Unlocking the Value of Quality Next-Generation Sequencing in APAC

Recognizing the value of next-generation sequencing and call-to-action for its quality assurance and standardization.

APACMed

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2 Foreward

We are extremely proud to share this report prepared in conjunction with our members Abbott, Guardant Health, Illumina, Janssen, Roche Diagnostics, Thermo Fisher Scientific and Vazyme.

Whilst the transformative powers and impact of next-generation sequencing (NGS) cannot be questioned, a multi-stakeholder perspective is needed on how we can standardize workflow optimisation, customization and data analysis to ensure quality and conformity.

The recommendations presented in this paper are intended to promote and support standardization and quality of NGS testing across the Asia-Pacific (APAC) region. To arrive at these recommendations, our experts discussed key issues such as: Why is NGS important? What quality standards are needed to ensure value of NGS, and how can these be implemented?

Leveraging best practices from across the world, we present a customized set of recommendations for APAC in this paper as a first step towards establishing region-wide quality assurance. This paper, and the recommendations it contains are primarily for regulatory experts / policy makers. However, other stakeholders, namely industry experts, oncologists, pathologists, medical associations, and patients would benefit from understanding the value of quality NGS and the recommended way forward on implementing use of NGS in the region.

By taking this foundational step, we hope to lay the groundwork for a harmonized and standardized set of testing procedures. Ultimately, NGS is important because of the quantifiable value it can deliver, both in terms of improved patient outcomes and cost efficiencies within the healthcare system.

We look forward to continuing this work with our members.

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Chief Executive Officer
Asia Pacific Medical Technology Association (APACMed)

3 Executive Summary

With advances in NGS technology, its decreasing cost and an increased focused of APAC governments on Precision Medicine, there is an opportunity for NGS to change the paradigm in oncology diagnostics and treatment decision-making.

For this to be a reality, there is a need to establish effective and market-appropriate national policy strategies, with a focus on reinforcing the value of quality NGS, as well as the need for quality assurance and standardization.

We define quality NGS as a test that accurately reports clinically relevant, actionable and reproducible results.

To this end, in May 2022, APACMed convened two roundtable sessions with regional and international experts, including oncologists, pathologists, geneticists, regulators / policy makers and industry experts.

Following extensive discussions, the roundtable participants agreed on a set of recommendations to ensure quality of NGS testing. The recommendations are intended to be practical and achievable by all markets in APAC. It was recognised that the process of setting a minimum standard for quality must take into consideration the region's regulatory heterogeneity.

Beyond quality, the roundtable attendees also highlighted that there are several other components of existing healthcare systems hindering realization of the true value of NGS. These components will be considered as focus points for future position papers. Examples include lack of reimbursement of NGS tests, resulting in high out-of-pocket costs for patients and barrier to access; lack of physician awareness; and low availability / lack of coverage for matched treatments. Enforcing quality NGS is the first, fundamental step which will, hopefully, lay the ground for better NGS access, and ultimately better treatment of cancer patients.

Challenge

Lack of standardization and quality in molecular testing procedures

- In a survey by IASLC, lack of quality and standardization was the second most frequent barrier for molecular testing in patients with lung cancer in Asia after cost. Given the current lack of guidelines in many APAC countries, there is a need for NGS quality guidelines to be established.

Recommendation

Public authority bodies to publish guidelines to ensure standardisation and quality NGS, across the entire workflow.

Challenge

No consistency on how laboratories performing NGS tests are regulated

- Not all markets have formalized regulations of labs performing NGS-based tests; labs are left to self-regulate. As a result, variations in NGS test results have been observed between laboratories with the same sample, raising concerns on capabilities and user's confidence in outcomes.

Recommendation

Public authority bodies to establish a list of recognized accreditations/ certifications to apply to NGS laboratories, including international accreditations/certifications to ensure standardisation and quality as per national/regional guidelines.

