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Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1531

Considering a Baby? Responsible Screening for the Future

Ethical and social implications for implementation and use of preconception expanded carrier screening in Sweden

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2019

ISSN 1651-6206
ISBN 978-91-513-0553-0
urn:nbn:se:uu:diva-372736

Dissertation presented at Uppsala University to be publicly examined in Sal IV, Universtetshuset, Biskopsgatan 3, Uppsala, Thursday, 28 February 2019 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Lars Sandman (Linköpings universitet).

Abstract
Matar, A. 2019. Considering a Baby? Responsible Screening for the Future. Ethical and social implications for implementation and use of preconception expanded carrier screening in Sweden. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1531. 53 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0553-0.

Preconception expanded carrier screening is a novel technology that involves the offer of a screening test for many recessive diseases (via an expanded screening panel) to prospective parents, with no priori risk. Test positive couples have a number of reproductive choices; prenatal diagnosis and aborting affected fetus, IVF and preimplantation genetic diagnosis, sperm or ovum donation or simply accept the risk. The test had been piloted in studies and can potentially be implemented in Europe. Therefore, it seemed pertinent to evaluate stakeholders' perspectives on ethical and social implications of implementing and using preconception ECS in Sweden.

Two main stakeholders were examined; healthcare professionals and health policymaking experts, via a mix of qualitative methods for data collection and data analysis. In Study I, we employed in-depth interviews to collect data and content analysis to analyze it. In Studies III and IV, expert interviews were used to gather data while thematic analysis was utilized to interpret it. Furthermore, in Study II, an ethical concept namely; reproductive autonomy, was critically discussed within a setting that expects a couple to make a conjoint reproductive decision about preconception ECS, while each partner still upholds his or her individual autonomy.

The main findings of the empirical studies (Studies I, III and IV) echo to a great extent the prevailing ethical and social debates associated with the novel technology. Respondents expressed concerns with reproductive autonomy, medicalization, prioritization of health resources, discrimination and long term societal changes. Furthermore, respondents emphasized the importance to observe Swedish values, such as human dignity, equality and solidarity, when assessing a preconception ECS program. In addition, they described practicalities of implementation and political considerations that are pertinent to the Swedish context. Finally, some respondents recognized the advantages of reduced suffering and decrease in fetal anomalies and abortion as a consequence of preconception ECS.

Study II, proposed a notion of couple autonomy, where certain demands if met, a couple's reproductive decision can be accepted by healthcare staff as autonomous.

The findings, in this thesis, steer towards non implementation of preconception ECS in its current status within the publicly-funded healthcare system in Sweden. This is because healthcare providers and experts were of the opinion that it would not solve a medical need, threaten Swedish values and use up resources extensively.

Keywords: Preconception expanded carrier screening, reproductive autonomy, solidarity, popula-tion screening, genomics, ELSI

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ISSN 1651-6206
ISBN 978-91-513-0553-0
urn:nbn:se:uu:diva-372736 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-372736)

To Amany, Ebtihal and Alaa

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Matar, A., Kihlbom, U., Höglund, A. T. (2016) Swedish healthcare providers' perceptions of preconception expanded carrier screening (ECS)—a qualitative study. *Journal of Community Genetics,* 7(3), 203-214

II Matar, A., Höglund, A. T., Segerdahl, P., Kihlbom, U. (2018) Couple autonomy in preconception expanded carrier screening. *BMC Medical Ethics*, under review.

III Matar, A., Hansson, M. G., Höglund, A. T. (2018) "A perfect society"—Swedish policymakers' ethical and social views on preconception expanded carrier screening. *Journal of Community Genetics,* 1-14

IV Matar, A., Hansson, M. G., & Höglund, A. T. (2018). Value and value conflicts in implementation and use of preconception expanded carrier screening – An expert interview study. *BMC Medical Ethics*, under review.

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Contents

Abbreviations

AR	Autosomal recessive
ART	Assisted Reproductive Technologies
cfDNA	fetal cell free DNA
CRB	Center for Research Ethics and Bioethics
CUB	Combined ultrasound and biochemical
ECS	Expanded carrier screening
ELSI	Ethical, legal and social implications
EU	European Union
HGC	The Human Genetic Commission
HT	Health technology
HTA	Health technology assessment
IVF	In vitro fertilization
MERETI	Middle East Research Ethics Training Initiative
NGS	Next generation sequencing
NIH	National Institute of Health
NIPT	Non-invasive prenatal screening
PB	Procreative beneficence
PGD	Pre-implantation genetic diagnosis
PKU	Phenylketonuria
SBU	Statens beredning för medicinsk och social utvärdering
SFS	Svensk författningssamling
SMER	Statens Medicinsk-Etiska Råd
USA	United States of America

A Prologue

Life has an interesting way of changing direction last minute. I was living in Cairo, Egypt, having just recently completed my MSc. in biotechnology and working for Middle East Research Ethics Training Initiative (MERETI), I was contemplating my future steps. During the time, Egypt's attempt at democracy was taking a plunge: violence, sectarian rifts and deepening of military embroilment in politics.

Fortunately, amidst all the chaos, I secured a bioethics fellowship at National Institute of Health (NIH), in Washington DC. I was preparing for my travels, when I came across a PhD announcement by Center for Research Ethics and Bioethics (CRB) at Uppsala University. I was quite intrigued by the post and after managing to apply last minute, I was invited for a skype interview, and voilá, I was accepted for the post. It seemed to me that all of the sudden, my travel plans changed from USA to Sweden.

I readily switched direction to Sweden for two reasons. Firstly, in order to experience a European academic culture, having only been exposed to American and Egyptian academia, and secondly, to explore a new area of bioethics which is reproductive ethics. My training and experience, thus far, was focused on research ethics, particularly in an international setting.

Preconception screening is a compelling topic, because I commonly encountered patients with severe recessive diseases during my medical training and my years in transfusion medicine. The most common ones were thalassemia major, an autosomal recessive disease, and hemophilia A, an X-linked condition. Both diseases could be prevented by an offer of a preconception screening program, which Egypt lacked. The patients had a short life expectancy and experienced many complications and a poor quality of life. Therefore, delving in the ethics of such programs was very intriguing and allowed me to view the subject with a different set of spectacles.

Introduction

This dissertation describes and discusses ethical and social implications associated with implementation and use of preconception Expanded Carrier Screening (ECS) within the Swedish healthcare system, as perceived by stakeholders. Preconception ECS is proposed to be offered to couples, who are planning a pregnancy, to detect carriers of autosomal recessive (AR) conditions. If a couple tests positive, there is a 25% risk of delivering a baby with the disease with every pregnancy (Marcus, 2010).

The subsequent text delivers a historical overview of the development of genetic screening as well as describes the main concepts used in the thesis such as, genetic screening, preconception screening and expanded screening panels. This followed by a section that details the current reproductive genetic screening practices and the regulations and guidelines used by Swedish practitioners. Subsequent to that is a review of some of the main ethical concerns associated with preconception ECS as presented in the literature.

The sections succeeding the literature describe the overall rationale of the dissertation and overview of the four studies, which encompasses aims, procedures and main findings. The discussion section briefly explains our choice of title, studies, reflects on main findings and relationship between the articles. In addition, there is a discussion of the methods utilized in the studies. Finally, the thesis ends with sections on conclusions as well as prospective research.

Background

Genetic Screening

The first genetic screening in the USA was performed to test for phenylketonuria (PKU) in newborns, where test positive neonates followed a special diet to preserve brain function and protect against mental impairment. This was followed, in 1970, by carrier screening of sickle cell trait among African Americans in 12 US states. However, it was met with mistrust for fear of stigmatization because, at the time, there was no treatment or means to prevent the birth of affected offspring. In 1972, the National Sickle Cell Anemia Control Act was issued in an effort to curb stigmatization (Lewis, 2008). The Act facilitated voluntary screening and counseling programs, spreading information to the public and healthcare personnel and providing funds for research (Nixon, 1972). By 1980, treatment was offered in the form of antibiotics and bone marrow transplantation (Lewis, 2008).

Likewise, a Tay-Sachs carrier screening program for the Ashkenazi Jews on the US east coast began in the 1970s. The program screened individuals in their reproductive age, who firstly engaged in informative sessions in synagogues before being proffered the test. Over the course of 30 years, around 1.4 million persons were screened and over 1300 carriers were identified. The program resulted in 90% reduction of the disease among the Ashkenazi community (Zlotogora, 2009).

This program was not popular among the ultra-orthodox Jews, since it could result in termination of pregnancy among test positive cases after 40 days of conception. According to their religious rules, termination of pregnancy is permitted only during first 40 days of pregnancy. To address this an alternative procedure Dor Yeshorim was established in 1983. In the program, each of the high school students who were screened for the Tay-Sachs disease received a specific number. The tested individuals did not receive their test result but they were kept at the Dor Yeshorim office and only revealed to match makers. In this community, young couples are married with the help of a match-maker, who could access the results and decides if a couple is compatible or not, judging by their risk to the Tay-Sachs disease (whether they or their parents are carriers) among other factors (Zlotogora, 2009).

