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Guideline for the Accreditation of Laboratories carrying out Genetic Testing using Next Generation Sequencing (NGS) Techniques

PURPOSE

This document is intended for National Accreditation Bodies (NABs) that assess laboratories carrying out genetic testing using NGS techniques, including whole genome sequencing (WGS). This document is applicable to all types of testing and medical laboratories so, accreditation may be to EN ISO 15189:2022 “Medical laboratories - Requirements for quality and competence” or EN ISO/IEC 17025: 2017 “General requirements for the competence of testing and calibration laboratories”. It aims to provide guidelines to NABs on how to approach the assessment of such laboratories in a harmonized way. Furthermore, the document aims to provide to NAB’s guidelines regarding the possible issues, which are critical in the assessment of the competency of the laboratories. These key aspects include topics, such as, when a (critical) part of the technique is externally provided/referred to on a permanent basis, the assessment of bioinformatics associated with these techniques, the assessment of the IT systems/storage of data, the competence of personnel, the reporting of results and the use of genetic (medical) data bases not belonging to the accredited organisation/ conformity assessment body

Authorship

The publication has been prepared by EA Laboratory Committee working group on Healthcare – Laboratory Medicine.

Official language

The text may be translated into other languages as required. The English language version remains the definitive version.

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CONTENTS

1 INTRODUCTION

This document provides guidelines to help NABs with the harmonization of the assessment of laboratories that perform testing or examinations using NGS techniques.

CABs shall meet all the requirements of EN ISO 15189 or EN ISO/IEC 17025; this document provides specific guidance on how those requirements may be met in the context of NGS services. It does not reproduce all requirements of the applicable ISO standard.

In many cases, these laboratories may use external service providers to carry out parts of the examination/testing pathway. These external service providers often belong to a different legal entity and may or may not be accredited for these activities.

The interaction between, and combination of, wet and dry lab activities must be considered when performing assessments in this field of testing since, both parts are critical and tightly linked in any successful NGS workflow. In addition, the use of reference data from databases not directly under the control of the accredited laboratory is an additional risk to consider during assessments.

This guidance document refers to the assessment of medical or testing laboratories that receive samples for testing or examination and they are responsible for carrying out genetic testing using NGS technique and for ensuring conformity to EN ISO 15189 or EN ISO/IEC 17025, respectively. A laboratory only performing wet laboratory activities shall be accredited for its activities to EN ISO 15189 or EN ISO/IEC 17025.

NABs should develop their own policy regarding accreditation of stand-alone “dry” laboratories. “Dry” laboratories will receive input from “wet laboratories” and might report results directly to laboratory users, or might return bioinformatics data to the ‘wet’ laboratory for interpretation and reporting. In either scenario, dry lab activities are a key part of the testing pathway. This activity shall be accredited to EN ISO/IEC 17025 or EN ISO 15189 (if the laboratory fulfils the requirements of the medical laboratory).

2 TERMS AND DEFINITIONS

Next Generation Sequencing (NGS): next generation sequencing (NGS) massively parallel nucleotide sequencing high throughput nucleotide sequencing method capable of determining multiple DNA sequences simultaneously and in parallel.
Note 1 to entry: The data from a single massively parallel sequencing analysis comprises of millions of sequences and the output is a file containing all sequence (ISO 24480:2024 , clause 3.16).

Bioinformatics pipeline: individual programs, scripts, or pieces of software linked together, where raw data or output from one program is used as input for the next step in data processing.
Example: The output from a base quality trimming program may be used as input to a de-novo assembler (ISO 20397-2:2021, clause 3.4 / ISO 23418:2022, clause 3.7).

Scope of accreditation: specific conformity assessment activities for which accreditation is sought or has been granted (EN ISO/IEC 17011:2017 clause 3.6).

Examination: set of operations having the objective of determining the numerical value, text value or characteristics of a property (ISO 15189:2022 clause 3.8).

Note 1: An examination may be the total of a number of activities, observations or measurements required to determine a value or characteristic.

Note 2: Laboratory examinations that determine a numerical value of a property are called "quantitative examinations"; those that determine the characteristics of a property are called "qualitative examinations".

Note 3: Laboratory examinations are also called "assays" or "tests".

