



**ORGANISATION FOR ECONOMIC  
CO-OPERATION AND DEVELOPMENT**

**DRAFT GUIDELINES FOR QUALITY ASSURANCE IN  
MOLECULAR GENETIC TESTING**

**2006**

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This version of the Guidelines is being released to elicit public comment. While the document reflects the discussions held at expert meetings and within the OECD Working Party on Biotechnology, it does not necessarily represent the views of the Working Party on Biotechnology or the member countries of the OECD.

## NOTE BY THE SECRETARIAT

This document provides a third revised version of the draft Guidelines for Quality Assurance in Molecular Genetic Testing first submitted to the OECD Working Party on Biotechnology (WPB) as document DSTI/STP/BIO(2005)23. Revisions to the document were made according to country comments and as recommended by the WPB at its meeting of 20-21 February 2006.

The structure of the guidelines is based on the approved elements outlined in the work plan for the project, and is reported in document DSTI/STP/BIO(2004)24. A first outline and coverage of the guidelines [DSTI/STP/BIO(2005)6] were discussed and approved by experts at their OECD steering meeting of 18-19 April 2005 [DSTI/STP/BIO/M(2005)1].

Two small drafting meetings (Manchester, 12 July 2005; Paris, 29 August 2005) were organised in 2005 to take forward the guidelines. A further expert meeting to discuss the chapter on Ensuring Quality in Molecular Genetic Test Result Reporting was hosted by the US-CDC in Washington on 19 September 2005. Complete drafts of the guidelines were further discussed by experts at their second OECD Steering Meeting in Rome, 19-20 October 2005 and at their third steering meeting held in Berlin, Germany on 29-31 January 2006.

The document is structured largely as it is intended to be published. The heart of the document is the Principles and Best Practices in "Part I", currently set out in five chapters. Prior to these Principles and Best Practices are short sections providing Background to the work and a Preface to the Principles and Best Practices. Part II of the document provides relevant background information to the Principles and Best Practices. These have been developed on the basis of discussions and recommendations at the Rome and Berlin OECD Steering Meetings. Part III will include a list of relevant references and documentation and Part IV a list of terms and abbreviations. Parts III has yet to be developed.

At its meeting of 23-24 March 2006, the Committee for Scientific, Technological Policy agreed to the proposal for a public consultation process of the present guidelines as described in document DSTI/STP/BIO(2006)12.

Pursuant to that decision, Delegates to the OECD Committee for Scientific and Technological Policy, to the Working Party on Biotechnology and its Working Group on Human Health-related Biotechnologies are invited to:

- **Agree and declassify** this document **according to written parallel procedure**. In the absence of comments **by 16 June 2006** both the WPB and the CSTP will be deemed to be in agreement with the document.

## BACKGROUND

1. Since the 1980's, the use of genetic testing as an aid in diagnosing disease and to predict future disease risk has grown steadily. Genetic testing is also just beginning to be used to inform prescribing of drug therapy based on individual genetic variation (pharmacogenetics). In 2006, testing is offered internationally, through both public and private sector genetic testing services, and there is evidence that human samples and related data are being exchanged across borders in an environment where regulatory and oversight procedures vary significantly between jurisdictions. This expanded use and "internationalisation" of genetic testing raises novel issues and is challenging the current regulatory frameworks governing genetic services.

2. In 2002, OECD's Working Party on Biotechnology decided to carry out a survey to document the availability and extent of molecular genetic testing throughout the OECD member countries. It also documented existing quality assurance practices in use in testing laboratories, including policies regarding the handling of samples and genetic data, and transborder flow of specimens. Eighteen OECD member countries (Austria, Belgium, Canada, the Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States) participated in this survey, which ran from June to October 2003. The results of the survey were published as "Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Summary Report of a Survey of 18 OECD Member Countries", OECD (2005).

3. The survey confirmed the steady growth of molecular genetic testing and its widespread availability. The survey also showed that laboratories in all countries use both formal and informal professional referral networks that exist either within or outside each country to send samples across borders. A number of mechanisms are in place in all OECD member countries to reduce risk from inappropriate and inaccurate testing and to assure the quality of molecular genetic testing procedures. Some countries have well established licensing, accreditation and certification procedures to provide regulation and oversight and to promote the quality of laboratories involved in medical testing.

4. However, these regulatory and oversight procedures have not penetrated diagnostic molecular genetic testing laboratories across OECD countries to a high degree and with any consistency. One reason for this is that most regulations with which laboratories must comply are not specifically designed for molecular genetic testing. Considerable differences exist in the use of licensing, certification, and accreditation procedures and this poses a number of challenges for molecular genetic testing, particularly with respect to the standards under which tests are performed and results are reported for clinical application, and the training and qualifications required by laboratory personnel.

5. Consequently, there is uncertainty about terminology and the choice of the most appropriate quality system. There is also a lack of understanding amongst the international community on the mutual acceptability of quality assurance systems. As laboratories increasingly provide their services to both national and international customers there is a need to develop international consensus and best practice to assure consistency in the quality of services available.

6. OECD member countries have thus agreed to develop these guidelines setting out principles and best practices for quality assurance in molecular genetic testing for clinical purposes in consultation with experts and interested parties. The Principles set out in these guidelines are recommendations for policy action (to be agreed by OECD Council) and are specifically directed to Governments and those involved in the regulation of genetic services. Best Practices are recommendations that aim to provide operational guidance in implementing the Principles and are directed to professional bodies and providers of molecular genetic testing services in developed and developing economies.

## PREFACE

7. Genetic tests may be highly predictive of the future health of the individual and can be carried out at any stage of life even in the embryo before implantation. They are relevant to healthy people as well as those showing symptoms of a condition and may have important implications for the relatives of the person tested. Given the rapid translation from research into clinical practice, research laboratories play a valuable role in service provision. The genotype established by a single laboratory test is usually not repeated and forms a permanent part of the medical record. Consequently it is important that services are provided with the appropriate level of support to the patient and their family prior to the offer of a genetic test and following the result. All these features of molecular genetic testing place an enhanced duty on laboratories to assure the quality of their services. In turn Governments regulators and professional bodies have a responsibility to ensure that these services are offered within a framework that retains the confidence of the public.

