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REVIEW

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Recommendations to improve the clinical adoption of NGS-based cancer diagnostics in Singapore

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Abstract

Next-generation sequencing (NGS)-based diagnostics have demonstrated clinical utility in predicting improved survival benefits with targeted treatment in certain cancer types, and positive cost–benefit in several healthcare systems. However, clinical adoption in Singapore remains low despite commercial availability of these diagnostics. This expert opinion review examines the key challenges to the clinical adoption of NGS-based diagnostics in Singapore, provides recommendations on impactful initiatives to improve adoption, and also offers practical guidance on specific cancer types in which NGS-based diagnostics are appropriate for use in Singapore. Limited patient affordability is one major challenge to clinical adoption of NGS-based diagnostics, which could be improved by enabling patient access to more funds for specific cancer types with clear benefits. Expert opinion based on current evidence and clinical experience supports the upfront use of hotspot panels in advanced non–small cell lung cancer (NSCLC), metastatic colorectal cancer, advanced and recurrent ovarian cancer, and acute myeloid leukemia. Comprehensive genomic profiling could be considered for upfront use in select patients with NSCLC and ovarian cancer, or in refractory patients with the four cancer types. Wider adoption of NGS-based diagnostics will improve the delivery of cancer care in Singapore and Asia-Pacific, and thus lead to better patient outcomes.

KEYWORDS

cancer genetics, group 1: major specialty, molecular genetics, group 3: other specific research areas, tumor markers, group 3: other specific research areas

1 | INTRODUCTION

With the advent of next-generation sequencing (NGS) technologies, significant achievements have been made in the field of cancer diagnostics to better understand the genomic profiles of individual patients and tumor types.[1] In recent years, NGS-based diagnostics that profile somatic mutations in tumors have demonstrated clinical utility and positive cost–benefit in cancer care. These NGS-based diagnostics include hotspot or targeted panels that sequence specific parts of genes commonly altered in cancer (typically ≤50 genes), and comprehensive genomic profiling (CGP) through sequencing of entire coding regions (all exons and in some cases introns) of multiple genes (typically >50 genes).

Prospective and retrospective clinical studies have shown that NGS profiling can predict overall survival (OS) and progression-free survival (PFS) benefits associated with chemotherapy and targeted

therapy in select patient cohorts. Non–small cell lung cancer (NSCLC) patients with high tumor mutational burden (TMB) as determined by NGS-based diagnostics achieved significantly longer PFS following treatment with both targeted therapy and chemotherapy.[2–4] Similarly, as informed by NGS-based diagnostics, addition of targeted therapy to chemotherapy improved survival amongst metastatic colorectal cancer (CRC) patients with high TMB and those with wild-type *KRAS* and *NRAS* genes.[5,6] Besides lung and colorectal cancer, NGS profiling has also been shown to predict OS and PFS improvements associated with chemotherapy and targeted therapy in breast and ovarian cancer, acute myeloid leukemia (AML) and several refractory cancers.[7–10]

In addition to improving patient outcomes, NGS profiling also reduces treatment costs and time to diagnosis compared with single biomarker tests. In two cost-impact model studies, investigators showed that NGS profiling helped to lower total cost of treatment for advanced NSCLC patients by US$2.7 million due to decreased costs incurred from nontargeted therapy and adverse events,[11] and achieved US$1.5 million in savings using NGS-based diagnostics compared to sequential single-gene tests with rebiopsies.[12] Time to diagnosis was also reduced by 2.8 weeks compared to sequential single-biomarker testing. In light of the clinical benefits associated with NGS-based diagnostics, international clinical oncology organizations such as the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) have issued guidelines recommending the use of broader molecular profiling tests such as hotspot panels and CGP for specific cancer types (e.g. advanced NSCLC).

As the body of clinical evidence and advocacy within the medical community continue to grow, countries such as the United States and Japan are already seeing high adoption rates of NGS-based diagnostics, particularly for NSCLC and CRC.[2–6,13,14] Wider clinical adoption of advanced diagnostics is expected to address evolving diagnostic and treatment needs of cancer patients, improve patient outcomes and lower healthcare costs for some patient populations.[11,12,15]

In Singapore, there is prevalent use of single-gene/biomarker cancer diagnostic tests, but the adoption rate for NGS-based tests remains low despite the regulatory approvals and commercial availability of these tests (Supporting information Appendix I). As such, the goals of this expert opinion paper are to:

1. Discuss the key challenges of adopting NGS-based diagnostics in clinical practice for the management of somatic cancers in Singapore.
2. Provide practical recommendations based on published evidence and expert opinion, taking into account the perspectives of multiple stakeholders, i.e., clinicians, patient advocacy groups, policymakers, academics and industry participants.

Based on a review of published evidence, the types of cancer in which NGS-based diagnostics have demonstrated the highest clinical utility and cost–benefit are profiled in this paper. The expert panel also provided their opinions on which of these cancer indications may be suited for wider clinical use of NGS-based diagnostics in Singapore.

