OECD GUIDELINES FOR QUALITY ASSURANCE IN MOLECULAR GENETIC TESTING

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Background

Since the 1980s, 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.[1]

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 molecular genetic testing laboratories and policies for the handling of samples and genetic data including transfers across borders. 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. 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).

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 the risk of harm 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

1. "Genetic Testing: Policy Issues for the New Millennium", OECD, 2000.

provide regulation and oversight and to promote the quality of laboratories involved in medical testing.

However, these regulatory and oversight procedures have not penetrated diagnostic molecular genetic testing laboratories across OECD Member countries to a high degree and with any consistency. One reason for this could be that 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.

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.

The need to take international action to resolve the issues was endorsed by OECD's Committee for Scientific and Technological Policy meeting at ministerial level in January 2004 as well as by OECD health ministers at their meeting in May 2004. OECD Member countries thus agreed to develop guidelines setting out principles and best practices for quality assurance in molecular genetic testing for clinical purposes in consultation with experts and interested parties. This work led to the *Recommendation on Quality Assurance in Molecular Genetic Testing* adopted by the OECD Council on 10 May 2007 (see C(2007)48)[2] which sets out, *inter alia*, a number of principles and best practices relevant to this field of activity. The Principles are policy recommendations 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.

2 . While a Recommendation of the OECD Council is a non-legally binding document, it represents an important political commitment on the part of the Member countries.

Preface

Genetic tests may be highly predictive of the future health of the individual. 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. The single laboratory test to establish a genotype is usually not repeated and its result 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. Whilst good laboratory practices and adherence to quality standards are the responsibility of all medical testing laboratories, these features of molecular genetic testing place an enhanced duty on laboratories to assure the quality of their services. Research laboratories play a valuable role in the development and validation of new tests particularly in the provision of genetic testing for rare diseases. Governments, regulators and professional bodies have a responsibility to ensure that all genetic testing services are offered within a quality assurance framework that retains the confidence of the public.

These Guidelines comprise Principles and Best Practices for quality assurance in molecular genetic testing for clinical purposes. The Guidelines seek to assist both OECD and non-OECD Member countries in the development and introduction of appropriate quality assurance procedures to:

- Promote minimum standards internationally for quality assurance systems and molecular genetic testing laboratory practices.
- Facilitate mutual recognition of quality assurance frameworks.
- Strengthen international co-operation and facilitate, where appropriate, the cross-border flow of samples for clinical purposes in accordance with recognised principles for their handling, storage, safety privacy and confidentiality.
- Increase public confidence in the governance of molecular genetic testing.

Principles are directed primarily at governments and those involved in the regulation of genetic services, whereas Best Practices primarily are aimed at professional associations and directors of molecular genetic testing laboratories and others involved in the provision of molecular genetic testing. The ethical and legal principles set out in international declarations and agreements and the diversity of systems and jurisdictions within and between countries have been recognised during the development of these Guidelines.

These Guidelines focus on certain aspects of the provision of genetic services. They concern molecular genetic testing 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.

The Guidelines 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.

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.

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.

These Guidelines are intended to be evolutionary in nature and will therefore need to be reviewed within four years of adoption and thereafter 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.

Part One sets out the Principles applicable to quality assurance in molecular genetic testing together with related Best Practices that were adopted as an OECD Council Recommendation. The Principles provide a framework within which to conceive measures that assure all aspects of quality, including competence to carry out and report molecular genetic tests as well as the education and training of laboratory personnel. The Best Practices are practical means for putting into place that framework. Part Two of the Guidelines contains explanatory Annotations which elaborate on the Principles and Best Practices in Part One. Finally, a glossary of terms as well as a list of other relevant publications is provided.

Part I

PRINCIPLES AND BEST PRACTICES FOR QUALITY ASSURANCE OF MOLECULAR GENETIC TESTING

1. Scope

This Recommendation applies to quality assurance of molecular genetic testing offered in a clinical context. It addresses 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.

It focuses 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. It is 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. It does not address testing carried out only for research purposes.

2. Principles and Best Practices

A. General principles and best practices for molecular genetic testing

Principles

A.1 Applicable legal, ethical, and professional standards should be respected in the practice of molecular genetic testing.

A.2. Molecular genetic testing should be delivered within the framework of health care.