8. These principles and best practices form guidelines for quality assurance in molecular genetic testing (MGT) for clinical purposes. Statements of Principle are directed at governments and those involved in the regulation of genetic services, whereas Best Practice statements are aimed at directors of molecular genetic testing laboratories and others involved in the provision of molecular genetic testing. The guidelines seek to assist both OECD and non-OECD Member countries in the development and introduction of appropriate quality assurance procedures to:

- Ensure minimum international requirements for quality assurance systems and molecular genetic testing laboratory practices.
- Facilitate mutual recognition of national or regional quality assurance frameworks.
- Strengthen international co-operation and facilitate where appropriate the cross border flow of samples for clinical purposes in accordance with recognized principles for their handling, storage, safety, privacy and confidentiality.
- Increase public confidence in the governance of Molecular Genetic Testing.

9. The ethical and legal principles set out in international declarations and agreements and the diversity of systems in different national jurisdictions have been recognised during development of these guidelines.

### Scope

10. These guidelines relate to aspects of the provision of genetic services, more particularly these guidelines concern molecular genetic tests on human DNA offered in a clinical context and the quality assurance practices of laboratories that carry out such tests. They do not address testing carried out only for research purposes. They address genetic testing for variations in germ line DNA sequences or products arising directly from changes in heritable genomic sequences that predict effects on the health, or influence the health management, of an individual. They focus on molecular genetic testing for the diagnosis of a particular disease or condition and predictive genetic testing often carried out before any clinical signs of the disease or condition appear. They are relevant to tests for heritable DNA variants that predict the response profile of an individual to a drug or course of therapy and that affect susceptibility to disease, patient prognosis, counselling, treatment and family planning.

11. Molecular genetic tests require particular consideration since these tests may be performed on asymptomatic individuals and results may have relevance to important lifetime decisions both for the individuals being tested and for their family and children. The guidelines reflect this particular responsibility of molecular genetic testing and place emphasis on the accuracy of all aspects of the testing and reporting process including forming links to appropriate levels of counselling.

12. In part these guidelines are also relevant and applicable to aspects of clinical cytogenetics testing and biochemical genetic testing. They are not designed to address directly the areas of testing for somatic mutations, variants important in tissue matching, genetic analysis of pathogenic organisms and identity testing, though all share related technologies.

### **Nature and structure of the document**

13. These guidelines are intended to be evolutionary in nature and will therefore need to be reviewed periodically in light of new genetic knowledge, technological advances, evolution of quality management and societal needs and to ensure that they are achieving the desired objectives.

14. The document describing these guidelines consists of four main parts. Part one establishes the principles and best practices for quality assurance in molecular genetic testing. It provides a framework for all aspects of quality assurance, from licensing, certification and accreditation to the education and training of laboratory personnel. Part two of the guidelines contains additional information. This is included to assure a common understanding of the wording used and as an aid to those readers who are less familiar with and/or have no direct experience with genetic testing. Part three includes references to relevant documentation as well as relevant analytical papers. Finally, Part four gives a glossary of terms.

## **PART I**

### **A. *General principles and practices for molecular genetic testing***

#### **Principles**

- A.1 International and national medical and ethical principles should be respected in the practice of molecular genetic testing.
- A.2 Molecular genetic testing should be delivered under the governance framework of a health care system.
- A.3 All molecular genetic testing services should be provided and practised under a common quality assurance framework.
- A.4 Informed consent to test should be regulated, within national and regional frameworks.
- A.5 Pre and post test counselling should be available. It should be proportionate and appropriate to the characteristics of the test, the test limitations, the potential for harm, and the relevance of test results to individuals and their relatives.
- A.6 Personal genetic information should be subject to a high level of privacy protection and security in accordance with applicable law and consistent with the principles articulated in the *OECD Guidelines on the Protection of Privacy and Transborder Data Flows and Guidelines for the Security of Information Systems and Networks*.
- A.7 The need for cross border exchange of patient samples and personal information should be recognized.
- A.8 Regulation concerning advertising and promotional claims for molecular genetic testing should ensure that they accurately describe the characteristics and limitations of the tests offered.

#### **Best Practices**

- A.i Regulatory and professional bodies should review whether the instruments available to manage a quality assurance framework require adaptation and interpretation for laboratories providing molecular genetic testing.
- A.ii Laboratories should provide information on the analytical and clinical validity of tests to inform users.
- A.iii. Molecular genetic tests should be reported back to the referring health care professional to enable counselling and healthcare decision making.

**B. *Quality Assurance Systems in Molecular Genetic Testing***

**Principles**

B.1 Governments and regulatory bodies should recognise that accreditation is the most effective measure for assuring quality assurance. All molecular genetic testing results for clinical care purposes should be released by accredited laboratories.

B.2 Accreditation, certification and licensing of laboratories should be based on internationally recognised standards and guidelines to facilitate mutual recognition of molecular genetic testing services.

B.3 Regulatory bodies should apply available instruments and measures proportionately to the characteristics of the genetic tests.

B.4 The legal, regulatory and professional requirements for licensing, certification and accreditation of laboratories should be accessible, clearly stated, transparent and enforceable.

B.5 Regulation and incentives should be introduced to facilitate the development and implementation of accreditation, certification and licensing of laboratories.

B.6 Impediments to achieving the requirements for licensing, certification and accreditation should be identified and addressed.

B.7 Governments and regulatory bodies should ensure that systems are in place to monitor and address instances where laboratories do not fulfil quality assurance requirements.

B.8 Governments should encourage international collaboration for the development, verification and use of reference materials for molecular genetic testing.

**Best practices**

B.i Whilst recognising and supporting the continuing contribution of research laboratories to testing services, all research laboratories releasing molecular genetic testing results for clinical care purposes should be accredited or arrange for diagnostic results to be confirmed in an accredited laboratory before reporting.

B.ii. Internationally agreed terminology should be adopted and used consistently with respect to quality assurance systems.

B.iii. Laboratory assessors acting on behalf of regulatory bodies should have qualifications, training and experience relevant to molecular genetic testing.

B.iv. Laboratories should have policies and procedures to document the analytical validity of all tests performed.

B.v. Laboratories should document current evidence concerning the clinical validity and utility of tests offered, with particular respect to the populations they serve. Laboratories should collaborate to establish the clinical validity of tests for rare disorders.

B.vi. Laboratories should seek to cooperate with relevant national and international institutions to collect, develop and verify reference materials for molecular genetic tests.