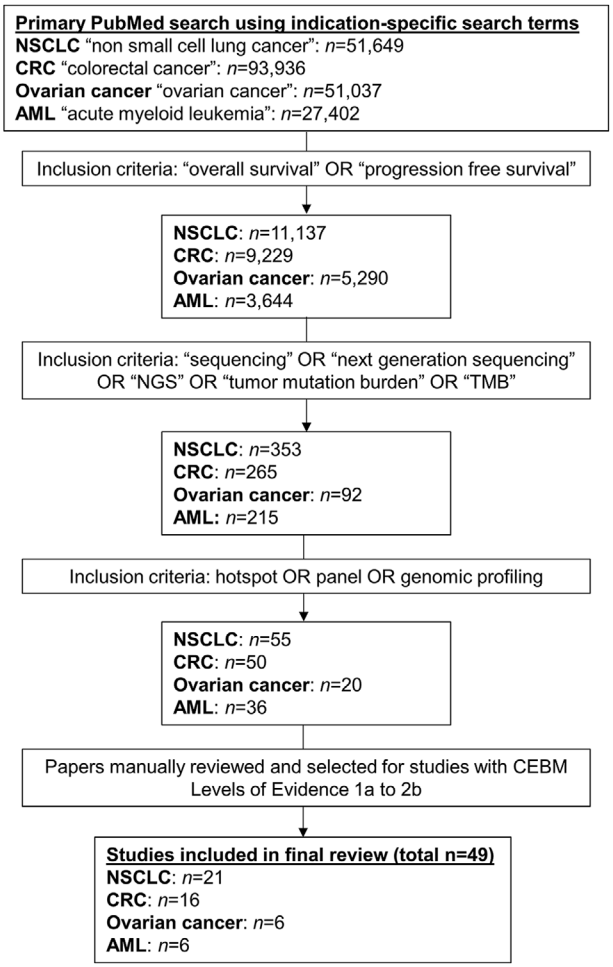

FIGURE 1 Summary of literature search strategy and selection for the specified indications. NSCLC, non-small cell lung cancer; CRC, colorectal cancer; AML, acute myeloid leukemia; CEBM, Oxford Centre for Evidence-based Medicine

2 | METHODS

2.1 | Literature search

A literature search for clinical studies evaluating NSCLC, CRC, ovarian cancers and AML with primary endpoints of OS or PFS was performed using PubMed. Search results were filtered for terms describing NGS technologies, and manually curated to select for studies with Oxford Centre for Evidence-based Medicine (CEBM) Levels of Evidence 1a to 2b to achieve high stringency for the clinical utility data present (Figure 1). The last search was performed in September 2019.

2.2 | RAND / UCLA appropriateness method

The expert opinion was gathered based on a modified form of the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method.[16] The expert panel, comprising of seven key clinicians from public and private hospitals in Singapore, reviewed the clinical literature, case studies from other countries and interview findings with stakeholders in Singapore (including clin-

icians, patient advocacy groups, policymakers, academics and industry participants). The experts rated each challenge and initiative for their impact, as well as the appropriateness of using NGS diagnostics in selected cancer types based on provided evidence and personal clinical experience. This validated method has been used widely to develop practice guidelines and align expert opinions.[17,18] The aligned recommendations form the final output of this expert opinion paper.

3 | RESULTS

3.1 | Utility of NGS diagnostics in selected cancer indications

We identified four cancers, namely advanced NSCLC, metastatic CRC, advanced and recurrent ovarian cancers and AML, which have high numbers of actionable mutations and targeted therapies based on a review of the current precision oncology landscape and expert opinion. A targeted literature review of these cancers identified studies demonstrating high clinical utility for upfront use of NGS-based diagnostics during the diagnosis process, especially in NSCLC and CRC (Figure 1, Supporting information Appendix II).

In NSCLC, hotspot panels are sufficient for detection of most common gene alterations, such as *EGFR*, *KRAS*, *BRAF*, *ERBB2* mutations, and *ALK* and *ROS1* rearrangements.[19–21] However, CGP can detect more targetable alterations with higher coverage and other classes of genomic alterations such as TMB. High TMB detected by CGP has been used to identify patients suitable for targeted therapy with improved survival benefits.[3,22–26] For example, patients with high blood TMB that were treated with PD-1/PD-L1 blockage therapy demonstrated superior PFS compared to patients with low blood TMB (hazard ratio = 0.39; 95% confidence interval, 0.18–0.84; $P = 0.01$).[23] In another study, higher TMB score significantly predicted improved OS (hazard ratio = 0.10; $P = 0.003$) in NSCLC patients treated with anti-PD-1/PD-L1 therapy.[26] However, the role of TMB as a predictive biomarker for clinical benefit is still controversial given the lack of standardization of TMB assessment across studies, and recent clinical trial results that reported comparable OS benefit in patients with high or low TMB.[27]

For CRC, hotspot panels are able to detect most actionable alterations, such as *KRAS*, *NRAS*, *BRAF* and *PIK3CA* mutations.[5,28,29] CGP is able to test for additional biomarkers, including TMB and microsatellite instability (MSI), which are also predictive of improved survival outcomes in patients treated with chemotherapy and targeted agents.[6,30] Although MSI status has been established as a strong prognostic factor for CRC, evidence for its use as a marker for guiding treatment decisions is still controversial and warrants further studies, as MSI-High phenotypes can exhibit significant molecular heterogeneity.[31,32]

For ovarian cancer, hotspot panels can cover several predictive biomarkers, such as mutations in DNA repair genes including *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *BRIP1*, *RAD51B*, *RAD51C*, *RAD51D* and *ATM*,[33] which are not always concentrated in hotspot regions.[34] Furthermore, cancer genomes with DNA repair gene mutations also often harbor chromosomal aberrations, so broader molecular profiling by CGP is needed to detect the full repertoire of actionable somatic alterations, and to quantify the extent of chromosomal abnormalities—namely telomeric allelic imbalance (TAI), loss of heterozygosity (LOH) and large-scale transition, which are jointly termed "genomic scar" assays or "homologous recombination deficiency (HRD)" score assays[33]—in these tumors. Profiling the extent of HRD with *BRCA1/2* mutation status has been shown to influence response to treatment with poly(ADP-ribose) polymerase inhibitors, highlighting the importance of CGP-based measurement of HRD as a clinical biomarker in the management of primary and recurrent ovarian cancers.[7,35–40]

Finally, in the context of AML, associated target genes including *DNMT3A*, *KIT*, *NPM1*, *IDH1/2* and *CEBPA* are typically covered in hotspot panels. As there are relatively fewer targeted therapies for AML, most studies have focused on linking individual biomarkers to patient risk stratification and prognosis.[41] Due to the limited number of studies, the clinical value of CGP in AML remains to be ascertained. With increased knowledge of the molecular landscape of AML, greater adoption of hotspot panels and CGP will likely follow to better guide treatment decisions for patients who would benefit from combination therapy or investigational treatments.