Targeted carrier genetic screening programs exist in many countries, such as Italy (Sardinia), Cyprus, Israel, Iran and Saudi Arabia to identify carriers of

recessive diseases such as beta thalassemia, cystic fibrosis, Tay-Sachs (Zlotogora, 2009).

The Council of Europe defined genetic screening as a medical test systematically offered to "a defined group" of people to detect "an early stage, a preliminary stage, risk factor/s of a disease" with the goal to "to cure the disease or prevent or delay its progression or onset by early intervention" (Godard, ten Kate, Evers-Kiebooms, & Aymé, 2003). Typically, a healthcare provider proffers screening programs as a means to identify those who are likely to, or already have developed a disease. This distinguishes it from routine medical testing, where an individual seeks medical help when s/he falls ill and undergoes medical tests to reach a diagnosis (Juth & Munthe, 2011).

The discovery, in 1970s, that amniotic fluid of pregnant women contains fetal chromosomes paved the way for expanding genetic screening to pregnant women, a process called prenatal genetic screening. In later years, it was found that most genetic disorders can be detected in maternal amniotic fluid, for example, sickle cell disease, cystic fibrosis (Press, 2008). Prenatal care expanded to encompass pre-implantation genetic diagnosis (PGD) for high risk couples, where In vitro fertilization (IVF) embryos are screened for genetic diseases and only those testing negative are implanted intrauterine (Godard et al., 2003).

Identifying the genetic basis of some cancers, such as breast and colon cancer, contributed to further expanding genetic screening to encompass hereditary cancers. This came about when Mary King, in the 1990s, discovered that some types of breast cancers ran in families (Press, 2008).

Recently, the scene has changed with the introduction of expanded screening panels, which have become reasonably priced and more reliable. The panels test for several genetic diseases simultaneously and may have implications for newborn and reproductive screening programs. A single testing panel can be utilized to screen for AR traits as well as hereditary cancers (Burke, Tarini, Press, & Evans, 2011). These new tests have been described as "genomic" rather than genetic because the whole genome of a patient is checked. An example of such a panel, described by Kingsmore, included 448 severe recessive diseases. The panel utilizes next generation sequencing (NGS) technology and can be used for preconception carrier screening at population level (Kingsmore, 2012).

It has been argued that for such a test to be implemented as a screening program it should provide a substantial public health benefit and fulfill certain criteria (Andermann, Blancquaert, Beauchamp, & Déry, 2008). According to Kingsmore (2012), Mendelian diseases account for around 20 % of pediatric mortality and hospitalization. Wilson and Jungner, in 1968 have put forth criteria for screening programs, which have been regarded as the gold standard (Andermann et al., 2008). They were subjected to revisions to appropriate them for genomic screening. The criteria include the scale of the health problem posed by the disease, appraisal of potential benefits vs. harms in early

disease discovery, the validity and the cost effectiveness of the tests (Grosse et al., 2010). Even if a screening program fulfilled those criteria, issues such as logistics, ethical and social implications can hamper implementation (Andermann et al., 2008).

Reproductive Genetic Screening in Sweden

This section outlines the Swedish healthcare context in terms of governance, laws and guidelines of genetic screening and present-day operation in reproductive clinics with particular focus on reproductive screening. The intention is to provide the reader with a frame of reference to better understand the circumstances surrounding our choice of stakeholders and methods.

Healthcare decision making in Sweden

There are two levels of governance in Sweden, a national one constituted by the Parliament and government departments, and a local level formed of 21 county councils and 290 municipalities. The role of the former is to set a political agenda and establish values and standards for Swedish healthcare (Clinical Studies Sweden, 2017; The Government Offices of Sweden, 2014). County councils function almost autonomously and are in charge of financing medical facilities and delivering medical care to local inhabitants, while municipalities provide medical care in schools, for disabled and elderly and lastly rehabilitation. Both comply with the agenda laid down by the national government (Carlsson, 2004; Swedish Research Council, 2017), yet they still possess much liberty in deciding on services and spending (Carlsson, 2004). Healthcare provision in Sweden is publicly funded through taxes (Carlsson, 2004).

Policymakers are informed by several institutions that provide expert advice. Among these are governmental boards such as SBU (Swedish Council on Technology Assessment in Healthcare and Assessment of Social Services), SMER (Swedish Medical Ethics Council) and Socialstyrelsen (National Board for Health and Welfare) (Socialdepartementet, 2018; Swedish Agency for Health Technology Assessment and Assessment of Social Services, 2018). Furthermore, there are non-governmental organizations which are frequently approached for input on certain healthcare policies. Examples of these are professional organizations such as Swedish Medical Association and the Swedish Society of Medicine (Svenska Läkaresällskapet, 2018; Sveriges Läkarförbund, 2016).

Laws and guidelines

In Sweden, genetic screening is regulated through a multi-tiered set of rules enabling flexibility and adjustments as the technology advances. Business ventures may view this type of regulation as arbitrary and vague (Godard et al., 2003). Law 1991:114, issued by the Ministry of Health and Social Affairs in March 1991, directly regulates specific gene technologies in healthcare context. Beside the law, there are professional guidelines and policy documents that indirectly regulate genetic screening, for example, guidelines for prenatal diagnosis in 1995 and the Swedish government contract with health insurance companies in 1999 (Godard et al., 2003).

In 2006, the Genetic Integrity Act was passed (SFS 2006:351) whose goal is to preserve the "integrity of individuals". The act provides provisions for PGD and for genetic investigation as part of medical care. The latter is only allowed upon consent of the user and a permission of the National Board of Health and Welfare in the event of a risk for serious illness. Information on prenatal genetic diagnosis and PGD would be offered to pregnant women at high risk of monogenetic or chromosomal diseases. PGD may not be used for non-medical reasons (SFS, 2006). There are no specific law or guidelines regarding preconception ECS yet.

Current practice

In Swedish antenatal clinics, pregnant women are routinely offered an ultrasound at week 18 to calculate expected delivery date, search for multiple pregnancies or major fetal malformations and locate the placenta (Vårdguiden 1177, 2018).

In addition, expectant mothers are proffered a Combined Ultrasound and Biochemical (CUB) test at week 11-14 or non-invasive prenatal testing (NIPT) to search for trisomy 21 (Down syndrome), 18 and 13. If either test has shown high probability for trisomies, a pregnant woman is offered an amniocentesis or a placenta test. Though they are associated with a risk of miscarriage (about 1 in 150), both tests present definite answers about trisomy 21, 18 and 13 (Vårdguiden 1177, 2018). If a woman tests positive, she can terminate her pregnancy until the end of week 18. For termination after 18 weeks of gestation, a committee within the National Board of Health and Welfare decides on termination of pregnancy (EUROCAT Central Registry, 2010). The type of prenatal testing vary according to county council or region (Ingvoldstad, Georgsson Öhman, & Lindgren, 2014; National Board of Health and Welfare, 2011).

Non-invasive prenatal testing (NIPT) is a new screening method that detects fetal chromosomal abnormalities in pregnant women's blood. The test detects fetal cell free DNA (cfDNA) in the blood of the pregnant woman (Lo et al., 1997). It is characterized by being less invasive and associated with no

risk of miscarriage. Moreover, it has higher detection rates and lower false positive results (Gil, Quezada, Revello, Akolekar, & Nicolaides, 2015). It is also possible to obtain an early ultrasound (from week 8) or CUB or NIPT at private clinics (Mama Mia AB, 2016).

Preconception Genetic Carrier Screening

Preconception ECS, sometimes also called preconception expanded universal genetic screening (van der Hout, Holtkamp, Henneman, de Wert, & Dondorp, 2017), is a proposed population-based program that screens couples of reproductive age without prior risk for autosomal recessive (AR) and X-linked condition using expanded genetic panels. Thus many AR diseases are screened simultaneously at one point in time. If both parents test positive for any single AR, the mother has a 25% risk of delivering a baby with the disease with each pregnancy. This distinguishes it from conventional screening, which targets specific high risk groups such as Ashkenazi Jews or individuals with positive family history of a carrier disease (De Wert, Dondorp, & Knoppers, 2012).

Reproductive ECS has been on the market for potential parents since 2010 (Chokoshvili, Vears, & Borry, 2018). To our knowledge, there are no preconception ECS programs in Europe as yet, however, a pilot study was conducted by University Medical Center Groningen. A panel of 50 serious, non-curable diseases, commonly associated with grave mental or physical disability, was offered to 1000 couples in northern Netherlands, who wished to start a family. The purpose of the pilot was to examine the feasibility of the screening program, investigate general practitioners' ability to convey information to users and users' views and ability to make informed decisions regarding the test (Plantinga et al., 2016; Universitair Medisch Centrum Groningen, 2015; University Medical Center Groningen, 2016).