Method/procedure: can be considered synonymous with the term “measurement procedure” as defined in ISO/IEC Guide 99.

Commercial procedure: procedure specified in the instructions for use of in vitro diagnosis medical devices (IVD-MD).

Published procedure: procedure that has been published in established/authoritative textbooks, peer-reviewed texts or journals, or in international consensus standards or guidelines, or national or regional regulations.

In-house method: laboratory-developed method

Test kit or testing kit: set of chemicals, materials and instructions for use, packaged together and intended for use as specified by the manufacturer of the kit (ISO 16577:2022, clause 3.3.80). In the document the term test kit is used.

Ref. XX, YY, ZZ, PPYY, PPZZ, IHM01: The reference of the method/procedure/instruction/ SOP(Standard Operating Procedure)/test kit can be any unique combination of letters and/or numbers.

Laboratory: The definitions for laboratory in EN ISO 15189: 2022 (clause 3.20) or EN ISO/IEC 17025:2017 (clause 3.6) apply. When the term laboratory is used in this document it refers to the entity that receives a sample for testing or examination and they are responsible for carrying out genetic testing using NGS technique and for ensuring conformity to EN ISO 15189 or EN ISO/IEC 17025. It applies the same when the term laboratories is used in this document.

External Service Provider: can perform part of the NGS testing pathway which the laboratory cannot perform.

The laboratory shall only be accredited for the range of laboratory activities it provides, which excludes externally provided laboratory activities on an ongoing basis.

In this document the term External Service Provider will be used to refer to both Standards.

Note 1: In the EN ISO/IEC 17025:2017 context an external service provider can provide testing services. In the context of EN ISO 15189:2022 (clause 3.27) services, also, include referral laboratories which is one to which laboratory management chooses to submit a sample or sub sample for examination, data for analysis or interpretation, or when routine examinations cannot be carried out.

Sample: A primary sample intended for an examination, as per EN ISO 15189:2022 (clause 3.25) definition and/or of test item for subsequent testing as referred in ISO/IEC 17025:2017. In the context of this document when the term sample is used, it refers to the primary sample or the test item received by the laboratory that is responsible for carrying out genetic testing using NGS technique and for ensuring conformity to EN ISO 15189 or EN ISO/IEC 17025.

“Wet” laboratory work: In a wet lab, testing and analyses are performed using physical samples, chemicals and liquids. Biological samples, drugs and fluids are all tested in a wet lab. In other words, “wet” materials are tested. In the field of NGS, a wet lab carries out part of the workflow where physical handling of biological samples and reagents is involved, including e.g., isolation and quantification of DNA/RNA, library preparation, template preparation and sequencing run.

“Dry” laboratory work: A dry lab is a type of laboratory that involves applied or computational mathematical analyses for a wide array of different applications. These analyses are completed on a computer-generated model, which means that computers and similar types of electronics are the main forms of equipment that are used in a dry lab. In the field of NGS, a dry lab carries out the data processing and bioinformatics (in silico analysis) in order to produce interpretable results from raw sequencing data (created by a wet lab), including e.g. base and/or variant calling, alignment to a reference sequence, gene expression analysis, metagenomic profiling.

3 ACCREDITATION CRITERIA

The accreditation criteria for laboratories performing NGS are:

- Standard EN ISO 15189, Medical laboratories. Requirements for quality and competence Or
- Standard EN ISO/IEC 17025, General requirements for the competence of testing and calibration laboratories

4 ORGANISATION/LEGAL ENTITY

The NAB assesses and accredits the legal entity, which takes responsibility for the delivery of NGS service and for ensuring conformity to EN ISO 15189 or EN ISO/IEC 17025. Some laboratories will carry out all end-to-end NGS activities. In other cases, laboratories will use externally provided parts of the NGS examinations. This external provider can belong to different legal entity and operate under different management system. In these cases, the requirements and responsibilities of parties should be clearly defined. The responsibilities need to be documented to ensure that it is clear which activities are performed by each party. The laboratory is responsible that all activities are carried out to meet the requirements but, will not be accredited for the parts of the NGS activity undertaken by an external service provider

5 ROLES AND RESPONSIBILITIES

5.1 Management System

The laboratory shall define its relationships with any external service provider. It shall ensure that externally provided laboratory activities performed by another legal entity meet its quality/accreditation requirements through negotiated agreements.

