologists, pathologists, cancer nurses, and other such professionals in each hospital.

Instead of limiting genetic testing to after the completion of standard treatment, these countries generally recommend CGP prior to first-line treatment or concurrent with standard treatment while considering family history and centered on advanced or recurrent cancer, demonstrating an emphasis on a more proactive approach to genomic screening in cancer care.

The health economic burden of CGP

Performing CGP prior to standard treatment will increase healthcare costs to a certain degree, however, it will contribute to longer survival for patients

A study by Tang et al. (2023) compared the budget impact of CGP in Japan for three types of untreated advanced or recurrent solid cancers (biliary tract cancer, non-squamous non-small cell lung cancer, and colorectal cancer).[xvii] It estimated that the cost per patient per month would increase by 19,600 yen for biliary tract cancer, 2,900 yen for non-squamous non-small cell lung cancer, and 2,200 yen for colorectal cancer when CGP was performed prior to standard treatment (in cases it was considered likely to lead to more effective treatments) compared to when it was performed after the completion of standard treatment (in accordance with current restrictions in the medical service fee schedule). Patient number estimates for 2026 are 27,570 cases of biliary tract cancer, 153,686 cases of lung cancer, and 158,498 cases of colorectal cancer. With CGP, the estimated annual increase in healthcare cost is 916 million yen for testing and 911 million yen for treatment for biliary tract cancer; 1.299 billion yen for testing and 2.678 billion yen for treatment for non-squamous non-small cell lung cancer; and 1.364 billion yen for testing and 4.365 billion yen for treatment for colorectal cancer.[xviii] In this scenario, the group that undergoes CGP is more likely to receive molecularly targeted therapies that are more appropriate for their genetic mutation (including through clinical trials), which is likely to contribute to longer survival. Another item observed by the study was that increased clinical trial participation would offset the increase in public healthcare expenditures from performing CGP. Making full use of CGP for necessary cases prior to standard treatment will make it possible to reduce the number of treatments that have little effect, place physical burdens on patients, and waste financial resources.

A number of studies have been conducted outside of Japan, as well. These include the Proudan et al. (2022) study on expanding first-line use of CGP for advanced and metastatic colorectal cancer in the US;[xix] the Harbey et al. (2021) study on the budget impact of increasing the rate at which CGP is performed in patients with advanced non-small cell lung cancer in the US;[xx] and the Tsai et al. (2022) study on budget impact of performing CGP prior to chemotherapy for advanced non-small cell lung cancer in Taiwan.[xxi] While all of these studies found that performing CGP increases budgets to a certain degree, this increase was thought to be limited and controllable, and that CGP could contribute to longer survival through increased use of more effective treatments, so efforts to provide reimbursements for CGP should be developed and reinforced with patients' well-being and clinical benefit in mind.

Clinical benefits

When considering insurance coverage eligibility for CGP or its requirements for coverage, in addition to cost-effectiveness, the value this medical technology delivers to patients should be evaluated in a multi-faceted manner. There has been an increasing number of reports in recent years on the benefits of matching therapy, in which molecularly-targeted drugs are administered according to genetic mutation. For example, in a randomized controlled trial called the CUPISCO trial, molecularly guided treatment strategies based on CGP results obtained before initial therapy significantly prolonged the primary endpoint of median progression-free survival compared to the chemotherapy group (the standard treatment) (6.1m vs. 4.4m, HR;0.72, p=0.079).[xxii] In the ROME trial, which was also a randomized controlled trial, the group receiving targeted therapy based on early CGP findings showed significant improvement in the primary endpoint of overall response rate compared to the standard treatment group (17.0% v.s. 9.5%, p=0.027). There was also significant improvement in the secondary endpoint of median progression-free survival (3.7m v.s. 2.8m, HR;0.64, p<0.0001).[xxiii] In Japan, a study by Hashimoto et al. (2024) that used data from the SCRUM-Japan MONSTAR-SCREEN consortium showed patients who participated in a matching clinical trial and received targeted therapy had significantly longer overall survival rates compared to those who did not (hazard ratio 0.77, 95% confidence interval, 0.71-0.83). Another study in Japan by Nakamura et al. (2024) using data from the GOZILA study found that patients with advanced gastrointestinal cancer who received targeted drug therapy based on ctDNA profiling had significantly improved overall survival compared with those who received non-targeted therapy (hazard ratio 0.54), and that patients who received targeted

