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REVIEW

Recommendations for the use of next-generation sequencing in patients with metastatic cancer in the Asia-Pacific region: a report from the APODDC working group

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Introduction: Next-generation sequencing (NGS) diagnostics have shown clinical utility in predicting survival benefits in patients with certain cancer types who are undergoing targeted drug therapies. Currently, there are no guidelines or recommendations for the use of NGS in patients with metastatic cancer from an Asian perspective. In this article, we present the Asia-Pacific Oncology Drug Development Consortium (APODDC) recommendations for the clinical use of NGS in metastatic cancers.

Methods: The APODDC set up a group of experts in the field of clinical cancer genomics to (i) understand the current NGS landscape for metastatic cancers in the Asia-Pacific (APAC) region; (ii) discuss key challenges in the adoption of NGS testing in clinical practice; and (iii) adapt/modify the European Society for Medical Oncology guidelines for local use. Nine cancer types [breast cancer (BC), gastric cancer (GC), nasopharyngeal cancer (NPC), ovarian cancer (OC), prostate cancer, lung cancer, and colorectal cancer (CRC) as well as cholangiocarcinoma and hepatocellular carcinoma (HCC)] were identified, and the applicability of NGS was evaluated in daily practice and/or clinical research. Asian ethnicity, accessibility of NGS testing, reimbursement, and socioeconomic and local practice characteristics were taken into consideration.

Results: The APODDC recommends NGS testing in metastatic non-small-cell lung cancer (NSCLC). Routine NGS testing is not recommended in metastatic BC, GC, and NPC as well as cholangiocarcinoma and HCC. The group suggested that patients with epithelial OC may be offered germline and/or somatic genetic testing for BReast CAncer gene 1 (*BRCA1*), *BRCA2*, and other OC susceptibility genes. Access to poly (ADP-ribose) polymerase inhibitors is required for NGS to be of clinical utility in prostate cancer. Allele-specific PCR or a small-panel multiplex-gene NGS was suggested to identify key alterations in CRC.

Conclusion: This document offers practical guidance on the clinical utility of NGS in specific cancer indications from an Asian perspective.

Key words: next-generation sequencing, metastatic cancers, Asia-Pacific, genomic alterations

INTRODUCTION

The burden, incidence, and mortality of cancer are rapidly increasing in Asia. According to Global Cancer Observatory: Cancer Today (Globocan), Asia accounted for one-half of all cases and 58.3% of the total cancer deaths in 2020.[1] Common cancer types identified in Asian women are

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breast cancer (BC), cervical cancer, lung cancer (LC), stomach cancer, colorectal cancer (CRC), and liver cancer, whereas LC, liver cancer, prostate cancer (PC), and CRC are the most frequently occurring cancer in men.[1-3] Asian countries have variable health services and infrastructure because of the differences in economic development, local practices, health care policies, and investments. The incidence rates for BC, LC, and CRC are higher in Asian countries with high human development index (HDI) scores, whereas BC, stomach cancer, and liver cancer are more common in countries with low and medium HDI.[2] More than 70% of cancer cases in low- and middle-income Asian countries are diagnosed at locally advanced or metastatic stages, with a 5-year overall survival (OS) rate of $<$50%.[2]

Precision oncology has transformed the management of patients with metastatic cancer through the application of advanced molecular profiling technologies to categorize subgroups of patients and match them to targeted therapy. The most commonly used assay technologies for identifying biomarkers (single gene) for precision medicine initiatives include (i) PCR to assess gene expression or DNA mutations; (ii) fluorescent *in situ* hybridization (FISH) to assess DNA copy number or genetic translocation; and (iii) immunohistochemistry (IHC) to assess protein expression and subcellular localization.[4] However, these assay technologies focus only on a small panel of genomic loci known to harbor common aberrations (hotspots).[5] In contrast, high-throughput next-generation sequencing (NGS) testing facilitates rapid and reliable identification of the most common and defined genetic aberrations in cancer patients beyond specific hotspot mutation loci.[6] Lately, NGS-based diagnostics that profile somatic mutations in tumors have demonstrated clinical utility in the identification of single-nucleotide mutations, insertions, deletions, and large genomic rearrangements.[7] Multigene NGS testing can provide a molecular portrait to the oncologist, which can offer additional insights into determining the response to targeted drug therapies.[7,8] In clinical trials, the use of NGS-based diagnostics in certain cancer types, including BC, ovarian cancer (OC), and nonsquamous non-small-cell lung cancer (NSCLC), improves patient survival outcomes with chemotherapy and targeted therapies.[9]

Recently, the European Society for Medical Oncology (ESMO) issued guidelines recommending the use of NGS on tumor samples in advanced NSCLC, PC, OC, and cholangiocarcinoma.[10] The ESMO Precision Medicine Working Group provided key recommendations for NGS testing in patients with metastatic cancer at three levels: (i) recommendations for use in daily practice (level 1 alterations where clinical trial data validate that the alteration-drug match results in a clinically meaningful improvement); (ii) for consideration of use only in clinical research centers where there may be a presence of matched clinical trials; and (iii) patient-centric recommendations.[10] However, these recommendations are Europe-centric and do not consider the socioeconomic and local practice characteristics associated with the treatment of metastatic cancer in the Asia-Pacific (APAC) region. Moreover, the American Society of Clinical Oncology (ASCO) has also recently published its provisional clinical opinion on somatic genomic testing in patients with metastatic or advanced cancer.[11] In most low-income and low- and middle-income Asian countries, cancer health services (diagnosis and treatment) are not adequately funded by the government and require high out-of-pocket imbursement by patients.[2] Patients are unable to access or have limited access to recommended care options because of the unavailability of sequencing-matched therapies, high cost of diagnostic tests, and inadequate government reimbursement plans.[12] Furthermore, access to novel targeted agents is often limited because of the unavailability of commercial or in-house companion diagnostic tests.[12] To get access to sequencing-matched therapies, cancer patients often enroll in clinical trials. In this article, we have summarized the current NGS landscape and the Asia-Pacific Oncology Drug Development Consortium (APODDC) recommendations for the use of NGS in patients with metastatic cancer in the APAC region.

