Not just a carrier – A qualitative study of psychosocial aspects of women’s experiences of living with an X-linked disorder

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PhD Thesis

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List of papers

Paper I:
von der Lippe C, Frich JC, Harris A, Solbrække KN.
Experiences of being heterozygous for Fabry disease: A qualitative study.

Paper II:
von der Lippe C, Frich JC, Harris A, Solbrække KN.
“It was a lot tougher than I thought it would be.” A qualitative study on the changing nature of being a hemophilia carrier.

Paper III:
von der Lippe C, Frich JC, Harris A, Solbraekke KN.
Treatment of hemophilia: A qualitative study of mothers’ perspectives.
Abbreviations

DNA – Deoxyribonucleic acid
ERT – Enzyme replacement therapy
GLA – Galactosidase alpha gene
GL-3 – Globotriaosylceramide
HIV – Human immunodeficiency virus
NIPT – Noninvasive prenatal test
OMIM – Online Mendelian Inheritance in Man
PGD – Preimplantation genetic diagnosis
PND – Prenatal diagnostics
QoL – Quality of life
WES – Whole exome sequencing
WHO – World Health Organization
WMA – World Medical Association
XCI – X-chromosome inactivation
Abstract

Background
Hemophilia and Fabry disease are rare X-linked disorders. Women who are carriers for hemophilia are rarely symptomatic, but those who are heterozygous for a *GLA* mutation often experience manifestations of Fabry disease. A carrier for an X-linked genetic disorder may have a son with the disorder. There is a paucity of research on psychosocial experiences of carriers or heterozygotes for X-linked conditions.

Aim
The aim of this study is to provide knowledge on how women who are heterozygous for a *GLA* mutation or carriers for hemophilia experience psychosocial aspects related to Fabry disease or hemophilia.

Materials and Methods
This study is based on semi-structured interviews with 26 women heterozygous for a *GLA* mutation (n=10) and carriers for hemophilia (n=16). Participants were between 24 and 77 years of age and had different demographic, educational, work, and civil status characteristics. Each participant was asked about the experience of learning that she was a carrier for hemophilia or heterozygous for a *GLA* mutation and how she experiences having a child with hemophilia or Fabry disease. In addition, participants were queried about how they communicated about the genetic condition within their families, how the condition affected their family life, and how they experienced encounters with healthcare professionals. The interviews were coded inductively and analyzed using a thematic analytical approach.

Results
The findings in this study are presented in three papers. Paper I describes the relief women with Fabry disease felt upon learning that they were manifesting heterozygotes because their symptoms were explained. Recognizing symptoms related to their heterozygous status as an expression of the disease, resulted in a major change in how they identified themselves and in how healthcare professionals interpreted their complaints. Despite this, they wanted to separate the disease from their daily lives.
Gratitude for available treatment was universal. However, several challenges remain, such as the time needed to plan for and carry out treatment, and absences from work. The women found healthcare professionals’ lack of knowledge about Fabry disease frustrating and they expressed feelings of guilt for having passed on the family’s mutation to their children and grandchildren.

Paper II concerns women who are carriers for hemophilia and mothers of boys with the disorder. The women described how the experience of being a carrier changed over time. It meant less to them when they were young and became more significant when potential consequences became apparent, for example when reproductive issues arose. Many who were aware of their carrier status prior to having children thought they were prepared for having a son with hemophilia, but nonetheless experienced sadness upon diagnosis. Several women described feelings of guilt that plagued women and men in their families over several generations because they had passed on the family’s mutation.

Paper III explores experiences of women who are carriers for hemophilia and mothers of boys with the disorder, focusing on challenges associated with the treatment of their sons. Hospital-based treatment led to less flexibility for the family, and a greater feeling of illness and being abnormal. In contrast, home treatment provided advantages in terms of flexibility and a retained sense of normality. Many of the participants had experienced that healthcare professionals lacked knowledge about the disorder. In some instances, this resulted in deterioration in the relationships between mothers and physicians.

**Conclusions**

Overall, the study shows that learning one is a carrier does not seem to be a “turning point” for women without disease manifestations, but rather a process that develops over time dependent on specific situations. Symptomatic women, however, appreciated diagnostic clarification, as their complaints could then be recognized as disease-related. Almost all participants felt guilty about having transmitted a mutation to one or more subsequent generations. Furthermore, the study reveals that a lack of knowledge about hemophilia and Fabry disease among healthcare professionals can have a negative impact on communication between physicians and patients or parents of children with
rare disorders. In a worst-case scenario, it may result in patients or parents avoiding contact with healthcare professionals.

This study has identified several issues related to women’s psychosocial experiences of living with hemophilia and Fabry disease. Healthcare professionals communicating with women who are carriers for hemophilia or heterozygous for Fabry disease may use this knowledge in caring for these women, especially in the context of genetic counseling.
Sammendrag

Bakgrunn

Mål
Det overordnede målet med denne studien er å få kunnskap om hvordan kvinner som er heterozygote for en GLA mutasjon, eller bærer av hemofili, erfarer psykososiale aspekt ved Fabry sykdom eller hemofili.

Materiale og metoder
Denne studien er basert på semi-strukturerte intervjuer med 26 kvinner som er heterozygote for en GLA mutasjon (n=10) eller bærere av hemofili (n=16). Deltagerne var mellom 24 og 77 år, og hadde ulik bakgrunn med tanke på demografi, utdannelse, arbeid og sivil status. I intervjuene ble kvinnene bedt om å utdype hvordan de opplevde å få vite at de var bærer av hemofili, eller heterozygote for en GLA mutasjon, og hvordan de opplevede å ha et barn med hemofili eller Fabry sykdom. Videre ble de spurt om hvordan de kommuniserte om den genetiske tilstanden i familien, hvordan tilstanden påvirket familielivet, og hvordan de opplevde kontakt med helsevesenet. Intervjuene ble kodet induktivt og analysert med tematisk analyse.

Resultater
Funnene i denne studien er presentert i tre individuelle artikler. Artikkel I viser at kvinner som er heterozygote for en GLA mutasjon opplever det som positivt å få diagnosen Fabry sykdom, fordi de får en forklaring på symptomer som tidligere ikke har blitt gjenkjent som sykdom. Gjenkjenning av symptomer relatert til Fabry sykdom resulterte i en stor forandring i hvordan de identifiserte seg selv, og hvordan helsepersonell tolket plagene deres. Kvinnene var likevel opptatt av å skille sykdommen
fra livet ellers. Alle var takknemlige for tilgjengelig behandling, men beskrev flere utfordringer med behandling som tidsbruk til planlegging og gjennomføring av behandling, samt fravær fra jobb. Kvinnene var frustrert over helsepersonells mangel på kunnskap om Fabry sykdom og kvinnene uttrykte skyldfølelse for å ha ført genfeilen videre til barn og barnebarn.

Artikkel II omhandler kvinner som er bærere av hemofili og mor til en sønn med hemofili. Kvinnene beskrev hvordan opplevelsen av det å være bærer endret seg med tiden. Da de var unge tenkte de ikke så mye på at de var bærer. Det å være bærer ble først noe de tenkte mye på da det kunne ha en konsekvens, for eksempel når familieplanlegging ble aktuelt. Mange som visste de var bærer før de fikk barn, trodde de var forberedt på å få en sønn med diagnosen, men opplevde likevel tristhet og sorg da sønnen fikk diagnosen. Flere av kvinnene beskrev skyldfølelse både hos seg selv, og i foreldre-, og besteforeldregenerasjonen, for å føre familiens genfeil videre.


Konklusjon
Samlet sett viser studien at det å få en bærerdiagnose ikke synes å være et «vendepunkt» for de som ikke selv har symptomer på sykdommen, men snarere er en prosess som utvikler seg over tid som også er knyttet til hvor i livet man er. For de som hadde symptomer var det å få bekreftet en diagnose, og bli «trodd» på sine symptomer, et viktig vendepunkt som de satte pris på. Felles for tilnærmet alle deltagerne var skyldfølelse over å ha før mutasjonen videre til nye generasjoner. Studien viser også at det er mangel på kunnskap i helsevesenet om de sjeldne diagnosene hemofili og Fabry sykdom. Mangel på kunnskap kan føre til dårlig kommunikasjon mellom leger og pasienter eller foreldre til barn med sjeldne diagnoser. I verste fall kan dette føre til at pasientene unngår kontakt med helsevesenet.
Denne studien gir ny kunnskap om kvinners psykososiale erfaringer med hemofili og Fabry sykdom. Helsepersonell kan bruke denne kunnskapen i kommunikasjon med kvinner som er bærere av hemofili eller heterozygote for Fabry sykdom, spesielt i forbindelse med genetisk veiledning, for å ivareta kvinnene best mulig.
1. Preface

“The journey of a thousand miles begins with a single step” (Chinese proverb)

In 2010, after several years as a trainee and specialist in clinical genetics, I started to work at the Center for Rare Disorders, at Oslo University Hospital, a multidisciplinary, nationwide socio-medical-educational center that provides information, advice, counseling, and seminars. The center provides services for individuals with one of approximately 70 rare disorders, as well as for their families and professionals.

As a clinical geneticist, I was well aware of the usefulness of a genetic diagnosis. A precise etiological diagnosis is important for the individual as well as for the parents of an affected child with a rare disorder. I had experienced many times just how important this information is for families. I appreciated that a molecular diagnosis is the best basis for answering a family’s questions about central issues, such as medical follow-up, treatment, and the likelihood of recurrence. However, I was much less familiar with how affected individuals, parents and families live their daily lives with rare disorders.

In a clinical setting at a university hospital, a doctor has brief encounters with individuals and parents. Life for those are is lived outside the clinic. Clinics and hospitals are tailored to a large degree around the specialist’s agenda: she has questions to ask and information to provide. The nature and consequences of a mutation, mode of inheritance, and likelihood of recurrence are important subjects covered in a genetic consultation. If information about prognosis and treatment is available, this will often be discussed as well. If a national or international center has expertise relating to the disorder, this is also conveyed. For some diagnoses, like Fabry disease and hemophilia, Norwegian lay organizations exist. For other rare disorders, there are no such organizations. However, increasingly there are national, Scandinavian, and international Facebook-groups dedicated to specific rare and ultra-rare disorders. Such groups are commonly initiated by affected individuals or their parents.

Over the years my work at the Center for Rare Disorders made me increasingly cognizant of the fact that although the information discussed in a genetic consultation is important, it might not be sufficient. Information about “how to live with the disorder?”
and “what it really means to the individual and the family?” is just, if not more, important in daily life.

I had thought a great deal about the mothers of boys with X-linked disorders. A mother must deal with her son’s disease and may be affected herself. Additionally, she faces the realization that she carries the mutation that is the cause of her son’s disease. In my experience, genetic counseling often revolved around the genetic cause of the disorder and information about the disorder in the child, information about carrier status in the mother, and the risk of recurrence in future children, as well as possibilities for prenatal diagnostics. My impression was that discussions regarding mothers’ experiences related specifically to their carrier status were less frequent. In what ways does it affect the mother’s role as caregiver knowing she carries the mutation that caused her son’s disorder? To what extent do healthcare professionals support these women in a helpful and caring manner? These questions led to the research project: “Experiences of being a carrier for an X-linked disorder: A qualitative study.”
2. Background

In this chapter, I place genetics and inheritance in a wider historical context. I also elaborate on rare disorders, X-linked disorders, and X-linked inheritance and the two diagnoses explored in this study, hemophilia and Fabry disease. I believe it is important for the reader to understand these topics to appreciate the psychosocial aspects of being a carrier for hemophilia or heterozygous for a GLA mutation. In this thesis, “heterozygous for Fabry disease” denotes a woman with a heterozygous mutation in the GLA gene. Further, I introduce concepts central to this thesis, such as disease, illness, women, and their role as mothers and caregivers in a Norwegian context, communication and genetic counseling, and stigmatization in a genetic context. Finally, I argue why a study of the psychosocial aspects of women’s experiences of being a carrier for hemophilia or heterozygous for Fabry disease is important.

2.1. Historicizing genetics and inheritance

Genetics is a relatively new specialty in medicine worldwide and in Norway (1). Ideas about inheritance, however, are old. For centuries, people have been interested in how we inherit various characteristics. Even in Hippocrates’ (460–377 b. Ch.) time, people held theories about inheritance. Hippocrates and Aristoteles had theories about how traits were passed on from generation to generation, although they did not agree on the mechanism. Both hypotheses were incorrect. Lamarck (1744–1829) introduced the idea that acquired characteristics could be inherited (referred to as “Lamarckism”). People mocked this theory for years. However, the relatively new field of epigenetics has provided several examples of environmental influences that can result in inheritable changes (2). A few years after Lamarck proposed his theory, Charles Darwin (1809–1892) presented his theory of natural selection. In 1866, the publication of George Mendel’s (1822–1884) principles for autosomal recessive and autosomal dominant inheritance delineated the basic laws of Mendelian inheritance. With the introduction of the microscope in the late 1800s, researchers discovered cells and chromosomes. The years from 1940–1970 are often referred to as the deoxyribonucleic acid (DNA) era, when knowledge about genes and DNA grew. In 1953, James Crick and Francis C. Watson described DNA’s double helix structure, a discovery for which they received the Nobel Prize in 1963.
As a rule, the discovery of single-gene disorders in the 19th and 20th centuries was based on the description of a disease affecting one or more families. It was not yet known that mutations in single genes were at the root of these disorders. In the 1980–90s, researchers identified more and more single genes that when mutated, e.g., in Fabry disease and hemophilia, cause disease.

Since the 1970s, the field of genetics has developed at an incredible speed. In 2003, researchers finished mapping 99% of the human genome in the Human Genome Project (3). The genome is the total DNA content of a cell or an organism and the exome is the protein-coding portion of the DNA, which constitutes ~1.5% of the genome in humans. In monogenetic disorders, a change or changes in a single gene, confer a high likelihood of having or acquiring the disorder. The increasingly ubiquitous availability and the falling cost of genetic testing are increasing the demand for, and use of, this new technology. Possibilities for genetic testing in diagnostic laboratories have increased rapidly over the last 10–15 years and in 2009, Ng and colleagues described how exome sequencing can be utilized to identify the cause of monogenic disorders (4). Laboratories that offer exome sequencing lower their prices each year. A few years ago, the cost for whole exome sequencing (WES) for a single individual was several thousand US dollars; today it is approximately one thousand dollars (5). Doctors now use exome sequencing as a tool for investigating patients with a suspected monogenetic disorder, especially in pediatrics (6). With these rapid changes it is important to be aware that changes in technology may change our opinions about disease and health (7).

Genetics is a word with a complex meaning for many people. We are still very aware of events during the Second World War and the eugenic movement in general. Most people today strongly reject the idea that reproduction should be allowed or encouraged based on selected characteristics. This change in opinion is however recent; in the 1930–70s, for example, the Norwegian Sterilization Act allowed the government to order the sterilization of people with intellectual disabilities. Today’s sterilization Act §2 (8) allows people to choose sterilization if “because of a heredity cause there is a major risk for a child to inherit severe disease or blemish.” This is, however, voluntary. If a person carries a gene with a mutation that predisposes him/her to disease later in life (late-onset disease), or that may cause a disease in a future child, this is private information. Individuals who request predictive or carrier testing for a genetic disorder
must receive genetic counseling before, during, and after testing, as mandated by The Norwegian Biotechnology Act (9) chapter 5. Further, §5-8 in this act states that the result of predictive or presymptomatic testing is private information. An individual has no obligation to inform anyone of his or her result and is advised of this during genetic counseling. It is up to each individual to inform, or not to inform, relatives of his/her potential carrier status.

2.2. Rare disorders

Fabry disease and hemophilia are rare disorders. Rare disorders, also called orphan diseases, are medical conditions that affect a limited number of individuals. In Europe, a rare disease is defined by a population prevalence of <1:2,000 (10). In the USA, a disease is considered rare if it affects <200,000 (<1:1,600) individuals (11). In Norway, the definition is under debate. Currently, a disorder with a prevalence of ≤1:10,000 is considered as a rare condition (12).