**C. Proficiency Testing: Monitoring the quality of laboratory performance**

**Principles**

- C.1 The performance of laboratories offering clinical molecular genetic tests should be measured.
- C.2 Governments, regulatory and professional bodies should support the availability of and access to proficiency testing.
- C.3 Providers of proficiency testing schemes should be accredited by a competent authority.
- C.4 Accreditation should be the basis for the international recognition of proficiency testing scheme providers.
- C.5 Governments, regulatory and professional bodies should take steps to encourage laboratories to participate in accredited proficiency testing schemes or, when not available, to use alternative methods to assess the quality of the tests they perform.
- C.6 Systems to monitor and address persistent poor performance in proficiency testing should be in place.

**Best Practices**

- Ci Proficiency testing providers and professional bodies should collaborate to establish acceptable performance levels for laboratories offering molecular genetic tests.
- C.ii. Regulatory and professional bodies responsible for monitoring laboratory performance against an agreed standard should identify persistent poor performance and ensure that timely corrective action is taken and documented.
- C.iii. Proficiency testing schemes should be structured to assess all phases of the laboratory analytical process, including result reporting.
- C.iv. Providers of proficiency testing should develop and modify proficiency testing schemes to take into account the evolution of analytical methods.
- C.v. The performance of individual laboratories in proficiency testing schemes may be disclosed on a voluntary basis but should not be made public unless so required by law.
- C.vi. Laboratories should participate in a proficiency testing scheme for every disease for which they test, where such schemes are available. When not available, they should participate in alternative methods relevant to the tests they perform.
- C.vii. Laboratories should make their participation in proficiency testing publicly known to inform and retain the confidence of the public in molecular genetic testing.

**D. *Quality of Result Reporting***

**Principles**

- D.1 Governments, regulatory and/or professional bodies should ensure that all laboratories meet the reporting requirements described in these guidelines
- D.2 All laboratories should issue molecular genetic testing results in the form of a written report to the referring clinician or health professional.
- D.3 Within jurisdictions where reports may be issued directly to patients, governments, regulatory and professional bodies should ensure that all laboratories performing clinical molecular genetic tests recommend patients to consult an appropriate clinician or health care professional to help them understand the implications of the test result.
- D.4 Governments and regulators should ensure that in issuing and archiving reports, all laboratories comply with existing legislation and regulations, including those concerning the confidentiality of information.
- D.5 The interpretation of test results should be evidence-based.

**Best Practices**

- D.i. Reports should communicate information effectively to their recipients, taking into account that the recipients may be specialist or non-specialist health care professionals or others.
- D.ii. Reports should be timely, accurate, concise, comprehensive, and communicate all essential information to enable effective healthcare decision-making by patients and physician (s), and should contain sufficient information that replication of the test can be carried out if needed.
- D.iii. Internationally accepted and unambiguous terminology and nomenclature and reference sequences should be used in reports.
- D.iv. A request for genetic testing should include all information necessary for the laboratory to perform appropriate testing and interpretation. The utility of a genetic test report is often dependent on the accuracy and adequacy of information provided to the laboratory.
- D.v. All the essential and relevant elements of test results and interpretation reported by a referral laboratory or sub-contractor should be communicated to the health care professional who ordered the test.
- D.vi. Where reports are entered into an electronic patient record, all the essential elements of test results and interpretation relevant to clinical care should be included in the record. This information should be subject to a high level of privacy protection and security in accordance with applicable law and consistent with the principles articulated in A 6.

D.vii. The following information should be included in the test result report at minimum:

- Two identifiers that unequivocally link the report to the patient.
- The name of the referring health care professional and their contact information.
- The indication for testing, or relevant specific referral information.
- The test performed and the methodology used (including the scope of the analysis and the analytical sensitivity and specificity).
- The sample type where necessary for the interpretation.
- The date of receipt of the sample.
- The name and location of laboratory(ies) which performed the actual testing on the sample.
- The test result.
- An interpretation of the genotype in the context of the indication for testing and other relevant demographic (*i.e.* race, ethnicity), clinical and family-specific information, including clinical sensitivity and specificity. The interpretation should be developed to ensure that the recipient of the report is able to understand the clinical usefulness and limitations of the test result.
- An indication of review and approval by the laboratory director or a qualified and designated individual.
- When appropriate, a recommendation for genetic counselling by a qualified health care professional.
- Implications for other family members as appropriate.
- Recommendations for follow up testing, as appropriate.
- Laboratory contact information.
- The date of issue of the report.

## **E. Education and Training Standards for laboratory personnel**

### **Principles**

- E.1 Appropriate professional qualifications and standards underpinned by education and training are necessary for assuring laboratory competence in the provision of molecular genetic testing.
- E.2 Laboratory accreditation standards should require that all molecular genetics personnel have a combination of education, training and experience that demonstrates their competence.
- E.3 Existing specialist education and training programmes relevant to molecular genetic testing that meet recognized standards should be formally adopted by governments, regulatory and/or professional bodies. Medical Genetics should be recognised as both a clinical and a laboratory specialty.
- E.4 Development of educational and training programmes should be encouraged where they do not exist.
- E.5 Where medical and scientific qualifications awarded by foreign institutions are recognised by governments, regulators and professional bodies, such recognition should be extended to equivalent qualifications in molecular genetic testing.
- E.6 All personnel should practice within the framework formed by the relevant legal statutes and codes of ethical practice within their jurisdiction.

### **Best Practices**

- E.i Measures to assure professional competence should be established. These measures should be comparable to those applied in other areas of laboratory medicine. They should include systems to validate requirements for education, training and qualifications specific to molecular genetic testing.
- E.ii Appropriate specialist qualifications, education and training standards for individuals directing molecular genetics laboratories should be established. The minimum qualification required to direct a laboratory should be an MD or PhD or recognised equivalent. Educational requirements should include formal training in molecular genetics and where available, certification in the specialty of clinical molecular genetics, molecular pathology, or another relevant discipline.
- E.iii All personnel should be trained and their competence documented prior to performing molecular genetic testing for the purpose of reporting a diagnostic result on any patient material.
- E.iv All personnel in molecular genetics laboratories should participate in education and training programmes appropriate to their roles and designed to ensure competence.
- E.v Education and training in genetics should be recognised as an essential element to strengthen professional competence to deliver molecular genetic testing.
- E.vi Educational programmes specific to molecular genetic testing should be made available and should aim to facilitate continued professional development and maintenance of competence.
- E.vii Comparison of specialist education and training systems between jurisdictions should be facilitated as a means to establish equivalence. .