METHODOLOGY

The APODDC set up a group of experts in the field of clinical cancer genomics to (i) understand the current NGS landscape in the APAC region; (ii) discuss key challenges in adopting NGS in clinical practice in the APAC region; and (iii) adapt/modify ESMO guidelines for local use. A literature review was conducted based on data from the PubMed database to identify relevant articles between January 2001 and November 2022 using keywords such as 'next-generation sequencing', 'metastatic cancer', 'Asia-Pacific', 'accessibility', 'funding', 'genomic alterations', and 'guidelines'. To discuss the current NGS landscape and the challenges in adopting NGS-based diagnostics in the APAC region, an advisory board meeting was conducted on 10 December 2021 on a virtual platform. A question-and-answer—based format was used to facilitate discussion on (i) the availability of NGS-based diagnostics in cancer with actionable targets; (ii) patient access to NGS tests and therapy; and (iii) challenges related to funding and availability of reimbursement plans for NGS testing in the APAC region. In subsequent discussions, nine cancer types were identified [BC, gastric cancer (GC), nasopharyngeal carcinoma (NPC), OC, PC, LC, cholangiocarcinoma, CRC, and hepatocellular carcinoma (HCC)] where the applicability of NGS-based diagnostics was evaluated on two levels (public health and academic clinical research). Asian ethnicity, accessibility of NGS testing, reimbursement, and socioeconomic and local practice characteristics associated with the treatment of metastatic cancer were taken into consideration while drafting recommendations on the use of NGS in daily practice and/or clinical research. Perspectives of multiple stakeholders (clinicians, academics, and industry participants involved in clinical and/or translational research activities) have been incorporated into this manuscript.

CURRENT NGS LANDSCAPE AND CHALLENGES IN ADOPTING NGS-BASED DIAGNOSTICS IN THE APAC REGION

The clinical adoption of NGS testing in patients with metastatic cancer is heterogeneous across different countries in the APAC region due to diversity in health care access, local practice guidelines, and socioeconomic status (Table 1).

Table 1. Accessibility of NGS testing across different countries in the APAC region

Countries	Accessibility of NGS at the authors' institution	Accessibility of NGS in other institutions (academic or nonacademic) within the country	Accessibility of NGS in community oncologists/nonacademic units within the country
Thailand	• The testing depends on the patients' health care scheme and drug accessibility. - UC: Hotspot testing for specific drugs that are reimbursed by this scheme, such as *EGFR* (LC) and *HER2* (FISH and IHC for BC) - SSS: Similar to UC - CSMBS: Hotspot testing for specific drugs that are reimbursed by this scheme, such as *EGFR* and *ALK* for LC, *KRAS* (all *RAS*) and *BRAF* for CRC, *HER2* (FISH and IHC) for BC, *BRCA* (germline mutation) for BC and OC - Private insurance or pay-out-of-pocket: Multigene panel NGS or comprehensive NGS testing and PD-L1 (IHC) are preferred for LC and others are similar to CSMBS • Participate in clinical trials (both pharmaceutical company-sponsored trials and investigator-initiated trials)	• Similar approaches in other institutions in the country • UC, SSS, and CSMBS are mostly adopted by university-based hospitals and government hospitals • Private insurance and pay-out-of-pocket are mostly adopted by private hospitals and private sections in university-based hospitals and government hospitals	Mostly adopted
Australia	• Routine • Easy to refer • Reasonably affordable Patients are charged essentially at cost price • Very accessible • Relatively accessible when required	• Routine • Accessible if the patient can fund it themselves • Very accessible • Accessible to self-funded patients and is not reimbursed	• Routine • Accessible if the patient can fund it themselves • Very accessible • Accessible to self-funded patients and is not reimbursed
Japan	NGS assay (three multiplex panels including one liquid CDx panel) is part of routine care in patients with advanced cancers in Japan owing to its reimbursement by the Japanese universal health care system; however, reimbursement is limited to patients who finished standard treatment with advanced cancer, accepting responsibility for 10%-30% of these costs while the government pays the remaining 70%-90% (depending on both age and income of each patient).		
Hong Kong	• Mainly paid service from outside of the institutions or through clinical trials • In-house tests coming online at academic institutions and high-volume centers		
South Korea	• Conducted as an in-house test of paid service outside of the institution • Cost with 50% support from national reimbursement in certain solid cancers at the time point of initial diagnosis and disease recurrence	• Accessible in major institutions and university hospitals • Mostly accessible to NGS in tertiary centers using in-house NGS testing. For the institution without in-house NGS testing, samples are sent to outsource NGS testing facilities (TAT is similar to in-house testing)	• Oncology practice is usually not conducted in the community center and there is little opportunity to handle tumor samples
Singapore	• Accessible to trial-eligible patients • Commercial panels are accessible at a cost • In-house panels are available depending on grant funding	• Accessible to trial-eligible patients in academic institutions • In nonacademic institutions, depending on funding capabilities (self-funded, insurance, or referral into an academic institution for NGS)	• Depending on funding capabilities, else suitable patients are referred to academic units
Malaysia	• Accessible via clinical research activities • Commercial panels (targeted and comprehensive genomic panels) at a cost	• Accessible via clinical research activities • Commercial panels (targeted and comprehensive genomic panels) at a cost • Ongoing establishment of centralized NGS genomic testing for public hospitals nationwide	• Commercial panels (targeted and comprehensive genomic panels) at a cost
Philippines	• Commercial panels are available, but patients pay out of their pocket • Does not have an in-house NGS facility and sends samples to outsourced laboratories • Specimens are sent to Manila (the capital of the Philippines) and then sent abroad		May avail of commercial panels at a cost but sending out specimens is a logistical concern
New Zealand	• Accessible for some cancer types via clinical research activities • Commercial panels are accessible at a cost	• Variable access via clinical research activities for some cancer types • Commercial panels are accessible at a cost	• Variable access via clinical research activities for some cancer types • Commercial panels are accessible at a cost

ALK, anaplastic lymphoma kinase; APAC, Asia-Pacific; BC, breast cancer; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *BRCA*, breast cancer gene; CDx, companion diagnostics; CRC, colorectal cancer; CSMBS, civil servant medical benefit scheme; *EGFR*, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; *KRAS*, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LC, lung cancer; NGS, next-generation sequencing; OC, ovarian cancer; PD-L1, programmed death-ligand 1; SSS, social security scheme; TAT, turnaround time; UC, universal coverage.

Currently, NGS-based diagnostics for metastatic cancer patients are reimbursed in Japan, Australia, and South Korea. However, in countries such as Thailand, Hong Kong, Singapore, Malaysia, and the Philippines, NGS testing is not reimbursed and the uptake of NGS has not been as apparent due to the high out-of-pocket expenditures. In Japan, health insurance is generally provided through the Universal Health Insurance System, which covers over 70% of the medical costs, including NGS testing.