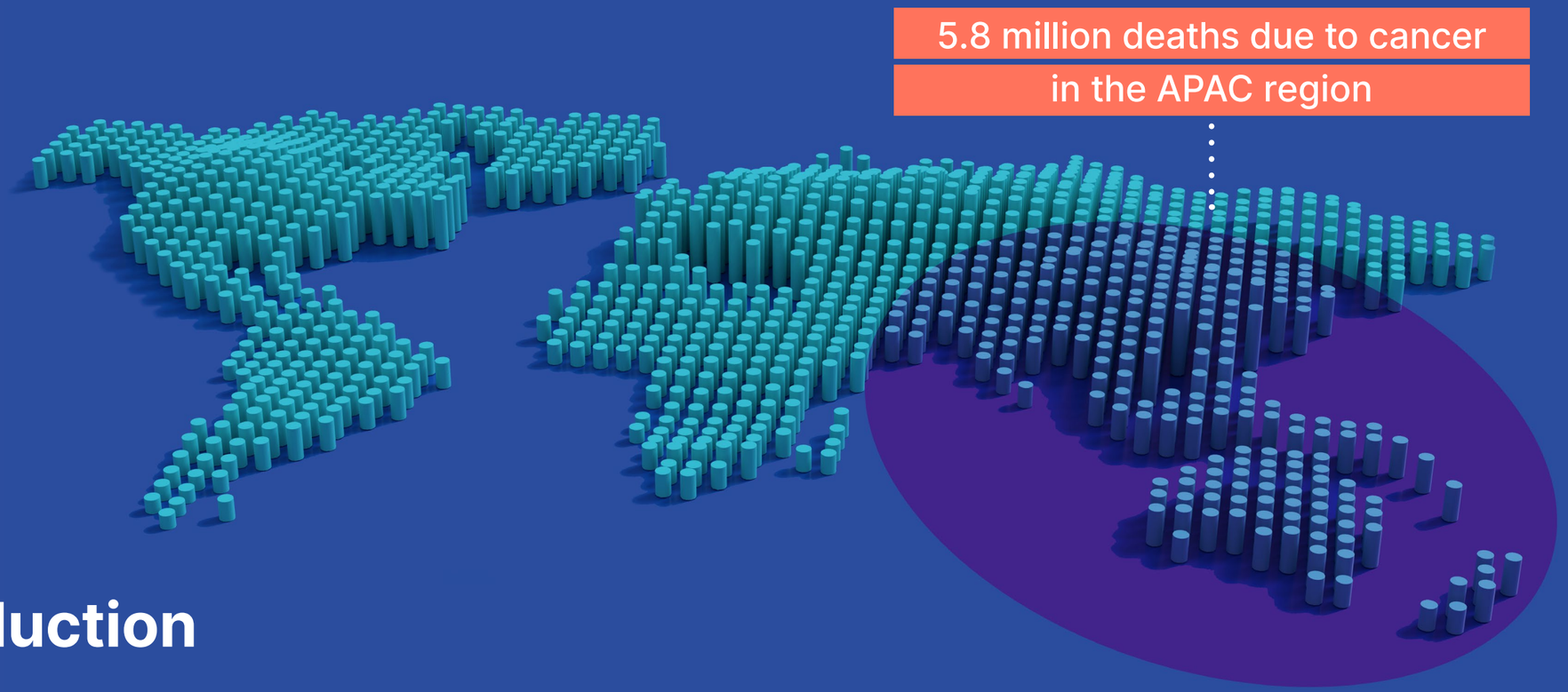
Challenge

Undesired outcomes for patients

- The US FDA has published many case studies where lack of quality assurance in lab-developed tests (LDTs) may have led to undesired outcomes. Several cases have shown lack of validation of test performance in clinical use and have led to patients inappropriately treated.

Recommendation

Public authority bodies to limit routine clinical use to only tests validated (pre-analytical, analytical, clinical validity) with clear clinical utility.



4 Introduction

Cancer burden in the APAC region is high, with 5.8 million deaths recorded in 2020,[1] accounting for almost 50% of global cancer deaths.[2] Advances in NGS testing and its decreasing cost mean there is potential for this technology to change the paradigm of oncology diagnostics and treatment for the growing cancer population by matching patients with effective treatments[1] and providing cancer recurrence risk assessment for improved monitoring.[2] Advancement in the sequencing technology has led to a rapid clinical adoption of NGS testing platforms and put the promises of "personalized" or "precision" medicine within reach. As with other in vitro diagnostics (IVDs), high-quality (i.e. accurate and reliable) NGS tests are key foundations to protect and promote public health. An inaccurate NGS test can lead to misdiagnosis and/or mistreatment that can impose unnecessary costs on healthcare systems and compromise patient care. With more APAC governments driving national initiatives in precision medicine (e.g., Australia Cancer Plan, Singapore's PRECISE) – NGS being one of its key pillars – there is a need to consider quality and standardization in NGS development and usage, to leverage the full potential of NGS technology.

Implementation and enforcement of quality and standardization of NGS helps assure clinicians that NGS tests are accurate, reliable, and clinically relevant. In the US, Europe and some early-adopting APAC markets, detailed NGS quality and guidelines have been established. However, many APAC markets have yet to define NGS quality standards for clinical use.

In a study conducted by the International Association for the Study of Lung Cancer (IASLC), many Asian participants reported that there are currently no strategies to address the quality of molecular testing, which encompasses NGS, in their market, despite the fact that lack of quality and standardization was the second most frequent barrier to molecular testing after cost.[3]

This highlights the need for establishment and enforcement of quality and standardization of NGS in APAC. This paper will articulate the value and benefits of quality NGS in terms of both patient outcomes and cost efficiencies within the healthcare system and provides a call-to-action for setting quality standards for NGS in APAC.

In the roundtable discussions and throughout this paper, the term next-generation sequencing (NGS) refers to a high-throughput technology that determines the sequence of DNA or RNA.

The following definitions of NGS for clinical use* are used:

- **Test use:** Includes NGS for prognosis, screening, treatment decision-making, minimal residual disease testing, and recurrence monitoring purposes.
- **Test type:** Includes small gene panels, hotspot panels, comprehensive genomic profiling (CGP), whole genome sequencing (WGS), whole exome sequencing (WES).
- **Disease type:** Oncology

* Encompasses both tissue and liquid samples and involves all providers for the whole NGS process, including in-house testing labs and overseas labs

5 The Value of Next-Generation Sequencing

NGS has the potential to deliver improved patient outcomes and cost efficiencies in the APAC region.

NGS could:

- allow for patients to be matched with effective and personalized treatment regimens, including clinical trials, as well as identifying more actionable biomarkers than standard testing.
- reduce time to diagnosis and provide increased accuracy of results for diagnosis and monitoring of recurrence.
- improve cost efficiencies within the healthcare system by reducing hospitalization visits, length of stay in hospital, treatment costs, and/or wastage from use of inaccurate tests – as well as, potentially, by identifying treatment-resistant mutations before treatment commences.

The value and benefits of NGS testing were acknowledged by experts attending the roundtable meetings. NGS has the potential to deliver improved patient outcomes and cost efficiencies in APAC, as demonstrated by the examples provided below. Experts convened across two roundtable meetings agreed that these quantifiable benefits encapsulate the importance and value of quality NGS – and agreed that they are applicable across the APAC region.

Improves patient outcomes

NGS can improve patient outcomes by matching patients to effective and personalized treatment regimens and appropriate clinical trials, leading to better survival (PFS, OS) and improved quality of life for people with cancer

- A 2020 study of patients with biliary tract cancer (BTC), who were tested with NGS and consequently matched to a treatment regimen, demonstrated longer progression-free survival (PFS) and higher disease control rate compared with patients treated with conventional treatment regimens (e.g., chemotherapy/surgery), which demonstrate low overall prognosis for BTC.[4] Patients who were NGS-tested and matched to therapies had a higher disease control rate of 61% vs. 35% and higher PFS of 4.3 months, compared with 3 months for patients who were not tested with NGS and did not receive matched to therapies.
- The 2021 MAST study demonstrated an improvement in clinical outcomes with use of NGS testing in patients with advanced solid tumors. Patients who received matched therapy had a higher median PFS of 6.47 months compared with 2.76 months amongst patients who received standard therapy.[5]
- In a retrospective study of patients in the US with late-stage cancer, patients who received NGS, which allowed patients to be matched to targeted therapy had a median overall survival of 51.7 weeks compared with 25.8 weeks for the control group.[6]

NGS can improve patient outcomes by identifying more actionable biomarkers compared to non-NGS tests, providing more options for treatment, which is especially important for patients who have exhausted current standard of care

