Electronic Genealogy and Cancer Databases in Cancer Genetic Counselling

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Thesis for the degree of Philosophiae Doctor

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Notkun rafrænna gagnagrunna í krabbameinserfðaráðgjöf

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Ágrip

Megintilgangur þessarar rannsóknar var að kanna á heildrænan máta notkun ættfræði- og krabbameinsgrunna í erfðaráðgjöf og hvernig slíkir grunnar nýtast til að búa til rafræn ættartré fyrir áhættumat í krabbameinserfðaráðgjöf. Íslenska landnemabreytingin í *BRCA2* geni var notuð sem dæmi. Einnig var reiknað hver væri besta stærð ættartrjáa í krabbameinserfðaráðgjöf fyrir nákvæmt áhættumat. Ritgerðin byggir á þremur birtum greinum.

Við rannsóknina voru þrjár mismunandi aðferðir notaðar. Í rannsókn I var gerð kerfisbundin leit að greinum sem lýstu notkun rafrænna ættfræði- og krabbameinsgrunna í klínískri þjónustu. Meginniðurstöður: Notkun slíkra grunna reyndist lítil eins og búist hafði verið við og eingöngu fjórar greinar lýstu notkun eða mögulegri notkun. Tvær greinanna voru umræðugreinar og ein var greinin var íslensk þar sem lýst var notkun upplýsinga frá Erfðafræðinefnd Háskóla Íslands, ættfræðigrunninum sem notaður var í þessari rannsókn.

Rannsókn II var eigindleg og könnuð var upplifun og reynsla ráðþega í krabbameinserfðaráðgjöf þar sem notuð eru rafræn ættartré. Gögnum var safnað gegnum vef-rýnihópa og öll umræða fór fram á netinu. Í erfðaráðgjöf þarf að safna upplýsingum fyrir ættartré. Þær upplýsingar eru notaðar til að skýra erfðir og erfðamáta sjúkdóma. Meginniðurstöður: Þeir sem voru í rýnihópunum sögðust flestir hafa haft upplýsingar um og þekkingu á erfðaráðgjöf áður en þeir komu í erfðaráðgjöf. Flestir höfðu komið í erfðaráðgjöf vegna sterkrar fjölskyldusögu um krabbamein. Þátttakendur voru jákvæðir gagnvart notkun rafrænna ættfræðigrunna og treystu bæði fagfólki og þeim upplýsingum sem notaðar voru í erfðaráðgjöfinni með aðstoð ættfræðigrunns og krabbameinsskrár. Sumir höfðu áhyggjur af því að tryggingafélög gætu nálgast upplýsingar um þá og það gæti orðið til þess iðgjöld hækkuðu eða að erfitt yrði að fá tryggingar. Lög og reglugerðir um mismunun vegna erfðaeiginleika eru til staðar, bæði hér á landi og erlendis. Fjölskyldusamskipti voru ýmist óbreytt eða höfðu batnað í kjölfar niðurstöðu erfðarannsóknar. Þar sem niðurstöður slíkra rannsókna hafa áhrif bæði á ráðþega og ættingja er mikilvægt að samskipti innan fjölskyldunnar séu góð. Í rannsókn III var reynsla af rafrænum ættartrjám í erfðaráðgjöf metin ásamt því að reikna út bestu mögulegu stærð fyrir áhættumat. Meginniðurstöður: Notkun rafrænna ættartrjáa í krabbameinserfðaráðgjöf gefur möguleika á nákvæmu og yfirgripsmiklu áhættumati og minnkar kostnað frá því að nota hefðbundin handteiknuð ættartré. Við reiknuðum ROC línurit (Reciver Operation Curves) og C-gildi sem byggt var á samaburði paraðra gilda til að

meta áhrif stækkandi ættartrjáa varðandi líkur á því að bera íslenska landnemabreytingu í *BRCA2* geni. Bestu niðurstöður fengust með 3° ættartrjám. Engu breytti að bæta 4° við. Engin vandamál urðu við að afla upplýst samþykkis og ekki voru nein vandamál við notkun ættartrjánna.

Ritgerðin endurspeglar klíníska reynslu við notkun rafrænna ættartrjáa. Þessi aðferð er vel þróuð á Íslandi og hefur verið notuð í 13 ár í krabbameinserfðaráðgjöf. Mikilvæg niðurstaða rannsóknarinnar er að besta stærð ættartrjáa eru 3° ættartré en þau geta náð yfir fimm kynslóðir. Slík ættartré er erfitt að gera öðruvísi en með hjálp rafrænna gagnagrunna.

Í heild benda niðurstöður til þess að rafræn ættartré sem sækja gögn í rafrænan ættfræðigrunn og krabbameinsskrá, spari vinnu og mannafla í erfðaheilbrigðisþjónustu. Víða um heim eru til viðamikil ættfræðigögn sem nota mætti til að gera slík ættartré og á Vesturlöndum a.m.k. eru víða nákvæmar krabbameinsskrár sem mögulegt væri að nota á sama hátt og gert er á Íslandi. Það gæti gert að verkum að bið eftir krabbameinserfðaráðgjöf yrði styttri, að áhættumat yrði nákvæmara og að hægt væri að bjóða fleirum ráðgjöf.

Lykilorð:

Áhættumat, krabbameinserfðaráðgjöf, ættfræðigrunnur, rafræn ættartré, gagnagrunnar, erfðaráðgjöf, *BRCA1*, *BRCA2*, arfgeng brjósta- og eggjastokkamein, ættartré.

Abstract

The overall aim of this PhD thesis was to cohesively assess the availability and use of electronic genealogy databases and information from cancer registries to construct electronically generated pedigrees for risk assessment in genetic counselling. The thesis is built upon three published papers. Hereditary breast and ovarian cancer (HBOC), due to the Icelandic founder *BRCA2* PV was used as an example. A second objective was to determine the optimal size of pedigrees for risk assessment in cancer genetic counselling.

Three different approaches were used. Study I was a systematic literature review for articles describing the use of electronic genealogy and cancer databases in clinical service. Key findings: Published data on the use of such databases was limited, and the search identified only four articles fitting the search terms. Two of the papers were discussion papers. One of the four articles described an Icelandic study which applied information from the Genetical Committee of the University of Iceland. Study II was qualitative, on the experience of counsellees where electronically generated pedigrees (EGPs) were used in hereditary breast and ovarian cancer (HBOC) genetic counselling. Data was collected via an online focus group using an online discussion board. In genetic counselling, family health and genealogical history are collected to assess risk and clarify the inheritance mode of a suspected or known disorder. Key findings: Prior to genetic counselling, the majority of participants said that they had known about genetic counselling, and the most common reason for GC was a strong family history of cancer. Most participants were positive towards the use of electronic pedigrees and had trust in both the professionals and the information from the databases used to generate the pedigrees. Some, however, worried that insurance companies would obtain the information from the databases and possibly raise premiums or even deny insurance outright based on the information. Laws against genetic discrimination and the protection of personal data exist, both in health insurance and employment. The majority of participants had either unchanged or better family communication following genetic counselling. As relatives may have a diverse reaction to the offer of genetic testing, good family communication is essential.

In Study III, the clinical use of electronically generated pedigrees was assessed, and the optimal pedigree size was calculated. Key findings: Using EGPs for risk assessment in cancer genetic counselling enabled accurate

and comprehensive risk assessment in HBOC families. Further, such use is cost-effective and reduces work. We used Receiver Operation Curves (ROC) and C-statistics based on pair-wise comparison to evaluate the effect of pedigree size on the prediction of the presence of the Icelandic founder *BRCA2* PV. Optimal results were attained using pedigrees with 3° relatives. Adding 4° relatives did not improve the outcome. Obtaining informed consent for the construction of pedigrees was straightforward, and no breaches of security (i.e. leakage of classified or restricted information) were observed. Conventional methods of collecting and constructing large enough pedigrees are time-consuming and difficult compared to our approach.

This thesis reflects the experience of a clinical genetic service using electronically generated pedigrees in clinical practice. This approach is well established in Iceland and has been used for over 13 years in cancer genetic counselling. It is efficient and without complications such as breach of data and mistrust on behalf of the counsellees. A significant result from this work is that the optimal size of cancer pedigree, 3° pedigree which can take up to five generations. Such a pedigree is very difficult and impractical to generate using the conventional handmade technique. This should create a motive to use EGPs in other countries where some or all the resources are readily available.

Keywords:

Risk assessment, cancer genetic counselling, genealogy database, electronic generated pedigrees, genetic counselling, *BRCA1*, *BRCA2*, hereditary breast- and ovarian cancer.

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I want to express my sincere gratitude to those participating in the qualitative research, which provided valuable information, leading to a wider understanding on the impact of cancer genetic counselling. Likewise, to the numerous individuals I have met through the genetic counselling service, allowing me to better understand their genetic counselling journey. This has been a much-appreciated experience.

The project was performed alongside the clinical work at Landspitali, and I am grateful for having had the opportunity to do so. Doing what one enjoys whilst at the same time being able to turn it into academic work must be the best of both worlds.

I dedicate this work to my parents, whose greatest wish for me was to pursue higher education.

Maybe, somewhere far, far away, they are smiling now…

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List of abbreviations

AES	Atomic Energy Commission
AGNC	Association of Genetic Nurses and Counsellors
AIMA	Australasian Integrative Medicine Association
BIC	Breast Cancer Information Core
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CGC	Cancer genetic counselling
CR	Cancer Registry
EGP	Electronically generated pedigree
EHR	Electronic health records
ENCR	European Network of Cancer Registries
EU	European Union
EUROSTAT	Statistical Office of the European Union
Fhx	Family history
GC	Genetic counselling
GDPR	General Data Protection Regulation
GCUI	The Genetical Committee of the University of Iceland
GMM	Dept. of Genetics and Molecular Medicine at Landspitali
HBOC	Hereditary Breast and Ovarian Cancer syndrome
IACR	International Association of Cancer Registries
ID number	Identification number
ICD	International Classification of Diseases
ICR	Icelandic Cancer Registry
IOM	Institute of Medicine
IRB	Institutional Review Board
MPLA	Multiplex ligation-dependent probe amplification
NCCN	National Comprehensive Cancer Network

NGS	Next generation sequencing
NORDCAN	Cancer statistics for the Nordic countries
PV	Pathogenic variant
RR	Relative risk
ROC	Receiver Operating Curves
UPDB	Utah Population Database
US AEC	United States Atomic Energy Commission
USA	United States of America
WGS	Whole Genome Sequencing

List of original papers

This thesis is based on the following original publications, which are referred to in the text by the appropriate Roman numeral.

1 **The use of genealogy databases for risk assessment in genetic health service: a systematic review.** Stefansdottir, V., Johannsson, O. T., Skirton, H., Tryggvadottir, L., Tulinius, H., & Jonsson, J. J. (Angelina Jolie). Journal of Community Genetics, 4(United Nations - Economic and Social Council), 1–7.

2 **Counsellee's experience of cancer genetic counselling with pedigrees that automatically incorporate genealogical and cancer database information.** Stefansdottir, V., Johannsson, O. T., Skirton, H., & Jonsson, J. J. (2016). Journal of Community Genetics, 7, 229–235.

3 **Electronically ascertained extended pedigrees in breast cancer genetic counselling.** Stefansdottir, V., Skirton, H., Johannsson, O.T. et al. Familial Cancer (2018).

Papers were reprinted with kind permission of the publishers.

Supporting work not included in the thesis:

Experience of Social Media Support Group for BRCA Carriers (2016). Stefansdottir, V. J Genet Couns, 25(6),1342-1344.

Fjölskyldusaga og ættartré. Vigdís Stefánsdóttir, Reynir Arngrímsson, Jón Jóhannes Jónsson**.** Læknablaðið (The Icelandic Medical Journal) (2014). 100(11):624-625.

Erfðaráðgjöf og sálfélagslegir þætti. Vigdís Stefánsdóttir, Reynir Arngrímsson, Jón Jóhannes Jónsson (2014). Læknablaðið (The Icelandic Medical Journal) 100(09)486.

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Iceland-genetic counseling services. Stefansdottir V, Arngrimsson R, Jonsson J.J. **(**2013**).** J Genet Couns. 22(6):907-10.

Declaration of contribution

I am responsible for writing this thesis in cooperation with my supervisor, advisor and the PhD committee. Contribution to each paper is listed below:

Paper I. I designed the study with the supervisor Jon Johannes Jonsson and the advisor Heather Skirton, organised the data collection and wrote the paper with the co-authors.

