ACCREDITATION SCHEME FOR LABORATORIES

TECHNICAL NOTES MED 002

Specific Criteria for Genomics and Genetics Testing

Technical Notes MED 002 – Genomics and Genetics Testing, 5 November 2025
The SAC Accreditation Programme is managed by Enterprise Singapore

TABLE OF CONTENTS

1 INTRODUCTION AND SCOPE

1.1 This document describes the specific requirements for clinical laboratories performing genetic and genomic testing

1.2 This document shall be read in conjunction with ISO 15189 Medical laboratories – Requirements for quality and competence, SAC-SINGLAS documents, Proficiency Testing Technical Note 001, other MEDICAL Series Technical Notes published by SAC-SINGLAS (such as Technical Note MED 001 General Criteria for Medical Testing Laboratories; and Technical Note MED 002 Specific Criteria for Molecular Pathology Section)

1.3 Laboratories shall also adhere to the local regulations in the area of genetics and genomics testing.

1.4 In this document, 'Genetic and Genomic Testing' refers to the analysis of nucleic acids (DNA and/or RNA) from patient samples or microbial cultures. Although sequencing-based technologies, such as capillary electrophoresis- and next-generation sequencing-based technologies (both short and long reads), comprise the main technologies under the scope of this Technical Note, other technologies that analyze sequence variation in a high-throughput manner, such as microarrays and optical genome mapping, may fall under the scope of this Technical Note.

1.5 Broadly, the clinical domains that fall under the scope of this Technical Note include infectious diseases, oncology, hereditary conditions/rare diseases, prenatal diagnostics, pharmacogenomics and histocompatibility and immunogenetics.

1.6 Infectious Diseases

1.6.1 Sequencing is used for the detection and characterisation of micro-organisms from primary specimens or cultures, including the following:

- Sequencing is used for the detection and characterisation of micro-organisms from primary specimens or cultures, including the following:
- Pathogen identification and characterisation
- Antimicrobial resistance determination
- Virulence factors
- Host response markers
- Clinical metagenomics
- Microbiome studies

1.7 Oncology

1.7.1 DNA and RNA sequencing of cancers for diagnostic, prognostic and therapeutic purposes is considered standard of care. There is increasing interest to apply next-generation sequencing technologies for cancer screening (i.e. early cancer detection) residual/minimal disease detection, disease monitoring (e.g. post-treatment), and evaluating genetic predisposition.

1.8 Hereditary conditions/rare diseases

1.8.1 Hereditary conditions, also known as inherited diseases or genetic disorders, are caused by changes in the genetic material or DNA (i.e. germline mutations). These diseases are transmitted from the parents to their children and can be passed on from generation to generation. Genetic testing approaches including next-generation sequencing have provided insight into the molecular etiology of genetic disorders.

1.9 Prenatal diagnostics

1.9.1 Prenatal diagnostics refers to a set of tests that are carried out during pregnancy in order to monitor the formation and development of the foetus. Prenatal screening tests done using foetal DNA can be used to identify if the fetus has certain birth

defects, many of which are genetic disorders. The application of next-generation sequencing has improved diagnostic yield in fetuses with abnormal ultrasounds.

1.10 Pharmacogenomics

1.10.1 Pharmacogenomics refers to the analysis of sequence variation of genes that either is predictive of an adverse drug reaction in an individual, or that suggest the need for dosage alteration so as to increase efficacy or reduce side-effects.

1.11 Histocompatibility and immunogenetics

1.11.1 Histocompatibility and immunogenetics refers to the study of the human leukocyte antigen system primarily for the matching of organ and hematopoietic stem cell transplants.

2 DEFINITIONS

2.1 Germline variants

An alteration in DNA that is present within the germ cells (sperm or egg). Such a variant is usually also found in all other cells. A germline variant may be passed on to the next generation (i.e. heritable).

2.2 Somatic variants

An alteration in DNA that occurs after conception and is not present within the germ cells (sperm or egg). A somatic variant cannot be passed on to the next generation (i.e. non-heritable).

