Points to consider for prioritizing clinical genetics services. Results from a European consensus process oriented at the principles of Accountability for Reasonableness

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Abstract [Maximum word count for abstract: 250]

Context: Given the cost constraints of European health care systems, criteria are needed to decide which genetic services to fund from public health care budgets if not all can be covered. To ensure that high priority services are available equitably within and across European countries, a shared set of prioritization criteria would be desirable.

Methods: A decision process oriented towards the framework of accountability for reasonableness was conducted, including a multidisciplinary EuroGentest/PPPC-ESHG workshop to identify shared prioritization criteria.

Results: Resources are too limited to provide all beneficial genetic testing services available the next decade. Ethically and economically reflected prioritization criteria are needed. Prioritization should be based on considerations of (1) intervention need / benefits, (2) health need and (3) costs. (1) includes evidence of benefit in terms of medical benefit, benefit of information for important life decisions, and benefit for other persons apart from the person tested; it may be subject to a finite time window. (2) includes the patient-specific likelihood of being affected by the condition tested for; its severity; and its potential progression at the time of testing. Further discussion and better evidence is needed before clearly defined recommendations can be made or a prioritization algorithm proposed.

Conclusions: To our knowledge, this is the first time a clinical society has initiated a decision process about health care prioritization on a European level, oriented towards accountability for reasonableness. This guidance aims to stimulate this discussion across the EU and to serve as a point of reference for improving patient management.

Key words: Health care prioritization, genetic testing, accountability for reasonableness

Background

The availability and application of genetic testing services are expanding rapidly.[1-3] Although technical improvements are leading to a decrease in laboratory costs per test the evidence that genetic tests produce overall savings in health care systems is weak[4] and limited to a minority of tests.[5,6] It is conceivable that the costs of data analysis and storage, interpreting the test results, patients' counseling services and follow-up care can easily lead to an increase in overall health care costs associated with genetic testing. As financial resources fail to maintain parity with the increasing opportunities for genetic testing, decisions have to be made about which tests to cover from public health care budgets.

To date there is a lack of structured guidance for decision-makers on how to prioritize genetic testing services. In a Canadian survey, health care providers reported that given the absence of coordinated approaches, resource allocation decisions are often left to local providers of genetic tests.[7] It is likely that this is also the case in European health care systems.[8] Due to limited resources, tests may be withheld or only available to individuals with a high ability to pay, based on contingency of daily practice rather than on well reflected considerations regarding the best use of scarce resources for the population as a whole. As an alternative, explicit prioritization decisions could be made on a higher level than daily practice, e.g. by a committee which develops standard operating criteria for assigning patients to immediate care or waiting lists on an institution level. However, without a shared set of prioritization criteria, decision makers might be accused of overprovision by health care financers or of underprovision of genetic services by patients. Given this situation, it has been argued that the development of agreed standards for resource allocation decisions based on sound medical, economic, and ethical considerations would be beneficial for both decision-makers and those who potentially benefit from health care.[9] As fair and reasonable priority setting has to account for

a range of context-specific issues, this study is aimed at contributing to the development of prioritization criteria specifically for genetics services.

The question of how health care services should be prioritized has a long history of debate within the scientific, medical, economic and ethical literatures. The challenge for the prioritization of genetic tests is to determine a set of ranking criteria specific to genetics that can be applied to order different tests according to their relative priority. Choosing prioritization criteria requires an extensive use of knowledge from various disciplines, but also the understanding of patient needs. A recent study has developed a theoretical framework of criteria to allocate scarce health care funds for genetic tests.[10] Furthermore, an approach has been developed to establish weights for the different criteria based on state-of-the-art health economic methods to elicit value judgments.[11]

However, it has been argued that neither theoretical, ethical and economic reflections nor empirical evidence of value judgments alone can solve all the conflicts which arise in prioritizing scarce health care resources. This is because reasonable people may still disagree about which criteria should be applied and, in decisions where more than one criterion is considered, about the weighting they should receive.[12] Instead, it has been proposed that besides the sound theoretical and empirical basis of decision criteria, the decision procedure is also relevant for obtaining legitimate guidance for prioritizing health care resources. A widely cited framework of procedural fairness is “Accountability for Reasonableness” [13]. The following study describes the results from a consensus process which is oriented around this framework. The aim of the study is to develop a shared set of criteria and considerations for prioritizing genetic tests on a regional and local level of decision-making.