Paper II. I planned the study, organised the data collection and wrote the paper with the supervisor and advisor and other co-authors.

Paper III. I planned the study, organised the data collection and wrote the paper with the supervisor and advisor and other co-authors.

I applied for the appropriate ethical and research approval with the supervision of Jon Johannes Jonsson. Statistical analyses were done in cooperation with the supervisor, advisor and co-authors.

Ethical approval for the study was obtained from the National Bioethics Committee (no. 11-147).

1 Introduction

> I trace the interest in genealogy in Iceland to the lack of trees. Because of the sparsity of trees, people opt for family trees and find themselves forests among their forebears.
>
> Einar Már Guðmundsson, in Angels of the Universe.

The theme of this thesis, which is based on three published studies, is family history based on information from electronic databases, in cancer genetic counselling. Different motives and views were used in each of the three studies. The first study was a systematic literature review on the use of family history based on electronic databases in clinical settings (Stefansdottir, V., Johannsson, et al., 2013). The second study using qualitative methods and online focus groups assessed the counsellees experience of using electronically generated pedigrees (EGPs) in cancer genetic counselling (GC) (Stefansdottir, V. et al., 2016). Lastly, we conducted a study on the clinical experience of using EGPs. The numerical EGP data was used to calculate the optimal size of pedigrees for risk assessment in hereditary breast and ovarian cancer (HBOC) genetic counselling (Stefansdottir, V. et al., 2018).

In Iceland, a high-quality cancer registry and an extensive, comprehensive genealogy database exist. Within the clinical genetic service there is a permission to use both databases for the construction of pedigrees and risk assessment. Taking advantage of this, we choose to use EGPs in HBOC genetic counselling as a topic in this study due to the number of cases.

1.1 The family history

Among the many health conditions from which people suffer, various cancers are common (Bray, F. et al., 2018). Pathogenic inherited germline genetic variants are thought to be the cause of about 5-10% of all cancers (The National Cancer Institute 2017; Tomasetti et al., 2017).

The family history once kept on scrolls, or perhaps the first page of the family Bible has gradually made its way into medicine. The journey from merely recording the growing number of kin as the family got more extensive, to using the pedigree to determine the risk of an inherited disorder is long and winding, yet illuminating. Several important stages in its evolution are:

- Recording the growing number of kin, either orally or written on skin or paper. As examples, the Maoris made an art-form of reciting their Whakapapa, the layered order of their genealogies (R.N., 2001), while Icelanders used the hide of animals to write on and record their information

- Connecting families into pedigrees, containing more genealogy data and understanding that family history could indicate patterns of inheritance, was an important step (Eisinger et al., 1998)

- Adding information to electronic databases, enabling easy access and using the data in various ways to interpret inheritance (Faria-Campos et al., 2015; Roque et al., 2011).

Familiarity with one's family history holds value for both the identification of relatives and the possible inheritance patterns of familial disorders. Well documented family history, including medical information, can help identify those at risk of familial disorder (Brennett, 2010; Robson et al., 2015).

The recognition of the inheritance of disorders through family history is an old story. In the old Babylonic Talmud, quoted in "Innocent Blood: A History of Hemorrhagic Disease of the Newborn" (United Nations - Economic and Social Council), a reference exists to what is believed to have been haemophilia. Presumably, the children in question are boys:

> "If she circumcised her first child and he died, and a second one also died, she must not circumcise her third child" (Obladen, 2015).

Early in the 20th century, A.E. Garrod published a paper in The Lancet titled "The incidence of alkaptonuria: a study of chemical individuality" (Garrod, 1996) where he described several cases of alkaptonuria within the closely related kinship. In this paper, he acknowledged the interpretation of William Bateson that the mode of inheritance of the disease seemed to follow a recessive inheritance pattern. Bateson was a Mendel protagonist and had corresponded with Garrod a few times about his research (Garrod, 1996).

One of the earliest known documentation of a family history of hereditary breast cancer was published in Mémoires de l'Académie Royale de Chirugie (1757) and referenced in The Lancet (Eisinger et al., 1998). The paper described how the surgeon, Le Dran, told a story from a colleague who had recently diagnosed one of his patients, a 19-year-old nun, with breast cancer. She had refused mastectomy as she believed that she would die from her

disease, just as other people in the family had. Her prediction turned out to be correct (Eisinger et al., 1998). Much later, the Breast Cancer Gene 1 (*BRCA1)* was linked to early-onset breast cancer (Hall et al., 1990; Margaritte et al., 1992).

Others shared similar stories. In 1895, Alfred Warthin, who was a medical doctor at the University of Michigan in 1892-1931 (Warthin, 1913), discovered that his seamstress was very depressed and asked her why. She believed that she would die of cancer either in the gastrointestinal tract or her female organs, as so many in her family had done before her. Warthin became interested in her story and compiled her pedigree with the aid of a tumour registry at the University. He confirmed the family history and that the cancers she had described had indeed been known in her family for at least four generations. The seamstress herself died of metastatic endometrial carcinoma at an early age. In an article published in 1913, Warthin described her family as “Family G”, underlining how cancer appeared to have a strong familial component (Warthin, 1913).

Henry Lynch was a resident of Internal Medicine University of Nebraska College of Medicine, Omaha in 1962. He visited a patient who told Lynch that he would die from colorectal cancer as it was highly prevalent in his family. This belief later proved to be correct, and the patient died as he had predicted. When a pedigree was made for his family, it showed segregation not only of colorectal cancer but also ovarian and endometrial cancers. From this family, the cancer syndrome, which later became known as Lynch syndrome, was documented for the first time (Lynch et al., 1966).

Nathan et al. (2016) concluded that family history is still important in order to assess the risk of a familial disorder (Nathan et al., 2016). Genetic and genomic technology has advanced to the point where the entire sequence of a person’s genome can be studied (Aworunse et al., 2018; Heather & Chain, 2016). As the science of genomics advances, the question of whether family history has a role in genetics has risen. In this context, one might ask if it is enough to sequence the genome, without the family history. In 2012, Pyeritz concluded that family history was still relevant in the light of genomic medicine to bridge the knowledge gap between the outcome of genetic testing and phenotypes. The article states that the family history needs to be reviewed as a clinical tool, for its validity and utility (Pyeritz, 2012).

Further, Reuter (2018) in concluded that family history continues to have an important role in predicting the risk associated with specific variations in the genome (Pyeritz, 2012; Reuter et al., 2018). The above examples show that the application of family history in genetics is far from being irrelevant and has evolved.

1.2 Guidelines for a clinical family history

In genetic counselling, family history is usually presented as a pedigree with standard nomenclature and symbolism (Bennett, 2012). Women are demonstrated as circles and males as squares. Affected family individuals are indicated with either a pattern or colour within the symbol. Documentation of three generations of the family is in most cases essential to determine the inheritance pattern in the case of Mendelian disorders. In Figure 1, degrees of relatedness for 1-3°of relatedness are explained. In a genetic health service, the gold-standard pedigree includes at least three-generations or 3° of relatedness if possible (National Institute for Health and Clinical Excellence, 2013) (NCCN, 2016). The third-degree pedigree is notably more extensive than the three-generation pedigree.

First-degree relations are parents, children and full siblings. Second-degree relations are comprised of grandparents, aunts/uncles, nieces/nephews, grandchildren, and half-siblings. Third-degree relations include great grandparents, great grandchildren and first cousins.

Figure 1. Degrees of relatedness.

Several guidelines exist on the size and content of a pedigree for risk assessment in cancer genetic counselling. The two most commonly used are the guidelines of the National Health and Care Institute (NICE) in the UK and National Comprehensive Cancer Network in the US (NCCN) (National Comprehensive Cancer Network, 2018; National Institute for Health and Clinical Excellence, 2013). The NICE guidelines for HBOC assessment are slightly different for individuals depending on if they have a personal history of cancer or not and whether the family history is obtained in primary or secondary care. In primary care, the recommendation is that a first- and second-degree family history should be taken, while in secondary care, such as in genetic services, third-degree family history is recommended. The third-degree family history on both paternal and maternal side should include the age of diagnosis, type and site of tumours, the age of death, the current age of unaffected relatives and if relevant, whether the counsellee belongs to a population with known founder pathogenic variants in cancer genes. The NCCN guidelines recommends taking a third-degree expanded family history, including medical history on both paternal and maternal side, with attention to close relatives who have cancer. The pedigree information should include

types and sites of cancer, primary cancers pathology reports and the age at diagnosis. These guidelines are similar, although the NCCN guidelines ask for more detailed medical history. For clinical practice, the collection of relevant documents can be time-consuming. However, it can be challenging to assess the risk appropriately in the absence of adequate family and medical history.

1.2.1 Barriers in collecting family history

Collecting family information from counsellees in order to make an extensive pedigree in a cancer clinic may not always be possible. This can be in part due to lack of staff, full schedule and the limited clinical time allowed for such work (Ozanne et al., 2013). To determine the completeness of family history in medical records, Wood (2014) reviewed records for over 10,000 patients from 212 practices in the United States of America (USA). They found that first-degree cancer family history had been recorded for nearly 80% of patients with breast or colorectal cancer, and almost 65% for second-degree family history. Only 32.9% of patients with breast cancer and 22% with colorectal cancer had a complete family history, comprised of the type of cancers, age at diagnosis, dates of birth and dates of death (Wood et al., 2014).

Other known barriers for obtaining a large enough family history are small family size, limited knowledge of family history, or a lack of communication within the family (K. et al., 2003). As families grow, it may be more difficult for family members to obtain information about each other. Therefore, people may have less information about more distant relatives than closer ones (Augustinsson et al., 2017; Chang et al., 2006).

To be able to provide an appropriate family history in cancer genetic counselling, counsellees must understand what kind of information is required. Lim & Hewison (2014) found that little over half (54%) of 300 participants, all members of the staff at the Faculty of Medicine and Health, University of Leeds, United Kingdom (UK), understood the meaning of clinical family history and the extent of information required. Some of the other participants in the study erroneously believed that step-parents and their siblings, in-laws, spouses and even friends and colleagues were relevant to the clinical family history (Lim & Hewison, 2014). Considering the participant´s workplace, it is interesting that nearly half did not understand the meaning of clinical history fully. No similar study with a different population was found for comparison, but it would be interesting to study.

1.2.2 The clinical family history

Exome and whole-genome sequencing have become more common in genetic testing. Those methods can lead to the identification of pathogenic variants (Gong et al., 2018; Ku et al., 2016). In this context, the importance of family history in genetic counselling must be evaluated. Further, a reason for assessing family history in genetic counselling could be to ensure the efficient use of resources by, i.e. indicating if genetic testing is needed and who would be the best candidate for testing.

In the case of familial cancer, family history can prove informative of likely future cancer types in family members. In such cases, the family history can assist in the design of appropriate clinical surveillance and risk reduction strategies (NCCN, 2016). Supporting this, Nathan (2016) states that high-quality and comprehensive pedigrees remain relevant at this time (Nathan et al., 2016).

Several methods are used to record family history in clinical settings. One common way is to send questionnaires to the person who is coming to the service (Armel et al., 2009). When finished, the counsellee returns the questionnaire which is then used to outline a pedigree, and document the family history before the counselling session. Issuing questionnaires to the counsellee for completion allows them to seek genealogy information from their relatives before their clinic appointment, which has proven to be an efficient way of obtaining data (Armel et al., 2009). Another method is interview via telephone, where a professional and a counsellee, discuss the family history prior to the counselling session. There are also numerous electronic tools available for family history collection. Welsch et al. (2018) compared and reviewed 17 available electronic family health history (FHx) tools. Some of them allow patients to collect and record their FHx, thus reducing the time and work of the professionals in question. The authors concluded that the various tools had different approaches for collecting the family history, adding familial connections and providing disease information. They underscored the need to standardise these tools, and to enable integration with electronic hospital records (EHR). As the study only used FHx tools available in mid-2017 and due to the constant change in the availability of tools, the authors planned to keep an active inventory of such tools on the Global Alliance for Genomics and Health website (Welch et al., 2018). Using electronic databases enables for safe storage and electronic documentation of all changes (Mahon, 2016). However, the information collected into the FHx tools are usually provided by the counsellee or

counsellees, and medical history must be confirmed. The relevant healthcare services need to confirm the history following consent from the individual in question.

During the counselling session, family history can be further explored. If none has been collected prior to the in-clinic appointment, the counsellor can draw a pedigree on a paper. In my experience, in the Icelandic settings, drawing a pedigree in the clinic is helpful as it offers the opportunity to connect with the counsellee or family, establishes a relationship and enables for a better understanding of the family dynamics.