2.3 Gene panels

A curated set of genes relevant to a particular phenotype, disease condition and/or testing indication. Exome- or genome-based panels, where the entire exome or genome is sequenced, but only indication-relevant genes are analysed, fall under this category of gene panels.

2.4 Exome sequencing (also referred to as whole-exome sequencing)

The analysis of coding regions of the human genome.

2.5 Genome sequencing (also referred to as whole-genome sequencing)

The analysis of the vast majority or entire genome. This is relevant to both human and microbial testing.

2.6 Transcriptome sequencing (also referred to as RNA-sequencing)

The analysis of complementary DNA (cDNA) that has been reverse-transcribed from RNA.

2.7 Cell-free DNA/RNA sequencing

The analysis of non-cellular DNA/RNA within a sample.

2.8 Clinical metagenomics

Both hypothesis-free, untargeted comprehensive analysis of microbial and host (human) genomic material, as well as targeted analysis where only specific regions (e.g. 16S) are analysed.

2.9 Microbiome

The analysis of a mixed population of microorganisms.

3 FACILITY AND ENVIRONMENTAL CONDITIONS

3.1 The laboratory shall ensure that facility and environmental conditions are suitable for the performance of genetic and genomic testing; in particular, with regard to the avoidance of amplicon contamination.

3.2 Should a distributive testing process be employed, the laboratory ought to have defined processes for selection and evaluation of referral laboratories. These are expected to fulfil requirements outlined in this document. Specimen traceability must be maintained throughout.

3.3 For laboratories performing clinical metagenomic testing, there shall be appropriate controls, as well as safeguards against cross contamination and environmental contamination.

4 REAGENTS AND CONSUMABLES

4.1 The laboratory shall ensure that each new lot/shipment of reagents is evaluated for performance before use in examinations or before release of results.

4.2 There shall be safeguards to prevent and/or minimize contamination from reagent sources, and where appropriate, limit contamination and prevent the reporting of low-level contaminants.

5 PRE-EXAMINATION PROCESS

5.1 Laboratories shall ensure that specimens meet the expected specimen collection and transport requirements (for example, volume/amount/type of specimen) as stated in the standard operating procedure.

5.2 The laboratory shall ensure compliance with prevailing national regulatory requirements in genomic testing.

5.3 Laboratories shall ensure that test request forms contain all relevant patient information including race/ethnicity and pedigree information if appropriate. For non-invasive prenatal testing (NIPT), information on gestational age at the time of specimen collection and other pregnancy-related information shall be provided if relevant.

5.4 Specimens shall be collected, handled and processed in a manner that prevents specimen contamination, tampering, loss or substitution/mix-ups.

5.5 The ordering clinician shall be promptly notified when a specimen is inadequate or if insufficient nucleic acid is obtained.

5.6 The laboratory shall store specimens appropriately prior to processing and testing to ensure successful extraction of analysable DNA and /or RNA from various specimen types. Repeated freeze-thaw cycles should be avoided.

5.7 The laboratory shall retain the original patient sample until all testing is completed and reported.

5.8 The laboratory shall retain specimens in compliance with applicable laws and regulations.

6 EXAMINATION PROCESSES: SPECIMEN PROCESSING FOR GENOMIC SEQUENCING

6.1 A written procedure providing adequate and precise information on the analytical wet bench process, reagents and methods used for generating NGS data must be available for each test.

6.1.1 Controls used should be adequately described, while validated specimen types should be specified.

6.1.2 If target enrichment is performed, the process and captured regions should be detailed.

6.1.3 For each step of the wet bench process – such as nucleic acid extraction, library preparation, and sequencing – laboratories shall define appropriate evaluation means, together with associated acceptance and rejection criteria.

6.2 Nucleic acid extraction and quantitation methods should be appropriate for intended clinical purpose and assay sensitivity.

6.2.1 For specimen types such as formalin-fixed paraffin-embedded (FFPE) tumour specimens and decalcified specimens, the laboratory should have written procedures to safeguard against erroneous reporting arising from sequence artefacts and/or suboptimal nucleic acid yield.

