

## ETHICS AND QUALITY ASSESSMENT IN GENETIC TESTING

Michael Neumaier

Corresponding author's address:  
Prof. Dr. med. Michael Neumaier  
Chair for Clinical Chemistry  
Director of the Institute for Clinical  
Chemistry  
University Hospital Mannheim of the  
University Heidelberg  
Theodor-Kutzer-Ufer 1-3  
D-68167 Mannheim

Ever since Jim Watson and Francis Crick deciphered the structure of DNA, scientists have tried to unravel the mysteries of life. The boldest approach in genetic research has certainly been the launch of the Human Genome Project (HGP), which came to its successful conclusion in the year 2001. The HGP was organized as a massive international effort to map and sequence the entire human genetic code. Its primary goal with respect to medicine was to link certain diseases with abnormal genes that may be possessed by certain people. It had been hoped that access to the entire genome will enable researchers to detect disease predisposition in individuals at risk or even screen whole populations for certain disease predispositions. While it is still too early to assess the implications that genetic testing will have on our public health care systems, it is fair to say that, like any medical procedure, genetic testing poses both benefits as well as potential harm. A major issue has been the questions on diagnostic specificity and sensitivity of the tests applied, as well as the safety and effectiveness of medical interventions that can be offered to the individuals identified to carry disease-associated DNA variations. Finally, the fact that a genetic finding is affixed to a tested individual for his lifetime touches human rights in a way so far unprecedented by other diagnostic procedures.

Accordingly, most if not all applications in genetic testing are closely linked to ethical questions and corresponding legal issues. These include areas of preimplantation diagnostics (PID) embryo and foetal screening, screening of neonates and carriers, but also genetic testing for reasons primarily linked to economic interests e.g. by insurance companies or health care plans. Most significant are the questions regarding ethical issues in the context with genetic screening programs. Predictive genetic testing has real potential to provide options for personal choice. However, it is imperative to recognise both the right to know and the right not to know as important individual rights. In contrast to the genetic screening or testing for disease predisposition, the testing of gene expression

appears much less problematic in terms of ethics. This certainly is owed to the fact that mRNA gene expression analysis is

- 1) functionally close to a biochemical phenotype and
- 2) a dynamic and not permanently affixed label for its carrier.

### 14.1 Arguments against genetic screening

There are a number of often-discussed arguments against genetic screening. For example, people fear that they may be discriminated or feel stigmatized by possessing "inferior" genes when testing positive for a genetic screening parameter that can be associated with a disease predisposition. Also, couples may base reproductive decisions on genetic test results either of their own genomes or the genome of their (unborn) child. Knowledge of genetic conditions may change the way humans reproduce and, if not so for reasons of limited technical capacities in the near future, a significant shift of so far naturally inherited gene pool may well be the ultimate consequence. All this has led to the view that genetic findings are exceptional and their significance cannot be placed on the same level as other medical findings or diagnostics (so-called concept of "Genetic Exceptionalism").

### 14.2 Arguments for genetic screening

In contrast, there are protagonists voting for genetic screening with a comparably valid set of arguments. These include the notion that the correct identification of a disease predisposition in an individual may enable the doctor to prescribe specific drugs or influence the behaviour prior to the onset of clinical symptoms, thus increasing the quality of life for individuals carrying that predisposition. Also, in the case of learning of an incurable condition, affected persons may be able to make appropriate adjustments to their lives rather than being surprised by it in the later phases of their lives (however, it is equally possible that an individual may not want to learn about such future inevitable condition).

### 14.3 Programs to deal with the legal and ethical issues of genetic testing

A key document relating to ethical questions in Medicine in general is the Declaration of Helsinki, an official policy document of the World Medical Association, the global representative body for physicians. First adopted in 1964 (Helsinki, Finland) it has been revised several times during the WMA General Assembly in 2002 in Washington.

Medical professionalism is attracting a great deal of attention nowadays, both from doctors and their medical associations and from the media and general public.