- A study of patients with advanced non–small cell lung cancer (NSCLC) in South Korea demonstrated that using a tissue NGS panel led to detection of 84% of actionable mutations, compared with 65% using tissue-based single-gene testing. This study also demonstrates the benefit of using circulating tumor DNA (ctDNA) based NGS testing in addition to tissue-based NGS and single-gene testing for detecting additional patients with actionable genomic[7]
- NGS tests provide high sensitivity and specificity, which is critical to ensure accuracy of diagnostic results, resulting in reduced false positive or negative results. This is important since false results can be detrimental to patient treatment. A US study, investigating the ability of PCR and NGS to comprehensively identify mutations in the EGFR gene amongst patients with NSCLC, demonstrated that commonly-used PCR tests would have identified only 305 (48.6%) of the 627 patients with an EGFR mutation, which were identified by NGS testing.[8]
- In melanoma patients, BRAF inhibitors have shown high response rates for patients with BRAF V600-mutated advanced melanoma. CGP testing, using NGS, was able to identify BRAF alterations in 37% of patients where no alterations were detected with PCR-based methods.[9]

NGS can improve patient outcomes by providing prognostic value in monitoring potential recurrence

- NGS can detect biomarkers that predict cancer recurrence, allowing physicians to proactively monitor for recurrence; in turn, chances of early detection can be increased, which is correlated with improved patient outcomes.[10]
- For example, NGS on plasma-only circulating tumor DNA can help to monitor patients post-curative-intent colon cancer surgery, in order to identify patients who may be at high risk of recurrence. In these cases, as tumor tissue has been removed, NGS provides an option to predict recurrence without the tumor tissue. This is also useful in cases where there is not enough residual tumor tissue from the surgery, as the tumor has been treated with neoadjuvant therapy to reduce size.[11]

The extent of value delivered by NGS will differ by clinical scenario (e.g., type and stage of cancer), treatment availability, efficacy, as well as treatment paradigms.

Cost efficiencies

NGS may offset cost by increasing clinical trial enrolment

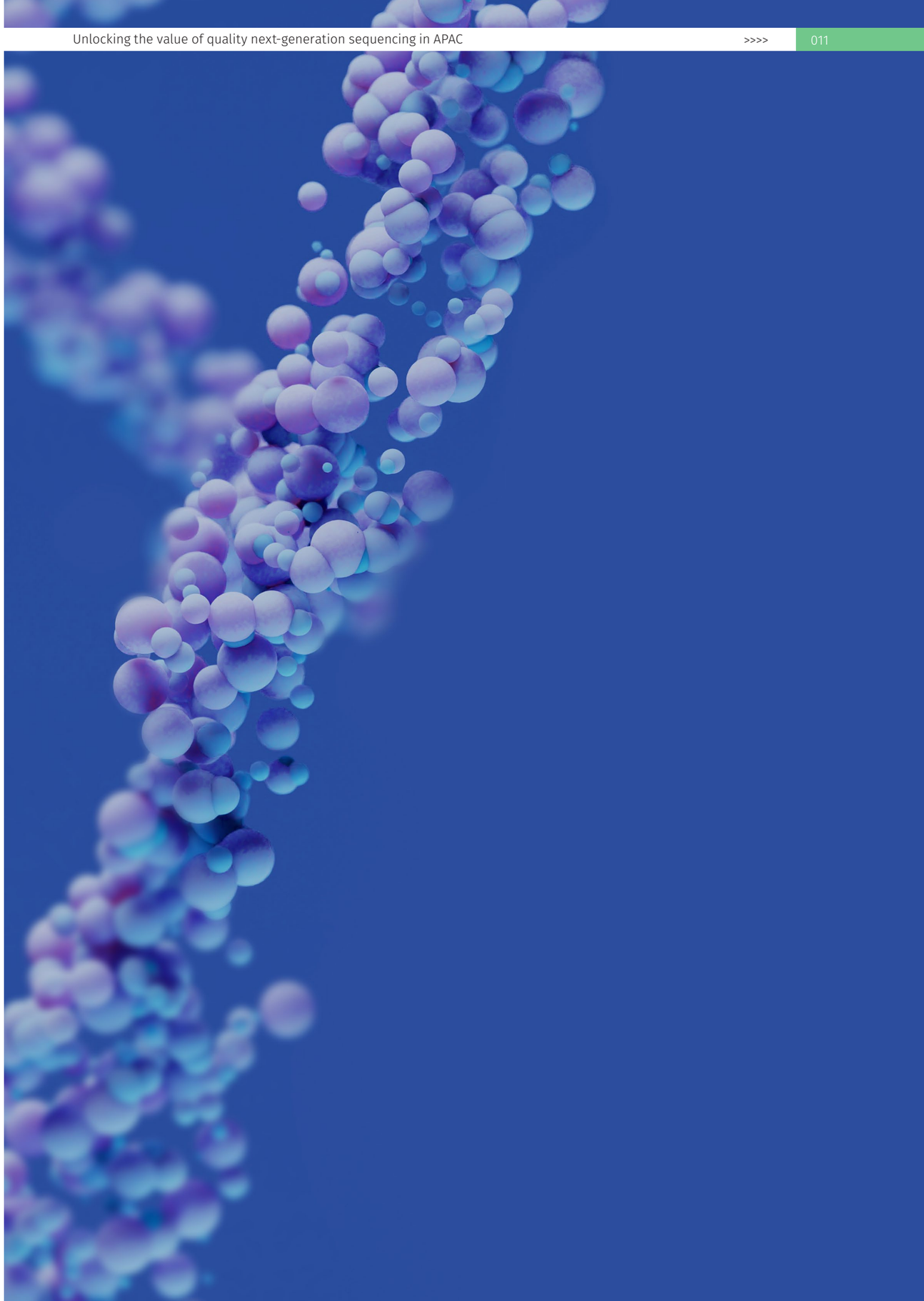
- NGS can provide cost offsets with the consolidation of tests[12] and reduced need of biopsy.[13,14]
- In an observational impact study comparing patients' pathways before and after their NGS results showed a significant increase in proposition of inclusion in clinical trials with experimental treatments. The proportion increased from 5% (n = 31 of 614) to 28% (n = 178 of 614) after NGS analysis (ref: https://www.sciencedirect.com/science/article/pii/S1098301520301819) . In a separate 3-year retrospective cost diversion analysis, study showed that for patients who enrolled in phase 1 clinical trials there could be an estimated $25,000 per-patient cost-benefit accrued to the payer (https://www.jmcp.org/doi/10.18553/jmcp.2019.18309?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed).