Methods

According to Daniels and Sabin, a decision process complies with accountability for reasonableness (A4R) if; decisions and their rationales rest on relevant reasons, they are made transparent, there exists a mechanism of challenge and appeal and the enforcement is ensured during the whole process.[13,14] It was assumed that the framework is applicable both for singular resource allocation decisions and for decisions about general frameworks for resource allocation. Different from pharmaceuticals or decisions about mass screening programs, it is likely that in clinical genetics there is a multitude of new services each of which has a comparatively low budget impact. Therefore, more general prioritization frameworks are likely to be more relevant here.

The following section illustrates how these conditions were addressed during the decision process. One central element in the decision process was a two day (28-29th November 2012) workshop in which potentially relevant criteria for resource allocation decisions in genetics were discussed by 25 participants representing different stakeholders from a multidisciplinary background (clinical genetics, molecular genetics, economics, ethics, public health, sociology). They included representatives of two patient organizations. Participants collaborated in the EU funded research project EuroGentest (www.eurogentest.org) and/or the Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG) (www.eshg.org/pppc.0.html).

Publicity

Decision making according to A4R requires that the rationales for resource allocation decisions should be accessible to relevant stakeholders. This refers to the publicity condition. It was assumed that health care providers and patients are the key stakeholders for the vertical

prioritization of budgets for genetic services. Further stakeholders include health care funders, regulatory agencies, industry representatives and the general population.

Information about this prioritization activity was provided through different channels such as relevant newsletters, websites (e.g. the EuroGentest website) and personal communications. Furthermore, it was presented at the EuroGentest General Assembly March 2013 in Prague and at the Annual conference of the European Society of Human Genetics June 2013 in Paris.

Relevance

The relevance condition of A4R requires that the prioritization rests on reasons that appeal to evidence and that fair-minded people can agree are relevant to the decision problem.[13] Hence as a starting point for the discussion, evidence on criteria used in prioritization decisions was collected and a theoretical normative framework for reasonable prioritization of genetic tests was developed.[10] A qualitative survey amongst patient representatives was conducted[15] and the resulting set of criteria was tested amongst geneticists within the framework of a discrete-choice experiment (DCE).[11] Scientific publication of this document also contributes to the relevance criterion, because it facilitates further debate in a transparent way.

Revisability/appeals

Those affected by a decision should have the chance to challenge it on the basis of relevant arguments that have not been considered duly during the original decision-making process.[13] In order to ensure that as many rationales as possible were considered during the workshop, a broad range of expertise and various stakeholders were involved in the workshop and its preparation. The acknowledgments section provides the names of the workshop participants. Appendix Table 1 presents further information on their expertise and country of origin. Unanimous assent was reached which ensured that the value judgments of minority groups were also accounted for.

Preliminary versions of this recommendation statement were and *will be shared for comments and revisions among the workshop participants as well as on the website of the European Society of Human Genetics (ESHG) and EuroGentest. A broad range of stakeholders will be contacted by email and invited to comment. The document will then be submitted to the standard process of ESHG recommendations including approval by the ESHG board. The preliminary version and all written stakeholder comments made before the final version are available from the lead author upon request.*

Enforcement

Apart from the conditions of publicity, relevance and revisability/appeals, A4R requires that procedures are in place to ensure that the prioritization activity complies with these conditions. To facilitate enforcement for this rather singular process of developing a general decision framework for prioritization decisions, this study draws upon the standard process for documents to formally become ESHG statements. These processes always have to include website publication (publicity), open discussion on the website (relevance) and incorporate comments (revisability/appeals).

Results

Scope and context of prioritization of genetic tests

In the following, "Genetic test" refers to genetics service as a whole. This includes, first, the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites to detect heritable disorders or treatment responses. Second, it includes the process of interpreting the tests result and communicating the meaning to the patient. From the discussion we excluded transgenerational aspects of genetic testing (e.g. pre-implantation and prenatal testing) as these tests involve a range of very specific issues that are discussed elsewhere. Population screening

programs were excluded as well as they are expected to undergo separate kinds of prioritization considerations in comparison to other public health programs.