In consideration of the published evidence and feedback from key stakeholders interviewed, the expert panel identified the top six key challenges that limit clinical adoption of NGS-based diagnostics in Singapore, and recommended potential initiatives to overcome these challenges (Figure 2, Supporting information Appendix III and IV).

3.2 | Challenges and recommendations

3.2.1 | Lack of patient affordability

Challenge

The lack of patient affordability is the top challenge to clinical adoption of NGS-based diagnostics in Singapore. Currently, the use of the national medical savings scheme (MediSave) for cancer diagnostics is capped at S$600 per year and is insufficient to cover NGS-based diagnostics, as the full quantum is typically consumed during initial diagnosis, before treatment selection is discussed. Imaging and molecular tests for initial diagnosis of NSCLC cost between S$5,000 and S$17,000 (Supporting information Appendix V). In such cases, patients may opt not to use NGS-based diagnostics due to the associated out-of-pocket cost (ranging from S$1,500 to S$5,500).

Recommendations

To reduce out-of-pocket costs for patients, insurance agencies could consider enhancing coverage for these NGS tests, as these tests could lead to optimization of therapy by lowering the likelihood of utilizing ineffective drugs. The government could also consider higher withdrawal limits for cancer diagnostics under MediSave or insurance coverage of NGS-based diagnostics under MediShield Life for selected indications with clear clinical benefits, such as advanced NSCLC, CRC and ovarian cancers.[2–7] For example, S$5,000 could be the baseline amount that advanced NSCLC patients are able to access through MediSave or MediShield Life since 90% of these patients require initial

Challenges	Recommendations
Lack of patient affordability	• Insurance companies to enhance coverage for selected NGS diagnostics tests • Government to allow more coverage for NGS diagnostics under MediSave and MediShield Life for selected cancer indications • Service providers and diagnostic companies to lower NGS diagnostics costs • Diagnostics and pharma companies to offer patient access programs for eligible patients
Long turnaround time	• Healthcare institutions and service providers to reduce overall turnaround time to ~2 weeks (e.g., Service providers could set up regional hubs in Asia-Pacific)
Lack of local guidelines	• Local clinical organizations to identify cancer indications where NGS diagnostics have demonstrated high clinical utility and craft well-defined guidelines
Insufficient education of the clinical community	• Healthcare institutions to incorporate NGS diagnostics into routine clinical workflow • Singapore Medical Council and medical schools to integrate NGS diagnostics education in CME programmes and medical school curriculum • Service providers and diagnostic companies to provide on-demand training to relevant healthcare practitioners
Insufficient education of patients	• Clinicians and genetic counsellors to provide dedicated patient education sessions • Service providers to support clinicians and healthcare institutions with communication training and patient education materials • Collaborative industry-healthcare institution effort to develop online resources for patients to facilitate easy access to up-to-date information
Lack of conclusive cost-benefit studies	• Payers to conduct local cost-utility study for NGS diagnostics, or contribute to design of studies conducted by third parties (e.g., industry, academia) • Payers to consider reimbursing selected patient segments where clear benefits of NGS diagnostics have been demonstrated in other healthcare systems

FIGURE 2 Overview of the top six challenges and recommendations for clinical adoption of NGS-based diagnostics in Singapore

tests that cost ~S$5,000 (Supporting information Appendix V). Additionally, NGS service providers and diagnostic companies could consider lowering costs through automation, bulk processing and process optimization. Diagnostics companies should also play a role in improving patient access by lowering the price of NGS-based diagnostics or providing financial assistance. They can also collaborate with pharmaceutical companies to offer innovative patient access programs to cover the cost of NGS-based diagnostics if the patient is eligible for the identified targeted therapies.

3.2.2 | Long turnaround time

Challenge

The current turnaround time for CGP of 4 weeks in Singapore is too long, resulting in some clinicians opting for single-biomarker tests instead of CGP for faster results. For patients with advanced cancers that would benefit from NGS-based diagnostics, such as stage III/IV NSCLC patients, quicker turnaround times are essential as a month-long wait for test results is substantial for a patient whose expected survival is less than 12 months.

Recommendations

To enable timely access to treatments, the expert panel recommends that the turnaround time for NGS-based diagnostics be reduced to 2 weeks. This includes the time it takes for pathology labs to process samples (~1 week) and for service providers to run the analysis (~1 week). Service providers could consider setting up regional hubs in Asia-Pacific to speed up sample transit times and improve coordination with local healthcare institutions. Service providers could thus meet a growing demand for genomic sequencing in Asia-Pacific, which accounts for nearly 50% of global cancer cases.[42] With the support of Singapore's Economic Development Board (EDB), service providers could consider making Singapore the regional hub for such testing services.

3.2.3 | Lack of local guidelines and recommendations

Challenges

The limited adoption of NGS-based diagnostics among oncologists in Singapore is also attributed to the lack of clinical guidelines and recommendations from local or regional clinical oncology organizations on which cancer indications will benefit. Despite published clinical evidence demonstrating the ability of NGS-based diagnostics to help predict improved survival benefits of targeted therapy and chemotherapy for NSCLC, CRC and ovarian cancer patients, clinical adoption varies significantly among clinicians in Singapore in the absence of clear guidelines on which cancer indications are likely to benefit.[2–7] This results in longer time to treatment for patients who receive sequential single-biomarker tests as per current clinical practice, and potential accumulation of overall diagnostics and treatment costs for patients receiving nontargeted treatment regimens.