6.2.2 Solid Tumour Samples are to be reviewed by an appropriately trained and certified pathologist, with corresponding documentation of tumour cell fraction estimation. Haematological specimens may require inference from separate analyses.

6.2.3 The laboratory is required to document appropriate Quality Control (QC) checks of extracted nucleic acid to ensure, as appropriate:

a) Integrity (e.g. DNA profiling),
b) Purity (e.g. Absorbance Ratio),
c) Yield sufficiency (e.g. Fluorometric methods; spectrophotometric methods are not recommended for NGS).

The laboratory is required to document the appropriate QC checks based on the manufacturer's recommendation or validation.

6.3 For laboratories that perform barcoding/indexing and pooling of samples prior to sequencing, written procedures to ensure accuracy and traceability of sample barcoding/indexing must be available.

6.3.1 Care must be taken to avoid sample swap, and to maintain specimen traceability. Examples could include having specific molecular barcodes, and having an independent technician verify the process. Independent means of verifying sample identity with respect to barcode used (e.g. spiking or adding specific DNA fragments to input specimen, SNP control test, or genome-wide SNP arrays) are strongly recommended.

6.3.2 For multi-target panels, measures to ensure equal representation across samples should be employed.

6.4 Where the regions of interest are pre-defined, the laboratory shall have a written procedure to ensure that coverage of the pre-defined regions of interest is adequate (e.g. include usage of orthogonal methods such as Sanger sequencing). This should be accompanied by details on monitoring mechanisms, and resolution measure(s) in the event of inadequate coverage.

6.5 Controls, Metrics and QC parameters, as established during validation, should be used for NGS analytical wet bench process monitoring and quality assessment. These may include:

a) Expected fragment size distribution and minimum concentration of prepared NGS libraries;
b) Minimum cluster generation;
c) Minimal sequencing run quality criteria (reads per sample, read depth, base quality and error rates, in NGS instrument output).

6.6 Laboratories shall define, and demonstrate compliance to, a confirmatory testing policy. This should also encompass means to ensure maintenance of assay quality, and/or define resolution measures for discordant results.

6.7 Laboratories shall ensure that documentation of specimen and analytic process quality is available. These include troubleshooting and resolution of quality issues arising from wet bench procedures. Communication of relevant issues to the ordering physicians should also be documented, regardless whether testing is proceeded with.

6.8 Laboratories shall ensure methods, instruments and reagents used throughout the wet bench process are traceable and verified for acceptability prior to usage or before release of results. Policies for monitoring, implementing and documenting upgrades should be available.

7 EXAMINATION PROCESS: TEST DEVELOPMENT AND VALIDATION

7.1 Test Development: Technical Considerations

7.1.1 Laboratories shall identify the relevant sample types required for the purpose of the test. They shall also ensure that the nucleic acid is isolated by a suitable method (uniform within sample type), and that there is quality control i.e. purity, good yield and absence of RNA contamination of the extracted DNA.

7.1.2 For laboratories performing pooling of DNA samples, equimolar pooling is recommended to obtain equal quantities of sequence data between samples. Also refer to sections 6.3.2 and 9.2.3.

7.1.3 The test's intended clinical use must be clearly described in a written procedure.

a)

7.1.4 Laboratories shall define the assay's target region(s). Regions that do not meet required quality metrics should either be tested by defined (documented) alternative method(s), or not reported from, with this removal from reported target region clearly indicated by the laboratory.

7.2 Test Development: Data Processing and Analysis

7.2.1 Laboratories shall assess and determine the overall quality of platform performance that includes the sequence generation data quality metrics and minimal experimental thresholds for raw data to be processed.

7.2.2 Laboratories shall establish and document the analysis pipelines developed in-house or in combination with described methods in scientific literature in the following areas, where applicable.

a) Base calling and quality assessment of raw data
   - Overall quality of raw data which is platform dependent shall be evaluated.
b) Mapping to the human genome
   - Methods, mapping software and target shall be defined and validated.

c) Reportable Range
   - Detection limits and threshold settings shall be established.

d) Coverage analysis
   - Coverage (vertical) depth shall be established according to the following recommendations:
     - ≥ 30X for germline testing
     - ≥ 20% variant read
     - ≥ 1000X for heterozygous variants in tissue specimen of low tumour cellularity
     - ≥ 5000X for heteroplasmic variants from mtDNA

e) Variant calling, annotation and interpretation
   - Bioinformatics tools shall be assessed for ability to reliably detect clinically relevant variant types. Evaluation and the eventual usage of multiple variant callers to maximise detection of different variant types, is recommended. Laboratories shall use published guidelines for variant classification and interpretation.