Most rare disorders are genetic (13). They are often chronic and may have substantial physical and psychological impacts on the affected individual’s life (14, 15). Based on the European definition, there are more than 6,000 rare diseases (10), and it has been estimated that as many as 30 million Europeans have a rare disease (16). Each rare disease affects a quite limited number of individuals, but taken together, rare diseases are not rare.

Individuals with rare disorders commonly experience that healthcare providers (17-19) and society (20-22) lack knowledge about their disorders. For an individual or family with a rare disorder, it is common to experience diagnostic delay, lack of access to peer support, and lack of psychological support (19, 23). Delayed diagnosis may have negative consequences, such as treatment delays, inappropriate treatment, anxiety, and reduced options for reproductive decision making (20, 24, 25). The absence of a diagnosis may also lead to a denial of social services (21).

For a few but growing number of rare disorders, treatment that can substantially alter disease course is available. However, common to almost all rare diseases is the lack of a curative therapy (26). Another challenge with rare disorders is that research may be limited, often slow, and perhaps not prestigious. Treatment including medications can be very expensive (27, 28). Because of the lack of available treatments, individuals and
parents may be willing to try unproven treatments (19, 29).

Many countries have a national plan for rare disorders in an attempt to increase awareness, knowledge, and research (30). However, national plans often lack translation into actions (31). In other words, although many countries intend to prioritize rare disorders, not all are successful. Norway appreciates a need but has not yet implemented a national plan.

2.3. **X-linked disorders and X-linked inheritance**

The most common modes of inheritance in monogenic disorders are autosomal dominant, autosomal recessive, and X-linked. Fabry disease and hemophilia are X-linked disorders.

Humans have 23 pairs of chromosomes, including 22 autosomal pairs and either two X chromosomes or an X and a Y chromosome. Every gene resides in a consistent chromosomal location. Approximately 200 protein coding genes are estimated to be located on the X-chromosome. In an X-linked disorder, the causative mutation is in a gene located on the X chromosome. Women usually have two X chromosomes, while men have one X and one Y chromosome. Women therefore have two copies of the genes located on the X chromosome. Men have a single copy of the majority of X-linked genes and are therefore generally more vulnerable to X-linked disorders. Women are often “protected” by having a second copy of a mutated gene that does not harbor the mutation. If a woman has a mutation in one of her copies of a gene, she is heterozygous, or a carrier, of the mutation. The distinction between carrier and heterozygous is important, as the designation “carrier” may the expectation of a benign outcome.

Many X-linked disorders only affect males, while heterozygous females are asymptomatic carriers. If an asymptomatic female with a mutation in a gene causing an X-linked disorder has children, each of her sons has a 50% probability of inheriting the mutation and developing the disorder. In some instances the likelihood of developing the disorder may be less than 50% due to reduced penetrance. Penetrance in genetics refers to the proportion of individuals with a particular genetic variant who also express an associated trait. Each of the female’s daughters has a 50% probability of inheriting
the mutation and becoming an asymptomatic carrier. This is, however, a generalization with some exceptions and modifications. One reason for this is a molecular mechanism known as X chromosome inactivation (XCI) (32). Usually random transcriptional silencing occurs in one of the X chromosomes in each female’s cell. Most genes on either the paternally or the maternally inherited X chromosome are expressed (“used”). This dosage compensation means that human females are mosaics for the expression of X-linked genes. The XCI pattern is often random; each X chromosome is active in approximately an equal number of cells. Skewed XCI, a marked deviation from a 50:50 ratio, where either the maternally or the paternally inherited X chromosome is preferentially inactivated in 80% or more of cells, occurs in some women (33). Skewing increases with age (34). In many severe X-linked disorders female carriers are usually asymptomatic and have extremely skewed XCI, most likely because of selective skewing in favor of the X chromosome harboring the non-mutated gene (35).

2.4.  Fabry disease

Johannes Fabry and William Anderson described the dermatological manifestations of Fabry disease (OMIM #301500 (36)) in 1898. The X-linked inheritance pattern was described in 1965 (37). Twenty years later, a mutation in the GLA gene in a man with Fabry disease was identified (38), and it was recognized that mutations in this gene cause Fabry disease. GLA mutations cause deficient activity of the enzyme alpha-galactosidase A, leading to progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body. The measurement of alpha-galactosidase A activity in leucocytes was the gold standard for diagnosing Fabry disease prior to the widespread availability of genetic testing. Enzyme activity is not, however, a reliable test for identifying heterozygous females (39). Genetic testing is necessary to determine if a woman is heterozygous for Fabry disease (40). The analysis of the GLA gene has been available in Norway since approximately 2001 (personal communication, senior researcher Kristin Eiklid, Dept. of Medical Genetics, Ullevål, Oslo University Hospital).

Periodic crises with severe burning pain in the extremities, angiookeratomas (vascular cutaneous lesions), hypohidrosis (reduced sweating), corneal and lenticular opacities, and proteinuria due to renal damage characterize classic Fabry disease (41). Fabry disease is a disorder with an onset in childhood (42, 43), although major organ damage typically occurs in adulthood (43). End-stage renal disease, cardiovascular and/or
cerebrovascular disease typically occurs in the third and fourth decades. Individuals with Fabry disease may also have hearing loss (44). Because of the involvement of several organ systems, diagnosing and treating Fabry disease require a multidisciplinary approach (45). Disease complications and pain negatively influence health-related quality of life in men and women with the disease (46).

Treatment consists of intravenous enzyme replacement therapy (ERT), which is effective and safe (47, 48). The current recommendation is to start ERT at the onset of clinically significant symptoms (49). In Norway, individuals usually receive infusions biweekly at a hospital or self-administer treatment at home. The Center for Rare Disorders at Oslo University Hospital offers certification for home treatment. Recently, a new treatment became available for patients with milder mutations in the GLA gene. These mutations reduce but do not obviate enzyme activity; affected individuals may respond to the orally administered small-molecule chaperone agent, migalastat (50). Gene therapy for Fabry disease is under development (51).

Females heterozygous for Fabry disease commonly manifest symptoms (52, 53), but the phenotype is more variable than in males (54). Whether or not skewed XCI influences the phenotype in females with Fabry disease is unclear (55-57). Some symptoms women experience may be “diffuse” and “common,” e.g., fatigue, pain and abdominal pain. A diagnosis of Fabry disease may be more difficult to make in women because of an attenuated phenotype and because the disease is historically viewed as only affecting men. Diagnostic delays and complications are common (58). Manifestations in women are usually milder than in men; nevertheless, women may have a significant disease burden and impaired quality of life (53). Unfortunately, women with Fabry disease describe negative experiences with healthcare professionals related to their gender, carrier status, and the rarity of the disease (59). Only about 10 years ago, researchers recommended that women heterozygous for Fabry disease should not be described as carriers, precisely because they often manifest symptoms (53). Early international studies estimated a heterozygous frequency of a mutated GLA gene as 1:117,000 (60). Newer studies from newborn screening programs indicate an incidence (boys and girls) of 1:3,000–1:4,000 (61-63), which seems high. A recent review of experiences with newborn screening in Taiwan shows that most identified newborns are suspected of being predisposed to later-onset (non-classic) disease (64).
Researchers also question whether some variants detected in GLA in newborn screening programs are misclassified and are neutral, i.e., without pathogenic effects (65-67).

There is no official registry for Fabry disease in Norway, thus there is no national record of symptomatic and asymptomatic heterozygous women. The Center for Rare Disorders enters individuals who contact the center in a voluntary registry and is aware of approximately 70 affected men and women in Norway.

2.5. **Hemophilia**

History teaches us that hemophilia is an inherited disease. Queen Victoria (1819–1901) of England was a carrier. She had an affected son, Leopold. Queen Victoria had daughters who were carriers, who married into other royal families, and had sons with hemophilia (68). Prolonged bleeding due to deficiency of factor VIII (hemophilia A, OMIM #306700 (69)) or IX (hemophilia B, OMIM # 306900 (70)) with deficient clotting activity characterizes hemophilia. In the beginning of the 1980’s researcher discovered deletions and mutations in the F8- and the F9 genes as causes of hemophilia A and hemophilia B, respectively (71). Genetic testing for hemophilia A and B has been available in Norway since 2009 and 2010 respectively, (personal communication Dr. Knut Erik Berge, Dept. of Medical Genetics, Ullevål, Oslo University Hospital).

The F8- and F9 genes are located on the X chromosome. Hemophilia A and B are X-linked disorders, mainly affecting males. The prevalence of hemophilia A worldwide is approximately 1:10,000 live male births (72) with some variation between countries (73). The prevalence of hemophilia B worldwide is 1:30,000 live male births (74). There is a voluntary registry for patients with hemophilia at the Center for Rare Disorders, and approximately 400 patients with hemophilia have enrolled. There is no registry for carriers for hemophilia in Norway.

Boys with hemophilia who are untreated typically experience prolonged and abnormal bleeding of skin wounds and after tooth extractions. Spontaneous bleeding especially in deep muscles and joints may result in muscle damage or chronic joint disease (72, 74). A very dramatic consequence of hemophilia is intracranial bleeding (75). Females with a mutation in the F8- or F9 gene are usually asymptomatic and are called carriers. However, females with a skewed XCI pattern may experience excessive bleeding (76).
Women who are carriers for hemophilia A may report excessive bleeding (especially increased menstrual blood loss) despite normal factor levels in their blood. Symptomatic women who are carriers of hemophilia A are at risk of experiencing inappropriate care and dismissive treatment from healthcare professionals (77).

Alternatively, causes for hemophilia in women may be mutations in both copies of the $F8$- (78) or $F9$ gene (79). Females with Turner syndrome (with karyotypes such as 45,X or 46,XX/45,X) and a single mutation in the $F8$-gene (80) or the $F9$ gene (81) may have hemophilia.

The treatment of hemophilia consists of intravenous administration of an external coagulation factor prophylactically and/or episodically (on-demand) when bleeding occurs. Prophylaxis for children with severe hemophilia requires the infusion of factor concentrate two or three times a week. On-demand therapy involves the immediate infusion of factor concentrate in an effort to halt bleeding and prevent joint or muscle damage.

Treatment regimens vary between countries (82-84). In Norway, medical personnel usually administer factor concentrate in hospital settings in children below four years of age (hospital treatment). Parents learn to administer factor concentrate when the child is around four years old (home treatment). Parents attend a five-day course at the national competence center for hemophilia (Center for Rare Disorders, Oslo University Hospital) to be certified to administer factor concentrate. At home, parents administer prophylactic treatment and on-demand treatment for uncomplicated bleeds. In the event of a serious injury, such as head trauma, or bleeds requiring more than two doses of factor concentrate, parents contact a hospital. The self-administration of infusions usually starts around age 12.

The treatment of hemophilia has a sad history starting from the 1980s. Several individuals treated with contaminated factor preparations developed hepatitis C and/or HIV (85). Public misconceptions arose regarding bleeding disorders, perhaps linked to the history of these unfortunate individuals (86). In the 1990s, the development of recombinant factors improved treatment availability and safety (87). In an attempt to develop more lasting treatment to reduce the numbers of repeatedly intravenous
injections, or even to develop a cure, researchers are focusing on gene therapy (88). Promising results (89) have led many to believe a cure will become available.

For families affected by hemophilia, the hope for a more convenient treatment or even a cure is important; hemophilia A and B are chronic disorders that place a medical and psychological burden on the individual and the family (20, 90, 91). Given the consequences of hemophilia, especially if not treated adequately, it is unsurprising that parents find it stressful to have a child with the disorder (91). Importantly, caregivers of children with hemophilia report a reduced health-related quality of life compared with caregivers of healthy children (92).

Not all women who are carriers for hemophilia are aware of their status. This is potentially because the mutation is \textit{de novo} (occurred for the first time) in the woman or the family has not been aware of, or not spoken of, the heredity nature of hemophilia. However, the mother of a boy with hemophilia is often a carrier for the mutation causing hemophilia (72). Some women might know about their carrier status because they have a father and a son with the disease (obligate carriers). However, if the only person in the family with hemophilia is a single boy, only a genetic test can reveal if the mother is a carrier. Prior to the availability of genetic testing, one might have known that “something ran in the family.” In the 1980–90s, it became possible to know more accurately the consequences of the family’s disorder for individual women.

2.6. \textit{Perspectives on disease and illness in a genetic context}

An individual’s health is related to disease and illness, two important concepts in discussing genetic disorders. The World Health Organization (WHO) defines health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.” Using this definition, we can view health as the ability to carry on with daily life; good health does not necessarily presuppose the absence of disease. How the concepts disease and illness are best defined is under debate (93) and beyond the scope of this thesis. However, to illustrate the potential difference in how individuals experience symptoms and how medical professions view disease, I choose to use Eisenberg’s definitions:
“Illnesses are experiences of disvalued changes of states of being and in social function; diseases, in the scientific paradigm of modern medicine, are abnormalities in the structure and function of body organs and systems” (94).

A genetic disorder is caused by an alteration in an individual’s genetic material. Genetic disorders can be caused by a mutation or mutations in a single gene, by variants in multiple genes (polygenetic disorders), by chromosomal aberrations (chromosomal or genomic disorders), or by a combination of genetic/genomic and environmental factors. When discussing disease and illness in a context of genetic disorders, we need to remind ourselves that we have approximately 20,000 protein coding genes (95). We all have many rare gene variants that deviate from the reference sequence (96). Some variants are pathogenic and cause disease, and others are neutral and do not cause or contribute to disease. Sometimes a variant will confer increased disease susceptibility; an individual with the variant may acquire the disease or not, dependent on other known or unknown factors. The likelihood of developing a disease is not the same as having it. Knowledge of risk may however cause anxiety and depression (97), and thereby potentially unrelated illness. Some mutations are incompletely penetrant and cause disease only in a proportion of individuals who harbor them. A mutation may also have variable expression: two people, even within the same family, with the same mutation may experience different manifestations or disease severity.

Individuals with undiagnosed genetic disorders may experience illness but genetic disorders are rare, and rarity may lead to a diagnostic delay (17-19). Doctors may recognize some symptoms as related to disease, even though a specific diagnosis is not recognized. However, in some cases, symptoms may not be appreciated as disease-related; still a person may experience illness. People may even underestimate and rationalize symptoms when chronic illness is experienced as an unwanted biographical disruption (98) with a loss of self (99).

For some genetic disorders, Eisenberg’s definition of illness and disease may be complicated. Not all genetic disorders cause a disease, or illness, even though the genetic alteration in a person may cause “abnormalities in the structure and function of body organs and systems.” An example is Down syndrome. Down syndrome, due to an extra copy of chromosome 21 (trisomy 21), is not a disease but a disorder. An
individual with Down syndrome may have a disease, such as heart failure secondary to a structural malformation, leukemia, or the flu. However, an individual with Down syndrome may feel well, and not ill. This challenges the concepts of illness and disease in genetic disorders. We should be mindful that many genetic disorders are just this: disorders, not diseases.

2.7. Women as mothers and caregivers

Historically, women have had a central role in taking care of children and the home. Increased gender equality from the 1970s has given women more options. Women in Norway today have in principle the same opportunities for education and work as men (100), and they are free to make their own decisions regarding family planning. For the last 50 years, oral contraceptives have been available in Norway (101). Contraception is easy to access, and sex education is taught in every Norwegian school (102). The law regulating self-determined abortion in Norway starting in the mid-1970s (103) allows a woman to terminate a pregnancy before 12 weeks of gestation. Women with a high probability of having a child with a serious genetic disorder have a right to prenatal testing. These rights are important for women; however, with rights come obligations. Women who carry mutations for genetic diseases feel an obligation to inform their partner of their status and to control pregnancy (104). Hence, women who are heterozygous or carry a mutation for a genetic disorder, have an extra aspect to consider in family planning. Women may not experience carrying a mutation as private, when they consider reproductive decisions. Moreover, although women today are often financially independent, they are usually the primary caretakers in the family (105, 106). In Norway, claimed to be one of the most gender balanced countries world-wide, more women than men take care of the home and children (107), and mothers take more responsibilities in planning and adjusting activities of family life (108).