Commercial voluntary insurance plans are also available in Japan, which support patients at diagnosis, during hospitalization, and for advanced medical care when needed. In Australia, patients with advanced NSCLC, CRC, and melanoma can receive government-reimbursed NGS testing for somatic mutations using a limited panel of selected genes to direct treatment. In addition, all high-grade ovarian carcinoma and BC patients with a significant family history are offered germline NGS testing using a selected gene panel. In other tumor types, where actionable mutations are limited to single genes, specific single-gene testing for actionable mutations is funded [e.g. BReast CAncer gene 1/2 (*BRCA1/2*) in castration-resistant PC]. Large-panel NGS is currently limited to academic initiatives where selected patient groups may undergo testing often free of charge, or through the private sector using commercial assays. In South Korea, NGS testing is usually conducted in academic university hospitals as either an in-house test or outside facilities depending on the type of NGS test. However, the turnaround time of NGS results is relatively long (6-8 weeks from sample submission to final report) compared to conventional tests. NGS is recommended at baseline and at the timepoint of tumor recurrence, and 50% of the testing price is reimbursed by national insurance in major solid cancers such as GC, LC, colon cancer, BC, and carcinoma of unknown origin.

Table 2 lists the APODDC group recommendations on the requirements of NGS precision testing in patients with metastatic cancer in the APAC region.

DISSECTION AND ADAPTATION OF ESMO GUIDELINES FOR THE USE OF NGS FOR PATIENTS WITH METASTATIC CANCER IN THE APAC REGION: KEY RECOMMENDATIONS FROM THE APODDC WORKING GROUP

Breast cancer

The management of BC in APAC and Western regions is similar. To date, routine NGS testing to guide therapy has been limited as testing for most markers of relevance to direct clinical management can be carried out via IHC [human epidermal growth factor receptor 2 (*HER2*) and programmed death-ligand 1 (PD-L1)] testing, *in situ* hybridization (ISH), or single-gene PCR. In patients with hormone receptor−positive (HR+), *HER*2− metastatic BC whose tumor harbors a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation, alpelisib, an alpha-specific phosphatidylinositol 3-kinase inhibitor, improves progression-free survival (PFS) and is approved in this group of patients.[13] Those with germline *BRCA1/2*-mutated early and metastatic BC also derive disease-free survival and PFS benefits, respectively, from poly (ADP-ribose) polymerase inhibitors (PARPis).[14-16] Current efficacy data are limited to patients with germline *BRCA1/2* mutation. For this reason, somatic testing to determine *BRCA1/2* status is not recommended. In other HR+, *HER2*− BC patients, estrogen receptor 1 (*ESR1*) mutations have emerged to be a key mechanism of resistance to aromatase inhibitors (AI), prompting a change of treatment to an estrogen receptor degrader.[17] In patients who progress on AI, it is common practice to change endocrine therapy irrespective of the emergence of *ESR1* mutation, negating the need for NGS testing. Tumor-agnostic therapeutics such as immune checkpoint inhibitors (ICIs) and tropomyosin receptor kinase (*TRK*) inhibitors demonstrate clinical activity in high tumor mutation burden (TMB) and microsatellite instability-high (MSI-H) solid tumors[18,19] as well as tumors harboring neurotrophic tyrosine receptor kinase (*NTRK*) fusions,[20] such as BC. Nevertheless, these aberrations are uncommon even though *NTRK* fusions are enriched in certain histological subtypes such as mammary analogue secretory BC.

Summary of recommendations: As most markers of relevance to direct clinical management can be carried out via IHC, ISH, or single-gene PCR, routine multigene NGS testing is not recommended by the APODDC Working Group in the APAC region. This is in agreement with the recommendations outlined by the ESMO Precision Medicine Working Group for BC. However, in clinical research centers with established molecular screening programs with an associated repertoire of biomarker-matched clinical trials, metastatic BC patients may be offered NGS testing to enhance the understanding of promising targets in BC.

Gastric cancer

NGS is not routinely used for patients in daily practice. *HER2* overexpression by IHC or amplification by ISH is recommended as an initial step approach. In addition, a PD-L1-combined positive score by IHC is recommended at the beginning of first-line treatment. Fibroblast growth factor receptor (*FGFR2*) IHC and claudin IHC will be mandatorily checked after the results of the phase III trial. However, several molecular targeted agents and ICIs such as trastuzumab,[21] nivolumab,[22] pembrolizumab,[23,24] trastuzumab deruxtecan,[25] and entrectinib[20]/larotrectinib[26] have been approved by the Food and Drug Administration (FDA) for treatment in patients with inoperable, locally advanced, recurrent, or metastatic adenocarcinoma GC. NGS may be considered for those patients via a validated assay for the identification of *NTRK* gene fusion, MSI status, and *HER2* amplification.

Summary of recommendation: Routine multigene testing is not recommended in cases with a limited number of actionable targets.* HER2 *amplification by FISH is not always concordant with copy number estimates inferred from NGS. NGS may be considered for institutions with access to a validated assay for the identification of* NTRK *gene fusion, MSI status, and* HER2 *amplification.

Table 2. Requirements of NGS precision testing in patients with metastatic cancer

