The challenge of implementing genetic tests with clinical utility while avoiding unsound applications

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Abstract Genetics and genomics have developed fast in the last decade, but have not revolutionized medicine, as some had expected. While translation of research findings to public health applications is lagging behind, direct-to-consumer (DTC) offers of genetic testing have become available, both for monogenic and severe genetic disorders and for genetic variants possibly associated with common complex diseases (susceptibility variants). The European Society of Human Genetics is concerned about the way in which commercial companies are currently introducing genetic tests into the market outside of the scope of the traditional health-care system. There is a sort of a paradox between the lagging implementation in health care of the few genetic tests with proven clinical utility, on the one hand, and the speedy DTC offer of tests, with or without clinical utility. To translate research findings into appropriate clinical applications, assessment of the clinical validity and utility is needed. Many of the

parameters needed in assessment frameworks are not available yet. Clinically relevant associations between genetic variants and disease risks have been established, e.g., in oncogenetics and cardiogenetics, and can be used to reflect on the possibilities and obstacles in using the new genetics in public health. In the absence of sufficient information on clinical validity and clinical utility, introduction of genetic tests in common complex disorders is often premature. Priority should be given to settings where clinical utility is proven or likely, to gain additional information concerning diagnosis, prognosis, and disease management. Monitoring and evaluation are essential.

Keywords Genetic testing · Translation · Evidence-based practice · Direct-to-consumer · Monogenic · Common complex · Clinical utility

Abbreviations

BRCA1/2	Breast cancer gene 1 or 2
DTC	Direct-to-consumer
ESHG	European Society of Human Genetics (www.eshg.org)
FAP	Familial adenomatous polyposis
HNPCC	Hereditary nonpolyposis colorectal cancer/Lynch syndrome
IPTS	Institute for Prospective Technological Studies (http://ipts.jrc.ec.europa.eu/)
LQTS	Long QT syndrome
MODY	Maturity onset diabetes of the young
PPPC	Public and Professional Policy Committee of ESHG
SNPs	Single-nucleotide polymorphisms

Introduction

More than 10 years ago, the draft sequence of the human genome was published. This raised expectations that

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“genome science will have a real impact on all our lives—and even more, on the lives of our children. It will revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases” (Collins 2010). In 2001, Francis Collins and Victor McKusick predicted that by the year 2010 predictive genetic tests would be available for various common disorders, “allowing individuals who wish to know this information to learn their individual susceptibilities and to take steps to reduce those risks for which interventions are or will be available” (Collins and McKusick 2001). In retrospect, these views were clearly too optimistic. The same, Francis Collins admitted in a more recent publication that we invariably overestimated the short-term impacts of new technologies and underestimated their longer-term effects (Collins 2010).

In genomics *research*, many associations between single-nucleotide polymorphisms (SNPs) and risks for common complex diseases have been identified. Though this paved the way to a better understanding of the pathogenesis and etiology of common complex disorders such as type 2 diabetes, stroke, and obesity, the magnitude of the estimated genetic effects of many variants is not relevant for health purposes (Becker et al. 2011). In the light of the increasing amount of genomic information available, appropriate translation of those research findings that do have an impact in health care is crucial. On the one hand, it is important to avoid that implementation of useful research findings takes an unnecessary long time. Attempts to integrate genetic/genomic knowledge of common conditions into clinical practice are in the early stages, and as a result, many questions surround the current state of this translation (Scheuner et al. 2008).

Obstacles in implementation of research findings need to be identified and addressed if we want genetics and genomics to improve diagnosis, therapy, or preventive strategies (Khoury et al. 2009; Ginsburg 2008; Graham et al. 2006). On the other hand, we have observed in recent years an increasing number of genetic tests that are being sold directly-to-consumer (DTC). Most DTC genetic tests are based on one SNP or a panel of SNPs, still having limited predictive value for the susceptibility to common complex disorders.

While the anticipated implementation of genomic medicine has not taken place in the last decade within the traditional health-care system, various companies started to advertise and sell genetic tests over the counter. According to some authors, these companies may even “come to displace clinicians as the primary providers of genetic information related to health promotion” (Foster and Sharp 2008).