therapy as a primary treatment benefited most. It is particularly noteworthy that not only was there a trend toward improved overall survival regardless of line of treatment, but that the effect was even more pronounced when targeted therapy was provided as the first-line treatment. Although this finding is centered on gastrointestinal cancer, it clearly suggests that performing liquid biopsy is beneficial both before or after standard treatment.

Conclusion

Performing CGP prior to first-line treatment for advanced or recurrent solid cancer can increase healthcare costs to a certain extent, but studies from Japan and overseas suggest that CGP can benefit patients by extending survival and reducing physical and mental burdens by enabling the selection of therapeutics that target genetic mutations or by accelerating the transition to treatments with fewer side effects.

In other countries, CGP is used flexibly in accordance with clinical need, and its use is not restricted prior to standard treatment. It is urgent that Japan eliminate systemic bottlenecks that impact patients' treatment options and prognoses.

To advance measures for cancer control that leave no one behind, we must remove the medical service fee schedule's restriction on eligibility for CGP to those who have completed standard treatment and transition to a system designed to provide CGP in a timely manner to patients who need it the most.

Perspective 2: When considering the application of the Mixed Medical Services Program for the use of CGP from first-line treatment, discussions should be based on the intent of seeing public insurance coverage granted to CGP because it is being used to select standard treatments and because there are socioeconomic disparities in private insurance coverage rates.

Premise for recommendations in Perspective 2

Perspective 1 proposes eliminating restrictions on the timing of CGP ("after the completion of standard treatment," etc.) and recommends performing CGP at earlier stages, including prior to first-line treatment. This is the direction that should be taken to accelerate the selection of appropriate treatments as much as possible and to maximize each patient's chance for better a prognosis with coverage from public health insurance.

Discussions are currently underway on allowing CGP to be performed earlier (including prior to first-line treatment). However, rather than examining the elimination of restrictions in the medical service fee schedule, these discussions are advancing with the premise that such tests will be performed under the Mixed Medical Services Program. We believe any situation in which socioeconomic disparities narrow patient options is wholly undesirable, but because a Mixed Medical Service Program-based approach is what is being considered, we also recognize the need to offer recommendations for a minimal system design that will not place patients at a disadvantage if the use of that Program is adopted. Therefore, Perspective 2 will discuss key points of note when implementing the use of the Mixed Medical Services Program.

Circumstances surrounding the use of CGP to provide access to standard treatment

For breast and prostate cancer, CGP is recommended for selecting standard or first-line treatment

It has been reported that 5.7% to 10.4% of patients with breast cancer are linked to treatment when CGP is performed after the completion of standard therapy. However, a clinical trial in which CGP was performed prior to standard therapy resulted in over 70% of patients receiving recommendations for Evidence Level A drugs. CGP is indispensable for planning treatment strategies, particularly for hormone receptor-positive, HER2-negative (luminal) metastatic breast cancer; however, in principle, the medical service fee schedule limits its use to after the completion (or the expected completion) of standard treatment.

Despite the wide variety of standard treatment options for breast cancer, few patients receive all treatments up to the third line, so CGP must be performed at the optimal time based on evidence-based and updated medical judgment. Furthermore, as discussed in Perspective 1, efforts are currently advancing for the initial use of FoundationOne®CDx with the premium for companion diagnosis, then later applying additional points for CGP after holding an expert panel.

