Research article

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Implementing carrier screening for cystic fibrosis outside the clinic: ethical analysis in the light of the personalist view

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Abstract

Background. Cystic Fibrosis (CF) is an autosomal recessive genetic disease. Two models for screening CF are normally used: newborn screening and population-based CF carrier screening. In turn, there are three main models of population-based CF carrier screening: prenatal carrier screening, preconception carrier screening, and carrier screening outside clinical settings.

Aim. To evaluate, in the light of the personalist view, the use of carrier screenings for CF outside the clinic, i.e. in non-clinical settings, such as school and workplaces.

Methods. Analysis has been carried out according to the "Personalist approach" (also called "Triangular model"), an ethical method for performing ethical analysis within HTA process. It includes factual, anthropological and ethical data in a "triangular" normative reflection process.

Findings. Implementing carrier screening for cystic fibrosis outside the clinical settings allows acquisition of knowledge for informing reproductive choices, that can be considered as valuable; benefit-risk ratio seems to be not much favorable; autonomous and responsible decisions can be taken only under certain conditions; economic advantage is difficult to determine; therefore, from a personalist view, implementing carrier screenings outside the clinic seems not to be ethically justified.

Conclusion. In accordance with the personalist perspective, public health programs providing carrier screenings outside the clinic should not be implemented. ***Clin Ter 2018; 169(2):e71-76. doi: 10.7417/CT.2018.2057***

Key words: *carrier screening, cystic fibrosis, ethics, bioethics, health technology assessment, Personalism*

Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal recessive genetic disease which is characterised by abnormal transport of chloride and sodium. It is caused by mutations affecting a gene on the long arm of chromosome 7, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) (1-2).

Approximately 2.000 mutations have been discovered since 1989, when the most common CFTR allele, known as ΔF508.5, was described. More than 280 of these mutations are responsible for the majority of cases of this disease (3).

CF can be developed by people from both sexes, as well as all races and ethnic groups. Anyway, the incidence of CF varies across the globe. CF is particularly common among Caucasians of Northern European descent and among Latinos and American Indians. The incidence of CF in the European Union is about 1 in 2.000-3.000 newborns, even though there are some discrepancies among the different countries. On the contrary, the disease seems to be underdiagnosed in Asia, even though researches suggest that the prevalence is rare (4).

CF affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections. Other signs and symptoms may include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in males. People may have different degrees of symptoms (5).

In the most serious forms, the treatment burden associated with the disease is significant, with patients undertaking a minimum of twice-daily chest physiotherapy augmented by nebulised therapies, prophylactic antibiotics, fat-soluble vitamins and pancreatic enzyme supplements. These therapies are time-consuming and non-curative, targeting the symptoms rather than the cause of disease (6). New treatments are being developed that target specific mutations. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) was the first of these drugs and targets patients with the G551D mutation, which is present in around 5% of CF population (7).

The life expectancy of patients with CF is currently around 42 years, a considerable increase from around 6 months when the disease was first identified, and is expected to increase to at least 50 years for children born in 2000 (6; 8). Anyway, morbidity and mortality are associated with factors, including age of diagnosis, sex, genotype, pancreatic functional status, socioeconomic status, and respiratory flora.

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Screening for cystic fibrosis

To have cystic fibrosis, a child must inherit one copy of a CF gene mutation from each parent. People who have only one copy of a cystic fibrosis gene mutation do not have CF. They are "CF carriers". If both parents are carriers (a carrier couple), each pregnancy has a 1-in-4 chance of being affected by CF. When one parent has CF and one parent is a carrier, there is a 50% chance having a child with CF.

There are two models of screening for CF, newborn screening and population-based CF carrier screening. Newborn screening for CF is a three-step process: the first step is a screening test for immunoreactive trypsinogen (IRT) on the dried blood spot specimen; in those with elevated IRT levels, the second step is to test for common mutations in the gene responsible for CF; the third step is a sweat test for those with heterozygous DNA results. When positive, infants are then addressed to diagnostic services in order to confirm (true positives) or refute (false positives) the diagnosis. Newborn screening for CF has rapidly expanded over the past decade. In many industrialized countries, it has become part of public health programs. All babies born are potentially screened and those diagnosed with CF have access to early treatments.

