Using needs-based frameworks for evaluating new technologies: An application to genetic tests

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Highlights

- The European Society of Human Genetics assessed the prioritization of genetic tests
- This study develops a prioritization score for genetic tests to facilitate equitable allocation oriented at need-based claims
- It includes attributes of health need, alleviation of need, and costs for a genetic test
- A case study for quantifying the attributes is presented
- Evidence from discrete-choice experiments can be used to weight the attributes

Abstract

Given the multitude of newly available genetic tests in the face of limited healthcare budgets, the European Society of Human Genetics assessed how genetic services can be prioritized fairly. Using (health) benefit maximizing frameworks for this purpose has been criticized on the grounds that rather than maximization, fairness requires meeting claims (e.g. based on medical need) equitably. This study develops a prioritization score for genetic tests to facilitate equitable allocation based on need-based claims.

It includes attributes representing health need associated with hereditary conditions (severity and progression), a genetic service's suitability to alleviate need (evidence of benefit and likelihood of positive result) and costs to meet the needs. A case study for measuring the attributes is provided and a suggestion is made how need-based claims can be quantified in a priority function. Attribute weights can be informed by data from discrete-choice experiments.

Further work is needed to measure the attributes across the multitude of genetic tests and to determine appropriate weights. The priority score is most likely to be considered acceptable if developed within a decision process which meets criteria of procedural fairness and if the priority score is interpreted as "strength of recommendation" rather than a fixed cut-off value.

1. Introduction

A rapidly expanding number of new genetic tests is available and used in health care for personalized prognosis, prevention and care [1]. Using new tests consumes additional resources for genetic services despite the fact that already now, it is not economically feasible to conduct all desirable genetic tests at the expense of existing public health care budgets [2, 3]. Therefore, decisions need to be made about which tests are the most important to provide. This is usually referred to as "prioritization", i.e. placing genetic tests into a rank order based on their perceived importance [4].

"Genetic test" is understood here as the application of a laboratory test or assay (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) to a defined clinical context [5]. The prioritization thus does not relate solely to tests but to groups of patients in specific clinical situation described as the test attributes below.

The increasing financial pressures on public budgets for genetics services as well as the concern for harmonized high quality provision of essential genetics services across Europe lead the European Society for Human Genetics (ESHG) in collaboration with the EU-funded project EuroGentest [6] to address ways of prioritizing genetic tests in an ethically and economically sensible manner [7]. The aim was to work towards a prioritization framework which is acceptable to the ESHG members as well as the major stakeholders affected by genetics services such as clinicians and patients.

The question as to which criteria should guide the prioritization of public health care resources is a topic of long-standing discussion in the ethical and economic literatures. Therefore, the project also included an assessment of prioritization criteria acceptable for genetic tests. Even if most economic frameworks are based on welfarist maximization of

individual benefit or on extra-welfarist maximization of health outcomes, neither of these is likely to be widely accepted by decision makers and stakeholders of genetic services [5].

One prominent alternative to benefit maximization is to base coverage decisions on claims according to medical need, rather than on health benefits [8, 9]. Medical need is a key criterion all health care systems relate to in their decision processes [10]. Need-based allocation is also promoted by the World Health Organization (WHO) in the concepts of horizontal (health care to all individuals with the same medical need) and vertical (preferential health care for those with greatest need) equity [11]. Needs are fundamentally different from desires or preferences which are the only source of value in welfarism [12]: an individual might desire something without needing it, and vice versa. Furthermore, while unsatisfied preferences do not necessarily harm individuals, unmet needs necessarily do so [13].

However, "need" is an ethical concept without consented definition [14]. It therefore requires further specification regarding its dimensions relevant for decision making. These dimensions depend on the decision context [11]. This study develops a need-based prioritization framework in the context of decisions about using public budgets for genetic services accountably. It can serve as a theoretical basis for an evidence-based priority ranking of genetic tests, based on standardized information sources about priority-relevant attributes of genetic tests such as the Clinical Utility Gene Cards [15] and weights for these attributes established by discrete choice experiments [16, 17].

2. Methods

Currently, no needs-based framework for prioritizing genetic tests in the face of scarce resources is available in the literature. To develop such a framework, this study uses literature searches described elsewhere [5] and discussions during a consensus process on prioritizing genetic tests [18].

A set of attributes was developed, based on the following theoretical considerations: first, the attributes should be associated with relevant measures of medical need for genetic tests or its alleviation which was the normative basis of this framework; second, the attributes should be mutually independent to the largest possible extent; and third, the attributes should be susceptible to measurement with available data sources to facilitate the establishment of a score representing the strength of need-based claims and further analysis such as discrete-choice analysis to establish potential weights for the different attributes. To assess its feasibility, the framework was applied to the case study of genetic testing for hereditary hemochromatosis.