1.3 Electronically generated pedigrees (EGP´s) in Iceland

In the genetic counselling service at Landspitali, accurate genealogy- and tumour information can be available in a ready-made EGP at the time of the clinical visit (Stefansdottir, V., Arngrimsson, et al., 2013). Since 2007, the genetic services at Landspitali have been premitted to use genealogy information from The Genetical Committee of the University of Iceland (GCUI) and the Icelandic Cancer Registry (Sigurdardottir et al., 2012) to construct electronically generated pedigrees (EGPs) in order to establish a family history of cancer (Stefansdottir, V., Arngrimsson, et al., 2013). Initially, the pedigrees were small, with three generations and one pedigree for both sides of the family of the counselee. The first EGPs were similar to the hand-made pedigrees but differed in the amount and source of information. The pedigree size and degree of relation varied according to the age of the counselee. Younger people usually had smaller pedigrees than older ones.

The workflow constructing pedigrees in the Icelandic cancer genetic counselling service at Landspitali was and is as follows: The counsellee consents in writing to have a pedigree constructed. If another member of the family has already been to genetic counselling and given consen, some of the family information may already exist. Due to the size of the pedigrees, a relationship with a distant former counsellee with a known pathogenic variant can sometimes be observed. The consent form goes to the GCUI where the pedigree information is composed. Then the Icelandic Cancer Registry (Sigurdardottir et al., 2012) adds relevant tumour information. Pedigree information is never disclosed to counsellees during counselling (Stefansdottir, V., Arngrimsson, et al., 2013; Stefansdottir, V. et al., 2016; Stefansdottir, V., Johannsson, et al., 2013). The EGPs tend to be quite large, with the most common size between 3-500 individuals. Therefore, an overlap is considerable, and individuals can appear in many pedigrees.

During the initial clinical visit, a conventional pedigree is most often first made by hand to clarify the counsellee´s knowledge of the family history and to gain insight into new, unrecorded cancers in the family. A handmade, conventional pedigree can be seen in Figure 2. This is partly because the ICR has about 12 months lag in reporting of cases. It is also helpful for the counsellor to do a handmade pedigree to explore the counsellee´s expectations, prior experiences, and family dynamics. These pedigrees are usually not used for risk assessment, except in the rare cases when no electronic information is available for constructing an EGP. Should any additional cancer information be documented in the handmade pedigree, the counsellor tries to verify the information to be able to use it in the risk assessment. Such information could be a newly diagnosed relative or a relative diagnosed abroad and not included in the Icelandic cancer registry. However, this is unusual, and it may be difficult to verify diagnosis made in other countries. In those cases, the official information is used for the risk assessment, but the additional information kept in mind when risk and surveillance are discussed.

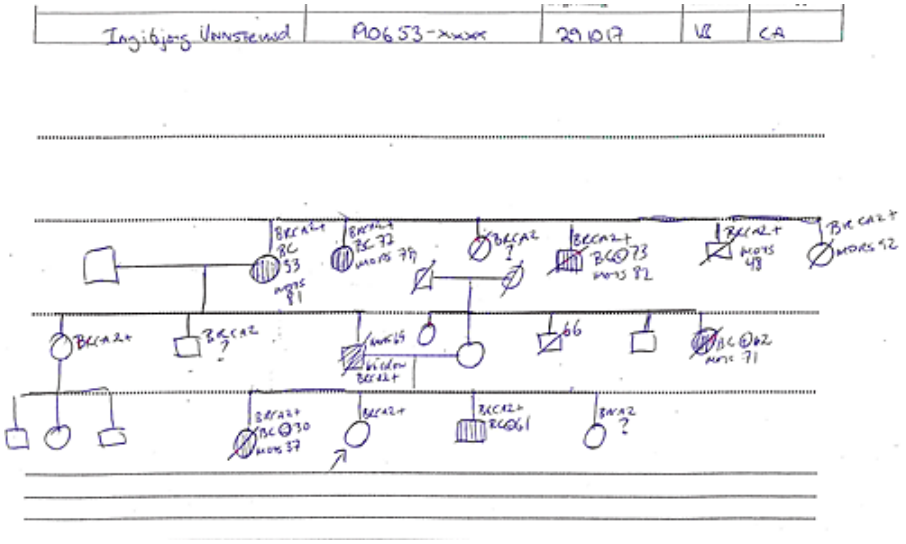

Figure 2. A fictional example of a handmade pedigree.

1.4 Presumed consent

In genetic counselling, the counsellee provides information about other family members, usually without explicit consent from most or all the relatives, i.e. the consent is presumed. The family history information is used for risk

assessment on the assumption that the process could benefit the counsellee and possibly other family members. The information is kept secure (similarly as medical information within health care) to ensure minimum risk of harm.

In medical genetics services, family history can be shared between professionals when needed, without consent from family members. This information may be used to assess risk for diagnosis or to help with surveillance or treatment (Lucassen & Hall, 2012). In the REFORM report in 2018, data collaboration between practices was noted that:

> "... when GPs and hospitals share information, they can identify which patients are most at risk of unnecessary hospital admissions, reducing admission by up to 30 per cent. Better information sharing between mental health nurses and police has seen the number detained for mental health issues reduce by 80 per cent in some areas." (Sarah Timmis S, 2018).

Extensive research databases form the foundation of genetic population studies and bio-banks. In many scientific studies, the use of presumed consent for genealogy, genetic, and other medical information is considered acceptable and ethical. (Bauer, 2014; Brewster et al., 2004; Trivedi, 2008; Wylie & Mineau, 2003).

1.5 Genealogy

The personal wish to learn one´s origin is common. People have systematically recorded their family history, either orally or in writing, for thousands of years. The Book of Genesis provides a precedent in its record of one of the earliest recorded genealogical accounts:

> "Cain knew his wife, and she conceived and bore Enoch, and he built a city, and named it Enoch after his son Enoch. To Enoch was born Irad, and Irad was the father of Mehujael, and Mehujael, the father of Methushael, and Methushael the father of Lamech. Lamech took two wives; the name of the one was Adah, and the name of the other Zillah", (Genesis 4:17).

One very well-established and extensive family history is that of Confucius (551-470 BC). It is the most extensive known genealogical history in the world, according to the 2005 Guinness Book of World Records (Jim Patttison Group, 2005). Initially written by hand, the Confucius Genealogy was printed in 1080 AD and has been revised five times since, each time with an

accurate listing of all family members (China.org.cn, 2008). Korea has a very long history of keeping family records and many families trace their lineage back 700 years or more based upon the male family line, as described in the South Korea Genealogies website (Howard, 2012). The registries are named JokBo - in Korean 族譜, 족보. Many Korean families publish their personal records on the Internet. This is partly done to cherish the family history and also to acknowledge that these records are a national treasure (Howard, 2012). Other interesting and long-term genealogy can be seen in the family history of the Royal Family of Japan, where one´s status has been determined according to place in the family tree (Agency, 2010) (Agency, 2010).

The Maoris have a strong sense of community, and in most families, someone is designated responsible for the collection and upkeep of the genealogy records. Initially recited orally, now many are kept on paper or electronically. Maoris can trace their ancestry back 30 generations or more in their 'Whakapapa.' The word *whakapapa* means to place something in layers, which is an appropriate description of genealogy (R.N., 2001).

Figure 3. Landnámabók - Book of Settlement. Published by Helgafell 1948. Photo by author.

In Ireland, the old Leabhar na nGenealoch, or book of genealogies, contains an extensive collection of Irish genealogy data. It has notes on families from all parts of Ireland - of Viking, Gaelic and Old English origin (Firbishigh, 1649) - and gives a detailed description of the genealogy and names of settlers.

Collection of family histories for personal or public use, has for a long time been a favourite interest in Iceland (Palomba et al., 2009; Palsson, 2002). In private and public libraries, a fair number of small and large genealogy books are available, allowing those interested in researching family histories. Initially, records of family history were kept for tracking assets and relationships. Examples can be seen in the Book of Settlement (Landnámabók Íslands), (Figure 3). The book includes a comprehensive overview of the settlement of Iceland in the 9th century and provides information regarding the distribution of land and assets. However, it is believed that much of what is described in the book, happened at least 200-400 years before it was written (Jóhannesson, 1941; Tulinius, 2011).

Icelanders began using paper in the 15th century. Until then, vellum, which is a prepared animal skin from sheep, goats or calves, was commonly used to write on (Gunnlaugsson, 2017). Many of the old scripts have been compiled and digitised and can be found at the website www.handrit.is and in museums such as the National Museum of Iceland.

In 1746, priests were ordered to keep parish records, through which they kept track of marriages, deaths and births (Hallgrímsson, 1934). These preserved parish accounts have proven to be an invaluable resource for the development of genealogy records.

1.5.1 Genealogy databases

Although large electronic genealogy databases exist online, access to most of them requires at least some form of registration. Many require fees for access. (Ancestry, 1997; NextAdvisor, 2016). Some examples of large online genealogy databases are:

- Scotland´s People database: an extensive genealogy database, holding much of Scotland´s birth, death, marriage, census and other information. Its statutory registers go back to 1855, the census back to 1841, and some of the church registers go back to 1560 (General Register Office for Scotland, 2007; Scotland, 2017).

- Ancestry.com, a for-profit genealogy company which also offers direct-to-consumer genealogical DNA tests. It has over 11 billion

connections, 100 million family trees, and 20 billion records from at least 80 countries (http://www.ancestry.com, retrieved 16.08.16).

- FamilySearch is an extensive public database, widely accessible and run by the Church of Jesus Christ of Latter-day Saints. The FamilySearch has gathered genealogical records worldwide for over 100 years and at present, has over 4 billion names in its databases (The Church of Jesus Christ of Latter-day Saints, 2016).

- The Verein für Computergenealogy, is not in itself a database but a significant genealogy portal for German genealogy databases. Retrieved from http://www.compgen.de, 2018.

- Geneanet, launched in 1996, is a searchable database of genealogy records, genealogy societies and commercial genealogy companies. Most of the data is free to access, but some of the content is charged for, according to the decision of the submitter. Geneanet can be found at the website http://en.geneanet.org.

- Cyndi´s list is a comprehensive genealogy research site with an index to online genealogical resources. (https://www.cyndislist.com, retrieved on 06.08.16).

Databases holding medical and genealogy information are also available online. One example is the Utah Population Database (UPDB) with restricted access to scientists. It comprises genetic, demographics, medical and epidemiological information for over 9 million people (Huntsman Cancer Institute at the University of Utah, 2016; Niazi et al., 2010). Another extensive database is the Anabaptist Genealogy Database of Old Order Amish of Lancaster County. This database was formed to map pathogenic genetic variations within the Lancaster Amish (Agarwala et al., 2003b). A third example is the Icelandic deCODE genetics database, comprising extensive medical, genealogical and genetic information on Icelanders (Helgadottir et al., 2018).

1.5.2 Icelandic genealogy databases

Over time, some of the Icelandic genealogy records have been organised into electronic databases, both private and public. Some of the largest ones include The Icelandic Genealogy Society (The Icelandic Genealogy Society, 2016), as a source of comprehensive data, and the IcelandicRoots database, which was initiated by Hálfdán Helgason, an Icelander with a keen interest in genealogy. The Icelandic Roots Heritage Organization in Fargo North

Dakota, USA now runs it. It is regularly updated and contains information on Icelanders living in Iceland and those who have emigrated, primarily to Canada and the USA (Icelandic Roots, 2016). Islendingabok (Book of Icelanders) at DeCODE Genetics, is particularly thorough. It is accessible, with restrictions, to anyone with an Icelandic ID number (Stefansson & Taylor, 2006). Unlike the databases mentioned above, the Genealogical Institute (ORG ættfræðiþjónusta) does not have a database accessible on the Internet, but, upon request, staff will help find genealogy information about Icelanders and those who have emigrated to Canada, USA and Brazil (Oddur Helgason, 1999).

