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CLINICAL SEQUENCING

Regulatory Frameworks and Quality Assurance for NGS-based Diagnostics

SAFER, SMARTER, GREENER

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Implementing quality in clinical NGS

This document aims to interpret high-level regulations through the lens of clinical NGS and to provide a list of resources to aid labs in developing high quality diagnostics, ensuring compliance with applicable regulations, and delivering a high standard of care within their organizations.

EXECUTIVE SUMMARY

The wide-spread adoption of NGS in clinical settings is a key prerequisite for precision medicine and has the potential to revolutionize diagnostics and treatment in a variety of therapeutic areas, but faces several challenges.

Legal and ethical frameworks, secure data sharing and computing, integration with existing hospital infrastructure, and the quality assurance of both physical and computational tools are all areas that must be addressed to ensure patient safety and to enable the broader use of clinical NGS and precision medicine.

In contrast to other medical specialties, clinical NGS employs a broad palette of technologies and tools, and standardization has been limited. Rapid improvements in technology and scientific knowledge, combined with the wide variety of application areas mean that custom workflows or laboratory developed tests (LDTs*), based on non-approved research use only (RUO) technologies are commonplace today and will likely remain so for the near future.

In contrast to many other healthcare areas, where hospital labs verify and use commercial tests approved for diagnostic use, clinical NGS labs currently serve the roles of both assay developer and user, and are generally responsible for the complete validation of their analytic pipelines. As such, while not necessarily manufacturers of medical devices, NGS labs processing patient samples for diagnostic use share some of the same quality and regulatory compliance requirements.

*Complete list of abbreviations on page 26

Partly due to a complex regulatory framework and lack of clear guidance, appropriate validation strategies and quality assurance systems are not universally implemented, and some labs may be unaware of their regulatory responsibilities.

In addition to presenting obvious risks to patient health, the lack of mechanisms to ensure the quality and trustworthiness of data hinders data sharing, a key requirement for the diagnosis and treatment of rare genetic disease.

This review summarizes three tiers of quality assurance for clinical NGS labs, consisting of regulatory frameworks; ISO standards applicable to medical laboratories, and technical, NGS-focused best practices. This document aims to interpret high-level regulations through the lens of clinical NGS and to provide a list of resources to aid labs in developing high quality diagnostics, ensuring compliance with applicable regulations, and delivering a high standard of care within their organizations.

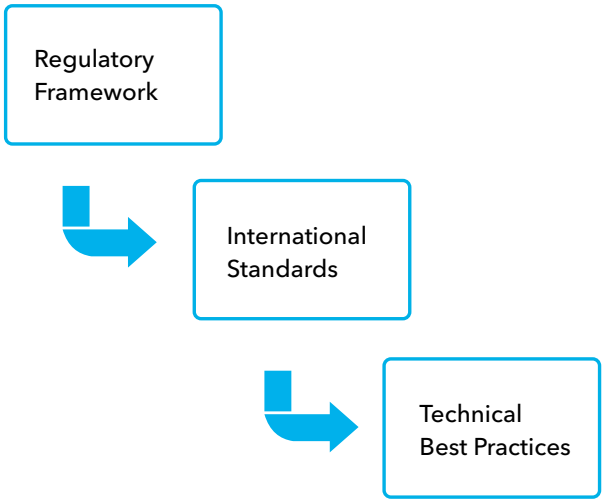

Figure 1. A three-tiered approach to quality assurance for clinical NGS labs

THE REGULATORY FRAMEWORK FOR CLINICAL NGS

While most medical systems in a modern healthcare setting undergo stringent approval processes and extensive clinical trials prior to use, the regulation of clinical NGS systems is still immature.

To date, only a small number of sequencers and gene panels, typically companion diagnostics or targeted assays for certain cancer indications, have undergone CE-IVD or FDA approval.

While most of the reagents and software modules used for clinical NGS are not intended or approved for clinical diagnostic use, clinical sequencing is quickly becoming an integral part of the modern health-care infrastructure. The vast majority of clinical NGS tests are performed with reagents and kits labeled 'for Research Use Only' (RUO). While some sequencers and assays are approved for IVD use, these are generally targeting low-throughput applications. For rare heritable disease diagnostics or applications that require higher read count, there are currently no instruments approved for IVD use, and even for low-throughput applications like cancer sequencing or companion diagnostics, IVD-approved assays and instruments are dwarfed by the number of RUO-labeled products.