7.3 Test Validation / Verification

7.3.1 Laboratories shall include validation procedures to confirm that the genomic assay fulfils the requirements for its specific intended use.

7.3.2 For laboratories performing end-to-end processes, validation procedures shall encompass the complete workflow that includes wet-laboratory steps and data analysis (bioinformatics) pipeline. As such, these are to be conducted only upon completion of design, development, optimisation and familiarisation of included components. Validation may also be for specific aspect of the workflow, for example bioinformatics pipeline only.

7.3.3 It is the laboratory's responsibility for validation and QC checks regardless if the tests are performed by the laboratory as an end-to-end process or sends out a portion of the testing process.

7.3.4 For laboratories that engage external service providers for wet lab processing, they remain responsible for the selection of, and assurance of data quality from, these providers.

7.3.5 Validation procedures shall include the following:

a) Definition of the type of samples and the number of cases that have to be assayed: these are to include and be representative of those tested by clinical assay;
b) Analysis of only good quality samples (per pre-defined criteria during test development);
c) Accurate description(s) of all NGS quality metrics used in the diagnostics procedure
d) Monitoring of run-specific and analysis / sample-specific features including quality measures for the platform, all assays and all samples processed
e) Means of sample identification and tracing (e.g. sample tracking and installation of barcoding, for laboratories conducting pooled sample analyses)
f) Establishment of workflow accuracy and precision. These should be part of the general platform validation; work does not have to be repeated for individual methods or tests
g) Evaluation of target genomic regions known or expected to cause errors in bioinformatic approaches e.g. pseudogenes, segmental duplication
h) Tailoring of bioinformatics pipeline for the technical platform used
i) Establishment of analytical performance matrix such as analytical sensitivity and specificity, reproducibility and repeatability. These are to be determined

separately for each type of variant (i.e. SNV, indel, CNV) during pipeline validation:

- large panel or genome-wide NGS assays shall include ≥ 60 positive variants of relevance and all variant types that are covered and reportable by the assay or deemed relevant by the laboratory.
- use well-characterised samples for which consensus variants are known
- establish minimum read depth required for a desired sensitivity

j) Implementation / usage of a structured database for all relevant variants with current annotations

k) For targeted panel, a defined 'reportable range' i.e. portion of clinical target for which reliable calls can be generated during test development, and this must be made available to the clinician

l) Checking of quality parameters and re-running samples when major changes are made

m) Defined steps taken towards long-term storage of all relevant data sets

7.4 Validation of genomic testing for rare, esoteric and/or unique identifying variants may be justified through the utility of an otherwise unmodified validated workflow, per a methods-based paradigm. Nevertheless, a representative target-positive specimen should be included with each clinical run, to guard against false-negativity.

7.5 Laboratories shall re-validate / verify if a previously-validated assay is modified; this should be appropriate to the extent of modification and documented. The type of samples and the number of cases that have to be assayed should be defined. Modifications include, but not limited to, the following:

- changes in chemistry and enrichment protocols
- adding gene to a previously validated panel
- changing version or updating any part of the bioinformatics pipeline tool
- assessing the in-house performance of a validated in vitro diagnostic medical device
- confirming that an assay meets defined quality metrics after minor test alteration
- change in reagent or consumables

8 EXAMINATION PROCESSES: DATA ANALYSIS (BIOINFORMATICS)

8.1 A written procedure providing adequate and precise information on the entire post-analytical data processing and analysis, including software type, infrastructure, quality checks and acceptance criteria, must be available for each test. Means of method traceability, including software version(s) used, must be accessible.