There is clearly much overlap between ethics and professionalism, and anyone interested in medical ethics needs to be aware of developments in medical professionalism. Specifically, since genetic test results may well be recognized as stigmata for their carriers, the various stakeholder groups (governmental institutions, researchers, physicians, personal interest groups and the healthcare industry) have come to recognize the ethical and social implications of genetic information and to acknowledge the need to regulate both access to and the use of genetic information. Consequently, there are numerous national and supranational programs, working groups and initiatives, and search terms like "recommendations for genetic testing" yield beyond 310,000 hits on the Internet. As examples, two such programs are addressed below:

In the USA the Department of Energy of the National Institutes of Health (NIH-DOE) Joint Working Group on the Ethical, Legal and Social Implications (ELSI) of Human Genome Research has launched the Task Force on Genetic Testing (<http://www.genome.gov/10001808>).

This committee has examined critical issues, such as:

- How will the safety, effectiveness, and correct interpretation of the tests be ensured?
- How accurate is genetic testing at identifying mutations?
- How reliable is a positive test result as a predictor of disease?
- How will the quality of laboratories providing the tests be ensured?
- What are the psychological effects of genetic testing?
- Which counseling services are needed for patients to make an informed decision about whether or not to have a genetic test?
  - What can individuals with an altered gene do to prevent the disease in the future?

A review and analysis of the ELSI Program that has supported more than 190 research or educational projects and a total expenditure of more than 76 million US\$ has been published very recently. Specifically, four program areas have been established in the course being referred to as "Privacy and Fair Use", "Clinical Integration", "Genetic Research" and "Education and Resources". A large body of publications that have resulted from these programs is available on the web (<http://www.genome.gov/10001727>).

The Directorate-General for Research of the European Commission has published 25 recommendations on the ethical, legal and social implications of genetic testing in 2004 ([http://europa.eu.int/comm/research/conferences/2004/genetic/recommendations\\_en.htm](http://europa.eu.int/comm/research/conferences/2004/genetic/recommendations_en.htm)). In contrast to the US program, the European nations decisively recommend involvement of various public and private bodies including the WHO, the Organisation of Economic Cooperation and Development, the EU commission, the International Federation of Genetic Societies and the International Conference on Harmonisation (recommendation 1). For example, the recommendation 3 states that the so-called "genetic exceptionalism" is inappropriate, i.e. the perception that genetic information represents a separate category of medical information. Indeed, genetic information (mostly germline information) is seen as an integral part of the entire spectrum of all health information and does not represent a separate entity.

The catalogue of recommendations reflects on the following issues:

#### **General Framework**

1. Need for universal standard definitions
2. Germinal and somatic genetic testing
3. "Genetic exceptionalism"
4. Public information and education
5. Public dialogue

#### **Implementation of genetic testing in healthcare systems**

6. Medical genetic testing and its context
7. Quality assurance
8. Population screening programmes
9. Genetic counselling
10. Data protection: confidentiality, privacy and autonomy
11. Protection from discrimination
12. Ethnicity and genetics
13. Gender issues and genetics
14. Social, cultural and economic consequences
15. Professional development
16. Partnerships and collaborations
17. Regulatory framework and criteria for test development and use
18. Rare diseases
19. Pharmacogenetics

#### **Genetic testing as a research tool**

20. Existing and new 'biobanks'
21. Collections of human biological material and associated data and their uses
22. Cross-border exchange of samples
23. Informed consent
24. Samples from the deceased
25. Consent procedures for children and vulnerable individuals in human genetic research

Within the "General framework" section of the EU program as well as within the section "Implementation of genetic testing in health care systems", some recommendations directly relate to clinical chemistry/laboratory medicine and their providers. Specifically, these respective recommendations involve development and distribution of materials and resources for genetic testing, the development of skill levels among researchers, physicians and technicians and the improvement of research frameworks within the EU community (see recommendation 4). Also, maintenance and improvement of analytical quality is being seen as an ethical issue of genetic testing (see recommendation 7). Moreover, tests must be meaningful and the conditions tested for must be serious, the results highly predictive, and post-test counselling must be warranted (see recommendations 8, 9 and 19).

Recommendations 15 and 16 call for professional development of the care providers and partnerships between the different groups of stakeholders.

Clearly, this paper calls for close interaction between the clinicians and the laboratories, particularly with respect to the combination of genetic tests performed in a diagnostic setting and their interpretation in context with the patient's phenotype, i.e. laboratory results from classical biochemical analyses.