3. A needs-based framework for allocating health care resources to genetic tests

Health or health care need is a key criterion for decision making under health care resource constraints. While the basic need for physical health is universal, the goods and health care services required to satisfy the need may vary [19]. Furthermore, health can be affected differently in different medical areas. Therefore, to develop a prioritization framework addressing the dimensions of health and health care need which are of specific relevance for the prioritization of genetic services, the terms of health or health care need require further specification. Unlike a welfarist approach, not all attributes of genetic tests which play a role in satisfying the patients' preferences for genetic tests are relevant for this specification. Instead, only the attributes objectively relevant to physical health are relevant [19].

There is a special feature of genetic tests which can easily blur the lines between welfarist and need-based approaches to prioritization in genetic testing: frequently, genetic tests are performed only for the purpose of providing information to facilitate patient empowerment [20, 21], rather than for improving health. This study starts by assuming that the information

as such is always considered beneficial because otherwise, the test would not have been requested. Any health benefits are additional to these knowledge based benefits. This excludes tests for multifactorial conditions where clinical impact and patient benefit are unclear and misleading information may be detrimental for patients so that the ESHG has recently made a recommendation against their use [22]. It also assumes that the test results cannot be obtained by less costly means. Furthermore, it excludes prenatal and preconceptive tests as well as screening tests which involves specific issues in the evaluation which have been discussed elsewhere [23-26]. Furthermore, the study assumes that the test results cannot be obtained by less costly means. Also, it excludes prenatal and preconceptive tests as well as screening tests which involve specific issues in the evaluation which have been discussed elsewhere [23-26].

3.1. Health-related need

"Need" can be defined as the gap between an actual state of an individual and a normal individual state as, for instance, Daniels' normal species functioning [27]. A "health-related need" constitutes a gap between actual and normal health states and is independent of whether there is anything that can currently be done to reduce the gap [28, p.131 ff.]. In the context of genetic testing, two different dimensions of health need are relevant for decision making.

Severity

Hereditary conditions can differ greatly with regard to their impact on life expectancy and health-related quality of life – for example, a test for Chorea Huntington compared with a test for susceptibility to periodontal disease. Different degrees of need according to this dimension are captured by an approach which is frequently labelled "fair innings" [14]. Measuring need according to this approach involves a comparison of the total health individuals experience over their lifetime with an average amount they could have expected. This expected health

can relate to the life expectancy at birth, or to life expectancy adjusted by a weight for health-related quality of life [29]. In the following, this concept of health-related need is termed "severity".

Severity (S) of a hereditary disorder targeted by a genetic test could be measured, independent of the age of the tested person, e.g. on a cardinal scale between a minimum of 0 (not severe at all) and a maximum of 1 (highest imaginable severity). This measure of severity would require information about life expectancy with this condition and, potentially, its impact on measures of health-related quality of life at the onset of disease. Estimating S in terms of this concept of severity requires subtracting the ratio of life expectancy with the disease (d) and average life expectancy (a) from one. The higher S, the higher is the health gap (decrement of life expectancy) the affected individuals suffer from:

(1) $S = 1- (d / a); S \in [0,1]$

Progression

The second dimension of "health need" can be based on a norm that rescuing individuals is more important the higher their immediate risk of disease is [14]. In the decision to test for hereditary hemochromatosis, for example, this dimension of health need does make a difference if a test is conducted in a healthy 18 years old male (h) who is very unlikely to have developed clinical manifestations such as liver cirrhosis yet, if it is conducted for early detection (e) in a 40 years old male where in case of C282Y homozygosis liver fibrosis may already have progressed silently or, whether it is conducted for diagnosis (d) in a 40 years old male who seeks a medical appointment because of fatigue and joint pain which may be a sign of clinical manifestation. In the following, this dimension of health need is termed "progression". It could be based on whether a test is for predictive purposes in an individual without symptoms and at an age prior to disease onset, whether it is for screening purposes in individuals at an age where the disease may already have progressed or for the purpose of

diagnosis in an individual with symptoms which may point towards the disease. The further the potential progression, the higher the health need may be considered because the need is more immediate. Progression (P) could thus be measured on an ordinal scale for the three settings of h for "healthy", e for "early detection" and d for "diagnosis":

(2) $P \in \{h, e, d\}$ with given ordering $\{h < e < d\}$

3.2. Alleviation of need

Even if an health-related need forms the basis of justified claims for medical interventions, the claims' degree of justification also depends on the extent to which the advised intervention can alleviate the need [28, p. 131ff.].