In reviewing the literature about the burden of caregiving it is important to be aware that “caregiver burden” is multi-dimensional and context dependent. There appears to be no consensus on how to define the concept (109). For the purpose of this thesis, I have chosen to use the definition proposed by George and Gwyther (110), who define it “as the physical, psychological, emotional, social and financial problems that individuals experience due to providing care.” The risk factors for caregiver burden include female sex and a lack of choice of being a caregiver (111), two criteria mothers of children with
rare disorders fulfill. Furthermore, taking care of a child with a chronic disease is demanding and stressful (112, 113), and caregivers of children with health problems have a greater risk of having health problems than those of healthy children (114). Mothers of chronically ill children in particular, report increased levels of anxiety and depression (115). Parents of a child with a rare disorder, have an extra dimension to having a child that is chronically ill because of the rarity of the diagnosis (24). Indeed, parents of a child with a rare diagnosis, and especially mothers, experience increased physical and emotional stress (116, 117).

A lack of knowledge about rare disorders among healthcare professionals is an extra burden for families with a child with a rare disorder (106, 117-119). The rarity of the disorder and the lack of knowledge may empower parents as they educate themselves and become “expert” caregivers (106, 118-120). A review describing the needs of parents with chronically sick children stressed three important areas: the need for normality and certainty, the need for information, and the need for partnership via, for example, an alliance with helpful healthcare professionals (121). Healthcare professionals and family caregivers should base collaboration on mutual recognition and respect, trust, and open communication (122). Caregivers reported better experience with healthcare services when they perceived that their services were valued and their knowledge was respected (123).

Caring for a chronically ill child may have financial as well as physical or psychological consequences. International research shows that mothers caring for chronically ill children are more likely to quit their jobs than men, and this negatively affects economic status, and maternal mental health (117, 124). The parents’ resources — social, physical, mental, and financial — are all factors shaping daily life in families with a chronically ill child. Family resources and the adjustment of chronically ill and handicapped children are significantly related (125). A country’s economic welfare system may have a disproportionate influence on how families are able to care for a child with a chronic disease.

2.8. **Family communication about genetic disorders**

Communicating within the family about genetic risk and testing can be a difficult and complex process (126-129). An individual who is aware of a genetic disorder must
decide if, how, when, and what to communicate to her/his children and other relatives (130). Several studies report that sharing information about genetic conditions and carrier risk is difficult (131, 132). The result may be no communication, misinformation, or misunderstandings (130). Non-disclosure can affect family dynamics (133), increase tension, and comprise coping and adaption (130).

Furthermore, parents may find discussing genetic risk with their children difficult and emotionally painful (128). However, of note is that open communication about risk starting in childhood seems to help children and parents cope with the implications of a genetic condition (128).

Caretaking has several dimensions, and women tend to take major responsibility for their families’ health (134), and are more likely to communicate information concerning inherited conditions (128, 135). Mothers often play a central role in discussions about carrier testing (128, 136). However, mothers may also act as “gate-keepers” who prevent the transmission of genetic information to children (137).

This thesis focuses on women who are carriers for hemophilia or heterozygous for Fabry disease keeping in mind that gender, the socially constructed characteristics of women and men (138), is a significant social dimension in communicating about genetic disorders.

2.9. Communicating about genetic disorders in the public sphere
In blogs, magazines, newspapers, and books, and on Facebook, people share experiences with illness and family life as well as opinions. Much of this information is freely available for anyone with internet access via a simple search for the diagnosis of interest. Openness about experiences with illness, thoughts, and opinions has increased over time. Today, for example, blogs written by individuals undergoing treatment for cancer, and cancer survivors, are numerous. For rare disorders like Fabry disease and hemophilia there are fewer blogs (139, 140), and the information shared is often about the manifestations of the disorder, rather than experiences related to carrier status.

The internet is a well-utilized source of information about health and disease for lay people as well as for clinicians (141). Diagnosing rare disorders is often an odyssey and
affected individuals and parents may go online for health information and diagnose themselves (142). It is also well documented that parents of children with rare diseases go online to find information, to share experiences, and to connect with others for support (143-145). This shows that patients and parents have a need for information and a need for a network with individuals with the same diagnosis as themselves or their children.

2.10. Healthcare, genetic disorders, and communication

In Norway, individuals with genetic disorders, carriers, and relatives at risk are entitled to genetic counseling. Genetic counseling entails more than providing risk information. In 2006, the Genetic Counseling Task Force of the National Society of Genetic Counselors (USA), proposed a broad definition that includes addressing psychosocial as well as familial aspects of individuals’ situations (146). Genetic counseling traditionally seeks to be nondirective. It aims to present and to discuss positive and negative implications of various alternatives. However, several authors have discussed the difficulties inherent in a non-directive philosophy (147-149). Clarke (150) claims that neutral genetic counseling is not consistent with the social objective of preventing disease and argues that a non-directive approach can do harm rather than promote health by transferring the burden of decision-making to the counselee.

In Norway, genetic counseling usually takes place under the auspices of a genetic counselor with a master’s degree or a physician who is a specialist or trainee in medical genetics. Individuals in both professions are trained in communication. “Genetic counselor” is however not a protected title in Norway.

Few studies have focused on how carriers for hemophilia or heterozygotes for Fabry disease are met by healthcare workers. However, hemophilia carriers may experience inappropriate care (77), and the diagnosis in women with Fabry disease is often delayed resulting in medical complications, such as under treatment of hypertrophic cardiomyopathy (58).

Hemophilia and Fabry disease are rare disorders, and non-geneticists may lack familiarity with the disorders, especially with presentations in females. Some doctors may still be unaware that female carriers and heterozygotes for some X-linked disorders
may experience disease manifestations. A lack of knowledge about rare disorders among healthcare providers may affect communication with affected individuals or parents (17-19). Information supplied by professionals may be perceived as inadequate, incomplete (18, 19) or contradictory (151). The significance of symptoms that are non-specific or difficult to explain may be disregarded, and females may present differently than males with same disorder. A lack of awareness of the influence of gender on disease manifestations has the potential to reduce the quality of healthcare, a phenomenon described as the “gender trap” (152).

2.11. Stigma, shame, and guilt in a genetic context
Stigmatization and social misconceptions are commonly reported as consequences of having a rare disorder (20, 22, 25, 151, 153-156). The Greek work stigma originally described a marking burned into the skin to allow the ready identification of traitors and criminals. Goffman defined stigma as “something that deviates from the society’s conception of what is normal or accepted” (157). Link and Phelan claim that how stigma is defined depends upon social, economic, and political power, “stigma exists when elements of labeling, stereotyping, separating, status loss, and discrimination co-occur in a power situation that allows these processes to unfold” (158). Both definitions are relevant for genetic disorders.

Carriers who have a child affected by a genetic disorder may experience guilt and blame (159). Guilt is an emotional experience in which a person assumes responsibility for his/her actions including subsequent harm (160). Shame—the painful feeling of being no good, inadequate, and unworthy—and guilt often occur together, and it can be useful to conceptualize them as an integrative construct (160). Importantly, guilt can interact with stigma (161).

A family may perceive its genetic disorder as stigmatizing; information about genetic risk becomes so difficult that silence ensues. Knowledge of a genetic disorder may thus become a secret with restricted access within a family, as described in the Norwegian novelist T. Steen’s book “Det hvite badehuset” [in English: “The white bathhouse”] (162). Stigma may even be experienced as a threat to personal identity, social life, and economic opportunities (163).
Although a genetic diagnosis may cause stigma, for many people a genetic diagnosis comes as a relief and provides an explanation. A Norwegian study of parental attitudes to genetic testing in autism revealed that most parents were positive because of the possibility of determining a cause of their child’s difficulties (164). A genetic diagnosis may also reduce stigma. Colorectal cancer or extreme obesity, for example, can be the result, at least in part, of an unhealthy lifestyle, or alternatively be manifestations of single gene disorders (165, 166).

2.12. Coping strategies
Several coping strategies have been described that ease the challenges associated with a rare disorder. People try to live a normal life, to the extent possible (18, 29, 156), living day by day without looking to the future (25). Some protect themselves from other peoples’ misconceptions by keeping a diagnosis a secret (22, 25). Another way of coping is to become an expert on the rare disease and its treatment (154, 156). Some chose to compare themselves to others whom they consider have more serious diseases (153). Caregivers may also use coping strategies, such as praying, talking to friends, and educating themselves (167). Taking brief breaks and using common forms of relaxation, such as the companionship of pets, shopping, and “eating chocolate” as well as enjoying support from friends, family members, and peer organizations, are other coping strategies reported by caregivers (168).

Lazarus and Folkman (169) define coping as “constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person.” The word manage is important because it includes minimizing, tolerating, accepting as well as avoiding stressful events or conditions. Thus, coping may be explained as efforts to prevent or diminish threat or harm, or to reduce associated distress (170).

Lazarus and Folkman further outline coping as a process (169). Coping depends on what the individual thinks or does, what the context is, and what the individual changes in thoughts or acts. Various coping strategies combine to form a coping process. Importantly, coping depends on an individual’s resources: health, existential beliefs, commitments, problem-solving skills, social skills and support, and material resources (169). If an individual believes that she can do nothing to manage a specific perceived
stressful instance, emotion-focused forms of coping are more likely. Problem-focused forms of coping are more probable when individuals perceive a situation as amenable to change (169).

Stress often relates to what an individual is trying to cope with. One definition of stress is “a function of the interaction of the subjectively defined demands of a situation and the capabilities of an individual or group to respond to these demands” (171). Stress depends on the relationship between the individual and the environment (169). Stress may thus be seen as an unstable mix of circumstances and experiences, as well as resources, all of which vary among caregivers, and thus vary in their impact on caregivers’ health and behavior (172). Appraising an outcome as controllable may be stress-reducing (169), and thus a coping mechanism.

2.13. Rationale for this study
Research on the experience of being a carrier or heterozygous for a mutation causing an X-linked disorder is largely lacking. A primary focus has often been issues pertinent to carrier testing and only to a limited degree issues relevant to the experience of being a carrier.

A few studies have shown that being a carrier for an X-linked disorder provokes feelings of guilt and a reconsideration of life plans, especially the decision to have children (104, 173, 174). In one study of Fragile X syndrome, an X-linked disorder that results in intellectual disability, some women even regretted determining their carrier status because they would have otherwise had more children (174). Another study on Fragile X syndrome showed that non-carriers felt better about themselves and were especially relieved not to have passed the family’s mutation on to a child (175). James and colleagues reported that mothers of children with X-linked disorders were more likely to blame themselves for their child’s condition, than those of children with autosomal recessive diseases (173). In James’ study, some fathers of children with X-linked conditions blamed their partners for their child’s disorder (173).

There is a lack of qualitative research on how carriers or heterozygous women for X-linked disorders experience the psychosocial dimensions of being a carrier or heterozygous, internationally and in a Norwegian context. To understand and help
women who are carriers for hemophilia or heterozygous for Fabry disease, healthcare professionals must understand the women’s experiences and how women give meaning to their experiences. We therefore designed a qualitative study to explore psychosocial aspects of carrier status or heterozygosity for two X-linked disorders, hemophilia and Fabry disease. We also aimed to explore how the disorders are understood and communicated about within the family as well as how women experience encounters with healthcare professionals. Research that contributes to increased knowledge in this field has the potential to improve healthcare for women who are carriers or heterozygotes for X-linked disorders. This study is a contribution to exploring the complex dynamics through which social and biological processes combine (176) to influence health.
3. Aims

The aim of this study is to provide knowledge about how women who are heterozygous for Fabry disease or carriers for hemophilia experience psychosocial aspects related to these conditions. To explore this, we developed the following research questions:

- What psychosocial issues do women heterozygous for Fabry disease experience, and how do they experience encounters with healthcare professionals?

- How does a woman’s experience of the psychosocial aspects of being a carrier for hemophilia change over time?

- How do mothers who are carriers for hemophilia experience the treatment of their son’s hemophilia in a hospital setting and at home?
4. Methods and research process

Below I describe the methods used in this study and the research process. I also discuss reflexivity and selected ethical considerations, and offer some methodological reflections.

4.1. Introduction

The aim of this study is to provide knowledge about how women who are carriers for hemophilia or heterozygous for Fabry disease experience the psychosocial aspects related to their condition. I utilized a qualitative design with an explorative interpretative approach. A qualitative orientation implies attention to cultural aspects, daily life, and situation-specific aspects of human thinking, learning, knowledge, acting, and to the way we understand ourselves as individuals (177). Qualitative research aims to gain broader insight into experiences and to understand the meaning of experiences (178) and qualitative methods address how something happens or is experienced (177). In the present study I used semi-structured interviews to collect data. A qualitative research interview is inspired by a phenomenological approach (177): through the interview the researcher seeks qualitative knowledge and tries to understand the meaning of central themes in the participants’ life.

In this study, I used a thematic analytic approach (179). In thematic analysis, the researcher seeks patterns of meaning and accommodates and explores discrepancies and contrarieties within the data (178). A phenomenological approach is used to investigate how people experience phenomena in their lifeworld, and a hermeneutic approach is concerned with the interpretation of meaning (177). Human experiences of understanding and interpretation through language, history, and culture are within us. Hermeneutics emphasizes the necessity of understanding our pre-understandings. Gadamer states that, according to hermeneutic philosophy, as we acquire new experiences our understandings of different phenomena are in constant change (180). The participant in a qualitative study can only understand and retell her lived experience in relation to her pre-understandings (177).

4.2. Selection of cases and recruitment

The overall aim of this study was to explore how women experience being a carrier for
an X-linked disorder. Many X-linked disorders involve intellectual disability, and/or serious progressive neurological disease in boys, including early lethality. Other X-linked disorders include chronic diseases, which do not entail progressive neurologic deterioration or intellectual disability.

When I planned the project, I knew that X-linked disorders were individually rare, and that there was no official national registry of individuals with X-linked disorders, heterozygotes, or carriers. I chose three X-linked disorders, Fabry disease, hemophilia, and Alport syndrome for which the Center for Rare Disorders serves as a national competence center. I originally aimed to recruit 10 women who were carriers for hemophilia, 10 who were heterozygous carriers for Alport syndrome, and 10 who were heterozygous for Fabry disease. These disorders have some similarities, and I thought it would be feasible to recruit participants for the study through the Center for Rare Disorders.

The Center for Rare Disorders has very few women known to be heterozygous for Alport syndrome registered. A nurse from the center contacted three women about the study, and they accepted the invitation; however, two were unable to participate during the period the interviews were scheduled, resulting in only one interview with a woman heterozygous for Alport syndrome. Alport syndrome does not have a patient support group in Norway, so I knew of no other means of recruiting heterozygous women. Because I only had one interview, I did not include Alport syndrome in the study, and Alport syndrome will thus not be discussed in this thesis.

One reason for choosing Fabry disease and hemophilia was that the diagnoses do not involve neurocognitive deficits or neuromuscular manifestations. I believed it would be less sensitive for the participants to talk about experiences of being a carrier for hemophilia or heterozygous for Fabry disease than to verbalize experiences of being carriers for disorders associated with neurocognitive or neuromuscular manifestations. In hemophilia and especially in Fabry disease, women who are carriers or heterozygotes may develop disease features. Fabry disease and hemophilia are chronic disorders, and mortality rates are low in childhood. For both disorders, effective symptomatic treatment is available and consists of intravenous infusions—enzyme replacement in Fabry disease and clotting factor supplementation in hemophilia. A difference between
Fabry disease and hemophilia is, however, the frequency of administration of the treatment. Boys with hemophilia usually undergo treatment with factor concentrate several times a week. Female carriers for hemophilia rarely require such treatment. Individuals with Fabry disease, men and women, typically receive infusions every two weeks. It is less common to treat Fabry disease than hemophilia in children.

The sampling process for qualitative research is guided by the research question, and the understanding that qualitative research is based on experiences and construction of meaning (181). I thus decided to use purposeful case sampling (181). Nurses working at the Center for Rare Disorders, who are familiar with the two diagnoses, selected a varied sample of women who are carriers for hemophilia or heterozygous for Fabry disease and invited them to participate. Directed sampling helps to ensure the recruitment of informative participants.