CGP is also necessary in prostate cancer, where it is used for metastatic Castration-Sensitive Prostate Cancer (mCSPC). FoundationOne®CDx is the only approved companion diagnostic for talazoparib, the standard treatment for mCSPC. While it is also possible to use olaparib for mCSPC, doing so involves the use of the BRACAnalysis Diagnostic System®, which is not a form of CGP and can only detect germline mutations. The proportions of germline and somatic mutations of BRCA2 (the targeted genetic mutation) are approximately equal, so from the perspective of rationality of testing, it is desirable that FoundationOne®CDx is used as the companion diagnostic.

Overseas, CGP is performed for mCSPC patients at initial diagnosis, but this is not the case in Japan, where it has been reported that over half of mCSPC patients are not receiving standard treatment.

Situation surrounding private insurance coverage (including for riders for advanced medical care)

Enrollment is relatively high, but socioeconomic factors result in disparities in enrollment rates

According to the Japan Institute of Life Insurance (JILI) "2024 National Field Survey on Life Insurance (Preliminary Ed.),"[xxiv] 89.2% of households are enrolled in life insurance.[6] Among life insurance enrollees, 95.1% have medical insurance or medical care riders, 68.2% have cancer insurance or cancer riders, and 54.0% have advanced medical care riders. As a proportion of all households, these figures correspond to 84%, 60.8%, and 48.2%, respectively.

[6] Includes private insurance (and Japan Post Insurance), Postal Insurance, JA, Prefectural Mutual Aid, Co-op, etc.

Household enrollment rates for cancer insurance and cancer riders increase proportionally with annual income, with the lowest being among households earning under 2 million yen (56.0%) and the highest being among households earning 10 million yen or more (75%). For advanced medical care riders, households earning less than 2 million yen have the lowest enrollment rate (35.2%) while households earning 7 to 10 million yen have the highest (62.2%). Another JILI survey, the "FY2022 Survey on Life Security,"[xxv] found that between households with annual incomes below and above 5 million yen, there was an enrollment rate gap of 17% (53% vs. 70%) for medical insurance and 11% (31% vs. 42%) for cancer insurance. Furthermore, enrollment in cancer insurance is 11% lower among non-regular employees than regular employees (27% vs 38%). Another trend that was observed was particularly high enrollment among middle-income groups compared to relatively low enrollment among low- and high-income groups.

Based on the data discussed above, according to socioeconomic status, there are disparities in coverage from medical care insurance, cancer insurance, and advanced medical care riders, with less than half of all households having riders for advanced medical care. This means that when CGP is performed using private insurance under the Mixed Medical Services Program, it will be necessary to keep in mind the possibility that disparities in treatment selection due to socioeconomic status may emerge.

The effects of expanding the Mixed Medical Services Program with the use of private insurance

Premiums (such as for advanced medical care riders) may become more expensive

CGP performed after the completion (or expected completion) of standard treatment in accordance with the medical service fee schedule is covered by the High-Cost Medical Expense Benefit system. When CGP is performed at other times, such as from first-line treatment, however, it is not granted such coverage; rather, it is covered by the Mixed Medical Services Program and is paid out-of-pocket. In existing private insurance policies, such tests are eligible for coverage under advanced medical care riders.

It is currently possible to add advanced medical care riders to private insurance policies for only a few hundred yen per month. However, such premiums are calculated based on factors that include current access to advanced medical care.[7] As such, if concerns toward health finances lead to future expansions of the Mixed Medical Services Program rather than providing coverage through public insurance (like in recent discussions on CGP), it may become difficult to maintain relatively low premiums as more people throughout the country access advanced medical care and similar services. As previously mentioned, this will widen the existing treatment access gap that is rooted in socioeconomic disparities.

The intent of Japan's National Health Insurance system is to ensure all citizens have access to the health services they need, regardless of their economic status and income. If this principle is to be upheld, rather than relying on the Mixed Medical Services Program to cover proven treatments, the basic approach should be to provide coverage through public health insurance.

It will be necessary to consider regulations, guidelines, etc. for CGP performed under the framework of voluntary healthcare, which is offered at many health institutions

Most CGP is currently performed under the framework of insured health services at hospitals with systems that provide g genomic therapy, such as designated core hospitals for genomic cancer medicine. However, an increasing number of designated core hospitals for genomic cancer medicine and some clinics are offering CGP within the framework of voluntary treatment, in which services are covered by out-of-pocket payments.