Currently, there are a few ECS suppliers, the majority of which are private companies and mostly located in the US. However, the Medical Hospital in Amsterdam, offers ECS tests for 50 genetic conditions. The number of genes screened vary widely among providers, from 40 to 1556, and the methods of screening also differ; either targeted genotyping or genetic sequencing or both (Chokoshvili et al., 2018).

In the UK, the Human Genetic Commission (HGC) issued a report stating there are no special ethical barriers to offering preconception ECS to couples before they conceive, nevertheless, such programs share ethical issues associated with other screening programs. The report emphasized the importance of enhancing reproductive autonomy and informed choice, and educating youths on genetic risks. It highlighted the significance of sharing genetic information with family members and cascade screening, and offering appropriate counseling for test-positive couples. Moreover, the report underscored the importance of ensuring equitable access to screening programs, which should be

based on concrete evidence, and providing therapy and support of those living with conditions being screened for (Human Genetics Commission, 2011).

Ethical issues associated with preconception ECS

In the following paragraphs, we are mapping some of the major ethical debates that have been raised in association with preconception ECS.

Reproductive Autonomy

One suggested motivation for implementing preconception ECS is enhancing reproductive autonomy of potential parents through offering more reproductive choices such as prenatal diagnosis (PGD), sperm or ova donation or adoption (De Wert et al., 2012). Reproductive autonomy has been defined as "the ability and opportunity to make one's own, well-considered decisions concerning procreation" (Health Council of the Netherlands, 2007). However, the ability and the opportunity can be restricted by internal elements such as inadequate mental capacity or external factors such as legal restrictions. Reproductive autonomy has also been regarded as a subdivision of autonomy but concerned with reproduction only (Zeiler, 2004). The term has been utilized synonymously with "procreative/reproductive liberty/freedom", "reproductive choice" and "right to choose" or "individual autonomy" (Priaulx, 2009).

Autonomy is one of the major principles of bioethics (Beauchamp & Childress, 2001) and has been connected to many concepts such as and not limited to: freedom of choice, self-governance and self-determination, individuality, human rights and empowerment (Zeiler, 2004). Moreover, reproductive autonomy has been established as a negative right: an individual is free to exercise that right by selecting their optimal reproductive choice without interference from state or others, so long as no harm is posed to others by such a choice (Robertson, 1996). In addition to being described as a principle and a negative right, S.I. Benn (1975) has viewed autonomy as an ideal to be a sought after. It is a value that a person relentlessly strives to embrace.

However, this individualized view of reproductive autonomy has been challenged. In an article titled "Reproductive autonomy is an illusion", Lucke outlined the relational aspect of reproductive autonomy, which is influenced by cultural, political, financial and personal considerations (Lucke, 2012). In addition to such factors, a person is usually embedded in a web of relationships including intimate ones, which influence their reproductive decisions and independence (Mackenzie & Stoljar, 2000).

The main premise proposed by De Wert et al., (2012) that preconception genetic screening enhances reproductive autonomy through offering couples more reproductive options, is challenged. Analysis of interviews with gynecologists and clinical geneticists showed a gap between theoretical discussions of reproductive autonomy and the actual practice (Zeiler, 2004). Though this study by (Zeiler) examined PGD, the results are pertinent to preconception

ECS. Reproductive autonomy was affected unfavorably by psychological and physical distress of couples, which were precipitated by repeated cycles of IVF some parents had to undergo. The results indicated that some healthcare professionals conveyed either too little or biased information, which affected couples' capacity to make informed decisions. In addition, the study demonstrated that offering more alternatives might hinder free choice. As one interviewee stated, "information about choices forced couples to make a choice" and some felt a compulsion to utilize the new technology. Moreover, some couples could not express their concerns freely because of the fear that healthcare professionals would dismiss them as "not serious" about IVF/PGD and run the risk of not using the technology (Zeiler, 2004).

To sum up, commentators described reproductive autonomy in different ways, as a principle, a right, an ideal, a combination of opportunity and ability and relational. No single definition seems encompassing and acceptable to all.

To complicate things further, autonomy becomes more elusive when joint decisions are expected from parents. In their article "autonomy and couples' joint decision-making in healthcare", Osamor & Grady explored the effect of gender, culture, couple's dynamics and dependency on joint decisions made by women in the context of healthcare. They developed a continuum where, on one end, a decision can be regarded as ethically admissible and thus respecting the woman's autonomy, if the partners demonstrated that they understood the medical procedure and no one partner has unduly persuaded or coerced the other partner. Ethically unacceptable decisions lie at the other end of the continuum, where the man hijacks the decision making with little or no input from the woman (Osamor & Grady, 2018).

Non-Maleficence and Beneficence

Yet another proposed motivation for implementing preconception ECS has been to diminish suffering by reducing the birth of babies with severe genetic diseases (De Wert et al., 2012). This follows the ethical principle of non-maleficence as described by Beauchamp and Childress (2001). Commentators have argued that parents hold a responsibility not to cause and protect their children from harm. They should love and care as well as provide for their basic necessities (Clarkeburn, 2000; van der Zee & De Beaufort, 2011).

By extending the principle of non-maleficence to *potential* parents, one could argue that individuals also hold a responsibility for the wellbeing of their children-to-be and thereby have a duty to protect these prospective children from harm. Such responsibility would include, but is not limited to, couples undergoing preconception testing for risks of debilitating diseases. However, this obligation would not apply to cases of "accidental" parents who were not planning a pregnancy. In fact, Van der Zee and Beaufort, have gone as far as arguing for all pregnancies to be planned, since accidental pregnancies could present a public health risk (van der Zee & De Beaufort, 2011).

In relation to the principle of non-maleficence, Clarkeburn (2000) developed the concept of parental duties associated with prenatal screening. Her argument is that parental duties should include not only non-maleficence but beneficence as well. The debate is relevant and can be extended to preconception ECS. In her article, Clarkeburn defined harm as "setting back the interests of one party by intentional and unintentional actions on behalf of another party". She further explained the term "welfare interests" as basic, which, if hindered, do not allow for advancement of any other interests, thus resulting in adversely affecting one's wellbeing. To her, severe genetic disease interferes with welfare interests of a person and consequently their existence (Clarkeburn, 2000).

To Clarkeburn, pregnancy could be classified as a harmful if it results in a child affected by a severe genetic disease. The question that arises is whether the non-existence of this baby with the severe ailment is better than his/her existence. To answer this question, Clarkeburn examines the criteria for life worthy of living, which includes, but is not limited to being able to "see oneself existing over time and a necessity to have self-awareness, self-control, and a capacity to relate to others". Violating such criteria, though, does not make a life worse than non-existence, because a person can still attain some sense of pleasure. So the author adds persistent severe non-curable pain to the criteria. In short, if there is a risk of giving birth to a child with severe mental disabilities associated with non-stop severe pain, his/her life would be considered as worse than non-existence. It is the moral duty of parents, following the beneficence principle, to prevent such existence (Clarkeburn, 2000).

The principle of beneficence has, also, been discussed in relation to preconception ECS. Savulescu and Kahane (2009) have proposed the concept of "procreative beneficence" (PB), which states that potential parents are, to an extent, morally required to give birth to the best possible child. Ensuring a minimum of well-being of a child-to-be is not enough, but parents should make use of all existing medical and non-medical information to choose the most advantageous child. Here, the parents have to select from among available children's traits to achieve the best outcome. Nevertheless, the concept is not absolute. Savulescu & Kahane (2009) emphasized that the principle is applicable so long as there are no "stronger" contending issues, for example, that the selection process can pose harm to parents or existing children.

Unsurprisingly, the PB principle has been under extensive criticism. Some commentators pointed out the adverse implications of such a principle, such as promoting discrimination against the (mentally and physically) handicapped (Bennett, 2014), supporting a new era of eugenics (Shakespeare, 1998), and challenging reproductive autonomy when one considers it as a moral obligation to give birth to the best possible child (Bennett, 2009). Other commentators contended the argument behind the principle. For instance defining a "best" child would be a challenge in practical terms (Herissone-Kelly, 2006). Rebecca Bennett deemed the notion of impersonal (or non-person)

harm upon which PB is founded as flawed, because harm can be morally wrong only if it affects existing persons. In the case of PB, the harmed ones do not yet exist, and therefore parents' selection of an embryo and not the other is regarded as a "preference". Such preferences should be morally neutral (Bennett, 2009).

Discrimination and Stigmatization

It has been argued that individuals with predisposition or carrier status of genetic diseases are at risk of genetic discrimination if their genetic make-up was revealed to third parties, such as employers or health insurance companies or government organizations. Such disclosure of information can affect the education or employment opportunities of those discriminated against. The discrimination may extend to stigmatization and shunning of carriers of certain genetic diseases (Burke, Coughlin, Lee, Weed, & Khoury, 2001; Hodge, 2004; Lea, Williams, & Donahue, 2005). Though carriers of AR diseases do not exhibit the disease phenotype, their genes carry the defect. This is in contrast with autosomal dominant diseases, where a genotype is mostly expressed phenotypically (Marcus, 2010).