A.3 All molecular genetic testing services should be provided and practised under a quality assurance framework.

A.4 Informed consent to test should be the norm and should be obtained in compliance with applicable legal, ethical, and professional standards.

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 privacy protection and security in accordance with applicable law.

A.7 The benefits of cross border exchange of patient samples and personal information for molecular genetic testing should be recognised.

A.8 The use, storage, transfer and disposal of patient samples collected for molecular genetic testing should be subject to applicable legal, ethical and professional standards.

A.9 Advertising, promotional and technical claims for molecular genetic tests and devices should accurately describe the characteristics and limitations of the tests offered.

Best Practices

A.i Regulatory and professional bodies should, as appropriate, 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 make available information on the analytical and clinical validity of tests.

A.iii Molecular genetic test results 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 of medical laboratories is an effective procedure for assuring quality.

B.2. All molecular genetic testing results for clinical care purposes should be reported by competent laboratories, as established by accreditation or other equivalent recognition consistent with these Guidelines.

B.3 Accreditation and other equivalent recognition should be based on internationally recognised standards and guidelines to facilitate mutual recognition of molecular genetic testing services.

B.4 The requirements adopted by legal, regulatory and professional bodies for laboratories to be recognised as competent through an accreditation or equivalent recognition should be accessible, clearly stated, and effective.

B.5 Regulation and incentives should be introduced to facilitate the development and implementation of accreditation or other equivalent recognition.

B.6 Impediments to achieving the requirements for accreditation or other equivalent recognition should be identified and addressed.

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

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

B.9 Governments should encourage international collaboration for the development and validation of molecular genetic tests.

Best Practices

B.i All laboratories reporting molecular genetic testing results for clinical care purposes should be accredited or hold an equivalent recognition. Research laboratories carrying out molecular genetic testing which are not accredited nor hold an equivalent recognition should arrange for such results to be verified and reported by a laboratory holding such an accreditation or recognition.

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

B.iii Technical assessors acting on behalf of accreditation bodies or bodies delivering equivalent recognition 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 have policies and procedures to regularly evaluate internal quality control measures and to document findings and any corrective actions taken to address deficiencies.

B.vi Laboratories should make available to service users current evidence concerning the clinical validity and utility of the tests they offer.

B.vii Developers, manufacturers, health care professionals and laboratories, as well as other relevant groups, should collaborate to establish the clinical validity and utility of tests, particularly for rare conditions.

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

B.ix Laboratories should use available reference materials and/or family-specific (private) mutation controls where appropriate and available.

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 competent to provide such schemes, as established by accreditation or equivalent recognition.

C.4 Accreditation or equivalent recognition 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 laboratory performance, and address persistent poor performance, should be in place.

Best Practices

C.i 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 agreed standards should identify persistent poor performance and ensure that timely corrective actions are taken and documented.

C.iii Proficiency testing schemes should be structured to assess all phases of the laboratory 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 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.vi Laboratories should make the fact that they participate in proficiency testing publicly known.

C.vii Individual laboratory performance in proficiency testing schemes may be disclosed on a voluntary basis by the laboratory concerned but should not be made public by proficiency testing scheme providers unless so required by law.

D. Quality of result reporting

Principles

D.1 All laboratories should issue molecular genetic testing results in the form of a written and/or electronic report to the referring clinician or health professional.

D.2 Within jurisdictions where reports may be issued directly to patients, governments, regulatory and professional bodies should encourage all laboratories performing clinical molecular genetic tests to recommend that patients consult an appropriate clinician or health care professional to help them understand the implications of the test result.

D.3 Governments and regulators should require that in issuing and archiving reports, all laboratories comply with applicable law and regulations, including those concerning the confidentiality of information.

D.4 The interpretation of molecular genetic test results should be appropriate to the individual patient and clinical situation and should be based on objective evidence.

Best Practices

D.i Reports should communicate information effectively taking into account that the recipient may not be a specialist health care professional.

D.ii Reports should be timely, accurate, concise, comprehensive, and communicate all essential information to enable effective decision-making by patients and health care professionals.

D.iii Reports should use applicable internationally accepted terminology and nomenclature including identification of reference sequences.

D.iv Laboratories should inform service users of the patient and family information the laboratory requires to ensure the appropriateness of the test request and to interpret the results.