Recommendations

The panel has identified cancer indications for which NGS-based diagnostics have shown high clinical utility. Specifically, upfront use of hotspot panels can help to predict survival benefits (OS and PFS) with targeted treatment in patients with advanced NSCLC, CRC and ovarian cancers, and also help to identify better prognosis in specific patient populations with AML.[2–8]

In view of the limited guidelines and recommendations to guide local clinical practice, the expert panel recommends that local oncology and hematology societies, as well as academic bodies, craft clear and detailed guidelines. For example, the following clinical use cases could be considered for NGS-based diagnostics (Supporting information Appendix IV):

- Hotspot panel: Upfront use for advanced NSCLC, metastatic CRC, advanced and recurrent ovarian cancer and AML.
- CGP: Subsequent use in advanced NSCLC, metastatic CRC, advanced and recurrent ovarian cancer for patients who have failed multiple therapies and who may be eligible for available clinical trials in Singapore. CGP can also be used upfront in selected patients with advanced NSCLC and selected patients with advanced primary and recurrent ovarian cancer.

As actionable mutations are dependent on the number of targeted therapeutics and clinical trials available in Singapore, the clinical utility of NGS-based diagnostics will continue to increase as these two factors improve over time.

3.2.4 | Insufficient education of the clinical community

Challenges

As advancements in the field of NGS-based diagnostics are evolving very quickly, the general community of healthcare professionals (e.g., doctors, nurses, genetic counsellors) do not receive sufficient ongoing education on these tests in their clinical practice or in continuing medical education (CME) programmes. This limits their awareness and consequently their understanding and adoption of these tests in clinical practice.

Recommendations

The panel recommends that education of the clinical community focus on incorporating NGS-based diagnostics into routine clinical workflow, and by integrating genomics into CME programmes. Singapore Medical Council could include short courses and seminars in CME that educate healthcare professionals on the clinical utility and limitations of NGS-based diagnostics, as well as interpretation of results and patient communication. For medical trainees, this could be included in the medical school curriculum. To increase awareness and product knowledge, service providers and diagnostic companies should also provide on-demand training for first-time users (e.g., workshops, online portal for easy access to training, triggering of online training modules when ordering a test for the first time via electronic medical records).

3.2.5 | Insufficient education of patients

Challenges

Patients who lack understanding of NGS-based diagnostics may demand unnecessary tests or expect NGS-based diagnostics to aid in highly efficacious treatment. If treatment strategies do not work as expected, patients may lose their trust in the test results and their clinicians' decisions. Decreased patient trust in NGS-based diagnostics may lead to lower adoption by clinicians. Hence, it is important for patients to be educated on the limitations of NGS-based diagnostics to manage their expectations.

Recommendations

The panel recommends that healthcare practitioners make conscious efforts to educate patients and their families to improve their understanding of the recommended NGS-based diagnostic tests, expected turnaround times and interpretation of test results. Clinicians and genetic counsellors could provide patient education sessions to specify the types of possible results and the potential for uncertainty, according to Singapore's clinical genetic and genomic testing standards. Service providers or manufacturers could also promote effective patient education by providing clinicians with communication training and patient education materials. Healthcare institutions could also work together with industry players to develop online resources with information that is up-to-date and easy to understand, which would be key to facilitate patients' access to information and their understanding of this sophisticated field.

3.2.6 | Lack of conclusive cost-benefit studies

Challenges

Although cost–benefit studies have supported the reimbursement decisions of NGS-based diagnostics in other countries, similar studies have not been conducted in Singapore. The lack of conclusive cost-benefit studies makes it difficult for policymakers to determine the need for funding support of NGS-based diagnostics. As a result, reimbursement for NGS-based diagnostics is insufficient, limiting clinical adoption of these tests due to poor patient affordability.

Recommendations

Studies in the United States have shown that the use of NGS-based diagnostics resulted in improved patient outcomes, minimal increase in cost and improved benefit-to-cost ratio for selected indications such as NSCLC.[11,12,15,43] However, in order to determine the impact of NGS-based diagnostics for Singapore, it is important for payers to actively generate local data on the cost-utility of NGS-based tests by analyzing survival benefits and impact on costs to the healthcare system. Alternatively, payers can participate in the design of such studies conducted by third parties (e.g., industry, academia) by providing inputs appropriate to Singapore's context. In the interim, authorities could also consider reimbursing selected patient segments, such as advanced NSCLC patients, where clear benefits from the use of NGS-based diagnostics have been demonstrated in other healthcare systems and thus influenced their reimbursement coverage.

Although it is beyond the scope of this paper to conduct specific cost–benefit analysis for Singapore, the expert panel urges payers to consider generating local cost-utility data for NGS-based diagnostics to identify high-priority cancer patient populations who will benefit from the use of these tests early and grant better funding access for them.

4 | DISCUSSION

To inform their recommendations, the expert panel examined several growth areas, from the emerging role of CGP, to the reimbursement landscape for NGS-based diagnostics in other countries, as well as the precision oncology ecosystem in Singapore. Forward-looking views of these key topics are discussed in this section.