One cause attributed to stigmatization and discrimination against carriers is genetic exceptionalism**,** which is handling genetic information differently from other clinical data and supporting the call for stricter privacy and protection of genetic results. Such procedures, it has been argued, may enhance the stigma associated with genetic testing (Hodge, 2004).

Among the ethical concerns raised in the literature are discrimination against disability and the fear of eugenic practices, in association with reproductive genetic screening. The claim is that if we screen against potentially disabling genetic diseases, this would increase the discrimination against currently existing people with the disease, as well as those couples who decide to bring a disabled child to life (Scully, 2008). Moreover, the author argues that the claim that state sponsored preconception screening increases reproductive choices of parents are in effect guiding people to improve the overall genetic pool. This is a form of eugenic practice affecting human genetic diversity unfavorably. Another concern raised is that such programs direct the focus and resources towards research to cure genetically-based disability only and shrug off other causes of disability (Scully, 2008).

Also the question of preconception sex selection has been debated. Sex selection can be carried out for medical reasons; for example, testing for X-linked diseases that primarily affect male offspring, such as Duchene Muscle Dystrophy. It could also be carried out for non-medical reasons such as choosing to give birth to boys over girls. The justification for such procedures is respecting parental reproductive autonomy and allowing families to decide the sex distribution among their offspring (Robertson, 2001).

Arguments against non-medical preconception sex selection include the risk of enhancing sexism, disruption of sex ratios, and the risk of demeaning

women's status particularly in patriarchal societies (Robertson, 2001). Also, disrupting birth order and, since tests are not perfectly accurate, a child of different sex may be born into a family that does not want him/her, have also been debated. Furthermore, inappropriate use of limited medical resources, the "playing God" argument, and the risk of social injustice are other arguments raised against this practice (Kalfoglou, Kammersell, Philpott, & Dahl, 2013).

Uncertainty of Genetic Test Results

Expanded screening panels detect disease either using genotyping or DNA sequencing. Genotyping detects with high accuracy well-established disease-producing mutations, while DNA sequencing, additionally, spots harmless variants, ones with unclear effect on gene function or ones with variable expression of a disease phenotype. Consequently, with the latter technique, practitioners cannot ascertain if some variants would lead to a disease phenotype (Edwards et al., 2015). In addition, there are many variants that have not yet been described at molecular level and as thus unknown to geneticists if they are disease-producing ones (Henneman et al., 2016) As a result, uncertainty associated with results depends on the technology used in ECS panels.

Furthermore, many commentators have stated the ineffectiveness of some genetic tests to detect all possible gene mutations and identify accurately predictive values for the genes expressing disease phenotypes are mostly due to lack of information regarding prevalence (Burke et al., 2001; Hodge, 2004; Lea et al., 2005). Such uncertainties can potentially affect parental reproductive autonomy and subsequently, their reproductive choices.

To address these setbacks, professional organizations in the USA and EU, have issued recommendations to laboratories designing panels and healthcare professional prescribing them. Test panels should include only disease-producing and probable-disease producing variants that are pertinent to the population where residual risk for negative screen parents is known. If not available, companies should continuously update their residual risk information when feasible. This would reduce the number of individuals requiring follow up and counseling. Moreover, the tests offered should have a "validated clinical association between the mutation(s) detected and the severity of the disorder" (Edwards et al., 2015; Grody et al., 2013; Henneman et al., 2016).

Medicalization

Medicalization has been mentioned as an ethical concern in relation to preconception ECS (De Wert et al., 2012). The term was portrayed prominently in sociology literature since the 1960s and more recently in anthropology, medical and public health literature, and lastly but not least in bioethics. In sociology the prominent depiction of medicalization has been "medicine as an institution of social control". At the time, defining deviant or eccentric behavior as a psychiatric problem was under criticism and was viewed as a form of

control by the medical institution (Conrad, 2013). According to Sadler et al., (2009), medicalization "describes a process by which human problems come to be defined and treated as medical problems". These definitions were criticized for being conflated into one medical model only.

In fact medicalization encompasses two distinctive processes: one of description and diagnosis and one of therapy and intervention. The former has been described as *pathologization* while the latter is *medicalization*. There are instances where either concepts occur independently of each other or where pathologization happens as a part of medicalization (Sholl, 2017). One example of pathologization without medicalization is when an individual declines prescribed treatments or doctors withdraw therapy from terminally ill patients because they are deemed more harmful. An example of medicalization without pathologization is the offer of numerous investigations to assess risk of genetic or cardiac disease or hypertension, to persons who are deemed *likely to* develop the disease but have not yet (Sholl, 2017).

In relation to reproduction, commentators believe many of its aspects have been medicalized; for example, conception and infertility by Assisted Reproductive Technologies (ART), prenatal care and contraception, abortion and child birth (Holm, 2009). In fact, prenatal medical care has been regarded as an example of medicalization of pregnancy without pathologization (Sholl, 2017).

Medicalization has various impacts, the most significant one being reduce suffering even in the absence of curative treatment. Another is achieving more control of one's life, the most prominent example is women's access to contraceptive pills. Pathologization, on the other hand, endorses certain social safeguards, allows certain concessions for afflicted individuals and redirects the blame toward the ailment rather than the individual (Sholl, 2017).

Attempts have been made in recent literature to formulate medicalization as a neutral construct and assess individual instances of medicalization as either good or bad (Parens, 2013; Sadler et al., 2009).

Rationale

With the advent of new reproductive technologies, families are given numerous reproductive options and thus, some believe, have more responsibility to select the right option, which is expected to comply with their medical/genetic status as well as with their beliefs and moral outlook.

Preconception ECS is a new genetic screening approach that is being considered in pilot studies and can potentially be offered to the general population in European countries. Though bioethical analysis has commonly been faulted for lagging behind while new technologies are introduced and implemented, (Shapiro, 1999) in the case of preconception ECS, it is taking the lead. Therefore, it is timely to describe and discuss ethical and social issues that are associated with preconception ECS particularly in the context of the Swedish public healthcare system. To our knowledge, there are very few empirical studies performed on the topic in Sweden (Ekstrand Ragnar, Tydén, Kihlbom, & Larsson, 2016).

Aims

The general aim of the project was to explore and critically discuss some of the ethical and social implications concerning preconception ECS from the perspectives of stakeholders and experts. Against the background of earlier ethical debates concerning preconception ECS, we sought to obtain the perspectives and opinions of some of the Swedish stakeholders who are anticipated to be involved in the implementation process, such as healthcare providers (for example: clinical geneticists, gynaecologists) and policymakers. The empirical results are intended to form the basis for theoretical reflection on some of the ethical and social concerns raised during the studies.

Specific Aims

Study I

To explore and describe Swedish healthcare professionals' perceptions of preconception ECS with focus on the ethical aspects of the technique.

Study II

To develop a normative interpretation of couples' autonomous decisions in the context of reproductive technologies in general and of preconception ECS in particular, while still acknowledging that it is essentially individuals that are autonomous.

Study III

To explore and describe how healthcare policymaking experts perceive ethical and social aspects of preconception ECS as a health technology (HT).

Study IV

To investigate values and value conflicts that experts recounted in relation to implementation and use of preconception ECS. In addition, to examine if experts assign different weights to the values they disclosed.

Methods

In this dissertation, we utilized both empirical and ethical analysis methods to examine ethical and social implications surrounding potential implementation and use of preconception ECS in Sweden. The results of the empirical method employed in Study I provided the base for normative analysis of concepts in Study II.

Article III and article IV were based on the same data set of healthcare policymaking experts, while the former investigated ethical and social implications for preconception ECS use and implementation in Sweden, the later identified values and value conflicts in the same study (Table 1).

Table 1. An overview of the methods used in Study I – Study IV

Study	Method	Data collection	Participants	Analysis
Study I	Qualitative	In depth interviews	Healthcare professionals (n = 11)	Content analysis
Study II	Ethical analysis	N/A	N/A	Conceptual analysis
Study III	Qualitative	Expert interviews	Healthcare policymakers (n = 10)	Thematic analysis
Study IV	Qualitative	Expert interviews	Healthcare policymakers (n = 10)	Thematic analysis

Study I

Study I had a qualitative descriptive design where in-depth interviews were employed.

Participants

We contacted eighteen healthcare professionals and eleven agreed to take part in the study. The participants included three gynecologists, three obstetricians (sub-specialty in fetal medicine), two clinical geneticists, a pediatrician, a

midwife and a genetic counselor from major hospitals and university hospitals Sweden (Table 2).