Prioritization should be preceded by efforts to improve the efficiency of care. This includes a focus on tests with both sufficient test performance and validity i.e. the sensitivity and specificity of the test and scientific validity for the analysis, and on information regarding the clinical implications of the test result. This is particularly relevant for multifactorial diseases where it is often unclear how the discoveries can be used to improve the patient treatment. Recently, the ESHG made a recommendation against the use of multifactorial tests where these preconditions for patient benefit are not sufficiently met.[16]

Prioritization of genetic tests is understood to mean placing tests into a rank order or into rank ordered categories. Prioritization (and, consequently, genetic services forgone) can occur in different ways. For example, local decision-making committees of health care providers may determine whether a testing service is in- or excluded from provision. Alternatively, it can relate to situations where tests are not provided fully (e.g. testing is only provided for the most frequent mutations rather than the whole gene). Furthermore, it can occur in terms of assigning services into priority categories which determine the place of the testing service on a waiting list so that individuals who seek testing may wait longer or shorter depending on the anticipated suffering from avoidable disease and uncertainty. The focus of this prioritization activity is on the efficient and fair allocation of collectively funded resources (e.g. taxes or contributions to statutory health insurance) on a regional or local level (e.g. to inform decisions by commissions on the management of genetics services of a hospital's genetics unit which has a fixed budget to spend). It is intended for situations where not all desirable genetics services which are technically available can be offered to all patients who may need them because of a lack of funding (e.g. because there are too few geneticists employed by the genetics unit to see all patients and no further geneticists can be employed given the existing

budget). This guidance can only serve as a complement to national reimbursement rules. It therefore focuses on decisions where national regulation is not sufficiently specific to solve the problem of prioritization.

Relevant criteria for prioritizing genetic tests

The following section outlines the criteria that have been found to be relevant for prioritization decisions. Generally, genetic tests are health care services provided to help individuals with medical need. Therefore, medical need should be a key criterion for health care priority setting also in genetics. Medical need can be, first, understood as "health need" in terms of need for medical care depending on the severity of the disease a patient is suffering from. The concept of "intervention need" additionally takes into consideration whether the health service can lead to health benefits (ameliorate the patient's need or avoid health damage).
The criteria of both health need and intervention need / benefits from testing, appeared to be most relevant. In general, it was considered desirable to operationalize and weight these criteria using empirical methods so that genetic tests can be ranked in a scientifically reflected manner. However, a number of points have to be considered before such quantitative methods can be used for prioritizing genetic tests.

Health need

Understanding medical need for genetic tests, first, in terms of "health need" which exists independently of whether a treatment is available to improve the patient's health, requires further specification.

Severity of the disease

One important aspect of health need is the impact that the condition targeted by the test has on the patient's health. It can be assumed that individuals at risk of a severe condition are worse

off than those at risk of a milder condition. Therefore testing for severe conditions should be assigned higher priority than testing for milder conditions. It was generally agreed that the severity of a genetic condition can be expressed in terms of reduced life expectancy, in reduced health related quality of life or a combination of these two. However, methodological details of measuring severity can cause concerns; for example concerns that have been expressed against the use of quality-adjusted life years (QALYs) if this metric was used to determine severity. Also, it needs to be determined to what extent "severity" should be based on objective measures or on the subjective patient experience.

Progression of disease

Another aspect of health that needs to be considered is how far the condition may already have developed in the tested individual. The test might be predictive in the sense that there are neither symptoms nor is it likely given the individual's age that the disease is already present. It may be a test for early detection in presymptomatic patients which do not display symptoms yet, but the disease may already have progressed silently. Alternatively it may be diagnostic if the test is performed in individuals with symptoms that may be indicative of the condition tested for. The more advanced a disease is, the higher the priority of the test. However, this can be highly context-sensitive; beyond a certain stage of progression, clinical signs and symptoms may be more accurate and make genetic testing redundant. Also, health need in terms of progression may be negatively correlated with intervention need in terms of health benefit (see below): in the case of hereditary cancer, for example, genetic tests are likely to be most important for healthy individuals because prevention is most effective at early stages.

Likelihood of disease

The patient's *a-priori* risk of developing the disease should also be considered. Identifying individuals at increased risk in advance is of key importance as testing high risk groups im-

proves the performance of the test in terms of cases detected. With this in mind, there might be justification to give priority to individuals who are likely to be at substantially greater risk of developing a condition than others in the population (in particular, close relatives). Also, high risk subpopulations can be considered of higher priority for genetic testing than individuals in populations with lower mutation prevalence.