ASCO provisional clinical opinion for genomic testing in patients with metastatic cancer	APODDC group recommendations for NGS testing in patients with metastatic cancer
Genomic testing should be carried out in patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios: (i) when there are genomic biomarker—linked therapies approved by regulatory agencies for their cancer; and (ii) when considering a treatment for which there are specific genomic biomarker—based contraindications or exclusions.	The APODDC group has agreed to this statement and can be adopted although it is important to acknowledge that potential lag times in local regulatory agencies relative to US FDA/EMA can limit treatment availability.
For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker—linked therapy that a regulatory agency has approved.	This will depend on local regulations, drug access, approval status, reimbursement status, and cost of sustaining treatment. There should be a provision/mechanism to apply for special permission for patients to have access to drugs currently not available in their respective nations but approved by other regulatory agencies for specific indications. It is important to have a systems approach to precision oncology in Asia.
Multigene panel—based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency—approved therapy.	Local epidemiology data, costs, and applicability in different cancer types need to be considered before the multigene panel—based testing can be recommended as most of the patients in the APAC region cannot afford NGS tests.
If genomic sequencing results are to be used to inform clinical care, such testing must be carried out in an appropriately certified laboratory.	A proportion of NGS testing is still research based in the APAC region. Appropriate certification of personnel and laboratories as well as test validation is required. Potential harmonization of certification requirements across the region shall be discussed by respective regulatory authorities.
Clinical decision making should incorporate (i) the known or predicted impact of a specific genomic alteration on protein expression or function, and (ii) clinical data on the efficacy of targeting that genomic alteration with a particular agent.	The APODDC group has agreed to this statement. In the APAC region, there should ideally be sufficient data on prevalence in the local population.
Germline testing for genetic alterations linked to approved therapies should be carried out in patients with metastatic or advanced solid tumors considered for such treatment. It should not be limited by family history—based or clinical criteria used for familial risk assessment. Patients with pathogenic or likely pathogenic variants should be referred for genetic counseling for education about secondary cancer risks, possible inheritance of germline mutations among blood relatives, and the differences between germline and somatic mutations, if they did not receive pretest counseling.	The APODDC group agreed to this statement but cautions that issues related to costs and resources need to be considered. A referral pathway in place for pretest counseling is strongly encouraged.
In patients with metastatic or advanced solid tumors, fusion testing should be carried out if there are fusion-targeted therapies with regulatory approval for that specific disease.	The APODDC group agreed to qualify the statement if the DNA panel or point mutation panel is negative. A stepwise approach should be considered.
NTRK fusion testing should be carried out in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types.	The APODDC group has agreed to this statement and can be adopted without modification in the APAC region.
Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large-panel DNA sequencing.	The APODDC group has agreed to this statement and can be adopted without modification in the APAC region.
Testing for *MET* exon 14 skipping should be carried out for patients with all types of non-small-cell lung cancer.	The APODDC group has agreed to this statement and can be adopted without modification in the APAC region.

Adapted from: ASCO provisional clinical opinion for genomic testing in patients with metastatic cancer from Chakravarty et al. 2022.[11]
APAC, Asia-Pacific; APODDC, Asia-Pacific Oncology Drug Development Consortium; ASCO, American Society of Clinical Oncology; EMA, European Medicines Agency; FDA, Food and Drug Administration; MET, mesenchymal—epithelial transition gene; NGS, next-generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is a rare cancer and is distinguished by its racial and geographical distribution. Although the incidence is only 0.5-2 cases per 100,000 in Western countries, incidences are as high as 20 in 100,000 in APAC regions where NPC is endemic.[27,28] To date, there is no evidence to support NGS testing of NPC to guide therapeutic management. Activating mutations in the nuclear factor kappa B (NF-κB) pathway have been identified in up to 40% of NPC cases.[29] However, there are currently no therapeutic agents targeting these genomic aberrations. Common targetable oncogenes including epidermal growth factor receptor (*EGFR*), *PIK3CA*, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), Erb-B2 receptor tyrosine kinase 2 (*ERBB2*), and *ERBB3* are rarely mutated in NPC and occur in $<$2% of cases.[30] Programmed cell death protein 1 (PD-1) inhibitors have documented activity in NPC irrespective of PD-L1 expression.[31,32] The correlation between anti-PD-1 clinical activity with TMB and MSI has not been determined. Therefore, we do not recommend routine NGS testing for patients with NPC, even when considering treatment with PD-1 inhibitors.

Summary of recommendation: Given that there are no validated genomic targets, routine NGS testing for patients with NPC is not recommended, even when considering treatment with PD-1 inhibitors.

Ovarian cancer

The trends in OC incidence rates vary widely across the globe. The highest age-adjusted incidence rates have been observed in more developed parts of the world, including North America, and Central and Eastern Europe.[33] Over the past three decades, the incidence and mortality rates of OC have gradually declined in most high-income countries,

largely North America and Europe.[33] On the contrary, less-developed countries with recent economic growth and lifestyle changes have seen a marked rise in OC incidence and mortality rates.[33] Women with a family history of OC have a higher risk of developing the disease. For patients with newly diagnosed, advanced, high-grade ovarian carcinoma, germline and somatic *BRCA* mutation testing is routinely recommended to identify patients who would derive the greatest magnitude of benefit from PARPi therapy in first-line maintenance settings.[34-36] For patients with newly diagnosed, advanced, high-grade ovarian carcinoma, who do not harbor germline or somatic *BRCA1/2* pathogenic mutations, a validated genomic scar—based somatic homologous recombination deficiency (HRD) test should be carried out to ascertain the magnitude of benefit from single-agent PARPi therapy or to guide therapy selection for PARPi in the presence or absence of bevacizumab versus bevacizumab monotherapy for first-line maintenance therapy.[34,36] Women diagnosed with clear cell, endometrioid, or mucinous OC should be offered somatic tumor testing for mismatch repair deficiency and/or TMB, if available.[37-39]

Summary of recommendations: All women diagnosed with epithelial OC should be offered germline and/or somatic genetic testing for* BRCA1, BRCA2, *and other OC susceptibility genes, irrespective of their clinical features or family cancer history. All patients with high-grade epithelial OC should be offered somatic HRD testing to determine the benefit of PARPi maintenance therapy. There is insufficient evidence to determine the clinical validity of individual or panels of non-*BRCA *homologous recombination repair genes for predicting a PARPi response and prospective collection of data is required. However, from the perspective of clinical research centers with established molecular screening programs, it is important to include OC patients in trials testing targeted therapies matched to genomic alterations to enhance our understanding of promising targets. Women diagnosed with clear cell, endometrioid, or mucinous OC should be offered somatic tumor testing for mismatch repair deficiency and/or TMB, if available.