Carrier screening detects couples who has for each pregnancy a 25% chance having affected child (9). The options available to carrier couples depend on whether they are screened before pregnancy (preconception carrier screening) or in the early phases of pregnancy (prenatal carrier screening) (10). Carrier couples identified during pregnancy may elect to have prenatal diagnosis, while carrier couples identified when the woman is not pregnant have the additional options of having no more children, adopting, or using donor oocytes or sperm or in vitro fertilization (IVF) with preimplantation genetic diagnosis. Three main models of a CF carrier screening program can be so implemented (10): prenatal carrier screening offered to all pregnant women or couples as part of their prenatal care; preconception carrier screening offered by general practitioners to individuals or couples before pregnancy; and carrier screening outside the clinic offered in non-clinical settings, such as school and workplaces. Carrier screening is less extensively used than newborn screening. Anyway, millions of tests have been performed (9, 11).

Aim

The aim of the present article is to evaluate, in the light of the personalist view, the use of carrier screenings for CF outside the clinic, i.e. in non-clinical settings, such as school and workplaces. More specifically, the article will examine if implementing carrier screenings for CF outside the clinic can be considered as ethically licit or ethically illicit in the light of the four principles of personalist bioethics: defense of human physical life, therapeuticity, freedom and responsibility, and sociality and subsidiarity.

Methods

This work is based on a previous ethical analysis on a similar topic carried out within a full Health Technology Assessment (HTA) process entitled "Health Technology Assessment Of The Genetic Tests For Cystic Fibrosis Carrier Screening In Italy" (12). The main difference regards the focus of the study, which in this case is restricted to a specific model of carrier screening, i.e. that one offered in non-clinical settings.

HTA is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner (13). Ethics in HTA aims at analysing the ethical issues raised by the use of a given technology: since technologies are always introduced into societies or organizations with their own set of values, their implementation can raise ethical consequences (13). A considerable number of models and frameworks can be successfully used to conduct ethical analysis in HTA (14-16). Furthermore, ethical analysis can be conducted in a descriptive or in a normative way. The descriptive way provides a list of ethical issues, which have to be identified, described, and addressed (the most widely used modality); the normative way provides a moral judgement (e.g., the use of the technology X is morally good/bad or ethically licit/illicit) (17).

The ethical analysis of the full HTA was conducted by a normative model, i.e. the Triangular model. The Triangular model, also known as the ''personalist model'', is rooted on the human person (body-soul unitotality) as reference-value in the reality, according the Aristotelian-Thomistic view. This approach includes factual, anthropological and ethical data in a ''triangular'' normative reflection process (Figure 1). The three steps of ethical process are: A. Data collection (knowledge level): an in-depth study of factual data concerning the object of the analysis; B. Ethical/anthropological analysis (justifying level) according to the following principles criteria: B1. the defense of human physical life; B2. the therapeutic principle, according to which the human person has to be treated as a totality of body and soul; B3. the interconnection between personal freedom and responsibility; B4. the principles of sociality and subsidiarity, for which public/private bodies are called to help all persons, namely when they are not able to fulfil their needs; C. Appraisal (normative) level, that should establish if implementing a certain technology is ethically licit/illicit, and, therefore, facilitate practical choices (18).

The ethical evaluation of implementing carrier screening in non-clinical settings has been carried out according to the Triangular Model too. Specifically, the present work reports the synthesis of the ethical analysis process carried out. The aim is to establish if implementing carrier screenings for CF outside the clinic can be considered as ethically licit or ethically illicit in the light of the personalist view.