Evidence that need can be alleviated

The proven ability of a medical technology to ameliorate health-related needs is a widespread criterion in explicit decision making regarding medical technology. Also for genetic tests, it is obviously relevant whether their findings can support prevention or treatment of the condition. Most agencies for health technology assessment and for coverage decision making assess the scientific evidence of a technology's effectiveness if explicit coverage decisions are made [30].

Established schemes such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) are available to determine in a standardized manner as to what extent one can be confident that the desirable effects of a genetic test outweigh the undesirable effects [31]. Prior to formulating recommendations, GRADE requires assessing the body of evidence related to the relevant outcomes of the test [32, 33]. GRADE distinguishes between strong and weak recommendations for or against the use of a technology. These may be complemented by a category of "recommended only in research". The strength of a recommendation is determined by the balance of desirable and undesirable effects of the

management strategies under consideration, the quality of the evidence and variability in values and preferences [31, 34]. Only strong or weak recommendations in favour of a test are considered here because the prioritization framework only addresses beneficial genetic tests. Also, recommendations only in research are included because weak evidence is a frequent characteristic of new genetic tests [7].

The different categories of recommendations can be labelled in terms of numbers or symbols. Evidence of benefit (E) could therefore be measured on an ordinal scale according to three levels {s, w, r} representing strong, weak and recommendations only in research according to the GRADE scheme.

(3) $E \in \{s, w, r\}$ with given ordering $\{r < w < s\}$

Likelihood of positive result

Besides the question of whether or not a genetic test alleviates medical need (the algebraic sign of benefit) also its size (the absolute value of benefit) is likely to be relevant for decisions surrounding genetic tests. Establishing the size of benefit for genetic tests in a standardized and comparable manner involves a range of methodological challenges which are difficult to resolve. For example, besides benefit in terms of improved medical endpoints like mortality, also the benefit of knowing about a condition may be of relevance in the case of an incurable disease like Chorea Huntington. Also, benefit can accrue to different individuals (e.g. to relatives who undergo increased preventive colonoscopy in the case of Lynch Syndrome) [35]. Therefore, and also because a precise estimate of benefit size is unlikely to be feasible for the large number of newly available genetic tests, it is likely that a structured prioritization tool has to rely on a simpler indicator of benefit size.

One such indicator which is likely to be of relevance to decision maker is the test's yield in terms of likelihood of detecting a disease, or the individuals' a-priori risk of having or

developing the disease phenotype. For example, first-degree relatives (FDR) of an individual affected by a hereditary disorder are likely to be considered of higher priority for genetic testing than individuals in the general population. Also, high-risk groups may be considered to have a higher priority than low risk groups. Using likelihood of positive result as a simplified measure of benefit size can also be motivated by the observation that frequently, health economic evaluations of genetic testing services report cases detected as outcome measure [36-38]. However, it has to be noted that following the definition above, it could also be seen as a measure of health-related need because it is independent of whether or not treatment for the detected cases is available.

Like severity, likelihood of positive result (L) could be measured on a cardinal scale between zero and one or 0-100%. To ensure that rare diseases are not discriminated against, it could also be classified into three categories on an ordinal scale. For example, these categories could be general population risk (g), a first-degree relatives risk group (f) and (i) a group of intermediate risk in between these two, e.g. when due to personal medical history an individual has specific risk factors.

(4) $L \in \{g, i, f\}$ with given ordering $\{g < i < f\}$

3.3. Costs to meet health-related need

Even if patients' claims relate to genetic tests to alleviate health needs, they are not limited to the claim that the tests should be made available – typically, it is possible for patients to see a private doctor if they can fund the genetic service out of their pocket. Instead, the question

addressed here is whether scarce health care resources devoted to genetic testing should be used to fund the tests[1].

Even in a need-based framework based on claims for medical interventions, these claims do not constitute absolute rights. This is because the judgment of whether it is appropriate to respond to a claim for a genetic test also depends on its costs as well as the available resources as there are also other patients' claims on the scarce resources [8, 39]. Therefore, the concept of "alleviation of need" could be extended by "at acceptable costs". This does not imply maximizing health or any other outcome but only that the balance of costs, health needs and the benefit of the intervention to ameliorate the health needs are considered adequate.

This study analyses prioritization decisions surrounding new genetic tests from the viewpoint of genetics services providers with public budgets devoted to genetic tests. The most relevant costs which accrue from this perspective include the time involved in genetic counselling and interpretation of the genetic test results, and the costs of the laboratory test in an in-house or external laboratory [40]. These costs (C) can be measured in Euros on a cardinal scale and contribute negatively to the priority of the test, such that a high cost test is of lower priority than a low cost test.

(5) $C \in [0\,€, \infty\,€[$

Table 1 provides an overview of the need-based principles for prioritizing genetic tests.