8.1.1 Analysis pipelines used must be detailed. Data flow and processing through these should be accessible to ensure transparency. Means of monitoring and tracking issues must be available.

8.1.2 Software version control must be present and tightly regulated. Changes, together with means of monitoring updates, must be documented, with appropriate validation of analysis reproducibility.

8.1.3 It is recommended to review the entire analysis workflow at least biennially. Otherwise, frequency of review and/or updates must be defined by the laboratory,

with justification. Documentation of these occurrences, including impact analysis (and corrective action(s) if applicable), are to be available.

8.2 Laboratories shall assess the overall run and sample quality according to quality metrics established during validation. These may include:

a) Total reads per sample
b) Fraction of bases/reads meeting specified quality thresholds,
c) % reads mapping/aligning to target region;
d) Average coverage per base and target region

8.3 Quality thresholds per metric, together with instructions on handling suboptimal results (e.g. flag for additional review/repeat from library preparation), should be available and documented.

8.4 Laboratories shall ensure the preservation and accuracy of specimen identity throughout each step of the Bioinformatics Pipeline analysis.

8.5 Bioinformatics tools used for variant calling, annotation and interpretation are to be periodically assessed for reliable detection of clinically relevant variant types. Published guidelines should be used for variant classification and interpretation.

8.6 Laboratories should include means of ensuring integrity of data files generated through the bioinformatics pipeline(s) employed.

9 POST-EXAMINATION PROCESSES

9.1 Reporting of Results

9.1.1 The laboratory shall have written procedures for result reporting, including the reporting of secondary or incidental genetic findings if applicable.

9.1.2 The laboratory shall refer and adhere to consensus guidelines for variant nomenclature and interpretation. Documentation of changes to software-generated annotations or nomenclature must be available and maintained.

9.1.3 Assay limitations should be identified and clearly indicated within the reporting workflow.

9.1.4 Laboratories shall follow the general principles of clinical genetic reporting that are in line with international diagnostic standards.

9.1.5 Laboratories shall include the following in the clinical report, as applicable:

a) Description of identified mutations according to the HGVS or prevailing international consensus nomenclature;
b) Genome build, version number and/or LRG sequence;
c) Reference sequence and genomic coordinates;
d) Test characteristics that includes technical and analytical test information;
e) Approach to acquiring sequencing data i.e. inheritance analysis model such as trio analysis for de novo mutations or specific analysis for autosomal or recessive inheritance;
f) Types of variants detected e.g. SNVs, indels, CNVs;
g) Variant of uncertain significance (VUS), as per laboratory reporting policy, limited to all relevant VUS or very strong candidate variants that suggest / predict functional impairment and warrant further testing in the family;
h) Whether pathogenic variants were confirmed by another independent method limitations in test performance and analysis that are both approach and pipeline-related.
i) Limitations in test performance and analysis

j) References

Information on regions and/or variants that do not meet satisfactory QC criteria should be available.

9.1.6 Laboratories shall define and disseminate policies regarding identification and reporting of incidental and secondary findings.

9.2 Data handling, storage and transfer

9.2.1 Laboratories shall establish and define the length of time of data storage in the various formats (such as, but not limited to, FASTQ, BAM/CRAM and VCF); recommendations are as follows:

a) FASTQ: ≥ 1 year
b) BAM/CRAM: ≥ 1 year
c) VCF: ≥ 2 years or unlimited time

9.2.2 Documentation of the method(s) through which the storage files were generated, together with relevant data statistics, should be available.

9.2.3 Laboratories shall ensure the confidentiality and accuracy of stored and/or transferred patient and genomic data, including during interim processes.

9.2.4 Laboratories are encouraged to create reference databases for the submission of identified and validated variants for diagnostic laboratory use.

9.2.5 Laboratories are to adhere to prevailing cybersecurity and data privacy requirements of local legislations and/or guidelines.

10 ENSURING THE VALIDITY OF EXAMINATION RESULTS

10.1 External Quality Assessment

10.1.1 The laboratory shall participate in an external quality assessment programme or proficiency testing programme appropriate to the examination. Where proficiency testing is not available, performance assessment must be conducted at suitable intervals as defined by the laboratory by appropriate procedures that may include split-sample analysis with other laboratories.