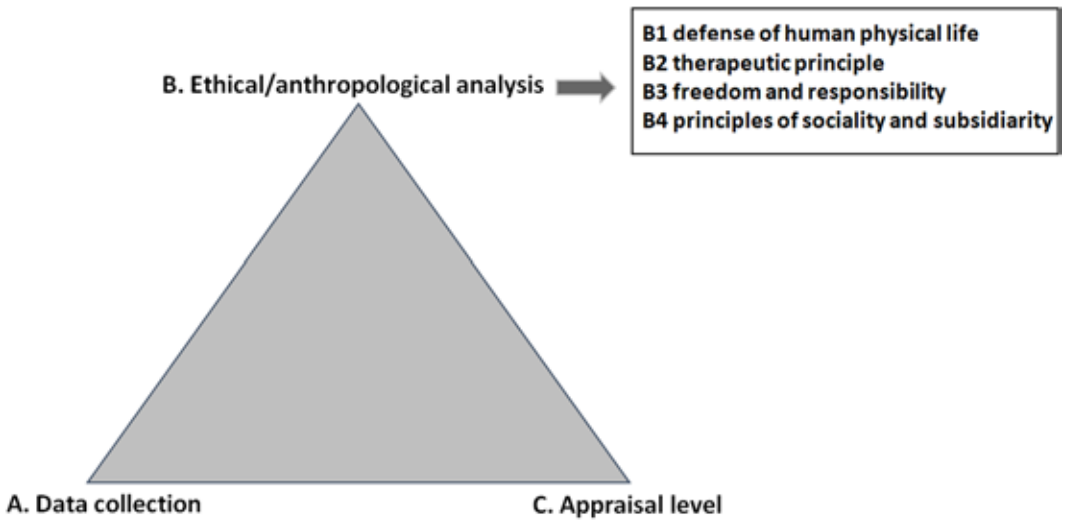

Fig. 1. The Triangular model for ethical analysis within HTA process

Ethical analysis

Data collection: carrier screening outside the clinic (A)

As mentioned, the first step of the ethical analysis is an in-depth study of the factual data concerning the object of the analysis.

The aim of CF carrier screening is to identify individuals at risk of having a child with CF. The sensitivity of screening test varies depending upon several factors, including the mutation panel being used and the race/ethnicity of the population. The sensitivity could range from less than 50% in those of Asian ancestry to 94% in the Ashkenazi Jewish. Furthermore, since screening is offered for only the most common mutations, a negative screening test reduces but does not exclude the chance of being a CF carrier (19).

Population-based CF carrier screening can be implemented at various life stages, including the neonatal stage, high school and college age, reproductive age, when planning a family, or during the early stage of pregnancy (20). It follows that carrier screening can be offered in clinical as well as non-clinical settings. "Non-clinical settings" refer to situation for which individuals are not planning pregnancy and test results can be used later.

In a number of countries (such as United States, Australia, United Kingdom, Canada, France), guidelines recommend that CF carrier screening be offered to all pregnant women and couples planning a pregnancy (clinical context) (20). No guideline recommends that CF carrier screening be offered in non-clinical settings. Anyway, it may be at the center of future health care policies. Moreover, carrier screening has been already offered in some Australian and Canadian Jewish high schools for many years (21). Experiences of workplace screening are also present (22).

Usually, CF carrier screening is performed in non-clinical settings by dedicated services.

Ethical/anthropological analysis (B)

The second step of the analysis consists in "comparing" the implementation of the technology with the four principle of the personalist bioethics: defense of human physical life, therapeuticity, freedom and responsibility, and sociality and subsidiarity.

Principle of defense of human physical life (B1)

Implementing carrier screening outside the clinic allows acquisition of knowledge for informing reproductive choices in any subsequent relationships (23). According to personalist model, some of these reproductive choices (e.g. abortion) are not ethically acceptable or are at least ethically questionable (e.g. preimplantation genetic diagnosis) (24). Following this view, carrier screening may be therefore linked with decision making against the defense of human physical life, and may generate "selection mentality", or a sort of "culture of perfect child".

This points to the importance of adequate counselling, in order to understand the ethical values of some reproductive decisions. Even though studies show that individual carrier status does not to affect reproductive intentions or behaviors, (20; 24-32), options are so much ethically questionable (such as abortion or preimplantation genetic diagnosis) that they should be well explained and highlighted through counselling.

Principle of therapeuticity (B2)

The main benefit of implementing carrier screening outside the clinic consists in acquisition of knowledge for informing reproductive decision making. Theoretically, this acquisition can be considered as valuable, since it is potentially able to reduce the birth prevalence of affected children.