"Likelihood of disease" refers to the risk of the phenotype. Therefore, incomplete penetrance, i.e. a low probability of overt symptoms in persons who have the underlying genetic defect, directly affects the risk assessment. Testing an individual with an elevated risk of a low-penetrance condition might be of lower priority than testing an individual with an equivalent prevalence of a mutation with a full-penetrance condition.

It may need to be considered that population groups with high mutation probabilities are more likely to be recognized as genetic cases in the clinical environment than those with lower probabilities and therefore will not benefit from special patient care. Therefore, like in the case of progression, this criterion may need to be adapted to the context.

Intervention need / Medical benefit

Three different dimensions of benefit need to be considered; medical benefit for the tested individual, benefit for life decision-making and benefit for others. When conducting a benefit assessment, it is important not only to include the positive effects but to weight benefits against harms that might be associated with the genetic test.

Medical benefit for the tested individual

From a medical perspective, the distinction between a test where effective clinical treatment or prevention options exist and a test where the disease progression cannot be altered with preventive measures or by treatment is of substantial importance. Detecting an individual with a condition for which medical interventions are available is more valuable than identifying an

individual with a similar risk of a condition with no evidence that the emergence of the disease can be prevented or that its course can be altered in a favorable way.

Particularly for rare disorders and for long-term benefits, the evidence is likely to be weak. Also, individual behavior patterns need to be accounted for when establishing the benefit of a genetic test. Although there might be a benefit from the genetic test *per se*, some individuals might not have it because they do not accept the next step of treatment or prevention. The medical benefit of genetic testing also includes reductions in anxiety if a close relative of a patient with a severe hereditary disease turns out to be non-carrier for the mutated allele.

Non-medical benefit for the tested individual

Genetic testing also induces benefits which are not covered by existing measures of medical benefit. An integrated part of the clinical care is to provide individuals with a more accurate prognosis including life span and quality of life. Although there might not be a treatment or prevention option available, the diagnosis itself may, in some cases, enable individuals and families to plan their lives in light of what is known about the particular condition.

Such non-medical consequences are frequently labeled patient empowerment[17] as they enable patients to get better mental and emotional control over their health and health care, and account for other aspects of their lives which are influenced by their health issues. These consequences should also be considered in the appraisal of a genetic test's priority. However, to be able to consider such benefits, there is a need for more scientific evidence from well-designed clinical studies on the empowerment produced by different genetic tests.

Non-medical benefits may also arise from information which neither leads to any action of clinicians nor of patients – also here, further evidence is needed and it needs to be determined which priority tests with such other benefit should have in the allocation of scarce public health care budgets.

Benefit for family members

The benefits from genetic testing may also apply to other individuals than the index patient since it may reveal elevated risks for other family members. For example, in the case of Lynch syndrome, testing is conducted not only for the benefit of the index case, but primarily for his or her relatives. This is because mutation carriers can choose to use aspirin prophylaxis or increased colonoscopic surveillance which improves their expected health outcomes[18,19]. Also, non-medical benefits may apply to the relatives of an index case if the disease risk of a relative is established. If in a Lynch syndrome family a mutation was detected so that relatives can undergo testing, some would experience relief from negative results. Therefore, the assessment of benefit and its impact on a test's priority relates not only to the tested individual but also to potentially affected relatives. However, particularly in the case of tests because of non-medical benefits for family members, relevant trade-offs with concerns for privacy or the right not to know may have to be taken into consideration.

Time window to obtain benefit

It may be that the benefit from a test can only be obtained within a finite time window. This is the case if there is a restricted time in which the clinical reaction on a positive diagnosis can still be effective. For example, in a newborn at risk of an inherited error of metabolism who (in the case of a positive diagnosis) would immediately need a special diet or, for those who accept termination of pregnancy as an acceptable medical option, there is a restricted time window in which prenatal testing can be conducted in pregnant women. Presymptomatic tests may be less urgent if therapy can be started somewhat later without negative effects on the course of the disease (for instance in hemochromatosis). Timing is, therefore, also a relevant aspect for priority setting.

Costs

Conducting one test in a situation of resource scarcity where not all tests can be funded implies that there are other tests which are omitted – and the benefits of these other tests are thus forgone. Therefore, also the resources consumed by a genetic test (and thus unavailable for alternative tests) should be considered for priority setting as one criterion among the others. Ideally, costs should be considered from a societal or at least a health care system perspective, including all costs that are associated with a genetic testing service, including counseling, follow-up testing and treatment. Also benefits should ideally be considered at a similar level. Even more ideally, "costs" should be considered in the economic use of the term "opportunity costs", which refers to benefit forgone because the resources have not been used for alternative purposes. From a societal perspective, costs may be much higher than for the genetic test alone – but they may also come with cost savings elsewhere in the health care system or society e.g. due to disease prevention.