There are several factors contributing to the current lack of standardization and regulation in clinical NGS:

- **Complex workflows:** In addition to the sequencing platform, chemistry, and assay, a complete workflow includes numerous other wet-lab steps including sample collection and handling, DNA or RNA extraction, quality control, and library preparation. After generating data, numerous software

modules, often implemented on one-off, custom computing infrastructures are required to process and analyze sequence data. Finally, the filtering, prioritization, interpretation and classification of variants by necessity requires the use of external databases, which have their own data governance models.

- **Large variety of clinical sequencing applications based on needs of specific therapeutic areas:** Each component of the pipeline must be specialized for a given application. While a clinic may want to call both CNVs and SNVs from an exome dataset, the bioinformatics pipelines for each type of variant will differ. Quantifying SNVs with a high-depth, tumour/normal pair of samples requires a drastically different workflow than profiling clinically relevant SNVs in trios for rare disease, and so on.

- **Development trajectory:** Many diagnostic pipelines are conceived in a translational or clinical research environment, where RUO algorithms and equipment are acceptable, and only later adapted for diagnostic use.

- **Rapid technological advancement:** Rapid evolution in technology means that the power and cost-efficiency of assays that have gone through a complete approval cycle will often be lower than the current state-of-the-art.

- **Changing scientific knowledge:** The knowledge underlying assay design advances rapidly, so there is a risk to patients due to assays not considering the most current knowledge and clinical best practices, particularly for complex disorders or diseases which are not completely understood.

- **NGS data challenges traditional performance criteria:** Historic clinical assays measure one or a small number of analytes, while NGS generates millions of data points and can generate non-anticipated results. Furthermore, as the field is relatively young, regulatory bodies may lack the technical expertise to provide informed guidance regarding the analytical validity of NGS-based diagnostics.

- **Lack of clear regulatory guidance:** In many jurisdictions, laws and regulations on diagnostics predate the era of genomics. Due to the lack of precedent and complex subject matter, it's often difficult for both clinical NGS labs and regulatory bodies to receive clear guidance.

- **Unclear regulatory responsibility:** In some instances, the national bodies responsible for the oversight of clinical NGS are not explicitly known. Without a responsible body to generate and enforce regulations, each lab must individually interpret and implement the best practices and recommendations guidelines supplied by a variety of organizations or groups, resulting in a heterogenous standard-of-care, even within a single healthcare system.

CLASSIFICATION OF CLINICAL NGS UNDER CURRENT REGULATORY FRAMEWORKS

While regulatory approaches vary between jurisdictions, human diagnostic assays intended for commercial sale or for provisioning as a commercial service must undergo an appropriate approval process. In the US, commercially available clinical NGS assays are considered *in vitro* diagnostic (IVD) medical devices, and are covered by a comprehensive regulatory framework provided by the FDA. In the EU, the *In Vitro* Diagnostic Regulation (IVDR 2017/746) regulates clinical diagnostics, including NGS-based assays. The IVDR was adopted in 2017, and the transition period from the previous EU directive 98/79/EC lasts until spring 2022.

The goals of the IVDR are to provide a more consistent and higher standard of safety across the EU and to modernise guidance with respect to new medical innovations. It's estimated that currently 10-20% of IVDs are regulated under 98/97/EC, and that this will rise to 80% under the IVDR*. In contrast to 98/97/EC, the new regulation puts a greater emphasis on risk assessment, transparency, and post-market surveillance, and include a new classification system for IVD medical devices.

With few notable exceptions, namely certain companion diagnostics and a limited number of gene panels meant to assay common pathogenic variants in certain cancers, the majority of assays provided by clinical NGS labs are not FDA- or CE-IVD approved. As a result, laboratories are tasked with providing clinical tests using a variety of research use only (RUO) designated reagents, equipment, and software. Both the FDA and EC make provisions for laboratory developed tests (LDT), which allow health institutions to offer cutting-edge diagnostics when approved devices are not available. The separation of LDT as a subset of IVD diagnostics creates a second level of regulation for health institutions that do not intend to manufacture or commercially market their assays.

*European Commission. "New EU rules to ensure safety of medical devices - factsheet." 2017.

This in turn limits undue regulatory burden on healthcare systems and preserves the rights of patients to access modern diagnostics, while still providing some level of regulatory oversight.