Prostate cancer

Although PC treatment has always revolved around targeting the androgen receptor as an oncogenic driver, it is only in recent years that a modern precision oncology approach using NGS has provided additional benefits. Based upon data supporting the use of PARPi and protein kinase B/AKT inhibitors in selected populations, the ESMO Precision Medicine Working Group has recommended that, in PC, NGS testing should be carried out on tumor samples to identify mutations in DNA repair genes, but only in countries where PARPi are accessible.[10] The group rationalized that the mutational status of at least *BRCA1/2* should be assessed, with the addition of phosphatase and tensin homolog gene (*PTEN*) alterations (optional), given the preliminary results of AKT inhibitors in that patient population.[10] These recommendations can be generalized to an Asian population; however, there are important caveats that need to be addressed. Firstly, although PC incidence is lower in Asian populations compared to Western populations, the incidence of PC is steadily increasing.[40] Prostate cancer has been reported to exhibit genetic variations among Asian and Western men, demonstrated by the presence of transmembrane protease serine 2—v-ets erythroblastosis virus E26 oncogene homolog (*TMPRSS2-ERG*) fusions in approximately 50% of Caucasian PC patients compared to 8%-21% of Asian PC patients. Furthermore, *PTEN* alterations are present in up to 70% of Caucasian PC patients; however, they are detected in only 34% of Asian PC patients as per a study conducted in China.[40] Specific to the ESMO precision medicine recommendations, data regarding *BRCA1/2* mutations are less clear. Some studies suggest that the rates of *BRCA1/2* mutations in Asian PC patients are similar to that of Caucasian patients.[41,42] The more pressing issue in implementing the working group recommendations is the diagnostic work-up of PC in Asian populations. The major impact of Asian PC on the ESMO recommendations lies in the way PC is diagnosed. National prostate-specific antigen screening programs are less common in Asian countries. Subsequently, the proportion of patients diagnosed with advanced disease is higher. In this scenario, the diagnosis is often made clinically, and the use of biopsies is less common.[40]

Summary of recommendations: To adopt NGS testing as recommended by the ESMO Precision Medicine Working Group, tumor tissue is required, which can help identify both germline and somatic mutations in* BRCA1/2 *and other DNA repair genes. Although the use of biopsies is increasing, it will need to be more widely adopted for NGS, particularly in patients presenting with advanced PC. In the absence of available tumor specimens, germline testing can be conducted as an alternative. Although this will assist in identifying all patients with hereditary PC for consideration of genetic counseling, it will only identify ∼50% of patients who would be eligible for molecularly matched therapy using PARPi, given that an equal proportion with somatic mutations will not be identified using this method. Lastly, as alluded to by the report, access to PARPi is required for NGS to be of clinical utility. In many Asian countries, access to novel treatments has trailed behind that of Western countries. In many developing Asian countries, the cost of novel treatments, as well as NGS, may be prohibitive. Given the rapid advancements in the diagnosis and treatment of PC patients, accelerating access to the latest approved therapies to United States (US)/European Union (EU) regulatory agencies remains a top priority.

Lung cancer

Targeted therapies that specifically act on pathways associated with the identified genomic alterations (*EGFR*, *ALK* [anaplastic lymphoma kinase], *ROS1*, *BRAF* [v-raf murine sarcoma viral oncogene homolog B1], *KRAS*, *MET*, *RET*, *HER2*, and *NTRK1*) have led to significant improvements in treatment responses in

metastatic NSCLC. The ESMO guidelines have recommended the use of multigene NGS in adenocarcinomas to assess level 1 alterations both in academic and clinical research centers and in community daily practice.[10] Moreover, the use of multigene NGS testing can also be considered in patients with squamous cell carcinomas (SqCC) who have been treated or have access to clinical research centers. These research centers conduct clinical trials involving novel targets that are increasingly detected in SqCC. However, there is a clear epidemiological difference in the subtypes of NSCLC found in East Asia. Specifically, *EGFR* gene mutations, which are found in only 10%-15% of Caucasian patients, are more frequently (>50%) observed in Asian populations.[43-45] The PIONEER study reported the prevalence of *EGFR*-mutant LC in seven countries in Asia, including Thailand, China, Hong Kong, Taiwan, Vietnam, Philippines, and India, at a prevalence of 47%-64%. However, India had a lower prevalence than the rest of the countries (22%).[43] As *EGFR* mutations are readily detected with single-analyte testing approaches such as tissue- or plasma-based PCR, which are less costly and have a shorter turnaround time, coupled with the consensus of mutual exclusivity between *EGFR* mutations and other actionable alterations. In the *de novo* disease setting, an exclusionary workflow approach of only carrying out NGS testing in samples from patients who have tested negative for *EGFR* has been proposed and modeled and was found to be cost- and time-saving for the overall population in Hong Kong.[46] In Singapore, however, a similar study indicated that upfront NGS in all patients may still be cost-effective, despite a high prevalence of *EGFR*-mutant LC.[47] This may be due to the relatively lower costs of NGS testing using an in-house, small-panel, multiplex-gene NGS assay.

Summary of recommendations: Given the expanding list of actionable alterations in LC, a small-panel, multiplex-gene NGS with adequate coverage of key alterations may be considered for NSCLC. This approach would save cost and have a shorter turnaround time compared to comprehensive genomic profiling NGS. There is a possibility for this to be done in-house as well, with the potential advantage of streamlining workflows for other IHC assays or orthogonal validation assays, for example, FISH. It is important to note that there are significant disparities in funding and access to health care in the APAC region and it will be most prudent if individual jurisdictions carry out dedicated health technology assessments to assess the viability of upfront NGS testing in NSCLC. Regardless of the findings of these dedicated analyses, the common thread in all cost-effectiveness assessments in NGS is that cost of NGS testing is inevitably a major barrier to more widespread adoption of NGS.

Cholangiocarcinoma

Cholangiocarcinoma is a rare cancer type worldwide. It is a heterogeneous disease with multiple risk factors. It also has a geographically variable distribution of risk factors in the APAC region.[48] For instance, it is a highly prevalent cancer in Thailand as the carcinogenic liver fluke *Opisthorchis viverrini* is endemic in the region.[49] However, the management of all cholangiocarcinoma is similar. There have been several breakthroughs in its treatment. According to the ESMO scale for clinical actionability of molecular targets, cholangiocarcinoma is one of the four cancer types in which NGS should be routinely carried out for the treatment of metastatic disease.[10] NGS could be used to test for the presence of isocitrate dehydrogenase 1 (*IDH1*) mutations, *FGFR2* fusions, MSI-H, and *NTRK* fusions in patients with metastatic cholangiocarcinoma.[10] The above-mentioned mutations are 'level 1' alterations. Ivosidenib, an *IDH1* inhibitor, significantly improved PFS in patients with cholangiocarcinoma who received at least one standard treatment in a randomized, phase III trial.[50] Although the OS analysis was not significant, the results could have been diluted by 70% of patients on placebo who received crossover ivosidenib upon progression.[50] Targeted therapy against cholangiocarcinoma with *FGFR* fusion or rearrangements, such as pemigatinib and infigratinib, showed significant anticancer activity and has been approved by the FDA in this setting.[51,52] MSI-H and *NTRK* fusions are rare but therapy against these alterations could also have superior efficacy as shown in both case series and basket trials.[53,54] Other genetic aberrations such as *BRAF* V600E mutation, *ERBB2* amplification or mutation, and *PIK3CA* mutation have been reported in cholangiocarcinoma. The utilization of targeted agents against these genetic aberrations in cholangiocarcinoma would require further clinical trials to confirm efficacy. For cholangiocarcinoma, it is challenging to obtain sufficient tumor tissue for testing. Among different testing methods such as IHC, ISH, or RNA sequencing, NGS has reasonable sensitivity and can provide results with minimal tissue.