However, to be confident that cost savings take place, well-designed health economic evaluations are necessary[5,20]. In practice, information about resource consumption over the whole care process is likely to be limited so that it may be necessary to restrict the assessment of costs to the total costs from a health care provider perspective, including only the relevant scarce budgets for laboratory testing and counseling. Also, determining the size of benefit (e.g. in terms of expected life-years lost for different target groups tested for hereditary hemochromatosis by decision-analytic modeling[21]) requires substantial scientific efforts which are unlikely to be feasible for the multitude of upcoming genetic tests.

To get an idea of the opportunity costs associated with the current service patterns, discussions about prioritizing genetic tests should attempt to incorporate information about the types of resource constraints and the types of tests currently withheld due to these resource constraints. The benefits and costs of these tests can serve as one qualitative benchmark for de-

ciding whether a new test should be funded from limited resources (in the context of the other prioritization criteria).

The overall budget impact of a genetic test is also relevant such that, the higher the budget impact, the better the evidence of the aforementioned relevant criteria should be in order to support its use in clinical practice. This is also to avoid discrimination against rare diseases which may have less evidence available but also less budget impact.

Establishing the relative importance of criteria

Genetic tests typically differ by more than one of these criteria simultaneously. Some testing situations might be clearly dominated by others - e.g. in the case of testing a first degree relative for a severe and treatable condition compared with testing someone without a family history for a mild and untreatable condition. However, most testing situations are likely to be less obvious. The resulting order of priority then depends on the weights given to each of these criteria. This is the case, for example, if a decision-maker has to decide between testing a high risk individual suspected of suffering from a mild condition and a low risk individual suspected of suffering from a very severe condition.

Generally, empirical methods such as discrete-choice experiments (DCE) can be used to determine weights for these criteria. The results of DCEs can be used qualitatively to appraise the relative importance of one criterion over the other.[11] Results from a DCE among patients and clinicians indicated that participants attached particularly high value to a proven medical benefit of the test, high risk of having the disease, and low costs of the test.[22] If the extent to which the criteria are met can be quantified, DCE results can be applied to create rank orders for different genetic tests. The field of organ transplantation is an example where sophisticated algorithms have been developed and are used for allocating a scarce resource.[23]

At the current point in time however, it is too premature to propose such an algorithm for genetic tests. This is, for example, because the evidence regarding the extent to which the criteria above are met is still too weak to allow for a valid quantitative ranking of tests. Also, fair and reasonable prioritization is highly context-specific and may depend on multiple further issues for which it is currently unclear how they can best be incorporated into or addressed alongside the use of such a prioritization algorithm.

How to use this prioritization framework

There is a need for guidance regarding the prioritization of genetic tests. However, at this point in time, the discussion about priority setting in Europe is still at an early stage and there is neither consensus about the most appropriate ethical frameworks, nor the economic tools and their practical implementation. Moreover, genetic services are currently undergoing tremendous technological change and the decision contexts are highly heterogeneous across European health care systems. Therefore, it is premature to give clear recommendations about how genetic tests are to be prioritized.

Instead, these criteria can be used for three purposes; firstly, they provide points to consider when prioritization decisions have to be made, e.g. at meetings on an annual basis when existing standard operating procedures for patient management are reviewed. Not only the criteria per se but also the procedural framework of A4R can provide a valuable orientation of fair and reasonable decisions about prioritizing genetic services. Secondly, they can serve as a starting point for the further development of quantitative approaches such as ranking lists established on the basis of DCE results. Thirdly, these points to consider can serve as a valuable basis for discussing current priorities for genetic care in order to identify which services are indispensable and where there is room for improvement regarding equitable access to high priority services. More frequently conducted tests for diseases like Lynch Syndrome or Factor

V Leiden which are likely to incur higher budget impact and there is likely to be a better evidence basis are likely to be good starting points for such prioritization activities. Going through the exercise of matching past decisions against the suggested set of criteria within a team of clinicians or regional administrators of public health funds can also have a positive impact on the consistency of allocation decisions with shared orders of priority.