One of the many decisions clinical NGS labs must address is whether to go through full FDA or CE-IVD approval, or to offer a diagnostic as an LDT. In general, the new IVDR applies more uniform requirements on IVD manufacturers, including the minority of clinical NGS labs that wish to market and manufacture diagnostic assays for use by secondary parties. While there is a growing trend for larger health institutions to pursue full regulatory approval, this review with focus mainly on the regulatory requirements for clinical labs offering LDTs, which describes most hospital sequencing facilities to date.

IN VITRO DIAGNOSTICS AND LAB-DEVELOPED TESTS UNDER THE IVDR

In the EU, IVDR 2017/746 clearly identifies genetic tests and companion diagnostics as IVDs. Based on a risk assessment, IVDs are placed into one of four risk classes ranging from A (low) to D (high). NGS tests are generally considered class C IVDs with the reasoning that they present a high risk to individuals (Annex VIII). Class C IVDs are subject to technical assessment by a notified body as part of the approval process. For labs not aiming at CE-IVD approval, article 5 of the IVDR contains several provisions pertinent to clinical NGS labs tasked with developing assays from RUO components.

Firstly, the regulations explicitly allow health institutions to develop LDTs or to modify approved IVDs.
Under Article 5, LDTs may only be developed by health institutions and cannot be manufactured on an industrial scale. The definition and language surrounding this provision is meant to remove the possibility of clinical diagnostics companies or service providers exploiting a loophole to classify themselves as health institutions to avoid IVD approval. LDTs developed by a health institution can only be provided within that health institution, and may not be transferred to other legal entities. This further differentiates commercial diagnostics from LDTs, but has implications when considering the distribution of clinical NGS resources between entities within a country's healthcare system or across borders.

While LDTs are not generally subject to the entirety of IVDR 2017/746, compliance to several regulatory requirements is still mandated. Labs that employ LDTs are required by

Both the FDA and EC make provisions for laboratory developed tests (LDT), which allow health institutions to offer cutting-edge diagnostics when approved devices are not available.

IVDR 2017/746 to have an appropriate quality management system (QMS) in place. Additionally, labs must hold a valid ISO 15189 certificate, or an appropriate national accreditation where available. While LDTs are exempt from some provisions of IVDR, primarily surrounding manufacturing, they must still fulfill the technical quality requirements detailed in Annex I.

An important caveat is that the exemption of LDTs from most sections of the IVDR is only possible if no equivalent assay is available on the market that meets the target patient group's specific needs. One interpretation of this is that if CE-IVD marked diagnostics are available for a particular application, compliance with the entirety of IVDR is necessary for labs seeking to offer an equivalent LDT. The goal of this provision is to ensure that LDTs must meet the minimum safety and efficacy requirements of commercially available assays, and are used for their primary purpose of fulfilling unmet clinical needs. This has immediate implications for the clinical validation of cancer diagnostics, where several CE-IVD marked cancer-specific panels and assays are already commercially available, and could have implications for rare disease diagnosis and whole genome sequencing (WGS) in the future as more approved diagnostics are available on the market.

Finally, health institutions developing LDTs must fulfill several documentation requirements addressed by standard quality management systems, such as the maintenance of versioned SOPs, reagent and sample tracking, and the ongoing documentation of risks. Additionally, labs should have a system in place for the systematic collection and review of clinical experience with the test. This is meant to mirror the provisions for post-market surveillance for IVDs. When interpreted through the lens of a clinical NGS lab, systematic collection and review of clinical experience with the device could include regular reviews with clinicians, adverse event tracking, or feedback sessions to identify and address areas for improvement.