10.2 Material Control

10.2.1 Laboratories shall have processes to ascertain acceptability of reagents prior to usage or before release or results and ensure usage only of acceptable reagents.

10.2.2 For software updates, laboratories shall ensure version control and conduct appropriate impact assessment.

10.2.3 For laboratories that conduct sample pooling, means of sample identity confirmation must be evaluated for accuracy. This may include methods that check sample identity with respect to barcode used and the original patient DNA stock.

10.3 Process Control

10.3.1 Laboratories shall include procedures to identify process failures and errors, such as defining relevant control materials and/or reagents, quality control stops, and quality monitoring.

10.3.2 Laboratories shall include procedures to detect and prevent contamination. These could include usage of No Template Controls from the point of library preparation through to sequencing, and/or bioinformatics analysis to monitor low-frequency variants in inherited disease testing.

10.3.3 Relevant procedures should be employed to ensure maintenance of validated lower limit of detection.

10.3.4 Bioinformatics software versions are to be tracked and monitored for updates.

10.4 Quality Monitoring

10.4.1 Laboratories shall maintain an exception log or record for documentation of processes that deviate from established procedures

10.4.2 Entries shall include linkage to affected specimen(s), reason for the deviation, and corrective and/or preventive actions (if applicable).

10.4.3 Exception logs are to be reviewed periodically by the laboratory director or designee.

10.4.4 Defined Quality Metrics are to be reviewed periodically by the laboratory director or designee

References:

1 Aziz, N., Zhao, Q., Bry, L., Driscoll, D. K., Funke, B., Gibson, J. S., Grody, W. W., Hegde, M. R., Hoeltge, G. A., Leonard, D. G., Merker, J. D., Nagarajan, R., Palicki, L. A., Robetorye, R. S., Schrijver, I., Weck, K. E., & Voelkerding, K. V. (2015). College of American Pathologists' laboratory standards for next-generation sequencing clinical tests. Archives of pathology & laboratory medicine, 139(4), 481–493. https://doi.org/10.5858/arpa.2014-0250-CP

2 Boycott K, Hartley T, Adam S, Bernier F, Chong K, Fernandez BA, Friedman JM, Geraghty MT, Hume S, Knoppers BM, Laberge AM, Majewski J, Mendoza-Londono R, Meyn MS, Michaud JL, Nelson TN, Richer J, Sadikovic B, Skidmore DL, Stockley T, TaylorS, van Karnebeek C, Zawati MH, Lauzon J, Armour CM. 2015. The clinical application of genome-wide sequencing for monogenic disease in Canada: position statement of the Canadian College of Medical Geneticists. J Med Genet 52:431-37.

3 Deans Z, Watson CM, Charlton R, Ellard S, Wallis Y, Mattocks C, Abbs S. 2015. Practice guidelines for targeted next generation sequencing analysis and interpretation. Association for Clinical Genetics Science: 1 – 13

4 Gargis, A. S., Kalman, L., Bick, D. P., da Silva, C., Dimmock, D. P., Funke, B. H., Gowrisankar, S., Hegde, M. R., Kulkarni, S., Mason, C. E., Nagarajan, R., Voelkerding, K. V., Worthey, E. A., Aziz, N., Barnes, J., Bennett, S. F., Bisht, H., Church, D. M., Dimitrova, Z., Gargis, S. R., … Lubin, I. M. (2015). Good laboratory practice for clinical next-generation sequencing informatics pipelines. Nature biotechnology, 33(7), 689–693. https://doi.org/10.1038/nbt.3237

5 Hume, S., Nelson, T.N., Speevak, M., McCready, E., Agatep, R., Feilotter, H., Parboosingh, J., Stavropoulos, D., Taylor, S., Stockley, T.L. (2019). CCMG practice guidelines: laboratory guidelines for next-generation sequencing. J Med Genet 56:792-800.

