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## Regulatory Issues for Genetic Testing in Clinical Practice

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### Summary

Whereas delivery of health care is nationally based with great differences in ways of service provision and financing between countries, and thus not subject to international regulations, genetic testing has become more exposed to international regulations and conventions. This is due to an interest of protecting the individual for abuse by inappropriate use of genetic information, but also to the fact that a specimen from a person aimed for a medical (clinical genetic) test is considered as “tradable goods”, and thus also subject to other non-medical associated regulations. There is a substantial transborder flow of samples for genetic testing thus requiring internationally accepted quality standards. Therefore, laboratories acting on an international market need to follow certain rules and regulations, also applicable to obtain high quality standards nationally. Further, genetic testing for rare disorders is often provided by a limited number of non-commercial laboratories and associated with research programmes for the individual disorders. International surveys have revealed that there is a general lack of high standards for quality assurance. This paper is aimed to give an introduction and overview of regulations, conventions and quality standards applicable for the laboratory who is seeking to improve their quality performance.

Key words: genetic testing, quality assurance, clinical genetic practice, regulations

### 1. Introduction

Genetic testing is often regarded as a laboratory procedure in a molecular genetic laboratory. However, for practical use in health care, this definition is too narrow. In the majority of cases,

the clinician is not using a genetic test for diagnostic purposes, but for confirming or excluding a clinical suspicion of an underlying disorder of presumed genetic background where there is a strong association between mutations in a specific gene and the disease. As an example, a confirmatory test could be requested by a paediatrician, who — after investigating an unhealthy child physically and with non-genetic tests — has the suspicion that the child has cystic fibrosis (CF) and orders a cystic fibrosis transmembrane conductance regulator (CFTR) mutation-scan. If mutations are found, the diagnosis is confirmed. Furthermore, the specific mutations detected may give prognostic information about the child's future health. The doctor will also have information that can be used for family investigations, and possibly for prenatal diagnosis. However, if only one or no mutations are found, this does not exclude the possibility that the child has CF. The test used may not detect all mutations, or the gene may have been silenced by other reasons, e.g., altering the regulation of the gene. An example of exclusion testing is a patient presenting with neurological symptoms, leading to a suspicion of Huntington's disease. A genetic test revealing a normal set of trinucleotide repeats in the IT-15 gene will indicate that the symptoms are not caused by this disorder. In genetic testing, the information given to the patients and their families must be an integral part of the process.

On the other hand, recent advances in molecular genetics have revealed information on the influence of genetic polymorphisms on common diseases. This opens for characterisation of genetic risk factors – susceptibility testing. Even if the implications for relatives might not be as foreseeable as when testing for rare genetic diseases, they still should be considered as genetic tests and only be performed in association with genetic testing.

Therefore, in clinical practice genetic testing must be seen in a wider context and may be defined as follows:

“Genetic testing is the process of information transfer within which the laboratory investigation is integral. It consists of any analysis of family data, of human chromosomes, DNA, RNA, protein or certain metabolites to detect heritable or acquired disease and related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include diagnostic, predictive, carrier, prenatal, preimplantation, or new-born testing, thus predicting risk of disease and/or identification of carriers, establishing prenatal or clinical diagnoses or prognoses in individuals,

families or populations” (1).

Such a wide definition encompasses all aspects of the testing procedure, including genetic counselling both before and after a genetic test is performed.

The aim of this chapter is to highlight some of the issues connected with the regulation and the use of genetic testing in clinical practice.

## **2. Regulations/Guidelines/Statements**

Laboratory genetic testing of suspected constitutional genetic disorders is legally more regulated than other medical investigations, including acquired genetic alterations, in order to protect family members from discrimination or misuse, mainly with regard to presymptomatic diagnosis.

### **2.1. International Documents**

Regulation of genetic services differs between different countries. In some, strong national regulations exist, whereas many countries have weak or a complete absence of regulations. However, a number of international bodies have published recommendations about individual rights as they relate to the development of genetic service. Important examples are the “Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine” by the Council of Europe (2), the “Universal Declaration of the Human Genome and Human Rights” by UNESCO (3), and the “Proposed Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Service” by WHO (4). Similarly many professional and scientific organisations have their codes of conduct. Examples are the HUGO “Statement on Principled Conduct of Genetics Research” (5), the “European Society of Human Genetics’ Statements by the Public and Professional Policy Committee” (6), the recommendations by the Europeans Society of Human Genetics’ Public and Professional Policy Committee (ESHG/PPPC), and the Guidelines for quality assessment in cytogenetics by the European Cytogeneticists Association (ECA) (7). Further, the Organization for Economic Cooperation and Development (OECD) took in 2000 an initiative to investigate the need for internationally harmonised guidelines for quality assessment in for molecular genetic testing (8,9,10). This initiative led to recommendations that were adopted by the council of

OECD in May 2007 (*11*).