For example, the increase in Non-Invasive Prenatal Testing (NIPT) being performed at uncertified facilities has led to the development of genetic counseling systems and other inappropriate systems for follow-up. This is giving rise to social and ethical issues that are currently being examined in ongoing discussions. A similar situation may occur with CGP and cause various issues. For example, there is no obligation to register data from CGP performed

[7] Among urban and rural areas, there are no significant disparities in enrollment for advanced medical care riders provided by private insurance policies. However, the ability to receive advanced medical care is greatly impacted by the presence or absence of health facilities offering advanced medical care where one lives. While people living in rural areas pay premiums for such riders, many of them do not actually receive advanced medical care. This is one factor that contributes to the low cost of premiums for such riders.

outside of insured health services in C-CAT, and there are no standards in place to verify the presence of systems for providing suitable medical support to patients and their families. It will be necessary to consider how to best structure regulations or create guidelines to prevent such problems from emerging.

Discussions must be held on cases already verified through Advanced Medical Care B usage to determine when it is appropriate to transition coverage from the Mixed Medical Services Program to public insurance and to identify exit strategies

The effectiveness of providing CGP from first-line treatment has already been verified through Advanced Medical Care B usage. Except when CGP is self-funded, it is no longer possible to perform CGP from first-line treatment for people who have already been accepted as new patients under the Advanced Medical Care framework. Given these circumstances and the fact that CGP is currently unlikely to be granted public insurance coverage, from a humanitarian standpoint, it will be necessary to provide opportunities to access CGP while using the Mixed Medical Services Program.

However, the framework for performing CGP under the Mixed Medical Services Program will require careful discussion and thorough evaluation. As previously discussed in the Background section, during the 146th meeting of the Advanced Medical Technology Review Committee, it was mentioned, “It has been shown that compared to the past, introducing CDx makes it possible for people to access non-standard therapies that are thought to be optimal prior to initiating standard treatment for a certain number of cases. This suggests that recommendations from expert panels could improve quantity, and could function even more effectively than before.” In other words, the usefulness of performing CGP prior to standard treatment has already been partially acknowledged.

At the same time, the report also points out the need to conduct additional evaluations on outcomes like survival time, stating, “It has not been verified if providing treatment with this scheme improves survival times or other outcomes, so to determine if this technology is truly effective, I think we must wait for the results of broader observational studies or validation studies conducted in the future.”

If efforts to further evaluate the effectiveness of CGP under the Advanced Medical Care framework (for category A or B) are to be pursued, from the perspective of patient access, steps should be taken to enable the use of systems at as many designated hospitals for genomic cancer medicine (including core, base, and cooperating hospitals) as possible throughout the country. Additionally, the usefulness of CGP prior to standard treatment has already been partially demonstrated, however, exit strategies must be clarified; in other words, it will be necessary to define what further conditions must be met under which research frameworks, or what outcomes must be achieved for CGP to be granted insurance coverage.

It is also desirable that applying the Mixed Medical Services Program to patient-selected extra medical services is avoided because a certain degree of efficacy has been verified through the results of Advanced Medical Care B and because doing so may restrict standard treatment access.

As mentioned in Perspective 1, AstraZeneca is implementing a program called the “TRUQAP® (capivasertib) Tablets Companion Diagnosis Results Support Program.” Examples of private pharmaceutical and biotech companies sponsoring CGP can also be seen in Canada, but some have voiced concerns about the quality of testing and follow-up, data protection, and sustainability issues that may emerge due to relying on the private sector. While it may be feasible to consider financial contributions from the private sector as an exit strategy, discussions on this topic should be advanced carefully while taking its advantages and disadvantages into account.

Perspective 3: Ongoing discussions should be held on eliminating the systemic divide between CGP and drug-agnostic companion diagnostics (CDx) in the medical service fee schedule as well as on the future integration of whole-genome sequencing while promoting the development of CDx as a transitional measure to improve future patient access.