INSERT TABLE 1 ABOUT HERE

[1] This study excludes the topic of organ allocation and the discussion of whether willingness and ability to pay does and should play a role in this setting. Also, prohibition of certain tests like pre-implantation genetic testing is excluded here.

3.4. Application to a case study

To explore whether it is feasible to quantify the five priority dimensions developed in the previous sections, the framework was applied to the clinical case study of testing for hereditary hemochromatosis (HH) in the 40 year old son of an affected individual. HH is an inherited disorder of iron metabolism. 90% of HH patients are homozygous for the C282Y mutation on the *HFE* gene. In the absence of early detection and preventive phlebotomy, a small percentage of homozygotes have been reported to develop liver cirrhosis, potentially associated with hepatocellular carcinoma and, as a consequence, increased mortality [41, 42].

The operationalization was based on public information sources which could have been identified through systematic searches of the published literature and other sources available on the internet. For the criteria of Severity, Progression, Evidence, and Likelihood, the information was based on a decision-analytic model [42] and a recommendation statement [43] which incorporated systematic literature searches. For the criterion of costs, a publicly available data base was used. The aim was to assess whether it is feasible to obtain all data necessary to add a priority score to structured information sources about genetic tests such as the Clinical Utility Gene Cards published by the EJHG [15] or the Gene Dossiers developed by the UKGTN.

Severity: A recent decision-analytic model estimated the undiscounted life expectancy of unaffected German males at birth to be 77.3 years and for German males who develop the disease to be 68.7 years [42]. From this, severity can be calculated to be:

$$S = 1 - (68.7 / 77.3) = 0.11$$

Progression: The potential progression of the disease depends on the age of the tested person. In the studies included in the decision-analytic model, the youngest age at which cirrhosis had developed was 33.4 years, the mean age was 54.3 years [42]. At an age of 40, the individual to be tested is therefore already at risk of clinical manifestation. Progression is, therefore:

$$P = \{e\}$$

Evidence of need: The C282Y mutation was detected in 1996 and since then, various studies have been conducted to increase the understanding of the impact of the disease. A recent evidence-based recommendation statement assigned the highest category of recommendation to testing for C282Y mutations in first-degree relatives [43]. As this is relevant for the case of a son of an affected patient, the evidence of benefit, therefore, is:

$$E = \{s\}$$

Likelihood: Even in first-degree relatives, the likelihood of developing manifestations is comparatively small. Nevertheless, it is of high impact on the cost-effectiveness results and screening among male first-degree relatives is much more cost-effective than screening male individuals at population risk. It can be calculated from the prevalence of C282Y homozygosis among first-degree relatives of 0.062 [see Appendix to: 42] and the risk of cirrhosis in homozygotes of 0.035. The a-priori risk is, therefore:

$$L = 6.2\% * 3.5\% = 0.22\%$$

or, alternatively, in ordinal categories: $R = \{f\}$

Costs to meet need: Frequently, costs differ by service provider and also depend on the utilization of existing testing facilities. If resource scarcity on a local level mainly refers to manpower, costs may primarily be the counselling time which is likely to depend on the complexity of the mutation tests. If the aim was to create a unified framework of priority

across different genetics service providers in Europe, European sources of test costs could be used as there are intermediaries who provide lab test services on a European level such as GENDIA. GENDIA provides lists of standardized test costs for mutation tests. It should be noted that this cost estimate is likely to be an underestimate because the costs of counselling are not included explicitly. However, given that the same underestimate applies to all tests prioritized within this framework, it is unlikely to have a large impact on the overall ranking of tests. For hereditary hemochromatosis, a bundle of tests for the four most frequent mutations which are likely to be tested for is available at a cost of €280. The test cost can therefore be estimated as:

$$C = €280$$

3.5. Establishing and interpreting a priority function

The overall priority of a genetic test can, therefore, be seen as a function of the different attributes above:

(6) $P = f(S, P, E, L, C)$

If one test clearly dominates all others, this information is sufficient to establish a rank order. Given that this is frequently not the case, it needs to be defined what form the priority function should take. For this purpose, value judgments about the relative importance of the different criteria for the overall priority have to be made.

In current health care practice, genetic tests are provided which score high or low on all of the five criteria above. Therefore, rather than assuming any kind of ex-ante priority ordering it could be assumed that the five criteria above are relevant independent of each other. If weights for each of the criteria can be established, the overall priority of a genetic test could be approximated by the following priority function:

(7) $P = S*\beta_1 + P*\beta_2 + E*\beta_3 + L*\beta_4 + C*\beta_5$

If empirically measurable value judgments are considered as an appropriate starting point for weighting the different criteria, it has been shown that standard methods of discrete-choice analysis are a feasible technique to estimate weights β_1 - β_5 for genetic tests to obtain a rank order [17, 44].