## **2.2. National Documents**

An overview on existing regulations in Europe and the United States was made by the European Society of Human Genetics' Public and Professional Policy Committee in a background paper to a workshop on Provision of Genetic Services in Europe (Helsinki, September 2000) (*6*). The EU-funded network of excellence EuroGentest ([www.eurogentest.org](http://www.eurogentest.org)) have further explored the field, and several reports are available on their website or under publication.

For those who work in countries with no or only rudimentary regulations who need to keep up with high international standards, these policy documents provide valuable information. A genetic testing laboratory operating in a relatively unregulated environment may benefit from having a written policy and guidelines based on these international documents and making their policies available to their clients. For example, the U.S. Clinical Laboratory Improvement regulations are available on the web (*12*) and constitute a sound basis for the provision of service.

## **3. Ethical Issues in the Molecular Genetics Laboratory**

There are no specific ethics for molecular genetics or molecular genetic tests, or for molecular genetics laboratories. The same premises and guidelines for good laboratory practice current in other medical laboratories should be achieved. However, in performing genetic investigations, many of the ethical issues become more evident. In addition to providing information that is highly predictive for future disease, molecular genetics tests often give information that is relevant to the person tested as well as to their relatives. Some important points have been published by a group of experts from science, industry and patient organisations under the auspices of the EU-commission (*13*)

### **3.1. Informed Consent**

Informed consent is of primary importance in presymptomatic testing and in other uses of genetic testing. The result of the genetic test may be of importance, not only to those tested but also to their relatives and the establishment of a genotype is usually a "once-in-a-lifetime-test."

For these reasons, the test provider must ensure that the patient or client has full information on the consequences of the test results. For diagnostic tests, the clinician should always inform the patient, or if applicable, the parents, children, or spouse, about the clinical suspicion of a heritable disorder. It is the obligation of the clinician who is responsible for referring the test sample to the laboratory to have an informed consent from the patient when presymptomatic testing is requested (*14*). The laboratory may request a clear statement from the referring clinician with the referral that the patient has given their informed consent for the test.

### **3.2. Ethical Committees**

In research laboratories, testing is most often performed as a part of the research program, and thus, ethical committees monitor the investigations. In clinical work, this is not mandatory. However, in a clinical laboratory, the staff must consider ethical implications of their work, e.g., if non-paternity is detected unexpectedly, or when analyzing the outcome of a newly introduced diagnostic test. Therefore, any laboratory is advised to have an ethical advisory board to consult, or at least be able to consult ethically trained persons.

## **4. Purpose of Testing**

A genetic test may be diagnostic, presymptomatic, prenatal, or carried out for screening purposes. These scenarios require different approaches, and the purpose of the testing must be made clear for the laboratory by the referring clinician.

Urgent tests such as prenatal and presymptomatic tests should have as short a turn-around time as possible. The mutation to be tested should preferably be known in advance, and the sample should be tested together with a sample from a relative with that particular mutation as a positive control.

The target turn-around time should be clear to the referring clinicians, and should be related to the realistic and normal capacity of the laboratory. For some complex molecular investigations such as for colon cancer or breast cancer, the necessary time period may exceed several months, whereas for Huntington's disease or cystic fibrosis, a normal turn-around time can generally be measured in days or weeks.

For more rare disorders, especially when service is offered as a part of a research program, the

time to results may be extended. In these cases, the referring clinician and the patient or family involved must be fully informed about the progress of testing, and that there may not be any results in any foreseen time period to avoid giving false hope to the patient and harming future clinical or research contacts.

Screening tests should have a high predictive value — the absolute majority of those at risk should be detected with as low a number of false-positives as possible. The screening test should also be cost-effective, and only performed if there is a treatment available for the disorder tested (15). Moreover, clinical resources for proper follow-up should be available. The methodology used should be targeted for large-scale analysis, and a positive result should always be confirmed by a diagnostic test. Screening tests could be neonatal, prenatal, or performed later in life. The screened group could be a whole population, or a subset selected on the basis of calculated increased risks. The decision to start such programs must carefully consider the costs and benefits, and should be made as a part of a public health care system. More information on the prerequisites for genetic screening is available through the statements of the European Society of Human Genetics (6).

## 5. The Importance of Genetic Counselling

A genetic test for a rare disorder should always related to clinical findings in a patient or to a person's family history. Based on this information, the referring clinician decides what type of test should be performed. Genetic counselling should be offered both before and after a genetic test is performed, and this is equally important whether a mutation is detected or not. One of the common misunderstandings is that when a genetic test does not reveal a mutation, the gene cannot be involved as a cause of the disorder—an interpretation that may be deleterious to the patient (11,14).