A large population-based genealogy database, (GCUI), in Iceland, has its origin in the great interest of genetics in the Western world following the Second World War. In the USA, specifically, one subject of interest was the relationship between the exposure of radiation and mutations during the height of the Cold War (Tulinius, 2011). Several population geneticists congregated to advise the United States Atomic Energy Commission (US AEC) on to the most efficacious means of performing research on the subject. At the time, some of these geneticists knew that Iceland had an isolated and concentrated population – an ideal environment for observation. One of the geneticists, Professor Luca Cavalli-Sforza, was also aware of the extensive genealogy information kept within the country, as well as the general interest in genealogy held by the nation (Olafsdottir, 2016). In 1965, the GCUI was formed with funds from the US AEC and has served since as a non-profit organisation (Olafsdottir, 2016; Tulinius, 2011). To ensure the exact relationship in families, a so-called, “mothers record,” was created for each mother, linking her to each of her children, as well as providing information on the father of the children (Tulinius, 2011). Initially, the database was generated from the information collected during the 1910 national census; birth records, death certificates, as well as information from the censuses from 1703 onwards. It contains records of Icelanders that lived as far back as the 1800s. Additionally, information was obtained from parish records created between the years 1840-1910. The database was computerised and linked to the National Registry in 1953 (Tulinius, 2011). One of the primary objectives of the Genetical Committee has been to link the demographic data of Icelanders into pedigrees for genetic studies, both large and small, but it also aims to help those who have an interest in genealogy, or those with a need to access genealogy information, such as priests and lawyers (Olafsdottir, 2016; Tulinius, 2011). In 2007, the Data Protection Authority approved the use of the database in genetic health

services at Landspitali Hospital, as can been seen in more detail in the section on genetic counselling (Stefansdottir, V., 2016b).

1.5.3 Collection of genealogy data from the Internet

The Internet is a vast source of genealogical data as can be seen in Figure 4, where many of the sources are demonstrated. In addition to the information provided via the databases mentioned above, collection of genealogy data from the Internet has proven to be successful. Kaplanis et al. (2018), understanding the importance that family trees have in many fields, used publicly available online data to collect over 86 million individual profiles. Both demographic information and geographical locations were extracted from online sources. For further evaluation, data on ~80.000 individuals, from the Vermont Department of Health were collected and compared to the dataset. The result was a pedigree containing 13 million individuals (Kaplanis et al., 2018).

The ongoing Veterans Genealogy Project is an extensive collection of genealogical data with linkage to phenotypic data (Cannon-Albright et al., 2013). The aim of the project is to create a genealogy/biomedical database of US citizens. In 2013, the database held genealogy data for over 22 million individuals in some areas of the US and was regarded to be the most extensive genealogy and medical data combination in the world. The Internet is the primary source of data for this project (Cannon-Albright et al., 2013).

As commercial genealogy DNA databases grow, with the voluntary submission of DNA and family history, the likelihood of finding related individuals in one of them increases. Such data has already been used to solve crimes, and the associated ethical issues are being debated widely (Court, 2018). Users or consumers of direct-to-consumer sites may not realise that their data can be used for solving crimes (Forensic Genetics Policy Initiative, 2017; Samuel et al., 2018).

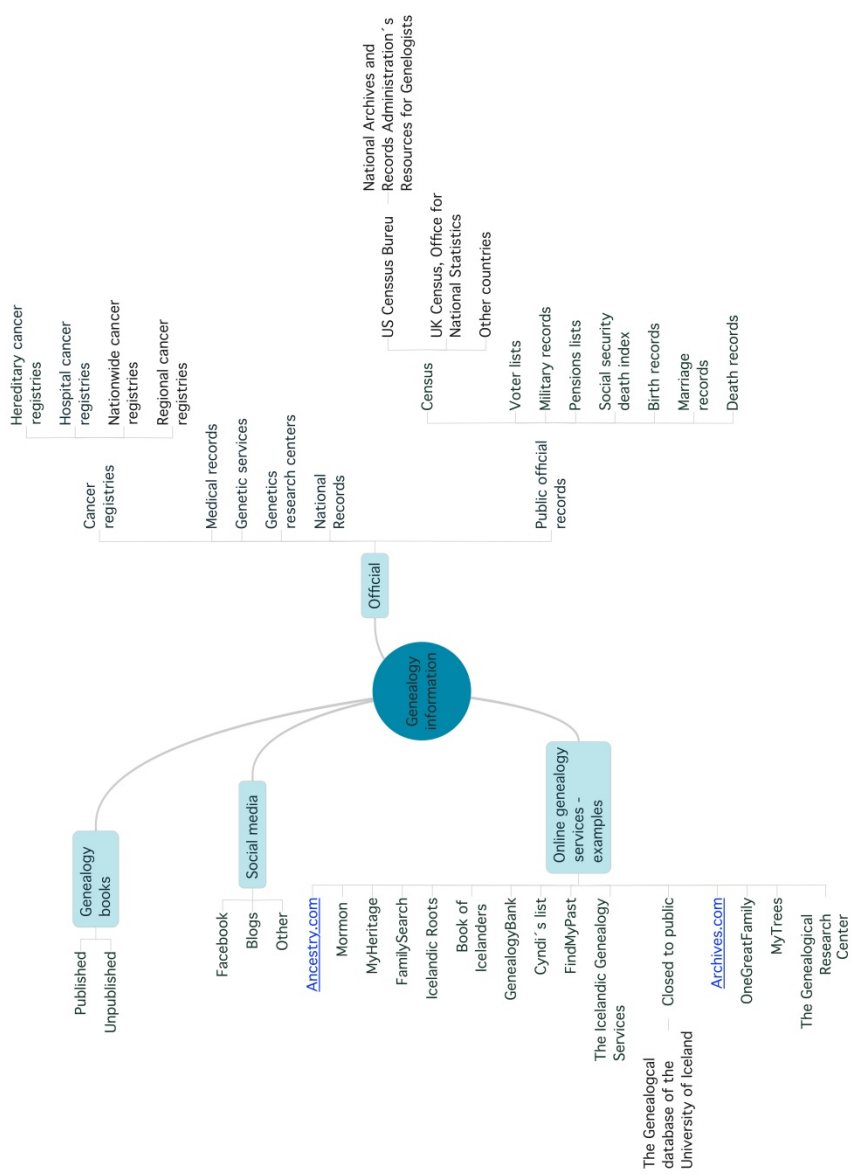

Figure 4 Geneology data, collected from the Internet

1.6 Census

The Statistical Division of the United Nations Economic Commission for Europe defines a population census as:

> "…the operation that produces at regular intervals the official counting (or benchmark) of the population in the territory of a country and its smallest geographical sub-territories together with information on a selected number of demographic and social characteristics of the total population (United Nations - Economic and Social Council), in 2015 conference of European Statisticians Recommendation, page 5)."

Likely the most famous census mandate, at least in Western countries, was the one described in the Bible. This story, in the Christmas Gospel, has likely been the first introduction to a census to many - the registration of every human being in a predefined area.

> "In those days, a decree went out from Caesar Augustus that the whole world should be enrolled. This was the first enrolment when Quirinius was governor of Syria. So all went to be enrolled, each to his own town" (Luke 2:1-6, English Standard Version).

Numerous large and small censuses have since been done for civilian, economic and military reasons. The first nationwide census of an entire country took place in 1703 in Iceland (Tulinius, 2011). The description of the motivation behind the census was:

> "to assemble a true accounting of all families in that country, from the best to the lowest person, in which shall be specified and explained the husband's and the wife's name, their children, and friends' names who at their home, also all servantmen, servant youths, servantwomen and girls, in summa no one omitted great and small, young and old, who are to be found in the whole country, wherewith the large number of poor at each location must be precisely observed and described." (Gudmundsson, E. G., 2015).

At the time, the entire population of Iceland numbered only about 50,000 persons. All information from the census still exists, although some of the original documents have now been lost (Tulinius, 2011). In Hagskinna, The Icelandic Historical Statistics, the following information can be found

(translated by VS): In 1769 the next census was undertaken in the whole of Denmark. As Iceland was under the authority of Denmark at the time, the census was also applied to Iceland. After that, a census was undertaken in 1801 and then every five years between 1835 -1860. After 1860, censuses were done in Denmark every ten years. Information from the Icelandic censuses was assessed in Iceland, instead of Denmark, from 1910. A nationwide census was performed regularly every ten years in Iceland until 1960. The last conventional census was undertaken in 1981 (Guðmundur Jónsson, 1997). In 2011, a new type of census was completed using only electronic information available from the National Registry. The demographic information has been collected electronically since 2011 (Iceland, 2016b).

1.7 National population registries

Most Western countries have national registries containing similar demographic information. The information generally includes names, dates of birth, dates of death, unique identification numbers, addresses, relationship statuses and other relevant information. The Nordic countries all have National Population Registries with regular updates (CPR-kontoret; Ekbom, 2011; Hagstofan, 2007; Population Register Centre, 2006; Registers Iceland, 2018; Skattedirektoratet, 2007).

The Icelandic National Registry (Þjóðskrá) was established in 1953 (Tulinius, 2011). Everyone born in Iceland is registered at birth, and all who immigrate to the country are registered as well. Similar to other Nordic countries, Icelanders are identified in the registry by a national identification number (kennitala), a number composed of the date of birth in the format ddmmyy and four additional generated digits. The third digit is a control digit, and the last one indicates the century in which the person was born; 9 for the 1900s and 0 for the 2000s (Iceland, 2016a). Companies and institutions are also provided identification numbers (The National Registry, 2016). Similarly, all bank accounts are inextricably linked to the national identification number of the owner. The National Registry is the basis for electoral registers (Ministry of Justice and Human Rights, 2016), such that the identification number is required in order to vote.

1.8 Cancer registries

Cancer registries can be hospital-based, pathology-based or population-based as well as hereditary registries. Cancer registries register information about cancer and tumour diseases in a defined geographically population (Tyczynski, 2003). They are key data providers for monitoring cancer burden.

In order to establish a cancer registry, reliable sources of information and a system for collecting clinical and pathological data hast to be in place. The collected information includes demographic information, medical history, diagnosis, age of onset, pathology, haematology, cytology, and tumour site (Bray, et al. 2014). From the data, various statistics, such as incidence, survival and mortality rates, are published (Forsea, 2016). Population-based cancer registries (PBCR), are available in over 700 countries. Some countries have separate regional cancer registries, covering a specific area (Parkin, 2006). Germany was first to set up a population-based cancer registry in 1926 (Isabel dos Santos Silva, 1999). Since then, cancer registries (national or regional-based, population-based, hospital-based, or pathology-based), have been established in many countries (Rodolfo Saracci and Christopher P. Wild, 2015). In most Western countries, registration into PBCRs is mandatory.

Hospital-based cancer registries are generally used to keep and maintain diagnostic data on cancer patients in one or more hospitals. These registries differ in purpose and use from national or regional cancer registries as data is collected on patients only (Ringborg et al., 2008). Some of the first such registries were a bone-sarcoma registry which Dr Ernest Amory Goodman described in an article published in the American College of Surgeons Bulletin, in 1924, reprinted in 2009 (Codman, 2009). Another one was the hospital-based cancer registry at Yale-New Haven Hospital in 1936 (Missouri State Tumor Registrars Association, 2018). Further, in St. Marks Hospital in Middlesex UK, the Polyposis Registry initiated the collection of data on polyps in 1924. Numerous colorectal and polyposis hereditary cancer registries have since been created following this trend (Rothenmund et al., 2013). Hereditary cancer registries help find individuals and families with specific hereditary cancers. Examples of hereditary cancer registries are the Breast Cancer Family Registry in the USA, which as the name implies, focusses on breast cancer (Breast Cancer Family Registry, 2017). In the Netherlands, the Dutch Hereditary Cancer Registry was established in 1985 with the aims of finding families with hereditary cancer, to encourage surveillance of high-risk individuals and promote research on improving surveillance protocols (Vasen et al., 2016). In general, hereditary cancer registries have diverse functions such as providing a basis for screening and surveillance recommendations, maintaining up-to-date information for families and health professionals, promote research, as well as to facilitate referral to genetic counsellors. The information is also used to assist with patient and family enrolment in research studies (Vasen et al., 2016).

1.8.1 The Icelandic Cancer Registry

> "In order to succeed in this fierce battle, one must acquire knowledge about the enemy". Professor Niels Dungal 1949.

Professor Niels Dungal, in 1949, asked all Icelandic doctors for information and documentation concerning all their cancer patients (Jon Gunnlaugur Jonasson and Laufey Tryggvadottir, 2004). Dungal, who was a professor in pathology at the University of Iceland, became the first chairman of the Icelandic Cancer Society in 1951 (Tryggvadottir, 2014). The ICR has registered all instances of cancer in Iceland since May 10th 1954, and as a nationwide population registry, it contains comprehensive information. In 2007, the ICR attained legal substantiation as one of the population-based health registries authorised by the Icelandic Directorate of Health and cancer registration was made mandatory (Sigurdardottir et al., 2012). The Icelandic Cancer Society continues to run the registry according to an agreement with the Directorate of Health, and electronic methods are used to collect and maintain most of the information. The completeness of the registry lies at around 99.15% (Sigurdardottir et al., 2012).