Summary of recommendations: In the APAC region, public financial support for an uncommon cancer is often less than that for highly prevalent cancer.* IDH1 *and* FGFR *inhibitors are very new, and most oncologists have no experience with these agents. Additionally, these drugs are not approved for clinical use in most jurisdictions in the APAC region. This may hinder the application of NGS. Access to* IDH1 *and* FGFR *inhibitors is required for NGS to be of clinical utility. In case novel therapies gain approval and become accessible, NGS can be considered specifically to detect* IDH1 *mutations,* FGFR *alterations, MSI-H, and* NTRK *fusions.

Colorectal cancer

Globally, CRC is the third most common cancer and a second leading cause of cancer mortality.[1] Over the past decade, age-standardized incidence rates are increasing in East Asia and Southeast Asia. Incidence rates are also increasing among younger adults, particularly in high-income countries.[55] In advanced CRC, approximately 45% of patients have hotspot mutations in exon 2 (codon 12,13), exon 3 (codon 61), and exon 4 (codon 117,146) in *KRAS* and neuroblastoma RAS viral oncogene homolog (*NRAS*), which predict resistance and rule out the use of

Table 3. Summary of the ESMO Precision Medicine Working Group recommendations versus APODDC recommendations for the use of NGS testing in patients with metastatic cancer

Tumor types	Recommendations for the use of NGS in patients with metastatic cancer by the ESMO Precision Medicine Working Group	Recommendations for the use of NGS in patients with metastatic cancer by the APODDC Working Group
BC	• Considering that somatic sequencing cannot fully substitute germline *BRCA* testing, *PIK3CA* status can be determined by PCR on three hotspots, and *HER2* testing is accurately done by IHC/ISH in the local center. There is currently no need to carry out tumor multigene NGS for patients with metastatic BC in the context of daily practice. • It is important to include metastatic BC patients in molecular screening programs and include them in trials testing targeted therapies matched to genomic alterations.	• Routine multigene NGS testing for daily practice is not recommended for metastatic BC patients. • In clinical research centers with established molecular screening programs with an associated repertoire of biomarker-matched clinical trials, metastatic BC patients may be offered NGS testing to enhance the understanding of promising targets in BC.
GC	• There is no current need to carry out tumor multigene NGS in patients with metastatic GC in daily practice. • Detection of MSI and *NTRK* fusions should be done using cheap standard methods.	• NGS is not routinely used in patients with advanced GC in daily practice. • NGS may be considered for institutions with access to a validated assay for the identification of *NTRK* gene fusion, MSI status, and *HER2* amplification.
NPC	• ESMO guidelines do not evaluate the utility of NGS testing in patients with nasopharyngeal carcinoma as the incidence of this disease is only 0.5-2 cases per 100,000 in Western countries.	• Routine NGS testing for patients with NPC is not recommended, even when considering treatment with PD-1 inhibitors.
OC	• Tumor multigene NGS can be used in OC to determine somatic *BRCA1/2* mutations and HRD status.	• All women diagnosed with epithelial OC should be offered germline and/or somatic genetic testing for *BRCA1*, *BRCA2*, and other OC susceptibility genes, irrespective of their clinical features or family cancer history. • All women with high-grade OC should be offered somatic HRD testing to determine the benefit of PARPi maintenance therapy. • There is insufficient evidence to determine the clinical validity of individuals or panels of non-*BRCA* HRR genes for predicting a PARPi response, and prospectively collected data are required. From the perspective of clinical research centers with established molecular screening programs, it is important to include OC patients in trials testing targeted therapies matched to genomic alterations to enhance our understanding of promising targets. • Women diagnosed with clear cell, endometrioid, or mucinous OC should be offered somatic tumor testing for mismatch repair deficiency and/or TMB, if available.
PC	• In countries where PARPis are accessible for patients with PC, it is recommended to carry out NGS on tumor samples to assess the mutational status of at least *BRCA1/2.* According to the preliminary results of the phase III trial with AKT inhibitors in patients with PTEN alterations, this gene could be added to the panel.	• To adopt NGS testing as recommended by the ESMO Precision Medicine Working Group, tumor tissue is required, which can help identify both germline and somatic mutations in *BRCA1/2* and other DNA repair genes. • In the absence of available tumor specimens, germline testing can be conducted as an alternative. • Access to PARPi is required for NGS to be of clinical utility.
LC	• It is recommended that a tumor (or plasma) sample from a patient with advanced nonsquamous NSCLC is profiled using NGS technology to detect level I alterations [*EGFR*, *ALK*, *ROS1*, *BRAF V600E*, *MET* (mutations ex 14 skipping), *RET*, and *NTRK*]. • It is highly recommended that clinical research centers carry out multigene sequencing in the context of molecular screening programs to increase access to innovative drugs and speed up clinical research.	• A focused panel multiplex-gene NGS assessing actionable mutations may be considered for NSCLC. This approach would save cost and have a shorter turnaround time compared to comprehensive genomic profiling NGS. There is a possibility for this to be done in-house as well. • It is important to note that there are significant disparities in funding and access to health care in the APAC region and it will be most prudent if individual jurisdictions carry out dedicated health technology assessments to assess the viability of upfront NGS testing in NSCLC.
Cholangiocarcinoma	• Tumor multigene NGS could be used to detect level I actionable alterations (*IDH*1 mutations, *FGFR2* fusions, MSI-H, and *NTRK* fusions) in cholangiocarcinoma.	• In case novel therapies gain approval and become accessible, NGS can be considered specifically to evaluate for *IDH1* mutations, FGFR alterations, MSI-H, and *NTRK* fusions.
CRC	• PCR tests for hotspot mutations, MSI by IHC or PCR. Multigene NGS can be an alternative only if it does not generate extra cost compared with standard techniques, NGS can detect *ERBB2*, *NTRK* fusions, and MSI status.	• PCR or small-panel NGS can be used for hotspot mutations. • MSI status is determined by IHC or PCR. *HER2* status is determined by IHC and FISH in a stepwise manner. • Multigene NGS can be an alternative only if it does not generate significant extra cost compared with standard techniques already implemented in routine practice.

