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Fuzzy Logic and Preconceptional Genetic Carrier Screening

Julia Inthorn[1]

1 Institute for Medical Ethics and History of Medicine, Göttingen University Medical Centre, Germany and Centre for Research Ethics and Bioethics, Uppsala University, Sweden

Email: Julia.Inthorn@medizin.uni-goettingen.de

Abstract

Medical screening programs have been established based on the idea of early treatment and prevention. The selection of tests as well as the diseases tested for that are included in a screening need to be ethically justified. This article looks at criteria for screening such as severity of a disease and efficiency of a test and their applicability for newly developed preconceptional genetic carrier screening. Preconceptional genetic carrier screening can be used by couples planning a pregnancy in order to learn it they are both carriers of a recessive inherited diseases und thus have an increased risk of having an affected child. It is argued that introducing fuzzy logic helps to overcome a binary logic of ethical decisions and to discuss ethical problems connected to the selection of diseases for preconceptional genetic carrier screening in a more nuanced way. With ongoing research about the relationship between genotype and phenotype as well as current development of new genetic screening methods the selection of tests and diseases will have to deal with knowledge deficits which fuzzy logic can help to handle.

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1 Introduction

Decisions in medical ethics often are described as crisp decisions between two distinct alternatives that have the structure of dilemmas (e.g. see case studies in journals like the Hasting Center Report or textbooks like [1], see also Inthorn et al. [2]). Most prominent examples are decisions at the end of life where decision about prolonging or withholding therapy can be framed as decisions between life and death. Technologies in reproductive medicine like prenatal or preimplantation diagnostics might also be understood in such a binary logic since these diagnostic tools provide information for a decision for or against continuing or terminating a pregnancy. In these textbook examples, there seems to be no grey area in between the two very distinct options. While the decision for or against an abortion or the question, if someone is dead or not clearly are (and need to be) crisp concepts this article will argue that not all ethical decisions need to be framed in this binary manner. Taking the currently developed chip technology for preconceptional genetic carrier screening as an example this article deals with the notion of crisp and fuzzy concepts in ethical decision making.

2 Medical background

Currently a technology is developed that can provide couples planning a pregnancy with information, if one or both partners are carriers of an autosomal recessive inherited diseases [3,4]. Examples for such diseases are severe early onset diseases such as Tay Sachs and Juvenile NCL (Batten disease) that lead to an early death in childhood, cystic fibrosis, a chronic illness mainly affecting the lungs with an average life expectancy of about 40 years but also MCAD deficiency, a metabolic disorder that is part of the new born screening in some countries and well treatable, if detected early or conditions like hereditary deafness. If both partners are carriers of the same condition, they (usually) have a 25% risk that their child will suffer from that disease. The diseases tested for are rare so in most cases there is no known family history of the disease. Carriers of such diseases are not affected and asymptomatic. Couples where both partners are carriers have different options when it comes to family planning. They can decide to live with the risk and choose not to do anything. Options to avoid the risk range from non-medical options like refraining from having children, adopting children or even changing partner, to the use of reproductive technologies like IVF and preimplantation diagnostics, prenatal diagnostics or sperm/egg donation [5]. The currently developed genetic carrier screenings (gcs) allow testing for a large number of diseases at the same time. Already available tests offer tests for 100+ different diseases (see https://www.counsyl.com/). In the US the National Center for Genome Resources and commercial companies with support of the patient organization *Beyond Batten Disease Foundation* had plans to develop an even larger chip [3]. This test aimed at testing for gen modifications of about 600 recessive inherited diseases. While some

diseases, that cause enormous suffering and an early death of affected children, might be uncontroversial to test for others like inherited deafness might cause more controversy [6].
By offering a large number of tests simultaneously, the test goes beyond the logic of current genetic test procedures. So far genetic counseling and testing had its starting point in a concrete problem like a known family history or parents who already have a sick child and a test was offered for a concrete disease or all known mutations responsible for that disease. Also existing genetic carrier screening programs like Dor Yeshorim among Ashkenazi Jews in Israel and the US [7] or screening for Beta thalassemia in Cyprus [8] were initiated because of a high prevalence of specific diseases within those communities. Those communities often have a long history of dealing with groups of affected persons. The newly developed chip technology is designed to – potentially – be offered to all couples planning a pregnancy thus aiming at a much broader group with no specific known risks. Therefore, the types and number of diseases the screening aims at is not already socially or culturally accepted.
The selection of diseases that are tested needs to be justified. This article deals with the question in how far switching from clear cut to fuzzy definitions of criteria for the selection process of diseases for the array chip technology can be helpful for ethical reflection.[1]