This study is based on interviews with 26 women, 16 carriers for hemophilia A or B, and 10 heterozygotes for Fabry disease (referred to from this point on as the hemophilia group and the Fabry group, respectively). Initial inclusion criteria were that women were:

- carriers for hemophilia, or heterozygous for Fabry disease or Alport syndrome.
- had at least one child with hemophilia, Alport syndrome, or Fabry disease.
- were able to understand and speak Norwegian or English.

The Center for Rare Disorders at Oslo University Hospital offers services for individuals and families with several rare disorders, including hemophilia and Fabry disease. All hemophilia patients have an annual follow up at Oslo University Hospital, and one of the nurses working at the Center for Rare Disorders usually participates. Mothers very often accompany their sons with hemophilia to these appointments. Women were the easiest to recruit from this group. The nurse selected 11 who had at least one son with hemophilia. The nurse approached seven women by phone and four in conjunction with their son’s annual appointment. All women received written information about the study. Five additional women contacted me directly by phone after hearing about the study from the Norwegian Hemophilia Society, and I mailed
them written information. All 16 women accepted the invitation to participate, gave written consent, and chose when and where they wanted their interviews to take place.

For the Fabry group, a nurse from the Center for Rare Disorders contacted the 14 potential participants known to the center to be heterozygous for Fabry disease, and recruitment was expanded via a mailing through the Norwegian patient support group for Fabry disease. I did not ask the patient support group how many women they invited, and I do not know if some women had received an invitation from both the center and from the patient support group. The exact number of women invited in the Fabry group is thus unknown. It was difficult to recruit 10 women with a child with Fabry disease. The response was poor despite several attempts. Upon re-application to the regional ethics committee, we were permitted to include women heterozygous for Fabry disease without a child with Fabry disease. After changing the inclusion criteria, 10 women accepted the invitation, gave written informed consent, and decided where and when they wanted their interviews to take place.

Participants in both the hemophilia and Fabry groups are ethnic Norwegians. Participants in the hemophilia group were aged 27–72 years (mean age 42 years). For demographic characteristics of the hemophilia group, see Table 1. All participants were given pseudonyms.
Table 1 – Clinical and demographic characteristics: hemophilia group

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age</th>
<th>Type of hemophilia (A or B)</th>
<th>Number of affected sons</th>
<th>Carrier status known prior to having a son with hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kari</td>
<td>35</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Lisa</td>
<td>32</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Anna</td>
<td>41</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Heidi</td>
<td>27</td>
<td>Hem. A</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Lisbeth</td>
<td>39</td>
<td>Hem. A</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Marianne</td>
<td>35</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Ingrid</td>
<td>27</td>
<td>Hem. B</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Thea</td>
<td>30</td>
<td>Hem. A</td>
<td>(1 early termination)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lena</td>
<td>40</td>
<td>Hem. B</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Tanja</td>
<td>65</td>
<td>Hem. A</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Wilma</td>
<td>55</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Mette</td>
<td>72</td>
<td>Hem. A</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Victoria</td>
<td>34</td>
<td>Hem. B</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Jane</td>
<td>56</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Therese</td>
<td>28</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>Astrid</td>
<td>49</td>
<td>Hem. A</td>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The participants in the Fabry group were aged 24–77 years (mean age 54 years). Five of
the women in the Fabry group had at least one child with Fabry disease, two did not
have children, and one had children who did not have Fabry disease. One participant
had children who were not tested for the disorder. For the demographic data for the
Fabry group, see Table 2.

Table 2 – Clinical and demographic characteristics: Fabry group

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age</th>
<th>Fabry disease symptoms</th>
<th>Enzyme replacement therapy (ERT)</th>
<th>Children with Fabry disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>77</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>P2</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>P3</td>
<td>50</td>
<td>Yes</td>
<td>No, but child w/ERT</td>
<td>Yes</td>
</tr>
<tr>
<td>P4</td>
<td>49</td>
<td>No</td>
<td>No, but child w/ERT</td>
<td>Yes</td>
</tr>
<tr>
<td>P5</td>
<td>63</td>
<td>Yes</td>
<td>Yes</td>
<td>? (not tested)</td>
</tr>
<tr>
<td>P6</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>No (tested)</td>
</tr>
<tr>
<td>P7</td>
<td>46</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>P8</td>
<td>24</td>
<td>Yes</td>
<td>Yes</td>
<td>No children</td>
</tr>
<tr>
<td>P9</td>
<td>30</td>
<td>Yes</td>
<td>Yes</td>
<td>No children</td>
</tr>
<tr>
<td>P10</td>
<td>42</td>
<td>Yes</td>
<td>No</td>
<td>No (tested)</td>
</tr>
</tbody>
</table>
4.3. **Data collection**

I called to introduce myself and explain the study in greater depth to the women who accepted our invitation and the women could then decide the time for the interview. This gave participants time to prepare and think about issues important to them before the interview.

I collected all data through in-depth semi-structured face-to-face interviews. The women decided where and when they wanted to the interview to take place. Two chose to be interviewed at home because it was most convenient. The 24 other participants were interviewed in an office at one of three university hospitals in Norway (Oslo, Bergen, and Trondheim). I conducted all interviews between February 2013 and March 2014 using an interview guide with open questions. An English translation of the main interview questions is attached in Appendix 4. The questions concerned what it was like finding out about being heterozygous for Fabry disease or being a carrier for hemophilia, experiences of living with being a carrier, thoughts about having, or potentially having, a child with one of the disorders, and experiences with the healthcare system. The interview guide was informed by literature published before October 2012 and was developed by the research team with input from professionals who had experience with managing the diseases.

Before initiating the interviews, I informed the participants once more about the study by repeating the written information they had received, emphasizing that they could withdraw from the study at any point. I informed them that they were free to skip questions they found difficult to answer for any reason. I advised them that my role in the project was as a researcher/PhD student, and not as a senior consultant in clinical genetics/medical advisor (my current position at the Center for Rare Disorders). I offered to organize a follow-up consultation after the interview with me or with a counselor at Center for Rare Disorders as needed. No participants were reluctant to answer any questions or asked for a follow-up consultation.

The interviews lasted from 40–100 minutes (average 60–70 minutes), and were recorded on a Sony digital voice recorder. I transcribed 12 interviews verbatim. Due to an inflammation in my elbow, a medical secretary transcribed the remaining 14
interviews verbatim. I listened to all 26 interviews while checking the transcripts and de-identified names and places.

4.4. **Data analysis**

Qualitative data can be analyzed in different ways: for example, by interpretative phenomenological analysis, grounded theory, or thematic analysis. I chose an inductive thematic analytical approach for analyzing the interviews (179). Thematic analysis is used to identify patterns of meaning across a dataset, a method which is appropriate for research questions concerning people’s experiences, thoughts, and perceptions. The method is theoretically flexible (178), not fixed to a single specific theoretical framework, and well-suited for larger datasets. An inductive approach aims to generate an analysis from the data without pre-set codes or themes. A code is a word or brief phrase that captures a piece of data the researcher thinks will be important and useful in the analysis (178).

Using an inductive approach and coding what interviewees actually say provides a better chance of finding what I did not know I was looking for. It was also important to seek out participants who did not agree with majority views, in an attempt to gain new insights and understanding of the participants’ experiences. The absence of something may be just as important as the presence of something (182). For example, one woman said she did not feel guilt or shame. I reviewed her interview to search for clues to why this was. She reflected in the interview that the reason she not to feel guilt was because her son had not had severe disease manifestations and his treatment had been straightforward.

I wrote a short summary for each interview, after the second reading, to get an overall impression of each woman’s experiences. I then coded all the material in detail using a software program called HyperResearch (183). A data program can be used as a tool for storing, ordering, and retrieving information (184) but cannot perform the analysis. I used the software program to organize the codes, which functioned as tools and organizing principles. The codes were used to create categories and to begin to read and think about the data in a systematic and organized way (185).
Analyzing qualitative data is more than coding and categorizing: analysis is also about the representation or reconstruction of social phenomena (185). Codes are the building blocks of analysis (178). I discussed the codes and analysis with the other authors of the papers, who also were my supervisors for my PhD. We identified patterns, categorized the codes into subthemes and themes, and selected the themes we believed captured important issues in relation to the research questions (179).

Qualitative data represent large amounts of information, and analysis implies abstraction and some degree of generalization (184). A theme can be used as a central organizing concept and conveys something about the content of the data that is meaningful in relation to the research question (178). A subtheme captures notable specific aspects of the central organizing concept of a single theme (178). Figure 1 shows an example of my analysis of the hemophilia group, which formed the basis for papers II and III.
Figure 1
Example of the analysis of the hemophilia group

Subthemes
- Guilt and sorrow in self
- Guilt and sorrow in fathers
- Guilt and sorrow in grandmothers
- When to test or not?
- Who, and when, to tell?
- To have children, or not?
- Prenatal diagnostics, or not?
- Believe to be prepared to have a son with hemophilia
- Shock and sadness when son is diagnosed
- Impact on daily life and healthy siblings
- Emotionally hard when the son has infusions
- Disruptive of daily life
- Less disruptive
- Can have treatment secretly; feel more normal
- Doctors' lack of knowledge about the diagnosis
- Parents' experience of not being taken seriously/being listened to

Themes
- Guilt and sorrow across generations
- Choices and consequences of genetic testing
- Preparing to have a child with hemophilia
- Challenges with treatment in the son with hemophilia
- Advantages with home treatment
- Trust and mistrust in doctors

Paper II
Paper III
I reviewed the themes by going back to the transcripts and research questions and collected extracts of data coded in relation to the themes. In writing the papers, I analyzed the themes further by relating them to various concepts that could enlighten and elaborate the findings. I translated the quotes from Norwegian to English. Because the language is oral in an interview, some words or phrases were altered slightly without changing their meaning.

When I initiated my research, I intended to analyze the 26 interviews together. Although the diagnoses differ, they also have features in common. However, while analyzing the interviews, I realized that the women in the two groups had several different concerns. I therefore decided to analyze the interviews from each group separately. As an example, the hemophilia group strongly expressed themes regarding the mothers’ experiences with their sons’ treatment and hospital visits. The results from this part of the study are presented in paper II.

Qualitative data may be presented in different ways and the use of numerical data is a topic of discussion, and to some degree controversial (186). However, within qualitative research using thematic analysis, the phrases “few,” “many,” “several,” “almost all,” and “the majority,” are commonly employed, and I chose to present the data using such phrases.

4.5. **Reflexivity**

In qualitative research, reflexivity may be understood as sensitivity to how the research process and researcher have influenced the results and conclusions; it is the process of critically reflecting on the knowledge we produce and the role we play in producing it (178). Reflexivity means that the researcher is self-disclosing her assumptions, beliefs and biases. The researcher should not eliminate her role, rather attempt to identify her influence and discuss it (187).

As researchers, we can never free ourselves from who we are, but we can be reflexive and transparent throughout the research process. A researcher needs to be aware of this and acknowledge her position and pre-understandings. Personal characteristics, for example sex, age, and profession, may create closeness to, or distance from, participants. Prior assumptions and experiences may influence which data are collected.
and analyzed. Close proximity to the subject or area you are researching may impede critical reflection. Importantly, much of our knowledge is tacit knowledge, bodily, and non-articulated. This knowledge is often taken for granted, and we neglect to reflect on it (188). The researcher should be conscious of, and acknowledge, this.

I am an ethnic Norwegian woman, married with two healthy children, a girl born 2006 and a boy born 2009. I have a Master of Science degree in molecular biology, and I am a medical doctor with a specialty in medical genetics. I have previously conducted quantitative research, and the field of qualitative research was new to me when I started this project in 2012. Since October 2012, I have had a 50% position as a senior consultant/medical advisor at the Center for Rare Disorders at Oslo University Hospital, and a 50% position as a PhD student. My main interests in medical genetics are syndromology and dysmorphology. I have also always been interested in communication—between people in general, but especially between physicians and patients and parents of children with rare disorders.

This PhD project built on my previous clinical experience as a medical geneticist. This background formed the basis for the research questions and motivated me to do the study. Research projects are commonly born out of curiosity or the need for specialization and reflection. Such motives are important parts of preconceptions (187). I was familiar with quantitative research from my work in molecular biology. In my experience within the tradition of medicine in Norway, the quantification of data is common, and qualitative methods have often had a less prominent role in medical research (189). However, I soon realized that my research questions, which were aimed at exploring experiences tied to a defined phenomenon, were not perfectly suited for quantification.

Malterud suggests that qualitative methods may cause methodological challenges to those trained in a quantitative research tradition (187). It may be difficult to see the role of the researcher, the prerequisites and consequences regarding the selection of participants, and the systematic handling of the organization and interpretation of the material in the analytical process. All these factors, with the exception of systematic handling, were relevant for me. I discussed this with colleagues who worked with qualitative methods, and I chose qualitative researchers as my supervisors. I worked
actively to reduce my prejudices, and I read books and papers on qualitative methods. Critical reading of papers written by others may enable useful learning (184). I concluded that my previous lack of knowledge about qualitative research caused many of my prejudices. I also had to reconsider my search strategies. As a doctor and quantitative researcher I commonly use PubMed (190). To find relevant literature for my PhD project, I had to supplement my searches using other databases and literature, such as Cinahl (191) and PsychINFO (192).

A consciousness of differences in language and culture between the researcher and participants is important, as the world presents itself through language and communication, and we shape our reality through words (193). The world for people with rare diagnoses is shaped in the relation to their realities. Individuals who have rare diagnoses and their families often experience that others lack knowledge of the diagnosis or the challenges the diagnosis entails (17, 20, 59, 154, 194).

Individuals who have rare disorders and their families often have extensive contact with doctors and the healthcare system. They frequently have expertise specific to their diagnosis (194, 195). They not only become experts in terms of experience and knowledge, but also in relevant medical language. In my study, I experienced that the participants were familiar with medical terminology and used many concepts usually unfamiliar to lay people. The fact that the participants knew I was a doctor and worked at the Center for Rare Disorders may have been a relief, as they did not have to explain medical terminology and treatment. On the other hand, it may have hindered them in relating certain experiences and understandings, even if I attempted to emphasize that I was acting as a non-judgmental researcher, not as a physician.

My background as a specialist in clinical genetics and my knowledge of medical conditions, rare disorders, and genetics may have prevented me from being open for all perspectives. My pre-understandings could have been limited and imprecise—hindering me from perceiving essential meanings in the interview. Being knowledgeable in a field where one is doing research might blind one to the obvious: pre-understandings can hinder new understandings (196), however, they can also facilitate them. When I entered the role of a researcher, it was difficult, not to take a therapeutic role with a wish to help and comfort. This was perhaps one of my greatest challenges as a
qualitative researcher. I tended to be keener to take care of the participant than to focus on the research questions. I experienced this as a problem especially in the first few interviews. However, being aware of this inclination I could focus on completing the interviews. Being a mother and a clinical geneticist may have helped me to connect and focus.

In a qualitative interview, researchers and participants alike have pre-understandings. Although I made my role as a researcher clear, the participants knew I was a physician and may have made suppositions about where my interests laid. They might have been prone to focus on medical issues instead of on issues I was interested in in the research context. They may also have wanted to discuss medical issues or ask questions and may have been afraid to recount negative experiences with the healthcare system.

I tried to address some of these challenges by outlining some premises before starting the interview. The participants and I agreed that if they had questions about genetics or other medical issues we would discuss them after the interview was concluded. If I believed they would benefit from an extra follow-up consultation, I would let them know. I also made it clear that it was important to me that they were honest about negative encounters with healthcare professionals including physicians. As best I can judge, they did not find this difficult.

My gender may also have influenced what I was told—or not told. Women might speak more easily to a female researcher and assume that she intuitively understands more than she does. My supervisors also have a set of pre-understandings that differ from mine. We were conscious of this and used it actively in discussions analyzing and interpreting the empirical data. My supervisors’ different backgrounds and pre-understandings were a strength that helped us to challenge each other’s assumptions and claims (184).

