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COMMENTARY

Points to consider in assessing and appraising predictive genetic tests

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Abstract The use of predictive genetic tests is expanding rapidly. Given limited health care budgets and few national coverage decisions specifically for genetic tests, evidence of benefits and harms is a key requirement in decision making; however, assessing the benefits and harms of genetic tests raises a number of challenging issues. Frequently, evidence of medical benefits and harms is limited due to practical and ethical limitations of conducting meaningful clinical trials. Also, clinical endpoints frequently do not capture the benefit appropriately because the main purpose of many genetic tests is personal utility of knowing the test results, and costs of the tests and counseling can be insufficient indicators of the total costs of care. This study provides an overview of points to consider for the assessment of benefits and harms from genetic tests in an ethically and economically reflected manner. We discuss whether genetic tests are sufficiently exceptional to warrant exceptional methods for assessment and appraisal.

Keywords Resource allocation · Genetic testing · Costs and cost analysis

Context

The use of genetic tests is expanding rapidly (Schmidtke et al. 2005; Javaher et al. 2008). Unless they replace other, more expensive tests or result in reduced costs of care through prevention or early, asymptomatic detection of disease, the introduction of new genetic tests will incur increased costs to health care systems. In spite of technical improvements, particularly in the field of sequencing

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technologies leading to steadily lowering laboratory costs per test (Rogowski 2006), the remaining and potentially increasing costs of genetic counseling and follow-up could outweigh the potential savings from early prevention and lead to an overall increase of health care expenditure (Rogowski 2007). A recent theoretical study showed a mismatch between medical need and available resources in genetics (Krawczak et al. 2007) which is likely to increase with the rising number of predictive genetic tests (Schmidtke et al. 2005). In a recent empirical study, Canadian decision makers reported insufficient resources to fund all desirable tests. Instead of being based on nationwide evidence-based guidance for predictive genetic tests, allocation decisions were mostly made on a local and ad hoc basis (Adair et al. 2009). This is likely also to be the case in Europe or USA (Rogowski et al. 2008).

A key criterion in health care decision making is evidence of medical net benefit, i.e., a positive balance of benefits and harms. This balance is often assessed by third-party payers before including new technologies among covered services (Rogowski et al. 2008); however, payers may disagree as to whether or when there is sufficient evidence of net benefit to endorse the widespread use of a screening test; the controversy over prostate-specific antigen screening for the detection of prostate cancer is an example.

In genetic testing, "clinical utility" as a criterion for prioritization is defined variably in terms of net medical benefit or whether clinical management is altered, regardless of medical outcomes (Grosse et al. 2010a; Grosse and Khoury 2006). The latter approach is reflected, for instance, in some of the prioritization principles of the Department of Health of New South Wales, Australia. Higher priority is assigned to diagnostic tests that alter clinical management, "When confirmation of a clinical diagnosis will lead to changes in management of an affected person," than if "genetic testing will not alter the patient's management or options".[1] The guidance has been adopted in a similar form by the Human Genetics Society of Australasia.

Genetic tests are associated with multiple benefits and harms which may be difficult to measure by standardized methods of clinical epidemiology. In addition to clinical outcomes, some observers call for the inclusion of non-medical benefits under the rubric of "personal utility" of genetic tests (Grosse et al. 2009). This study provides an overview of points to consider in assessing the usefulness of predictive genetic tests.

We define genetic tests here as the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to a heritable disorder or to specific reactions to medical treatments.[2] In the case of predictive testing, an individual (typically without symptoms) is offered a test on an individual basis, e.g., for personalized prevention; screening here denotes a situation where a test is offered actively to a group of individuals. To focus on issues involved with assessing benefits and harms from new and forthcoming genetic tests, we exclude from this study carrier-, pre-implantation, and prenatal testing for the purpose of family planning. These latter tests involve a range of very specific ethical issues which have been discussed elsewhere (de Jong et al. 2010; Grosse et al. 2010b; Kress 2007; Buchanan and Brock 2007).