The ICR collects tumour information from pathology and haematology laboratories, as well as from hospitals and other healthcare facilities. Information is also received and analysed regarding cancers notified on death certificates and in the population-based hospital discharge registry. This information relates mainly to clinically diagnosed cancer. In addition, cases of breast cancer have been registered since 1911 (Icelandic Cancer Society, 2016) as part of a broader study by G. Snaedal, who collected extensive information on breast cancer diagnosed between 1911-1965 nationwide (Snaedal, 1965).

The ICR and the clinical genetic services have developed a close, working relationship due to their collaboration (Stefansdottir, V., Arngrimsson, et al., 2013).

1.9 Risk assessment programs

Several breast cancer risk assessment programs are available. The majority of them relate to the assessment of breast cancer risk in families with a history of breast and ovarian cancer, such as the Gail model or the Breast Cancer Risk Assessment Tool (National Cancer Institute, 2017). It is free to use and can be accessed on this website: https://www.cancer.gov/bcrisktool. In a recent article, the Gail model was shown to predict female breast cancer

better in American and European population than in the Asian population (Wang et al., 2018). Another risk assessment program is the Tyler-Cuzik or IBIS Breast Cancer Risk Evaluation Tool, which uses family and medical history to assess the likelihood of having a pathogenic mutation that can increase breast cancer risk. The program, which is only available for Windows™, can be downloaded from the website: http://www.ems-trials.org/riskevaluator.

BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, is a program developed in Cambridge UK. It is used to calculate the risk of the probability of having a pathogenic variant in several genes such as the *BRCA1, BRCA2, PALB2, CHEK2 and ATM* genes. It also calculates the risk of getting breast or ovarian cancer based on family history. However, at the time of the study, only the *BRCA* genes were included. BOADICEA is free to use and can be assessed online with a user account (Jervis et al., 2015). The BOADICEA program was chosen for the risk assessment in cancer genetic counselling in Iceland, mainly due to its performance in comparison with other similar programs (Terry et al., 2019). Other reasons included the possibility of a plug-in to the pedigree program PedigreeAssistant, used for the construction of pedigrees. Moreover, the authors were ready to help to adapt the program to the Icelandic situation.

1.10 Breast cancer

Cancer treats everyone the same – the rich and the poor, the slave and the queen. In *Bathsheba´s Breast: Women, Cancer, and History,* James Olson followed the history of breast cancer through the ages. The story began in 490 BC when queen Atossa found a lump in her breast and ends in the modern era, where genetic tests determine the type of breast cancer and help with the treatment (Byler et al., 2014; Olson, 2002).

The incidence of breast cancer in women in Western countries is high, with one in every eight women is diagnosed with the disease in their lifetime (World Health Organizaition, 2016). The National Comprehensive Cancer Network (NORDCAN) database (Engholm G, 2016) has information concerning cancer incidence and distribution in Nordic countries and shows a similar trend in these countries regarding breast cancer. Figure 5 shows the age-standardised rates over time for incidence and mortality cancer in Iceland from 1960-2016.

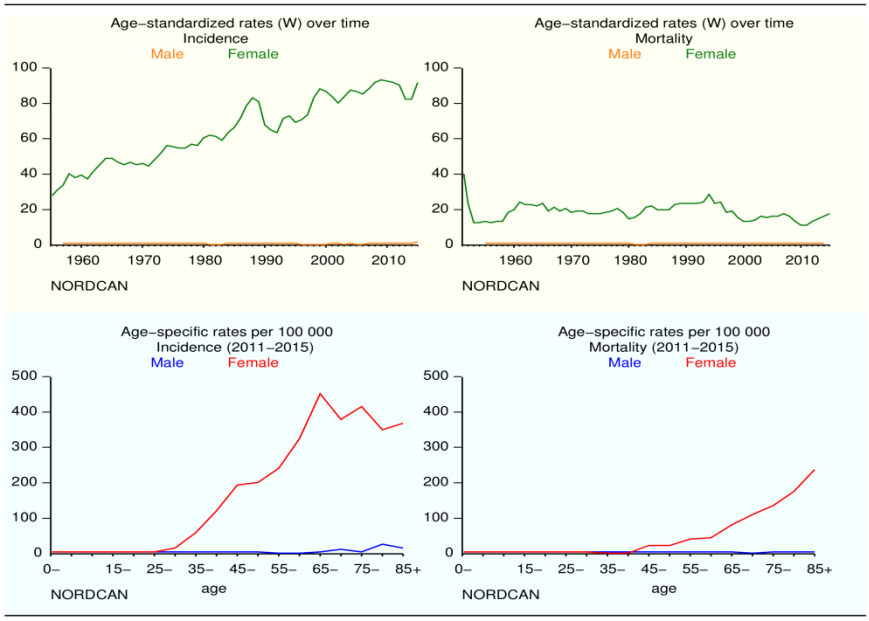

Figure 5 NORDCAN: Breast cancer incidence and mortality in Iceland 1960-2015. Age-specific rates per 100.000 (4.11.2017).

Breast cancer rarely occurs in males (Abdelwahab Yousef, 2017; Fentiman, 2009; Liu et al., 2018). However, those with the Icelandic founder *BRCA2* PV, NM_000059.3: *BRCA2:c.767_771delCAAAT* have a significantly increased risk, up to 69% at the age of 80 (Kuchenbaecker et al., 2017). According to information from Cancer Research UK, 250 males in the United Kingdom (UK) are diagnosed with breast cancer each year. In the USA, in 2014, 2141 males were diagnosed with breast cancer (U.S. Cancer Statistics Working Group, 2017). According to NORDCAN statistics, 149 males were diagnosed with breast cancer in 2012-2016 in the Nordic countries. This number accounts for 0.6% of all new breast cancers. In 2013-2017, the age-standardised rate per 100.000 (W) in Icelandic males was 1.1 as opposed to 86.8 in women (Icelandic Cancer Society, 2016).

On average, a little over 210 women were diagnosed in Iceland with breast cancer each year from 2013-2017 (Icelandic Cancer Society, 2018). Breast cancer accounts for about 27% of all cancers diagnosed in Icelandic women (Table 1). In contrast, three males were diagnosed with breast cancer on average per year in the same period (Icelandic Cancer Society, 2018). Approximately 40% of the males diagnosed with breast cancer in Iceland carry the Icelandic founder *BRCA2* PV (Giordano, 2005; Thorlacius et al., 1995), hereafter referred to as the Icelandic founder *BRCA2* PV.

Table 1. Breast cancer in Iceland 2013 - 2017 (Icelandic Cancer Society, 2018).

Breast cancer 2013 - 2017	Males	Females
No. of new cases	20	1052
Proportion of all cancers (%)	0.5	26.8
Average age at diagnosis (years)	69	62
Mortality (per year)	<1	50

To date, increased risk of breast cancer has not been observed in males who carry the Icelandic founder PV NM_007294.3: *BRCA1:c.5074G>A* (Thorlacius et al., 1995). However, this variant is very rare, making an accurate assessment difficult. In general, males with a PV in *BRCA1* gene have a very slightly higher risk of breast cancer than the general population, although the risk is much less than for those with PV in the *BRCA2* gene (Tai et al., 2007). The average age at breast cancer diagnosis in Iceland was 62 years for women and 71 years for men (Table I).

1.11 Hereditary breast and ovarian cancers

In families with numerous cases of breast and ovarian cancers, there is an increased likelihood that it is caused by inherited genetic predisposition. A PV in either of the *BRCA* genes is then most probable (Petrucelli et al., 2010) although PV´s in other genes can increase the breast cancer risk as well. Among them, each with moderate breast cancer risk associated, are the *ATM, CHEK2, PTEN, STK11, BRIP1, CDH1, PALB2, RAD51, TP53, BARD1, BLM, NBS1, RECQL and XRCC2* genes (Moran et al., 2017; Rousset-Jablonski & Gompel, 2017); Kurian et al., 2017). Cancers other than breast or ovarian are seen in families with hereditary breast and ovarian cancer syndromes. Within families with a PV in either of the *BRCA* genes, cancer penetrance is highly variable, depending partly on the gene position of the variant and by the change of function caused by the variant (Lesueur et al., 2018).

1.11.1 BRCA1 and BRCA2 PVs in the Icelandic population

In 1965, dr. Gunnlaugur Snaedal, a leading Icelandic obstetrician, published an article from his doctoral study. He had collected information on all breast cancer cases in Iceland from 1911-1955 (Snaedal, 1965). In 1982, Tulinus et al., drew attention to the increased risk of relatives of cancer patients, indicating a strong genetic component in some families (Tulinius et al., 1982).

In 1989, a study on the polymorphism of the HRAS proto-oncogene gene in breast cancer patients was published (Barkardottir et al., 1989). This was the first paper where many Icelandic researchers reported their joint efforts to identify genetic components that increased the risk of familial breast cancer. Results from linkage analysis on Icelandic hereditary breast cancer families played an important role in the cloning of the *BRCA2* gene. Specifically, the Icelandic data contributed to the rapid narrowing of the linkage peak, containing *BRCA2* gene on chromosome 13q (Arason et al., 1993; Gudmundsson, J. et al., 1996; Gudmundsson, J. et al., 1995; Tavtigian et al., 1996; Thorlacius et al., 1995; Wooster et al., 1995).

Shortly after the landmark paper by Mary-Claire King and her co-workers, in where the *BRCA1* gene, located on chromosome 17 was shown to be associated with a high risk of breast cancer (Hall et al., 1990), a scientific group from Landspitali published a paper supporting this finding (Arason et al., 1993). The paper reported chromosome 17q linkage in two of seven analysed families. They also showed an original observation suggesting that a potential breast cancer gene might also increase the risk of prostate cancer. This effect did not appear to be confined to the 17q-linked families. This was an interesting observation, especially in connection with results from a previous epidemiological study, based on data from the ICR, suggesting a relationship between prostate, ovarian, endometrial and breast cancers (Tulinius et al., 1992). These Icelandic findings attracted attention, as reflected in an editorial in the March 1994 issue of Nature Genetics ("The prognosis for prostate cancer," 1994). Later, the high risk of breast and prostate cancer in most of the remaining families included in the study by Arason (1993) turned out to be due to a PV in the *BRCA2* gene (Gudmundsson, J. et al., 1995).

A study on breast and prostate tumours, as well as other tumour types from those with a pathogenic variant (van der Kolk et al.2010) in the *BRCA2* gene showed a very high incidence of loss of the wild-type copy of the *BRCA2* gene in the tumour in all the cancer types studied (Gudmundsson, J. et al., 1995). The results, as well as results from other Icelandic studies, indicated a 2-3-fold increase of the occurrence of *BRCA2* PV in cancer patients diagnosed with cancer in organs other than breast and ovary (Johannesdottir et al., 1996). These were among the very first results strongly suggesting that *BRCA2* was a tumour suppressor gene and that it was not only involved in the development of breast- and ovarian cancer, but also of other cancers (Thorlacius et al., 1996; Tulinius et al., 1992).