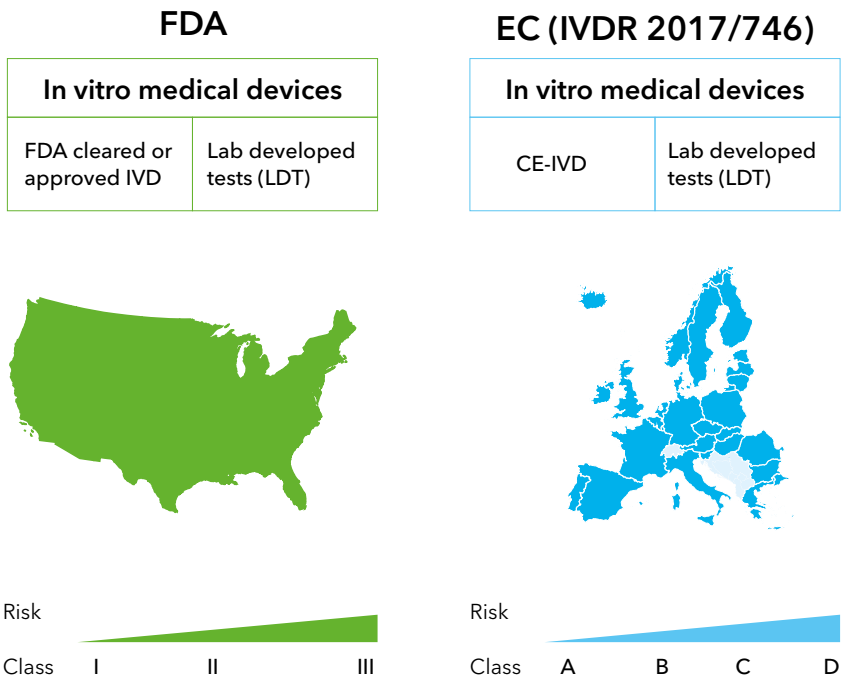

Figure 2. Comparison of IVD classification and risk categories in the US and Europe.

IN VITRO DIAGNOSTICS AND LAB DEVELOPED TESTS UNDER THE FDA

The FDA has purview over the approval of medical devices and clinical assays in the US. At the time of writing, examples of FDA-approved NGS software, assays, and sequencers are all available.

Depending on the intended application and associated risks, diagnostics are classified into one of three risk categories that dictate the controls necessary to ensure safety and effectiveness. The FDA maintains an exhaustive list of device classifications, and classification of new IVDs is usually grounded in prior precedent.

To date NGS assays are generally considered class II (moderate complexity and risk) or class III (high complexity and oversight) medical devices, although future assays could

conceivably have risk profiles that lead to class I designation.

The regulatory situation for LDTs in the US is complex. In a 2017 discussion paper the FDA clarified their stance, in which the FDA has held back on issuing final regulatory guidance for LDTs in favour of maintaining flexibility and applying focused oversight*. The FDA recognizes that the quality and validity of LDTs can vary significantly, and keeps broad oversight and regulatory options open for cases in which LDTs endanger patient safety, are not analytically valid, or the LDT developer has engaged in deceptive promotion, but has not gone so far as to issue a clear regulatory pathway, in contrast to the EC.

Many clinical NGS assays are not reviewed by the FDA, but are conducted as LDTs in labs compliant with the clinical laboratory improvement amendments (CLIA) or other quality standards issued by relevant professional societies. The 1988 CLIA regulations deliver standards for all clinical laboratories providing tests for the diagnosis, prevention, or treatment of disease, regardless of if they exclusively use FDA-approved diagnostics or if they develop custom assays. CLIA is jointly administered by the FDA (Food and Drug Administration), CMS (Center for Medicare and Medicaid Services), and CDC (Center for Disease Control), each of which provides different input into the program. CLIA sets standards for the operation of clinical labs and the provisioning of clinical assays, develops resources for proficiency testing, and conducts certification and audit activities.

While CLIA has historically offered a comprehensive mechanism for clinical labs to ensure the quality and validity of results, the addition of guidance for NGS-based tests is more recent. As an example, a strict interpretation of CLIA when determining the performance characteristics of an assay would require the analysis of a large number of samples to determine concordance

* See 2017 and 2018 FDA guidance documents, page 16.

The FDA has held back on issuing final regulatory guidance for LDTs in favour of maintaining flexibility and applying focused oversight.

and assay precision. While this is acceptable for a PCR-based test it quickly becomes financially untenable for NGS-based assays, particularly for high-depth applications like WGS or RNA-seq. Other challenges include the participation in both proficiency testing and inter-laboratory quality exchange programs and the existence of appropriate reference materials, neither of which are available for all clinical NGS applications. Despite some shortcomings, CLIA certification is a valuable mechanism for quality assurance in US-based labs, particularly when supported by more technical guidelines on NGS-based diagnostics.

Individual states may additionally require that labs offering LDTs are approved by a specific third-party organization/body. For example, clinical NGS labs located within or accepting specimens from New York are subject to third-party review by the NY State Department of Health's Clinical Laboratory Evaluation Program (NYSDOH CLEP). CLEP has developed standards for the provisioning of and for determining the validity of genetic tests, and offers in-depth technical guidelines for the development of NGS-based assays. Even for labs outside of the US, the CLEP technical guidelines on NGS assays can serve as valuable documents when validating new NGS assays.