This study is based on an exploratory review of the literature. It starts with an outline of the major issues to consider for genetic testing that have impacts on their benefits and harms and outlines approaches to assess these in a scientific manner. Following a framework outlined in a previous paper (Rogowski et al. 2009a, b), benefits and harms are divided into three categories. First, medical benefits and harms are presented, which include anxiety and distress and which are typically in the scope of evidence-based medicine. A second category is non-medical benefits and harms, which are of particular importance in genetics because frequently tests provide personal utility in terms of information for other life decision making; also, issues like concerns about privacy are of high relevance but not captured by medical outcome measures. Third, the category of financial benefits and costs is presented because in the face of scarce resources these are of relevance for decision making as well. The discussion addresses the questions whether genetic tests are sufficiently different from other health technologies to make specific recommendations necessary as well as implications for balancing benefits and harms of genetic tests depending on their expected application.

Establishing benefits and harms of genetic tests

Some genetic tests raise hardly any doubt regarding their benefits and that these benefits outweigh the harms. A classic example is neonatal screening for phenylketonuria, a condition in which severe sequelae can be prevented by dietary measures if the disease is detected soon after birth (Bodamer et al. 2007). For most genetic tests, however, establishing benefits and harms raises a number of challenging issues (Rogowski 2007).

[1] http://www.health.nsw.gov.au/policies/gl/2007/pdf/GL2007_013.pdf (downloaded on January 19, 2010)

[2] See http://www.genetests.org/servlet/access?id=8888891&key=Wt-CocgvbZFre&fcn=y&fw=FNL-&filename=/concepts/primer/primerwhatistest.html (downloaded on December 22, 2009; pharmacogenetics included)

Medical benefits and harms

Benefits

A first issue in the establishment of benefits is that the associations between genotypes detected by genetic tests and phenotypes related with disease are frequently weak and potentially overestimated (Ioannidis et al. 2001). In the case of hereditary hemochromatosis (HH), for example, early evaluations assumed that about half of male homozygotes would develop the life-threatening manifestations of cirrhosis, diabetes, or cardiomyopathy (El-Serag et al. 2000; Adams and Valberg 1999). According to a recent modeling study, based on the cross-sectional literature about 3.5% of adult male homozygotes for the HH-associated C282Y mutation have liver cirrhosis, and there is no excess risk of either diabetes or heart disease (Rogowski 2009). Among individuals detected by phenotypic tests, the cumulative incidence or risk of cirrhosis is likely to be considerably higher; another study reported that 16.7% of homozygotes with serum ferritin above 1,000 μg/L had documented liver cirrhosis or fibrosis (Allen et al. 2008).

For monogenic diseases caused by highly penetrant genotypes, mutation prevalence frequently is so low that screening studies would need to have very large sample sizes in order to establish a clinically relevant health impact of genetic markers with statistical significance.

The precision of risk prediction in itself is not necessarily meaningful from a medical management perspective. Detecting an individual at elevated risk of a condition for which no preventive options are available is less valuable than identifying someone with an equivalent risk for a condition with outcomes that can be prevented. For example, in the case of HH, outcomes such as liver cirrhosis can be prevented by therapeutic phlebotomy to lower blood iron levels if this is begun prior to the development of clinical disease (Rogowski 2009). To estimate clinical utility, the final health outcomes associated with decisions made following the results of a genetic test need to be established. To achieve this, a variety of additional factors need consideration, e.g., the availability and effectiveness of prevention or cure for the health consequences of the genetic defect.

Clinical trials, the "gold standard" in the establishment of effectiveness of an intervention, are not necessarily feasible for predictive testing/screening for highly penetrant genotypes. Consequently, the estimate of benefit from the early detection of genetic disorders typically must rely on observational evidence relating to separate components of a program (e.g., evidence relating to the accuracy of predictive testing/screening for early disease detection, and evidence on the health impact of early treatment) which frequently is uncertain as well (Rogowski 2007; Potter et al. 2008; Teutsch et al. 2009).

Also, psychological and behavioral issues play an important role in the establishment of the long-term medical benefit of genetic testing. Detection which is not followed by the adoption of preventive interventions does not provide medical benefit. The uptake of preventive services following the detection of a genotype associated with disease risk varies depending on the type of prevention strategy. Positive genetic test results for genotypes associated with hereditary cancers are associated with increased uptake of phenotype screening among carriers, but uptake of prophylactic surgeries is not as high. For Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC), uptake of frequent colonoscopies among mutation carriers ranged from 71% to 100% in published studies. Compliance with mammography in patients with hereditary breast and ovarian cancer mutations (BRCA1/2) ranged from 68% to 78% (Beery and Williams 2007). Given the difficulties of achieving long-term adherence for medication (McDonald et al. 2002), long-term adherence to demanding preventive interventions such as maintenance phlebotomy in conditions with lower penetrance like hereditary hemochromatosis is likely to be considerably lower.