D.v In jurisdictions that allow laboratories to enter reports into a conventional or electronic patient record, all essential and relevant elements should be included.

D.vi Reports should include at a minimum the following information:

1. Identification that unequivocally links the report to the patient.
2. The name of the referring health care professional and contact information.
3. The indication for testing and specific medical information where it is relevant to test interpretation.
4. The test performed and the methodology used (including the scope of the analysis, the limitations of the test and its analytical sensitivity and specificity).
5. The primary sample type where necessary for the interpretation.
6. The date of receipt of the sample.
7. The name and location of laboratory(ies), including any referral laboratory(ies), which performed the actual testing on the sample.
8. The test result.
9. An interpretation of the result in the context of the indication for testing and all other information provided to the laboratory.
10. The identity of the individual approving the report.
11. Laboratory contact information.
12. The date of issue of the report.

D.vii Where appropriate, the test report should also include the following information:

1. A recommendation for genetic counselling by a qualified health care professional.
2. Implications for other family members.
3. Recommendations for follow-up testing.

D.viii All the essential and relevant elements of test results and interpretation reported by a referral laboratory should be included in the report to the health care professional who ordered the test.

E. Education and training standards for laboratory personnel

Principles

E.1 Laboratory personnel should have appropriate professional qualifications that meet recognised standards, underpinned by education and training, to assure laboratory competence in the provision of molecular genetic testing.

E.2 Standards for laboratory accreditation or other equivalent recognition should require that all molecular genetics personnel have a combination of education, training, skills and experience that ensures their competence.

E.3 Existing specialist education and training programmes relevant to molecular genetic testing that meet recognised standards should be formally adopted by governments, regulatory and/or professional bodies.

E4. Development of educational and training programmes should be encouraged where they do not exist.

E5. Relevant government or professional authorities should recognise medical genetics as a discipline comprising both a clinical and a laboratory specialty.

E.6 Where governments, regulators and professional bodies recognise medical and scientific qualifications awarded by foreign institutions, such recognition should be extended, as appropriate, to equivalent qualifications in molecular genetic testing.

E.7 All personnel involved in molecular genetic testing should practice within the framework formed by applicable legal, ethical and professional standards.

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, qualifications and skills 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 a recognised equivalent qualification. Educational requirements should include formal training in molecular

genetics and where available, certification in the specialty of clinical laboratory molecular genetics, or another relevant discipline.

E.iii Laboratory directors should ensure that all laboratory personnel have relevant training and have their competence documented prior to performing molecular genetic testing for the purpose of reporting a diagnostic result on any patient material.

E.iv Education and training in genetics should be recognised by regulatory and/or professional bodies as an essential element to strengthen professional competence to deliver molecular genetic testing.

E.v Laboratory directors should ensure that all personnel involved in molecular genetic testing participate in continuing education and training programmes appropriate to their roles and designed to further develop and maintain competence.

E.vi 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 Practices. For ease of reference, Principles or Best Practices to which a specific annotation alludes to are included in parentheses at the end of the relevant paragraph.

2. These Guidelines offer principles and best practices for quality assurance in molecular genetic testing 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 their standards for quality assurance systems and molecular genetic testing laboratory practices. The Guidelines recognise the existence of regional, national and international quality assurance frameworks and seek to facilitate their mutual recognition.

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 the comprehensive availability of services through international collaboration. This mutual recognition can only be achieved through international consensus on minimum common standards to assure consistency in the quality of molecular genetic testing services.

4. Whilst most OECD Member countries have mechanisms in place to reduce the risk of inappropriate and inaccurate molecular genetic testing, these regulatory and oversight procedures have not penetrated molecular genetic testing laboratories across OECD Member 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.

General terminology

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

6. For the purpose of these Guidelines, quality assurance means all those planned and systematic activities implemented within a quality system, and

demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality.[3]

7. The Guidelines acknowledge that different mechanisms or procedures exist across OECD Member countries to promote quality assurance in laboratory medicine. Instruments relevant to quality assurance may include: accreditation, licensing, certification, proficiency testing, internal quality control measures, documentation of policies and procedures, and/or assurance of personnel competence that may include certification or registration of laboratory personnel.