For almost two decades, only two PVs in the *BRCA* genes were known in the Icelandic population; the *BRCA1*:5193G->A (Bergthorsson et al., 1998) and the Icelandic founder *BRCA2* PV (Johannesdottir et al., 1996; Tavtigian et al., 1996; Thorlacius et al., 1996). The *BRCA1:5193G->A* PV is very rare, with a carrier frequency of <0.01%, (Rosa B. Barkardottir, personal communication) and had until recently only been found in three Icelandic breast cancer families (Arason et al., 1998; Bergthorsson et al., 1998). Recently, two new families with the *BRCA1:5193G->A* PV were identified, bringing the total number of families to five (Stefansdottir V., unpublished data). In contrast, the carrier frequency of the Icelandic founder *BRCA2* PV is relatively high (0.6-0.8%) (Gudbjartsson et al., 2015; Thorlacius et al., 1997). Two studies found the frequency of the variant in Icelandic breast and ovarian cancer patients to be about 7%, highest (24-27%) in patients diagnosed with breast cancer younger than 40 years of age (Johannesdottir et al., 1996; Thorlacius et al., 1996). However, this may be an overestimation due to ascertainment bias and has not been established in newer studies. The frequency of the Icelandic founder *BRCA2* PV is thought to be approximately 5% in Icelandic breast cancer patients (unpublished data)

Recently, by sequencing the BRCA genes, using multiplex ligation-dependent probe amplification (MPLA) and cancer panel testing, numerous additional pathogenic variants have been found in the *BRCA* genes in the Icelandic population. Among them are the pathogenic variants: *BRCA1: c.386delG*, c.*981_982delAT*, *c.4096+3A>G, c.4041_4042del* and *BRCA2: c.8796del (*Stefansdottir*,* unpublished data*).* However, the Icelandic founder *BRCA2* PV (formally known as 999del5), remains by far the most common *BRCA* PV in Iceland (Janavicius, 2010). The *BRCA1: c.386delG* has been found in two large Icelandic families, connected by a common ancestor seven generations back (Stefansdottir, unpublished data). The *BRCA1: c.981_982delAT* has, to date, been found in only one family (Stefansdottir, unpublished data). The *BRCA1: c.4096+3A>G* has a carrier frequency of 0.2%. Icelandic data show that this variant carries up to a 3.5-fold risk of breast cancer and more than a ten-fold risk of ovarian cancer (Th.R. personal communication). To date, through the cancer genetic counselling at Landspitali, this PV has been found in four families, all from the same geographical area in the country. Two are related by a common ancestor eight generations back. This PV has been reported several times in the Breast Cancer Information Core (MacInnis et al., 2013), with varied clinical significance. The *BRCA1: c.4041_4042del and the BRCA2*: c.8796del were each found in one family. The *BRCA2* c.9234C>T has been found in one

family, where the Icelandic founder *BRCA2* PV is segregating as well. It is a benign synonymous variant with the allelic frequency of 0.263% in Iceland (Th.R. personal communication). These findings indicate that the carrier frequency of all *BRCA* PV together in the Icelandic population is about 1%.

1.11.2 Genetic counselling

The term “genetic counselling” was first used in 1947 by Sheldon Reed while serving as a director of the Dight Institute for Human Genetics at the University of Minnesota (Reed, S. C., 1957; Reed, Sheldon C., 1974; Resta, 2006). Reed understood that people had a great interest in how genetic diseases affected their family lives and found the need to devise a term to describe how individuals and families were helped to cope with effects of a genetic disease, without the eugenic overtones common at the time (Resta, 1997). However, the idea of establishing a formal profession of genetic counselling has been credited to Melissa Richter, a professor in the 1960´s at Sarah Lawrence College in New York, where the first genetic counselling training program was established (Stern, 2009). Genetic counsellors, as genetic health professionals, are trained to help their counsellees understand genetics, assist in making risk assessments, and advise on testing and surveillance. The profession´s primary purpose is to assist those in need of genetic information (Paneque et al., 2001). They help facilitate accurate diagnoses, discuss the appropriate options for testing or reproduction, and offer psychosocial support to families using the service. Genetic counsellors have advanced training in counselling and genetics in order to interpret genetic test results and explain the results to the counsellee (Rantanen et al., 2008). They ideally work within teams comprising medical geneticists, genetic nurses and clinical laboratory scientists working in molecular, biochemical and cytogenetics laboratories (Rantanen et al., 2008). A Master level degree in genetic counselling from an accredited program is the required training for new genetic counsellors in both Europe (Ingvoldstad et al., 2016) and the United States (National Society of Genetic Counselors' Definition Task et al., 2006). The need for trained genetic counsellors increases as genetic services expand (Cordier et al., 2012).

1.12 Genetic health services in Iceland

The population of Iceland at the end of January 2019 was 356.991, with approximately 10% of the inhabitants of different origin than Icelandic (Iceland, 2016a). Most of the population (64%) lives in the Reykjavik capital area. Literacy is high, and over 97% of the population has access to the

Internet (Sigurdsson, 2015). The health care system is a mixture of government-funded and private practice (Sigurgeirsdottir et al., 2014). Landspitali – The National University Hospital of Iceland is in the capital and is the only hospital offering genetic health services. The Department of Genetics and Molecular Medicine (GMM) belongs to the Division of Diagnostic Medicine. The GMM comprises clinical genetics and genetic counselling as well as molecular, cytogenetic and biochemical laboratories with both prenatal and newborn screening. The department serves the whole country including limited GC services in the northern town, Akureyri. The genetic counselling unit was formally established in mid-2006 and organised cancer genetic counselling began within the GMM in December 2006.

1.12.1 The team

During the study, the clinical genetic health service team at Landspitali consisted of two part-time medical geneticists, a full-time genetic counsellor (GC), a part-time clinical cytogeneticist and a part-time oncologist trained in cancer genetics. (Stefansdottir, V., Arngrimsson, et al., 2013). The office manager performed clerical work and constructed the electronically generated pedigrees (EGP´s) while also managing most of the communication with the ICR. The clinical diagnostic work was undertaken by the medical doctors, while the task of providing information on genetic risk and potential options to patients was shared between the doctors and the GC. Cases were seen by either the counsellor exclusively or by a medical geneticist and a GC, depending on the issue. This practice is similar to the standard followed by many genetic services in other Western countries. Genetic nurses were not yet a part of the genetic healthcare service in Iceland, although this may be changing.

1.12.2 Referral routes

Self-referral to the genetic health services in Iceland is accepted, and is in fact, the most common form of referral. Health professionals can refer to the genetic services by email, phone and through the hospital electronic medical record. Self-referral is most common in genetic cancer services, followed by referrals from oncologists and oncology nurses and other healthcare professionals. The contact details for the genetic health services are published on the hospital website.

1.12.3 Ethos of the clinical genetic service

In genetic services, the importance of individual confidentiality is high, and

the counsellee often prefers to keep the appointment private (Stefansdottir, et al., 2013). To ensure equal access, self-referral is important. Most individuals receiving cancer genetic counselling in Iceland are self-referred, but in other cases, they have been advised by a professional to use the service, without a formal referral. Increasingly, as the genetic services are better known, professionals refer formally.

Non-directiveness and freedom from coercion are one of the key features of genetic counselling. The following statement can be found on the website of the National Society of Genetic Counsellors, Code of Ethics in the USA, in Section II, Article 4:

> "Genetic Counsellors strive to enable their clients to make informed decisions, free of coercion, by providing or illuminating the necessary facts and clarifying the alternatives and anticipated consequences" (National Society of Genetic Counselors, 2017).

On their website, the Association of Genetic Nurses and Counsellors in the UK have a similar text in their Code of Ethics:

> "Enable clients to make informed and independent decisions, free from coercion, through the use of a range of counselling theories and styles. Respect the client's personal beliefs and their right to make their own decisions." (Association of Genetic Nurses and Counsellors (AGNC), 2018).

Counsellee´s decisions about issues such as surveillance and risk reducing surgeries, may not be the one most cost-effective, but one consistent with their values and place in life. This policy includes therapy decisions like, for example, a woman with a *BRCA* PV who may choose to have either a mastectomy or surveillance every six months, without regard to which option is more expensive for the society. The counsellors´ responsibility is to offer the counsellee the most accurate information, and support for any consequent decision making.

1.13 A genetic "storm"

In May 2013, the New York Times published a letter from the actress Angelina Jolie, revealing that she had a PV in the *BRCA1* gene (Angelina Jolie, 2013). She explained her choice of double mastectomy as a preventive measure, knowing that she had a high risk of getting breast cancer in her

lifetime (Angelina Jolie, 2013). This event marked the beginning of an unprecedented increase in cancer genetic counselling, genetic testing for BRCA PVs and requests for risk-reducing mastectomy worldwide (Evans et al., 2015). In Iceland, the effect was noted immediately, as the media responded quickly to the news (Arnason V, 2014). In the first few days after the publication of Jolie´s article, several hundred people called the GMM, asking for cancer genetic counselling. This increase in service volume called for a change in the standard approach for the genetics clinic, as there was no increase in staff to cope with the increased demand for services. The first change regarded the genetic clinic appointments. Instead of allowing 60-90 minutes for the first session, 30-40 minutes became the norm. Next were changes in the way of conveying the results of genetic testing. The number of telephone sessions increased, in place of many of the former standard in-clinic/in-house appointments. Initially, only individuals who tested negative received results by telephone, but soon it became apparent that this was not optimal.

Thus after 2014, the majority of counsellees received their results, whether positive or negative, by phone. However, initially during the pre-test counselling and then at the beginning of the telephone conversation when the results were communicated, all counsellees were asked in what way they wished to receive the results. Those who wanted more time or a session in the clinic could request this at any time. One of the benefits of using the telephone instead of in-clinic/in-house appointment was less waiting time for the return of results for the counsellee. All who received telephone genetic counselling were also offered a clinical appointment.

For counsellees living at a considerable distance from the genetic clinics, using a telephone or other means of telemedicine is often less troublesome than travel. Many families where the Icelandic founder *BRCA2* PV is segregating, live far from the cancer genetic counselling services in Reykjavik. Although this has not been formally assessed in Iceland, when asked, many counsellees found telephone sessions useful, and for some even better than an in-clinic session. Elsewhere, the use of telecommunication has increased as well (Hilgart et al., 2012). Studies comparing in-clinic and telephone genetic counselling for to HBOC have shown similar psychosocial and knowledge outcomes (Peshkin et al., 2016; Schwartz et al., 2014, Kinney et al., 2016). Of note, although the changes developed from pressure on the genetic services system, the change to giving test results by phone had at least the advantage of allowing the

counsellees time to adjust to the knowledge of their genetic status, before the clinical appointment.

1.14 Facebook support group

In 2013 a private Facebook support group for Icelandic women who tested positive for a *BRCA* PV was formed. The founders were two women with the Icelandic founder *BRCA2* PV and the author of this thesis, as a genetic counsellor (Stefansdottir, V., 2016a). The group size increased quickly and soon became not only a support group for patients but also partly for the cancer genetic counselling service. Having a genetic counsellor on-board enables easy access for group members seeking advice or information. As well as being a group of peers, supporting and advising each other, the group also serves the purpose of providing information quickly when needed to a larger group - the families of members. The BRCA society in Iceland was formed subsequently and has been active and vocal on behalf of the BRCA community. The BRCA society Facebook page is open to everyone and can be accessed here: https://www.facebook.com/brakkasamtokin. Recently, (in August 2018) males with a *BRCA* PV in Iceland formed a similar private support group on Facebook.

1.15 Summary

Conventional collection of medical and family information is a lengthy process. The genetic assessment usually calls for a pedigree covering at least three generations or 3° relatedness with accurate medical information, which is difficult to collect and labour-intensive.

Hereditary breast and ovarian cancer syndromes are identified and confirmed by genetic testing when possible. At the beginning of the study, only two *BRCA* pathogenic variants were tested for in HBOC cancer genetic counselling in Iceland. In many ways, circumstances in Iceland are unique, as interest in genealogy is extensive, and numerous databases exist alongside a comprehensive nationwide cancer registry. By using our databases, genetic services can generate electronic pedigrees with comprehensive data. This method leads to relatively large and more accurate pedigrees, which consequently improve risk assessment and surveillance plans. It also enhances the ability to identify those at risk in the family. While the use of electronic health records has increased over the years, utilising electronic genealogy databases in genetic health services is uncommon. Collection of family information through specific cancer registries and other disease registries is, however, well known, and family information does

accumulate over time in all genetic health care centres. Professionals exchange information as needed, with presumed consent from all included, to ensure excellent service to counsellees and their families.

In this thesis, I cohesively assessed the use of electronic genealogy databases in genetic health services and evaluated how using electronically generated pedigrees was perceived. Additionally, I evaluated how using EGPs influenced the genetic health service, and finally, assessed the optimal size of pedigrees for HBOC genetic counselling.

2 Aims

The overall aim of this PhD thesis was to cohesively assess the availability and use of electronic genealogy databases and information from cancer registries to construct electronically generated pedigrees for risk assessment in genetic counselling. Hereditary breast and ovarian cancer (HBOC), due to the Icelandic founder *BRCA2* PV was used as an example.

The thesis is built on three studies, published as three separate scientific papers. The specific aims of each study were as follows.

The use of genealogy databases for risk assessment in genetic health service: a systematic review. The aim of the literature review was to identify and analyse the existing work on the use of genealogical databases used to facilitate pedigree construction in genetic health care services.

Counsellee's experience of cancer genetic counselling with pedigrees that automatically incorporate genealogical and cancer database information. The aim of the qualitative study was to assess the counsellees´ experience where EGPs were used in HBOC genetic counselling.

Electronically ascertained extended pedigrees in breast cancer genetic counseling. We aimed to determine the practicality of using large EGP´s in HBOC genetic counselling. An additional aim was to calculate the optimal size of a pedigree for risk evaluation in cancer genetic counselling.