NGS can improve cost efficiencies within the healthcare system by reducing hospitalization visits, length of stay in hospital, treatment costs, and/or wastage from use of inaccurate tests[15,16]

- A 2018 US study showed weekly treatment costs of USD 2,720 for late-stage cancer patients who underwent NGS and received matched targeted therapy, compared with USD 3,453 for patients who did not receive NGS and matched targeted therapy.[17]
- An analysis of American patients with metastatic NSCLC revealed that relative to PCR testing strategies, using NGS for genomic profiling resulted in more patients positively identified for a mutation, lower mean testing cost per patient ($4,932 for NGS vs $6,605 for PCR), and faster time to initiation of appropriate targeted therapy (2 weeks for NGS vs 6 weeks for PCR). This was calculated based on a hypothetical coverage of 1 million members, with an estimated 1,119 tests for mNSCLC.[18]

NGS can potentially improve cost efficiencies in the healthcare system by identifying treatment-resistant mutations

- Early detection of treatment-resistant mutations has the potential to reduce costs associated with starting patients on ineffective treatments. For example, anti-EGFR antibody therapy is used to treat advanced colorectal cancer, but patients who have certain mutations in KRAS gene do not benefit from such therapy. Advanced colorectal cancer patients eligible for anti-EGFR treatment, should therefore be tested for these resistant mutations before treatment; however, tests for KRAS mutations by focused molecular hotspot testing were unable to pick up 88% of patients who had KRAS non-codon 12/13 alterations, which were picked up from CGP testing.[19]



6 Best Practice Guidelines and Reference for Quality Next-Generation Sequencing

In the previous section, we define the value and benefits of NGS compared to other methods. However, within NGS, there are many different standards. To achieve the full benefits of NGS, a set of quality standards need to be met. This best practice guideline section defines the quality standards by which NGS needs to comply to.

Quality must be ensured at every stage of the NGS testing workflow. There are several points along the workflow where guidance is needed for quality NGS testing.

Best practice guidelines are already established in certain markets, including the US, Europe and some early-adopting APAC markets, which provide examples to guide implementation of clinical and quality guidance in APAC.

The roundtable attendees agreed that quality must be ensured at every stage of the NGS testing workflow.

There are several critical junctures along the NGS testing workflow where guidance is needed on setting standards for quality NGS in the APAC region. At each of these stages, guidelines have already been established in certain markets, including the US, Europe, and some APAC markets with early NGS adoption (for example, in Japan and South Korea). Examples of guidance that have been implemented in these markets are provided on the next page.

OBJECTIVE TO ACHIEVE	STANDARDS OF GUIDANCE
To ensure accuracy, reproducibility, and repeatability of the test	Quality guidelines for NGS tests
To support consistent and reliable analysis and interpretation of data	Quality guidelines for NGS test data analysis and interpretation
To ensure patients and HCPs have necessary and accurate information to make informed decisions	Data reporting standards for NGS data generated
To ascertain that clinical utility of the NGS test has been proven, and test results can inform appropriate treatment and patients management	Clinical guidelines for NGS usage
To provide assurance of standardized testing, reliability and quality control for HCPs and patients	Quality guidelines for laboratories

Quality guidelines for NGS tests

Quality for NGS testing ensures accuracy, reproducibility, repeatability, and usefulness of the test, this can be divided into three key areas: analytical validity, clinical validity, and clinical utility.

Analytical validity

Analytical validity refers to how well NGS tests can predict the presence or absence of a particular gene or genetic change, accurately and reliably. Assessment of analytical validity involves measuring the test's performance over a set of predefined metrics, to demonstrate whether it is adequate for its indications of use and meets predefined performance specifications. Key quality metrics for analytical validity pertain to accuracy, precision, and limit of detection of NGS tests:

- **Accuracy**: The US FDA recommends that positive percent agreement, negative percent agreement, and technical positive predictive value be predefined and evaluated for each type of mutation.[20]

- **Precision (reproducibility and repeatability)**: Based on US FDA recommendations, thresholds for reproducibility and repeatability should be predefined and reported for each condition tested and genomic context, separately for each variant type. These thresholds should be justified using objective evidence and valid statistical techniques.[21] The Association of Molecular Pathology (AMP) and College of American Pathologists (CAP) Joint Guidelines also recommend assessing a minimum of three samples across all steps and over an extended period, to include all instruments, testing personnel, and multiple lots of reagents. Replicate (within run) and repeat (between run) testing should also be performed.[22]

- **Limit of detection**: The US FDA requires manufacturers to establish and document the minimum and maximum amount of DNA that will enable the test to provide expected results in 95% of test runs, with an acceptable level of invalid calls or no call results (i.e., without a loss of accuracy).[23]

Clinical validity

Clinical validity refers to how well NGS tests can detect or predict a clinical condition associated with the genotype. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are key properties to measure clinical validity.

- Based on the AMP and CAP Joint Guidelines, the clinical validity of an NGS test, including clinical sensitivity and specificity, must be determined during the assay design and evaluated during the validation process. Further, full-scale clinical validation is required for multianalyte NGS tests with prediction algorithms and should be performed using the guidelines and calculations as defined for an analytical validation.[25]

Clinical utility

Clinical utility refers to the usefulness of the results obtained from the NGS test, including whether they provide helpful information about disease diagnosis, treatment, management, and prevention. Important considerations in determining clinical utility include whether the test has led to improved health outcomes for patients.[26]

- The Australian National Pathology Accreditation Advisory Council (NPAAC) Requirements for in vitro diagnostic medical devices (IVDs) state IVDs for novel tests / use should only be offered in clinical settings where there is sufficient evidence of clinical utility for the specific patient population in which the assay is intended for use. Levels of evidence must be assessed in accordance with relevant criteria, such as from the National Health and Medical Research Council (NHMRC), the Evaluation of Genomic Applications in Practice and Prevention (EGAPP2), Eurogentest Clinical Utility Gene Cards, or other guidelines for the evaluation of such evidence.[27]

Quality guidelines for NGS data analysis and interpretation

Data analysis and interpretation involves processing substantial amount of data (raw sequence) to detect genomic alterations that ultimately impact disease management and patient care. The computationally complex process requires quality control and validation of the bioinformatic pipeline, analysis software, reference database and interpretation coupled with trained and qualified personnel. Without appropriately validated processes and quality assurance of data analysis and interpretation, output may generate inaccurate results leading to negative consequences in clinical interpretation and patient care.[28]

Clinical associations, accreditation bodies and policymakers should set standards and enforce compliance on data analysis and interpretation for NGS laboratories.