Some clinical NGS labs do seek FDA approval for their assays, and recent pilot programs with the FDA have set precedents for regulatory pathways for NGS-based diagnostics. The FDA recognizes that the quality and validity of an LDT is highly dependent on the competencies of the lab that develops it, and leverages existing lab certification schemes in its approval processes. Examples of this include CLIA, as well as third-party premarket oversight, such as that provided through CLEP by the NYSDOH, which has recently been accredited by the FDA as a third-party reviewer. As a case study, consider the 2017 approval of the MSK-IMPACT test. The assay had been developed and put into clinical use as an LDT, and had been evaluated by the NYSDOH. The NYSDOH certification provided the groundwork for approval as a class II device through a *de novo* premarket review pathway*, similar to other recent class II and class III genetic tests.

* FDA. "Evaluation of automatic class III designation for MSK-IMPACT." 2017.

Resources: Regulatory Frameworks

Content	Title	Year
Regulation of IVD medical devices and LDTs in Europe	EU/EC Regulation 2017/746 on *in vitro* diagnostic medical devices (IVDR)	2017
FDA discussion on LDT regulation	Discussion Paper on Laboratory Developed Tests (LDTs)	2017
Regulation of Medical Devices in Europe	EU/EC Regulation 2017/745 on medical devices (MDR)	2007
FDA news release on new authorization path and links to further information	FDA Unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action	2017
Example FDA requirements for Class II device	FDA MSK-IMPACT Decision Summary	2017
FDA guidelines for NGS test development	Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases	2018
FDA recommendations for assertions supported by variant databases	Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics	2018
Clarification of CLIA structure and links to resources	CDC links of interest to CLIA regulated laboratories	Kept current
Interpretation of CLIA and recommendations for NGS assays	Assuring the Quality of Next-Generation Sequencing in Clinical Laboratory Practice	2012

INTERNATIONAL STANDARDS FOR QUALITY ASSURANCE

Various ISO standards regarding quality management, data security, and the development of medical devices are available that can promote quality when applied in a clinical NGS setting.

Examples of these can generally be applied to multiple settings or industries, and include broad standards for quality management, data quality, or cybersecurity. In addition to general quality management standards, some documents provide guidance specifically for clinical labs, IVD assay development, or other industry-specific guidance. Before applying any particular ISO standard, labs should thoroughly consider the value it provides and weigh this versus other tools available for ensuring quality.

This section provides overviews of two widespread ISO standards. ISO 9001 describes quality management systems and is broadly used in the healthcare industry. ISO 15189 more specifically addresses quality management in a medical laboratory setting, and compliance is required for labs offering LDTs under the IVDR. Other ISO standards for data quality, cyber security, and the manufacturing and development of diagnostics are not discussed in detail but do address specific organizational needs.

ISO 9001:2015

The ISO 9001 standard provides generalized requirements for a quality management system for organizations that need to conform to and provide services according to a set of regulatory or other applicable requirements. The standard is broadly worded and can be applied to many settings, and many hospitals or clinics within hospitals hold ISO

9001 certifications. The standard focuses on the implementation and maintenance of a quality-management system, which can then be adapted for NGS labs.

ISO 9001:2015 includes the following aspects:

- The mapping of and description of responsibilities within the organization
- The development of policies for the management and maintenance of quality
- Defining metrics and processes for the continued monitoring of quality
- A description of documentation, process, and traceability requirements
- A focus on information flow, awareness, communication, and mechanisms for supporting staff
- Guidelines on planning periodic reviews and quality audits
- Processes for handling nonconformity and exceptions

Many lab-developed traceability and quality management systems may already fulfill parts of ISO 9001, so full adoption for many clinical NGS labs would begin with exercises in mapping and reviewing existing policies. One key challenge for clinical sequencing labs adopting ISO 9001 is the broad nature of its recommendations: while the quality management system framework is well-defined, implementation depends to a great extent on the setting.

ISO 15189:2012

The ISO 15189 standard offers guidelines for the competencies and quality management systems necessary for medical laboratories to deliver technically valid results. In contrast to ISO 9001, the language in ISO 15189 is directed to medical laboratories specifically and, in addition to elements of quality management, focuses on the technical processes and requirements of providing medical tests. Some of the requirements in this standard are aligned with ISO 9001, making it easier for labs to comply with both guidelines.

