Genetic Testing and Common Disorders

Proposed Recommendations of the European Society of Human Genetics

DRAFT version 18 May 2009, PLEASE DO NOT QUOTE

Introductory considerations

After the focus on monogenic and chromosomal disorders in the second half of the twentieth century, in the last two decades research in genetics and genomics increasingly turned to common complex diseases. Unravelling the contribution of monogenic subsets to the etiology of common disorders as well as the contributions to multifactorial etiology of susceptibility genes, including complex gene-gene and gene-environment interactions, this new research promised to give insights that might lead to improved diagnosis and prognosis, disease management and disease prevention in common complex disorders that are of major relevance for population health.

However, many of these claims have not substantiated yet, and might, in retrospect, have been too optimistic. Translation of research findings to health care applications appears to lag behind. In 2009 the genetics research community may be sceptical about the possibilities of genetic susceptibility testing and screening.

Many promises may be interpreted as "genohype": what was promised to funding agencies in order to obtain grants, was also published in scientific journals and picked up by the media. In retrospect several researchers have been aware of too high expectations.

On the other hand more and more research findings on susceptibility genes do become available through genome wide association studies. Whereas replication was difficult at first, various associations have increasingly been confirmed. Difficulties with the translation of research findings need to be understood and addressed if genetics and genomics research is to fulfil its promises.

To translate research findings to appropriate clinical applications, such as genetic testing, several stages of assessment are needed. For the assessment of genetic testing and screening several frameworks of criteria have been developed. Many of the parameters needed in these assessment frameworks are not available yet.

Furthermore, in Europe the current regulatory framework does not cover an independent evaluation procedure for genetic tests before marketing. Mechanisms for funding pre-market review and post market surveillance are lacking.

In the meanwhile the general public is increasingly confronted with genetic susceptibility tests being offered on the internet without adequate regulation or independent sources of information and result interpretation.

At present, genetic testing for common disorders has been implemented in health care only in the case of some monogenic subforms of common disorders with highly penetrant mutations such as breast and ovarian cancer and colon cancer. Whatever can be learnt from these examples should not currently be extrapolated to the situation of susceptibility testing or screening on the basis of low-risk genes. The framework for such an endeavour needs to be explored.

These issues were discussed at a workshop in Seville, Spain, in October 2007, which was jointly organized by the Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG),the EU-funded Network of Excellence EuroGentest and the Institute for Prospective Technological Studies (IPTS). Experts and key actors, such as

representatives of the Public Health Genomics Network (PHGen) were present at the meeting. For the PPPC the aim of the workshop was to produce statements and recommendations from the genetic health care professional point of view. In June 2008 the preliminary documents were discussed at the ESHG meetings of Board and PPPC in Barcelona. In order to further discuss some genetic epidemiological issues, a workshop was organized in September 2008 in Amsterdam. Suggestions were incorporated in both the background document and the recommendations. A draft of these statements and recommendations will be distributed and posted on the web to elicit comments. After this procedure the draft will be revised and the final text is expected to reflect the views of the human genetics scientific and professional community.

Statements and recommendations

Definition of susceptibility testing and screening

There are several valid definitions of genetic testing and screening available. For the purpose of this document we use the following definitions.

Genetic susceptibility testing may be defined as the analysis of DNA or biomarkers for the early evaluation of one or more genetic risk factors for a particular disease or disease group.

Genetic susceptibility screening may be defined as a systematic, proactive offer of genetic susceptibility testing to members of a certain group of individuals.

Evidence

For monogenic subtypes of common complex diseases the relation between genetic alterations in genes conferring a high disease risk and disease are well-established, for instance in the case of breast and ovarian cancer caused by BRCA1 and BRCA2 mutations, familial adenomatous polyposis (FAP), herereditary nonpolyposis colorectal cancer (HNPCC) and familial hypercholesterolaemia (FH).

The number of genome wide association studies revealing association between genetic variants and common complex disorders is rising rapidly. Though evidence is accumulating and several associations have been confirmed, still much work is needed on replication of research findings. Especially comparison between populations is a challenging issue. Furthermore gene-gene interactions as well as interactions between genetic and environmental factors merit further study.

Translation of research findings

As yet, promises about health care applications on the basis of research findings on low risks susceptibility genes have been overstated. There is hardly any effect on improving diagnosis and prognosis, treatment and prevention, such as life-style interventions or effective therapies concerning common complex disorders on the basis of these newly established associations. Translation of research findings on low-risk genes into health care practices – be it public health, primary or specialized health care, is problematic. Most genetic variants may only alter disease susceptibility risk by a factor of 1.1 to 1.6 at most, and usually a large number of genetic variants will have a bearing on risk, of which only a minority will be known or testable. In most cases of polymorphic variants, the risk alteration would be too small for any

intervention to be appropriate, but it may be that in the future a combination of risk variants could confer a sufficiently high relative risk to support the recommendation of testing or screening in the case risk-reducing interventions would be available. In the near future the use of multiple SNPs for predicting risks for for instance colorectal and breast cancer might allow individuals at substantially increased risk to be identified by using several markers. At present, however, for certain disorders, family history may often be a more discriminant factor in risk assessment.
In the case of moderate risk genes, there has been some success in improving diagnosis, for instance in the case of determining HLA subtypes to confirm the diagnoses Bechterew's disease and celiac disease. In case of several monogenic subtypes of common disorders diagnostic tests are in widespread use, as the earlier mentioned examples of breast and ovarian cancer related to BRCA1 and BRCA2 mutations, FAP, HNPCC and FH show.