- AMP and CAP have published guidance for validation of processes, including the bioinformatic pipeline. This includes confirming the appropriateness of the process for intended use, sample identity to be preserved throughout the process, and specified quality control/quality assurance parameters to be evaluated.[29] **These guidelines also highlight the importance of having a properly trained and qualified molecular professional for NGS data analysis.**

- Analysis quality metrics specified by the Association for Clinical and Genomic Science (ACGS) are depth of cover, region of interest and copy number analysis.[30]

- **For software used for data analysis, the ACGS requires validation of all software before it is used within the clinical setting.[31] AMP and CAP also recommend that for software and/or scripts developed and maintained by laboratories, appropriate code repository tools (e.g., GitHub, mercurial, and subversion) should be used to enforce version control and source code documentation.[32]**

- Further, AMP, CAP and the American Society of Clinical Oncology have published guidance for interpreting and reporting NGS results, covering recommended databases for NGS tests, resources to interpret mutations detected, and a tiered reporting system based on clinical significance of results.[33]

  - The US FDA has established reference databases for different applications. For example, for human genome reference, the FDA has assigned ClinGen Expert Curated Human Genetic Data, which is funded by the National Institute of Health, to serve as a reference genomic database.[34]

Data reporting guidelines for NGS data generated

Guidelines and standards on data reporting ensure all NGS reports include the information required for the ordering physician and the patient to understand the genotype tested, the results obtained, and any additional factors that may influence clinical interpretation of results. It is also crucial to report what a test does not find (i.e., pertinent negatives or suboptimal signals) as incomplete or unclear data representation can lead to clinical errors and incorrect patient management. Precision oncology is rapidly evolving, clinicians must understand that these reports are not static and will need to stay up to date on relevant changes.

- The European Society of Human Genetics has updated recommendations for reporting results of diagnostic genetic testing to provide the genomic community with guidance on reporting unambiguous results to avoid misinterpretation. Updates include the need for reporting additional information such as "the importance of understanding and reporting the limitations of the test performed in the context of current methodologies" as well as "reporting of no clinically significant findings, incidental findings and recommendations for further testing".[35]

- The Practice Guidelines for Targeted Next Generation Sequencing Analysis and Interpretation produced by the ACGS advises that reports should convey sufficient concise information such that the reader understands the basic approach taken (what has been sequenced); is assured that the results are reproducible (standardization of variant nomenclature; confirmation of variants); and understands the test limitations (sensitivity; coverage; technical constraints).[36]

- Globally, most guidelines recommend using the Human Genome Variation Society nomenclature, which merged into the HUGO Gene Nomenclature Committee (HGNC), when annotating and reporting all detected genetic alterations. The HGNC database is a curated online repository of HGNC-approved gene nomenclature, gene groups and associated resources, including links to genomic, proteomic, and phenotypic information.[37,38,39,40]

  - A joint consensus by AMP, CAP and American Society of Clinical Oncology recommended that genetic alterations should be clearly described including functional annotation of variants, whether fusions are tested and which ones, therapeutic implications, and mutational clonality. For example, not all variants that affect gene function are therapeutically actionable thus, the report should include specific information addressing its possible role in cancer and the therapeutic implication. On the other hand, if the variant is of unknown significant, it should also be clearly indicated, particularly in genes considered therapeutically actionable.[41]

Clinical guidelines for NGS usage

Clinical guidelines for NGS usage are critical to ensure that the clinical utility of the NGS test has been proven, and test results can inform appropriate treatment and patient care. At present, many physicians in APAC follow international guidelines for clinical usage of NGS, as local guidelines may not be available or up to date. Examples of international guidelines include:

- **Recommendations published by European Society for Medical Oncology (ESMO) Precision Medicine Working Group for use of NGS for patients with metastatic cancers**, such as the use of tumor multigene NGS in NSCLC, cholangiocarcinoma, prostate and ovarian cancers, as well as to test tumor mutational burden in well- and moderately-differentiated neuroendocrine tumors, cervical, salivary, thyroid and vulvar cancers.[42] Recently, **ESMO has also published recommendations for use of validated and sensitive ctDNA based NGS assays for patients with advanced cancer, in identifying actionable mutations to direct targeted therapy.**[43]

- Recommendations published by ASCO on somatic genomic testing in patients with metastatic or advanced cancer. **ASCO strongly recommends multigene panel-based genomic testing whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy. If these tests are to inform clinical care, testing must be performed in an appropriately certified laboratory.**[41]

Medical associations in some APAC markets, like China, Japan and South Korea, have published clinical practice guidelines to educate and share NGS best practices:

- The Chinese Society of Clinical Oncology has published guidance for NGS testing, which includes quality requirements of NGS, sample processing, sequencing and management of data generated.[44]

- The Japanese Society of Medical Oncology, the Japanese Society of Clinical Oncology and the Japanese Cancer Association jointly published a clinical guidance for NGS application in cancer profiling and treatment. It includes suggestions on selecting NGS tests based on their characteristics, collecting and handling samples, informing patients, handling test results, and establishing NGS systems and working groups within hospitals.[45]

- In South Korea, the Korean Society for Genetic Diagnostics has published clinical guidance for NGS application in detection of hematologic malignancies, which includes guidance on NGS instrument selection and NGS performance characteristics to consider, such as positive percentage agreement and PPV.[46]

- Korean Society of Medical Oncology and Korean Cancer Study Group have also published clinical guidance for use of NGS and Molecular Tumor Board for patients with advanced cancer, which includes guidance on considerations when obtaining samples for NGS and how molecular tumor boards should be operated.[47]

Quality guidelines for laboratories

Quality standards are needed to guide accreditation of laboratories that run clinical NGS testing, with a local or international organization in charge of such accreditation.

- In the US, laboratories that run NGS must be certified as compliant with Clinical Laboratory Improvement Amendments (CLIA), Clinical Laboratory Evaluation Program (CLEP) or other quality standards issued by relevant professional societies (e.g., College of American Pathologists laboratory accreditation).[48,49] The US FDA also requires LDTs to be designed, manufactured and used only by CLIA-accredited laboratories.