Discussion

Throughout Europe, clinicians are faced with resource constraints and the problem of implicit prioritization of health care services. Given limited budgets and the increasing availability of new interventions, it is likely that the need for prioritization will further increase. To our knowledge, this is the first time a clinical society has responded actively to these challenges and explicitly addressed the issue of prioritizing health services at a European level. The decision process resulted in a set of points to consider for prioritizing genetic tests.

As the field of genetics is subject to rapid technological change and given that decision practices are highly heterogeneous across Europe, it is currently too premature to develop definite and structured recommendations about how genetic tests are to be prioritized across Europe. Instead, these points to consider are intended to stimulate a longer process of identifying locally relevant prioritization criteria and acceptable prioritization tools. At this point in time, the results from this project are therefore just a first step towards a more harmonized and equitable provision of high priority genetic services across Europe.

Implications for future prioritization activities

Genetic exceptionalism for prioritization?

This study developed an approach for vertical prioritization of genetics services only. Generic measures that can inform prioritization between a range of medical technologies often rely on

generic concepts such as QALYs. While such generic concepts can also be used to assess the medical benefit of a genetic test, they are of limited sensitivity to the multi-faceted benefits and relevant issues in the provision of genetic tests. Also, for many genetic tests there is not sufficient evidence to parameterize meaningful cost-utility analyses and the budget impact of many single tests is unlikely to justify full economic evaluations. Furthermore, condition-neutral frameworks only account to a limited extent for the budgeting practice in many health care systems. This is because budgets are frequently assigned by legitimized decision-makers to different clinical areas, such as genetics services, and prioritization has to take place within these budgets. This framework, which is designed for clinical genetic services, may provide a more acceptable alternative because it accounts for specific attributes of genetic tests that are relevant for prioritization. As it has been developed in collaboration with experts and major stakeholders of genetic services and challenged in a transparent decision process, it also accounts for concerns about procedural fairness.

There are also other genetic services which are integrated into other clinical areas such as genetic screening programs which are funded from public health service budgets. Here, it is more likely that their benefits and costs have to be balanced against the benefits and costs of very different alternatives. Therefore, the use of more condition-neutral tools, such as evaluations of costs per QALY, is more likely to be applicable. Nevertheless, maximization of health outcomes like QALYs years is unlikely to be considered acceptable by all participating stakeholders.[24] This study can help in identifying relevant points which should also be considered. In addition, criteria of health need, such as the potential progression of disease or intervention need to obtain information for life decision making without tangible health benefit is likely to be relevant for other diagnostics as well.

Using accountability for reasonableness for prioritization

To our knowledge, this is also the first time a clinical society has specifically applied the widely cited "Accountability for Reasonableness" framework [13] to improve the legitimacy of the recommendations for priority setting.

This normative framework is sufficiently generic to allow for very different ways of implementation. In this context, it appeared very consistent with standards of good scientific practice. This case study may therefore also serve as an example for prioritization processes in other clinical areas.

Implications for further research

It is very unlikely that for all or most genetic tests a statistically significant establishment of benefit can be achieved. Particularly for benefits that are not strictly medical (yet still related to health such as anxiety etc.), the evidence is still weak. Instruments for measuring this type of benefit are needed in a context of scarce resources and evidence-based medicine where technologies without good evidence of benefit may be candidates for exclusion from services. Also, there is little evidence about the total effects and costs of genetic services from a health care system perspective. More health economic evidence is needed, in particular for genetic tests with a high budget impact and/or potential for major health benefits.

Apart from the criteria discussed above also the evidence that a priority criterion is met should be considered. Typically, prioritization decisions with a large population impact such as decisions in favor of a genetic screening program have to be based on high level evidence. Also on a local level, better evidence that a priority criterion is met should lead to a test receiving higher priority and "evidence" can serve as a meta-criterion for the criteria above. However, the lack of evidence for a test should not lead to exclusion of a test but rather be incorporated in the form of a conservative assessment of the priority criteria. This is particularly true for

very rare diseases, where the numbers of patients are too small to conduct reliable clinical studies. A future challenge that needs to be resolved is therefore, how the evidence gap can be filled in a reasonable and fair manner, and how weak levels of evidence should reasonably be accounted for in conservative assessment of priority criteria without inappropriately discriminating against patients with rare diseases.