Assessment

In the past decades criteria for assessing genetic tests and genetic screening programmes have been elaborated. The comprehensive ACCE framework from the Centers for Disease Control and Prevention (CDC, USA) has set a contemporary standard for assessing tests. The United Kingdom has further adapted this framework which evaluates not only the test characteristics, but also the medical setting in which the test is applied, as well as the legal, social and ethical context of the medical application. According to this framework a test should first of all have a good analytic validity: this is a measure for the technical accuracy of the test and defines the test's ability to measure accurately and reliably what the test is aiming to identify. Clinical validity defines a test's ability to detect or predict the associated disorder. Clinical utility refers to the likelihood that the test will lead to improved health conditions when introduced to clinical use. Information on analytic validity alone is insufficient to assess the usefulness and performance of a test in medical services.
However, at present many parameters needed for the assessment of susceptibility testing are not available yet (sensitivity, specificity, prevalence, severity, morbidity, reduced mortality). In addition, in many cases information is lacking regarding the relation between the tested genetic variant and other genes, gene variants or combinations of gene variants relevant for a certain disorder, and the safety and usefulness of interventions such as medication or life-style changes. Therefore, the PPPC statement from 2003 'It will take many years to be sure that the identification of groups at risk for common diseases, or for specific drug therapies and consequent interventions, is beneficial', is still valid for many health care settings.
In the absence of sufficient information on clinical validity and clinical utility, introduction of susceptibility tests is often premature. In the near future, in certain health care setting susceptibility tests may be introduced to gain additional information concerning diagnosis, prognosis and disease management. However, this introduction should be carefully monitored in order to obtain additional information regarding the usefulness and performance of the test in that specific setting.

Priorities

When considering implementation in health care priority should be given to genetic tests for common complex disease of proven clinical utility and cost effectiveness. Taking a family history first can be an adequate initial source of risk differentiation enhancing both efficiency and cost-effectiveness of further testing.
In case of monogenic subtypes of common disorders family history may be followed by cascade screening of family members at risk. This would provide ready opportunities to

health gain in the case of, for instance, breast and ovarian cancer related to BRCA1 and BRCA2 mutations, FAP, HNPCC and FH.
At present genetic susceptibility testing for common disorders in general is not generally considered useful. However, in some cases applications are feasible, such as in case of the systematic testing of mutations in breast cancer tumour tissue, or pharmacogenetic testing in case of certain adverse drug reactions or drug dose determination.

Direct-to-consumer-tests

Increasingly, genetic tests for common disorders can be obtained via the internet or over the counter as a direct-to-consumer test, without thorough assessment of the clinical validity and utility. Since information on analytic validity alone is insufficient to assess the usefulness and performance of a tests, this information should not be considered as sufficient pre-market evaluation.
The premature introduction of commercial genetic tests may have some serious disadvantages. The test results may be confusing or raise concern, and may cause false distress or reassurance, and people may need extra information from health professionals to explain the test results and possible consequences or courses of action. This would mean the extra use of scarce health care resources, or the test may simply be a waste of money. Premature introduction of genetic susceptibility tests may therefore also seriously undermine public trust in genetic testing for medical purposes.
Often, interpretation of test results in relation to other health and life style indicators of an individual is necessary, which may include relevant family history regarding a certain disorder. Therefore, we recommend that advice from sufficiently qualified health care professionals is available when direct-to-consumer genetic susceptibility tests are offered. Special attention is necessary regarding advertising for direct-to-consumer tests to ensure adequate information is given and truthful claims are made about the test and possible interventions.

Regulation

Regulation is necessary to improve the assessment procedures of genetic tests for common disorders, either to be used in health care or offered as direct-to-consumer tests on the internet.
In European regulation, many genetic tests fall under the heading of in vitro diagnostics (IVD). Currently, in the IVD Directive, these tests have often been categorized as low risk products and are therefore not subject to independent evaluation before coming to market. Thus clinical validity and utility may not be assessed.
The goal of the process of pre-market review is to ensure truth-in-labelling and truthful promotion of in vitro diagnostic devices. Mechanisms for post-marketing evaluation are not in place yet. It is recommended that internationally recognised regulation for mandatory pre-market review for genetic tests is established, including for common disorders. It would be desirable to develop a post-marketing evaluation procedure.

Harmonisation

Within the European Union, initiatives by various actors should lead to a combined effort to harmonise regulation concerning genetic testing and screening and genetic susceptibility testing and screening between the member states.