Table 2. Characteristics of participants in Study I

Specialty	Obstetrician/fetal medicine	Gynecologist	Clinical geneticist	Pediatrician	Genetic counselor	Midwife
Number	3	3	2	1	1	1

Duration of practice	0- 10 yrs	11 - 20 yrs	Above 20 yrs	Total
Number of professionals	5	2	4	11

Gender	Male	Female	Total
Number	4	7	11

Data collection

Data was collected from healthcare professionals during September 2014 until February 2015. An interview guide with semi-structured questions was designed after review of the main literature The interview guide was divided into four main sections; the first part addressed healthcare professionals' background and the remaining parts examined their views on the potential effects of preconception ECS on the individual/parents, the healthcare system and the society respectively (Table 3).

Table 3: Outline of the interview guide for Study I

Section	**Main questions**
Background information	• Specialty, duration of practice, previous knowledge of preconception ECS .
Challenges to parents/couples	• Preconception ECS and reproductive choices. • Preconception ECS and parental responsibility. • Preconception ECS and potentially complicating a natural process such as pregnancy. • Preconception ECS and couple's perception of pressure to test.
Challenges to healthcare system	• Main challenges for healthcare professionals if preconception ECS were offered. • Positive aspects for healthcare professionals if a preconception ECS program were to be implemented. • What should we be screening for in preconception ECS? What kind of diseases?

Challenges to the society	• Possible motives behind offering preconception ECS as part of healthcare system? What do you think of such motives? Why? • Do you think governments should include preconception ECS as part of basic healthcare system? Do you think it is feasible to have such a program? • Potential societal effects. • Preconception ECS and eugenic practices. • Preconception ECS and discrimination against the disabled

Procedures

Initially, informal interviews were carried out with a gynecologist and a clinical geneticist in order to decide which medical specialties to include in the study. The advice was to engage gynecologists, clinical geneticists, midwives, and pediatricians because they were expected to be the first line of contact with potential parents in case of implementation of preconception ECS. A participant list was drawn up by suggestions made during the informal meeting, followed by a snowballing approach to choose the remainder healthcare providers for the study. They were invited to partake in the research via an email, to which an overview of the project and its aims were attached. All the interviews were conducted in English. Ethical considerations of human subject research such as voluntary participation and confidentiality of data, were respected during the study.

Analysis

The interviews were recorded, transcribed verbatim by a transcription company and reviewed. The text was analyzed applying content analysis as described by Graneheim and Lundman (Graneheim & Lundman, 2004), where the focus was primarily on the manifest content to interpret the data. First, the transcripts were read through, meaning units were marked and preliminary codes were designated. Next, via a word processing document, meaning units were collected, condensed, and abstracted to codes, subcategories, and lastly categories.

Study II

In this study, a practical problem in the context of preconception ECS has been identified. The problem concerns a couple that has to make a conjoint decision regarding undergoing a preconception ECS test yet still uphold their individual reproductive autonomy. The healthcare professional is expected to respect each of the couple's individual reproductive autonomy on one hand, and yet s/he is presented with a conjoint reproductive decision from the couple. The

individualized notion of autonomy does not really address the question of conjoint decision-making (See scenario 1).

Based on this example the following research question was formulated: How can a couple make a conjoint autonomous decision while still maintaining their own individual reproductive autonomy?

There is little in the bioethical literature to address such an issue, which is partly conceptual and relate to reproductive autonomy and relational autonomy and partly a normative discussion, particularly when addressing problematic cases.

In order to answer the research question, conceptual analysis of reproductive autonomy and relational autonomy was performed. This was followed by analysis of some argumentation as has been presented in the literature followed by critical discussion and lastly a suggestion of a formulation of reproductive autonomy.

Scenario 1

Partner A and partner B have been thinking of having a baby for a while, but they are worried. Partner A's best friend Linda has recently given birth to a baby with X, a severe genetic disease. This was completely unexpected, as neither Linda nor her husband had a positive family history of the disease. Partner A and partner B plan a visit to their family doctor to discuss their concerns of begetting a child with a similar condition or another severe disease. Neither knows of a history of a genetic disease in their families. During their visit, the family doctor informs them about a preconception test for severe autosomal recessive genetic diseases and explains the test procedure, risks and benefits and the available reproductive options in case of positive results.

Study III and IV

In article III and IV, the expert interview was employed as a data collection method. It is a new approach, where research subjects are selected based on their expertise and knowledge in a certain subject (Bogner & Menz, 2009). In our case, it was the field of ethical evaluation of health procedures and technologies.

Participants

Out of thirty experts we contacted, ten agreed to take part in our study. All of the experts served on governmental and non-governmental boards that can impact healthcare policymaking in Sweden. These committees addressed,

among other things, ethical and social aspects of proposed healthcare procedures either as part of their primary operation, or via subcommittees.

The interviewees were chosen as supported by the social representation view of an expert defined in Bogner and Menz (Bogner & Menz, 2009). There were six males and four females. Their profession and affiliations are described in table 4.

Table 4. Characteristics of participants in Study III and IV

Profession	Committee	Gender
• 4 Physicians • 3 bioethicists • 1 legal expert • 1 theologian • 1 political party representative	• SMER • SBU regional board • Ethical board of Socialstyrelsen • Swedish Society of Medicine • Swedish Medical Association	• 4 females • 6 males

Data collection

The main purpose of collecting data from experts was to obtain their process and interpretative knowledge. Process knowledge describes practical experience of the expert, such as procedures and routines, while interpretative knowledge explains experts' decisions, interpretations, opinions, subjective reasoning etc. (Bogner, Littig, & Menz, 2009).

Data was collected from February to November, 2017. Initially, the contact details of the experts were acquired via websites of the different committees, after which we used snowballing to obtain interviewees details. A semi-structured questionnaire was drafted after thorough review of literature and was revised and accepted by all authors. The interview guide, composed of open ended questions, was divided into 3 sections; questions on the background of experts, healthcare decision making, and ethical and social aspects of preconception ECS (Table 5).

Table 5. Interview guide for Study III and IV

Section	Questions
Background	• Professional background, function as policymaker, description of their role as policymaker. • Have you heard of preconception ECS? If yes, in what context?

Healthcare decision making	• What would influence/impact your judgment in assessing preconception ECS? Are there certain ideologies? Values? Interests you would keep in consideration? What are they? • Would you advocate for public engagement in deciding on implementing preconception ECS in Sweden? Why and to what extent? • What type of research do you need to consider in evaluating preconception ECS? • What about economic considerations? In case of situations with limited resources, should preconception ECS be prioritized? Why?
Preconception ECS	• Can you think of any value conflicts when deciding on preconception ECS? What are these values and what obstacles can you foresee? • From your perspectives, what are the ethical issues to consider when evaluating preconception ECS? • From your perspectives, what are the social issues to consider when evaluating preconception ECS? • From your point of view, what are the positive consequences generated by implementing preconception expanded carrier screening? For parents, for healthcare system? For society? • What are the potentially negative consequences? For parents, for healthcare system? For society? • What would make Swedish healthcare consider implementation of preconception ECS? What is your stance on that?

Procedures

An invitation email was sent to all experts with an overview of the study, where aims and concepts were explained. Upon approval by the expert, a time and date was scheduled for the interview, where privacy of the interview was secured. The interviews were conducted in English and recorded, after which, they were transcribed verbatim by a transcription company. All the transcripts were double checked for accuracy of transcription. During the course of the study, ethical guidelines of human subject research were respected for example, voluntary participation, confidentiality of data etc.

Analysis

The transcripts were read through once, before we conducted an initial open coding. The codes were, then, grouped into major themes. Under each theme, the quotes were further analyzed to find subthemes. We were guided by thematic analysis as described by Ryan and Bernard (Ryan & Bernard, 2003). We utilized NVivo 11.4.3 software for the analysis.

For Study III, the analysis followed an inductive approach to locate the different themes and subthemes. The transcripts were cleared of the interview

questions and only answers to the questions were examined for major themes and subthemes.

In Study IV, by means of deductively inspired analysis, we conducted a secondary analysis on the transcripts from Study III. We identified texts referring to or describing moral values and principles in relation to preconception ECS. The definitions of values and principles were obtained from the literature addressing ethical values adopted in healthcare contexts. Some of the values or principles, we identified, ascribed to overarching values and we grouped them together as such (refer to section on findings).

Ethical Considerations

None of the studies in thesis required ethical approval per Swedish laws and regulations, because the studies did not handle sensitive personal information, nor encompass medical interventions and posed no physical or psychological risks to participants. In addition, our research subjects were authority figures; healthcare professionals and experts serving in a public capacity, which warranted no ethical approval from a research ethics committee (SFS, 2003).

Nevertheless, we followed the guidelines for conducting ethical research (General Assembly of the World Medical Association, 2014) by ensuring voluntariness of participation and obtaining informed consent from all interviewees after they received relevant information on the study. Additionally, we acquired participants' permission to record the interviews and maintained the confidentiality of data by securing the audios and transcripts in a password-protected computer that was only accessed by the researchers. The transcription company received audios assigned with numbers (1, 2, 3…) and cleared of any personal information such as names or professions to further secure confidentiality of data.