- In the EU, NGS LDTs must comply with the in vitro medical devices Regulation (IVDR) 2017/746 by having a quality management system in place and must hold a valid ISO 15189 certificate or appropriate national accreditation where available. NGS LDTs may be exempt from certain sections of the IVDR, such as manufacturing; however, exemption is only applicable if there are no commercially available tests. This ensures that LDTs must meet the minimum safety and efficacy requirements of commercially available assays.[50]

- In South Korea, the Korea Laboratory Accreditation Scheme (KOLAS) and Korean Institute of Genetic Testing Evaluation certify NGS laboratories[51]. The Korean Society of Pathologists has also developed laboratory guidelines for NGS cancer panel testing procedures and requirements for clinical NGS laboratories.[52]

- In China, the Medical Device Regulation, State Council Order No.739 allows qualified medical institutions to develop reagents themselves if no tests of the same variety are available in the China market and use these within the institution, according to clinical needs, if the same category product is not approved in China.[53]

- In Australia, LDTs are accredited by the National Association of Testing Authorities (NATA) for compliance with the NPAAC standard. NATA can request Therapeutic Goods Administration assistance in the technical evaluation of analytical and clinical performance of LDTs.[54]

- In Taiwan, the Ministry of Health and Welfare (MOHW) released Guidance on Laboratory Developed Test and Service for Precision Medicine Molecular Testing. These guidelines include regulations for LDTs performed at overseas laboratories. Quality standards for LDT laboratories include compliance with ISO 15189 for medical laboratories and CLIA certification, while TFDA laboratory certification will be mandatory from 2026.[55]

- In Singapore, the minimum required standards for provision of clinical genetic/genomic testing is defined in the published “Standards for the provision of clinical genetic/genomic testing services and clinical laboratory genetic/genomic testing services”. The published standard provides a list of approved laboratory accreditation bodies and agencies that provide external quality assessment schemes that is recognized by Singapore’s Ministry of Health, both for local and overseas testing.[56]

7 Challenges and Recommendations

APAC is a heterogenous region comprising many markets, with significant variation in healthcare systems and policies. This variation leads to large differences in accessibility, regulatory environment and quality of NGS tests.

The following recommendations – put forth by the roundtable participants following extensive discussion and consideration – are intended to ensure the quality of NGS testing, its ability to produce accurate, actionable and reproducible results. This is to ensure that NGS tests being provided can deliver on the value of the test mentioned, which are better patient outcomes and improve cost efficiency. The intention is not to create or increase existing obstacles to NGS testing; rather, it is to ensure those tests are consistently of the quality required.

This set of recommendations is intended to be practical and achievable by all countries across APAC. Therefore, they provide a minimal standard floor which is acceptable, applicable and can feasibly be implemented in all APAC markets, which will ensure elevation of quality NGS testing in the region. Markets with more stringent local standards should maintain current standards. Markets that currently do not have quality standards in place, can look to adopt quality standards that have been established in other markets.

In this initial step of establishing minimum acceptable NGS quality, this set of recommendations is intended to cover clinical use of targeted biomarker NGS tests for cancer for the more widely used targeted biomarker NGS tests, such as single biomarker, hotspot panel and CGP.

Recommendation 1:

Publication of guidelines ensuring standardisation and quality NGS across the entire workflow by public authority bodies

Recommendation 2:

Enforcement of laboratory accreditation/certification by public authority bodies

Recommendation 3:

Restrict routine clinical use to only tests validated (pre-analytical, analytical, clinical validity) with clear clinical utility

Lack of standardization and quality in molecular testing procedures in APAC

In order for the value of quality NGS to be realized, NGS testing must deliver as promised, with accurate reporting of actionable and reproducible results.

There are several concerns about lack of quality assurance with NGS testing, with the potential for repercussions that ultimately impact patient safety and treatment.

Challenge:

In a large survey carried out by the IASLC, lack of quality and standardization was the second most frequent barrier for molecular testing in patients with lung cancer in Asia after cost.[57] Lack of standardization and quality can be further split into three aspects of NGS: processing of sample from patients, bioinformatic analysis of results and reporting of results.

Processing of sample from patients: For instance, in the case of tissue samples, this included insufficient amount of tumor cells for testing (81%), inadequate tissue quality (52%), lack of sensitivity of assay or assay use failure (22%), and inadequate technical expertise in the laboratory (12%). Indeed, this study showed that <50% of patients received testing for biomarkers beyond EGFR, ALK and ROS-1, due to insufficient quantity or quality of biopsy tissue.[58]

Bioinformatics: Bioinformatics pipeline which are not validated and verified may lead to high rates of false-negative errors. A study investigating inconsistencies of mutation calls as high as 43% in databases such as the Genomics of Drug Sensitivity in Cancer and the Cancer Cell Line Encyclopaedia indicates that highly-multiplex NGS has a high rate of FN errors. FN errors may be an important factor for analysis of tissues with low-percentage cancer cells designed for extremely high-sensitivity detection of mutations.[59] This study supports prior reports, which noted significant errors in NGS, illustrating need for regulations around NGS testing to ensure reliable and accurate results.

Reporting of results: Concerns were raised at the roundtable meetings around the impact of non-standardized NGS reporting terminology, which could hinder both the physician's interpretation of results and the patient's understanding of the implications of those results. For example, confusion can occur when genomic alterations are reported using different terminologies. As specific genomic alterations may have a corresponding matched treatment, correctly interpreting the genomic alteration is important for oncologists to determine appropriate course of treatment.

It was agreed that, given the current lack of unified regulations for quality, there is a need for NGS quality standardization across APAC.

Recommendation:

Public authority bodies to publish guidelines to ensure standardisation and quality NGS, across the entire workflow. (Similar to what the US FDA, Singapore HSA and Japan PMDA do in the above examples)

- Best practices at the global and APAC level for each step of the NGS workflow has been elaborated in the previous section "Best Practice guidelines and reference for quality next-generation sequencing". Markets that do not have such guidelines in place may look to adopt guidelines that have been developed in other regions, or within the region.
- To give an example for one of the aspects mentioned – pre-analytical validation, there are examples of best practices within the region such as China and Japan where local medical associations have published clinical practice guidelines that include quality requirements and suggestions for sample handling, collecting, and processing. Given that biopsy sample input is very important to the quality of NGS, such guidance helps to ensure proper sampling and handling to mitigate delays in testing and resampling.