It might be a potential strength that I am a mother myself. It may give me an increased awareness of fundamental aspects of being a carrier, especially in relation to reproductive decision making. I can easily relate to wishing to become pregnant, for a healthy child, to be pregnant, and to have a child. However, not everybody has the same thoughts around pregnancy and children, and there are significant differences in having
a healthy child and having a child with a disability or medical disorder. Participants were in a different age group than me and their ages and individual histories may have influenced their pre-understandings.

Reflexivity toward all these factors was important in analyzing the empirical material. Our analyses and data interpretations cannot mirror real life but represent an interpretation of how we see the participants’ life told by them in research interviews. Qualitative data give us a new understanding and insights into other people’s lifeworld, but not evidence in the sense of how things exactly are.

4.6. Ethical considerations

In medical research, human beings are very often the research objects and the researcher must be aware of ethical issues at every step. The World Medical Association’s (WMA’s) Declaration of Helsinki is a summary of ethical principles for medical research involving human subjects, including research on identifiable human material and data (197).

The declaration states that medical research must follow ethical standards that show respect for all humans and protect their health and rights. We should only carry out medical research on human beings if its value outweighs the risk and strains it puts on the people who participate. The Regional Committee for Medical Research Ethics (Health Region South-East, reference number: 2012/1617) approved this PhD project (Appendix 1). All women were actively informed that participation was voluntary and that they could withdraw from the study at any time without explanation (Appendix 2). The participants gave written informed consent and agreed that I could publish results without identifying them in international journals (Appendix 3).

It is especially important to be careful when researching sensitive topics or focusing on vulnerable groups (187). I did ask myself if it was ethical to ask the women about sensitive topics, such as how they felt about being carriers or heterozygotes and their thoughts about having a child with hemophilia or Fabry disease. However, I do believe I can justify doing research on such sensitive topics, as I was well aware of the sensitivity of the topics and conducted the interviews in accordance with all relevant ethical principles and guidelines mentioned above. The intention of the study was to increase
knowledge about the women’s experiences. Previous research confirms that difficult situations are easier to handle with increased knowledge and experience (198). There may also be a therapeutic benefit for the women associated with using their experiences to help others.

People may, however, find it challenging and difficult to participate in research on sensitive topics. A qualitative interview may evoke feelings and thoughts that are new to the participant, and which may cause anxiety and sadness and alter her self-understanding (177). An example from one of my interviews is the woman who, in response to the question about feelings of guilt or sorrow for passing on a mutation, said: “I have never had such feelings. If I have them they are well hidden, and so they shall continue to be.” At her annual follow-up a year later, the nurse asked if she wanted to see me, and she did. She then expressed gratitude for having participated, and said that she was doing fine despite the fact that she had felt the interview setting had been challenging. Even though she had felt it had been difficult to talk about her feelings during the interview, she did not regret participating. She asked for the published paper, which I gave her. After reading the paper, she wrote to me to say: “I obviously do not remember what I said [in the interview], but I recognize my opinions after reading it [the paper], like you said. Your conclusions—as I read them—are something I agree with.”

The researcher, as well as the participant, can find research on sensitive topics demanding. Dickinson-Swift and colleagues discuss a number of challenges a researcher faces throughout the research process (199). When you do qualitative research on human beings, they do not simply offer you a blood sample—they offer you words. They give you words as part of their life story and let you enter their lives. Their stories may evoke different feelings in the researcher. Examples of feelings are vulnerability and a need to spend more time on the interview than planned. Furthermore, the researcher may feel a need for reciprocity, acquire a sense of being a secret-keeper, feel privileged in comparison to the interviewee, feel incapable of facing the participant’s feelings, or develop a fear of becoming desensitized or immune to sad stories.
My clinical experience made me more prepared to hear the dramatic stories and not letting them create bodily discomfort (200) that potentially could limit what I asked, and what I was told. As a clinician, I have developed skills relating to reading body language, helping people relax, and sensory awareness. Sensory awareness is an important route into the kinds of experiences that are difficult to articulate (201). I believe these skills are important for balancing distance and proximity, and for safeguarding the participant in a qualitative interview. Several times, I felt that the women achieved therapeutic benefit from the interviews. This was not the intention, but a potential consequence (202). Fortunately, I never felt a conflict between my roles as a researcher and as a clinician.

Rare disorders do present particular research challenges. First, it may be difficult to recruit participants, just because they are few. Individuals who have participated in research previously may develop “research fatigue” where they become “tired” of partaking in research. Anonymity is also a challenge. Norway is a small country and individuals with rare disorders may know each other—or know of each other. We therefore decided to de-identify the women by assigning numbers or pseudonyms. We also chose not to identify the total number of children they had, and we de-identified the names of healthcare workers and hospitals.

4.7. Discussion of methods
In this chapter, I will offer a coherent discussion of central aspects of the methods used: recruitment and representability, user involvement, and the qualitative interview. Further, I will discuss some central criteria in evaluating qualitative research: validity, reliability, transferability, triangulation and member checking.

4.7.1. Recruitment and representability
Both the hemophilia and Fabry groups included women of different ages and from different parts of Norway. In the hemophilia group, all the women had a son with hemophilia, while not all women in the Fabry group had children with Fabry disease. We believe the women represent a varied group of Norwegians with different experiences relating to being a carrier for hemophilia or heterozygous for Fabry disease. However, recruiting individuals or parents via a voluntary registry at the Center for Rare Disorders or a patient organization may introduce sampling bias.
Several factors may influence the decision to participate or not to participate in a research study. Believing that the research study is beneficial and worthwhile motivates people to participate (203). In our sample, we may thus have recruited those who have more problems with their son’s or their own disease and those who have had more contact with the healthcare system, and thus a greater need to tell their stories. The sample lacks ethnic diversity. However, hemophilia and Fabry disease are rare disorders, and there were a limited number of individuals we could invite to participate. We believe the women in this study represent a satisfactory amount of variation and depth of human experience to highlight our research questions.

The analysis of the data from the interviews revealed that some themes were shared by both groups. However, almost all women in the Fabry group reported having symptoms of the disease, while women in the hemophilia group were asymptomatic. This fits well with the literature that shows that women who are heterozygous for Fabry disease have symptoms, while carriers for hemophilia usually do not have excessive bleeding. The number of symptomatic women in the Fabry group may have been influenced by recruitment via the Center for Rare Disorders’ voluntary registry of patients and the Fabry patient organization. We recruited the women in the hemophilia group via their symptomatic sons. Because of the differences in how the disorders affected the women in the Fabry and hemophilia groups, we presented the results in separate papers. In retrospect, some themes were quite similar and could have been presented in a joint paper.

4.7.2. User involvement
User involvement means involving users or affected individuals in every step of research, from planning the project to publishing the results. We can view such collaboration as a validity lens that adds credibility (204). User involvement is a valuable policy for ensuring that research is focused on topics important to the people we study. User involvement has become a prioritized area the last few years. In 2012 when I started my project, it was not so common to have a reference group or user involvement. However, user involvement is a guiding principle and permeates all activities at the Center for Rare Disorders. The nurses at the center involved with hemophilia and Fabry disease provided important input regarding their knowledge of
what was important to affected individuals and families. I did not have a reference group, but I kept in contact with the nurses working with hemophilia and Fabry disease and the patient organizations throughout the study. During the study, I also presented preliminary findings at hemophilia and Fabry disease patient organization meetings and participants could give me feedback.

In Norway, user involvement is now a criterion for most agencies that provide research funding. In the absence of user involvement, the researcher has to “substantiate the reason for not collaborating with the users or patient group in applying for research grants in clinical studies” (205). User involvement is not only a criterion for applying for research grants; the patients in Norway have a right by the Norwegian law (206) to participate in research as well.

One challenge with user involvement in research on rare disorders is that the number of individuals with rare disorders, or parents of children with rare disorders, is by definition low. This can lead to “overuse” of the same people and exhaust them. The disease and illness may also hinder people in participating in user involvement. Researchers and institutions providing grants for research should be aware of this.

**4.7.3. The qualitative interview**

A qualitative interview attempts to grasp the different meanings of experiences and important issues for the interviewee (177). The interview is a conversation between the researcher and the interviewee, and it is this conversation that is the research instrument (207).

A qualitative research interview is a craft: a skill that must be learned (177). I had respect for this, as I knew I had more skills in doing a clinical anamnestic interview than a research interview. In an anamnestic interview, the doctor asks questions and analyzes and interprets information to understand the patient’s status— to treat and to help. A researcher asks questions to explore the participant’s experiences, meanings, or descriptions of the life she/he lives, in an attempt to interpret the meaning of the described phenomena. Usually researchers maintain a monopoly of interpretation over subjects’ statements (208). Interestingly, both anamnestic and qualitative interviews
involve power asymmetry in the sense that it is through the conversation the doctor or researcher achieves her goal.

When I started my PhD I was a novice in qualitative research, and I therefore asked my main supervisor to attend my first interview, with approval from the participant. My supervisor could then guide me in how I could improve my interview technique and verify that the interview guide was appropriate.

Many factors influence a qualitative interview—for example the physical setting, the participant and researcher’s ability to trust each other and relax, and the allotted time. Rich data material depends on the researcher’s investment of time and effort in establishing an atmosphere where the participant feels comfortable and relaxed, without feeling pressured or invaded (187). I did allow a generous amount of time for each interview, and I felt it was easy to help the interviewees relax. The women seemed comfortable and it did not seem difficult for them, for example, to tell stories about negative encounters with healthcare professionals.

The mothers of boys with hemophilia in particular had many stories about encounters with doctors who lacked knowledge and were unwilling to seek appropriate information. Some mothers had dramatic stories about how their sons were diagnosed with hemophilia after a trauma. Even though it was not my intention to investigate these dramatic stories in this study, I did not stop the women from telling these stories. I later, when listening to the interviews, drew some possible conclusions as to why I did not try to guide the women away from these stories. I had the impression it was extremely important for them to tell these stories, and I was afraid I would misuse their trust, and ruin the good atmosphere of the interview, if I cut them off. Moreover, I believe these stories influenced how these mothers viewed themselves as carriers. I was also aware that you cannot hurry a good interview or push the participant to disclose something she does not want to tell (209). However, I do not think the mothers would have told as many medical facts to a researcher without a medical background.

I did not take many notes during the interviews, as I wanted to focus on the participants. Digital records of interviews are a suitable means of collecting data, as the researcher can focus on the participant undistracted by note-taking. Digital records document
pauses, hesitation, laughter, and crying; however, nonverbal communication is missed. After each interview, I wrote a short summary with my immediate thoughts.

All research builds on interpretation. In this study, the results builds on what the participants presented in the interviews, our analyses and interpretations, together with relevant concepts and existing knowledge in the field. A face-to-face interview will be richer than a written text in terms of nuance and depth. To stay as true to the face-to-face interview as possible, I chose to note in the transcripts places in the interviews with pauses, laughter or crying. I felt these events were important in the analytical process. Sometimes a participant would pause, or cry and this made me more aware of how difficult she felt a topic was. Sometimes a woman used laughter to make a difficult topic less difficult to talk about. My previous clinical experience made me alert to such issues.

Data saturation is often cited as a criterion for sample size (178) and is usually defined as the point where additional data do not generate new information (178). In qualitative interviews, when a number of participants have been interviewed and the next interview fails to provide new information, saturation has been reached. The researcher’s point of view may influence her/his perception of saturation. One researcher may find something new and interesting in an interview, which another researcher overlooks. Consequently, the concept is contested (210). Nevertheless, research shows that six interviews may be enough, and the difference between six and 12 interviews is very small (211).

4.7.4. Validity

The results from research, quantitative or qualitative, do not constitute the “one and only” truth. Validity, or credibility, addresses whether a research method measures what it was intended to measure (177, 178). Validity can be classified as internal validity which refers to whether identified effects are caused by the variable(s) under study, or as external validity, which refers to whether results are generalizable from the sample to a wider population (178).

The aim of this study was to explore experiences of being a carrier for hemophilia or heterozygous for Fabry disease. I decided that a qualitative interview study was an appropriate method for the research question, as a criterion for internal validity. According to Kvale and Brinkmann (177), validity must be present throughout the
entire research process: from planning, to carrying out interviews, to transcription, to data analysis, to reporting results. Validation entails controlling every step in the research process, critical thinking and interrogating the analytic process and the reporting of results (177). I reflected a great deal about my role as a researcher and my pre-understandings, from the start of the project and throughout the research process. During the research period, I discussed every step of the process from the planning to the reporting of the results with my supervisors. Via discussion at the various steps, my supervisors provided guidance and asked questions that helped me reflect on validity.

I will discuss whether one can generalize the results to a wider population than our participants, as a criterion for external validity, in the section on Transferability.

4.7.5. Reliability
Reliability is present when the results are consistent over time and present an accurate representation of the total population under investigation—in other words, reliability is a measure of the trustworthiness of results (177). In quantitative research, the results are reliable when replicated in repeated experiments using the same methods. Qualitative research is, however, not an experiment with cells, chemicals or numbers, and will be influenced by context. For a qualitative interview, the context will, for example, include when and where the interview is conducted, the interviewer, the interviewee, and the interview format.

An altered context can change the results of an interview. The interviewee may, for example, experience events in the time between two identical interviews that can influence his or her responses. All stories are also likely to change with retelling (209). In qualitative research, the researcher is an instrument for collecting and analyzing data. Qualitative researchers indeed acknowledge that the researcher, whether she intends to or not, influences the research process and the knowledge produced (178). Therefore, reliability, in the sense of generating the same results when the same measurements are administered by different researchers to a different participant group, is not an appropriate criterion for assessing quality in qualitative research (178).

I reflected on my influence as a researcher throughout. I have justified my choices of methods in a transparent way, describing the recruitment, the conduction of the
interviews, and the analytical processes. In the interviews, I used open-ended questions, and avoided leading questions. I carefully checked the transcripts of all interviews for errors and nuances by listening to the taped records. The preparation of the interview guide and data analysis was informed by discussion with my supervisors, who co-authored my papers, and these factors strengthened the reliability of the study. I included verbatim quotations in the findings of papers I–III, which can assist the reader in assessing the trustworthiness of the research.

4.7.6. Transferability
Generalizability refers to the extent to which one can extend the account of a particular situation or population to other persons, times, or settings than those directly studied (177, 178). However, in qualitative research, the concept of transferability is more common. Transferability refers to how and if the qualitative research results can be transferred to other groups of people and contexts (178).

The researcher should provide a detailed contextual description and argue for transferability. The reader can be given a basis that allows her or him to evaluate the potential for applying the results to other participants and contexts (177, 178). I was transparent about the different steps in my research and provided detailed information about participants and contexts. The verbatim quotations I presented in the findings of papers I–III will help the reader to assess whether the findings may be transferable to their practice.

Norway has a publicly funded one-payer universal healthcare system. Home treatment, for hemophilia (since 1975) and Fabry (since 2007) has a long tradition. The situation in other countries may be quite different when it comes to both disorders, especially because treatment is expensive, thereby limiting the transferability of some of our findings.
In practicing and reading qualitative research, it is important to remember that qualitative research may provide some answers and explanations, and may give indications of how things are experienced. Qualitative studies do not provide facts that are applicable to an entire population, but rather descriptions, notions, or theories that can be applied within a given setting (184). The purpose of my study was not to quantify and generate generalizable data from a large population, but to gain increased
insight into and knowledge of experiences of being a carrier or heterozygous for an X-linked disorder. When discussing transferability, the identification of varying degrees of similarity and difference can provide a mental map of the sites to which transferability can, or cannot, be extended (212).

The two diagnoses represented in my study, hemophilia and Fabry disease, have some similarities and some differences, as discussed previously. The results from the two groups did, however, show that some experiences were shared. By identifying similarities and differences with other genetic diagnoses, I believe that women who are carriers or heterozygous for other X-linked disorders may also recognize themselves in what we describe. Furthermore, I believe that the mothers of children with rare disorders other than hemophilia may recognize the findings presented in paper III.

4.7.7. Triangulation

Triangulation and member checking are techniques used to improve the quality of qualitative research. The aim of triangulation is to increase the understanding of complex phenomena (184). Triangulation compares the results from two or more different methods of data collection, or from two or more data sources (178). This allows the researcher to capture multiple “voices” on a topic, look for convergence in the results, and make an overall interpretation.