Another issue is the potential benefit from predictive genetic testing/screening in terms of information for first-degree relatives, a positive test result in one member of a family may alert other family members to hitherto unexpected elevated risks. Thus, the genetic test can serve as a starting point for more cost-effective predictive cascade testing/screening strategies, as has recently been demonstrated in testing for Lynch syndrome (Mvundura et al. 2010). Hemochromatosis can also lead to unspecific symptoms like fatigue and joint pain. In such a situation, predictive and diagnostic test properties overlap.

Medical benefits may relate to different dimensions of health, e.g., pain, anxiety, mental and physical functioning, or life expectancy. To compare the size of medical benefits across a range of technologies, these different dimensions of benefit can be summarized by quality-adjusted life years (QALYs). QALYs are based on an estimation of length of life, multiplied by a factor between 0 and 1, representing the health-related quality of life within different periods under investigation. QALYs provide a tool for the establishment and comparison of health benefit in a scientific manner which is frequently used in health economic evaluations. QALY gains are an important input to cost–utility analysis, a tool to support decision makers in systematic priority setting (Brouwer et al. 2008); however, the first step of establishing QALY gains is a measurement of health outcomes by generic instruments like the EQ-5D which measures medical benefit in terms of changes in the following five categories: mobility, self-care, usual activities (e.g., work, study, housework, family, or leisure activities), pain/discomfort, and anxiety/depression with three

corresponding parameter values. While questionnaires like those used to score, the EQ-5D have a range of advantages, e.g., they facilitate quick health assessments, these generic health profiles frequently lack sensitivity for establishing the benefit of genetic testing (Rogowski 2007).

Genetics-specific survey instruments have been used to characterize psychosocial outcomes of clinical genetic testing (Payne et al. 2008). Domains addressed by these instruments include anxiety, worry, depression, coping, decision-making, health status, knowledge, perception of risk, perceived personal control, psychological impact, quality of life, self-esteem, or spiritual well-being (Payne et al. 2008); however, these outcome measures have generally been used and reported in only one article. Also, no clinical instrument is currently available which captures all relevant outcomes, and some important aspects of patient benefit from clinical genetic services are not covered by existing outcome measures (Payne et al. 2008).

Harms

Even a negative test result in at-risk families can incur net harms to certain individuals. This has been best studied for Huntington disease. In a study of psychological outcomes from predictive genetic tests for Huntington disease, not only carriers, but also 24% of non-carriers experienced depression during follow-up (Gargiulo et al. 2009). It has also been reported that suicidal ideation was increased after genetic testing for Huntington disease in both carriers and non-carriers (Larsson et al. 2006). Consequently, there is an ethical imperative for the offer of genetic testing for this disease, which must be preceded by thorough pre-test counseling, to be accompanied by careful screening for risk factors for poor mental health outcomes and for adequate post-testing support to be provided (Lickleder et al. 2008).

Also, in conditions where medical options for preventing the manifestations of disease are available, individuals who test positive may experience an immediate increase in health worries, regardless of the potential positive health impact associated with prevention (Anderson et al. 2006). In the long run, though, the earlier fear concerning negative impact of genetic test results on mental health has not been substantiated by scientific studies (Broadstock et al. 2000; Cohn et al. 2008; Douma et al. 2008; Smith et al. 2008; Beran et al. 2008; Foster et al. 2007).

Non-medical benefits and harms

Genetic testing also incurs benefits and harms which are not captured by the tools typically used in clinical and epidemiological research. These can be relatively minor medical consequences or strictly non-medical outcomes, such as individual autonomy and life planning; both are subsumed here under non-medical benefits and harms. It has been argued that non-medical outcomes should not be considered by health care decision makers (Brouwer et al. 2008).

