Accelerating clinical adoption of next-generation sequencing

Considerations for the clinical laboratory director

Key learnings

Understand the importance of adopting NGS technologies for population health strategies.

Understand the key role of lab directors in the adoption of NGS methods in clinical labs, including stakeholder education, data development, and engagement.

Understanding the NGS landscape

Many factors impact the full transition of NGS technology from its current position as a powerful research tool to what, for many, is the ultimate goal—the use of NGS to inform and guide diagnosis and treatment decisions for improved patient outcomes. Despite the fact that the majority of NGS applications are in the research space, some NGS assays with demonstrated clinical evidence are receiving in vitro diagnostic (IVD) approval.

According to Phillips et al. (2018), the clinical sequencing market is the fastest growing segment within diagnostics, fueled by expanding demand for tests with better performance characteristics and validation in areas such as prenatal testing and cancer care.[1] Investments in the use of NGS, multi-gene panel testing and collection of data are occurring globally.

With cancer care and prenatal testing leading the way, key trends influencing wider clinical adoption of NGS include the unmet clinical need for better tools to predict, diagnose, treat, and monitor disease, as well as increasingly efficient sequencing technologies. Other factors driving growth include: patient demand, industry investment, and regulations that allow the adoption of tests without Food and Drug Administration (FDA) approval.[2]

Technological advancement in sequencing platforms, library preparation, reagents, assays and analytics have gained much attention from both public and private health authorities. Research gathered from 2016–2020 shows that adoption of these technologies is largely based upon local policy priorities, research interests and clinical care strategies.

In addition, the growing body of clinical evidence for the potential to improve diagnosis and treatment decisions, as well as the gradual inclusion of NGS methods in relevant clinical guidelines, may be an additional factor in adoption.

Growing global cancer burden

The World Health Organization (WHO) reports cancer as one of the top two leading causes of premature death ages 30–69 in 134 of 183 countries evaluated, and cancer is the third or fourth cause of premature death in 45 additional countries. Of the 15.2 million premature deaths from non-communicable disease worldwide in 2016, 29.8% were due to cancer.[3]

Cancer has a significant economic consequence. In 2009, WHO researchers estimated the cost of care of $1.16 trillion (USD) per year, characterizing disease and economic cancer burden as a clear public health priority.[4] Given their impact on constituents and the economy, policymakers now recognize and are attempting to address the growing burden of cancer.[4]

Breast, lung and colorectal cases were reported to be the most common cancer types of new cases globally in 2020 (Figure 1).[5] Molecular diagnostic testing has been proven to accurately deliver prognostic and diagnostic information important for making treatment decisions unique to the needs of each cancer patient.

NGS, also known as massively parallel sequencing, offers multi-gene biomarker testing within a continuous workflow. Testing availability may include smaller panels (e.g., <50 genes), larger panels including comprehensive genomic panel (CGP) profiling,[a] or whole-exome or whole-genome sequencing.

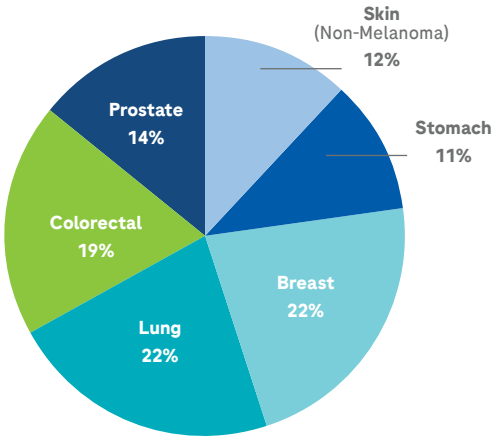

Figure 1: Common cancer types (WHO, 2020)

What are the barriers facing routine NGS testing?

Despite the rapid growth of the NGS market, there are several interrelated challenges to overcome to ensure uniform, routine, and global access to NGS tests and a transition to personalized healthcare in the future:

Proving cost-effectiveness

Economic stakeholders will consider the comparative cost of technologies relevant to their population health objectives. Whether funding is through delegated hospital systems, laboratory budgets, or public or private resources, the publication of comparative cost-effectiveness research relevant to stakeholder perspectives is essential.

Clinical interpretation and actionable data

Experience tells us that the adoption of a new technology—or even a new, improved standard clinical diagnostic assay—requires everyone from the laboratory, through clinical staff to policy makers, to develop an awareness and comfort level in the new paradigm. In particular, a barrier for genetic tests is the lack of confidence from clinicians in how to best act on genetic test results in treatment decisions, and the complexity of the clinical decision-making process. Published studies have identified a lack of confidence of clinicians in their ability to interpret sequencing data. For example, 22% of clinicians at a tertiary cancer center reported a lack of confidence in their genomic knowledge, demonstrating a need to educate oncologists in interpreting genomics data.[6]

a. Comprehensive genomic profiling, or "CGP", may be defined as a next-generation sequencing approach that detects novel and known variants of the four main classes of genomic alterations, as well as genomic signatures, to provide prognostic, diagnostic and predictive insights that inform research or treatment decisions for individual patients across all cancer types.