Anyway, this reduction can be achieved into practice in part by reproductive choices (e.g. abortion, or use of donor oocytes or sperm or in vitro fertilization (IVF) with preimplantation genetic diagnosis) not ethically acceptable from personalist perspective. Furthermore, carrier screening is not able to reduce the number of infants in which CF can neither be confirmed nor excluded after newborn screening (10). In personalist view, advantage seems to be therefore ethically questionable as well as more theoretical than practical.

Possible harms include a potential for misunderstanding the carrier status. As mentioned, the sensitivity of carrier screening test varies depending upon several factors, including the mutation panel being used and the race/ethnicity of the population. Studies show that some noncarriers believed that a negative test result meant they had no chance of having a child with CF (20; 28). The confusion regarding residual risk may have implications for a carrier if he or she will plan pregnancy in the future.

A potential psychological harm is anxiety on receiving a positive test result. Anyway, anxiety seems to be transient among carriers, with little to no anxiety present at 6-12 months or more after testing (20, 29).

Finally, psychological harms also include possible stigmatization and discrimination of individuals or the community. For ex., a positive result may have implications in finding a partner o in work activity (33) with an increasing risk of "geneticization". Geneticization is the identification of persons with their genes, a tendency to overemphasize the role of genes in disease causation, in medical practice and in social attitudes toward disease (34).

In the light of the above considerations, from the personalist perspective, benefit-risk ratio of implementing carrier screening outside the clinic seems to be not much positive.

Principles of freedom and responsibility (B3)

An important question is whether implementing carrier screening outside the clinical settings allows exercising responsible freedom and how this can be achieved (35).

Some argue that carrier screening outside the clinic may promote autonomous decision making, while in the clinical settings patients would accept any test, in the belief that they are "necessary" or "routine" (11). Offering the test in a non-clinical setting would encourage participants to exercise the type of agency they routinely use outside the clinic medical. Personalist view believes that this argument is ethically questionable since freedom cannot considered as the sole requirement for making good decisions. Freedom needs to be linked to responsibility. Freedom is not necessarily good in itself. In this sense, good reproductive options are not only those that are freely chosen but those by which good is achieved. Although freely chosen, options that do not ensure the respect for human life, human dignity and health, should be avoid.

This points to the importance of genetic counselling, in order to highlight the ethical value of some reproductive choices. In turn, this poses the question on how performing genetic counselling. Some perspectives argue that genetic counselling should be value-neutral and "non-directive": counselor should impart genetic risk information without offering direct advice, enabling clients to reach informed, voluntary decisions. Personalist view believes non-directiveness may be difficult or impossible to achieve for several reasons (24). Additionally, it argues that there are some values (for ex., the value of human life) that cannot be neutralized. Therefore, it promotes an exchange of clinical information and personal values from both patient and counsellor, leading to a shared decision-making process (24).

The milestone of this process is the informed consent, an important prerequisite to the beginning of any medical intervention. Informed consent is a process by which the health care provider discloses appropriate information to a competent patient, so that the patient can make a voluntary choice to accept or refuse the treatment. In this sense, informed consent is connected with the principles of autonomy and the issue of self-determination. In order to be valid, informed consent requires that: the individual should have the capacity to make the decision; his/her choice should be voluntary; s/he should be provided with appropriate information, in a format s/he can understand, regarding the benefits, risks, consequences and alternatives to the proposed treatment; and his/her decision should be accurately documented.

When a genetic test is offered within genetic screening programs to the general population, the individuals have not personally requested the test, and they may not know anything about the condition being tested. For these reasons, it is extremely important to adequately inform the public. Specifically, pre-test counseling information should include: 1. exploration of all pros and cons of testing; 2. elucidation of individual motives for testing; 3. identification of areas in which the individual's expectations might be unrealistic; 4. understanding the phenomenon of false negatives; 5. information about psychological, familiar, social and ethical aspects as well as the economic consequences.