8. Accreditation is a procedure by which an authoritative body gives formal recognition that a body is competent to carry out specific tasks.[4] It is a public recognition of a laboratory's competence. It is only granted after a thorough on-site assessment by technical assessors of the management, environment, policies and procedures of the laboratory in addition to specific scientific/technical competences measured against external standards. Accreditation is also applicable to organisations providing proficiency testing. The Guidelines also conceive of equivalent recognition (see paragraph 24). In 2003, the OECD quality assurance survey provided evidence that 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.[5]

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

10. 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 on a need for a continuous cycle of quality improvement at the centre of all policy making and operational decisions.

11. Establishing the competence of a laboratory through an accreditation procedure includes an assessment of the laboratory infrastructures and all

3. [ISO 9000].

4. [ISO/IEC17000:2004].

5. "Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Summary Report of a Survey of 18 OECD Member Countries", OECD (2005).

internal quality control and quality assessment measures. For example, to achieve accreditation a laboratory must, amongst other requirements, 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 scheme. It may also be obliged to demonstrate satisfactory performance and show that it is responsive to shortcomings demonstrated through proficiency testing as well as deviations in performance discovered as a result of routine internal laboratory quality control measures.

12. In contrast, licensing is a legal permit or a formal permission from a constituted authority or 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 types of service provided. In return, the laboratory is officially registered and may be publicly listed. Practice amongst licensing authorities varies. The granting of a licence may or may not require a formal audit of policies, procedures or practice by the responsible authority. In some jurisdictions licensing authorities require formal accreditation (see paragraph 8).

13. Certification is a procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements.[6] Certification is a well-recognised indicator of the quality management of an organisation but it is less stringent than accreditation. It involves a procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements 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. In contrast, a certification programme for persons that is accredited to ISO/IEC 17024 requires examination of the competence of persons.

14. Proficiency testing schemes are systems to determine laboratory performance for particular fields of testing.[7] They allow a laboratory to compare its performance for an individual test or technique against that of other laboratories. Typically, a proficiency testing scheme provides a number of biological samples of known and validated genotype to participating laboratories. Laboratories are asked to genotype the samples

6. [ISO/IEC17000:2004.].

7. Based on UKAS Accreditation of Providers of Proficiency Testing Schemes for Laboratory Testing. 2005.

and return their reports to the proficiency testing scheme 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 proficiency testing samples and asking participants to interpret the genotype results in the context of the clinical scenario and to report their findings in their usual reporting format.

1. General principles and practices for molecular genetic testing

15. 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. Therefore, support to the individuals concerned, appropriate to the potential outcomes of testing is important. The test may be used to support a diagnosis, or may be used to predict, with variable certainty, later onset of disease. In jurisdictions where permitted, genetic testing may be carried out to determine carrier status or for pre-implantation or prenatal testing. (A.2)

16. The Principles specify that all genetic testing services should be subject to a quality assurance framework. In this context, a framework is considered to be the totality of the mechanisms that directly or indirectly affect the quality of a laboratory service. These may include statutory, non statutory, regulatory and/or professional mechanisms such as code of practices and clinical guidelines. (A.3)

17. A process leading to informed consent is a necessary step for medical procedures including molecular genetic testing and the responsibility of health care professionals. Exceptions are recognised in regulation, law, and professional guidelines. 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 molecular genetic test. Informed consent should be considered as a process, following a dialogue, not simply a contractual agreement and should strive for patient education and understanding. 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 molecular genetic test. The process leading to informed consent should follow established regulation or professional guidelines. For some tests, in particular for predictive or pre-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. Relevant international recommendations and declarations on informed consent include the (1997 UNESCO) Universal Declaration on the Human Genome and Human Rights; the (2003 UNESCO) International Declaration on Human Genetic Data; and the (2005 UNESCO) Universal Declaration on Bioethics and Human Rights (A.4)

18. Together with the offer of a genetic test, consideration must be given by a health care professional to the need for pre-and post-test genetic counselling. For the purpose of these Guidelines, genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counselling to promote informed choices and adaptation to the risk or condition. [8]

19. The nature and duration of counselling should be dependent on the type of genetic test, its context and its potential outcomes. 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, and that confidentiality is respected. (A.5)

8. [National Society of Genetic Counselors' Definition Task Force; Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, Williams JL. A New Definition of Genetic Counselling: National Society of Genetic Counselors' Task Force Report. J Genet Couns. 2006;15(2):77-83.]