NGS global access and value creation

Funding laboratory services requires investment in facilities, technology, data infrastructure and analytics, as well as people, processes, quality systems, accreditation and procurement. Funding sources may include, but are not limited to: grants from public or private organizations, public or private resources, health system or hospital budgets, patient payments, research allocations or other revenue sources.

Understanding and addressing the unique needs of stakeholder groups within local care systems is vital to allowing lab directors to leverage the value drivers of NGS testing. Health strategies aligned with local policy and treatment objectives differentiate NGS from other diagnostic tools. Table 1 outlines the value drivers most closely associated with NGS.

Table 1: Next-generation sequencing (NGS) value drivers.

Risk identification	Application of validated tests using NGS platforms enables clinicians to identify individuals at higher risk of disease across multiple cancer types.
Risk stratification	Beyond informing the management of patients with advanced disease with respect to targeted therapies, the analysis of genomic alterations (for example, in plasma circulating tumor DNA, or ctDNA) has been shown to accurately provide early diagnosis, risk stratification, detection of minimal residual disease and tumor surveillance.
Personalized healthcare	Understanding individual characteristics and DNA, caretakers and patients may choose treatment pathways that are most likely to benefit the individual through clinical care, research or avoidance of therapies not likely to add clinically meaningful benefit. Policymakers in particular have shown strong interest in personalized health care, as may be seen through legislative reforms and appropriations.

Data on file with Roche.

Early evidence of NGS cost-effectiveness: Oncology

An emerging body of economic evidence suggests that NGS may be cost-effective in therapy selection for specific indications and applications. For example, Italian researcher Gancitano and colleagues (2018) compared three diagnostic strategies for locally advanced or metastasized non-small cell lung cancer (NSCLC) and concluded the availability of ctDNA sequencing data (from liquid biopsy) would support care optimization in both first- and second-line treatment selection.[7] The least cost-effective strategy proved to be the exclusive use of tissue biopsy, whereas a combined strategy, using liquid biopsy in cases where tissue biopsy was not conclusive, did improve the cost analysis. The most cost-effective strategy proved to be liquid biopsy NGS analysis which also correctly identified the most cases, supporting the prescription of the best oncological therapy.

Pennell et al. (2018) modeled the cost consequence of single-gene hotspot PCR-based testing compared with NGS methods for metastatic non-small cell lung cancer (mNSCLC) in the United States.[8] NGS was associated with shorter turnaround times and cost saving. Compared with single-gene testing for mNSCLC patients, NGS-based multi-gene panel testing may identify more patients who could benefit from targeted therapies with moderate cost-effectiveness. Steuten and colleagues (2019) modeled overall survival benefits favoring patients with NGS-guided therapies, with cost-sensitivities mostly impacted by the cost of the targeted treatments and immunotherapies.[9]

Carlson et al. used a population probabilistic model with six health states to evaluate NGS cost-effectiveness in the detection of minimal residual disease (MRD) for maintenance of patients diagnosed with multiple myeloma (MM): MRD+ or MRD- on or off treatment, relapsed, or dead; and compared yearly NGS MRD testing to no MRD testing over a lifetime horizon. Using U.S. cost inputs, MRD testing was projected to save $1,156,600 over each patients' remaining lifetime. Authors concluded that NGS-based MRD testing is cost-saving, with potential quality-adjusted life year (QALY) gains due to avoidance of treatment-related adverse events compared with no testing for multiple myeloma patients on maintenance therapy. They noted further clinical studies are needed to determine the health outcomes of NGS MRD testing during MM maintenance treatment.[10]

Tan et al. more recently published results from their review of Singapore nationals receiving care through Singapore General Hospital.[11] For periods January 2016 through September 2017, authors evaluated 174 samples using a targeted NGS panel for DNA alterations (29 selected genes including BRAF, EGFR, ERBB2 and TP53) and an RNA fusion panel (ALK, ROS1 and RET). PD-L1 immunohistochemistry was also performed. A cost-effectiveness analysis of NGS compared with standard molecular testing was conducted. The authors concluded that upfront NGS testing represents a feasible, cost-effective method of diagnostic molecular profiling compared with sequential testing strategies.

Araujo et al. concluded that the use of ctDNA analysis from blood is a valid alternative to EGFR testing in NSCLC when insufficient tissue is available (known as quantity not sufficient, or QNS). This allows more patients to be identified for matched and targeted therapies, thus reducing overall prescription of immunotherapies for patients who are not likely to benefit from them and reducing overall costs to the Brazilian health care system.[12] Researchers used a population probabilistic model guided by the diagnostic test. Models considered progression-free survival, disease progression and death. Savings were generated because ctDNA NGS identified more eligible patients for target therapies and reduced the prescription of immunotherapies to patients who would not benefit. Greater effectiveness was due to patient mapping with targeted therapies.