Challenges stemming from the need for one-to-one correspondence among medicines and diagnostics for approval and reimbursement

When access to standard treatment requires CDx that cannot be used

In the context of genomic cancer medicine, for drugs administered based on genetic mutations to be approved, CDx must be approved at the same time. Since the potential use of CDx for in vitro diagnostics (IVD) is evaluated in parallel with the clinical trial for the drug in question, CDx that have yet to be evaluated cannot be used when selecting therapeutics. IVD manufacturers can also seek approval for CDx afterward, but time and cost restrictions prevent them from immediately obtaining approval for all combinations.

As for the actual use of CDx, the cost of the testing and the efficiency of collecting tissue specimens required for testing means singleplex tests (tests on single genes) are used rarely, while multiplex tests (tests on multiple genes) are used often.[8] However, among multiplex tests, the types of drugs that can be used based on results may differ even when they detect the same genetic mutation. For example, when testing for EGFR gene mutations in non-small cell lung cancer patients, the Lung Cancer Compact Panel Dx Multiplex Companion Diagnostics Test cannot be used prescribe dacomitinib, while the therascreen EGFR Rotor-Gene Q PCR Kit Qiagen cannot be used to prescribe osimertinib. In other words, even for tests that detect the same EGFR mutation, there are times when therapeutics remain inaccessible. With the current state of affairs, patients have no way of knowing what CDx a health institution may use, and CDx selection on the part of health institutions can impact future treatment options for patients.

Furthermore, as mentioned in Perspective 1, there are already eight examples in which CGP is the only approved method of providing companion diagnosis. In that context, in Japan, the reimbursement for CDx is lower than the reimbursement for CGP, so the cost of performing CGP for companion diagnosis exceeds its reimbursement. This means the difference between the cost of performing CGP and the amount reimbursed must be covered by the hospital's budget, and this is preventing CGP from being performed and therapeutics from being used.[9]

Overseas, there are no restrictions in insurance systems that prevent the use of CGP at first-line treatment, and CDx and CGP are handled in the same manner as tests for making treatment decisions from the outset, so there is no need to develop CDx and CGP tests separately. Developing and obtaining approval for CDx separately only for certain drugs in Japan is not economically rational for pharmaceutical companies or IVD manufacturers, and is a factor that is limiting access to treatment.

Guidance on drug-agnostic CDx and current circumstances

Drug-agnostic CDx development has not progressed

There are growing expectations being placed on drug-agnostic CDx to address the circumstances described above.

Drug-agnostic CDx are diagnostics that can be used to evaluate responses for multiple molecular targeted therapies for the same genetic mutation or biomarker.

Discussions on this topic started in around 2019 and were led by the Pharmaceuticals and Medical Devices Agency (PMDA), which led to a notice from the Ministry of Health, Labour and Welfare (MHLW) titled "Notification on Handling of In Vitro Diagnostics and Medical Device Products aiming Drug-agnostic Companion Diagnostics" in

[8] It must be noted that studies comparing singleplex and multiplex testing for EGFR gene mutations have found detection rates to be higher for singleplex tests and lower for multiplex tests (for both false negatives and false positives).

[9] Demand for singleplex tests is declining and production of a singleplex test called ArcherMET ended in 2023. This led to concerns that access to tepotinib would become restricted. After related agencies came together to discuss this issue, the end of sales was postponed. In the meantime, a different multiplex test was approved for use as CDx for tepotinib, thus avoiding a restriction of access.

March 2022. Further guidance was provided in "Guidance on Drug-Agnostic Companion Diagnostics," which was issued in June 2022 and partially revised in May 2024.

The Guidance outlines concepts and procedures for linking the same molecular targeted therapies to CDx that detect the same genetic mutations so those CDx can be used to evaluate responses for all drugs that target said genetic mutations within the scope that is considered scientifically reasonable. The Japan Lung Cancer Society submitted a proposal on drug-agnostic CDx for EGFR gene testing in May 2023, and efforts in line with that proposal are currently underway. While it is expected that approval will be granted, a diagnostic has yet to be approved under this framework despite the fact that it has already been three years since the MHLW issued the aforementioned notification.