20. Thousands of 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 Member 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 Principles recognise the need to enable and facilitate this exchange through clearly stated, transparent, internationally agreed standards and procedures. (A.7)

21. 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 OECD Privacy Guidelines provide that, in general, Member countries should refrain from restricting the flow of personal data across countries 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. Furthermore, the storage, retention and use of samples, records and reports are subject to legal, ethical and professional standards. Examples are the (1997 UNESCO) Universal Declaration on the Human Genome and Human Rights; the (2003 UNESCO) International Declaration on Human Genetic Data; and the (2005 UNESCO) Universal Declaration on Bioethics and Human Rights. (A.6; A.8)

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

23. 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 Practices also draw special attention to the communication between the clinicians and the laboratory providing the testing. (A.ii; Aiii)[9]

2. Quality assurance systems in molecular genetic testing

24. Principle B2 refers to the concept of "equivalent recognition". This should include assessment of competence in services provided, including technical competence and relevant specialist education and training; and also compliance with relevant legal, professional and quality management standards. (B2)

25. Where accreditation or equivalent recognition is based on the same or compatible standards, such as ISO 15189 and ISO/IEC 17025, there is the potential for achieving similar levels of competence internationally. The mutual recognition arrangement (MRA), contemplated by the International Laboratory Accreditation Cooperation (ILAC), provides a basis for equivalence of laboratory services and is a base for laboratory accreditation reciprocity between countries. International comparability in genetic test quality assurance standards is essential to retain public confidence in molecular genetic testing. (B.3)

26. The type of instrument applied will depend on the nature and scope of oversight. Regulatory and/or professional oversight can be effective. Intervention should occur when necessary and should be appropriate to the risk of an erroneous genetic test result. The intent, meaning and process by which regulations are developed and administered should be transparent. Regulators must be able to justify their decisions and provide regulations that are practical and useful to implement. For example, the licensing of a molecular genetic testing laboratory does not contribute directly to the quality of its output. However, it may be a valuable tool which is used by authorities to monitor service providers. It may indicate a particular requirement 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. (B.4)

9. 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".

27. The implementation of regulation and appropriate incentives can act as major drivers to promote the quality of molecular genetic testing. The Guidelines recognise as a principle that achieving and maintaining compliance with the standards of accreditation or equivalent recognition requires resources to achieve this objective. They also recognise that establishment of formal arrangements for evaluation and benchmarking of processes, and structures to encourage performance improvement are necessary. (B.5, B.6)

28. Principles encourage active dissemination of 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. (B.6, B.7)

29. For most molecular genetic tests in use today, there are no reference materials available. The objective of the Principles is to encourage international collaboration and the establishment of appropriate mechanisms or programmes [10] for the collection, development, verification and use of reference materials. 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. (B.8)

30. International collaboration is particularly important for certain tests, including those for rare diseases and new tests, in establishing analytical and clinical validity. (B.9; Bvii)

31. Research laboratories play a valuable role in the development and validation of new tests particularly in the provision of genetic testing for rare diseases. Characterization of mutations in rare diseases is not always available in an accredited or recognized equivalent molecular genetic testing laboratory for a number of reasons, including the fact that the infrequency of such conditions makes this activity resource-prohibitive for such laboratories. Consequently, characterization of mutations in rare diseases is often only undertaken by a small number of research laboratories in the world that are studying causative genes and recruiting affected families to further the research in this area. The Best Practice recommends that results of clinical importance which are to be used for health care are verified and reported within an acceptable quality assurance framework. (Bi)

32. The OECD 2003 survey of quality assurance molecular genetic testing laboratory practice revealed a lack of clarity and consistency in the adoption and use of the existing terminology relevant to quality assurance; for example, different meanings are often assigned to the terms ‘accreditation’, ‘certification’ and ‘licensing’. Governments, regulatory and professional

10. For example: The US Centers for Disease Control and Prevention Genetic Testing Quality Control Materials Program (GTQC), EUROGentest.

bodies should encourage consistent use of internationally agreed terminologies and nomenclature. (B.ii)

33. The policies and procedures to document the analytical validity of tests should be sufficient to satisfy external assessment. (B.iv)