One way of performing triangulation is to use a mixed method of quantitative questionnaires and interviews. Another approach is to interview the same participants more than once, or to interview two different groups, for example affected individuals, and their family members, or their doctors. I chose to interview participants from two different groups.

A quantitative study with questionnaires regarding psychosocial aspects could have provided additional data for the study. However, Fabry disease and hemophilia are rare diagnoses, and I anticipated difficulty in achieving a sample size that would confer sufficient power.

I interviewed women, as the aim of the study was to explore women’s psychosocial experiences of being a carrier for hemophilia or heterozygous for Fabry disease, and not
those of their family members or healthcare workers. Looking back, however, it would have been interesting to have healthcare workers’, especially doctors’, views in paper III about mothers’ experiences on treatment of their sons. However, paper III grew out of an inductive analytic process, and I did not foresee that the mothers would be so concerned with this issue.

4.7.8. **Member checking**

With member checking, the researcher checks her analyses with study participants (178). One way of doing this is to let the participants read their interview transcripts and/or participate in the analyses. Another option is to present the analyses for the participants and identify whether they recognize the findings.

I presented the analyses and preliminary results, and later the results in all three papers at various national and international meetings. Some participants from my study may have attended these meetings, as well as many non-participants. My approach cannot be viewed as genuine “member checking” (178), but as a variant of internal validation. I also presented the results from the three papers at different international meetings for healthcare workers, nurses, and doctors and experienced that they recognized what I presented and related my findings to their experiences with carriers for hemophilia and heterozygous for Fabry disease. By not using member checking in the process of analyzing, I avoided several potential practical problems. Member checking may be problematic if participants are reluctant to be involved, if they disagree with the analyses, if they give contradictory feedback, or if they are reluctant to express doubts or argue with the researcher given the power dynamic (178).

The feedback I received from patients, carriers, heterozygotes, and healthcare workers was important guidance. In addition, I received an email from a carrier for hemophilia, who did not participate in the study, but who read a paper (paper II) and recognized experiences described therein. One of the participants in the Fabry-group wrote me a letter after reading paper I and said she could recognize the descriptions and confirmed that they were presented the way she experienced them. This feedback was also important to me, as it confirmed I was close in capturing the participant’s experiences. In conclusion, I feel that presenting the results to both participants of the study, and other carriers for hemophilia and heterozygous for Fabry disease, as well as healthcare
workers gave me a good indication that I was close in capturing the participants’ experiences and analyzed and presented them in a correct and respectful way.

4.7.9. **Strengths and weaknesses**

One could argue that individuals in (frequent) contact with the healthcare system and the Center for Rare Disorders have more health-related, and perhaps psychosocial, issues than others. As a consequence, the selection of participants in this study may be biased toward women who have experienced more challenges with their son’s or their own disorder. The sample is relatively homogenous culturally, which may be reflected in the consistency of viewpoints expressed. I may have recruited women who are more vocal after negative experience(s). The age range among participants may constitute a strength: opinions and viewpoints may vary with one’s stage in life. In this study, I asked women to remember how they felt at the time of diagnosis or when made aware of their carrier status; recall bias is therefore an issue. One way to reduce recall bias could be to perform a second interview with the participants.

I had not conducted qualitative research interviews previously, and this may be a weakness, as experience in doing qualitative research interviews improves skill. However, it may be a both a strength and a weakness that I have substantial experience in conducting anamnestic interviews. It may be a strength because I am familiar with interviewing individuals and grasping important elements of their stories. However, it may also be a weakness because I could potentially have lost focus of the research question in an attempt to care for the interviewee.

Because of the rarity of the diagnoses and potential challenge of recruiting participants, I did not perform a pilot interview: I was hesitant to “waste” an interview. In retrospect, I think I should have, as this would have left me better prepared me for the research interview. On the other hand, I believe preparation requires more than a single pilot interview, and a qualitative interview guide often evolves across the entire data-collection process. It may be a weakness that the interview guide lacked precision initially. However, it may also be a strength, as this let us “throw a wide net” and encompass many relevant aspects in the first few interviews. We reviewed the interview guide after the first few interviews and were able subsequently to focus on the main topics raised by the initial participants.
It may have been a strength that I am a doctor and familiar with the diagnoses and with medical terms. Because of this, the women did not have to explain things to me. On the other hand, it may have influenced the women to avoid conveying important aspects of how they experienced encounters with healthcare workers. Being a woman may have been a strength, as the participants may assume that I can relate to their stories more easily than a man might. However, it may be a weakness because they may have neglected to express or explain things because they took for granted that “a woman understands.” Being a mother and clinical geneticist may have helped me to connect with the women and focus on the issues that were important for them.

It is a weakness that I lacked a user reference group. However, it is a strength that I had close contact with the nurses involved in the treatment of participants or participants’ family members. Furthermore, it is a strength that I presented preliminary results at lay organization meetings several times where I had the opportunity to discuss our findings. It is also a strength that my supervisors, with their varied professional backgrounds, guided me through the process from developing the project and the interview guide, conducting the interviews and analyzing the data. It may be a strength that I conducted all the interviews, as this promoted consistency: it may also be a weakness. When a single researcher performs all the interviews, there is a potential for unrecognized blind spots or poor chemistry between the researcher and the participant.
5. Summary of the results

5.1. Paper I

von der Lippe C, Frich JC, Harris A, Solbrække KN.
Experiences of being heterozygous for Fabry disease: A qualitative study.

The aim of this paper was to explore women’s experiences of being heterozygous for Fabry disease. Our research questions were: What psychosocial issues related to the condition do women heterozygous for Fabry disease experience? How do they experience encounters with healthcare professionals?

This paper is based on empirical data from semi-structured interviews with 10 women heterozygous for Fabry disease. The women were ethnic Norwegians, aged 24–77 years (mean = 54), and lived in different parts of Norway. Five of the women had children with Fabry disease, three had children who did not have Fabry disease, and two did not have children. Six women received treatment for Fabry disease. We used an inductive thematic analytical approach in analyzing the interviews.

We identified three main themes: learning about being heterozygous for Fabry disease, coping with Fabry disease, and experiences with follow-up and treatment. We found that most participants had learned about the Fabry diagnosis/heterozygous status as adults after a father, brother, son, or daughter had been diagnosed with the disease. Even though some women had had symptoms for many years, some since childhood, they reported that no one had considered Fabry disease until another family member was diagnosed. They shared stories about not being taken seriously when reporting their symptoms. Thus, for most women, learning about one’s heterozygous status, as well as doctors’ acceptance of symptoms in women heterozygous for Fabry disease, provided a causal explanation and relief. The recognition of Fabry disease represented a major change in how the women regarded themselves and how healthcare professionals and others understood their symptoms. However, for a few, it was devastating to learn about
their heterozygous status, having a diagnosis of Fabry disease, and starting with treatment, as this changed their identity from “healthy” to “ill.”

Although many women did not consider themselves ill, especially compared to male relatives with Fabry disease, and thus wanted to identify themselves as “carriers,” they also wished to be acknowledged as more than “just carriers” by healthcare professionals.

Most participants described challenges in communicating about the genetic disorder with their family members, although they thought it was very important to be open to it. Even if the diagnosis explained many years of “unease,” it was essential for all the women to make a distinction between Fabry disease and daily life, and not draw attention to the diagnosis. It was very important for them to be able to have treatment without absence from work.

The participants were grateful for enzyme replacement therapy, although treatment involved time, planning, and absence from school and work. Women commonly experienced deep frustration and worries related to lack of healthcare providers’ knowledge of Fabry disease. Finally, we found that the women experienced feelings of guilt for passing on a mutation for Fabry disease to children and grandchildren.

We concluded that healthcare professionals should acknowledge the different ways women react to the knowledge of being heterozygous for Fabry disease; for some, the diagnosis is a relief, for others a disaster. It is important to stress that women are not “just carriers,” but remember that it is important for the women to separate their daily life from the diagnosis. Health professionals should acknowledge feelings of guilt and difficulties in communication about the genetic disorder in the family and provide personalized information, support, and management to patients with Fabry disease.
5.2. **Paper II**

von der Lippe C, Frich JC, Harris A, Solbække KN.

“It was a lot tougher than I thought it would be.” A qualitative study on the changing nature of being a hemophilia carrier.


The aim of this paper was to understand more about the psychosocial aspects of being a hemophilia carrier over time.

The empirical data used in this paper were drawn from semi-structured interviews with 16 women who are carriers for hemophilia A or B. The women, all ethnic Norwegians and from different parts of Norway, were aged 27–72 years old (mean = 42 years), and all had one or more sons with hemophilia A or B. We used a qualitative inductive analytical approach for analyzing the data retrieved from the interviews.

We identified three main themes: Guilt and sorrow across generations, choices relating to and consequences of genetic testing, and preparing to have a child with hemophilia. We found that experiences of guilt and sorrow ran through generations. The women expressed feelings of guilt and they also told stories about fathers and grandmothers who expressed feelings of guilt. However, not everyone felt guilt. One woman thought this was because her son never had experienced severe complications with his hemophilia and the treatment had been uncomplicated.

We also found that the experience of being a carrier for hemophilia changes over time. Most women expressed that they did not really worry much about the positive result of a genetic test when they were young, as the consequences felt far in the future. However, when it came to planning for a family and having children, when being a carrier could have an actual consequence, the women thought about difficulties a future son with hemophilia could face, as well as challenges for other family members. Thus, carrier status may create “mothers-in-waiting,” who live knowing of a risk of having an affected child in the future. Many women thought they were prepared to have a son with hemophilia but experienced more sadness than expected when a son was diagnosed.
We concluded that healthcare professionals, carriers, families, and patient organizations need to be aware that women’s experiences of being a carrier for hemophilia changes during life. Women may benefit from several rounds of genetic counseling at different stages. Follow-up counseling should be offered. Women may not be prepared for the shock of having a son with hemophilia, even if they believe they are. Healthcare professionals need to be aware of this and “stand-by” with support as needed.
5.3.  Paper III

von der Lippe C, Frich JC, Harris A, Solbraekke KN.
Treatment of hemophilia: A qualitative study of mothers’ perspectives

The aim of this paper was to investigate how women who are carriers for hemophilia and mothers of boys with hemophilia, experience the treatment of their sons in a hospital setting and at home.

The empirical data used in this paper drew on the same 16 semi-structured interviews as paper II. The participants were women who are carriers for hemophilia A or hemophilia B. The women were all ethnic Norwegians and from different parts of Norway, aged 27–72 years old (mean age = 42), and have or have had one or more son with hemophilia A or B. We used a qualitative inductive analytical approach to analyze the data retrieved from the interviews.

We identified three main themes: challenges with treatment, advantages with home treatment, and trust and mistrust in doctors. We found that mothers experienced both practical and emotional challenges in relation to their sons’ treatment. Repeated venipuncture was especially difficult emotionally. Going on vacation could also be a challenge, and the mothers preferred to travel to places and countries where they knew access to proper treatment in a hospital was available. Concerns were raised about healthy siblings and treating children differently. Parents preferred home treatment to hospital treatment because it was less time-consuming, less disruptive to family life, and provided a greater sense of control. Home treatment also allowed the children to be perceived as “normal” because they were able to avoid absence from kindergarten and school.

Encountering healthcare professionals who were unfamiliar with hemophilia was a major stress factor, especially when the parents felt that healthcare professionals lacked competency and were unwilling to seek advice. Mothers accepted that not all doctors had extensive knowledge of hemophilia but found it difficult when they perceived that physicians were unwilling to admit their shortcomings and seek information and advice.
Many mothers said it was most difficult when the doctors attempted to disguise their lack of knowledge. This could lead to mothers’ lack of trust in doctors and avoidance of contacting the hospital in situations when they should.

We concluded that while home treatment for hemophilia enables freedom, flexibility, and autonomy for the boys as well as for the families, mothers might experience treatment in general as a burden. Healthcare professionals should provide tailored practical and emotional support to parents by actively exploring their experiences with treating their sons’ hemophilia.
6. Discussion

The main question investigated in this study is: How do women heterozygous for Fabry disease or carriers for hemophilia experience the psychosocial aspects of these conditions? We found that women who are heterozygous for Fabry disease may react with relief, but also in some cases be devastated when diagnosed. In many instances, the diagnosis provided an explanation for chronically unexplained symptoms, thus eliciting acceptance from healthcare providers and opening the avenue for treatment. Participants who were asymptomatic carriers for hemophilia reacted differently to a carrier diagnosis. Their experiences changed over time, depending on whether a carrier status raised questions about reproductive issues. Further, we found that feelings of guilt and sorrow were common in both the Fabry and hemophilia groups. In addition, we confirmed that communication about genetic disorders can be challenging, both within a family and in the healthcare system. Healthcare professionals’ lack of knowledge about Fabry disease and hemophilia, and especially their unwillingness to admit to a lack of knowledge, was worrisome and frustrating.

In this chapter, I will discuss the impact of our findings, focusing on the social dynamics of being a carrier, and guilt and stigma associated with genetic disorders. Finally, I will contextualize selected aspects of genetic counseling and communication about genetic disorders.

6.1. The social dynamics of being a carrier

The distinction between illness and disease is important in a genetic context and in interpreting the results of this study. It is also important in discussing the social dynamics of being a carrier. The present study showed that women who are heterozygous for Fabry disease had experienced symptoms and illness for years, without recognition of their disease by medical professionals (physicians). It is reasonable that the first doctor a patient sees, usually a general practitioner (GP), does not recognize the presence of Fabry disease. The disorder is rare, and there is often a substantial delay in diagnosing rare disorders in general (17-19, 213). Moreover, symptoms of Fabry disease are often common and non-specific, e.g., stomachaches, muscle pain, and tiredness. There is overlap with more common disorders, such as fibromyalgia, a condition many medical professionals view as low in prestige (214).
Furthermore, medical professionals may assume that women over-report complaints. In their study on patients in primary care in the USA, Kroenke and colleagues concluded that women reported more symptoms than men and that medically unexplained symptoms were more common in women (215). However, another study based on a survey of a selection of the general population in Scotland on how men and women report illness concluded that the likelihood of reporting a condition was not higher in women (216). Nevertheless, when a woman seeks medical help, the doctor should pay attention to her story. If doctors do not take women’s illness narratives seriously, women may not disclose symptoms (217). Diagnostic clues may be present in the family history. However, GPs may not have sufficient time and knowledge of genetics to obtain a family history (218).

Importantly, a woman is commonly the primary caretaker in a family, and one can assume it is important for a caretaker to take care of herself. Healthcare professionals and lay people may even view good health as a moral responsibility, and individuals may fear stigma for not responding to symptoms (219). However, because the symptoms of Fabry disease may be so “common” in the general population and symptoms may be stigmatizing, women may not seek medical attention. Some women may not even experience their symptoms as illness because a close family member has more severe symptoms and they do not feel ill by comparison. Comparing oneself to others with more severe symptoms may also serve as a coping strategy (153).

Good health may be essential in managing caretaking. A recent study from the USA concluded that health-related quality of life among adults living with a rare disorder is poorer than in the general population (213). Interestingly, this study demonstrated an association between time to diagnosis and well-being: shorter time to diagnosis correlated with reduced fatigue, anxiety and depression, and an increased ability to partake in social roles and activities (213). Individuals may experience relief upon reaching a diagnosis, even if it initially comes as a shock (220). This is analogous to our finding that living with the symptoms of Fabry disease was more difficult when the underlying diagnosis was unrecognized. Although carriers for hemophilia in the present study did not report excessive bleeding it was important for them that a cause of their sons’ serious disorder was identified. This illustrates the importance of identifying a
causal explanation, even if the disease diagnosed is serious and inheritable. This is in line with van Manen’s theory of the healing effect of explanation (221).