## **PART II: ANNOTATIONS**

### **Introduction**

1. The purpose of these Annotations is to provide additional information on the Principles and Best Practices found in Part One of the Guidelines. The Annotations follow the structure of the Principles and Best Practice statements.

2. These guidelines offer principles and best practices for quality assurance in molecular genetic testing (MGT) for clinical purposes. They are addressed to all those involved in the regulation and provision of molecular genetic testing. The Guidelines are intended to assist both OECD and non-OECD governments in the development and introduction of requirements for quality assurance systems and molecular genetic testing laboratory practices. They also seek to facilitate mutual recognition of local, national or regional quality assurance frameworks.

3. OECD member countries have expressed the view that internationally and mutually recognised quality assurance systems are essential to securing and maintaining public confidence and ensuring comprehensive availability of services through international collaboration. This mutual recognition can only be achieved through international consensus on minimum common requirements to assure consistency in the quality of molecular genetic testing services.

4. Whilst most OECD countries have mechanisms in place to prevent risk from inappropriate and inaccurate MGT testing, these regulatory and oversight procedures have not penetrated molecular genetic testing laboratories across OECD countries to a high degree and with any consistency. It has been suggested that many factors may contribute to this including uncertainty about terminology and the choice of the most appropriate quality system. This poses a number of challenges for molecular genetic testing, particularly with respect to the standards under which tests are performed for clinical application, results are reported, and the training and qualifications needed by laboratory personnel.

### **General Terminology**

5. The Guidelines apply to molecular genetic tests offered in a clinical context.

6. In particular they apply to testing for the diagnosis or carrier risk assessment of a particular disease or condition and predictive genetic testing often carried out before any clinical signs of the disease or condition appear. They also apply to related recent developments such as testing to predict the response profile of an individual to a drug or course of therapy and patient prognosis.

7. Whilst the term genetic testing used in these guidelines is intended to be broad and many of the principles and best practices have relevance beyond testing for single gene conditions these guidelines are not intended to cover areas such as identity testing, testing for variants important in somatic disease, tissue matching and DNA analysis of pathogenic organisms involved in human diseases, though all share related technologies.

8. Molecular genetic testing, as defined above places a special responsibility on the laboratory, particularly in the pre- and post-analytical phases as test results often can be predictive of the future health of the individual. Test results may have relevance to important lifetime decisions both for the individuals being tested and for their family and children and counselling appropriate to the nature and risk of an adverse outcome may be essential<sup>1</sup>.

9. The guidelines acknowledge the different ways in which quality assurance may be regulated. Instruments relevant to regulation of quality assurance may include: accreditation of laboratories, certification of laboratories, licensing of laboratories, Proficiency Testing, internal quality control measures, documentation of policies and procedures; in addition the individual accreditation, board certification and state registration of laboratory personnel.

10. Licensing is permission from a governmental agency to operate a laboratory. It may involve documenting the existence, institutional accountability and, in general terms, the activities of the facility, for example the menu of services provided. In return, the laboratory is officially registered and may be publicly listed. The granting of a licence may not require a formal audit of policies, procedures or practice.

11. Accreditation is a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks. It is a public recognition of a laboratory's competence. It is only granted after a thorough on-site assessment by inspectors of the management, environment, policies and procedures of the laboratory in addition to specific scientific/technical competences measured against external standards.

12. International standards are relevant to the design of jurisdiction specific accreditation systems. The ISO 17025 standard is designed for the accreditation of testing and calibration laboratories of all types. The ISO 15189 standard is related to ISO 17025 and is relevant to all general medical laboratories but not specific to MGT laboratories. These standards are not themselves accreditation systems but may be referred to by the authoritative national bodies that award accreditation.

13. Modern accreditation standards related to clinical laboratories place emphasis on having an effective quality assurance system in place; on a commitment to meeting the needs of patients and their doctors as users of laboratory services; and placing a continuous cycle of quality improvement at the heart of all policy making and operational decisions.

14. The accreditation process includes an assessment of the laboratory infrastructures and all internal quality control and quality assessment measures. To achieve accreditation a laboratory must be adequately staffed by personnel with appropriate qualifications and training. It must maintain adequate documentation, including standard operating procedures for analytical tests. In addition it must demonstrate external assessment of its tests preferably through participation in a recognised laboratory Proficiency Testing (PT) scheme. It may also be obliged to demonstrate satisfactory performance and show that it is responsive to performance shortcomings demonstrated through PT as well as deviations in performance discovered as a result of routine internal laboratory quality control measures.

15. Certification is a well-recognised indicator of the quality management of an organisation but it is less stringent than accreditation. It involves an audit of an internally defined quality management system but does not require examination of specific competences against external standards. ISO9001:2000 is an example of a certification standard that can be applied to any manufacturing process or service.

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1. As an example, a patient tested for fV Leiden as a consequence of a thrombotic event should be counselled as to his/her future risk and interventions will be offered to reduce the risk of recurrence.

16. Proficiency testing (PT) schemes are a means by which a laboratory can compare its performance for an individual test or technique against that of other laboratories. Typically a PT scheme provider such as the European Molecular Genetics Quality (EMQN) Network or the College of American Pathologists (CAP) provides a number of biological samples of known and validated genotype to participating laboratories. Laboratories are asked to genotype the samples (for mutations in a gene associated with a particular genetic condition, for example Huntington disease) and return their reports to the PT organiser. Genotype accuracy is assessed by a panel of experts and individual comments on performance are returned to participating laboratories. Laboratories are asked to act on shortcomings to improve their performance. Proficiency Testing schemes may also assess the reporting practices of the participating laboratories, by providing mock clinical scenarios with the PT samples and asking participants to interpret the genotype results in the context of the clinical scenario, and report their findings in their usual reporting format.

17. Accreditation is the most effective way to improve quality assurance, but it is not widespread in diagnostic molecular genetic testing laboratories in OECD member countries.