Continued

Table 3. Continued

Tumor types	Recommendations for the use of NGS in patients with metastatic cancer by the ESMO Precision Medicine Working Group	Recommendations for the use of NGS in patients with metastatic cancer by the APODDC Working Group
		• NGS can be used simultaneously to determine MSI-H status in CRC and can identify *HER2* amplification and gene fusions involving drug targets (*NTRK*, *NRG1*, *ROS1,* and *ALK*). Other targets relevant to clinical trials may be identified. The use of NGS should thus consider diagnostic cost and access to academic centers, novel therapeutics, and trials.
HCC	• Tumor multigene NGS is not recommended in advanced HCC in daily practice.	• Current standard HCC treatment is not biomarker driven, and due to the lack of high-level evidence on using NGS results to guide treatment, routine NGS testing for patients with HCC is not recommended.

Adapted recommendations for the use of NGS in patients with metastatic cancer by ESMO Precision Medicine Working Group from Mosele et al. 2020.[10]
ALK, anaplastic lymphoma kinase; APAC, Asia-Pacific; APODDC, Asia-Pacific Oncology Drug Development Consortium; BC, breast cancer; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *BRCA*, breast cancer gene; CRC, colorectal cancer; *EGFR*, epidermal growth factor receptor; *ERBB2*, Erb-B2 receptor tyrosine kinase 2; ESMO, European Society for Medical Oncology; *FGFR*; fibroblast growth factor receptor; FISH, fluorescent *in situ* hybridization; GC, gastric cancer; HCC, hepatocellular carcinoma; *HER2,* human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; HRR, homologous recombination repair; *IDH1*, isocitrate dehydrogenase 1; IHC, immunohistochemistry; LC, lung cancer; *MET*, mesenchymal—epithelial transition; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NPC, nasopharyngeal carcinoma; NSCLC, non-small-cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; OC, ovarian cancer; PARPi, polyadenosine diphosphate-ribose polymerase inhibitor; PC, prostate cancer; PCR, polymerase chain reaction; PD-1, programmed cell death protein 1; *PIK3R,* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *ROS1*, ROS proto-oncogene 1 receptor tyrosine kinase; TMB, tumor mutational burden.

anti-*EGFR* antibodies, cetuximab, and panitumumab.[56] Approximately 8% have *BRAF* V600E mutations, which both relate to worse prognosis and also select patients who will benefit from the encorafenib—cetuximab combination, based on the phase III BEACON trial.[57] Among *BRAF* mutants, non-V600 mutations are associated with improved prognosis but do not predict therapy.[58] Patients with microsatellite instability benefit from PD-1/PD-L1 or cytotoxic T-lymphocyte—associated antigen 4 immune checkpoint blockade with survival benefits and long-term disease control.[59] MSI-H status is typically tested with loss of expression of mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) either by IHC or by PCR to detect variations in the length of a panel of microsatellites. *HER2*-directed therapeutics may be considered for patients with *HER2* overexpression by IHC or amplification by FISH.[60,61] Putting these together, a small-panel NGS assay or allele-specific real-time PCR assays, together with IHC for mismatch repair proteins and *HER2*, represent the most cost-effective and widely accessible upfront profiling approach to capture the breath of biomarkers to inform therapy selection in CRC. NGS can capture the relevant somatic mutations. Recently, the College of American Pathologists (CAP) guidelines allow for the use of a validated MSI by NGS assay for ascertainment of MSI-H status, specifically in CRC.[62] The CAP guidelines have been endorsed by ASCO.[63] NGS can identify *HER2* amplification, though there is no evidence for use of NGS to ascertain *HER2* status to select or rule out patients for *HER2*-directed therapy. NGS may identify *NTRK*, *NRG1*, *ROS1,* and *ALK* fusions, which may benefit from the respective inhibitors.

Summary of recommendations: Allele-specific PCRs or a small-panel, multiplex-gene NGS can provide adequate coverage of key alterations in CRC. MSI status is determined by IHC or PCR.* HER2 *status is determined by IHC and FISH in a stepwise manner. Multigene NGS can be an alternative only if it does not generate significant extra cost compared with standard techniques already implemented in routine practice. NGS can be used simultaneously to determine MSI-H status in CRC and can identify* HER2 *amplification and gene fusions involving drug targets (*NTRK, NRG1, ROS1*, and* ALK*). Other targets relevant to clinical trials may be identified. The use of NGS should thus consider diagnostic cost and access to academic centers, novel therapeutics, and trials.

Hepatocellular carcinoma

For the last decade, NGS has advanced the understanding of the genetic mutational profile and deregulated signaling pathways of HCC. Based on NGS findings, a number of molecular classifications were proposed for HCC to associate with prognosis (e.g. recurrence and death) and phenotype of HCC (e.g. serum levels of alpha-fetoprotein and viral etiology).[64] However, most of the studies fail to identify druggable targets or predictive biomarkers for the existing treatment of HCC. Recently, a prospective study attempted to evaluate the feasibility of using NGS results to predict outcomes of treatment in HCC.[65] In the study, 24% of 127 patients harbored at least one actionable mutation but no patients had a level 1 or 2A alteration, due to the lack of validated predictive biomarkers for specific drugs in HCC.[65] Despite this limitation, a small number of patients received off-label use of mechanistic target of rapamycin or mesenchymal—epithelial transition (*MET*) inhibitors, which were matched to the findings of tuberous sclerosis complex 1/2 alterations or *MET* amplifications by NGS.[65-67] The study also suggested that the presence of activating the alteration of Wnt/β-catenin signaling was associated with fewer benefits from ICIs.[65] Another study made use of an integrative genomic approach to use a 20-gene signature to predict the inflammatory phenotype of HCC, which was associated with more benefits from immunotherapy.[68] In

particular, it was found that although up to 85% of HCC with Wnt/β-catenin pathway shows features of immune exclusion or immune cell paucity, another 15% demonstrated features of inflammatory phenotype.[68] Further studies are required to validate the clinical role of the Wnt/β-catenin and gene signature on the decision of treatment. Another challenge to the applications of NGS in HCC is the lack of biopsy tissue in advanced settings because biopsy is historically not required for diagnosis in a large number of patients. To solve this problem, researchers have gradually accepted the conduct of biopsy procedures in advanced HCC to obtain tumors or even nontumorous liver tissue for research purposes.[69,70] Another method is the use of liquid biopsy. Multiple studies show that the NGS of circulating nucleic acid is feasible in HCC.[71,72]

Summary of recommendation: Given the fact that current standard HCC treatment is not biomarker driven and the lack of high-level evidence on using NGS results to guide treatment, routine NGS testing for patients with HCC is not recommended.