Points under this standard include:

- Organization mapping, quality management, and document control systems (similar to ISO 9001)
- Guidance on the test provisioning process, including using or providing services for external

parties, identifying and correcting non-conformities, and the continuous monitoring and improvement of quality.

- Recommendations for the acceptance testing and control of reagents, consumables, and QC materials.

- Guidelines on sample acquisition, transport, testing, reporting, advising on clinical cases, and the handling of clinical samples and data.

ISO 15189 provides a valuable framework for labs offering clinical NGS services, as it addresses elements of both quality management and the practical provisioning of clinical tests in a medical setting. Additionally, ISO 15189 accreditation is a requirement under IVDR 2017/746, so is essential for labs within the EU that develop LDTs. Similar to ISO 9001, this standard is technology-agnostic and could be implemented in a variety of settings, where again a key challenge for labs will be in determining how to best implement it in concrete and specific terms.

Other ISO Standards

Various other ISO standards can be applied to clinical genetics. ISO 8000-8 describes standards for quantifying and describing data quality, and ISO 27000 details security management systems for data. For labs that choose to pursue EU or FDA approval for their diagnostics, ISO 13485 describes quality management systems applicable to medical device manufacturers, and ISO 23640 contains information on the assessment of reagent stability, an important aspect of assay development. When implementing an NGS pipeline in a clinical context, ISO 20428 and 25720 both describe data formats that can be used to integrate genetic data into patient records. Numerous other standards that could be applied to the development and implementation of clinical sequencing assays. While adherence to some of these documents is mandatory under certain regulations, these should be seen as a resource that can help labs design their systems in a documented and standardized way and not simply as a regulatory hurdle.

Resources: ISO Standards

Content	Title	Year
Requirements for quality management systems	ISO 9001:2015	2015
Requirements for quality and systems in medical laboratories	ISO 15189:2012	2012
Application of risk management to medical devices, including *in vitro* medical devices	ISO 14971:2007	2007
Standards for measuring information quality in the context of quality management	ISO 8000-8:2015	2015
Security management standards for data	ISO/IEC 27000:2018	2018
Stability evaluation of IVD reagents	ISO 23640:2011	2011
Requirements for quality management systems for medical device developers	ISO 13485:2016	2016
Data elements for describing sequence information in electronic health records	ISO/TS 20428:2017	2017
Description of Genomic Sequence Variation Markup Language	ISO 25720:2009	2009

TECHNICAL BEST PRACTICES FOR CLINICAL NGS

While broad-reaching ISO standards like 9001 or 15189 provide thorough descriptions of various aspects of data handling and quality management, it must be recognized that they lack technical depth, and at most can provide a framework for a system promoting quality.

To put the recommendations included in these standards into practice, various technical resources, best practices, and NGS-specific guidelines are needed. Additionally, as a relatively young and rapidly advancing field, it must be recognized that various de facto standards and widespread international best practices have emerged that are not reflected in ISO standards, but which provide a great deal more practical value when developing systems to promote quality in the lab.

A variety of technical guidance documents are available, reflecting the opinions of professional societies, individual research groups, and other organizations. When choosing specific documents to follow, labs should generally aim to implement guidelines that reflect the broad consensus of the field. As such, best practices issued by national or international professional societies are a valuable resource. Labs should also thoroughly evaluate whether guidelines are intended for the specific NGS application in question. Finally, as the field is rapidly evolving, guidelines are regularly updated, and labs should ensure that they have a process in place to remain current.

Below, we present a non-exhaustive list of literature that may be helpful when instituting quality systems or developing clinical assays for common therapeutic areas.