## 1. General Features of Molecular Genetic Testing

18. (A.1). These guidelines attest the need of consistency with the ethical and legal principles set out in international declarations and accords such as the 1997 UNESCO declaration on the Human Genome and Human Rights, and the 2003 UNESCO international Declaration on Human Genetic Data and recognise the need to guarantee patients informed consent and confidentiality of information

19. (A.2). Molecular genetic testing within the scope of these guidelines may have important consequences for the health and well-being of an individual and their relatives. For example, genetic tests may be used to predict, in healthy individuals, what their medical problems might be in the future. The test, is used to support conclusions based on the physician's current assessment of the patient, and in addition may be used to predict, with variable certainty, late onset of disease (*e.g.* Huntington disease) and future patient outcomes. Genetic testing may also be carried out to determine carrier status or to test before birth for a childhood onset recessive disorder such as Fragile X syndrome (pre-natal testing)<sup>2</sup>. Today it is also possible to test an embryo before implantation (pre-implantation genetic diagnosis). In the light of the above a statement of principle places emphasis on molecular genetic testing being carried out within the framework and governance of a healthcare system which can offer the appropriate level of support to the patient and their family prior to the offer of a genetic test and following the result

20. (A.3). Regulators should make no exceptions amongst providers regarding the quality standards of genetic testing services. The guideline principles specify that all genetic testing services should be subject to a common quality assurance framework. In this context a framework is considered to be the totality of the statutory, regulatory and professional mechanisms that directly or indirectly affect the quality of a laboratory service. Statutory mechanisms include legislation and associated, regulation and codes of practice. Non statutory mechanisms may include controlling provision and access to services through resource allocation (*e.g.* reimbursement) or health care management guidelines (*e.g.* clinical guidelines).

21. (A.4). A procedure leading to informed consent is considered a necessary step for genetic testing. Within these guidelines informed consent is intended as a safeguard to ensure the patient's autonomy and to provide an opportunity to learn and understand information with respect to both the positive and negative consequences of a genetic test. Informed consent should be considered as a process, following a dialogue, not simply a contractual agreement. The nature and duration of the process may vary depending on the patient, his/her age and ability to consent, and the nature of the genetic test. The process leading to informed consent should follow professional guidelines. For some tests, in particular for predictive or pre-

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2. Fragile X syndrome results from a trinucleotide repeat expansion and is a heritable condition.

symptomatic testing, it may take the form of a written statement describing the risks and benefits and limitations of genetic testing for the patient to read and sign before the evaluation and/or test is performed. Documenting evidence of an informed consent process should be preserved in the patient record. Information such as length of time the sample will be stored, duty to re-contact if samples might be retested (*e.g.* due to relevant advances in knowledge and technologies), possible secondary use(s), potential third-party access to samples, procedures to protect confidentiality (coding/de-identification), may also be included

22. (A.5) Together with the offer of a genetic test, consideration must be given to the need for pre- and post-test genetic counselling. Genetic counselling provides individuals and families with a heritable disorder with accurate, full and unbiased information and offers support in the decision making process. It may be a complex process, which seeks to help families to cope with the diagnosis of a heritable disorder, to face its implications and to make decisions on the basis of their medical and non-medical options. It is of particular relevance in predictive and pre-symptomatic testing. Counselling ensures that the individual's prerogatives include autonomy of choice to undertake or not to undertake the test, freedom from third party pressures, access to a test even if the result has a deferred clinical utility (*e.g.* in terms of access to available therapy), and that confidentiality is respected.

23. (A.6) Molecular genetic testing involves the processing and exchange – sometimes across borders – of diagnostic tissue samples and clinical details. These are personal data that may be considered sensitive. Such exchange should be facilitated, as appropriate, except where the OECD Privacy Guidelines are not substantially observed, including their security safeguards principle. The OECD *Guidelines on the Protection of Privacy and Transborder Data Flows* and *Guidelines for the Security of Information Systems and Networks* provide minimum standards for the protection of personal data and the security of the systems and networks used for their processing and exchange. These standards may be supplemented in national law by additional protective measures, in particular with respect to transborder data flow. The OECD Privacy Guidelines provide that, in general, member countries should refrain from restricting the transborder flow of personal data where the Guidelines are substantially observed. They also provide that restrictions may be imposed in respect of certain categories of personal data (*e.g.* sensitive data) for which no equivalent protection has been provided in the other country.

24. (A.7) More than 1700 different molecular genetic tests are available to patients at risk of heritable single gene conditions. Most of these conditions are very rare. Given the large number of genetic disorders, and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of molecular genetic testing. This results in exchange of patient material and genetic testing across national borders. In 2003, the OECD quality assurance survey reported that at least 18 000 samples crossed 18 OECD countries' borders. Transborder flow is clearly a mechanism to fill a significant gap in the availability of tests for rare disorders in many countries. The guideline recognise the need to enable and facilitate this exchange through clearly stated, transparent, internationally agreed standards and procedures

25. (A.8) Governments and regulators should consider the responsibility of the genetic test service provider to temper commercial requirements and pressures with the rights and protection of the consumer. Regulators should make no exceptions amongst providers regarding the quality standards of genetic testing services.

26. **(A.i)** Best Practices recognise that the principal instruments to manage a quality assurance framework for medical laboratories are already available. These instruments should be used for this purpose. Best Practices also suggest that they may require adaptation and interpretation. This may include the training of assessors, promotion of quality assurance schemes, availability of high quality reference materials, promotion and extension of Proficiency Testing schemes and drafting of competencies specific to molecular genetic testing personnel.

27. **(A.ii)**<sup>3</sup> Best Practices recognise that laboratories are responsible for ensuring that test results are fit for their clinical purpose by setting and maintaining the quality of their analytical methods, and the methods used are appropriate for the given clinical application. The Best Practice statements also draw special attention to the communication between the clinicians and the laboratory providing the testing.

28. **(A.iii.)** For better protection of the patient, Best Practices state that molecular genetic tests used for clinical management of a patient should be reported back to the referring health care professional.

## 2. Implementing quality assurance systems in Molecular Genetic Testing

29. **(B.1.)** Principles recognise that accreditation of laboratories is the most effective measure for assuring quality and for the maintenance of a process of continuous improvement. Accreditation is defined in the guidelines as a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks. Accreditation requires having the laboratory assessed against external standards by an independent agency.

30. **(B.2)** Principles recognise that when establishing or revising requirements for quality assurance systems within their jurisdiction, governments and regulatory bodies should aim to base requirements on existing international standards and guidelines. Where national accreditation agencies base their systems on the same or compatible standards, such as ISO/IEC 17025 and ISO 15189, there is the potential for achieving similar levels of competence internationally. The mutual recognition arrangement (MRA), detailed in ISO/IEC 17025, and maintained by the International Laboratory Accreditation Cooperation (ILAC) provides a basis for equivalence of laboratory services between nations and is a base for laboratory accreditation reciprocity between nations. International comparability in genetic test quality assurance standards is essential to retain public confidence in Molecular Genetic Testing.