Summary of Findings

Study I

Healthcare professionals brought forward several ethical and non-ethical concerns. Six major categories were obtained, via a content analysis procedure. These were issues related to implementation, medicalization of pregnancy and parenthood, prioritization of healthcare funds, discrimination against the disabled, uncertainty associated with preconception ECS and lastly reproductive freedom. Under each of these categories, a couple of subcategories surfaced (Table 6).

Implementing preconception ECS was expected to become expensive and logistically burdensome for the Swedish healthcare system. Reaching informed consent with expanded panels was also seen as a challenge. Furthermore, some healthcare professionals believed that there is a risk that parents would feel a pressure to test, if preconception ECS were implemented. Finally, healthcare professionals also expressed worries that preconception ECS would increase medicalization and strive for control of pregnancy and parenthood. However, it was also mentioned that preconception ECS might enhance reproductive autonomy and could reduce abortion incidence, since it allows parents to opt for alternative reproductive choices. Also, it may reduce workload of obstetricians dealing with intrauterine fetal diseases because such conditions could decrease.

Table 6. Findings of Study I

Categories	Subcategories
Implementation of preconception ECS	• Stakeholders • Effects • Motivations • Regulations
Medicalization	• Striving for control • Increased anxiety • Shift of paradigm
Prioritization	• Costs • Health equity
Discrimination	• Eugenics • Stigmatization

Uncertainty	• What should we test for? • Interpretations of results • Need for Information
Reproductive freedom	• Pressure to test • Responsibility

Study II

The theoretical discussion of autonomy resulted in a formulation of couple autonomy, which is a normative interpretation that sheds light on the interdependency, the shared values, emotions and goals and the relational aspect of decision making within a couple. If certain demands are met, couple's reproductive decision can be accepted by healthcare staff as autonomous (Table 7). The suggested demands on couple autonomy include that both partners are individually autonomous and that the decision is reached through a communication process which enables expression of concerns and preferences by each partner and free of coercion, manipulation and miscommunication. Further, the decision-making process should allow them enough time to weigh options and reach a decision that feels right for both parties; and, lastly, there is consensus over the final decision by both partners. In certain cases, one partner can autonomously transfer some aspects of the decision to the other partner. This characterization of couple autonomy aims to help resolve some of real-life scenarios occurring inside reproductive clinics.

Table 7. Proposed criteria for autonomous decisions made by a couple

A reproductive choice made by a couple is autonomous at the couple level if and only if:	
1	Both partners are individually autonomous.
2	The decision is reached through a communicative process characterized by for instance: a) Each feels free to express his or her concerns and preferences so no one partner dominates the discussion, either by coercion or manipulation b) There is adequate time for the couple to negotiate possible differences and conclude that the decision is right for them. c) The final decision is reached through consensus of both partners, where persuasion may be used
3	One partner can autonomously transfer aspects of the decision to the other partner (e.g., permit some of the features above to be less prominent).

Study III

According to policymakers, Sweden presently is not ready to incorporate a preconception ECS program in its healthcare system. This is due to several ethical and social concerns as delivered by the study. The main motivation for

ECS, as advocated by European Society of Human Genetics, is facilitating informed reproductive decision-making, which respondents regarded as a dubious reason to spend taxpayers' money on. In addition, respondents were afraid of potential long-term consequences of preconception ECS on Swedish values, such as prizing human dignity and allocating priority of care to the most vulnerable.

However, respondents acknowledged the different stakeholders and were open to engaging the public's views in the policymaking process. This is a way to combat the current status of healthcare policymaking in Sweden, which was viewed to rely mainly on politicians, experts, and authoritative entities. Moreover, they recognized the potential influences of EU and worldwide healthcare policies on the Swedish ones (Table 8).

Table 8. Findings of Study III

Themes	Subthemes
Economics	• Alternative financing • Prioritization of resources • Reduce cost for healthcare
Political considerations	• International context • Swedish context
Considerations of implementing preconception ECS	• Interests groups • Preparation • Post screening measures • Quality of service • Anti-preconception ECS views and alternatives
Role of public engagement	• Who? • How? • Why?
Research	• Research on ethical issues • Health economics research • Research in relation to test panel
Responsibility	• Parental responsibility • Societal responsibility • Responsibilization
Societal effects	• A disabled friendly society • A perfect society • Long term effects

Study IV

The analysis of the interviews disclosed that respect for persons, solidarity, human dignity, do no harm, health, love and trust were the main values mentioned by experts (Table 9). In addition, they discussed value conflicts between autonomy and integrity, and, for instance, priority setting and human dignity. Moreover, the analysis revealed that certain values were deemed more

important than others, judging by the extent and frequency of occurrence; for example, respect for persons and solidarity were on top of the list (figure 1).

We also examined how experts described various values and principles and compared them to definitions existing in bioethical literature with special emphasis on European bioethics and regulations. As these were mostly in agreement, it can be concluded that experts highlighted values and concepts that are distinctive of welfare states such as Sweden.

Table 9. Themes and subthemes for Study IV

	Themes	**Subthemes**
Values	Respect for persons	Autonomy
		Integrity
		Privacy
	Trust	
	Love	
	Solidarity	Justice
		Equality
		Social Care
	Health	
	Do no harm	Parental worry
		Reduce suffering
	Human dignity	Tolerance

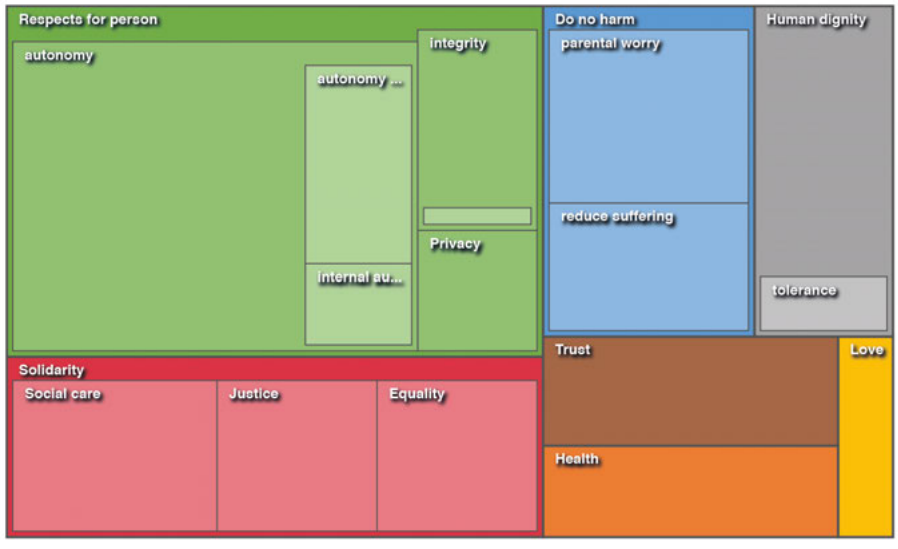

Figure 1. A tree map illustrating the results of Study IV. Each color denotes a theme and the lighter colors within the theme denote subthemes. Judging by the number/size of quotes respect for persons and solidarity are the largest two themes.

Discussion

This dissertation contributes to the current ELSI (ethical, legal and social implications) debate on preconception ECS with emphasis on a Swedish milieu. The question in the title of the thesis - “considering a baby?" demonstrates a prospective consideration for parents-to-be who are expected to be offered the screening test. The second part of the title - “responsible screening for the future” - reflects the effort within the dissertation to propose an ethically and a socially acceptable way to screen parents-to-be preconceptionally using expanded screening panels in Sweden.

Preconception ECS is regarded more advantageous to prenatal screening because it offers alternative reproductive options to termination of pregnancy (gamete donor, change of partners and IVF & PGD) and bypasses the small time window available for parents to undertake often complex decisions resulting in either termination of pregnancy or delivering an affected child (Langlois, Benn, & Wilkins-Haug, 2015). In addition, prenatal screening examines a pregnant woman and not a couple, and therefore informed consent is expected to be communicated by her primarily. Moreover, prenatal screening in Sweden encompasses testing for trisomies only, and not a list of AR conditions on a test panel as expected in ECS (Vårdguiden 1177, 2018).

The main findings, elicited by the studies in this thesis, echo to a great extent the prevailing ethical and social concerns associated with the novel technology (De Wert et al., 2012; Henneman et al., 2016; Holtkamp et al., 2017; van der Hout et al., 2017). In addition, stakeholders (healthcare professionals and experts) in our studies called attention to non-ethical implications such as lack of personnel. Furthermore, healthcare professionals in Study I raised similar issues to those described by experts in Study III. Nevertheless, each group put emphasis on certain themes more than others.