4.1 | Emerging role of CGP

In the coming years, the role for CGP will evolve as more clinical evidence emerges. Although the current expert panel opinion recommends upfront use of hotspot panels in the four selected cancers (advanced NSCLC, metastatic CRC, advanced and recurrent ovarian cancer and AML), given that hotspot panels are sufficient for detection of the <50 biomarkers associated with the limited targeted therapeutics available, it is important to recognize the expanding clinical value of CGP. CGP simultaneously interrogates all four of the main classes of genomic alterations in cancer, which include insertions/deletions (indels), base pair substitutions, copy number variations (CNVs) and rearrangements. Compared to hotspot panels, CGP can detect driver alterations (especially structural alterations such as chromosomal CNVs and complex genomic rearrangements) more comprehensively and at higher resolution.[1,44]

Given the more comprehensive genomic coverage, CGP can support clinicians in making more informed molecular-guided therapy decisions as more targeted therapeutics for different biomarkers become available.[45,46] In the near term, CGP can also support clinicians in selecting targeted therapeutics for off-label treatment of refractory patients based on their genomic profiles. Furthermore, the value of CGP in detecting complex gene signatures (e.g., TMB, MSI and LOH) and predicting survival benefits is undergoing further clinical validation, and may provide additional evidence to guide prognosis and treatment decisions in a personalized manner in the near future, particularly for combination therapies.[10] Some CGP tests also capture transcriptomic information, which may supplement the genomic information to guide therapy recommendations.[47] From a forward-looking perspective, CGP may also impact future clinical care through its use in the identification of pan-tumor biomarkers such as *NTRK* genes and support the enrolment of patients into basket trials.

In addition, given that current diagnostic tests use the tissue biopsy as the standard sampling approach, upfront use of CGP can play a critical role in patients with limited fresh or archival tissue samples as the test requires less material and avoids multiple sequential testing. For instance, 30% of NSCLC patients do not have adequate tissue samples available for diagnosis using standard biomarker testing.[48–50] Alternatively, with increasing clinical evidence, CGP using liquid biopsy samples may also be considered as an option for these patients.[51,52]

Although the relatively high costs of CGP today and limited number of targeted therapeutics have contributed to limited adoption of CGP, the body of evidence supporting the clinical utility of CGP and the number of targeted agents are increasing for multiple cancer types, in addition to the four selected cancers reviewed in this paper.[53–55] This includes several other cancers with some of the highest mortality rates in Singapore, such as liver cancer, gastric cancer, pancreatic cancer, as well as prostate cancer in men.[57-62] For pancreatic cancer in particular, patients receiving molecularly matched therapy using CGP have shown improved survival outcomes in a recent study, and about 8% of the pancreatic cancer patient population has genetic alterations with available targeted therapies.[60] Taken together, this signals an expansion in the role that CGP can play in delivering effective cancer care for specific indications in the future.

4.2 | Reimbursement for NGS-based diagnostics

NGS-based diagnostics for cancer patients are already reimbursed in many countries across the globe (e.g., United States, Japan). Although health systems in these countries are larger and may have different payer structures compared to Singapore, the reimbursement landscape in other countries still serve as valuable case studies that could inform and potentially guide Singapore's own reimbursement decisions. Ultimately, the availability of reimbursement plans for NGS-based diagnostics in selected advanced cancer patients remains a key driver in increasing clinical adoption and patient access to NGS diagnostics.

A number of countries, such as Australia, France, Japan, Korea, the United States and the United Kingdom, provide funding mechanisms for NGS-based diagnostics today (Table 1). These countries justified reimbursement through a combination of published clinical evidence for enhanced patient outcomes and expected healthcare cost savings. The key patient outcomes that influenced reimbursement decisions are improved survival data using NGS-based diagnostics (Supporting information Appendix II), though other improved clinical outcomes include reduced adverse events and reduced time to diagnosis. Based on micro-costing analysis and cost-effectiveness studies in specific cancer patient populations, NGS-based diagnostics are also expected to result in healthcare cost savings due to a reduction in the number of diagnostics tests that would have been performed sequentially, as well as decreased use of more expensive nontargeted therapies.[11,12,15,43]

For example, the US Centers for Medicare & Medicaid Services (CMS) and Japan's Ministry of Health, Labour and Welfare (MHLW) provide reimbursement for both hotspot panels and CGP up to US$3,500 per test (Table 1). In the United States, test reimbursement and funding is dependent on proven clinical utility in clinical trials, whereas in Japan, reimbursement is dependent on the test's clinical effectiveness compared to other reimbursed tests.[56]

With reference to the reimbursement practices in other countries and evidence of the clinical utility of NGS-based diagnostics in selected

TABLE 1 Regulatory framework and reimbursement options of NGS-based diagnostics across different countries

Country	Regulatory framework	Hotspot panel	CGP	Reimbursed amount
United States	• The FDA regulates NGS-based diagnostics as a class II device requiring 510(k) submission/premarket notification (PMN) or class III device via premarket authorization (PMA) • Most companion diagnostics (CDx) are class III devices requiring PMA and clinical data showing safety and efficacy	✓	✓	Up to US$3,500 per test for advanced cancer diagnostics
United Kingdom	• MHRA expects to follow the new EU IVDR framework • NGS-based diagnostics are considered class C devices requiring a CE mark; without predicate, clinical data showing safety and efficacy is required	✓	✓	Full reimbursement, estimated around US$500 per test
France	• Under the new EU IVDR framework NGS-based diagnostics are expected to be regulated as Class C devices requiring a CE mark; without predicate, clinical data showing safety and efficacy is required	✓		Full reimbursement, estimated around US$700 per test
Australia	• Under the proposed TGA framework, NGS-based diagnostics are expected to be regulated as Class III IVDs (similar to CDx); the proposal also calls for mandatory audits and inclusion in the Australian Register of Therapeutic Goods (ARTG)	✓	✓	Not specified, will be based on cost-effectiveness as evaluated by MSAC
Japan	• PMDA regulates NGS-based diagnostics as class II or III medical devices; clinical performance of CGP test is evaluated by expert panel and clinical utility established through implementation	✓	✓	Up to 70% reimbursement, estimated up to around ~US$4,000 per test
Korea	• MFDS regulates NGS-based diagnostics as class II or III devices, similar to the US FDA; most IVDs require additional testing to Korean product standards;	✓	✓	Up to 80% reimbursement expected if included in MoHW reimbursed list
Singapore	• HSA's draft guidance regulates NGS-based diagnostics as IVDs, and the draft will be updated after consultation and feedback from stakeholders in 2H2019 • Documentation of methods, data analysis, preclinical studies and clinical studies are required, as well as evidence-based assessment to justify gene inclusion	✓	✓	Limited to around US$430 in MediSave for all cancer diagnostics, though the amount is insufficient as imaging and other diagnostics often exhaust this expenditure cap