In view of these contradicting tendencies, the European Society of Human Genetics (ESHG) has recently prepared three documents with regard to the incorporation of genomic medicine into current clinical and public health practice, and its position in the need for regulation of direct-to-

consumer companies. In this manuscript, based on material that was presented at the symposium “Predictive genetic testing, risk communication and risk perception” at the Robert Koch-Institute Berlin, 21 November 2011, we aim to summarize the main findings of these documents. For a full discussion, we kindly refer to these original documents. The first document is a background document on genetic testing in a public health framework (Becker et al. 2011). This document provides a reflection on the paradigm shift in the field of human genetics from rare monogenic to common disorders with a genetic component. It continues a tradition of documents and initiatives that were set up to assess and harmonize genetic testing services in Europe (Godard et al. 2003; Ibarreta et al. 2004; (Cassiman 2005). This first background document led to the second document: recommendations that aim “to reflect the view of the European human genetics scientific and professional community” on genetic testing and common disorders in a public health framework at that moment (van El et al. 2011). The third document is a formal policy statement of the ESHG with regard to the advertising and selling of genetic tests directly to consumers (European Society of Human Genetics 2010). These documents did not pay special attention to pharmacogenomics and nutrigenomics, due to their currently limited relevance for health-care purposes.

History of documents

The two first documents on genetic testing and common disorders were initiated on the basis of a first workshop on “Clinical validity and utility of genetic susceptibility testing in common disorders” that was organized in Seville, Spain, in 2007. This meeting was organized by the Public and Professional Policy Committee (PPPC) of the ESHG, together with Eurogentest (www.eurogentest.org) and the Institute for Prospective Technological Studies (IPTS; <http://ipts.jrc.ec.europa.eu/>). Based on literature, a background document was prepared and circulated among participants and ESHG members. Comments were integrated in the document and further discussed at a meeting in Amsterdam in 2008, where mainly genetic epidemiological issues were discussed. The PPPC developed recommendations based on the workshop and background document. The background document and recommendations were posted on the ESHG website in 2009, inviting comments. After integrating these comments, the PPPC and board of ESHG approved the final versions, which were published in 2011.

In the same years, the PPPC also developed recommendations on DTC genetic testing. Several articles were already available summarizing the scientific developments and the ethical, legal, and societal issues. Building on this earlier work, a first draft of recommendations on DTC was

developed by Pascal Borry, Christine Patch, and Martina Cornel for a PPPC meeting in January 2010. Comments of other PPPC members were integrated, and in April–May 2010 the text was available on the ESHG website to solicit comments from members, and for external review. The final version was sent to the ESHG Board, which approved the recommendations in June 2010.

Differentiating patients, improving implementation

New possibilities for genetic testing confront health-care workers with the question of whom to test and which test to use. Apart from tests for rare conditions, in the last decade, genetic testing for monogenic subforms of common disorders, such as cardiovascular disease, stroke, diabetes, cancer, dementia, and depression, became available. “For a health-care practitioner seeing a patient—unlike a geneticist or an epidemiologist—it may not be clear whether such a common disorder is due to one gene with a high risk of serious disease, or due to a combination of several genes and several environmental factors” (Becker et al. 2011). For disorders in which both etiologies exist, monogenic and multifactorial, the etiology can be thought of as “complex”. A clear distinction between disorders with monogenic and multifactorial etiology does however not exist (Becker et al. 2011; Bompreszi et al. 2003; Manolio et al. 2009).

To improve the implementation of currently available tests with proven clinical utility, when a patient enters health care, it is relevant to discern monogenic subtypes of common complex disorders from other cases that have a multifactorial etiology. In monogenic subtypes, treatment and prognosis may be different. Health-care practitioners have numerous ways to recognize these monogenic subtypes: positive family history, relatively young age of onset in the probands, and bilaterality or multilocality in the case of cancer. For a patient with breast cancer at a young age, a positive result of breast cancer (BRCA) testing has consequences for her surgery and follow-up, as well as for the risk of cancer in her family members. Genetic testing will also modify health-care needs in case of monogenic subtypes of colon cancer (familial adenomatous polyposis (FAP) and Hereditary nonpolyposis colorectal cancer (HNPCC)), cardiovascular disorders (familial hypercholesterolaemia, hypertrophic cardiomyopathy), and diabetes (MODY subtypes) (Grosse et al. 2010; Rahner et al. 2010).

Discerning tests with and without clinical utility

A genetic test has clinical utility if a positive result would alter the treatment or intervention. Especially if gene–environment interactions exist, individuals at “high risk” may

profit from tailoring interventions (Becker et al. 2011). In most of the monogenic subtypes of common disorders, cascade screening (inviting family members) is a very effective approach to organize health-care services.

A summary of evidence available on specific genetic tests in specific settings, sometimes in relation to a specific phenotype, can be found in ACCE and EGAPP reviews (Grosse et al. 2010) and Clinical Utility Gene Cards (Schmidtke and Cassiman 2010).

The assessment of pros and cons according to the different schemes mentioned above, builds on the evaluation of a specific genetic test in a specific setting according to the criteria specified in the ACCE framework (Sanderson et al. 2005):

- Analytic validity defines the ability of a test to accurately and reliably measure the genotype of interest: the genetic variant(s) that the test is aiming to identify.
- Clinical validity is defined as the ability of the test to detect or predict the phenotype of interest.
- Clinical utility is defined as the likelihood that the test will lead to an improved outcome.
- Ethical, legal, and social aspects include patient information needs, informed consent, impact on insurance.