34. Information pertaining to the clinical validity and utility of a test, relevant to the patients served, should be made available to service users (healthcare professionals and patients). It should be based on relevant existing medical guidelines and peer reviewed literature and may include or be supplemented by in-house studies appropriate for peer review. Sources of data should be cited. (B.vi)

35. Clinical validation of a genetic test reflects its ability to correctly classify individuals with respect to their disease status or risk. Measurements of validity include sensitivity, specificity, positive predictive value, and negative predictive value[11]. 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 to the general population. Thus, an assessment of who should be offered the test is part of the assessment of clinical validity. Clinical utility refers to the anticipated effect(s) of the clinical use of the test result, including on health outcomes, recognising that a variety of factors influence this outcome. (B.vi; Bvii)

3. Proficiency testing: monitoring the quality of laboratory performance

36. For the purpose of these Guidelines, the term "proficiency testing" is taken in a broad sense to include assessment of all phases of the laboratory analytical process, including test result reporting. Some proficiency testing programmes may also refer to the term external quality assessment. In these Guidelines the terms are deemed to be equivalent.

37. Across OECD Member countries, proficiency testing 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

11. Important limitations of molecular 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 for the patient's subpopulations is often crucial in defining their residual risk in the event of a negative test result.

specific molecular genetic tests means that it is not practicable to provide a proficiency testing scheme for each genetic test. In addition, considering the large variability in methodologies and diagnostic approaches, the comprehensive availability of proficiency testing remains challenging.

38. The Guidelines recommend the use of an external review process and recommend that organisations providing proficiency testing schemes should be competent to do so as established by accreditation or equivalent recognition. This recommendation is based upon the requirements contained in the International Laboratory Accreditation Cooperation (ILAC) guidelines for the Requirements for the Competence of Providers of Proficiency Testing (ILAC-G13:2000) and on ISO/IEC Guide 43-1:1996.[12] 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. (C.3, C.4)

39. Many genetic diseases are rare and testing may be carried out by only one or a few laboratories in the world which are studying the causative genes, have recruited affected families and have developed in-house assays. This makes development of proficiency testing schemes for these disease services impractical since they rely 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 Principles acknowledge these issues and include provisions for disease testing for which proficiency testing is unavailable by recommending under Principle C.5 that alternative methods for measuring laboratory performance should be made available.[13] The Best Practices encourage laboratories to make use of these alternative methods. Alternative methods include blind sample exchanges and review of results between laboratories, blind repeat testing, testing by different independent methods, and correlation of results to clinical and laboratory parameters. If 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). (C.5, C.v)

12. ISO/CASCO 322: ISO/IEC Guide 43: Proficiency Testing by inter-laboratory comparisons -Part 1: Development and operation of proficiency testing schemes. 1996.

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

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. For example, proficiency tests can, by design, include statistical techniques to monitor a participant's performance. 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. (C.6)

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

41. To ensure that standards are being met and effectively address persistent poor performance, regular monitoring and documentation of corrective actions are necessary. Regulatory and professional bodies should consider what body will have authority to intervene in case standards are not being met and what interventions these will be. (C.ii)

4. Ensuring quality in molecular genetic test result reporting

42. For the purpose of these Guidelines, the test result report is the factual presentation of results of tests done in a laboratory useful for patient management and counselling.

44. When genetic testing is ordered to determine a genotype associated with disease, predisposition to a disease, or to predict an individual's response to a medicine, the genotype, in itself, can be uninformative or misinterpreted if appropriate test, patient or family-specific information is not taken into consideration. Genetic test results may 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 test result report communicates the certainty or uncertainty of the analytic test result, its limitations and, where appropriate, the implications for the patients tested and their family.

45. Principles recommend that all laboratories reporting clinical molecular genetic test results issue a written and/or electronic report to the referring health professional. Within the Guidelines, health professionals are persons authorised by local and/or national bodies to use molecular genetic tests for patient counselling and/or management. Health professionals may include

physicians, nurses, midwives, physician assistants, and genetic counsellors. (D.1)

46. While it is recognised best practice that genetic test results should be provided to patients by a health care professional, this does not always happen. Some jurisdictions permit ordering of genetic tests directly by members of the public, and such individuals may receive results without the involvement of a health care professional. In other situations, patients may receive a copy of their genetic test report which has also been sent to their health care professional. This Principle seeks to ensure that all patients receiving reports directly from a laboratory also receive a recommendation to consult a health care professional about the result and its possible implications. (D.2)