3 Established Criteria

There are a number of already existing examples of carrier screening programs in different communities. These programs were initiated as a reaction on specific problems within those communities and based on specific selection criteria. The communities usually are small, such as a Beduin tribe in Israel or the population of an island like Cyprus. Due to their special (often geographic) situation they have a tradition of intermarriage or can be dated back to one or a few founder families [9]. In the case of preconception genetic carrier screening, experiences from those specific community based carrier tests come together with more general ethical reflections on public health measures such as general screening programs.
There is an ongoing discussion about criteria for screening programs already starting in 1968 when Wilson and Jungner proposed ten criteria for screening programs [10]. Their criteria were widely acknowledged [11]. They were developed for a medical context different from the one today. Genetic tests had not yet been available and therefore the criteria are aiming at structuring screening programs within the logic of early diagnosis and treatment. With genetic testing new options for decisions developed, especially in the field of reproductive choices and around use of genetic information in preimplantation and prenatal screening contexts. Central criteria for

[1] This article will not deal with the ethical questions connected to the use of such tests, implications for family planning, responsible parenthood or the controversy about prevention against therapy.

screening such as the availability of treatment for a disease seem to be less relevant within that context [11]. A broad discussion followed how to adapt the list of criteria to the "genomic age" [12, 13]. Andermann [13] and colleagues provide a list of ten screening criteria applicable to genetic as well as other types of screening:

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm. [13]

The criteria do not define clear thresholds when a screening program is appropriate and when not, but rather provide dimensions of reflection for the implementation and evaluation of such programs. While some might argue that the vagueness of the criteria is problematic, opening up possibilities for screenings that are ethically not justified, the vagueness of the criteria can also be seen as their strength. It enables to weigh the criteria for each individual case, critically assessing the characteristics of the disease or condition as well as the test used for screening. For example the recognized need can vary between very low to very high within different parts of the population calling for different levels of effectiveness. Degrees of probability can be used to describe a specific level of risk such as high risk or low risk without the necessity to ascribe probability in exact numbers. And the criteria can be adopted for different types of genetic screenings such as preconceptional genetic carrier screening where the genetic information is the sole basis for risk assessment as opposed to genetic information within rheumatoid arthritis screenings where genetic information is one risk factor within a multitude of different risk factors. The relationship and interdependency of different criteria can be assessed for each specific context.

While the vagueness of the criteria might be seen as positive on a more general level because different screening programs can be compared with regard to the criteria one might argue that for concrete screening programs there need to be criteria that are precise and not fuzzy. In the following, I will therefore have a closer look at criteria that have been used to describe the selection of diseases within preconceptional genetic carrier screenings. The analysis will focus on criteria connected to two established preconceptional screening programs, Dor Yeshorim

and Beta Thalassemia screening on Cyprus and Sardinia.

4 Severity: Dor Yeshorim

Within the community of Askenazi Jews there is a higher prevalence of some monogenetic recessive diseases, especially Tay-Sachs disease. Dor Yeshorim is a platform within the orthodox community of Ashkenazi Jews offering couples information, if they are compatible or incompatible (e.g. both are carriers of the same disease) with regard to ten hereditary diseases. There is an increased risk for those diseases within the community of Ashkenazi Jews compared to other groups. While in Israel there is a population wide offer for screening based on individual genetic counseling [9] Dor Yeshorim is an especially designed service for the orthodox community that does not allow abortions and where most marriages are arranged. The program is strongly supported by religious leaders and genetic information is used only to arrange marriages when there is no increased risk for sick children. Since its start in 1983, the program reduced the prevalence of Tay Sachs disease by over 90% [14]. The program started with screening only for Tay Sachs, integrating cystic fibrosis and Canavan disease in a first step [15] and now also screening for Bloom's syndrome, Familial Dysautonomia, Fanconi anemia type C, Morbus Gaucher, Glycogen storage disease type 1, Mucolipidosis type IV and Niemann-Pick disease. Reasons for the selection of diseases within the screening program were the possibility to avoid the birth of affected children by choosing a different partner, the severity of the disease, as well as the increased risk (higher prevalence) [7].