Regarding implementation of a preconception ECS program in Sweden, both studied groups elaborated on who the stakeholders are. While healthcare professionals acknowledged three stakeholders: Politicians, parents and themselves, experts identified additionally many “interests groups,” which included patients organizations, commercial and professional entities. Both groups cautioned against commercial interests driving the implementation process and as thus endorsing a mostly for-profit agenda rather than fulfilling a medical need. Moreover, they endorsed proper evaluation of the program and establishing good quality of its service.

Additionally, both groups communicated the significance of adequately assessing preconception ECS in terms of prioritization of health resources, to ensure that the program would not deplete resources from areas with more urgent needs. However, healthcare professionals recognized that such a function lies within the politicians' domain and medical personnel is responsible for providing best possible care to patients without regard to costs. In addition, concepts of justice and equity in management and distribution of preconception ECS services were of paramount importance to both stakeholders.

Conventional screening is offered to high-risk groups which are often identified based on ethnicity. Proponents of ECS, stressed that ECS would be better suited to diverse, multi-ethnic populations, where it is becoming harder to determine a specific ethnic background (van der Hout et al., 2017). However, neither healthcare professionals nor experts, in our studies, regarded ECS as an opportunity for an "equitable access to genomic technology" when it is set up.

Likewise, both healthcare professionals and experts in this thesis required more information and research on preconception ECS to dispel much of the uncertainty associated with it. This included the science behind it, analysis of potential ethical and social effects and the economics of implementing it. The research ideally would not only examine the Swedish context, but other countries as well. Evidently much of the uncertainty can be attributed to the fact that most of the research participants were unaware of the new technology. This was confounded by the scarcity of studies at the time of the inquiry, particularly during Study I.

Since then, however, much more research have been performed and elucidated the complexity of the technology. There are many aspects to assess (Chokoshvili, Janssens, Vears, & Borry, 2016; Edwards et al., 2015; Henneman et al., 2016; Lazarin et al., 2014) such as,

- the type of technology used (NGS or monogenetic test);
- analytic validity;
- the characteristics of diseases to screen for;
- clinical validity and utility;
- professional guidelines to comply with.

For example, the clinical utility of ECS was examined among adopted persons (Spencer, Ewing, Calcagno, & O'Neill, 2018) and at-risk couples who carried the same severe genetic condition (Ghiossi, Goldberg, Haque, Lazarin, & Wong, 2018). Since many adoptees might have insufficient information on their biological family history or their ethnic background, ECS may prove useful to them. The study surveyed 124 adoptees' attitudes and opinions on the utility of ECS to identify their procreative risks. Most of the adoptees were in favor of use of ECS regardless of their knowledge of medical family history, and were willing to pay a reasonable amount, out of pocket, for the service

(Spencer et al., 2018). In the other study, the demographics of the identified 64 couples-at-risk were largely Caucasian, with a university degree and well-to-do. Out of 45 non-pregnant couples-at-risk, 28 have altered their reproductive decisions following test-positive results for a severe condition using preconception ECS, while 13 couples did not adjust their plans and 4 couples were undecided at the time of the study. (Ghiossi et al., 2018).

Furthermore, some form of consensus has been reached regarding the characterization of recessive conditions to screen for: Severe diseases, early-onset conditions, those leading to substantial cognitive and physical disability or low quality of life (Chokoshvili et al., 2016; Edwards et al., 2015; Henneman et al., 2016). Moreover, Consyl, a commercial entity offering preconception ECS, formulated an algorithm based on responses of 192 healthcare professionals to classify genetic diseases according to severity into: Profound, severe, moderate and mild, where factors such as cognitive disability and early onset of mortality contributed to severity of disease (Lazarin et al., 2014).

The notion of *responsibility* surfaced while interviewing both groups in our project. Experts regarded the offer of preconception ECS as an opportunity and assigned no responsibility for parents to get screened. This was reiterated by healthcare professionals, who viewed the designation of responsibility as a form of "compulsion" to test and accordingly tamper with parental autonomy. Comparable ideas were described in a similar study conducted in the Netherlands, where the societal view on "reproductive responsibility" would alter with programs such as preconception ECS, so that couples would feel obligated to get screened against their own wishes. Another potential result was disinclination of society to look after affected children, hence coercing parents to screen and making reproductive decisions that do not comply with their beliefs and values (van der Hout et al., 2017).

The stakeholders in our studies brought up two comparable notions; namely *striving for control* (healthcare professionals) and *seeking a perfect society* (experts). They are similar because they reflect the general tendency to desire more control, whether by an individual, a family or by a society. This inclination has become more pronounced within healthcare contexts where some commentators stated that medicalization of "at-risk" individuals is occurring (Sholl, 2017). In the case of preconception ECS, parents want to control the traits of their offspring, and society assists with such an endeavor to control risks of diseases in generations-to-be.

Even though there is no corresponding study on value and value conflicts carried out with healthcare professionals, the analysis identified two values that have been deliberated upon by healthcare professionals and policymakers: Reproductive autonomy and health equity. Healthcare professionals referred to reproductive autonomy by words such as informed decisions, reproductive choices and reproductive freedom. Moreover, as policymakers, healthcare professionals underlined the importance of voluntariness of participation in

such programs without any pressure to test by the society or the healthcare system. Policymakers were more detailed in their discussion of autonomy as indicated in Study IV.

Health equity was the second value highlighted by both stakeholders. There was worry that preconception ECS would increase health inequity between the *have* and *have not*, on one hand if it is offered by private companies, or it would import health inequalities hitherto existing in the society on to the screening program, on the other hand. Thus, more advantaged socio-economic classes would benefit most from it. The studies also revealed that much attention was given to values such as justice and health equity of health resources as to be expected in a welfare state.

The previous paragraphs described the results that were common between the two groups of stakeholders. However, there were also differences. Healthcare professionals have raised notions alluding to medicalization and even geneticization, which were deemed less important to policymakers. Moreover, discussion of discrimination, a main theme for healthcare professionals, was only hinted at as a long term societal effect by experts.

The themes of *role of public engagement* and *political considerations both within Sweden and internationally*, were of concerns for experts only. These aspects are particularly relevant to the Swedish context and seldom mentioned in previous research. Engaging the public in healthcare matters and Health Technology Assessment (HTA), especially those with ethical and social implications, should gain more prominence in Sweden, where currently only experts' and politicians' input are effectual. Other European countries such as Germany, France and the UK, have well-established public engagement procedures to influence health policy and HTA (Kreis & Schmidt, 2013).

Political considerations referred to effects such as free movement within EU would have on Swedish parents-to-be. Swedish couples could access preconception programs in other EU countries, in case of non-implementation in Sweden. Another political aspect mentioned was the employment of "Swedish values" such as solidarity, human dignity and equality, in appraising new technologies. However, such appraisal could be still influenced by uptake of such programs elsewhere, like in the USA or within the EU.

Discussion of Methodology

The use of empirical methods in ethics, such as those employed in this thesis, has always been under scrutiny and criticism. Commentators usually debate the function and the setting of empirical methods in relation to ethical theory. Nevertheless, many ethicists recognize the value of incorporating empirical research within ethics, as it serves several functions, which include describing, appraising, explaining and improving a particular social practice, as well as

contributing to moral theory or methodological development (Molewijk, Stiggelbout, Otten, Dupuis, & Kievit, 2004; van der Scheer & Widdershoven, 2004).

There are several approaches to harness empirical data in ethics, the most relevant of which to this thesis, is integrated empirical ethics. It involves the integration of descriptive and prescriptive disciplines, where empirical data acts as the subject of inquiry. In other words, there is deep interaction between empirical data and moral theory. The objective of using empirical data, within this approach, is primarily for interpretation or evaluation of a social practice or for methodological improvement (Molewijk et al., 2004). The interpretative goal is most pertinent for the purpose of this thesis, where qualitative methods of inquiry (Study I, III and IV) and ethical normative analysis (Study II) have been used.

Furthermore, preconception ECS is a novel technology and little to no research was available at the onset of the project, particularly studies addressing the Nordic countries. Therefore, the qualitative interpretative methodology of inquiry was deemed the most suitable. In addition, one of the aims of the dissertation is to examine and describe stakeholders' perspectives regarding social and ethical implications, which arguably are unquantifiable, further justifying the use of a qualitative scrutiny (Berg, 2000; Britten, 1995). In addition, the thesis incorporates a mix of methods, where different populations (healthcare professionals, experts) and hence different data sets, and analysis methods (content analysis, thematic analysis) were utilized, which by definition is triangulation of research (Berg, 2000). The use of triangulation is beneficial to identify the various vantage points of a concept or to study a phenomenon in depth or confirm accuracy of results (Berg, 2000; Hussein, 2009).

Moreover, we employed expert interviews for data collection to access specialty knowledge and obtain standpoints from crystalizing points of experience, namely the expert. Commentators uphold that the expert interview is less time consuming, can be a means for good quality data and experts can become a source for other appropriate informants. However, the method can reinforce assumptions underpinning social hierarchies without proper substantiation (Bogner et al., 2009).