Unlike the standard preference-based interpretation of DCE results, such an analysis would not aim at positively describing preferences which are assumed to be exogenous, stable individual rank orders and which are considered the only relevant sources of value for the tests. Instead, it would reveal value judgments which are normative and susceptible to reasoned discussion and modification. Rather than representing which tests the respondents would prefer for themselves they can be seen as considered judgments about whether the test should be conducted, or, in other words, what relative priority, on average, the respondents assign the different genetic tests, balancing health needs, evidence that the need can be alleviated and costs [45]. The use of this framework as well as DCE results related to the framework should therefore be complemented with a process of stakeholder deliberation (see discussion section).

As long as there is still room for improving the sum of priority scores of all tests provided by a genetics unit this implies that there have been tests provided to individuals with lower needs and more highly needed tests have been forgone. Allocating scarce health care resources to genetic tests in such a way as to maximize the overall priority score obtained from the scarce resources would therefore be equivalent to treating patients equally according to need. Maximizing this needs-based index therefore corresponds with the neoclassical tradition of an axiomatic concept of benefit maximization rather than the utilitarian tradition of a hedonistic concept of benefit and benefit maximization [46, p. 19 ff., 47].

4. Discussion

One frequent objection to utility- or health maximizing economic evaluation frameworks is that equal claims rather than net benefit should be the basis for fair allocation of scarce health care resources [48]. To our knowledge, this is the first study which develops a needs-based framework to quantify the strength of claims to a genetic test, to facilitate equitable allocation based on medical need.

This study evolved from a prioritization activity of the European Society of Human Genetics which is the first clinical society that aims at developing a formal recommendation statement on the vertical prioritization of scarce health care resources to genetics services. Given that need is a key criterion for allocating scarce health care resources also in genetics [49], it used an inductive approach to needs assessment, starting with specific types of medical need relevant for genetics. This provides a condition-specific alternative to the more general specification of an aim of health care (e.g. based on quality-adjusted life years) which may only be applicable to genetic testing to a limited extent. It also provides an alternative to standard welfarist frameworks which can incorporate the multitude of benefits associated with genetics services but do not match with the requirement of fair health care resource allocation to be based on medical need.

Using HH as a case study, it has been demonstrated that evidence about the characteristic values of the attributes used in this framework can be established. Also, first evidence of weights elicited within DCE to reveal value judgments of a large group of stakeholders about these attributes has been collected recently [16, 17] which may be an appropriate starting point for implementing the framework developed here.

4.1. Using the results

Following a procedural approach to fair and reasonable priority setting, it is likely that using such a prioritization framework is more likely to be considered acceptable if it has been challenged within a transparent decision process which includes experts and key stakeholders and allows for revision and appeal [50]. It is likely that such a process would include deliberation about three aspects: firstly, whether the underlying prioritization principles are indeed considered reasonable by decision makers and affected stakeholders; secondly, whether the operationalization for measuring to what extent the principles are met are considered feasible and scientifically sound; and thirdly, whether the weights and the ranking which results from applying the prioritization tool to selected case studies is considered plausible and fair. Given that genetic tests are an evolving area of clinical care and given the early stage of discussions about priority setting in an international context, this deliberation and further methods development is likely to be an iterative process.

The stakeholder workshop after the first iteration concluded that, generally, such a needs-based prioritization framework as well as the use of DCE to elicit weights for a prioritization algorithm is considered desirable. However, further work is needed before this framework can be used in decision practice which is described below. Given that it is likely that not all aspects relevant for priority setting can be incorporated into a structured framework, it is also likely that in the long run, a score resulting from a prioritization algorithm may better be understood in a weak manner as "strength of recommendation" rather than as a definite value to be compared to a fixed cut-off in an algorithmic decision process [18].

4.2. Limitations

This study is subject to a number of limitations which also need to be addressed by further research.

Validation of attributes and functional form

Regarding the attributes, not only the evidence of benefit but also its size is likely to play a role in priority setting, and the diverse benefits associated with genetic testing [20, 21] could have been addressed in more detail. However, the evaluation of genetic tests is generally faced with limited evidence which was one of the motivations to conduct a study on the prioritization of medical interventions specifically in this area [35]. This study focuses on attributes for which it can realistically be assumed that at least some evidence can be identified which is currently collected in Clinical Utility Gene Cards as part of the EuroGentest project [15] or the UKGTN gene dossiers. Further work is necessary, to improve the standardized synthesis of evidence around genetic tests; the collection of new evidence regarding the effects of genetic testing in terms of "weak" endpoints such as patient empowerment, and on exploring the usability of a more complex set of effects in this framework.