When considering implementation in health care, priority should be given to genetic tests for common complex diseases of proven clinical utility and cost effectiveness. As an example, a population cascade screening program for familial hypercholesterolemia has been in operation in the Netherlands since 1994 and has reduced morbidity among affected patients (Grosse et al. 2010). HNPCC testing in healthy first-degree relatives may lead to the advice for (bi)annual colorectal cancer screening with complete colonoscopy and gynecological examination, while family members that do not carry the mutation do not need intensified screening (Rahner et al. 2010). On the other hand, testing patients with venous thromboembolism for factor V Leiden (FVL) was of low clinical utility despite high analytic and clinical validity for FVL because of lack of evidence that genetic test results appropriately change clinical management or improve outcomes (Grosse et al. 2010). For the latter, implementation in health care should receive lower priority than the first two.

In the near future, in a certain health-care setting, genetic tests in common complex disorders may be introduced for tests and settings where clinical utility is likely, to gain additional information concerning diagnosis, prognosis and alter disease management. Mammaprint® and OncotypeDX® are new tests that differentiate breast tumors according to prognosis (Kohli-Laven et al. 2011). In a platform, several genes with prognostic value are tested. Retrospective studies informed the development of the products. Ongoing prospective trials will show whether the prognostic value is confirmed

(Rutgers et al. 2011). The introduction of new products with insufficient evidence of clinical utility should be carefully monitored in order to obtain additional information regarding the usefulness and performance of the test in that specific setting.

Concerns on direct-to-consumer genetic testing

In the last decade, several tests have been introduced direct-to-consumer. The tests range from (1) single-gene tests for monogenic disorders or monogenic subsets of common disorders, (2) one or several SNPs or genetic variants found to be associated with common disorders such as diabetes, (3) genomic profiles combining gene variants or SNPs, (4) genome-wide scans for a particular range of conditions such as cancer or cardiovascular problems, and also (5) tests to learn more about for instance ancestry or traits (Becker 2011). Even tests based on whole genome sequencing techniques can already be commercially obtained. However, most DTC tests are SNP-based and lack assessment of clinical validity or utility. Several authors and professional organizations have criticized this development, as test results may be confusing or raise concern, and may cause false distress or reassurance, or may lead to unnecessary or potentially harmful interventions (European Society of Human Genetics 2010) (European Academies Science Advisory Council and Federation of European Academies of Medicine 2012). If consumers have questions on the test results, they may consult regular health care, leading to an unwanted impact on health-care resources. Media attention for DTC genetic testing lacking clinical utility might furthermore undermine public trust in genetic testing for medical purposes. Whereas SNP-based tests may simply be a waste of money, to interpret genetic risk information, especially for serious medical problems, advice is necessary from sufficiently qualified health-care professionals (European Society of Human Genetics 2010).

Regulation

If indeed clinically useful tests are to be promoted and less useful tests are to be discouraged, regulation is necessary to improve the assessment procedures of genetic tests for common disorders, either to be used in health care or to be offered as direct-to-consumer tests on the internet. Discussion is needed on the strategy: legislation, professional guidelines, and self-regulation by commercial parties. Regulation should address first of all the transparency of the evidence of claims, before tests come to the market and also in advertising and promotional materials (Patch et al. 2009). For common conditions, only tests for which there is

evidence of clinical utility should be approved by professional bodies. Reimbursement of routine testing should be available only if tests have been evaluated effectively. For rare disorders, other levels of evidence apply. Testing of minors should be allowed only if tests are ordered by health-care professionals.

The In Vitro Diagnostics Medical Devices Directive already guarantees pre-market review and truth-in-labeling to a certain extent. However, the current risk stratification is not suitable for genetic testing for high risks and/or serious disorders.

Harmonization of genetic testing regulation would be facilitated by ensuring consistency with the Council of Europe's Additional protocol to the Convention of Human Rights and Biomedicine, concerning genetic testing for health purposes (2008).

Ethical, legal, and social aspects

Promises of personalized medicine are becoming more realistic, although only few genetic tests nowadays contribute to clinically useful stratification. The solidarity in the provision of health-care needs to be guaranteed in the wake of personalized medicine. Several countries have enacted non-discrimination legislation in relation to genetic information. While innovation needs commercial parties to develop new products, patents owned by commercial parties may also be an obstacle for implementation. The interests of the industry need to be balanced with the requirements of furthering the availability of testing devices in a responsible manner. More research is necessary to understand the ways in which people will respond to receiving this kind of risk information, as well as the social and ethical consequences of susceptibility testing and screening. Developing countries have increasing numbers of adults that might profit from genetic testing with clinical utility. Attention is needed for their specific situation, both in terms of different disorders and organization of health care.