31. **(B.3, B4)** The type of instrument applied will depend on the nature and scope of the regulatory oversight. Regulation should intervene when necessary and should be appropriate to the risk to the individual posed by an erroneous genetic test and to the potential consequences. Regulations should also be transparent. Regulators must be able to justify their decisions and keep regulations simple and user friendly. For example the, licensing of a MGT laboratory does not contribute directly to the quality of its output. However, it may be a valuable tool which is used by regional, national or local authorities to monitor service providers. It may indicate a particular concern for oversight, particularly where highly predictive tests such as prenatal diagnosis are offered. By contrast, accreditation is a powerful tool to improve quality assurance. It requires having the laboratory assessed against external standards by independent audit.

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3. The Best Practice is based on ISO 15189, 5.6.2, which requires that “The laboratory shall determine the uncertainty of results, where relevant and possible”.

32. **(B.5)** The implementation of regulation and appropriate incentives can act as major drivers to promote the quality of clinical molecular genetic testing. The guidelines recognise as a principle that achieving and maintaining compliance with accreditation standards requires responsible management that has the tools and resources needed to achieve this goal. They also recognise that establishment of formal arrangements for evaluation and benchmarking of processes, and structures to encourage performance improvement are necessary.

33. **(B.6, B.7)** Principles encourage active dissemination of governmental requirements for quality standards through training and facilitation. Regular monitoring and specific actions may be necessary to ensure that standards are being met and performance improvements are maintained.

34. **(B.8)** For most molecular genetic tests in use today there are no quality reference and quality control materials (defined in the glossary) available. The objective of the guideline statement is to encourage international collaboration and the establishment of appropriate mechanisms for the collection, development, verification and use of reference material. To achieve this it is also necessary to facilitate cross-border flow of diagnostic samples when needed for precise diagnosis or as reference/quality control materials – as stated in Principle A7.

35. **(B.i)** These guidelines recognise that research laboratories perform a vital role in providing tests for rare disorders, which would otherwise not be available, They also acknowledge the need to ensure a high quality of service. This can be achieved by encouraging research laboratories to attain accreditation for diagnostic activities or alternatively to make arrangements with accredited laboratories to confirm research results and report diagnostic tests. This ensures that results are reported within an acceptable quality assurance framework.

36. **(B.ii)** The OECD 2003 survey of quality assurance molecular genetic testing laboratory practice revealed a lack of clarity and consistency in the use of the existing terminology (defined in the glossary) relevant to quality assurance; for example different meanings are often assigned to the terms ‘accreditation, certification and licensing’. Governments, regulatory and professional bodies should alter their practice to make consistent use of agreed terminologies and to disseminate their understanding of the terminologies to laboratories.

37. **(B.iii)** The guidelines also recognise the need for laboratory assessors to be aware of the specific features and range of applications of molecular genetic testing and hence have the appropriate qualifications, training and experience.

38. **(B.iv, B.v)** Before genetic tests are made available, the issues of analytical and clinical validity and clinical utility (defined in glossary) should be addressed. Laboratories should make this information available to service users (healthcare professionals and patients).

39. Clinical validation of a genetic test reflects its ability to correctly classify people who have or will develop disease as test-positive and those who will not develop disease as test-negative. Measurements of validity include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Clinical utility generally refers to the likelihood that a genetic test will result in an improved health outcome (see definition in the glossary)<sup>4</sup>.

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<sup>4</sup> Important limitations of genetic tests are 1) that they may not detect every mutation associated with a disorder and 2) that the clinical presentation cannot always be predicted from the variants detected. A single gene can have many different mutations and these can occur anywhere along the gene. In addition, the frequency of common mutations may vary among population groups. An understanding of the detection rate of the test

40. **(B.vi)** The Best Practice follows from Principle B.8. The international genetic testing community is encouraged to collaborate with relevant institutions to collect, develop, verify and make available at a reasonable cost quality control materials for molecular genetic testing.

### 3. Monitoring quality in laboratory performance through Proficiency Testing

41. External Quality Assessment and Proficiency Testing (PT) are terms used interchangeably and define an externally moderated system for inter-laboratory comparison of test results. The latter term has been adopted in these guidelines.

42. Proficiency Testing is the formal process by which laboratories measure their performance against their peers using externally validated materials. This definition is based on ISO/IEC Guide 2 (“General terms and their definitions concerning standardisation and related activity”, 1996) and has been expanded in the guidelines to include assessment of all phases of the laboratory analytical process, including result reporting.

43. Across OECD countries, PT for many molecular genetic tests has not been implemented on a routine basis. This limitation is particularly evident for rare diseases and for diagnostic tests being performed in a research context. The large number of gene target specific molecular genetic tests means that it is not practicable to provide a PT scheme for each genetic test. In addition, considering the large variability in methodologies and diagnostic approaches, the comprehensive availability of PT remains challenging.

44. **(C.1, C.2)** The guidelines recognise as a principle the importance of measuring laboratory performance and encourage governments to facilitate development, availability and access of test-specific PT schemes.

45. **(C.3, C.4)** Principles recommend the use of an external review process and recommend that PT scheme providers should be accredited by a competent authority. This recommendation is based upon the requirements contained in the ILAC (International Laboratory Accreditation Cooperation) guidelines for the Requirements for the Competence of Providers of Proficiency Testing (ILAC-G13:2000) and on ISO Guide 43-1 (ISO/CASCO 322: ISO/IEC guide 43-1): Proficiency testing by inter-laboratory comparisons - Part 1: Development and operation of proficiency testing schemes. 1996.). This ISO Guide gives recommendations for the development and operation of proficiency testing schemes and provides a basis for recognition of equivalence of Proficiency Testing schemes between jurisdictions.

46. **(C.5, C.vi)** Many genetic diseases are rare and may be carried out by only one or two laboratories in the world which are studying the causative genes, have recruited affected families and have developed in-house assays. This makes development of PT schemes for these disease services impractical since PT relies on the possibility of comparing practices, on the participation of a minimum number of centres for inter-laboratory sample exchange and on a critical volume of testing. The guideline principles acknowledge these issues and include provisions for ultra rare disease testing for which PT is unavailable by recommending under Principle C.5 that alternative methods for measuring laboratory performance should be made available<sup>5</sup>. Best Practices encourage laboratories to make use of these alternative methods. Alternative methods include blind sample exchanges between laboratories, blind repeat testing, testing by different independent methods, and correlation of results to clinical and laboratory parameters. If

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for the patient’s respective race/ethnicity is often crucial in defining their residual risk in the event of a negative test result.