Benefits

Some part of the benefit of a genetic test may be impossible to establish by medical or psychological instruments, particularly if a primary purpose of a genetic test is enhancing patient autonomy. This is, for example, the case in testing for Huntington disease which may have lifestyle consequences, such as decisions about employment or residence. Such testing will also likely have psychosocial consequences, e.g., anxiety, which can be assessed in terms of medical benefits and harms. Autonomy is particularly an issue in the case of preconceptional and prenatal genetic screening for family planning (Rogowski 2007). Also, such tests may have medical consequences, e.g., when results constitute an indication for prenatal diagnosis or other methods for family planning.

Harms

It is widely accepted that genetic tests must involve informed consent and that an individual has the right to decline receiving information. Consent implies more than just a patient agreeing to or not refusing a medical intervention. One gives an informed consent to an intervention if (perhaps only if) one is competent to act, receives a thorough disclosure, comprehends the related information, acts voluntarily, and consents to the intervention (Beauchamp and Childress 2009, p. 120). There have been concerns that the results of genetic tests can very easily be misunderstood; patients may not be familiar with epidemiological concepts of risks and over- or underestimate the precision of a prediction as well as the meaning of relative risk information for their personal health (Potter et al. 2008). Informed consent is also difficult to obtain if parents make decisions on behalf of their children (e.g., in the case of newborn screening). Thorough genetic counseling may be particularly difficult in the case of a mass screening program (Potter et al. 2008). Research results have reported difficulties inherent in obtaining truly informed and voluntary consent (Sugarman and Sulmasy 2001, 269f).

Regulation of genetic testing in a number of countries requires counseling and written informed consent prior to genetic testing (Javaher et al. 2008). The Human Genetic Examination Act in Germany which became effective on February 1, 2010 requires, for example, that genetic diagnosis must be preceded by written informed consent. This consent includes “the decision in regard to the scope

of the given genetic examination as well as regarding the decisions if, and if so to which extent, the examination results may be disclosed or, as the case may be, destroyed"[3]; however, genetic information is inherited and thus shared within a family. The decision to obtain genetic information may therefore potentially impact other family members (Burnett et al. 2007; Denny et al. 2008). This is, for example, the case, if a young adult conducts a predictive genetic test for Huntington disease which had been found in a grandparent; a positive test result implies the knowledge that the parent must also be a carrier, even if he or she declined undergoing the genetic test. If results are shared within a family, genetic testing may thus violate a relative's right not to know his or her genetic predisposition.

Furthermore, information about inherited risks may not be considered beneficial. Some people may prefer the innocence of simply letting things evolve as they will rather than being confronted with having to make a choice to undergo a predictive genetic test and to know the results.

Additionally, there have been concerns about a potential for unfair discrimination, e.g., in the labor or insurance market. A number of countries have established laws for genetic tests which address these issues (Javaher et al. 2008). The potential impact of unfair discrimination may thus differ according to a patient's national legal context.

Financial benefits and costs

Financial benefits may arise from genetic testing if it leads to cost savings elsewhere in the system—e.g., due to more targeted prevention. Predictive testing and screening for HH, for example, can reduce the costs of liver cirrhosis in at-risk individuals. In the case of HH screening, these reductions of health care expenditure are outweighed by the costs involved with a screening program (Rogowski 2009).

Some types of genetic screening can possibly lead to overall cost savings in the health care system. This may be the case for familial adenomatous polyposis (FAP), a hereditary colorectal cancer syndrome where affected patients develop multiple polyps. Due to its autosomal-dominant inheritance pattern, offspring of patients with FAP have a prior probability of 50% of developing the disease. Consequently, in the absence of genetic testing all offspring of a parent affected with FAP should receive increased prophylactic colonoscopy. If a causal mutation for this syndrome is detected in the index case, specific clinical surveillance can be restricted to individuals who carry this mutation. The cost savings from a 50% reduction of additional colonoscopies among test negative first-degree relatives, if it occurs, would exceed the costs incurred by the genetic test for the index case and the genetic test among the relatives (Rogowski 2006); however, that presumes that FAP is diagnosed in the absence of genetic testing. A cost-effectiveness analysis of genetic testing for index patients in the other common form of hereditary cancer, HNPCC, concluded that testing is not cost saving but may be cost-effective (Mvundura et al. 2010). This differs from the FAP case because few relatives would undergo colonoscopies in the absence of genetic testing.