In the case of tests offered within school programs, specific attention should be paid to capacity of children and adolescents to understand information. Anyway, many guidelines are in agreement that minors preferably should not undergo carrier testing and that testing of children ideally should be deferred until he/she will have the intellectual capacity for discerning if and when to be tested (36-37). If minors are tested, it is clearly needful the support of the parents.

Individuals may also decide not to accept the test. Studies shows that the percentage of individuals who accepted an offer of CF carrier screening of the total number of individual offered ranged from 2 to 96% in the general population (20).

Genetic test offered within genetic screening programs should also provide an appropriate counseling after the test (post-test counseling). During the post-test counselling the counselor discusses the relevance of the patient's test results with the patient and/or his or her family members (in the case of minors). All information has to be disclosed in confidential setting and patient's privacy protected. A strategy for informing other family members about increased risk should be discussed. Depending on the resources available as well as the context, follow-up contacts with the genetic counselling unit should be offered. A written summary of the test result and issues discussed during the counseling should be given to the counsellee.

Individuals may also decide not to know the test results. This poses a further complex question about counsellor's responsibility to inform relatives. Probably, counsellors should not make direct contact with relatives but rather they should act as mediators by instilling a feeling of duty and responsibility towards relatives in the counsellees. Anyway, this topic needs to be better debated.

In the light of the above considerations, from the personalist perspective, implementing carrier screening outside the clinical settings could promote autonomous and responsible decisions under certain conditions. Specifically, the greatest attention should be paid to genetic counselling.

Principles of sociality and subsidiarity (B4)

Some argue that implementing carrier screening outside the clinic may promote distributive justice to a broad cross-section of population (11). Indeed, this advantage seems to be more theoretical than practical: current healthcare systems are dominated by increasing scarcity of resources, so sustainability of all health care interventions need to be closely assessed. Resources required to meet health needs have to be divided fairly among increasing competing demands. However, one preliminary question may consist in wondering if acquisition of knowledge for informing reproductive choices can be per se considered as health need.

Sustainability assessment requires well-identified dashboards of indicators. One of the most important is cost-effective analysis. It is often thought that carrier screening is cost-effective simply because it would mean that cases could be either prevented and/or found earlier. Indeed, overview of the evidence on the costs and consequences of community CF carrier screening shows widespread variation in the published literature (38). The main difficulty consists in great amount of variables which have be taken into consideration. Even though one recent study (39) has shown that cost savings are possible, on these basis, it is rather difficult to make any evidence-based recommendations about whether a CF carrier-screening program should be undertaken on economic grounds.

Normative level (C)

The previous analysis has shown the following results:

a. implementing carrier screening for cystic fibrosis outside the clinical settings allows acquisition of knowledge for informing reproductive choices, that can be considered as valuable;
b. benefit-risk ratio seems to be not much favorable;
c. autonomous and responsible decisions can be taken only under certain conditions;
d. economic advantage is difficult to determine.

For these reasons, since principles of defense of human physical life, therapeuticity, freedom and responsibility, and sociality and subsidiarity are only partially fulfilled, from a personalist view, implementing carrier screenings outside the clinic seems not to be ethically justified.

Conclusions

Cystic Fibrosis (CF) is an autosomal recessive genetic disease, to which a significant burden is often associated. To have cystic fibrosis, an individual must inherit one copy of a CF gene mutation from each parent. Implementing carrier screening outside the clinic, i.e. in non-clinical settings, such as school and workplaces, allows acquisition of knowledge for informing reproductive choices in any subsequent relationships. Nevertheless, in a personalist perspective, using this type pf technology is not ethically justified, since principles of defense of human physical life, therapeuticity, freedom and responsibility, and sociality and subsidiarity are only partially fulfilled. Therefore, according to personalist viewpoint, decision-makers should not be implement this technology within public health program.

The result of this evaluation is closely connected to the approach used. As mentioned, a considerable number of models and frameworks can be used to conduct ethical analysis in HTA. Perhaps, other methods could determine different results. However, the overall aim of HTA is to support decision-making. Therefore, even though not everyone would agree with the method used, the information collected in this work could be useful in order to make a decision on implementing this type of technology.

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