Structural issues and accuracy control-related challenges that hinder drug-agnostic CDx development

In terms of economic feasibility, individual companies face high hurdles to development (e.g. due to development cost)

While the PMDA has formulated the "Guidance on Drug-Agnostic Companion Diagnostics," considering the fact that there has yet to be a single example of an approval under that system, establishing guidance is insufficient. Further action for the development of drug-agnostic CDx will be necessary.

Both clinicians and pharmaceutical companies would like to see further development of drug-agnostic CDx as an interim measure for delivering treatment to as many patients as possible, as efficiently as possible, and within the framework of the current system. However, for IVD manufacturers, drug-agnostic CDx development is not commercially viable, and there are background structural challenges that mean developing CDx poses a risk of damaging their products' value. Factors for this include the fact that drug-agnostic development involves more combinations between genetic mutations and drugs, leading to greater costs for accuracy control and equivalence testing. Furthermore, even if the number of drugs covered by a diagnostic increase, the number of tests does not increase, so for IVD manufacturers, the only result is higher R&D expenditures.

In the approval process for follow-on CDx (which are new diagnostics that target the same biomarkers as already-approved drugs) including drug-agnostic CDx, neither the PMDA in Japan nor the FDA in the US require new clinical trials on the efficacy and safety of approved drugs in patient populations selected by follow-on CDx. Instead, they must demonstrate clinical concordance (a high rate of concordance) with existing CDx using specimens used in clinical trials or collected under equivalent conditions to show that they can be used to select patients who will respond to treatment in a similar manner. The Japan Lung Cancer Society and the FDA have also specified that "If a CDx targets the same genetic mutation, it should be used for treatment selection even if the CDx is different," so both advocate for a system that ensures CDx can be used interchangeably. However, some have expressed concerns that showing clinical concordance (such as having positive or negative concordance) is insufficient and that clinical usefulness cannot be fully demonstrated without verifying the drug's clinical outcomes (efficacy and safety) for selected patients, so such practices carry the possibility of being detrimental to patients.

Improving future patient access

Drug-agnostic CDx currently have the potential to improve access to medicines in Japan, but this need is driven by restrictions on CDx and CGP that are unique to Japan. In fact, demand for drug-agnostic CDx in other countries is limited. For non-Japanese pharmaceutical companies and medical device manufacturers involved in genomic cancer medicine in particular, it is irrational to independently advance R&D for drug-agnostic CDx for the sole purpose of complying with rules that are unique to Japan. If efforts to further the development and accuracy management for drug-agnostic CDx are to be advanced to improve patient access to treatment, progress is unlikely to occur from efforts from individual companies; rather, it will require multi-stakeholder collaboration involving pharmaceutical companies and medical device manufacturers.

To address the fundamental issue of patient access to treatment, discussions must be held on how to eliminate the division between CDx and CGP. As previously discussed, Japan has a unique systemic framework for CDx that has given rise to a new form of drug lag. Moving forward, new genetic mutations are likely to be discovered, followed by the introduction of new therapeutics that target them, so discussions must be held on how long to

maintain the current frameworks for CDx and CGP. Astonishing progress is also being made in research related to whole genome sequencing, and in countries like the Netherlands, the UK, and Denmark, whole-genome sequencing is already being actively used in clinical diagnosis. In Japan, research and other efforts are currently advancing under the “Action Plan for Whole Genome Analysis” to encourage the timely adoption of whole-genome sequencing in routine clinical practice. Continuous discussions must be held to examine the integration of CDx, CGP, and whole-genome sequencing as well as their combined use.

April 2025

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Project sponsors (in Japanese syllabary order)

Guardant Health Japan Corp.
Chugai Pharmaceutical Co., Ltd.
Janssen Pharmaceutical K.K.

April 2025

Regarding the independent nature of these recommendations

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