Another key aim of the dissertation is to critically discuss some of the findings; this has been attended to in Study II and to a less extend in Study IV. There, an ethical reflection on reproductive autonomy, values and value conflicts in connection to preconception ECS was carried out.

Selection of subjects

At the start of the PhD project, an informal meeting was held with a gynecologist and a clinical geneticist, to identify the main healthcare actors that may

be connected to a setting of a preconception ECS program in Sweden . Their input formed the basis for selection of healthcare specialties in Study I.

The literature review that was carried out before Study I guided the design of the semi-structured questionnaire used for interviewing Swedish healthcare professionals. Furthermore, it directed our the attention towards a possible problem for healthcare professionals when they are counseling couples for preconception ECS. A couple makes conjoint decisions regarding reproductive choices, even though it is expected that each individual maintains their independent reproductive autonomy. This quandary was also consolidated by the results obtained in Study I. Accordingly, it was addressed in Study II via a conceptual analysis of autonomy-related notions such as reproductive autonomy and relational autonomy.

Moreover, healthcare professionals in Study I indicated the importance of insights from different stakeholders on preconception ECS, policymakers included. Consequently, we decided to examine their perspectives on ethical and social aspects of the proposed technology in Study III. To do so, it was suggested to interview members of SMER (Socialdepartementet, 2018), whose sole function is to evaluate ethical and social ramifications of new technologies. This was, however, reconsidered because most members declined our invitation to participate in the research. Fortunately, with further enquiry, I discovered that other governmental and non-governmental boards in Sweden assess ethical and social ramifications and influence the national government's policies.

Most policymakers in Study III repeatedly pointed to "Swedish values" in healthcare as well as laws and guidelines in place to protect these values. In addition, much data was generated during the interviews that warranted further analysis. As a result, it was decided that Study IV would attend to values and value conflicts as discussed by policymakers in association with preconception ECS.

Trustworthiness of qualitative methods

To reach trustworthiness of findings, *credibility, dependability, confirmability* and *transferability* should be considered in the method of inquiry. *Credibility* reflects the extent by which the method has captured the truth of what it is examining. *Transferability* indicates whether the findings are applicable to other contexts or other research subjects, while *dependability* denotes the consistency of results across similar settings or with similar research subjects. Lastly, *confirmability* signifies the extent to which the findings are a function of respondents and context, with limited influence by researcher's partialities or interests (Guba, 1981).

For each empirical study within this thesis, there is a detailed description of how aspects of trustworthiness were fulfilled. Nonetheless, when reflecting on the overall trustworthiness of the thesis, it is reasonable to claim that

credibility was improved by enrolling research subjects with different professions or specialties, genders, years of experience and serving on varying boards or hospitals. The goal was to capture the diverse perspectives on preconception ECS. Moreover, during the analysis process, attention was given to choose appropriate meaning units that best reflected the data, so they were neither redundant nor too vague. However, the meaning units were not always mutually exclusive so that some quotes could conceivably fit more than one category or theme (Graneheim & Lundman, 2004).

Regarding *dependability*, a complete and detailed description of the methods, selection of participants, and the use of peer reviewed analysis procedures have been incorporated in the studies. In addition, the sections on results have been enriched with direct quotes from respondents, as evidence for the meaning units selected. Moreover, some commentators stated that triangulation can add to dependability of findings, which we believe has been achieved in this thesis (Williams & Morrow, 2009). However, the users as a stakeholder, have not contributed to the findings, which can negatively affect dependability.

To achieve *confirmability*, Guba (1981) proposed two means; triangulation and reflexivity. Triangulation of different data sets, methods and analyses has been employed to examine preconception ECS. Moreover, during the course of the thesis, reflexivity was attained and expressed through regular meetings with the supervisors, which occurred periodically at the different stages of the research. The goal was to discuss and reflect on selection of participants, analytic processes and results and meaning units. Unfortunately, reflexivity procedure as described by Guba, has not been fulfilled.

Lastly, the final aspect of trustworthiness is *transferability*. Within this work the Swedish context was elaborated upon; the healthcare system; its governance and operation, functions of different advisory committees and relevant aspects of reproductive screening. Moreover, within the studies, findings were thoroughly delineated and supported by direct quotes from respondents. In this manner, readers and researchers can judge whether our data are applicable in similar contexts and settings (Graneheim & Lundman, 2004).

Conclusions

There have been claims that the bioethical discourse lags behind the implementation of new technologies (Shapiro, 1999). In the case of preconception ECS, bioethical inquiry is instead taking the lead. This thesis has contributed to the growing literature on preconception ECS. It focused on ethical and social implications of implementation and use in Sweden, a Nordic country with a welfare system.

The findings reiterate much of what has been discussed about ELSI of preconception ECS in the literature. However, some findings are pertinent to the Swedish context, such as practicalities of implementation and political considerations. Nonetheless, it is reasonable to claim that the findings steer towards non implementation of the new technology in its current status within the publicly-funded healthcare system, because healthcare providers and experts were of the opinion that it would not solve a medical need, threaten Swedish values and use up resources extensively.

There are a few possible outcomes as a result, one of which is people with the necessary means accessing the tests through commercial providers online, or across borders within EU countries. It is, therefore, difficult to imagine how that access could be effectively regulated. Consequently, many of the concerns leading to non-implementation could still be realized. Therefore, one can argue non implementation has not effectively protected Swedish values such as health equity, solidarity and human dignity. In fact, it reasonable to expect that new technologies would continuously emerge, each with its own ethical and social challenges. Therefore, a more pragmatic approach is suggested and that is to formulate a course of action that promotes dialogue, interaction and active participation within the society about values and ways to protect them.

Future Research

Though we acknowledge the importance of potential parents' input as a main stakeholder, as well as primary users of preconception ECS, due to time and financial constraints and anticipated practical obstacles such as translation from English to Swedish and vice versa, we have decided not to include parents' views in the present project. But as pointed out by healthcare professionals and experts, engaging potential parents is crucial. This can be achieved not only by conducting research utilizing citizen panels, in depth interviews, or vignette studies to obtain their perspectives and views, but also by public engagement procedures as a strategy to enable societal dialogue and strengthen democracy. As underlined by politicians, public engagement is lacking in Sweden and engaging parents in preconception ECS debate is an opportunity to institute this much needed practice.

A study comparing results as raised by each of the stakeholders - parents, policymakers and healthcare professionals - could prove beneficial to further understand what each group prioritized in terms of values and ethical and social implications of preconception ECS in Sweden. Additionally, conducting conceptual analysis of ethical notions such as medicalization, geneticization or responsibilization, in relation to preconception ECS may culminate in normative frameworks that could be useful and of practical function.

In fields other than bioethics, further research is needed to decrease the uncertainty surrounding the technique; for example to ensure accuracy of results, their clinical validity and utility; research on characteristic of disease to screen for; as well as the health economics aspects. The latter would encompass cost/benefit analysis; estimates of total cost, which should include the prices for training professionals, genetic counseling and treatments post testing such as PGD.

Moreover, sociological research may be required to address potential long term effects, the change in public mindset and intolerance, effects of what respondents named "genetic revolution" on parents, the society and the healthcare system.

Acknowledgments

There are many people that I will be forever grateful because of their continuous support and encouragement during the course of my PhD. The first and foremost is Anna T. Höglund, my supervisor who rescued me from despair and burn out. She was always accessible to give advice and guidance when all seemed lost. I thank you for your patience and your genuineness, your modesty and your happy smile, your thoroughness and professionality.

My gratitude is endless to Gunnar Fridborg my landlord, my driving instructor, my friend and my *fika* partner. Thanks for listening and being there when hopelessness hit.

I would like to express my gratefulness to colleagues and friends at the Center for Research Ethics and Bioethics, especially Heidi Howard, thank you for your support and encouragement, Jennifer Viberg Johansson, Mona Petterson, Mirko Ancilloti, Tove Godskesen, Kathinka Evers, Elisabeth Furberg, Stefan Eriksson, Joanna Stjernschantz Forsberg and Camilla Östergren. Thank you for the advice, pep talks and brainstorming sessions.

I would like to thank Ulrik Kihlbom, Mats G. Hansson and Pär Segerdahl for their contribution, input and advice on my thesis work. I also extend my thanks to Josepine Fernow and Anna Holm for their help on the best ways to present my work in conferences and to the public.

I am indebted forever to Henry Silverman, my mentor and role model. You had confidence in me and instructed me on how to be a researcher, a writer and a presenter. It was through your earnest mentoring and advice that I am able to achieve this milestone in my life.

To my sisters Amany, Ebtihal and Alaa Matar, you were my motivation and my inspiration and I appreciate your continuous support and love. I also thank my parents for their understanding and care.

Last but not least, I would like to express my gratitude to David Eller, for your love, support, patience and valuable advice.

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