6 Hutchins RJ, Phan KLSaboor A, Miller JD, Muehlenbachs A. 2019. Practical Guidance to Implementing Quality Management Systems in Public Health Laboratories Performing Next-Generation Sequencing: Personnel, Equipment, and Process Management (Phase 1). J Clin Microbiol 57:10.1128/jcm.00261-19.https://doi.org/10.1128/jcm.00261-19

7 Jennings LJ, Arcila ME, Corless C, Kamel-Reid S, Lubin IM, Pfeifer J, Temple-Smolkin RL, Voelkerding KV, Nikiforova MN. 2017. 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. J Mol Diagn 19(3):341-65.

8 Kim, J., Park, W. Y., Kim, N. K. D., Jang, S. J., Chun, S. M., Sung, C. O., Choi, J., Ko, Y. H., Choi, Y. L., Shim, H. S., Won, J. K., The Molecular Pathology Study Group of Korean Society of Pathologists (2017). Good Laboratory Standards for Clinical Next-Generation Sequencing Cancer Panel Tests. Journal of Pathology and Translational Medicine, 51(3), 191–204.

9 Matthijs, G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, Race V, Sistermans E, Sturm M, Weiss H, Bakker E, Scheffer H, Bauer P. 2016. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016 Jan;24(1):2-5. doi:10.1038/ejhg.2015.226. Epub 2015 Oct 28.

10 New York State Department of Health. “Next Generation” Sequencing (NGS) guidelines for somatic genetic variant detection. Available online: https://www.wadsworth.org/sites/default/files/WebDoc/NextGenSeqONCOGuidelines%20_April_2021.pdf (accessed on 06 October 2024).

11 Rehder, C., Bean, L.J.H., Bick, D., Chao, E., Chung, W., Das, S., O’Daniel, J., Rehm, H., Shashi, V., Vincent, L.M. (2021). Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 23(8), 1399-1415. https://doi.org/10.1038/s41436-021-01139-4.

12 Roy, S., Coldren, C., Karunamurthy, A., Kip, N. S., Klee, E. W., Lincoln, S. E., Leon, A., Pullambhatla, M., Temple-Smolkin, R. L., Voelkerding, K. V., Wang, C., & Carter, A. B. (2018). Standards and Guidelines for Validating Next-Generation Sequencing Bioinformatics Pipelines: A Joint Recommendation of the Association for Molecular Pathology and the College of American Pathologists. The Journal of molecular diagnostics : JMD, 20(1), 4–27. https://doi.org/10.1016/j.jmoldx.2017.11.003

13 Santani A, Simen BB, Briggs M, Lebo M, Merker JD, Nikiforova M, Vasalos P, Voelkerding K, Pfeiffer J, Funke B. 2019. Designing and implementing NGS tests for inherited disorders - A practical framework with step-by-step guidance for clinical laboratories. J Mol Diagn 21(3):369-374

14 Souche E, Beltran S, Brosens E, Belmont JW, Fossum M, Riess O, Gilissen C, Ardeshirdavani A, Houge G, van Gijn M, Clayton-Smith J, Synofzik M, de Leeuw N, Deans ZC, Dincer Y, Eck SH, van der Crabben S, Balasubrmanian M, Graessner H, Sturm M, Firth H, Ferlini A, Nabbout R, De Baere E, Liehr T, Macek M, Matthijs G, Scheffer H, Bauer P, Yntema HG, Weiss MM. 2022. Recommendations for whole genome sequencing in diagnostics for rare diseases. Eur J Hum Genet. 2022 Sep;30(9):1017-1021. doi: 10.1038/s41431-022-01113-x. Epub 2022 May 16.

15 Weiss, M.M., Van der Zwaag, B., Jongbloed, J.D., Vogel, M.J., Brüggenwirth, H.T., Lekanne Deprez, R.H., Mook, O., Ruivenkamp, C.A., van Slegtenhorst, M.A., van den Wijngaard, A., Waisfisz, Q., Nelen, M.R., van der Stoep, N. (2013). Best practice guidelines for the use of next-generation sequencing applications in genome diagnostics: a national collaborative study of Dutch genome diagnostic laboratories. Hum Mutat. Oct;34(10):1313-21. doi: 10.1002/humu.22368. Epub 2013 Aug 19.