No consistency on how laboratories performing NGS tests are regulated

Challenge:

Traditional IVDs are tests developed and extensively validated by companies and regulated by regulatory bodies. They require approval by regulatory bodies in all markets, and so end-users are assured of their quality. However, in the case of NGS based IVDs which are highly complex assays; laboratory processes such as sample processing, library preparation and sequencing, bioinformatics analysis, laboratory personal training and quality management systems are crucial to ensure the quality of the NGS tests.

LDTs on the other hand are typically developed used within a single laboratory. In some markets, there are no formalized regulations and external validation in place for LDTs, raising concerns regarding their quality. Experts noted high usage of LDTs in the region, and that LDTs are typically conducted by smaller labs in APAC, compared with larger centralized labs in markets like the US and EU. This impacts quality, since LDTs are not typically regulated at test level, but at laboratory level, and larger laboratories have more resources to validate processes and quality.

Further, in certain APAC countries (e.g., South Korea) validated NGS tests which are conducted in overseas laboratories, which are CLIA, CAP certificated and ISO 15189 compliant are discriminated against the locally conducted NGS tests in terms of clinical adoption or for reimbursements purposes. Additionally, matched therapy reimbursement decision also depends on where the NGS tests are conducted (local vs overseas labs) which limits the accessibility of validated, high quality NGS tests to improve patient outcomes in such countries.

In some markets, there are guidelines and regulations for laboratories performing NGS tests:

- In the US, laboratories are required to be accredited by CLIA, CLEP or CAP.
- Implementation of the IVDR in EU is bringing the regulations of IVDs and LDTs closer to reality, as NGS labs performing LDTs will be regulated under IVDR
- Examples in APAC include regulations/guidelines that are enforced/published by National Pathology Accreditation Advisory Council in Australia, Ministry of Health and Welfare in Taiwan and Ministry of Health in Singapore.[60,61,62]

While in others there are no regulations, leaving those to self-regulate. Variations in outcome have been observed between laboratories given the same sample, raising concerns on capabilities and user's confidence in outcomes.[63,64]

Recommendation:

Public authority bodies to establish a list of recognized NGS laboratory accreditations/certifications, including international accreditations/certifications to ensure standardisation and quality as per national/regional guidelines.

- All laboratories, both local and overseas, should be accredited similar to how pharmaceutical manufacturers require GMP accreditation to ensure quality.
- Such a list will provide flexibility to local regulatory bodies on the accreditations/certifications that are recognized. There are established international accreditations/certifications that should be accepted; since the industry is at an early stage of development, many useful NGS tests and competent NGS laboratories are available outside the market where the patient sample was collected.
  - » Accreditations highlighted by experts included ISO 15189, CLIA and CAP.
- Singapore's Ministry of Health has published a list of laboratory accreditation bodies and overseas agencies that it recognizes for local and overseas testing.[65]

Undesired outcomes for patients

Challenge:

The US FDA has published case studies where lack of quality assurance in lab-developed tests (LDTs) may have led to undesired outcomes, such as patients not receiving necessary care.[66] An example that illustrates the risk is a lab-developed prognostic genetic panel that provided treatment recommendations for prostate cancer. Based on test results, patients would either be recommended monitoring or treatment. Treatment options included SOC procedures, such as hormone therapy, surgery, radiation or chemotherapy. However, there was no prospective study to validate whether these treatment recommendations were appropriate, so patients could have been either overtreated or undertreated for prostate cancer.

Recommendation:

Public authority bodies to limit routine clinical use to only tests validated (pre-analytical, analytical, clinical validity) with clear clinical utility

- In relation to setting the guidelines, there will also need to be a mechanism to limit routine clinical use to tests that have been validated with clear clinical utility
- For example, The Australian NPAAC only allows use of novel IVDs in clinical settings where there is sufficient evidence of clinical utility for the specific patient population in which the assay is intended for use. The levels of evidence must be assessed in accordance with relevant criteria, such as from the NHMRC or other guidelines for the evaluation of such evidence.

While these recommendations should be implemented as first steps to NGS quality assurance and standardization, there are several other considerations to be taken into account. These next steps include understanding of test applicability and purpose, report readability, alignment on terminology, publication of evidence and consideration of bias in reference databases.

8 Quality Considerations for Next-Generation Sequencing

Following implementation of the recommendations outlined so far in this paper, the following additional considerations should also be taken into account to support NGS quality assurance and standardization.

Validate applicability of test to local population

Current bioinformatic databases are largely based on data from European individuals.[69] Most NGS tests are validated based on these databases, which may or may not be representative of ethnicities in APAC. For regulated tests, some markets, such as Australia and China, require validation of the NGS testing with local samples prior to approval. In other markets, manufacturers should conduct post-marketing clinical validation of tests with local samples.

Ensure clear understanding of test applicability and purpose

Healthcare professionals ordering NGS tests should understand the applicability of the test (e.g., particular stage of cancer) and its limitations (e.g., other tests required for diagnosis) prior to ordering the test, and thus should receive training, accordingly. Training could be provided as a professional development course or a seminar by industry or other training provider. To the above points, experts highlighted the importance for clinicians to understand the limitations of different panel designs.

Align reporting terminology

Use of differing terminology amongst stakeholders must be reconciled to avoid misinterpretation of results. Certain nomenclatures, such as colloquial nomenclature and Human Genome Variation Society (HGVS) nomenclature, have been developed to facilitate common understanding. However, there is no consistent use of one nomenclature across the board.

This results in different report terminologies (e.g., hTERT promoter variants are reported as c.1-124C>T in HGVS, and TERT C228T in colloquial nomenclature).[68] Adoption of standardized nomenclature, such as HGVS, would improve universal ability to interpret results.

Improve report readability

NGS reports can be lengthy and important information can be hard to identify, since reporting guidelines are focused on ensuring all required information is included.[67,68] This makes it difficult for end users (physician specialists and patients) to understand NGS results. In addition to ensuring all required information is included, there must also be effort made to improve readability of reports. End users could be consulted to increase clinical usability of reports.