Women who are heterozygous for Fabry disease and mothers who are carriers for hemophilia shared a desire to separate daily life from disease, for themselves and their sons. It was important for them, or their children, to have treatment while minimizing absences from work or school. They appreciated the option of having treatment at home or in a hospital setting at a convenient time. The mothers of boys with hemophilia mentioned home treatment as one important dimension in feeling normal. Participants reported that visits to the doctor or hospital exacerbated their and their children’s feelings of illness. By reducing the number of hospital visits, they reduced their feelings of illness and felt that normality was promoted. This fits well with research on both rare and more common disorders, where mothers report that avoiding making the child feel “ill” is of utmost importance for preserving normality (220). For Goffman (157), visibility is the prime marker of stigma. Visibility does not have to be related to appearance. The absence from work or school and IV-infusions are indeed visible to others. The present study indicated that receiving treatment at home reduced visibility and perceived disease-associated stigma. Importantly, the number of hospitalizations and the degree of a child’s functional impairment correlate with increased parental emotional problems (222). Healthcare professionals can help normalize daily life, and improve health, for patients and families by facilitating home treatment and reducing patients and families’ contact with the healthcare system.

The present study revealed that the presence or absence of symptoms was important for how women thought about their status as carriers or heterozygotes. Women who were unaffected carriers for hemophilia reacted differently than women with Fabry disease. Carriers for hemophilia had learned of their status at different stages in life. Some knew about hemophilia in the family and learned about their carrier status around 16 years of age, while others first learned of their carrier status following their son’s diagnosis. Those who learned about their status at a young age did not experience a significant impact initially. However, as they grew older and reproductive issues became relevant; their carrier status acquired a different meaning. Learning about one’s carrier status was not a “telling moment” (223), but rather a process that developed over time similar to a diagnostic process (224). Carriers face different challenges at different stages in life.
Carrier testing for hemophilia, and perhaps other X-linked disorders, may create “mothers-in-waiting” contemplating the risk of having a sick child. Women who knew they were carriers and thought themselves prepared to have a child with hemophilia, experienced an unexpected degree of shock and sadness upon their son’s diagnosis. There are things in life one cannot fully prepare oneself for, and healthcare professionals should offer extra support flexibly as needed.

The present study demonstrates that there are several dimensions in the social dynamics of being a carrier for, or heterozygous for, a genetic disorder. Clinical geneticists and genetic counselors should be aware of these dimensions. As genetic technology makes personalized treatment increasingly possible, healthcare providers who counsel women who are carriers for X-linked disorders also need to be cognizant of the need for personalized counseling at different stages in life.

6.2. Guilt and stigma in genetic disorders

We found that feelings of guilt were a common theme in both groups of women. This fits well with previous research showing that feelings of guilt are common in heritable disorders (104, 159, 173). Our results demonstrate the additional finding of “trans-generational” guilt, in that feelings of guilt may plague women and men in more than one generation. Even in the late 1940s, medical geneticists working in the earliest genetic clinics recognized that families confronted with hereditary diseases faced dilemmas concerning reproductive decisions. They also acknowledged that guilt, blame and stigma are often experienced as a result of having, or passing on, a genetic disorder (225). The present study demonstrated that although healthcare professionals may be aware of guilt and shame related to genetic disorders, this does not translate into strategies that lessen or alleviate people’s feelings of guilt and shame. Within families, negative emotions present in several generations may be considered “normal” and therefore be difficult to eliminate.

Reviewing the history of genetics may provide a partial explanation of the survival of guilt through generations. Genetics is a word with complex meanings in contemporary society. For some, the word may be associated with “genetic hygiene.” In the past, doctors gave medical advice to discourage reproduction in those considered “unfit,” aiming to reduce the incidence of certain diseases or conditions that were regarded as
burdens on society (225). Löwy’s historical work on prenatal diagnostics (PND) showed that physicians have considered genetic disorders incurable and that the only means of prevention was viewed as preventing the birth of persons with such disorders (226). Although information about PND is provided with good intentions today, healthcare professionals need to be aware of the potential side effects of risk communication (227). Providing health education may inadvertently create fear, humiliation and shame (227).

Most people know that you cannot influence the genes with which you are born. However, people have several choices when it comes to reproductive decision-making. Options can include choosing not to have children, abstaining from prenatal testing, a noninvasive prenatal test (NIPT) to determine the child’s sex, PND to determine if the fetus has inherited the family’s mutation(s), and termination (or not) of the pregnancy with an affected fetus. Preimplantation genetic diagnostics (PGD) is technically often possible but may not be readily available. PGD is not performed in Norway, and publicly funded financial assistance at a center outside Norway requires that a couple has a high probability for the transmission of a serious, non-treatable disorder. Applications for financial assistance are made to a board comprised of pediatricians, medical geneticists, lawyers, and lay people: the PGD-nemnda (228). However, who can decide if a disease is severe “enough”? The doctor? Society? Alternatively, is it the woman who is a carrier and perhaps has lived her life with a child or relative who has the disease? In addition, what does it really mean that treatment is available? Moreover, what costs does treatment entail, not just economically but psychosocially?

There is no curative treatment for most genetic disorders; treatment is usually symptomatic. Women in both groups in this study were grateful to live in a country where symptomatic treatment is available. However, they described several treatment-related psychosocial challenges regarding their own treatment (Fabry group) or their son’s treatment (hemophilia group). They specifically mentioned the lack of flexibility, the need for planning, time requirements, and absences from school or work. Chronic illness can be understood as a biographical disruption (98). Only the individual and his/her family can fully appreciate the consequences the disease and illness confer on daily life, expectations, plans, and the future.
Another element that may have a negative impact on people with genetic disorders or their relatives is how the media refer to rare disorders. What does it mean to become aware that others may consider individuals with rare disorders to have “less worth”? What are the effects of publicizing the high costs of medications for rare disorders? Moreover, how will it affect an individual to know that there is treatment that may be effective, but that it is not available? The expression of such opinions and discussions in the public sphere may create, or increase, feelings of guilt. Thus, healthcare professionals need to be aware of how these discussions can potentially affect people already facing extra demands and difficult decisions.

Another and even more relevant question to raise in the context of stigma and shame is the following: To what extent do people who carry a mutation have a real choice about decisions regarding PND? Schwarz discusses choice as a cultural phenomenon, arguing that culture shapes choice, the set of alternatives, choice processes and the ascription of choice (229). Our participants were not asked for their opinions about PND; however, while discussing guilt one could question whether the available choices of PND can contribute to or create feelings of guilt. In a society in which advanced technology is available (and publicly funded) choices may be both shaped and restricted. One could argue that the increased accessibility of genetic testing creates a standard of what society expects people to choose. As a result, carriers may not perceive PND as a choice, but as mandatory. A woman may feel she should choose society’s “acceptable” choice. A perceived “acceptable” choice for one woman may, however, not be the same for another. Nevertheless, technology is without a doubt helping many individuals and families with rare disorders, providing causal explanations, knowledge about prognosis, and in some cases, specific treatment, as well as choices in reproductive decision making.

Although in the final analysis a woman makes her choice, she deserves support from professionals involved in her care. Based upon the results in this study, it is relevant to argue that healthcare professionals should probe a woman’s social, cultural, and psychological background, counsel her individually, and support her choices. Healthcare professionals should address problematic questions and support patients, mothers, and other relatives in challenging situations that may involve compromises. If a woman decides to continue a pregnancy with a fetus with a genetic disorder, she
should be reassured that the healthcare system and society will provide services and support for her and for her child. Support and the normalization of difficult feelings may not hinder negative emotions, but may ease the pain associated with them.

Increased possibilities for genetic testing before and after birth is an issue we need to reflect on in a discussion of guilt. Healthcare professionals should be aware of the possible psychosocial “side effects” created by increased accessibility of and choices in genetic testing. That is, by offering extended genetic testing, healthcare professionals need to be aware that genetic information has the potential to change one’s personal life through labelling and stigmatization. Healthcare professionals need to remember the personal and social costs involved in being confronted with moral responsibility and choice (135, 230, 231) and the risk of discrimination (232). Healthcare professionals should remind themselves of the basis of the Norwegian Biotechnology Act:

The purpose of this Act is to ensure that medical applications of biotechnology are utilized for the benefit of everyone in an inclusive society. This shall be done in accordance with the principles of respect for human dignity, human rights and personal integrity and without any discrimination on the basis of genetic constitution, on the basis of the ethical norms that form part of our Western cultural heritage. The Biotechnology Act, 2003, § 1-1, official English translation (233).

When people recognize that they have done something wrong, or not done something they should have done, guilt arises. Guilt may help individuals to understand if they do things they should not and allow them to say, “Sorry.” However, for women heterozygous for Fabry disease or carriers for hemophilia feelings of guilt may be destructive and inhibitory on a personal level as well as on a family level. This study shows that the severity of the child’s symptoms, or lack of serious symptoms, influenced the amount of guilt mothers felt. An example is the mother of a boy with hemophilia without severe symptoms who did not have feelings of guilt and hypothesized herself that this could be related to her son’s benign course. Viewing this in light of Link’s and Phelan’s definition of stigma where elements of labeling, stereotyping, separation, status loss, and discrimination co-occur in a power situation (158), one could argue that the grounds for stigmatization are not very strong in a
disorder with the absence of severe symptoms and without visible characteristics, and therefore less feelings of guilt result. A choice not to focus on negative feelings or thoughts can also be a coping mechanism (234).

Social norms that presume “perfect health” most likely influenced the women in this study and may strengthen carriers’ feelings of guilt and stigma in a genetic context. If a mother feels shame, it may impair the relationship she has with her affected child and with her healthy children. Mothers in this study did express concerns about treating their children differently. Some felt they were overprotective of, and reluctant to be equally strict with, an affected child. A review of the psychosocial well-being of children with chronic diseases, their parents, and siblings showed that psychosocial functioning, peer activities, and cognitive development were lower for siblings compared to controls (222).

Although shame and blame are often not mentioned in a medical encounter, they do exist. Guilt, shame, and stigma are often interrelated. Patients with lifestyle diseases may experience feelings of guilt, due in part to interactions with medical professionals (235, 236). Patients also blame themselves for diseases, and for some the self-blame coupled with fear of blame from healthcare professionals may contribute to their reluctance to seek healthcare (237). Shame is something we begin to develop as young children, and there is a gender difference. Girls experience shame more often than boys (238). This difference is present in adults as well. Women, especially women with typical female gender roles, report higher levels of shame and guilt than men (239, 240). If a family has not communicated about their genetic disorder, it may create shame, as secretiveness can perpetuate feelings of shame (241). Many mothers in the present study blamed themselves for transmitting the family’s mutation to the next generation and felt sadness for “causing” illness and pain in a child. This adds an extra dimension to motherhood. Mothers will likely not tell their doctors directly that they feel ashamed or have feelings of guilt. Not addressing shame and guilt in the medical encounter may lead to it becoming “the elephant in the room” (242). Most doctors will probably be hesitant to address shame and guilt for several reasons. To ask a mother to acknowledge feelings of shame or guilt may make matters worse. The discussion of sensitive and difficult issues may be time-consuming and challenging for all parties. The lack of time is unfortunately often an issue in medical consultations. However, related to the
findings in the present study, I suggest that the doctor pays close attention to the mother’s non-verbal communication, and if she seems sad, the doctor could gently probe the issues of shame and guilt, for example, by saying: “I know this can be difficult [knowing you carry the mutation]. Not all, but some mothers have told me they feel guilty for passing on the mutation to their child.” Confirming that others harbor similar feelings of guilt or shame can have a “normalizing” and thereby therapeutic effect. In contrast and somewhat paradoxically, expressing an understanding of these emotions can have the unintended effect of strengthening their potency (243, 244).

Many participants had experienced doctors with a lack of knowledge of their rare disorder and doctors who were reluctant to seek information or advice. This may enhance negative feelings, including frustration and anger. Externalizing defenses, such as anger, may signal a defense against shame (245). Healthcare professionals should consider this dimension of externalizing defense if they perceive patients or parents as hostile or angry. Anger may also create a fighting spirit, and mothers of children with rare disorders, in my experience, are generally strong advocates for their children. A poor mother–physician relationship may be devastating for the child, for example if a mother avoids seeking necessary medical attention on her child’s behalf.

Although genetic testing and the subsequent knowledge of a mutation may cause sadness and sorrow, genetic test results can also serve as a “meaning-organizer” and an emotional organizer, rendering the “problem” concrete and promoting a sense of control (246). This fits well with my findings where, in some instances, genetic testing finally provided an explanation for symptoms. Knowing you have, or will likely develop, your family’s disorder can also create a sense of belonging (247). On the other hand, being the only one in the family with a mutation can create a feeling of loneliness, as described by one participant in this study. Healthcare professionals can provide individually tailored counseling if they recognize that women who are carriers for genetic conditions may feel guilt or shame.

6.3. **Contextualizing genetic counseling and communication**

This study revealed the importance of communication in the context of rare genetic disorders. Participants described difficulties in communicating about the disorder in the family, and the study demonstrated that the experienced value of genetic information
about carrier status was dynamic over time. This shows that genetic counseling may be perceived differently at different times in life. It may also matter whether a clinical geneticist or a genetic counselor provides the information as they may use different approaches. The clinical geneticist may use a more medical approach than the genetic counselor.

Genetic counselors represent a relatively new profession (248) and make important contributions to the care and management of individuals and families with genetic disorders. The Master of Science program for genetic counselors in Norway was initiated in 2001, and the first students graduated in 2003. Genetic counselors practice across a diverse range of disorders. The Norwegian Biotechnology Advisory Board and the Norwegian Society for Medical Genetics suggested in the latest evaluation of the Norwegian Biotechnology Act that genetic counseling should be divided into different categories, dependent upon severity of the condition in question and the individual’s and family’s needs (249). One reason for this suggestion is that with the rapidly increasing possibilities for genetic testing in many different areas of medicine, there will not be enough genetic counselors or clinical geneticists to provide services, including genetic counseling, and that task-shifting is necessary and appropriate (250).

There are several barriers to integrating genetics in mainstream medicine and utilizing non-genetic specialists and primary care physicians as counselors, e.g., a lack of knowledge about genetics (251, 252). Different healthcare professionals may, however, provide genetic counseling at different levels, based on the severity of the disorder and the complexity of the information to be conveyed. More complex genetics may lead to communication challenges for non-genetic physicians because of confusion regarding genomic and genetic terminology, difficulty with the volume or complexity of information, and difficulties in communicating risk information (253). One way to address this, in addition to the increased use of genetic counselors, is to educate non-genetic specialists, in genetics and in communication, so that they can provide counseling for more common and genetically speaking straightforward disorders, such as cystic fibrosis.

The way information is communicated as well as the content of the information may influence how individuals perceive the value of genetic counseling. In other clinical
specialties, communication is more effective when it is supportive, honest, and attentive in contrast to domineering and argumentative (254) and it is safe to assume that the same will hold true in medical genetics. Communication in genetic counseling may benefit from going beyond an education focus in some circumstances to a more emotional and supportive approach (255). Patient-centered communication is a skill that must be learned and practiced (256). I believe it is important that clinical geneticists, during and after their specialization, focus on improving their communication skills. Clinical geneticists and genetic counselors should be aware of the different experiences and perspectives women may have in the context of X-linked disorders throughout life. This may, in other words, be an issue in many genetic disorders, not just the two we studied.

In a genetic counseling session, and in encounters with physicians, parents of children with chronic diseases have information needs regarding their child’s diagnosis, treatment, and prognosis (257, 258). For rare diagnoses in particular, the scarcity of information from healthcare professionals may enhance patients’ or parents’ feelings of isolation and uncertainty and be conducive to misunderstandings (258). A perception of inadequate help or the lack of interest in their child’s welfare may lead parents to seek alternative sources of information (145, 258). Consulting the internet is often, but not always, helpful: information overload, misinformation, and triggering of unpleasant feelings may result (145).