Table 3 provides a comparative overview of ESMO Precision Medicine Working Group recommendations versus APODDC recommendations for the use of NGS testing in patients with metastatic cancer prevalent in the APAC region.

Implications

Figure 1 lists the implications of NGS testing in selected cancer types in the APAC region. NGS profiling can reduce the time to diagnosis as compared with single biomarker tests and improve patient outcomes in selected cancer types (NSCLC, GC, and PC). In addition, NGS profiling can broadly determine mutations and potentially identify emerging biomarkers for immunotherapy (e.g. TMB, MSI-H) that may otherwise not be detected with conventional molecular testing.[73]

CONCLUSION

Outside of clinical trials, NGS testing in most APAC countries is primarily self-funded. Furthermore, access to therapeutics that target genetic aberrations is limited to a restricted number of sites with drug development expertise. Even when approved by the FDA, there are delays in local regulatory approvals and the prohibitive cost of novel therapies remains a barrier. Routine NGS testing to guide therapy has been limited to date as most markers of relevance that direct clinical management are detected via IHC or single-gene PCR. The lack of convincing cost—benefit studies makes it difficult for policymakers to determine the need for funding support for NGS testing in most low- and middle-income Asian countries. Considering these factors, the APODDC Working Group recommends routine multigene NGS testing for daily practice in patients presenting with advanced NSCLC. Access to PARPi is required for NGS to be of clinical utility for the management of PC in the APAC region. A small-panel, multiplex-gene NGS can provide adequate coverage of key alterations in CRC. Routine multigene NGS testing for daily practice is not recommended

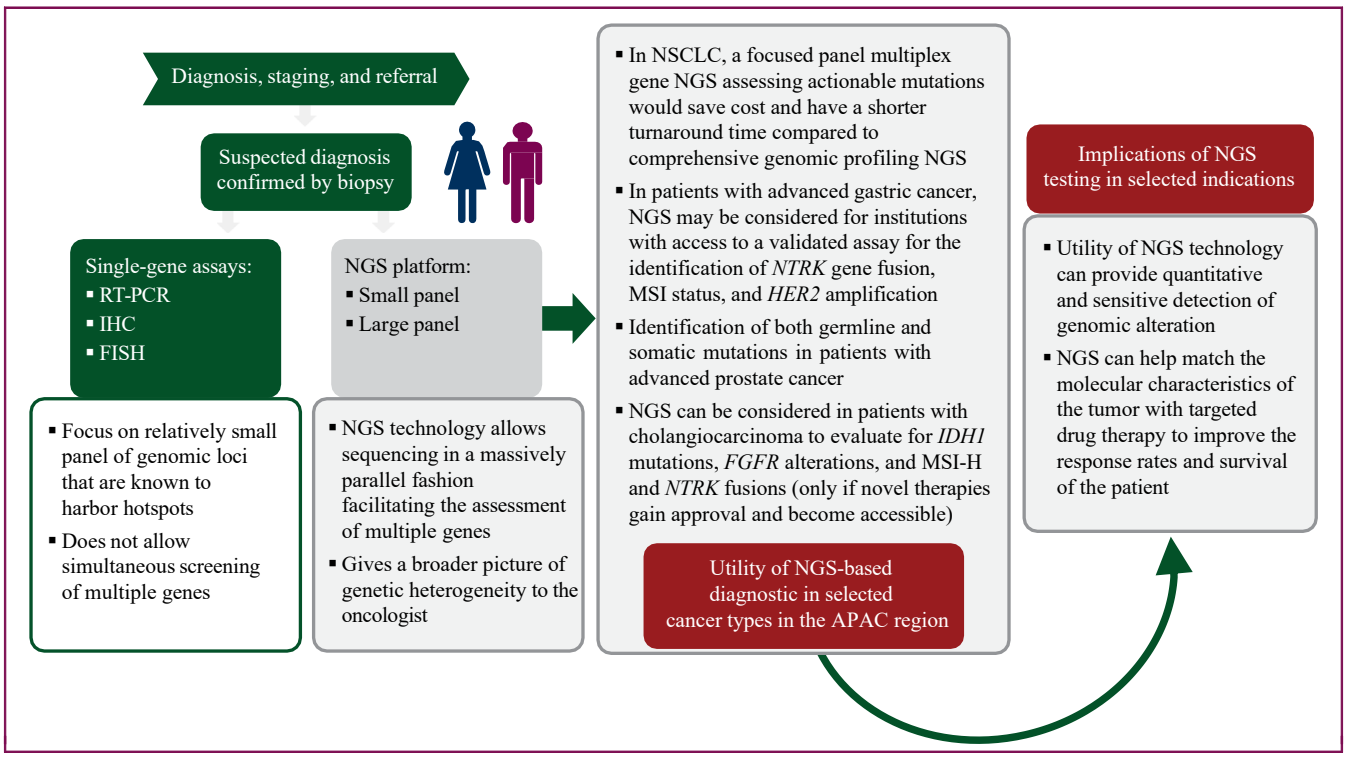

Figure 1. Implications of NGS profiling in certain cancer types in the APAC region.
APAC, Asia-Pacific; *FGFR*, fibroblast growth factor receptor; FISH, fluorescent *in situ* hybridization; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription-polymerase chain reaction; TMB, tumor mutation burden.

for patients with advanced GC, cholangiocarcinoma, NPC, BC, and HCC. The APODDC group recommends an end-to-end systems approach to precision oncology in Asia. Greater availability and awareness of NGS testing in both clinicians and patients can ensure rapid adoption of these tests in clinical practice. There should be enhanced mechanisms for patients to access the latest cancer drugs that might be currently unavailable but approved by other regulatory agencies for specific indications.

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