Resources: Best Practices

	Content	Title	Year
GA4GH	Resources for consent, ethics, and responsible data sharing	Global Alliance for Genomics and Health Regulatory and Ethics Toolkit	Kept current
GA4GH	Technical standards for integration and data formats	Global Alliance for Genomics and Health Genomics Data Toolkit	Kept current
GA4GH	Privacy and Security Infrastructure and Policy for Clinical NGS Data	Global Alliance for Genomics and Health Data Security Toolkit	Kept current
General	Benchmarking methodology	Best Practices for Benchmarking Germline Small Variant Calls in Human Genomes	2018
General	Checklist for clinical NGS testing	College of American Pathologists' Laboratory Standards for Next-Generation Sequencing Clinical Tests	2014
General	Guidelines for the validation of bioinformatics pipelines	Standards and Guidelines for Validating Next-Generation Sequencing Bioinformatics Pipelines: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists	2017
General	Broad Institute best practices for data analysis	GATK Best Practices	Kept current
General	GLP guidelines for bioinformatics pipelines	Good laboratory practice for clinical next-generation sequencing informatics pipelines	2015
General	Technical standards for integration and data formats	FHIR Release 3: Genomics Implementation Guidance	Kept current
General	Guidelines for using variant file formats	Principles and Recommendations for Standardizing the Use of the Next-Generation Sequencing Variant File in Clinical Settings	2017
NIPT	General considerations for NIPT/PGD, with focus on WGS and exomes	Joint Position Statement from the International Society of Prenatal Diagnosis (ISPD), the Society of Maternal Fetal Medicine (SMFM) and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis	2018

	Content	Title	Year
Rare Disease	Interpreting variants: focus on germline testing/constituent variants in heritable disease	Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology	2015
	Recommendations for reporting secondary findings	ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing	2013
	2016 Update to ACMG secondary findings list	Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics.	2017
	Guidelines for clinical NGS, focus on inherited disease and exome/WGS	ACMG clinical laboratory standards for next-generation sequencing	2013
Cancer	General LDT implementation, with a focus on somatic variant detection with gene panels	CLEP standards and NGS guidelines for somatic variant detection	Kept current
	Guidance on developing exome and amplification-based panels, focus on tumour assays	Guidelines for Validation of Next-Generation Sequencing- Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists	2017
	Interpreting variants: focus on somatic testing in the context of cancer diagnostics	Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists	2017
	Updated standards for clinical NGS and lung cancer	Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology	2018
	Standardized data elements for describing cancer variants	Somatic cancer variant curation and harmonization through consensus minimum variant level data.	2016

CONCLUSIONS

As a newly-emerging and rapidly changing field, the development and wide-spread adoption of NGS-based diagnostics in precision medicine faces several regulatory and quality assurance hurdles.

Regulations specifically addressing clinical genomics are recent, and both regulators and laboratories may be unaware of applicable frameworks. In the US, the FDA, CLIA, and various state-run programs regulate the development and manufacture of custom assays and IVD products, although the FDA has maintained a flexible stance on the regulation of LDTs. Europe is currently under transition to the 2017 IVDR, which is expected to normalize the regulation of *in vitro* diagnostics in the EU.

International standards pertaining to several aspects of the clinical NGS workflow exist, including ISO standards for quality management, data security, and the integration of data into existing hospital infrastructure. While compliance with ISO standards may be mandatory under certain regulations (for example, ISO 15189 will be mandatory for labs offering LDTs under the IVDR), the various standards that could be applied in a clinical setting should be viewed as tools for improving quality and patient safety, and not simply as regulatory hurdles.

While important, compliance with ISO standards is likely insufficient for clinical NGS labs to support adequate quality. Due to the breadth of therapeutic areas and the high complexity of NGS data, best practices documents issued and maintained by the ACMG, GA4GH,

AMP, ASCO, and numerous other professional organizations serve as a key resource when implementing and validating clinical pipelines. When combined with international standards for quality management, data security, and risk management and placed in the context of applicable regulatory frameworks, these continually developing technical resources provide the backbone of a solid quality management system.

We present here a tiered approach to quality in the clinical NGS setting, taking into account regulatory structures, international standards, and concrete, NGS-specific best practices. We hope that this document can serve to guide clinical NGS labs when implementing quality systems, and can instigate broader discussions on ensuring data quality, analytical validity, and minimizing risks to patients.

ABBREVATIONS

ACMG	American College of Medical Genetics
AMP	Association for Molecular Pathology
ASCO	American Society for Clinical Oncology
CDC	Center for Disease Control
CE	European Conformity
CLEP	Clinical Laboratory Evaluation Program
CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
EC	European Commission
FDA	Food and Drug Administration
GA4GH	Global Alliance for Genomic Health
IVD	*In Vitro* Diagnostic
IVDR	*In Vitro* Diagnostic Regulation (IVDR 2017/746)
LDT	Laboratory Developed Tests
MD	Medical Device
NGS	Next-Generation Sequencing
NYSDOH	New York State Department of Health
QMS	Quality Management System
RUO	Research Use Only
SOP	Standard Operating Procedure
WGS	Whole Genome Sequencing

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