Also, there is a need to further validate the exact functional because the attributes may not be mutually independent but interactions may have to be taken into consideration. For example, progression may sometimes be inversely related with medical benefit as for hereditary conditions where effective prevention is available, testing can be considered of highest value at an early stage where the progression of disease can still be averted [18]. However, this may also be a special case restricted to selected predictive tests which is not sufficiently generic to be included into an overall prioritization function (counterexamples may be, for example, pharmacogenetic tests). Therefore, further discussion of case studies and rankings evolving from the algorithm are needed to validate or confirm the prioritization function. In case of modification, also further elicitation of value judgments [16, 17] may be necessary.

Lack of consequent objectivity

The study starts with an objective notion of need but finally proposes a needs function which is based on subjective weights to be established by preference elicitation methods. This appeared necessary for three reasons: firstly, because no objectivist function relating the attributes to measures of physical health or disability could be detected in the literature. Secondly, and more importantly, measuring health and disability necessarily involves value judgments, including the researcher's choice of one among the multiple outcome measures, the choice of responders to evaluate health states, and, in case health-related quality of life is traded off with length of life, the value judgments associated with calculating QALYs [see e.g. 51, 52, 53]. This choice is particularly difficult for genetics services because they include a large variety of clinical manifestations. Thirdly, the priority function contains both the benefit of an intervention to ameliorate the needs and indicators of the needs' gravity so that not one single link between these attributes and an objective measure of health or disablement from an objectivist perspective is possible.

Nevertheless, further research is necessary to explore whether it is possible to increase the share of objective elements in the priority function. Given that the normative basis of using the algorithm was based on its acceptability rather than on its objectivity, this is seen as a limitation but not as an inconsistency of the approach.

New dimensions of discrimination

This framework used risk group as one priority category (high risk, FDR). Even if this framework is oriented at the equitable allocation of health care resources, this may introduce a new issue of discrimination, particularly against patients suffering from rare diseases. This framework addressed this by using types of evidence which are also likely to be available for comparatively rare disorders. Additionally, it can be based on categories of risk rather than absolute percentage values so that rare and other diseases are treated equally. However,

further work is necessary to explore the implications of frameworks like the one proposed here for different ethical frameworks of equitable health care resource allocation.

5. Conclusions

It is frequently claimed that rather than maximizing health or satisfying consumer preferences, scarce health care resources should be allocated to facilitate equitable service provision, based on claims relative to medical need. This study is the first to propose a needs-based approach to prioritizing health care services to genetic testing. It demonstrates how a priority score could be established so that funding tests in a way to maximize the aggregated priority score is consistent with serving patients equitably according to medical need. Further stakeholder deliberation is necessary to validate this approach, and further research to address its remaining limitations.

References

[1] Schmidtke J, Pabst B, Nippert I. DNA-based genetic testing is rising steeply in a national health care system with open access to services: a survey of genetic test use in Germany, 1996-2002. Genet Test 2005; 9:80-4.

[2] Krawczak M, Caliebe A, Croucher PJ, Schmidtke J. On the testing load incurred by cascade genetic carrier screening for Mendelian disorders: a brief report. Genet Test 2007; 11:417-9.

[3] Adair A, Hyde-Lay R, Einsiedel E, Caulfield T. Technology assessment and resource allocation for predictive genetic testing: a study of the perspectives of Canadian genetic health care providers. BMC Med Ethics 2009; 10:6.

[4] Giacomini M, Miller F, Browman G. Confronting the "gray zones" of technology assessment: Evaluating genetic testing services for public insurance coverage in Canada. Int J Technol Assess 2003; 19:301-16.

[5] Rogowski WH, Grosse SD, Schmidtke J, Marckmann G. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? Eur J Hum Genet 2013.

[6] Cassiman JJ. Research network: EuroGentest--a European Network of Excellence aimed at harmonizing genetic testing services. Eur J Hum Genet 2005; 13:1103-5.

[7] Rogowski WH, Grosse SD, Khoury MJ. Challenges of translating genetic tests into clinical and public health practice. Nat Rev Genet 2009; 10:489-95.

[8] Cuadras-Morato X, Pinto-Prades JL, Abellan-Perpinan JM. Equity considerations in health care: the relevance of claims. Health Econ 2001; 10:187-205.

[9] Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. Lancet 2009; 373:423-31.

[10] Golan O, Hansen P, Kaplan G, Tal O. Health technology prioritization: which criteria for prioritizing new technologies and what are their relative weights? Health Policy 2011; 102:126-35.

[11] Guindo LA, Wagner M, Baltussen R, Rindress D, van Til J, Kind P, Goetghebeur MM. From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decisionmaking. Cost Eff Resour Alloc 2012; 10:9.