FDA, U.S. Food and Drug Administration; MHRA, UK Medicines and Healthcare products Regulatory Agency; IVDR, European In Vitro Diagnostic Regulation; CE, Symbol of free marketability within European Economic Area; TGA, Australia Therapeutic Goods Administration; MSAC, Australia Medical Services Advisory Committee; IVD, in vitro diagnostic; PMDA, Japan Pharmaceuticals and Medical Devices Agency; MFDS, Korea Ministry of Food and Drug Safety; MoHW, Korea Ministry of Health and Welfare; Class I medical devices, low-to-moderate risk (most do not require regulatory approval); class II medical devices, moderate-to-high risk (some require product testing/clinical data); class III medical devices: high risk (most require clinical trials).

patient populations, Singapore should consider providing reimbursement for NGS-based diagnostics in these patient populations, or grant increased coverage by MediSave or MediShield Life. For both patients and payers, this would mean a shorter time to targeted treatment, reduced subsequent cost of care, and reduced costs of unnecessary treatment as only eligible patients predicted to respond will be given targeted therapies. With clearly defined biomarkers identified in the NGS-based diagnostics test reports, both public and private (e.g., insurance) payers will be able to validate patients' claims for eligible diagnostics and drugs more efficiently.

4.3 | The present and future of Singapore's precision oncology ecosystem

Although clinical adoption of NGS-based diagnostics is low, Singapore's precision oncology ecosystem has done well in several other areas. Nation-wide initiatives such as the Singapore Translational Cancer Consortium (STCC) have been established to lead precision oncology efforts to improve care for cancer patients, and leverage on established data infrastructure such as the Health Data Grid. In addition, Singapore has short regulatory approval timelines typically under 1 year, accounting for the many targeted therapeutics and diagnostics being made commercially-available in Singapore. Singapore's Health Sciences Authority (HSA) is also working on a draft guidance for NGS-based diagnostics as of mid-2019, which will enable better regulation and quality control of NGS-based diagnostics here. Furthermore, Singapore has unique reimbursement flexibility that enables better patient access to targeted treatments compared to other countries, as the national basic health insurance plan MediShield Life allows coverage of off-label use of targeted therapeutics in oncology when there is a lack of existing options.

To further improve the precision oncology ecosystem in Singapore, there will be a need to increase the availability and access to targeted treatments. Given the limited number of targeted therapeutics avail-

able globally, increased research is needed to identify more targeted agents. By investing more in clinical research, Singapore could play a significant role in identifying new targeted therapeutics for biomarkers specific to the Asian or Singaporean population. Reimbursement limits for cancer treatments in Singapore should also be reviewed periodically to determine if patients are able to access the care needed, taking into account the clinical utility and value provided by the targeted treatments.

In planning for the future, Singapore should consider a value-based approach in healthcare delivery. Presently, healthcare delivery for cancer patients is often a one-way street from diagnosis to treatment. A better healthcare delivery model would encompass a continuous feedback loop, where real world data generated from the diagnosis and treatment of cancer patients is used to identify better treatment options for subsequent cancer patients. This model has been increasingly adopted in systems around the world such as Intermountain Healthcare in the United States and multiple cancer centers in Japan. The proliferation of value-based healthcare is changing the way physicians and hospitals provide care. New healthcare delivery models stress a team-oriented approach to patient care and sharing of patient data so that care pipelines are coordinated and outcomes can be measured easily. In adopting this healthcare delivery model, Singapore will be able to continuously improve and thus deliver cancer care more effectively in the coming years.

5 | CONCLUSION

In this era of genomic medicine, rapid research developments and innovative clinical advancements in oncology have helped to transform the understanding of tumor biology and cancer therapy for individual patients. As clinicians, we should change the way we think about cancer management for our patients and keep pace with the developments. The clinical utility and cost–benefit of NGS-based diagnostics have been demonstrated in numerous studies and widely adopted in countries that are moving ahead in precision oncology efforts. In Singapore, wider adoption of NGS-based diagnostics will improve patient outcomes for specific cancer patient populations, such as in advanced NSCLC, metastatic CRC, advanced and recurrent ovarian cancer and AML patients. The panel's guidance of upfront and subsequent use of NGS-based diagnostics for the recommended clinical use cases involving the four cancer types provide a starting point to guide clinicians in their choice of advanced molecular diagnostics. With the increased adoption of NGS, the disease burden for specific cancer patients is expected to decrease, bringing more value to both payers and patients due to overall improvements in outcomes. It is therefore worth reviewing the current funding mechanisms for cancer diagnostics (e.g., MediSave, MediShield Life, private insurance) to improve patient access. Increased clinical usage of NGS-based diagnostics will strengthen the growth of the precision medicine ecosystem in Singapore, as genomic data obtained from NGS test results will enhance delivery of precision oncology to patients, support value-based healthcare, broaden cancer research and innovative drug discovery. Given the Singapore ecosystem is comparatively small, there is a greater potential for a whole-of-nation effort to drive precision oncology delivery. National initiatives, such as the STCC and the National Precision Medicine Programme, are taking steps in the right direction to increase collaboration among all stakeholders involved in delivery of this key service. Finally, while the recommendations here are targeted for Singapore and provided by clinical experts in Singapore, most of the key constraints and lessons are broadly relevant to other Asia-Pacific countries, and could guide further discussion to improve value-based healthcare in this region.