5. The principle is based on CSLI document GP29-A: “Validation of Laboratory Tests When Proficiency Testing is not available”.

practicable, blind sample exchanges between laboratories is the preferred approach. These alternative methods could also include generic schemes designed to test laboratory performance of individual steps in the analytical process (*e.g.* DNA sequencing or PCR).

47. (C.6) The guidelines recognise as a principle that systems to monitor and address poor performance in proficiency testing are needed. In the context of these Guidelines the term *systems to monitor proficiency testing* refers to the procedures and statistical techniques needed to adequately establish whether or not each participant laboratory has met satisfactory performance levels over time. For example, proficiency tests can, by design, include statistical techniques to monitor a participant's performance over time. These statistics can be used to determine a participant's performance variability, identify general trends and spot inconsistencies. Procedures must be in place to provide laboratories with the appropriate feedback.

48. (C.i) Guidelines recognise that in establishing acceptable performance levels, collaboration between proficiency testing providers and professional bodies is necessary.

49. (C.ii) To ensure that standards are being met and effectively address persistent poor performance, regular monitoring and documentation of corrective actions are necessary.

50. (C.iii) The usefulness of any medical test requires results to be reported, understood and used appropriately for patient management. Guidelines recommend that PT schemes are structured to assess all phases of the laboratory analytical process, including result reporting.

51. (C.iv) Given the rapid progress in scientific and technological, proficiency testing schemes must be flexible and evolve to take account of progress in analytical methods.

52. (C.v, Cvii) Laboratories that participate in PT are encouraged to make this activity and their performance publicly known as a measure to improve the confidence of the public in molecular genetic testing.

#### **4. Ensuring Quality in Molecular Genetic Test Result Reporting**

53. Molecular genetic testing is often ordered to determine a genotype associated with disease or its predisposition. However, the genotype, in itself, can be uninformative or misinterpreted if certain test, patient and family-specific information is not used in developing an interpretation. Molecular genetic test results often have implications for other family members, and it is important that the health-care professional receiving the report understands these implications. For carrier, pre-symptomatic and susceptibility testing, the patient is often asymptomatic and the test result may be the sole indicator of increased risk. As such, it is essential that the report communicates the certainty or uncertainty of the analytic test result, its limitations and the implications for the patient tested and their family.

54. (D1) Molecular genetic tests, especially those for rare diseases, are often only available in research settings. Laboratories in such settings may not subscribe to the full range of quality assurance practices found in a dedicated clinical testing laboratory. Whilst recognising the special issues of rare disease testing, Principles recommend that all laboratories including research laboratories, have policies and procedures in place to ensure that the reporting requirements described in these guidelines are met. This can be achieved through attaining accreditation or confirming and reporting results through an accredited laboratory.

55. **(D.2)** Principles recommend that all laboratories releasing clinical molecular genetic test results should issue a written report to the referring clinician of health professional. Within the guidelines, health professionals are persons authorized by local and/or national bodies to use genetic tests for patient counselling and/or management. Health professionals may include physicians, nurses, midwives, physician assistants, and genetic counsellors.

56. **(D.3)** In some jurisdictions, testing can be ordered by members of the public in the absence of referral by a health care professional and individuals may receive results without the consultation of a trained health professional. In such cases, reports should comply with existing legislation and regulations, including those pertaining to the confidentiality of information and encourage consultation with a health care professional.

57. **(D.4)** Reports include personal data that may be considered sensitive. In issuing and archiving reports, laboratories should be aware of and comply with existing legislation and regulations.

58. **(D.5)** Principles recommend that the interpretation of test results should be based on clinical, scientific and technical evidence.

59. **(D.i, D.ii)** The report should be clear and complete, to ensure both understanding of the test result by health-care professionals (who may not be familiar with the technologies used) and subsequent effective communication with the patient. The Guidelines recommend that when reporting the results of a genetic test, the laboratory should report the raw test result, information on the method by which it was reached and the genetic interpretation of the result. Test results may have far reaching consequences for the individual patient and their family particularly in the case of a highly penetrant disorder. It is important that there should be adequate means of tracing how a genetic interpretation was reached. It might be necessary to replicate the test and determine that appropriateness of a conclusion reached by the laboratory. furthermore, in case of challenge such a trace or log might be a valuable element for the clinical practitioner. '

60. **(D.iii)** For historical reasons, a number of common mutations have names that do not conform to standard nomenclature schemes. To avoid confusion, Best Practices recommend that the common designation of such mutations should continue to be used alongside standardised nomenclature. Reports should indicate which system is being used.

61. **(D.iv)** Best Practices recommend that all essential and relevant elements necessary for the laboratory to perform appropriate testing should follow the patient specimen through the entire testing process including the transfer of a specimen to a referral laboratory.

62. **(D.v)** Best Practices also recommend that all the essential and relevant elements of tests results , including elements reported by a referral laboratory, are communicated to the health care professional who ordered the test.

63. **(D.vi)** In some jurisdictions the question of whether reports may be entered into an electronic patient record as a principle is regulated. Best practices recommend that where jurisdiction allows the reports to be entered into an electronic patient record, all essential and relevant elements should be comprehensively included.

64. **(D.vii)** Best Practices also recommend that care should be taken so that when analytical sensitivity is included in information concerning test characteristics, it is presented in a manner that is not confused with clinical sensitivity.

## 5. Education and Training standards of molecular genetic testing laboratory personnel

65. **(E.1)** The levels of competence of the laboratory personnel who provide and interpret clinical molecular genetic tests are essential to the quality of services. Personnel should be educated and trained to possess expert knowledge of genetic principles, the technologies employed, the limitations of the tests used, an appropriate understanding of the clinical implications of the test result and how to communicate this information.

66. **(E.2)** Laboratory accreditation standards should require that all personnel who provide and interpret clinical molecular genetic tests have a combination of education, training and experience appropriate for their role in a diagnostic molecular genetics laboratory.