In any case, covering a genetic test always incurs financial costs to health care systems; scarce resources are spent for a genetic test which could also have been spent for an alternative purpose. From a health care system's perspective, the analysis of genetic tests needs to account for the total costs of care associated with genetic testing. This includes the costs of counseling, follow-up testing, treatment and prevention, avoided costs of prevented medical conditions or, in the case of screening programs, the costs of achieving test uptake (Rogowski 2006; Rogowski 2007). Furthermore, despite the stability of germ line genetic information over lifetime, duplicate genetic testing can be found in medical practice (Riegert-Johnson et al. 2008). While the costs of DNA-based tests are currently decreasing substantially, the total costs associated with genetic testing might increase rather than fall over time because of rising uptake rates as well as increasing options for follow-up testing and treatment.

An important issue complicating prioritization of genetic tests within a budget for genetics services (vertical prioritization) is the perspective of which costs need to be taken into consideration. In a situation where genetic tests are conducted by a genetics specialist or where decisions have to be made about scarce resources specifically for genetic tests, it is unclear how financial benefits and costs of other health care sectors and beyond should be taken into consideration.

Such budgets for specific types of health care services and problems associated with a "budget silo mentality" have been described and analyzed for pharmaceuticals (Garrison and Towse 2003). For genetic tests, similar arrangements can be found in Sweden, where hospitals are assigned budgets for genetic services. Also, reimbursement arrangements where the amount of reimbursement is tied to whether the total number of services meets or exceeds a budgeted number (so-called "Regelleisungsvolumen" in Germany) can have a similar effect.

In the case of testing for FAP or HNPCC, a rather expensive full sequencing test is necessary for the index case to detect a mutation which can then be used for predictive cascade testing/screening (Rogowski 2006). While this mutation test may be initiated in a hospital setting for an individual who undergoes colon cancer

[3] See: http://www.eurogentest.org/uploads/1247230263295/GenDG_German_English.pdf (uploaded on May 17, 2010)

treatment, financial benefits from testing accrue elsewhere due to savings from avoided colonoscopies in ambulatory care for family members. Likewise, a genetic test for HH may be conducted by an outpatient geneticist, but in case the patient then experiences worries and either undergoes psychological treatment or increases his amount of diagnostic checks and prevention to an unnecessary amount, this is likely to fall on other than the genetics budget. Health economics textbooks typically favor a rather broad perspective for economic evaluation—society as a whole or at least the health care system (Gold 1996; Drummond 2005); however, such a broad perspective for decision making is difficult to achieve if the incentives implied by the sectoral or regional budgets are at odds with the efficient use of scarce resources from the broader perspective. One additional aspect to discuss apart from prioritization of genetic tests within one budget may therefore be whether the budgeting system is adequate. For example, the costs of a test which incurs savings in another sector may need to be charged to a global or to a different sector's budget to achieve efficient allocation of scarce health care resources.

Dealing with future benefits and harms

Frequently, the (expected) benefits from predictive genetic tests accrue in the future. Screening for hereditary hemochromatosis, for example, can avoid future liver cirrhosis which increases life expectancy by approximately 8.6 years, comparing cirrhosis patients with the normal population. Yet for a male Caucasian who is tested at the age of 30, these gains are expected to accrue after an additional 25 years (Rogowski 2009). It is unclear whether they should be valued equal to an immediate reduction of mortality risk from a treatment which improves life expectancy of a patient presenting to his doctor with liver cirrhosis. On one hand, there is empirical evidence that individuals value immediate health gains higher than health gains in the future (Frederick et al. 2002). On the other hand, a lower valuation of future health gains may be considered unfair discrimination against those who could benefit from prevention or against future generations (Bos et al. 2005). In health economic evaluation, it is current practice to apply discount rates to future benefits and costs, both financial and health, although it is an issue of debate (Claxton et al. 2006; Gravelle et al. 2007).

Dealing with uncertain benefits and harms

A problem tightly connected with the question of future benefits and harms is the question of how to deal with uncertain information. Especially for long-term effects of multifactorial disease, the evidence is usually very weak. While evidence-based medicine primarily demands that decisions should be based on the best available evidence of benefits and harms, the practice in prioritization decisions is frequently to accept a treatment as beneficial only if the benefits have been established by studies of high quality with statistical significance and thus give little weight to uncertain benefits (Rogowski 2009).