47. 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 molecular genetic test, the laboratory should report the 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. (D.i, D.ii)

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

49. The utility of a molecular genetic test report is often dependent on the accuracy and adequacy of information provided to the laboratory. The 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. (D.iv, D.viii)

50. A referral laboratory is an external laboratory to which a sample is submitted for a specialist, supplementary or confirmatory examination procedure and testing. It is important that the integrity of the report from the referral laboratory is maintained in the report provided to the health care professional (D.viii)

51. Information provided by the referring health care professional and used in the interpretation of the genotype may include: relevant demographic information, clinical data and information about a family history and 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. Where the quantity or quality or the adequacy of the sample received may affect the result, this should be noted in the report. Identification must unequivocally link the patient to the report. (D.vi)

5. Education and training standards for laboratory personnel

52. 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. (E.1)

53. Laboratory accreditation standards or other equivalent recognition 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. (E.2)

54. 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 professional competency. 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. (E.3, E.5)

55. Lack of specialist training programmes in molecular genetics may lead to inadequate availability of competent staff with consequences for quality assurance. Education and training programmes may be necessary to meet the growing personnel requirements of diagnostic molecular genetic testing laboratories. Jurisdictions lacking such programmes are encouraged to consider the adoption or development of such programmes. (E.4)

56. 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. (E.6, E.vi)

57. 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. (E.7)

58. An appropriately 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/or professional bodies, as applicable, should establish a process whereby an MD, PhD, or recognised equivalent, as well as formal training in molecular genetics are deemed important qualifications for a director of a molecular genetics laboratory. A recognised equivalent may be defined by governments and/or professional bodies within each jurisdiction. Training of a diagnostic molecular genetics laboratory director should be appropriate to their 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 of a molecular genetics laboratory 6) establish and ensure the maintenance of a quality management system. (E.ii)

Glossary

The following definitions are provided for ease of reference. They are drawn from definitions commonly used in international instruments and do not represent an effort by OECD to agree on interpretations of these definitions or develop new ones. The source material reference is acknowledged in square brackets following the definition.

Accreditation is a procedure by which an authoritative body gives formal recognition that a body is competent to carry out specific tasks. [ISO/IEC 17000: 2004]

Audit: systematic, independent and documented process for obtaining evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled. [ISO 9000: 2000 Quality Management Systems: Fundamentals and Vocabulary]

Competence is the product of basic academic, postgraduate and continuing education, as well as training and experience of several years in a medical laboratory. [ISO 15189: 2003].

Informed consent: a process by which a subject voluntarily confirms his or her willingness in a particular testing act, after having been informed of all aspects of the act that are relevant to the subject's decision to participate in the act .Informed consent is a process, following a dialogue, not simply a contractual agreement, should strive for patient education and understanding and should follow established regulation or professional guidelines. [Based on ICH Good Clinical Practice Guidelines E6]

Laboratory director: competent person with responsibility for, and authority over a laboratory [ISO 15189: 2003].

Objective evidence: data supporting the existence or to verify something. Objective evidence may be obtained though observation, measurement, test, or other means. [ISO 9000: 2000]

Proficiency testing is the formal process by which laboratories measure their performance against that of their peers using externally validated materials. [ISO/IEC 17000: 2004]

Quality assurance means all those planned and systematic activities implemented within a quality system, and demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality. [ISO 9000: 2000]

Referral laboratory: external laboratory to which a sample is submitted for a supplementary or confirmatory examination procedure and report. [ISO/WD 15189 v1.05]

Reference material: material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process. [ISO Guide 35:2006]

Note 1: Reference material is a generic term.

Note 2: Properties can be quantitative or qualitative, *e.g.* identity of substances or species.

Note 3: Uses can include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.

Note 4: A Reference Material can only be used for a single purpose in a given measurement.

Technical assessor: an assessor who conducts the assessment of the technical competence of the laboratory or inspection body for specific area(s) of the desired scope of accreditation. [ILAC G11:07/2006 ILAC Guidelines on Qualification and Competence of Assessors and Technical experts.]

Validation: confirmation by examination and provision of objective evidence that the requirements for a specific intended use are fulfilled. [ISO 8402; 1994 Quality Management and Quality Assurance - Vocabulary (Glossary)]