Publish evidence

Sharing information in the public domain, such as evidence-based clinical validity and utility benefits of NGS testing, will help to build a body of knowledge towards the advancement of the field. **In the absence of regulations for LDTs, clinical validity evidence to validate NGS tests (IVD & LDT) should be published so quality may be cross-checked by users and other industry professionals.**

9 Initiatives for Quality Next-Generation Sequencing

Collaborative initiatives for quality NGS in APAC and other regions

Brazil

Peru

Chile

A consortium of seven companies in Brazil is providing free quality NGS tests for patients with NSCLC. This support ensures the NGS tests provided are of high quality, whilst also facilitating access.[70] This consortium model has been replicated in Peru and Chile, as well.

Australia

A collaboration between industry and research institutes in Australia aims to provide the expertise, equipment and process required to elevate NGS tests in clinical use.[71] This public-private partnership has also committed to providing quality NGS for cancer patients to enable clinical trials, and establish Australia as a hub for cancer drug development, helping future-proof its healthcare system.[72]

Another collaboration between industry and the Australian government co-funds a study that will generate high quality, real world, clinical and medical data about the impact and value of CGP, precision medicine and personalised healthcare (PHC). This will establish a blueprint for how CGP and PHC can be incorporated into clinical practice and become the standard of care in treating cancer in Australia.[73]

Singapore

China

Japan

India

Efforts are ongoing in Singapore, China and Japan to address the bias in bioinformatic databases, by sequencing the local population and building population-specific databases.[74,75]

10 Closing Remarks

A panel of experts convened across two industry roundtables provided recommendations to ensure standardization and quality of NGS testing across APAC. These recommendations aim to protect public interest by setting standards for quality NGS.

Quality NGS testing can deliver value both in terms of improved patient outcomes and cost efficiencies within the healthcare system. To ensure this value is delivered, there must be an ongoing focus on quality assurance and standardization. A customised set of recommendations for APAC has been presented as a first step to establishing region-wide quality assurance, based on examples of best practice within the APAC region, and globally.

The panel noted that this discussion should be part of a larger conversation, since implementation of quality assurance standards is only the first step to ensuring NGS tests can deliver value. In addition to quality, the roundtable participants noted that there are several other components within the healthcare ecosystem that are hindering realization of the true value of NGS.

Importantly, lack of reimbursement of NGS tests, which results in high out-of-pocket costs for patients, reduces accessibility for the majority of people. More work is needed to make NGS more accessible in the region.

Beyond this, a lack of physician awareness and familiarity with NGS and, indeed, the low availability and lack of coverage for matched treatments means physicians may be hesitant to order NGS tests for their patients.

Following establishment of NGS quality standards for clinical use, these substantial challenges to implementation of NGS testing should be considered as next steps.

11 Glossary and Abbreviations

Abr'v	Terms	Definition
	Actionable mutation/ gene/ biomarker	Associated with a targeted treatment, with the potential to mitigate symptoms or disease
	Bioinformatic pipeline	A series of software algorithms that process raw sequencing data and generate interpretations from the dataset
CDx	Companion diagnostics	Diagnostic tests used as a companion to a therapeutic drug to determine its applicability to a specific person
CGP	Comprehensive genomic profiling	Test that detects all four classes of genomic alterations (substitutions, insertion and deletion alterations [indels], copy number alterations [CNAs], and gene rearrangements) across a broader panel of genes (typically >50 genes up to 500+ genes)
	Copy number analysis	The process of analysing data produced by a test to identify somatic or germline events
FN	False negative	An error in which a test result incorrectly indicates the absence of a condition when it is actually present
	Gene panel	Test that analyzes multiple genes at once
GA	Genomic alterations	Gene alterations including cancer-driving mutations, gene fusions and copy number variations
HGNC	HUGO Gene Nomenclature Committee	The HGNC curates an online database of approved gene nomenclature, gene groups and associated resources, including links to genomic, proteomic, and phenotypic information
	Hotspot panel (also known as 'small gene panel)	Gene panel that sequences specific parts of multiple genes (typically ≤ 50 genes) commonly altered in cancer; also known as targeted panel
IVD	In-vitro diagnostics	Tests that have been developed, manufactured and intended for in vitro examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes. In the context of this paper, it is used to refer to commercialised IVD tests, tests that are used by laboratories that did not manufacture the test.
LDT	Laboratory-developed tests	IVDs that have been developed, manufactured and are used within a single laboratory. Some health authorities refer to it as 'in-house' IVDs
	Liquid biopsy	The sampling of non-solid biological tissue, primarily blood, for further tests
	Molecular profiling	Form of testing that classifies tumors based on their genetic make-up for diagnosis and treatment
NGS	Next-generation sequencing	A high-throughput technology that determines the sequence of DNA or RNA
PCR	Polymerase chain reaction	A low throughput technique to test if there is a DNA mutation in a gene, conducted on DNA obtained from liquid or tissue biopsy
PFS	Progression free survival	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse
	Targeted biomarker NGS test	Test that sequences pre-determined selected genes, this is in contrast to WES or WGS that sequences all genes
	Variant/mutation calls	Process by which variants are identified from sequence data
WES	Whole exome sequencing	NGS technique that sequences the exome to identify variations in the protein-coding region of any gene (exons)
WGS	Whole genome sequencing	NGS technique that determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome

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APACMed
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The Asia Pacific Medical Technology Association (APACMed) represents manufacturers and suppliers of medical equipment, devices and in vitro diagnostics, industry associations, and other key stakeholders associated with the medical technology industry in the Asia Pacific region. APACMed's mission is to improve the standards of care for patients through innovative collaborations among stakeholders to jointly shape the future of healthcare in Asia-Pacific. In 2020, APACMed established a Digital Health Committee to support its members in addressing regional challenges in digital health. For more information, visit: www.apacmed.org

"Asia Pacific" means the countries and/or economies in the Asia Pacific region, namely: Australia, Bangladesh, Bhutan, Cambodia, DPR Korea, Hong Kong (China), Independent State of Papua New Guinea, India, Indonesia, Japan, Lao People's Democratic Republic, Macau (China), Malaysia, Mongolia, Myanmar, Negara Brunei Darussalam, Nepal, New Zealand, Pacific Islands, Pakistan, People's Republic of China, Chinese Taipei, Philippines, Singapore, South Korea, Sri Lanka, Thailand, Timor Leste, Vietnam;"

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