Finally, the European recommendations address genetic testing in research. Specifically, they suggest that legal frameworks and organisational structures have to be developed for the implementation and the ethically correct use of "biobanks" containing tissues, cells or body fluids. Recent surveys have shown

that a substantial number of clinical studies lack surveillance by institutional review boards and ethics committees.

#### 14.4 Ethics of genetic testing in context with commercial interests

One important concern touching ethical issues in genetic testing is the practice of patenting disease information. This may interfere with diagnostic procedures as has been argued by Jon F. Merz and colleagues at the Center for Bioethics in Philadelphia. Legislative initiatives like the 2002 "Genomic research and Diagnostic Accessibility Act" have tried to exempt, from patent infringement lawsuits, medical practitioners (and their hospitals) or non-profit organisations performing tests based on patented gene sequences. However, there are grave biotech industry concerns about the loss of marketing exclusivity. It is feared that regulation will inhibit the process of development of new genetic diagnostic tests. In addition, universities often hold patents and prefer to grant exclusive licenses to individual companies after having obtained, in a large percentage of cases, their patent rights by using public funding. The question may be legitimate, why the use of this genetic information should not be public domain in the first place. Also, it has been argued that exclusive licensing will block competition in the development of cheaper and better tests. This may increase costs and thus limit the access to genetic testing. Finally, Cho et al. have presented a study suggesting that genetic testing in a diagnostic setting has been withheld from patients, since laboratories have feared patent infringement lawsuits, or do not have access to clinically important diagnostic tests altogether, as is shown by the discussion about BRCA1 testing (<http://www.cmg.org/patents.htm>).

Technological advances have to be seen with respect to their ethical impact. It is highly significant that, with the advent of array technologies (i.e. DNA chip, DNA array) a further quantum leap is about to become a commonplace reality in diagnostics allowing genetic testing to be performed in a multiparametric setting. DNA chips will become commonplace for a number of obvious reasons: Firstly, the higher cost efficiency of DNA chips versus single parameter testing. Secondly, the increased information density of DNA chips, presumably providing more medical information. Thirdly, the low predictive power of single nucleotide polymorphisms (SNP) with odds ratios below 1.5 in the polygenic/multifactorial diseases requires the use of multiple genetic parameter sets to be diagnostically valuable. Next to the bioinformatics issues associated with medical interpretation of complex multiparametric test results, there is the unsolved question of external independent quality assurance for this methodology. The high throughput and quasi-industrial setting under which genetic information will be gathered with DNA chips will even require development of appropriate standardisation schemes and control measures including external quality control assessments. However, so far no quality control program has been implemented to control this type of mass genetic testing (see below).

#### 14.5 External Quality Assessment (EQA) in Molecular Diagnostics

It can be concluded from the arguments above and the guidelines that distributing the knowledge and skills and securing the quality of genetic testing is an important integral part of ethics in genetic

analysis. EQA schemes are common tools in clinical laboratory diagnostics and, on an international level, are mandatory in patient health care. There are a number of quality programs available that cover genetic testing in microbiology/virology (<http://www.qcmd.org/Index2.htm>), the Human Genetics of inherited mendelian disorders (<http://www.emqn.org/eqa.php>) or Molecular Diagnostics that test for SNPs associated with disease predisposition ([http://www.dgkl-rfb.de/index\\_E.shtml](http://www.dgkl-rfb.de/index_E.shtml)).

For example, since 1997 the German Society for Clinical Chemistry and Laboratory Medicine (DGKL), a non-profit organisation has established an external quality assessment (EQA) program, the tasks of which are:

- 1) the implementation and extension of external quality assessment (EQA) schemes;
- 2) the establishment of a proficiency network and database between participating laboratories and organisations and
- 3) educational training programs.