67. **(E.3)** Many jurisdictions have regulations and guidelines for specialist qualifications, education and training in laboratory medicine. Governments and professional bodies are encouraged to establish regulations and guidelines relevant to the practice of diagnostic molecular genetics where they are not available. The guidelines also recognise that linking molecular genetic testing to an appropriate clinical speciality is an important means to promote a strong professional governance framework. Moreover, education and training programmes and requirements leading to specialist competence in molecular genetic testing can be strengthened by being accountable to a medical genetics or other recognised professional discipline.

68. **(E.4)** Lack of specialist training programmes in molecular genetics may lead to inadequate availability of competent staff with consequences for quality assurance. In public health systems a planning process may be required to ensure that education and training programmes can meet the growing personnel requirements of diagnostic molecular genetic testing laboratories. Jurisdictions lacking such programmes are encouraged to adopt or develop such programmes.

69. **(E.5, E.vii)** The definition of core competencies for diagnostic molecular genetic testing laboratory personnel at all levels may differ across jurisdictions and even within the same country. The guidelines recognise that there is a need to facilitate mutual recognition of equivalent qualifications and establish mechanisms for comparison of specialist education and training programmes between jurisdictions.

70. **(E.6)** Clinical genetics can potentially raise a number of ethical issues. All personnel involved in the analytical process of a molecular genetic test should have sound knowledge of the ethical and legal principles guiding their profession.

71. **(E.i)** The guidelines recognise that there is a need to establish systems to validate requirements for education, training and qualifications specific to molecular genetic testing.

72. **(E.ii)** An adequately educated and trained laboratory director is a key influence on quality markers in diagnostic molecular genetic testing. Whilst qualification and certification of laboratory directors is regulated in a number of jurisdictions, this is often limited to recognition of an MD without regard for relevant specialty training or certification. Governments and professional bodies should establish a process whereby individuals with an MD, PhD, or recognised equivalent, as well as formal training in molecular genetics can be certified as laboratory directors. A recognised equivalent may be defined by governments and professional bodies within each jurisdiction. Training of a diagnostic molecular genetics laboratory director and/or another qualified and designated individuals should be appropriate to his/her role and, at a minimum, provide the knowledge and skills to 1) review test request for appropriateness; 2) validate and perform tests; 3) identify and interpret molecular abnormalities; 4) communicate this

information to referrers whether specialists or non-specialists; and 5) assume the day-to-day responsibilities for the operation and standards of a molecular genetics laboratory.

73. **(E.iii, E.iv, E.v.)** All personnel should be trained and their competence documented. Training of technical personnel should provide the knowledge and skills necessary for competence within their profession. Minimum educational qualification for technical personnel should be at the Bachelor's (BA, BS, or BSc) level or recognised equivalent education for laboratory technicians. Education and training in genetics is recognised by Best Practices as an essential element to strengthen professional competence to deliver molecular genetic testing.

74. **(E.vi)** Access to continuing education and training is important for all grades of laboratory staff. Participation in educational programmes for continuing professional development is a method to achieve this.

## TERMS AND ABBREVIATIONS

In the context of these guidelines, it is necessary to point out that several terms are used differently across OECD countries. The following terms were agreed by the group of experts reporting to the Working Party on Biotechnology and are provided for ease of reference:

**Accreditation:** a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks.

**Accuracy:** closeness of the agreement between the result of a measurement and a true value of the measure and (from the terms and definitions given in ISO 9000, ISO/IEC Guide 2).

**Acquired variants:** changes in DNA sequence which occur in the somatic cells of an individual during their lifetime, rather than being inherited.

**Analytical sensitivity:** the probability that a test is positive if the genetic mutation is present.

**Analytical specificity:** the probability that a test is negative if the genetic mutation is not present.

**Analytical validity:** gives a measure of how well the test measures the property or characteristic it is intended to measure. It includes measures of analytical sensitivity and specificity.

**Audit:** systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled.

**Certification:** procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements.

**Clinical validity:** clinical validity measures the extent to which the test predicts a clinical outcome. It is described in terms of clinical sensitivity and specificity; and in terms of a test's predictive values. Positive and negative predictive values are the extent to which a test accurately predicts the presence or absence, respectively of a clinical condition. Predictive values are heavily dependent on the prevalence of the condition in the population being tested. As a result a test may be clinically valid when applied to individuals from a high risk population, but not so when applied in the general population. Thus an assessment of who should be offered the test is part of the assessment of clinical validity.

**Competence:** properly qualified to carry out defined activities.

**Consent:** any freely given specific, informed and express agreement of an individual to his or her genetic data being collected, processed, used and stored.

**Corrective action:** action to eliminate the cause of a detected non conformity or other undesirable situation.

**Electronic patient record:** a repository of information regarding the health of a subject of care, in computer processable form.

**Evidence-based:** a claim validated by documented studies.

**Formal report:** a report of laboratory findings useful for patient management and counselling.

**Genetic counselling:** a procedure to explain the possible implications of the findings of genetic testing or screening, its advantages and risks and where applicable to assist the individual in the long-term handling of the consequences. It takes place before and after genetic testing and screening.

**Genotype:** DNA base composition and sequence for a particular region of a gene or multiple genes.

**Health care professional:** a person who helps in identifying or preventing or treating illness or disability.

**Informed consent:** the process of effectively communicating pertinent information to the patient such that an informed decision can be made.

**Interpretation:** the conclusions reached from a genetic test in the context of a clinical referral.

**Laboratory director:** competent person(s) with responsibility for, and authority over a laboratory.

**Licence:** permission, permit from a governmental agency to operate a laboratory.

**Nomenclature:** a naming convention that can be applied uniformly.

**Proficiency testing:** the formal process by which laboratories measure their performance against their peers using externally validated materials. This definition is based on ISO/IEC Guide 2 (“General terms and their definitions concerning standardisation and related activity”, 1996) and has been expanded in the guidelines to include assessment of all phases of the laboratory analytical process, including result reporting.

**Proficiency testing scheme:** a system to determine laboratory performance for particular fields of testing. A scheme might cover a particular type of test related to a disease specific service or a technology.

**Professional qualification:** a quality, ability, or accomplishment that makes a person suitable for a particular position or task

**Referral laboratory:** external laboratory to which a sample is submitted for a supplementary or confirmatory examination procedure and report.

**Reference material:** a material or substance, one or more of whose properties are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.

**Requirement:** need or expectation that is stated, generally implied or obligatory.

**Terminology:** the science of proper use of terms.

**Validation:** validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled. (ISO17025 Section 5.4.5.1).