Harmonisation between the European Union and the United States regarding the assessment of genetic tests for common disorders is desirable.
However, harmonisation should not be restricted to regulation per se. Actors from various fields of interest should reach common ground, for instance, regarding professional protocols, standards for referral, and codes of practice applicable in health care and public health.

Commercial valorisation and responsible entrepreneurship

At present funding for a pre-market assessment procedure is lacking. On the other hand, research funding is often based on promises of valorisation of research findings, thus giving an extra impetus for quick marketing of applications. In order to organise and fund pre-market assessment a combined effort of stakeholders is recommended. The European Diagnostic Manufacturers Association (EDMA) may serve as an example of self organisation (or function as a platform) to unite industry and stimulate interaction with regulatory bodies in drawing new guidelines.

Solidarity in the wake of personalized medicine

In the near future, it might become increasingly possible to understand the functioning of the genome on the individual level and tailor prevention, medication, therapies, or life-style interventions to individual needs. This will only be possible if people are to be reimbursed for a substantial part of their health care cost. A system of collective insurance is needed to realize the potential of individualized medicine.
In this way the danger of furthering inequalities, or unfair discrimination in health care as a consequence of increasing genetic knowledge, may be reduced.

Legal aspects

We recommend that governments proceed with additional non-discrimination legislation in relation to genetic information in order to facilitate both employers and insurance companies to use genetic information in a responsible and ethically justified manner. Fear of social and economic drawbacks should not discourage people from obtaining information about their genetic constitution for health purposes. Unfair discrimination on the basis of the constitution of one's genome should be avoided.
Research and development of new test devices are costly. Patenting may be a way to ensure return on investment, however, research may be hampered by legal restrictions on use and dissemination of genetic knowledge. A concerted action between stakeholders in industry, health care, professional and patient organisations and governmental bodies is necessary to balance the interests of industry with the requirements of furthering the availability of testing devices in a responsible manner.
Storage of tissue and information on health and life-style of individuals in biobanks is vital for research. Legislation is necessary to secure privacy and non-discrimination regarding genetic information to ensure an enduring public trust.

Ethical and social aspects

The information that comes available through genetic susceptibility testing differs in several respects from genetic testing for monogenic disorders, including monogenic subsets of common complex disorders. Since a genetic susceptibility test only reveals a higher (or lower) risk to develop a certain disorder, the psychological impact, as well as the societal

consequences for insurers and employers, will probably be less evident. Nonetheless, more research is necessary to understand the ways people will respond to receiving this kind of risk information as well as the social and ethical consequences of susceptibility testing and screening.

Role for clinical geneticists in health care

Since genetic knowledge will become more important in managing various disorders, the specialist knowledge of clinical genetics should be made available and should be easily accessible for other professionals in health care settings. To prepare health care for genetic testing in common disorders, cooperation between geneticists and other professionals in health care is paramount. Initiatives to form multidisciplinary teams, genetic resource centers, knowledge transfer centers, genetic knowledge parks, et cetera, should be encouraged.

Counselling in relation to susceptibility screening

Since susceptibility testing differs from testing for monogenic disorders, the need for counselling may differ for different types of disorders and the established risk.
If the test is or is claimed to be capable of detecting high relative risks for serious conditions and thus has implications for treatment or prevention in the person or his/her near relatives, then pre- and post test genetic counselling is needed. At present, this is rarely the case in common complex diseases when testing healthy individuals with a non-contributory family history. However, should the need for counselling arise in certain case, the experience of clinical geneticists can be valuable to support or educate other health care providers.

Training

Genetic literacy of health care professionals should be improved to enable them to assess whether genetic testing, including genetic susceptibility testing may be of use, as well as to respond to the questions from patients regarding genetic (susceptibility) testing or the information obtained from commercial genetic testing.

The public

High-quality information on genetic (susceptibility) testing for common disorders should be readily available for the public at large. One of the means to achieve this would be using national and supranational trusted websites offering independent high-quality information on genetic tests, including genetic susceptibility tests, and benefits versus drawbacks of genetic testing. A concerted effort is necessary in secondary education and public education to stimulate genetic literacy.
Patient organisations may have an intermediary role in informing the public. Written documentation (leaflets, brochures) based on expertise from patient organisations and genetic specialists may be used by patients to inform primary care professionals that often lack sufficient knowledge to detect or manage disorders with a genetic component.

Developing countries

Applications of genetic (susceptibility) testing for common disorders have mainly been developed for health care in wealthy countries. For the prevention and control of common complex disorders in the poorest countries much is to be gained by raising standards of living

conditions (nutrition, avoidance of deleterious environmental agents) and access to primary health care. In countries where infectious diseases and nutritional problems start to have a smaller impact, genetic (susceptibility) testing for common disorders may become relevant for reducing the impact of common diseases. Genetic research in pathogenic organisms may need prioritisation here. Research should focus on the specific genetic structure and health needs of populations. Health care priorities of developing countries should be reflected in global research priorities.