Researchers cited above collectively suggest opportunities to consider which application, indication and strategy may utilize NGS testing to achieve both policy and clinical objectives of the health care system, clinician and patient.

Professional society guidelines and consensus statements

As further evidence of clinical utility and cost effectiveness becomes available, expanded coverage and funding of NGS-based solutions are expected. Adoption of NGS technologies is further informed by professional society guidelines, a sample of which is outlined in Table 2. These clinical guidelines play an important role in influencing the use and coverage of these tests, particularly in the genetic oncology testing space. It is also important to recognize that different countries and regions may have regulations and government mandates that impact test usage and treatment options, and that the timing of testing and treatment may also impact treatment efficacy, regardless of NGS test results.

Table 2 : Society guideline illustrations. NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; NSCLC = Non-small cell lung cancer; IHC = Immunohistochemistry; NGS = Next-generation sequencing; FISH = Fluorescence in situ hybridization; PCR = Polymerase chain reaction.

Indication	Last updated guidelines	Guideline issued by	Recommended biomarker testing	Recommended technologies	Comments
Advanced or metastatic non-small cell lung cancer (NSCLC)	Version 1.2023 – Dec 2022[13]	NCCN	PD-L1, ALK, ROS1, NTRK, RET, MET (MET ex14 and optimally MET amplification), BRAF, KRAS, ERBB2 (HER2)	IHC, NGS, FISH, PCR	*"It is recommended at this time when feasible, testing be performed via a broad, panel-based approach, most typically performed by NGS."*
Advanced nonsquamous NSCLC, and metastatic prostate cancers, ovarian cancers, cholangio-carcinoma	Aug 2020[14]	ESMO	Various based on indication	Multigene NGS, broad panel	*"ESMO recommends that clinical research centers develop multigene sequencing as a tool to screen patients eligible for clinical trials and to accelerate drug development, and prospectively capture the data that could further inform how to optimize the use of this [NGS] technology."*

How can lab directors drive future adoption?

Lab directors play a primary role in adoption and access to advanced testing, including NGS. Ongoing engagement with internal and external stakeholders is paramount to ensure financial and human resources are adequate to meet health system requirements, including outcomes derived through personalized health care. Table 3 provides a brief summary of lab director actions that have proven effective in adoption of NGS technologies.

Table 3: Key actions for laboratory directors.

Stakeholder education & awareness	• Ongoing stakeholder awareness and education about diagnostic testing, NGS, and indications for when this class of technologies is indicated in support of clinical decision-making for cancer screening, diagnosis and prognosis. • Proactively engaging with local policymakers, technology assessment organizations, clinicians, and other budget holders influencing access and funding of NGS for indicated patients. • Delivering stakeholder-relevant information concisely, and through the most effective communication channels, is an area of opportunity for the lab director.
Data development, publication & communication	• Organization and, when available, analysis of NGS laboratory data by policymakers and relevant budget holders. • As appropriate and if available, publication of NGS laboratory experience, including specific use cases informing clinical decision making and improving quality of care.
Advocacy for access to NGS testing for cancer applications	• Proactive engagement with access stakeholders, encouraging NGS availability consistent with indicated use and local standards of care. • When appropriate, active participation in patient-specific prior authorization, utilization review and appeal processes when pursued by the patient, caretaker or prescriber.[b]
Guidelines & position statements reflecting local community care standards	• Participation and publication of guidelines reflecting standard utilization of NGS methods for oncology applications, in collaboration with the community of health care providers and patients.
Quality assurance & laboratory accreditation	• Active engagement and support for ongoing development, implementation and enforcement of quality assurance standards, and accreditation of laboratories performing NGS.
Uptake, experience & coordination of diagnostic care	• Use of NGS portfolio of technologies and services, including sequencing platform, reagents, sample preparation tools, data analytics and reporting. • Sharing direct NGS experience with internal and external stakeholders, about how NGS data can inform clinical decision making by prescribers, caretakers and patients.

b. Adherence to local privacy laws and compliance is required.

Conclusion

NGS is one of the fastest growing types of technology advancing precision medicine research. Many peer-reviewed publications highlight the scope and breadth of clinical areas where NGS has the potential to improve clinical practice and patient outcomes. Importantly, those responsible for financing healthcare systems—public, private and institutional bodies, for example—are releasing funds for further research and translational efforts.

Although access to NGS is heterogeneous, ongoing investments in data development, infrastructure, and experience—coupled with emerging evidence of the impact of NGS in precision medicine—are fueling adoption.

Lab directors play a key role in the adoption of NGS, including stakeholder education, data development, and engagement in policy reform. These key influencers can further inform care guidelines, incorporating NGS use by indication and application of each test. They establish quality assurance standards, ensuring tests which inform clinical decision making are reproducible and accurate. Through proactive stakeholder engagements, lab directors are uniquely positioned to shape and deliver the promise of NGS to health systems and their patients.

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