This program has found broad acceptance in countries within the EU and also abroad with approximately 230 laboratories participating in the EQAs twice a year ([http://www.dgkl-rfb.de/index\\_E.shtml](http://www.dgkl-rfb.de/index_E.shtml)). The parameter spectrum of this program is being constantly expanded and currently includes Factor V, Factor II (Prothrombin 20210), Factor XIII, MTHFR, Glycoprotein II b III a (GPIIb/IIIa), PAI 1 (Plasminogen-Activator Inhibitor 1), ApoE, ApoB100, aAT1 (Proteinase-Inhibitor 1), ACE I/D, CETP (Cholesterol Ester Transfer Protein), HFE, TPMT (Thiopurin-S-Methyltransferase), CYP2D6 (Cytochrom p450 2D6) and UGT-1A. Other EQA that have been performed in the past address methodological issues including preanalytics, DNA sequencing and SSCP for mutational screening. Some of the results from these programs have been communicated. A number of conclusions can be drawn from this program at present:

- Preanalytical factors (material quality, transportation time and modalities, inhibitors etc.) are critical for the quality of the molecular test result.
- Molecular methods used for the amplification in genotyping assays appear to be very robust with respect to technical performance of the assays.
- With respect to correct findings, simple methods work as well as new techniques. Specifically, there is no correlation between the sophistication of the method and the quality of the genetic test result.
- Validities of test results have been observed to decline steeply in the diagnostic setting, even when minor template contaminations (1:8 to 1:16; w:w) were present in the sample. This emphasizes the importance of laboratory procedures that use DNA amplification methods.
- Most mistakes are not caused by faulty primary data, but postanalytical validation and interpretation.

Very recently, the European Community has funded a new EQA program in genetic testing called EQUAL (<http://www.ec-4.org/equal/>) based on a national EQA. EQUAL addresses important methodological aspects of genetic testing and currently organizes three different EQA aiming at genotyping, quantitative gene expression analysis and DNA sequencing. It is hoped that in compliance with the recommendations set forward by the Commission, EQUAL will help to improve the quality of genetic testing through these EQA and training programmes. Finally, dissemination of experiences in genetic testing to countries less experienced in the field has prompted the International Federation for Clinical Chemistry (IFCC) to publish draft documents and implement the official working group "Committee for Molecular

Biology Curriculum” (C-MBC, chair: Prof. Maurizio Ferrari, Milan, Italy) within its Education and Management Division (EMD).

Taken together, an impressive number of professional activities have resulted from the knowledge that ethics and quality are of utmost importance in diagnostic genetic testing of human disease. The positive results obtained in the multinational EQA programs show that molecular testing has successfully arrived in medical diagnostic procedures. Still, the experiences also justify the continued effort to improve the external quality. It is important to note that the supranational programmes encourage concerted actions and cooperation on different medical, technical and educational levels.

## References

1. Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., et al. (2001) *Nature* 409, 860-921.
2. Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., et al. (2001) *Science* 291, 1304-51.
3. Merz, J. F., Leonard, D. G. & Miller, E. R. (1999) *Science* 283, 1647-8.
4. Merz, J. F., Kriss, A. G., Leonard, D. G. & Cho, M. K. (2002) *Nature* 415, 577-9.
5. Chahine, K. (2002) *Nat Biotechnol* 20, 419.
6. Merz, J. F., Leonard, D. G., Kriss, A. G. & Cho, M. K. (2002) *Nat Biotechnol* 20, 657; author reply 657.
7. Cho, M. K., Illangasekare, S., Weaver, M. A., Leonard, D. G. & Merz, J. F. (2003) *J Mol Diagn* 5, 3-8.
8. Funke, H., Cullen, P., Gessner, R., Klein, H.-G., Knabbe, C., Langmann, T. & Neumaier, M. (2003) *J. Lab. Med.* 27, 131-136.
9. Neumaier, M., Braun, A. & Wagener, C. (1998) *Clin Chem* 44, 12-26.
10. Neumaier, M., Braun, A., Gessner, R. & Funke, H. (2000) *Clin Chem Lab Med* 38, 161-3.
11. Braun, A., Deufel, T., Geilenkeuser, W. J., Neumaier, M., Rohle, G., Roscher, A. & Wagener, C. (1998) *Clin Chem Lab Med* 36, 231-4.
12. Raggi, C. C., Pinzani, P., Paradiso, A., Pazzagli, M. & Orlando, C. (2003) *Clin Chem* 49, 782-91.