5.2 Personnel

The laboratory should define the competence requirements and qualifications for all activities, ‘wet’ and ‘dry’.

When part of the NGS activities is externally provided (i.e.bioinformatics), the laboratory shall ensure that the external provider has processes in place to assess that there are sufficient, competent personnel to perform the externally provided activities.

When part of the NGS activity is externally provided, the laboratory should ensure that its own personnel has sufficient knowledge and competence to understand and evaluate the externally provided activity.

5.3 Externally provided services

The laboratory shall ensure that, where possible, accredited externally provided laboratory activities are used when part of the NGS examination is externally provided. This shall be done by defining and documenting the criteria for selection of external provider through contractual arrangements or service agreements. A risk-based approach of the NGS process shall be used to define the criteria for the selection, evaluation and approval of externally provided services’ laboratories.

Arrangements or service agreements should include but, not limited to:

1. Accreditation requirements (EN ISO 15189 or EN ISO/IEC 17025) to confirm the continuous accreditation of the externally provided activity and the obligation for the external provider to keep the laboratory informed of any changes in the accreditation status.
2. The identification of the externally provided activity.
3. Confidentiality agreement between the parties to ensure that confidentiality of information is maintained.
4. Details of the lines of communication between the laboratory and the external provider, and the responsibilities of involved personnel.
5. Confirmation that the external provider has processes in place to ensure and monitor the competence of its personnel involved in the is externally provided activity.
6. When any part of the testing/examination pathway is externally provided then, the external provider shall confirm to the laboratory that the externally provided activity/pipeline (i.e bioinformatics pipeline) has been validated/verified to meet the laboratory's requirements. When changes are made or intended to be made in any activity/pipeline (i.e. bioinformatics pipeline), the external provider shall inform the laboratory and to have processes in place to perform re-validation/re-verification, and confirm to the laboratory that this has been completed and the activity/pipeline remains fit for purpose. It should also be ensured that data are available with respect to the performance characteristics of the activity (e.g. sensitivity, specificity, measurement uncertainty, limitations) and any other information required for incorporation into the report."
7. Confirmation the external provider has access to facilities, equipment, reagents and consumables that are required for the correct performance of the externally provided activity that can influence the validity of results. This should include appropriate maintenance and service of equipment.
8. The expected turnaround times of the externally provided activity. These shall reflect clinical needs, when appropriate.
9. The procedures that the external provider has in place to review and evaluate its quality control strategy and results to ensure that the requirements are met.
10. Definition of the responsibilities for the reporting of the results of the externally provided activity, including details of whom and when the external provider should inform of critical results.
11. Definition of the processes that the external provider has in place for ensuring the accuracy/completeness of the results provided to the laboratory. The laboratory is responsible for ensuring that the results from the external provider are transcribed accurately and completely into the final test report.
12. The transport conditions and requirements for the samples.
13. Agreed data security and protection details, including patient confidentiality, for covering data transfer between organisations, and data storage/use by the external provider.

14. When the external provider does not hold accreditation for the externally provided activity, the arrangements or service agreements shall include mechanisms to ensure the external provider is competent to deliver valid results with regard to the externally provided activity. These mechanisms may include review of quality assurance processes and results, validation/verification reports, training/competency records, internal audits, user feedback, and/or reports by any relevant external body.

5.4 Examination methods

The laboratory shall document performance characteristics for the testing/examination pathway.

If any part of the NGS testing/examination pathway has been developed in-house (i.e bioinformatics, DNA extraction method), full validation is required. If the pathway used is a commercially available, the laboratory is required to verify that it meets its needs, based on defined performance criteria.

Any changes made to any part of the analysis pathway, shall be validated / verified before being introduced into routine use. All validations and verifications shall be documented and the record should be reviewed and approved by competent personnel.

Measurement uncertainty should be stated, when available. This measurement uncertainty should also include the bioinformatics pipeline, if possible, and any externally provided activity, when available or relevant.