[12] Brouwer WB, Culyer AJ, van Exel NJ, Rutten FF. Welfarism vs. extra-welfarism. J Health Econ 2008; 27:325–38.

[13] Wiggins D, Dermen S. Needs, need, needing. J Med Ethics 1987; 13:62-8.

[14] Stolk EA, Pickee SJ, Ament AH, Busschbach JJ. Equity in health care prioritisation: an empirical inquiry into social value. Health Policy 2005; 74:343-55.

[15] Schmidtke J, Cassiman JJ. The EuroGentest clinical utility gene cards. Eur J Hum Genet 2010; 18:1068.

[16] Severin F, Schmidtke J, Muhlbacher A, Rogowski WH. Eliciting preferences for priority setting in genetic testing: a pilot study comparing best-worst scaling and discrete-choice experiments. Eur J Hum Genet 2013; 21:1202-8.

[17] Severin F, Hess W, Schmidtke J, Mühlbacher A, Rogowski W. Value judgments for priority setting criteria in genetic testing: a discrete choice experiment (accepted for publication in Health Policy). 2014.

[18] Severin F, Borry P, Cornel M, Daniels N, Fellmann F, Hodgson SV, Howard H, John J, Kääriäinen H, Kayserili H, Koerber F, Kroese M, Lewis C, Marckmann G, Meyer P, Schmidtke J, Skirton H, Tranebjærg L, Rogowski W, Consortium ftEaEPP. Points to consider for prioritizing clinical genetic testing services. A European consensus process oriented at Accountability for Reasonableness (Eur J Hum Genet, in press). 2014.

[19] Gough I. Lists and thresholds: comparing the Doyal-Gough theory of human need with Nussbaum's capabilities approach. In: Comim F, Nussbaum M, editors. Capabilities, Gender, Equality: Towards Fundamental Entitlements. New York: Cambridge University Press, forthcoming.
[20] McAllister M, Payne K, Macleod R, Nicholls S, Dian D, Davies L. Patient empowerment in clinical genetics services. J Health Psychol 2008; 13:895-905.
[21] Payne K, Nicholls S, McAllister M, Macleod R, Donnai D, Davies LM. Outcome measurement in clinical genetics services: a systematic review of validated measures. Value Health 2008; 11:497-508.
[22] Becker F, van El CG, Ibarreta D, Zika E, Hogarth S, Borry P, Cambon-Thomsen A, Cassiman JJ, Evers-Kiebooms G, Hodgson S, Janssens AC, Kaariainen H, Krawczak M, Kristoffersson U, Lubinski J, Patch C, Penchaszadeh VB, Read A, Rogowski W, Sequeiros J, Tranebjaerg L, van Langen IM, Wallace H, Zimmern R, Schmidtke J, Cornel MC. Genetic testing and common disorders in a public health framework: how to assess relevance and possibilities. Background Document to the ESHG recommendations on genetic testing and common disorders. Eur J Hum Genet 2011; 19 Suppl 1:S6-44.
[23] Eisenberg VH, Schenker JJ. The moral aspects of prenatal diagnosis. Eur J Obstet Gynecol Reprod Biol 1997; 72:35-45.
[24] West R. Ethical aspects of genetic disease and genetic counselling. J Med Ethics 1988; 14:194-7.
[25] Johnson SR, Elkins TE. Ethical issues in prenatal diagnosis. Clin Obstet Gynecol 1988; 31:408-17.
[26] Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics. Public Health Genomics 2010; 13:106-15.
[27] Daniels N. Just health : meeting health needs fairly. Cambridge [u.a.]: Cambridge University Press, 2008.
[28] PrioriteringsCentrum. Resolving Health Care's Difficult Choices. Survey of Priority Setting in Sweden and an Analysis of Principles and Guidelines on Priorities in Health Care. Rapport 2008:2. Linköping: National Centre for Prioritiy Setting in Health Care, 2008.
[29] Williams A. Intergenerational equity: an exploration of the 'fair innings' argument. Health Econ 1997; 6:117-32.
[30] Rogowski WH, Hartz SC, John JH. Clearing up the hazy road from bench to bedside: a framework for integrating the fourth hurdle into translational medicine. BMC Health Serv Res 2008; 8:1-12.
[31] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schunemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013; 66:719-25.
[32] Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64:401-6.
[33] Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schunemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013; 66:151-7.
[34] Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R,

Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013; 66:726-35.
[35] Rogowski WH, Grosse SD, John J, Kääriäinen H, Kent A, Kristofferson U, Schmidtke J. Points to consider in assessing and appraising predictive genetic tests. J Community Genet 2010; 1:185-94.
[36] Assasi N, Schwartz L, Tarride JE, Goeree R, Xie F. Economic evaluations conducted for assessment of genetic testing technologies: a systematic review. Genet Test Mol Biomarkers 2012; 16:1322-35.
[37] Carlson JJ, Henrikson NB, Veenstra DL, Ramsey SD. Economic analyses of human genetics services: a systematic review. Genet Med 2005; 7:519-23.
[38] Rogowski W. Genetic screening by DNA technology. A systematic review of health economic evidence. Int J Technol Assess Health Care 2006; 22:327-37.
[39] Hope T, Osterdal LP, Hasman A. An inquiry into the principles of needs-based allocation of health care. Bioethics 2010; 24:470-80.
[40] Rogowski W. Current impact of gene technology on healthcare. A map of economic assessments. Health Policy 2007; 80:340-57.
[41] Adams PC, Barton JC. Haemochromatosis. Lancet 2007; 370:1855-60.
[42] Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: a remodeling study. Med Decis Making 2009; 29:224-38.
[43] Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011; 54:328-43.
[44] Severin F, Schmidtke J, Muhlbacher A, Rogowski WH. Eliciting preferences for priority setting in genetic testing: a pilot study comparing best-worst scaling and discrete-choice experiments. Eur J Hum Genet 2013.
[45] Cookson R. QALYs and the capability approach. Health Econ 2005; 14:817-29.
[46] Hicks JR. Value and capital : an inquiry into some fundamental principles of economic theory. Oxford: Clarendon Press, 1946.
[47] Klonschinski A. [The cost-effectiveness ratio as criterion for prioritization? A philosophical and historical analysis of the economic paradigm of value maximization]. In: Schmitz-Luhn B, Bohmeier A, editors. [Prioritization in medicine Criteria in dialogue] (Book in German). Heidelberg: Springer, 2013:79-106.
[48] Klonschinski A, Lübbe W. [QALYs and fairness: health economic approaches to the fairness issue and their problems]. Gesundheitswesen 2011; 73:688-95.
[49] Rogowski WH, Grosse SD, Schmidtke J, Marckmann G. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? Eur J Hum Genet 2014; 22:25-31.
[50] Daniels N, Sabin J. The ethics of accountability in managed care reform. Health Aff (Millwood) 1998; 17:50-64.
[51] Bowling A. Measuring health : a review of quality of life measurement scales. Buckingham ; Philadelphia: Open University Press, 1997.
[52] Bowling A. Measuring disease : a review of disease-specific quality of life measurement scales. Buckingham ; Phildelphia: Open University Press, 2001.
[53] Brazier J. Valuing health States for use in cost-effectiveness analysis. Pharmacoeconomics 2008; 26:769-79.

Tables

Category	Criterion for prioritization	Rationale	Values	Operationalization for case study: HH testing in FDR
Health need	(1) Severity	Those at risk of a severe disease if left untreated are worse off and thus of higher priority than those at risk of a mild condition.	S ∈ [0,1]	S = 1 - (68.7 / 77.3) = 0.11
	(2) Progression	The further the (potential) progression of the condition in the tested individual, the higher the priority of the test: h: healthy individuals younger than the typical age of onset; e: early detection in asymptomatic individuals at an age where the disease may already have progressed silently; d: diagnosis in individuals who see a doctor because of symptoms which may be caused by the condition tested for	P ∈ {h, e, d} with given ordering {h < e < d}	P = {e}
Alleviation of need	(3) Evidence of benefit	Care need additionally requires that a medical intervention exists which can improve the patient's situation. A genetic test with a GRADE class I (here: s) recommendation for testing can be seen as more needed than a test with a class II (here: w) recommendation or a recommendation only in medical research (here: r).	E ∈ {r, w, s} with given ordering {r < w < s}	E = {s}
	(4) Likelihood of positive result	The higher the risk of a disease, the worse off the person seeking the test thus the higher his or her priority; risk groups: general population risk (g), a first-degree relatives risk group (f) and (i) a group of intermediate risk	L ∈ {g, i, f} with given ordering {g < i < f} or, on a cardinal scale: R ∈ [0-100%]	R = 6.2% * 3.5% = 0.22% or, alternatively, in ordinal categories: R = {f}
Costs to alleviate need	Cost of test to address (1)-(4)	Meeting the needs (1)-(4) is associated with test costs which also need to be considered in decision making – the lower the cost, the higher the priority of the test.	C ∈ [0 €, ∞ €[	C = €280

Abbreviations: C = cost; e = early detection; E = evidence of intervention need; d = diagnostic testing; FDR = first-degree relatives; f = first-degree relative risk group; g = general population risk group; h = healthy individuals; HH = hereditary hemochromatosis; L = likelihood of positive result; P = progression; r = recommendation only in research; S = severity; s = strong recommendation; w = weak recommendation;

Table 1: Need-based principles for prioritizing genetic tests