Research on genetic counseling focuses mainly on the role of genetic counselors. Why is this? Is genetic counseling provided by medical geneticists considered “good enough”? Are medical geneticists less likely to experience counseling dilemmas? Or do clinical geneticists consider research on counseling provided by them unimportant or unnecessary? Clinical genetics has not been a prestigious medical specialty or field of research (259, 260). We may look to research from other medical specialties for clues. Norredam and Album point out in their review (259) that prestige is inter-subjective and part of a culture, our shared and common understanding of the world, and our collective perceptions. These authors concluded that medical professionals considered active specialties such as surgery as having higher status than “passive” specialties such as psychiatry that use “talking therapies.”
Clinical genetics is an active specialty because it employs the newest hi-tech diagnostic modalities, and a passive specialty because of its major counseling (“talking”) focus. Album (214) ranked prestige associated with various diseases but did not include genetic disorders. However, the majority of genetic disorders are chronic and curative therapy is unavailable, two characteristics of diseases with low prestige (214). It may follow that genetic counseling is less valued than diagnostics in clinical genetics. Is it perhaps more interesting to find the cause of a disease than to provide counseling? If this is the case, a pitfall for the doctor is to focus more on genetic testing and less on the communication with the individual or parents.

Clinical genetics has evolved enormously during the last ten years, in large part driven by developments in diagnostic laboratory testing and increased international collaboration facilitated by collaborative networks such as GeneMatcher (261). We have entered a new era, the genomic era (262). Technology is shaping clinical genetics, and the practice of genetic counseling (263). The future will probably hold more use of technology including tools such as educational videos and chat-interactions (263). A recent study of alternatives for returning carrier results from exome sequencing to well-educated individuals in the post reproductive age group, demonstrated that web-based return of results may be sufficient for certain subsets of test results (264). This study highlights that the perception of test results vary with age and context. Genetic counseling always aims to be personalized, especially when reproductive decision-making is pertinent. Increasing opportunities for genetic testing necessitate more research about and a better understanding of challenges in communicating complex information and uncertainty in a manner that is helpful (265). Genetic counselors are likely to take responsibility for more counseling. One model that could help meet an increased demand for genetic counseling in selected cases would be to have the counselee(s) meet a clinical geneticist and a genetic counselor initially, and then provide follow-up consultations as needed by the genetic counselor alone with the option for re-consultation with the geneticist.

This study revealed that participants had encountered healthcare professionals without knowledge of Fabry disease and hemophilia: the women emphasized that it was not lack of knowledge they found most distressing, but rather the unwillingness of healthcare professionals to probe the women’s knowledge or to seek information and help
appropriately. Mothers in this study were expert caregivers (266). However, it takes time to become an expert caregiver, and in the process parents may have difficulty identifying and expressing their information needs (257).

Finally, this study emphasizes the need for healthcare professionals to be open to, actively seek, and appreciate the expertise that individuals and families with rare disorders possess. Healthcare professionals must gather information and knowledge about rare disorders via national and international collaboration, and provide understandable and relevant information for individuals and families who have rare disorders. These are essential elements of comprehensive care.
7. **Conclusions**

The aim of this study was to provide knowledge regarding how women who are heterozygous for Fabry disease or carriers for hemophilia experience psychosocial issues related to these conditions. The findings, based on qualitative interviews with ten women heterozygous for Fabry disease and 16 who are carriers for hemophilia, offer valuable insights. In addition, this study contributes to knowledge regarding having a rare disorder and being the mother of a child with a rare disorder. In sum, this study shows that: being a carrier is not just being a carrier.

The main conclusions, including suggestions for implications for practice, are as follows:

- **Learning about one’s carrier status is not a “telling moment,” but a process that evolves over time.** Healthcare professionals need to be cognizant of this and genetic counseling must be personalized with this in mind. Healthcare professionals should probe a woman’s social, cultural and psychological background and counsel and support each woman in her choices.

- **Carrier testing may create “mothers-in-waiting,” contemplating the likelihood of having an affected child.** Individuals’ reactions are not always in keeping with their assumptions and predictions. Carriers for hemophilia who thought they were prepared to have a son with hemophilia, experienced unexpected shock and sadness when their son was diagnosed with the disorder. Healthcare professionals should be aware of this discordance and provide support when needed. A provider of genetic counseling must acknowledge that information on PND may contribute to difficult emotions, such as ambivalence and guilt. A woman should be assured that she (and her future children) will be supported irrespective of her choices related to reproductive decisions.

- **Being diagnosed as heterozygous for Fabry disease is a relief and a positive event for many women.** However, if a woman is asymptomatic, or considers herself unaffected, the revelation may be devastating. Healthcare professionals should acknowledge that different women react differently to the same message.
• Home treatment is valued as a flexible alternative compared to hospital-based treatment. Individuals felt less ill with home treatment, and it had a normalizing effect on daily life.

• Women who are heterozygous for Fabry disease or carriers for hemophilia report experiencing guilt and sorrow. Such emotions may transverse generations. Healthcare professionals should normalize such feelings, without presuming to understand them, and offer time and space to discuss these topics when women wish to do so.

• The mothers of children with hemophilia express concerns about treating their children with hemophilia differently than their healthy children. Quality of life issues for the family as a whole and for unaffected siblings in particular should be addressed and managed on an individual basis.

• Participants in both the Fabry and hemophilia groups had encountered healthcare professionals with a lack of medical knowledge and reluctance to seek advice. Such experiences may predispose them to having a negative relationship with their doctors. Actively seeking out the patients’ or parents’ expertise combined with supportive, honest, and attentive communication are a winning combination.
8. **Suggestions for future research**

- More qualitative research on the psychosocial impact of receiving a diagnosis of Fabry disease, and the personal costs on receiving enzyme replacement therapy, may provide a better understanding of how women view the diagnosis and living with it. A quantitative survey of psychosocial wellbeing could offer additional insight into these issues.

- Research on how carriers for other X-linked, recessive, and dominant disorders experience being carriers over time may provide more insight into gender-specific issues, how women experience genetic counseling at different stages in life, and how different contexts influence outcomes in genetic counseling.

- This study shows that the mothers of boys with hemophilia experience several challenges related to the treatment of their sons in their encounters with healthcare professionals. A study of healthcare professionals’ experiences of these encounters could provide valuable insight into these challenges from a different perspective.

- Research on how counselees experience genetic counseling at different stages in life is necessary to evaluate outcomes. Such research can also be used to develop guidelines and content checklists. This is especially important to complement the increasing use of advanced technological tools in genetic diagnostics. Developing guidelines and checklists should be done in cooperation with affected individuals and/or caregivers.

- Longitudinal research on how people experience being a carrier, or heterozygous, may overcome the limitations of retrospective data by exploring women’s experiences at different time points in their healthcare trajectories.

- There is, in general, limited qualitative research on experiences of living with a rare genetic disorder. Much of the available research focuses with a quantitative or descriptive view on specific diagnoses. More qualitative research on how people experience living with a rare disorder, parenting a child with a rare disorder, and growing old with a rare disorder is necessary if we are to better understand what these disorders mean for people’s lives.
9. References


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10. Appendices

10.1. Appendix 1: Approvals from the Regional committee for medical research ethics

Appendix 1: Approvals from the Regional committee for medical research ethics

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Forskningsansvarlig: Universitetet i Oslo
Projektleder: Kari Nyheim Solbakk

Vi viser til søknad om forhåndsgodkjenning av ommannvaske forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetisk (REK sør-øst) i møtet 18.10.2012.

Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jfr. forskningsetikklovens § 4.

Prosjektomtale

X-bundne tilstrender er forårsaket av enkeltsidige genmutations i et gen på X-bromosomet. Bærere av X-bundne tilstrender mener flere utfordringer både i forhold til personlig helse og psykososiale faktorer, inkludert risiko for å få en sykdom, eller syke barn/barn (dattersønn), risiko for å overfore mutasjonen til fremtidige generasjoner, risiko for å få symptomer selv, følelser som det å være "skyldt" sykdommen hos barnet og skam rundt dette, stigmatisering ved å være bærer av en alvorlig sykdom og negative følelser som sorg, angst og depression. Slike faktorer kan påvirke strengt aspekter ved dagliglivet, som relation til partner, syke barn, friske barn, andre familiemedlemmer, kollegaer og venner. Selvbildet, identitet og synet på egen helse kan også påvirkes. Hovedformål med studien er å undersøke åpner erfaringer med å være bærer av X-bundne tilstrender for å få kunnskap om hvordan de ser på seg selv i rollen som bærer og hvilke utfordringer dette gir. 30 kvinner skal rekrutteres til kvalitative intervjuer.

Vurdering

Komiteen mener dette er en godt forberedt og interessant søknad, og minker seg at det er beskrevet rutiner for håndtering av spørsmål knyttet til genetikk, blant annet ved at deltakere kan få tillid om genetisk veiledning som en del av prosjektet. Komiteen anser dette som positivt, og legger til grunn at tilsvarende gode beredskap eksisterer dersom noen av deltakere skulle ha behov for psykologoppfølgning ved eventuell reaktivering av vanskelige følelser knyttet til intervjuet.

Vedtak

Prosjektet godkjennes, jf. helseforskningslovens §§ 9 og 33.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og prosjekten, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2018. Opplysningene skal deretter settes eller anonymisere, senest innen et halvt år fra denne dato. Prosjektet skal sende sluttnotering på eget skjemma, jf. helseforskningsloven § 12,
senest et halv år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

\textit{Søknad om prosjektendring}
Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

\textit{Klagegang}

Med vennlig hilsen

Arvid Helberg
prof. dr.med
leder REK sør-øst C

\underline{Tor Evin Svanes}
seniørrådgiver

\underline{Kopi til: Universitetet i Oslo v/ ansvarlig for forskning: univerzetetsdirektør@ui.no}
\underline{j.h.magnus@spridning.uio.no}
Til Kari Nyheim Solbrække


**Forskningsansvarlig:** Universitetet i Oslo

**Prosjektleder:** Kari Nyheim Solbrække

Vi viser til søknad om prosjektendring datert 19.11.2013 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst C på fullmakt, med hjemmel i helseforskningsloven § 11.

**Vurdering**

De omsøkte endringene består av en endring i inklusjonskriteriene. Det var i det opprinnelige prosjektet et krav at deltakere i tillegg til å være bærere av en gitt tilstand, også måtte ha barn som var diagnostisert. Dette tilleggskriteriet har vanskeliggjort rekruttering for gruppene med tilstandene Alport og Fabry. Protokollen endres på dette punktet, slik at tilleggskriteriet om diagnostiserte barn bortfaller.

Komitéen har ingen forskningsetiske innvendinger til prosjektet slik det nå foreligger.

**Vedtak**

Komitéen har vurdert endringsmeldingen og godkjener prosjektet slik det nå foreligger med hjemmel i helseforskningslovens § 11. Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarelig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: [http://helseforskning.etikkom.no](http://helseforskning.etikkom.no). Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no
**Klageadgang**


Med vennlig hilsen

Britt-Ingrid Nesheim prof. dr. med.
leder REK sør-øst C

Marianne Eidem
forstekonsulent

*Jeanette Magnus, UiO*: j.h.magnus@medisin.uio.no

*Universitetet i Oslo ved øverste administrative ledelse*: universitetsdirektør@uio.no
10.2. Appendix 2: Forespørsel om deltagelse

Forespørsel om deltakelse i forskningsprosjektet
"Å være bærer av X-bundet sykdom. En kvalitativ studie"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie hvor vi ønsker å få mer kunnskap om det å være bærer av X-bundet sykdom, henholdsvis Hemofili, Alport syndrom eller Fabry sykdom. Du blir spurt om å delta fordi du er bærer av en X-bundet sykdom.

Tidligere forskning har stort sett hatt fokus på psykososiale faktorer rundt den genetiske testingen for å vite om man er bærer eller ikke, og det er gjort lite forskning på det å leve som bærer. Vi ønsker å få mer kunnskap om hvilke konsekvenser det har å få vite at man er bærer, hvilke følelsesmessige og sosiale utfordringer det innebærer og hva det gjør med ens egen identitet. Vi ønsker også å få mer kunnskap om hvordan man håndterer informasjon om genetisk sykdom i en familie, og om hvordan kvinnelige bærere blir møtt av helsevesenet. Målet er å gjøre den genetiske veiledningen og oppfølgingen som kvinnelige bærere får i helsevesenet mer kunnskapsbasert.

Hva innebærer studien?

Mulige fordeler og ulemper
Fordelen for deg er at du kan dele dine erfaringer om noe som du muligens aldri har delt med andre før, samt at vi kan utnytte kunnskapen som kommer fram til å forbedre oppfølgingen av kvinner som er bærere av X-bundne sykdommer. Ulempen er at du må bruke ca. 2 timer av din tid til et intervju. Du bestemmer selv om du ønsker å bli intervjuet hjemme hos deg selv eller om vi skal finne et annet egnet sted for intervjuet, for eksempel intervjuers kontor. Dette kan vise seg å være vanskelige temaer å snakke om, virke belastende. Skulle du oppleve det slik, vil vi på best mulig måte ivareta deg. Det vil blant annet bli gitt tilbud om ettersamtale til de som ønsker det.

Hva skjer med informasjonen om deg?
Intervjuene vil bli tatt opp på bånd. Dette er et hjelpemiddel, slik at man kan gjøre om samtalen til tekst etter intervjuet. På denne måten sikrer vi at det ikke går tapt viktig informasjon ved notering, og at det ikke brukes unødvendig tid til skriving under

**Frivillig deltakelse**

**Personvern**
Opplysninger som registreres om deg er det som kommer fram i intervjuet. Forskningsprosjektet er godkjent av Regional etisk komité. Avdelingsleder ved Nasjonalt kompetansesenter for sjeldne diagnoser og funksjonshemninger, Oslo Universitetssykehus, Solveig Ervik, er databehandlingsansvarlig.

**Rett til innsyn og sletting av opplysninger om deg**
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigeret eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien kan du kreve å få slettet opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

**Økonomi**
Studien er finansiert av Senter for sjeldne diagnoser.

**Informasjon om utfallet av studien**
Du har rett til å få informasjon om utfallet av studien. Dette kan du få ved å henvende deg til Charlotte von der Lippe, tlf. 23075340.

**Deltakelse**
Dersom du ønsker å delta i forskningsprosjektet, gjør du det ved å underskrive vedlagte samtykkeerklæring (side 3) og returnere det i vedlagte frankerte konvolutt. Undertegnede tar så kontakt med deg for å avtale tidspunkt for intervju. Dersom du
ønsker mer utdypende informasjon om studien eller har andre spørsmål kan du kontakte undertegnede på telefonnr. 23075340.

Vennlig hilsen,
Charlotte von der Lippe
Overlege/Medisinsk rådgiver
Senter for sjeldne diagnoser, Rikshospitalet
Oslo Universitetssykehus
e-post: uhelc@ous-hf.no
Tlf. nr. 23075340/23075355/Mobil: 9001566
10.3. Appendix 3: Samtykkeerklæring

Samtykke til deltagelse i studien
"Å være bærer av X-bundet sykdom. En kvalitativ studie"

For deltaker:
Jeg har lest den vedlagte informasjonen og er villig til å delta i studien

__________________________________________________________________________
(Signert av prosjektdeltaker, sted, dato)

For å lage avtale om intervju kan Charlotte von der Lippe kontakte meg på
Telefon nummer _______________

Det passer best å bli kontaktet i tidsrommet:
______________________________ (dag/klokkeslett)

For hovedforsker:
Jeg bekrefter å ha gitt informasjon om studien

__________________________________________________________________________
(Signert Charlotte von der Lippe, hovedforsker, sted, dato)
10.4. Appendix 4: Main questions in the interview guide

I. What thoughts do you have concerning being a carrier for an X-linked genetic disease?
   Tell me about the moment when you learned you are a carrier/heterozygote, and how you experienced this.
   What thoughts and feelings do you have about the risk of having a child with the disease, or of actually having a child with the disease?
   What thoughts do you have about your own risk for getting ill?

II. What is the communication of genetic information in your family like?
   When did you learn about the disorder in your family, if it was known?
   If it was known, how did the health of the affected person influence how you considered the disorder?
   When, and how, did you inform your partner?
   What are your experiences on how your family talks about the genetic disorder – if they talk?

III. Tell me about your experience with encounters with the healthcare system?
   Have you been offered genetic counseling?
   If you had genetic counseling, to what extent were your thoughts around being a carrier discussed?
   If you have symptoms, tell me about your experiences in encounters with the healthcare system regarding your symptoms?
Papers I-III