3 Materials and methods

The overall design of this thesis was based on exploratory sequential mixed methods (Ivankova et al., 2006). This approach can be used in studies focussing on an area of research, which is mainly exploratory and where the use of different research methods will enable diverse aspects of the topic to be dissected. I found it important to explore the use of EGPs from the perspectives of the key users – namely patients and professionals.

The first part of the study was a systematic literature review to ascertain the previous use of EGPs in a range of settings. This was followed by a qualitative study to determine the impact on patients. The last study was done by quantitative methods to examine the use and impact of EGPs in clinical care.

3.1 Study I design

The litereature review question was: 'What is known about the use of electronic genealogy databases, to generate electronic pedigrees in clinical genetics and genetic counselling? To answer the question, I did a systematic literature review using 12 combined search terms in five literature databases and the grey literature to find as many relevant papers as possible.

The original search for the systematic review was performed in October 2011 and is described in Study I (Stefansdottir, V., Johannsson, et al., 2013). As an update for this thesis, the search was repeated in December 2018. The updated review was done using a systematic rapid-review approach (Ganann et al., 2010). The databases, but not the grey literature, were searched using the same terms as in the first search to capture all papers with a title, abstract, or topic that included any of the phrases. The data limits were 2017 and 2018. The searches were refined to exclude case reports and non-peer reviewed journal articles (newspaper and magazines), non-English papers, and animal studies. The original review was to provide a foundation for the subsequent study, and the update was used to determine changes to the peer-reviewed evidence base since the original study. Additionally, although not a part of a formal study, the author has been a subscriber of alerts from Google and Google Scholar, with the same search terms used in the study, since 2013 and has read the relevant daily alerts. The inclusion and exclusion criteria for the original systematic review can be seen in Table 2.

3.2 Study I, data sources

The databases PubMed, Web of Science, EBSCOhost, OVID, and CINAHL were used to search for papers published in peer-reviewed journals, as well as the reference lists of relevant papers, theses, and articles in the grey literature. The Penn Libraries determined the grey literature as:

> *"…created by researchers and practitioners in various fields, but is not controlled by commercial publishing. The groups that produce grey literature may be government, industry, advocacy or other organizations that disseminate information in the form of reports or working papers rather than by publishing scholarly articles in commercial journals" (University of Pennsylvania, 2017).*

3.3 Search terms

The following 11 combined search terms were used for the review:

- Genealogy database* AND genetic risk AND family history
- Genealogy database* AND clinical genetics
- Genealogy Database* AND medical AND family history
- Cancer registry AND genetic service
- Cancer registration AND clinical genetics AND genealogy
- Database* AND family history AND genetic risk assessment
- Genealogy database* AND cancer registry
- Database* AND genealogy AND genetics
- Genealogy AND database
- Genetic counsel* AND clinical genetics AND genealogy
- Cancer genetic counsel* AND genealogy.

Collectively those search terms should identify articles in the literature that discuss the use of electronic databases in genetic counselling.

Table 2. Inclusion and exlusion criteria for the literature review

.	Included	Excluded
Main theme	Focus on the use of genealogy data-bases in genetic health services	Focus solely on use of genealogy databases for the purposes of genetic research rather than clinical service (e.g., mapping a gene)
Timeframe	1970-2010, later updated to include 2011 to 2018.	
Population	Humans	Not human, statistics, computer programs,
Concept	Electronic genealogy databases and cancer registries related to clinical genetic services, electronic databases used in health care, electronic health records used in clinical services, experience of pedigree making in clinic, literature review on electronic databases in clinical genetic services	Non-clinical settings, statistical family history related, impact of genetic test results, familial disease description, risk assessment outcome, non-clinical settings, non-humans, computer programs, statistical papers, genetic test results, suggestions for guidelines
Context	Qualitative and quantitative original research articles, published in English, genetic clinical services setting, communication about electronic databases and family history, outcomes from published genetic services papers, conference papers, discussion papers, thesis, dissertations, genetic services setting, how to make family history, using electronic databases	Magazine and newspaper articles, epidemical studies, description and computer programs, treatment settings, palliative care settings, family history related, non-clinical, guidelines or suggestions for guidelines, statistical papers, genetic test results, editorials, commentaries, molecular research, description of registries, relative risk outcome, genetic services follow-up, description of available genealogy databases, ethical issues, population studies, case control studies, general discussion on genetics

(Stefansdottir, V. et al., 2013)

3.4 Study II, design

In this study, a qualitative descriptive approach was used, with online focus groups, (Sandelowski, 2000) to experience, emotions, values and perceptions of participants who had undergone genetic counselling with EGP´s.

Online focus groups (OFG) are commonly used in business for marketing research. Specific websites, such as iResearch allow researchers and interested participants to connect with a promise of anonymity in online focus group studies (iResearch, 2018). Those participating in focus groups for business, usually get paid or compensated for their time (Petrescu, 2018). This contrasts with academic studies where participants usually participate for free. Another platform, Facebook™, can be used for focus groups. The negative side of Facebook™ is that it is impossible to be anonymous and Facebook™ owns all the data added. However, using a secret Facebook™ group allows the participants at least some sort of privacy as the group is invisible to non-members (Lijadi & van Schalkwyk, 2015).

In qualitative research, OFGs enable a different approach from face-to-face groups (Hansen, 2006). The methods used can be either written (email, discussion boards) or audio/video meetings. Studies using OFGs can be performed either synchronously or asynchronously. The difference is the log-on time; participants must all log on at the same time using the synchronous way (Fox et al., 2007) while they can log on when convenient in the asynchronous method (Zwaanswijk & van Dulmen, 2014). In both methods, facilitators moderate the group or groups to collect data through an exploration of topics (Kevern & Webb, 2001). The method chosen depends on the availability of participants and the topic.

The asynchronous method was chosen mainly to enable participants to log on at their convenience and not to be bound to a specific timeframe or have to travel. These features would possibly encourage more active participation. In market research, online focus group studies are well known, but at the time of the study, less so in academia.

The strength of using OFGs instead of a face-to-face focus group is mainly the anonymity among participants and easier recruitment (Newington & Metcalfe, 2014). Another benefit is that group members do not have to travel to a specific place for a meeting and therefore can participate when convenient, at home or elsewhere. (Zwaanswijk & van Dulmen, 2014). As for the information shared, some find it easier to share sensitive information

without personal identification (Tates et al., 2009). For the researcher, the data is accurate and already in a textual form which eliminates the need for transcribing and editing, saving workload and money (Kenny, 2005).

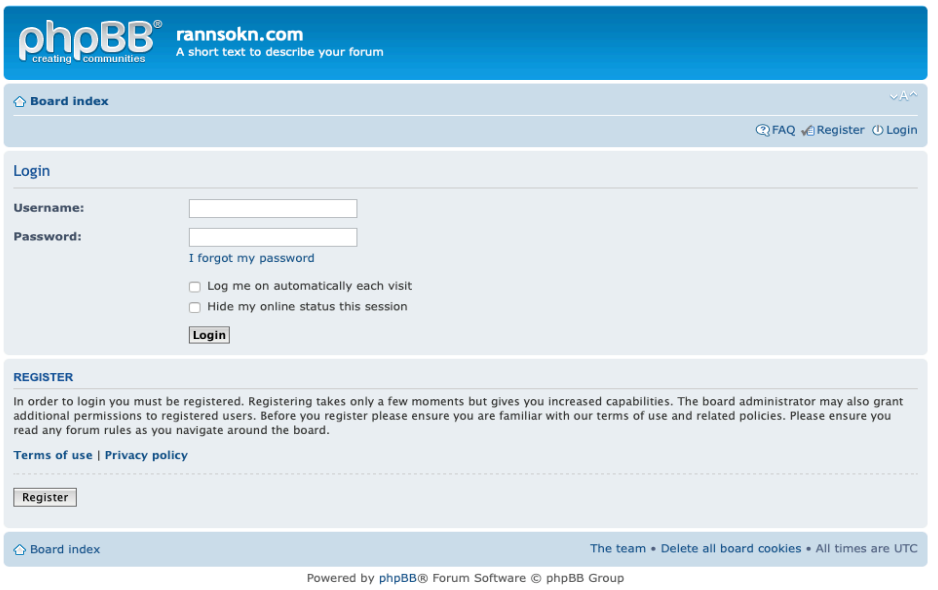

Figure 6 The registration page of the phpBB Forum.

Body language is an important factor in conversation. One of the main weakness of using an online focus group is the complete absence of body language and facial aspect, resulting in different group dynamics than in a conventional focus group. (Zwaanswijk & van Dulmen, 2014). Participants may also be multi-tasking and not with full attention on the task at hand when online. For some, not knowing who is corresponding, (anonymity) can be difficult. Lastly, not having access to a computer or not being comfortable with computer technology could be a barrier to participation.

Weighting the pros and cons of OFGs, such as anonymity, the possibility to log on when convenient as described in the Introduction, overall, we felt that the advantages were greater than the disadvantages. Therefore, we decided to use this method.

Several online discussion/bulletin boards or forum are available. For this study, a phpBB forum which could be downloaded from the webpage https://www.phpbb.com was chosen. It is a free, open-source bulletin board accessible from anywhere, with an Internet connection. Figure 6 shows the registration page of the forum. The Icelandic Human Genetics Society hosted the forum for the study. The forum was kept secure and closed to the public to ensure the privacy and discussion of participants,. The host ensured that the IP numbers and email addresses of participants could not be accessible by anyone. Each participant chose a username and a password at registration. After each group had finished, the communication board was completely deleted. Figure 7 shows the outlook of the forum.

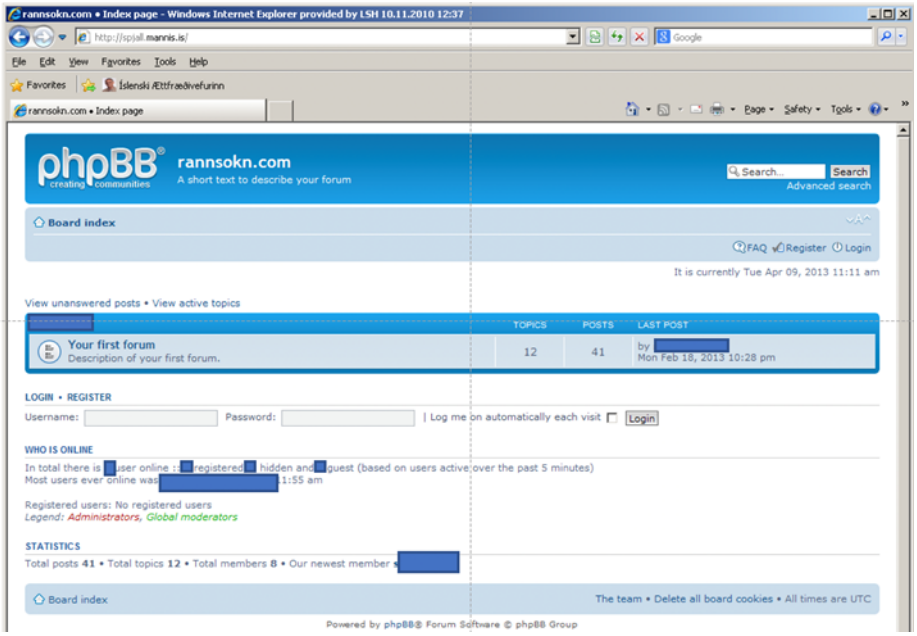

Figure 7. The outlook of the forum.

3.5 Cohort. Study II

Participants (n=19) were of Icelandic origin and had received cancer genetic counselling between 01.01.2007 and 31.12.2012 at Landspitali. Both males and females were invited to the study, in all 225 individuals - 158 females and 67 males. All invited to the study had been tested for either one or both known Icelandic founder PV´s.

Four online focus groups were selected (Stancanelli, 2010). From the original group of 225 individuals, 50 were selected randomly for each of

group one to four, using the RAND function in the Microsoft program Excel™ (Microsoft). The number, average age and age range of participants is shown in Table 3. An invitation letter was sent by mail to each of the participants, first for group one. Their names were then removed from the original group (selection without replacement). The same method was used for groups two and three (50 each), but for group four only males who had not been in the selection of the first three groups were invited to the study.

No males participated in the first three groups although some had shown interest. Males with a PV in the BRCA genes have a different experience and risk than females. We found it important to invite males only to the last group to obtain their views as well as learning more about their experiences

Table 3 Number and age range of participants in the online focus groups.