5.5 Ensuring the validity of results

a. Internal quality control (IQC):

The IQC plan should cover the performance of each critical activity within the complete process of the analysis pathway from sample reception to reporting. This process should also include bioinformatic analysis and interpretation.

b. External Quality Assessments (EQA) / Proficiency Testing (PT)

The EQA/PT plan shall cover the whole NGS process including, where relevant, clinical interpretation of variants and reporting.

The materials/products, the analytes (or group of analytes) /parameters and/or the technique of the NGS process included in the Scope of Accreditation should be included in the EQA/PT plan and should be assessed at a defined frequency.

When parts of the NGS examination are externally provided then the laboratory should ensure the validity of the results of the externally provided activity through agreements or service agreements with the external provider, as mentioned in clause 5.3 of this document.

The frequency of EQA/PT participation should be based on a risk analysis.

5.6 IT Systems

Where data is stored outside of the laboratory, legal requirements and other arrangements and responsibilities shall be documented.

The laboratory shall ensure there is adequate data storage capacity available, including consideration for future capacity requirements. Capacity should be periodically checked for ongoing adequacy.

5.7 Reporting of Results

When parts of the technique are performed by an external service provider the laboratory shall follow the NAB's policy when making reference to accreditation so, to avoid instances where accreditation is implied or suggested for non-accredited activities reported by the laboratory that are not part of its Scope of Accreditation.

5.8 Risk-assessment

In order to prepare for the assessment the NAB should take a risk-based approach to cover the activities performed by the laboratory. This risk based approach should take into account factors in addition to the usual risks associated with accreditation processes and operation of NABs (see EA-2/19 INF:2022), that confirm that there are ongoing controls and effective implementation, for the following areas, but not limited to:

- Definition of responsibilities and communication channels between the laboratory and the external provider
- Confidentiality/ Impartiality
- Competence and training of personnel involved with the activities, competence of the laboratory on the full process and especially on the externally provided part
- The competence of the external service provider (selection, criteria, review and evaluation) as documented by the laboratory
- Method verification/ validation
- Maintenance, handling and suitability of equipment
- Quality assurance mechanisms
- Transport of samples between different sites, the transfer of data and communication between the different sites
- Storage and transfer of data
- Availability and adequacy of agreement or contractual arrangements to cover responsibilities, communication, competence, equipment, QC mechanisms, transport, storage/transfer of data, method verification/validation, confidentiality/impartiality related to the externally provided part

6 SCOPE OF ACCREDITATION

The NAB shall clearly define, in the Scope of Accreditation, the examinations and tests performed by the laboratory.

The technique used should be presented in terms of Extraction + Library prep + Sequencing + Bioinformatics.

When there is Flexible Scope of Accreditation the NAB shall define the level of flexibility concerned. For flexible Scope accreditation the requirements of EA 2/15: 2022 apply.

When there is a non-flexible Scope of accreditation then, the presentation of the Scope may additionally indicate the version of the kit used, the equipment (and supplier, if necessary) and the pipeline (including version code) for equipment and / or method and / or procedure references. For the bioinformatics software there should be indicated if its in-house or commercial and its latest version.

For medical laboratories, the requirements of EA 4/17 apply for Scope presentation.

If parts of the technique are performed by an external service provider then, the Scope shall include the parts of the technique that are performed by the laboratory. If a NAB chooses to include the externally performed parts in the Scope, it may define in its policy how this should be stated.

Note: In Annex are listed examples of Scope presentation.

7 COMPETENCE OF THE ASSESSMENT TEAM

The assessment team shall have appropriate experience in the field of NGS and should be able to evaluate the whole NGS workflow in the assessment process.

In the specific case of bioinformatics, if a commercial bioinformatics pipeline is used, an assessor with experience and competence in the use of bioinformatics pipelines should suffice. In cases when an in-house developed pipeline is used then the assessment team should include experts in the development and the management of bioinformatics pipelines.

Not every activity in the NGS pathway must be assessed every year. Any decision on which activities to assess must be risk-based. For example, a laboratory using a commercial bioinformatics pipeline with no changes might require a bioinformatics assessor to be part of the assessment team less frequently than a laboratory developing and managing in-house pipelines.