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CONFLICTS OF INTEREST

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REFERENCES

1. Horak P, Frohling S, Glimm H. Integrating next-generation sequencing into clinical oncology: Strategies, promises and pitfalls. *ESMO Open*. 2016;1(5):e000094.
2. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093-2104.
3. Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): Outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. *J Clin Oncol*. 2019;37(12):992-1000.
4. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. *Cancer Cell*. 2018;33(5):843-852 e4.
5. Ciardiello F, Normanno N, Maiello E, et al. Clinical activity of FOLFIRI plus cetuximab according to extended gene mutation status by next-generation sequencing: findings from the CAPRI-GOIM trial. *Ann Oncol*. 2014;25(9):1756-1761.
6. Innocenti F, Ou FS, Qu X, et al. Mutational analysis of patients with colorectal cancer in CALGB/SWOG 80405 identifies new roles of microsatellite instability and tumor mutational burden for patient outcome. *J Clin Oncol*. 2019;37(14):1217-1227.
7. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10106):1949-1961.
8. Klco JM, Miller CA, Griffith M, et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. *JAMA*. 2015;314(8):811-822.
9. Radovich M, Kiel PJ, Nance SM, et al. Clinical benefit of a precision medicine based approach for guiding treatment of refractory cancers. *Oncotarget*. 2016;7(35):56491-56500.

10. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: The I-PREDICT study. *Nat Med*. 2019;25(5):744-750.
11. Sabatini LM, Mathews C, Ptak D, et al. Genomic sequencing procedure microcosting analysis and health economic cost-impact analysis: A report of the association for molecular pathology. *J Mol Diagn*. 2016;18(3):319-328.
12. Pennell NA, Mutebi A, Zhou Z-Y, et al. Economic impact of next generation sequencing vs sequential single-gene testing modalities to detect genomic alterations in metastatic non-small cell lung cancer using a decision analytic model. *Journal of Clinical Oncology*. 2018;36(15_suppl):9031.
13. Freedman AN, Klabunde CN, Wiant K, et al. Use of next-generation sequencing tests to guide cancer treatment: Results from a nationally representative survey of oncologists in the United States. *JCO Precision Oncol*. 2018(2):1-13.
14. Takeda M, Sakai K, Takahama T, Fukuoka K, Nakagawa K, Nishio K. New era for next-generation sequencing in Japan. *Cancers (Basel)*. 2019;11(6):742.
15. Haslem DS, Chakravarty I, Fulde G, et al. Precision oncology in advanced cancer patients improves overall survival with lower weekly healthcare costs. *Oncotarget*. 2018;9(15):12316-12322.
16. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: Rand Corp.; 2001.
17. Cheung PP, Lahiri M, Teng GG, et al. Consensus development on eligibility of government subsidization of biologic disease modifying antirheumatic agents for treatment of ankylosing spondylitis: The Singapore experience. *Int J Rheum Dis*. 2017;20(10):1517-1526.
18. Teng GG, Cheung PP, Lahiri M, et al. Singapore chapter of rheumatologists consensus statement on the eligibility for government subsidy of biologic disease modifying antirheumatic agents for treatment of rheumatoid arthritis (RA). *Ann Acad Med Singapore*. 2014;43(8):400-411.
19. Kostenko A, Michels SYF, Fassunke J, et al. Survival following implementation of next-generation sequencing in routine diagnostics of advanced lung cancer: Results of the German Network Genomic Medicine. *J Clin Oncol*. 2016;34(15_suppl):9085.
20. Aisner D, Sholl LM, Berry LD, et al. Effect of expanded genomic testing in lung adenocarcinoma (LUCA) on survival benefit: The Lung Cancer Mutation Consortium II (LCMC II) experience. *J Clin Oncol*. 2016;34(15_suppl):11510.
21. Seto T, Matsumoto S, Yoh K, et al. Contribution of nationwide genome screening in Japan (LC-SCRUM-Japan) to the development of precision medicine for non-small cell lung cancer. *J Clin Oncol*. 2018;36(15_suppl):9085.
22. Campesato LF, Barroso-Sousa R, Jimenez L, et al. Comprehensive cancer-gene panels can be used to estimate mutational load and predict clinical benefit to PD-1 blockade in clinical practice. *Oncotarget*. 2015;6(33):34221-34227.
23. Wang Z, Duan J, Cai S, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol*. 2019;5(5):696-702.
24. Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. *JAMA*. 2019;321(14):1391-1399.
25. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598-2608.
26. Chae YK, Davis AA, Raparia K, et al. Association of tumor mutational burden with DNA repair mutations and response to anti-PD-1/PD-L1 therapy in non-small-cell lung cancer. *Clin Lung Cancer*. 2019;20(2):88-96.e6.
27. Bristol-Myers Squibb Provides Update on the Ongoing Regulatory Review of Opdivo Plus Low-Dose Yervoy in First-Line Lung Cancer Patients with Tumor Mutational Burden ≥10 mut/Mb [press release]; 19 October 2018.
28. Yao J, Zang W, Ge Y, et al. RAS/BRAF circulating tumor DNA mutations as a predictor of response to first-line chemotherapy in metastatic colorectal cancer patients. *Can J Gastroenterol Hepatol*. 2018;2018:4248971.
29. Udar N, Lofton-Day C, Dong J, et al. Clinical validation of the next-generation sequencing-based extended RAS Panel assay using metastatic colorectal cancer patient samples from the phase 3 PRIME study. *J Cancer Res Clin Oncol*. 2018;144(10):2001-2010.
30. Pai SG, Carneiro BA, Chae YK, et al. Correlation of tumor mutational burden and treatment outcomes in patients with colorectal cancer. *J Gastrointest Oncol*. 2017;8(5):858-866.
31. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer: A personalized approach to clinical decision making. *Ann Oncol*. 2012;23(10):2479-2516.
32. Battaglin F, Naseem M, Lenz HJ, Salem ME. Microsatellite instability in colorectal cancer: Overview of its clinical significance and novel perspectives. *Clin Adv Hematol Oncol*. 2018;16(11):735-745.
33. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. *J Natl Cancer Inst*. 2018;110(7):704-713.
34. Hirst J, Crow J, Godwin A. Ovarian cancer genetics: Subtypes and risk factors. In: Devaja O, Papadopoulos A, eds. *Ovarian Cancer - From Pathogenesis to Treatment*. London, United Kingdom; IntechOpen; 2018.
35. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(1):75-87.
36. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381:2391-2402.
37. Ray-Coquard IL, Pautier P, Pignata S, et al. LBA2_PRPhase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology*. 2019;30(supp_5):v851-934.
38. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505.
39. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(9):1274-1284.
40. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375(22):2154-2164.
41. Gu R, Yang X, Wei H. Molecular landscape and targeted therapy of acute myeloid leukemia. *Biomark Res*. 2018;6:32.
42. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: gLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
43. Yu TM, Morrison C, Gold EJ, Tradonsky A, Arnold RJG. Budget impact of next-generation sequencing for molecular assessment of advanced non-small cell lung cancer. *Value Health*. 2018;21(11):1278-1285.
44. Consortium APG. AACR Project GENIE: Powering precision medicine through an International Consortium. *Cancer Discov*. 2017;7(8):818-831.