The first argument given refers to possible options of dealing with a known risk. Treatability as a criterion has been highly important for screenings for non-genetic diseases, but is not applicable in the context of carrier screening. The idea behind that criterion is the relevance of the information for decision making and further action. This idea has been transformed for the context of genetic screening into the more general idea of having options to avoid a disease. While the option to choose a different partner might not be culturally acceptable in communities outside the orthodox Ashkenazi, it still shows that the genetic risk information opens up options how to deal with the genetic risk. In other cultural contexts, where abortion is not generally forbidden, preimplantation diagnostics and prenatal diagnostics are further options for carrier couples. This criterion serves as a strictly binary yes/no criterion. Screening would not be justified, if there were no options for dealing with the risk information.[2]

The second criterion refers to the *severity of the disease*. First, there is a broad consensus based on the distinction of health and disease that genetic testing should not be used to select "designer babies" but only to avoid suffering. Still the notion of

[2] The relevance of information is highly debatable. While some follow the line of this argument, that information is only relevant, if it opens up choices, results from empirical studies show that having information about one's own condition is valued in itself by patients, even if nothing derived from this information.

suffering or severity of a disease needs to be defined in order to be able to distinguish between those two. While extreme examples like Tay Sachs on the one hand and eye color on the other hand might be easy to distinguish, there is a large "grey area" where the distinction between severe disease and pure lifestyle wishes seems less clear. On very prominent example with conflicting opinions is hereditary deafness. Deaf couples already have actively sought to increase their chances to have a deaf child and argued for that in US courts starting an international debate [6]. Within the screening program offered in Israel Gaucher Disease is another example where there is no common agreement on the severity of the disease. [15] Gaucher disease can manifest in very different forms from (almost) asymptomatic persons to severe forms form early childhood on. Bell et al. [3] aim at developing a test for "severe childhood recessive diseases" and claim that they include all conditions that are severe, even if they are so only with a small percentage within the group of affected persons. Thus they make no distinction between potentially server and (always) severe diseases. Gaucher Disease thus falls under their definition. Instead of either leaving out diseases or simply integrating all of them based on a definition like that, fuzzy logic could be used to distinguish between different types of the severity of a disease and different average times of onset. Diseases where all persons are affected in the same severe way thus can be compared to diseases with different variants of different severity.

Another problem connected to the description of severity is who should be allowed to decide, if a diseases is considered severe or not. Firstly, there are cultural differences when it comes to assessing severity of a disease [16]. Therefore, the severity of a disease for which a carrier screening program is set up should always be discussed with representatives of the community. In communities, like the above mentioned ones on islands like Sardinia or Cyprus, Beduin tribes or religious communities like orthodox Ashkenazim Jews, there might be established ways to find an accepted threshold between severe an non-severe diseases. But even within culturally (relatively) homogenous communities there is no simple agreement on the severity of a disease. Affected persons will have a different perspective on the severity of a disease than indirectly affected persons like parents or other relatives and this will differ from the perspective of doctors or non-affected persons [17]. Within a public discourse these different perspectives on the question of severity need to be brought together. Sagi argues that the voice of those affected by the disease should be given priority in the assessment [15]. Their assessment of the quality of life is a major factor for assessing severity but the principle of not harming can also be extended to other groups of persons such as the parents who care for a sick child. Therefore, their perspective needs to be integrated as well.

This adds another dimension to the problem of defining severity, showing the necessity to integrate different (even opposing) perspectives. Here fuzzy logic can also be used to describe differences and similarities. By choosing prototype diseases like Tay Sachs as a reference point the similarity regarding severity of a disease can be expressed in numbers for each disease (by each speaker) and thus there is a possibility to have a formal way of comparing severity between otherwise very different diseases. The notion of severity can remain vague for this purpose and

open to individual assessment. At the same time, fuzzy logic provides a possibility to grasp this vagueness formally.
The last criterion to be discussed here, that was brought forward by Eckstein and Katzenstein [7] is a statistical one based on the prevalence of a diseases in a certain community. A similar criterion could be the carrier rate within a community. While the prevalence of diseases has been remarkably reduced by programs like Dor Yeshorim, the carrier frequency remains stable. While there is a large number of publications on carrier rates (e.g. see contributions in [18]) it is difficult to assess the frequency within larger communities especially when a larger number of mutations are associated with a disease. Therefore clear thresholds like 1 in 1000 pose enormous methodological problems. It seems to be more appropriate to use more general categories such as high and low frequencies that can be described as fuzzy concepts. Thus prevalence can be considered despite lack of knowledge and ongonig research.
Ethically the prevalence of a disease is a controversial criterion. On a public health level prevalence is an important factor to calculate efficiency of a screening program. This is not only economically necessary (based on the principle of justice, [19]) but also is essential for trust of the community in a screening program. Resources spend on a screening program should translate into benefits for individuals as well as the community. This would not be the case, if no carrier couples would be detected. Efficiency therefore does not only refer to prevalence but also to the efficiency of the test itself. Only with high validity and low false positive and false negative rates of a test can a screening program be efficient. On an individual level prevalence might not count as an argument, especially among affected couples. The criterion of efficiency is discussed more in depth in the next section:

5 Efficiency: Beta Thalassemia screening on Cyprus and Sardinia

In Cyprus and Sardinia (Italy), there is a genetic screening program for beta thalassemia. The program was initiated due to a high prevalence of beta thalassemia on both islands. With the life expectancy of persons suffering from beta thalassemia rising due to an available but expensive treatment especially Cyprus was facing an increase in health care costs unbearable for the community. Furthermore, life quality of those affected was still reduced even with available treatment. The screening program was introduced on a strictly voluntary basis, but it is strongly supported by the Orthodox Church. The church asks for a certificate that both partners know about their carrier status (regardless if positive or not) for beta thalassemia before performing a church wedding. On Sardinia the results were due to an intensive education program both for medical professionals as well as for the population [8]. On Cyprus besides questions of life quality of people affected and reducing harm also economic reasons played a major role in introducing the screening program. The screening on Sardinia reduced the prevalence of beta thalassemia by 90%. Reasons given for the screening for beta Thalassemia besides the above mentioned

were also its efficiency.
Efficiency can have different dimensions: The first refers to the already mentioned prevalence. The more carriers are detected the higher the reduction rate – provided that couples decide to take measures not to have affected children.[3] Efficiency is also connected to the knowledge about the causal link between genotype and phenotype. While for diseases like Tay Sachs and Huntington's the genetic risk factor is a very valid predictor of the future condition, the causal link is much looser for diseases like beta thalassemia or the risk for specific types of cancer (like BRCA1 and BRCA2). In [20], Knoppers and Isasi discuss this as "substantial risk" and describe different regulatory approaches to pinpoint the distinction between a high and low probability of the disease to break out based on genetic risk information. The mechanisms translating a genotype into a specific disease have not yet been fully understood. Precise probabilities for this relationship between genotype and phenotype will therefore be not available for many diseases for some time. Once more I want to suggest to use fuzzy logic to grasp this and to have a more general distinction between a strong connection and a weak connection. Since this type of "substantial risk" gains more or less relevance in combination with other criteria already discussed. Research in genetics is generating new insights as well as new questions. Both can be modelled and integrated using fuzzy logic and explicitly leaving issues that are still vague as such. All those criteria could be integrated into a more holistic model to describe the different facets relevant for genetic carrier screening

6 Conclusion

The discussion of the criteria for preconceptional genetic carrier screenings showed, that it might be helpful to understand those criteria as fuzzy concepts operationalizing them in the way Sadegh-Zadeh described in his resemblance theory [21], [22].
Sadegh-Zadeh suggests to introduce fuzzy logic to get a more fine grained view on the distinction of disease and health and the distinction between different diagnoses. His idea can be transformed and made useful for the classification of the severity of diseases in combination with the other criteria. A first and simple approach would be to say that severity is a fuzzy notion in itself. Between the two poles of severe (like a heart attack or multiple trauma) and not severe (like having a cold or aching muscles) there is a continuum of more or less severe diseases. The criteria discussed here could either be used to differentiate between different aspects for ethical reflection or a mathematical model could be developed to integrate these different aspects to assess the overall importance to integrate a disease into the screening.
While in the above mentioned communities the prevalence of the diseases is comparably high and the severity of (most of) the diseases well known and accepted

[3] This is not always the case and depends on the circumstances of the screening: Despite a mandatory premarital screening in Saudi Arabia the vast majority of participants proceeded this their marriage plans [8].

– not only within the medical community but also within the communities themselves, the currently developed genetic carrier screening by Kingsmore and team [3] does not aim at a special community. They announce that their test is for severe early onset diseases and claim that they are "scaling up" already existing screening programs like the above mentioned. Their main example is juvenile batten disease, a condition that affects children around the age of 6 months to two years leading to an early death before 5. Based on Sadegh-Zadeh's fuzzy notion of diseases and ways to compare them [23], it can be argued that severity can be interpreted as one dimension of resemblances between diseases. The methodological background of fuzzy logic can be used to create a model for this comparison. Such a model would need further ethical reflection about how the different dimensions are brought together and maybe weighed against each other. Such a model could be used in two ways: It could serve as a basis for ethical reflection and discussion by making the different dimensions transparent. It could also be used to assess individual preferences of patients before carrier screenings in order to get a general picture of which diseases they want to be tested for. Thus informed consent procedures can be facilitated by providing this specific individual information.

Medical ethics can profit from integrating notions of fuzzy logic into its line of thinking. Discussing the example of criteria for genetic screening showed that criteria often need to be vague to pinpoint the many facets of an ethical problem that in most cases cannot be reduced to a simple binary distinction or clear definition. Especially in practical contexts where lack of knowledge and different practices play an important role, fuzzy concepts help to grasp the complexity of a problem without negating it or surrender because of the complexity.

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