8 REFERENCES

Normative references

EN ISO/IEC 17011: 2017 “Conformity assessment — Requirements for accreditation bodies accrediting conformity assessment bodies”

EN ISO 15189:2022 “Medical laboratories — Requirements for quality and competence”

EN ISO/IEC 17025: 2017 “General requirements for the competence of testing and calibration laboratories”

ISO/IEC DIR 2:2016 - ISO/IEC Directives Part 2 Principles and rules for the structure and drafting of ISO and IEC documents.

EA 2/15: 2023 “EA requirements for the Accreditation of Flexible Scopes”

EA 4/17: 2022 ‘Description of scopes of accreditation for medical laboratories’

EA-3/01M:2021 ‘EA Conditions for the use of Accreditation Symbols, Logos and other claims of accreditation and reference to the EA MLA Signatory status’

9 ANNEX: SCOPE PRESENTATION

The examples of Scope Presentation provided below are to illustrate the presentation of a Scope of accreditation but, they are not intended to be the definitive approach for all NABs.

Each NAB's policy specifies whether the part of the examination performed by an external provider is presented. For this document the part of the examination performed by an external provider is not presented in the examples provided

Example 1 - Scope of accreditation

Scope presentation (established by the NAB)

Material and / or System and / or Matrix	Analyte and / or Parameter	Technique	Equipment and / or Method and / or Procedure reference	Location/site
Blood FFPE tissue Fresh tissue DNA	Detection and quantification of mutations/variants of nucleotides + pathology + list of genes	- type of extraction (manual versus automated) - Library prep - Type of sequencing - bio-informatics	IVD-MD instruction (Ref. XX including version code) + kit + equipment + supplier + pipeline (including version code + in-house versus commercial)	extraction + library prep + sequencing + bio-informatics
Material and / or System and / or Matrix	Analyte and / or Parameter	Technique	Equipment and / or Method and / or Procedure reference	Location/site
Blood FFPE tissue Fresh tissue DNA	Detection and quantification of mutations/variants of nucleotides + pathology + list of genes	- type of extraction (manual versus automated) - Library prep - Type of sequencing - bio-informatics	IVD-MD instruction (Ref. XX including version code) + kit + equipment + supplier + pipeline (including version code + in-house versus commercial)	extraction + library prep + sequencing + bio-informatics Or multisite Site 1: extraction + library prep + sequencing Site 2: bio-informatics

Example 2 - Flexible scope of accreditation

Scope presentation (established by the NAB)

Material and / or System and / or Matrix	Analyte and / or Parameter	Technique	Equipment and / or Method and / or Procedure reference	Location/site
Blood tissue DNA	Detection and quantification of mutations/variants of nucleotides + pathology (level to be determined by the NAB)	- type of extraction (manual versus automated) - Library prep - Type of sequencing - bio-informatics	Commercial methods / procedures, in-house methods	extraction + library prep + sequencing + bio-informatics Or multisite: Site 1 and Site 2 Site 1: extraction + library prep + sequencing Site 2: bio-informatics

The current detailed list of accredited activities/site is available from the laboratory

Example 3- Scope of Accreditation when part of the examination is externally provided i.e. bioinformatics

Scope presentation (established by the NAB)

Material and / or System and / or Matrix	Analyte and / or Parameter	Technique	Equipment and / or Method and / or Procedure reference	Location/site
Blood FFPE tissue Fresh tissue DNA	Detection and quantification of mutations/variants of nucleotides + pathology + list of genes	- type of extraction (manual versus automated) - Library prep - Type of sequencing	IVD-MD instruction (Ref. XX including version code) + kit + equipment + supplier + pipeline (including version code + in-house versus commercial)	extraction + library prep + sequencing

Example 4- Flexible Scope of Accreditation when part of the examination is externally provided i.e. bioinformatics

Scope presentation (established by the NAB)

Material and / or System and / or Matrix	Analyte and / or Parameter	Technique	Equipment and / or Method and / or Procedure reference	Location/site of the Laboratory
Blood tissue DNA	Detection and quantification of mutations/variants of nucleotides + pathology (level to be determined by the NAB)	- type of extraction (manual versus automated) - Library prep - Type of sequencing	Commercial methods / procedures, in-house methods	extraction + library prep + sequencing

The current detailed list of accredited activities is available from the laboratory