Clinical genetic guidance

If more tests become available for common complex disorders, the role for clinical geneticists in health care will change, as well as the role for genetic counselors. Counseling is especially needed in relation to testing for common complex disorders when a high risk of serious disorders may be at stake (BRCA, FAP, and LQTS). Guided by clinical geneticists and counselors, other medical professionals will increasingly be involved in genetic testing and informing individuals that might profit from tests with clinical utility. Genetic literacy of health-care professionals should be

considerably improved to differentiate between groups of patients meriting genetic testing and optimize referral. High quality information on genetic testing for common disorders should be readily available to the public at large, both via internet and medical professionals.

The changing landscape of DTC

Proponents of DTC genetic testing stress the right to genetic information, which we support, provided that it is transparent and adequate. DTC advertising of genetic testing for recreational purposes (ancestry and non-medical traits) can perhaps be thought of as relatively unproblematic, though ill-founded claims of ethnic origin may cause distress. However, as soon as severe medical problems are at stake, the criteria of clinical utility, truth-in-advertising, and medical supervision are paramount. In general, DTC may create unrealistic expectations because of overstated claims, and may induce confusion and anxiety (European Academies Science Advisory Council and Federation of European Academies of Medicine 2012).

The quality of genetic testing services in terms of their analytical validity, clinical validity, and utility must be guaranteed in the same way as in regular health care. Quality assurance of the laboratories should be required, preferably by accreditation. Proper qualifications, training, and education of the personnel involved in genetic testing for serious medical indications are needed. In case of severe disorders, individualized medical supervision of DTC will help to guarantee that patients get appropriate care.

Information and genetic counseling before genetic testing

In clinical genetic service provision, a practice has developed that is relevant for all genetic testing. Informed consent has to be given before a test is performed. This requires appropriate pre-test information and genetic counseling, especially when high risks or serious disorders are involved. In case of DTC testing, because of the limitations of an internet procedure in establishing interaction, there is concern whether consent can be really informed and is not reduced to ticking a box. Increasingly, DTC genetic testing companies try to include health-care professionals in the provision of their services (Howard and Borry 2012). In case companies hire or link up with professionals, their impartiality may not be guaranteed. “If a company’s profits are dependent on selling tests, then how could employees hired by that same company or representing that company be completely impartial and not (routinely) suggest testing to potential clients?” (Professional and Public Policy Committee of the European Society of

Human Genetics 2009) In case a company uses samples for research, this should be made clear to customers and separate adequate consent should be obtained. Nowadays also, complex techniques such as whole exome or genome analysis require appropriate counseling. In minors, these new forms of genetic testing can be responsibly performed if in the interest of the minor, but not otherwise.

Privacy and confidentiality

Genetic test should be performed with due respect for privacy. “In particular, companies offering DTC genetic tests should preserve the customer’s privacy, keep their data confidential, inform them about their security procedures, explain what will happen to the sample and the data when the testing process is concluded, and have a clearly laid-out plan as to what will happen to the samples and data should the company be sold or go bankrupt. Companies inviting their customers to share their genetic information via a web community or forum should inform people about the potential risks for disclosure of this type of sensitive information. The ESHG disapproves any use of personal details or genetic information by test providers (or other companies) for DTC marketing of medicines, vitamins, or dietary supplements” (European Society of Human Genetics 2010).

A sustained effort for a responsible implementation of genetic testing in health care

If indeed clinically useful tests are to be promoted and less useful tests are to be discouraged, there is a need for assessment procedures of genetic tests for common disorders, either to be used in health care or to be offered as direct-to-consumer tests on the internet. Premature translation of genomic services into the market or clinical practice may be prevented by different strategies, ranging from legislation, professional guidelines, self-regulation by commercial parties, and regulatory oversight. At the European level, regulatory mechanisms, and in particular the adaptation of the European In Vitro Diagnostic Devices Directive (to consider genetic tests of high risk), the implementation of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, and the implementation of the OECD Council Recommendation on Quality Assurance in Molecular Genetic Testing will be necessary to ensure appropriate introduction of genetic tests into the health-care system (Council of Europe 2008; Organisation of Economic Cooperation and Development 2007).

The impact of innovation in genetic testing on the health-care system has the potential to personalize medicine, to

identify risks before symptoms occur and thus protect individuals. However, attunement is needed with many other actors, including companies, non-genetic health-care professionals, regulatory bodies, ethicists, and legal experts to allow for a responsible implementation of genetic testing in health care.

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