If tests are only conducted if their effectiveness is well established, it is likely that very few genetic tests can achieve high priority for evidence-based practice. This would particularly be the case in a situation where the benefits and harms of predictive genetic tests are compared to those from other medical treatments like drugs for which typically solid evidence of effectiveness from randomized clinical trials is available (horizontal prioritization).

Discussion

Do the issues call for genetic exceptionalism?

There has been a discussion in scientific discussion and health policy about whether genetic tests are sufficiently different from other medical tests to justify a "genetic exceptionalism" that would require tighter regulation (Murray 1997). Indeed, predictive genetic tests share many characteristics with other screening or diagnostic technologies. For all diagnostic technologies, long-term health outcomes depend on treatment and patient adherence and hence are uncertain (Rogowski 2007; Gazelle et al. 2005). This is also the case with more specific aspects, for example, the diagnosis of an infectious disease has implications for the health of other family members and predictive information from laboratory tests can lead to discrimination by the insurance industry.

Furthermore, the current literature suggests that, despite the availability of an increasing number of genetic tests, the prevalence of conditions with high penetrance where genetic exceptionalism may be of particular relevance remains low. Instead, gene–environment interaction appears to play an important role, and genetic tests should undergo the same analysis of predictive power as phenotype-based tests. In most cases, a brief look at a patient's body weight as well as a brief family history of disease may tell a doctor much more about his or her risk for diabetes or myocardial infarction than a predictive genetic test (van der Net et al. 2009; van Hoek et al. 2008; Janssens and van Duijn 2008). Consequently, the additional value of predictive genetic testing may be quite limited, even if the genotype is significantly associated with the risk of the disease outcome.

However, there also are good reasons in favor of genetic exceptionalism in allocating resources to genetic tests in the

sense that specific solutions to genetics-specific problems are needed.

First, the value of some tests cannot adequately be addressed by standard methods for the assessment and appraisal of health technologies. The question therefore remains which genetic tests result in desirable medical treatments even if the frequently proposed methods of prioritization of health services (e.g., priority based on cost per QALY) do not adequately capture their desirability because of information for personal life decision making, and if scientific evidence is accepted as a major criterion of coverage decision making, it needs to be determined which methods should be applied if randomized clinical trials are not feasible for ethical, financial, or other practical reasons.

Second, there is a need for advice on prioritization which is specific for predictive genetic tests as far as it addresses prioritization within budgets made available for genetic services. If prioritization of genetic tests can draw upon experiences from prioritization in other, similar technologies, this is an argument in favor of rather than against such transfer of knowledge because it increases its chances of success; however, the concepts for prioritization developed by ethicists and economists are typically too generic to be applicable in health care practice. In circumstances where laboratory managers or heads of genetics units oversee a fixed budget for genetic services, they have to make decisions, the criteria of which will differ from those by gatekeepers in emergency rooms or networks of organ transplantation.

Balancing the benefits and harms of genetic tests

The most appropriate method for assessing and weighting or valuing benefits and harms as well as the need for genetics-specific solutions is likely to differ depending on the context of testing:

1) Diagnostic testing: Genetic testing to validate or further specify the diagnosis of monogenic diseases frequently results in little or no improvement in health outcomes; however, the budget impact of such tests is low compared with other technologies like drug treatment. In addition, a genetic diagnosis may provide value by excluding other potential causes which might warrant additional testing and treatment. These reasons are likely to be sufficient for decision makers to treat genetic tests for individual monogenic diseases as exceptional in a sense of lower requirements for establishing effectiveness or cost-effectiveness by classical methods.
2) Screening: For active screening programs (e.g., for hereditary hemochromatosis, familial hypercholesterolemia, or HNPCC), there are good reasons to apply the same high standards of assessing effectiveness and cost-effectiveness to genetic tests as to any other screening program. This is because the problems of assessing predictive power, effectiveness, and cost-effectiveness of genetic screening tests are similar to those for other screening tests and one of the key questions in the assessment is whether genotypic or phenotypic markers perform better in terms of effectiveness and cost-effectiveness (Rogowski 2009). In addition, exceptionalism in terms of informed consent for genotypic screening may be warranted because of concerns that problems in confidentiality and data security could potentially result in unfair discrimination and stigmatization.
3) Predictive testing associated with well-established health gains: Finally, for the multitude of upcoming predictive genetic tests, the specific issues to address are likely to depend on the resources available and the payers' policies. The benefits and costs of predictive tests for severe diseases like hereditary cancer with the clear aim of reducing cancer-related morbidity may be straightforward to assess in terms of cost per life year or QALY saved. Evidence-based approaches like the process developed by the Evaluation of Genomic Applications in Practice and Prevention initiative (Teutsch et al. 2009) provide valuable genetics-specific guidance concerning the existing evidence. Given that testing is not offered actively but more likely to be upon request from well-informed individuals, the concerns about potential harms and informed consent are likely to be lower here. Nevertheless, as opposed to the case of diagnostic testing, there is more reason for health care payers to fund only tests for which evidence of effectiveness and, potentially, cost-effectiveness has been established.
4) Predictive testing without well-established health gains: For other tests, e.g., tests for incurable diseases like Huntington disease in asymptomatic individuals, tests with lower predictive power or tests for conditions with lower severity, it first needs to be specified whether payers accept funding tests without clear evidence of major health effects. In the absence of robust evidence of health effects, novel methods of establishing and valuing other types of benefits need to be applied, in particular for tests with the highest budget impact.

An economic measure of benefit which does not depend on evidence of health effects is willingness to pay (WTP) (Grosse et al. 2008). WTP methods have recently been applied to different types of genetic tests in general (Ries et al. 2010) and to genetic tests for unexplained developmental disability (Regier et al. 2009). In WTP surveys, individuals

trade off the utility they expect to gain from the test in question with the utility from alternative uses of their money. The WTP metric allows for a direct comparison with the costs of tests, although this may be difficult to apply in health care because of expectations of third-party payment. A recent Canadian study found that few people were willing to pay the full cost of a molecular genetic test, in part because they felt that this was the responsibility of health payers (Ries et al. 2010). WTP can also be estimated through choice experiment (conjoint analysis) surveys in which individuals are asked to trade off among bundles of attributes, including cost and the probability of detection (Regier et al. 2009). Due to a number of methodological limitations (Donaldson et al. 2006), the use of WTP techniques has to be handled with care. Also, it is unclear whether health care decision makers consider WTP estimates to be relevant for prioritization (Brouwer et al. 2008) (Grosse et al. 2008).

If payers are unwilling to pay for predictive tests without well-established health gains, a case can be made in favor of out-of-pocket funding of such tests where the comparison of benefits and costs is left to those who ask for testing and are expected to pay for it (it has to be noted that tests for reproductive decision making were excluded from this analysis; here, additional ethical and economic issues would need to be considered). As autonomous consumers, they are free to purchase a test if its perceived benefit exceeds its costs. Consumer sovereignty is also supported by the high importance of informed consent, the comparatively the low cost of genetic tests and, typically, the limited urgency of decisions about genetic testing; however, as with other goods on the market, there remains the need to regulate their acquisition to prevent harm to consumers. In addition, there is the danger that if clinical geneticists have to fund their work by offering their tests like other services, they may have incentives to sell unnecessary or potentially even harmful tests. Quality standards of genetic counseling for those who offer the test or even a prohibition of certain marketing methods like direct-to-consumer sale via Internet (Wasson et al. 2006) may be necessary to prevent consumers from the potential harms listed above. To prevent financial harms to the health care system, additional measures should be taken to ensure that these tests do not lead to extensively unnecessary confirmatory testing (McGuire and Burke 2008).

Conclusion

In conclusion, we have addressed what we consider the important issues to be considered in the assessment and appraisal of predictive genetic testing (excluding reproductive testing). The way that benefits and harms of genetic tests are to be assessed and weighted is likely to depend on whether the genetic test is used in symptomatic individuals, active screening, or predictive testing upon request for conditions with or without well-established health gains. For the latter, out-of-pocket payment may be considered more appropriate than funding by social health insurance. Therefore, the following are among the most important topics associated with genetic testing which ought to be addressed by future work: First, how can we ensure that the distinction between publicly and privately funded genetic tests is made in a reasonable and fair manner? Second, how should we trade off the aims of protecting patients against the multiple potential harms from genetic tests through adequate regulation and increasing customer sovereignty through deregulation of a (former) public service?

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