Furthermore, this study revealed the need for standards regarding the operationalization of the criteria. For example, the criterion "severity of disease" can be measured in terms of future health prospects without treatment (i.e. severity of illness concept[25]) or in terms of health loss compared with the average amount of health individuals could have expected (i.e. the fair innings concept[26]). Also, an appropriate measure of "health" needs to be chosen. Further work is needed to ensure that the value judgments in such methodological decisions reflect the value judgments of the relevant stakeholders.

While the accountability for reasonableness framework is highly cited in the literature, there is still little known on the acceptance and the impact of procedural fairness on health care practice. To account for this limitation, the acceptability of the final results from this guideline as well as its uptake and impact of use in health care practice needs to be assessed further.

Finally, besides clinical genetic services, it is likely that this framework is applicable for genetic tests in health care generally. However, it is also likely that other clinical areas where genetic tests are used (e.g. oncology, cardiology) also have different specific prioritization criteria. Further work is needed to explore the applicably of this framework for prioritizing genetic tests in other medical specialties. The A4R framework appears to serve as a valuable basis for such exercises.

Conclusion

Explicit, fair and reasonable priority setting of health care resources in Europe is still at an early stage. The results from this study provide important points to consider for prioritizing genetic tests and highlight issues that need further development.

Within this study we provide results from a decision process oriented at the A4R principles about prioritization criteria for genetic testing services. Key criteria were; evidence of medical benefit for the individual being tested, benefit for life decision-making, benefit for other persons and timing to obtain the benefit, the likelihood of disease or benefit, severity and progression of the disease, and the costs of the test (see Table 1). These criteria should not be seen as fixed or final, but rather as a starting point for further discussions towards a more harmonized and considered approach to priority setting for genetic services across the European Union.

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Table 1: Points to consider for prioritizing genetic tests

Criterion		Explanation	Selected challenges for measurement and use
Health need	Severity	Tests for conditions with a severe impact on the patient's health should be of higher priority than tests for comparatively mild diseases.	Severity can be expressed in reduced life expectancy or in reduced health related quality of life. Methodological details of measuring severity need to be considered because they can cause concerns, e.g. if QALYs are used.
	Progression	Tests for conditions which may already have developed silently or even overtly in the tested individual should be of higher priority than predictive tests in healthy individuals before the onset of disease.	Needs to be applied in context-dependent manner: • At a certain stage of progression clinical signs and symptoms may be more accurate and make genetic testing obsolete. • May be inversely related to medical benefit if benefit primarily arises from prevention in healthy or presymptomatic carriers.
	Likelihood	Tests for patients with high a-priori risk of developing the disease (e.g. high-risk populations or even first-degree relatives) should be of higher priority than tests for patients with low a-priori risk.	• Incomplete penetrance, i.e. a low probability of overt symptoms needs to be incorporated in risk assessment. • High-risk individuals may be more likely to be detected as genetic cases in clinical practice than medium-risk individuals
Intervention need	Medical benefit	Tests where, based on the results, effective clinical treatment or prevention options exist, should be of higher priority than tests without effective interventions.	• For rare diseases and long-benefit, evidence frequently is weak. • Individual behavior patterns (e.g. whether the treatment would be pursued) need to be accounted for to establish the benefit of a genetic test.
	Non-medical benefit	Consideration of intervention need also should include benefit of health-related information by itself which may assist individuals and families in planning their life.	• There is a need for more scientific evidence about the benefit for life decision making ("empowerment") incurred by different genetic tests. • It is unclear how non-actionable information should be accounted for.
	Benefit for family members	Consideration of intervention need also should include benefits for family members.	• Also, the non-medical benefits may apply to relatives. • Particularly for tests because of non-medical benefits, trade-offs with concerns for privacy or the right not to know may be relevant.
	Time window	It may be that the benefit from a test can only be obtained within a finite time window.	Criterion likely to be of higher relevance for a local perspective which also includes management issues than from a health care system perspective.
Costs	Costs	Tests with lower costs (and, thus, less other tests displaced) should be of higher priority than high cost tests.	• Consideration of costs should include savings elsewhere in health care. • Further evidence from well-designed economic evaluations are needed. • Costs should not be the dominant but only one criterion among others.
	Weighing the criteria	Typically, tests differ across different criteria simultaneously so that the criteria need to be weighted. A score based on empirical methods of measuring and weighting the criteria would be desirable. However, currently, it is too premature for such quantitative ranking algorithm, e.g. because of too limited evidence about whether the criteria are met and unresolved questions about which value judgments should be incorporated into the empirical analysis.	

Appendix Table 1: Workshop Participants

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