45. Alvarez RH, Thomas JW, Chalmers ZR, et al. Comparison of comprehensive genomic profiling (CGP) and hotspot next generation sequencing (NGS) assays in identifying treatment options for care of patients with metastatic cancer in in the community setting. *Journal of Clinical Oncology*. 2016;34(15_suppl):e23120.
46. Wheler JJ, Janku F, Naing A, et al. Cancer therapy directed by comprehensive genomic profiling: A single center study. *Cancer Res*. 2016;76(13):3690-3701.
47. Rodon J, Soria JC, Berger R, et al. Genomic and transcriptomic profiling expands precision cancer medicine: The WINTHER trial. *Nat Med*. 2019;25(5):751-758.
48. Lim C, Tsao MS, Le LW, et al. Biomarker testing and time to treatment decision in patients with advanced non-small cell lung cancer. *Ann Oncol*. 2015;26(7):1415-1421.
49. Green MR, Willey J, Buettner A, Lankford M, Neely DB, Ramalingam SS. Molecular testing prior to first-line therapy in patients with stage IV nonsquamous non-small cell lung cancer (NSCLC): A survey of U.S. medical oncologists. *J Clin Oncol*. 2014;32(15_suppl):8097.
50. Kim E, Peters M, Tischer B, Hirsh V. *Physician patterns of care in patients with EGFR mutation+ NSCLC: An international survey into testing and treatment choice*. Vienna, Austria: World Conference on Lung Cancer; 2016.
51. Schwaederle M, Husain H, Fanta PT, et al. Use of liquid biopsies in clinical oncology: Pilot experience in 168 patients. *Clin Cancer Res*. 2016;22(22):5497-5505.
52. Rothwell DG, Ayub M, Cook N, et al. Utility of ctDNA to support patient selection for early phase clinical trials: The TARGET study. *Nat Med*. 2019;25(5):738-743.
53. Hyman DM, Taylor BS, Baselga J. Implementing genome-driven oncology. *Cell*. 2017;168(4):584-599.
54. Remon J, Dienstmann R. Precision oncology: Separating the wheat from the chaff. *ESMO Open*. 2018;3(6):e000446.
55. Fountzilas E, Tsimberidou AM. Overview of precision oncology trials: Challenges and opportunities. *Expert Rev Clin Pharmacol*. 2018;11(8):797-804.
56. Jean NS, Pinto C, Tenente I, Murray G. Collaboration is key to accelerating diagnostics access to optimize benefits of precision medicines. *Per Med*. 2018;15(3):157-161.
57. Lee J, Kim ST, Kim K, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VIKTORY umbrella trial. *Cancer Discov*. 2019;9(10):1388-1405.
58. Chen S, Cao Q, Wen W, et al. Targeted therapy for hepatocellular carcinoma: Challenges and opportunities. *Cancer Lett*. 2019;460:1-9.
59. Lee R, Tebbutt N. Systemic treatment of advanced hepatocellular cancer: New hope on the horizon. *Expert Rev Anticancer Ther*. 2019;19(4):343-353.
60. Pishvaian MJ, Blais EM, Brody JR, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: A retrospective analysis of the Know Your Tumor registry trial. *Lancet Oncol*. 2020.
61. Chung JH, Dewal N, Sokol E, et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis Oncol*. 2019;3. https://doi.org/10.1200/PO.18.00283.
62. Zhu J, Tucker M, Marin D, et al. Clinical utility of FoundationOne tissue molecular profiling in men with metastatic prostate cancer. *Urol Oncol*. 2019;37:813.e1-813.e9.

SUPPORTING INFORMATION

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

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