Depending on the indication for investigation, pre- and post-test counselling is of varying importance. Whereas in the case of a diagnostic test for CF the post-test counselling to the patient and/or the parents may be the most important factor, in the case of a presymptomatic test for Huntington's disease, the pre-test counselling is of equal importance. In this situation, the clinician is dependent on the accuracy of the laboratory report. It is important that the results are clearly stated and interpreted in a way that is understandable for the non-specialist to ensure a high standard of genetic counselling.

With regard to susceptibility testing, the reason for testing may be different than for rare disease testing. The test result reveals a risk factor that has to be interpreted together with other health information for the individual. Therefore implications for relatives might be less evident. However, these tests must be considered as genetic tests and accompanied by relevant pre- and post test counselling.

## **6. Training and Workload of Laboratory Staff**

Effective staffing is a prerequisite for providing high-quality service. This includes both appropriate training and qualification for the personnel who perform the analyses and supervision, as well as a level of staffing that enables the laboratory to present results without unnecessary delay. If not a part of the laboratory staff, medical expertise must be available on a regular basis. The laboratory should also have policies for referral elsewhere in cases that require specialized expertise that it cannot provide.

Staff should be offered continuous education on a regular basis that is relevant to their position in the laboratory. Their competence should be documented and regularly updated.

The workload of each staff member is difficult to estimate, as it is influenced by many factors such as the degree of automation and the type of samples processed in the laboratory. However, the number of staff should be sufficient to ensure that no unnecessary delay occurs in the processing of the samples. Sufficient staff to ensure continuity of service in a clinical laboratory during absences and vacations is recommended, and lack of space or appropriate equipment must not be a quality-limiting factor.

## **7. Validation of the Laboratory — Quality Issues**

The validation of the laboratory should focus not only on process, but also include staffing, education of staff and supervisors, reporting, and recording. It should include external and internal quality assessment, with emphasis on standardization of operational procedures using recognized laboratory standards. The EMQN best practice protocols are very useful (*16*).

To maintain public confidence to reach high standards and to avoid abuse of molecular genetic investigations, participation in External Quality Assessment activities, including a transparent organization and a willingness to allow public inspections of the laboratory, are necessary (*11*).



There is at present no simple and reliable way to identify, for a particular diagnostic test, a laboratory with a strong quality system, nor conversely to determine for a given laboratory what is included in its Quality Assurance (QAu) system. EuroGentest is, in collaboration with Orphanet ([www.orpha.net](http://www.orpha.net)) performing a survey on the status of quality assurance in European genetic laboratories., This information will be available on their websites.

## **8. Clinical Significance of Test Results**

The clinician who sends samples to the laboratory may have little knowledge about how the work is performed in the laboratory. The results must always be written with this in mind so that the interpretation of the laboratory results is absolutely clear. Reporting of polymorphisms may sometimes cause problems. It may be difficult for the clinician to understand the nature of the molecular finding, and the clinical significance of the absence of a mutation. An even greater problem is when a finding—for example, a missense mutation—not previously described and of unknown function is reported. The clinician must have full information, especially if the laboratory requests an extended family investigation to be able to further delineate the clinical significance of the molecular findings. In these cases, careful, repeated genetic counselling is often required to avoid the risk that the patient and their family will misunderstand the clinical significance of the molecular findings. The OECD recommendations, the ECA and the EMQN guidelines provide valuable information on what information is considered important when reporting, and how it should be structured ([7,11,16](#)).

## **9. Transition of Research to Clinical Testing**

Many research laboratories offer genetic testing to families who have contributed to their research, and to other families or clinicians asking for help with molecular diagnosis of the diseases in which the laboratory has research interests. Although the core members of the research families often are well-informed about the disease and risks and benefits of genetic testing, this may not be the case in the extended family. In addition, many researchers and scientists may not be trained to talk to patients and family members about presymptomatic or prenatal testing. Genetic testing in a research context should therefore have a clinical geneticist or genetic counsellor associated to the team to communicate information to family members.

As research progresses, the research scientist must make sure that a clinical laboratory can continue to offer a service to patients and families. The researcher, in collaboration with the health care providers, must develop a mechanism that allows the transition from research to clinical service.

For the families and patient organizations who have been involved in research, it is traumatic to realize that tests that have been offered suddenly are not available. A failure in this transition of research into clinical service may detract from families' interest to participate in future research.

Several factors must be considered in the decision to transfer a genetic test from research to clinical practice: Is there a need for a clinical test? Are the methods used reliable, and how will the test be validated? There is a danger of offering inadequately evaluated, unregulated tests of potential, but unproven value as a service. The researcher has the responsibility to have an open discussion about the benefits and drawbacks of the clinical practice of his/her research.

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