N=225	Group 1	Group 2	Group 3	Group 4
Invited	50	50	50	7
Consent to participate	8	8	7	3
Actual no. of participants	3	7	7	2
Females	3	7	7	0
Males	0	0	0	2
Average age	49	52	53	53
Age range of participants	44-54	33-69	36-64	38-68

Stefansdottir, V. et al., 2016)

The average age of invited individuals (n=225) was 50.4 years (range 23-86), but the participants´ average age was 52.2 years (Table 3). The youngest participant was 33 years and the oldest 69 years. Eleven were positive for either one of the Icelandic founder PV in BRCA genes, and eight were negative (Table 4). In the invitation letter, participants were informed that consent for participation was defined as either the return of signed form sent with the invitation letter or by email stating willingness to participate.

Table 4. *BRCA* PV status and age of participants in the online focus groups.

Group 1	Group 2	Group 3	Group 4 (males only)
Negative, 54	Negative, 66	Positive, 64	Positive, 36
Negative, 45	Positive, 33,	Positive, 57,	Negative, 67
Positive, 44,	Positive, 45	Positive, 56	
	Positive, 55,	Negative, 36,	
	Negative, 67,	Negative, 41,	
	Positive, 34,	Positive, 55,	
	Negative, 69	Negative, 64	

(Stefansdottir, V. et al., 2016)

3.6 Instructions to participants

Those who agreed to take part in the study received instructions about how to sign on to the forum and what to do to be a part of the group. Below information letter translated by the thesis author, can be seen. The original is in the supplemental files (Information letter):

Dear participant

Start by going to the Internet address: spjall.mannis.is.

Before you start, you can make a new email address for yourself, for the purpose of this study, if you like. The IP numbers used when signing on to the website, cannot be observed and will not be collected.

You need to click on „register“, in the right upper corner. There you can make your own username and password.

When all have registered, I will get notified will add you to the board where we can discuss the question as you like before you reply to it.

I would like everyone to reply to all questions if possible. It would be nice to have a chat as well, on the board. It is rewarding and can be great and informative for all, to have conversations on the board.

All exchanges are done without personal identification, and it should be impossible to find out who you are, without your permission. However, any of you can send a private email to other participants at will.

You can also exchange information or mail within the board, among yourselves by private messages.

Thank you for participating.

Vigdis Stefansdottir, genetic counsellor.

3.6.1 The questions

At the time of the study the formal cancer genetic counselling service had only been available for a few years, or since the end of 2006. Early on, it was decided to seek permission to use the extensive genealogy database GCUI for the construction of EGPs in order to do better for risk assessment in cancer genetic counselling. Simultaneously, permission to add information from the Icelandic Cancer Registry was applied for. Both permissions were granted. This was a novel approach to cancer genetic counselling. Due to the novelty of the EGPs, it was of interest to survey the overall experience of the counsellees of the genetic counselling service as well as the EGPs. Thus, the questions were prepared not only to explore the experience of using the EGPs but also the genetic counselling service. We wanted to know if there was any change in the family dynamics following genetic testing (McInerney-Leo et al., 2005), and how the family communication had changed (MacDonald et al., 2007). Lastly, we were interested in knowing how the overall experience of the genetic services had been (McAllister et al., 2011).

The first two groups received identical questions posted sequentially to the forum. Each time a question had been posted, participants received notification by email. A week later, another reminder was sent if few or no replies had been posted on the board. Both on the discussion board and in the reminder email, the administrator encouraged participants to engage in communication and to post their own questions and comments.

When the first two rounds had finished, the replies and communication were reviewed, and a decision was made to make small changes to the questions. The content of the questionnaire stayed the same, but the wording was changed in some of the questions. Therefore, instead of 10 questions, groups three and four received 15 questions, with some of the more complex questions made simpler and divided into two. The content of the questions remained the same for all groups. This is common in qualitative studies, where concurrent data analysis influences the data collection (Green et al., 2007).

Another change was made in the third and fourth group to prompt faster replies in the group and more engagement on behalf of the participants in the third and fourth group. This involved adding the questions to the board in two parts instead of one by one. The first seven questions were added together and the last eight shortly after.

3.6.2 Group 1 and 2, questions

1. Why did you go for genetic counselling and what were your ideas about it beforehand?

   (An explanatory comment on the board, from the admin, for the questions below). “I would like you to ponder about the EGP´s we use for the risk assessment, made with the information from the genealogy database and Cancer Registry.

2. Did you know anything about them beforehand – if it was possible to make them? What were your thoughts about the capability to make such extensive pedigrees?

3. Did you have anything against using EGP´s in the genetic counselling and were you worried about other family member’s issues or attitude regarding the extensive information in the pedigree?

4. Do you trust the information in the EGP? Any thoughts?

5. What did you think about also having to give your information for a handmade pedigree?

6. When you had to decide on genetic testing, how did you feel about your decision? Describe your feelings during the waiting period.

7. Can you describe your emotions right after and for the first few days after you got the results? What about later?

8. Has the family dynamics and communication changed after the genetic counselling? In what way?

9. Do you think that anyone in your family is suffering from survival guilt? (Survival guilt can be described as when one feels “guilty” when not having a genetic mutation when others in the family have it).

10. This question is a bit complicated and long: What do you think was well done during the genetic counselling? What do you think can be done better?

    a. Information before the testing,

    b. Information after the testing,

    c. Anything else?

    d. Lastly, is there anything else you want to share?

3.6.3 Group 3 and 4, questions

1. Why did you come for genetic counselling?
2. What ideas had you about the genetic counselling prior to your visit?
3. Did you know anything about EGP´s prior to genetic counselling?
4. Can you tell us about your thoughts when you knew that it was possible to get the extensive information from the electronic databases?
5. Were you against using EGP´s in the genetic counselling?
6. Did you worry about others in the family because of the use of the EGP and the information they contained?
7. What did you think about also having to give your information for a handmade pedigree? (A comment from admin: This is only for those who had no relatives that have come before to genetic counselling).
8. Did you trust the information in the EGPs? Any thoughts?
9. When you had to decide on genetic testing, how did you feel about your decision?
10. The waiting period for the results – can you say something about that?
11. Can you describe your emotions right after and for the first few days after you got the results? What about later?
12. Has the family dynamics and communication changed after the genetic counselling? In what way?
13. Do you think that anyone in your family is suffering from survival guilt? (Survival guilt can be described as when one feels “guilty” when not having a genetic mutation, when others in the family have it).
14. What do you think the genetic counselling has done well?
15. What do you think we can do better?

    a) Information before the genetic testing

    b) Information after the genetic testing

    c) Is there anything else you want to add?

3.7 Study III, design

For this study, we used genealogical and PV data from those individuals who had received cancer genetic counselling due to HBOC at Landspitali between 1.12.2006 - 31.12.2015. All were of Icelandic origin and had been tested for the Icelandic founder *BRCA2* PV. Some had also been tested for the founder PV in the *BRCA1:G5193A* (n=1352). Families, with at least one family member positive for either of the founder *BRCA* PV, were defined as "families with BRCA PV."

After subtracting individuals with the *BRCA1:G5193A* (n=58) 1294 remained and were divided into two sub-groups: a) those who belonged to a family with the Icelandic founder *BRCA2* PV (sub-group I, n=523) and those without (sub-group II, n=771).

In all, 104 women who had tested positive and 105 who had tested negative for the Icelandic founder *BRCA2* PV were randomly selected from the groups by the Randbetween function in Excel (Microsoft). Each participant was given a unique number and was removed from the group after selection in order to not to choose the same number twice.

For each proband, up to eight EGPs were made, with descendants from each of the eight great-grandparents. Some individuals appeared in multiple EGPs, either as a member of the family or married into the family.

We estimated the average cost of generating ten EGPs within the genetic counselling service in Iceland. This was done by timing the consent process, the data transfer time, the upload of data, the time used for reviewing the data, and the final output with all relevant information for several pedigrees of different sizes to find the average workload.

3.8 Data analysis

3.8.1 Study I

The papers were analysed for key codes, categories, and themes within and across papers. Meta-analysis was not possible, given the limited data found, and the findings were presented in textual form, under themes.

The quality appraisal tool CASP checklist for cohort studies (Health) designed by the Critical Appraisal Skills Program (Critical Appraisal Skills Programme, 2010) was used to evaluate the research-based paper (Brewster et al., 2004) with the score set at 93%. It was not possible to formally appraise the quality of the discussion-based papers.

3.8.2 Study II

A thematic analysis method was chosen for this study as it enables rich data to be collected and analysed without restrictive prior categories. Thematic analysis has minimal organisational effects. It allows for searching for patterns across the entire data set, rather than within each interview or data for each participant separately (Braun & Clarke, 2006).

In thematic analysis, a theme or a pattern is found by looking at the frequency of the appearance in the text. Still, the researcher must make the judgement himself as a number alone cannot be a qualifier. This relates more to ascertain if the alleged theme captures essential issues related to the overall research question. We found it important not to try to fit the data into any pre-existing coding frame, rather to allow the pattern to emerge. The replies were coded into topics, categories and the following themes; motivation, information and trust, impact of testing, emotional response and electronic pedigrees. Two of the authors (VS and HS) independently coded the replies using descriptive coding by hand. Thematic analysis of data was made by the approach used by Braun and Clarke (Braun & Clarke, 2006), which includes identifying and analysing patterns or themes within the data, in a non-theoretical way. Examples of the analysis can be seen in Table 5. Categories were independently coded using descriptive coding.

Codes, categories, and themes were discussed between two of the authors (VS and HS) until consensus was reached.

Table 5. Examples of the thematic data analysis in Study II.

Original text	Topic	Category
I had had breast cancer myself and later one of my aunts. She was tested and found to have BRCA 2 and then the doctors wanted to know which of her parents had it. My brother turned out to have the gene and following that I decided to get tested. And I had it.	Breast cancer self	Experience of disease
	Aunt w breast cancer	Family history
	Relatives tested positive	Experience of mutation/testing
	Where from	
	Self-testing	Experience of mutation/testing
	Self with mutation	Experience of mutation/testing
I had not thought about it, but I think for the sake of research that it should be possible. Could I get a tree like that?	No previous thoughts	
	Should be possible	Positive attitude (EGP)
	Want data	Information
I did not know they were used.	No prior knowledge	Information (not)
No	Thoughts (not wanting to share them)	Sharing
I trust the information and would really like to see it.	Trusts the information (EGP)	Information and trust
It goes without saying (Icelandic well-known phrase)	Self-explanatory	Positive attitude (towards EP information)

3.9 Study III

In study III, detailed one to six generation pedigrees were constructed within the pedigree software Clinical Pedigree™ (Cyril Chapman, 2016) using data from the GCUI (Tulinius, 2011) and the population-based Icelandic Cancer Registry (Sigurdardottir et al., 2012).

The predictive model BOADICEA™ (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) (Lee et al., 2014; MacInnis et al., 2013) was used to calculate the likelihood of being a carrier for the Icelandic founder *BRCA2* PV. The likelihood of having the *BRCA1* founder PV was not used in this study as the variant is very rare. The program used the Icelandic allele frequency 0.3 for the Icelandic founder *BRCA2* PV and cancer incidence rates for Iceland (Gudbjartsson et al., 2015). Search sensitivity was overall 0.8 (Lee et al., 2014; MacInnis et al., 2013). Microsoft Excel was used as a datasheet for descriptive statistical analysis. The MedCalc™ Receiver Operating Characteristic (ROC) Curve Analysis (Hanley & Mcneil, 1982) was used to evaluate the effect of pedigree size on risk calculation for (MedCalc Software, 2016). The Area Under the Curve (AUC) - C-statistic for paired samples, based on exact binomial functions was used to assess how increasing the degree of relatives included in a pedigree would affect the classification of probands with regard to the Icelandic founder *BRCA2* PV positive and the Icelandic founder *BRCA2* PV negative.

Statistical tests were two-sided. The difference, standard error, and 95% confidence interval (CI), and p-value of the differences between C-statistics were calculated with a significance level of 0.05 (95% CI did not include zero) (Delong et al., 1988).

To further assess if the difference was because of an increased number of individuals or degree of relatedness, both the 3° and the 4° pedigrees were divided into two groups, according to size. The MedCalc program was used to calculate the statistical significance of the difference between the ROC curves for independent samples.

We also converted the lower number group in the 3° pedigrees into 4° relative pedigrees to assess this further. This was done within the ClinicalPedigree program which allows for truncating and increasing the size of the pedigree according to the degree of relatedness.

4 Results

4.1 Study I

The systematic literature review was undertaken to assess the use of electronic genealogy databases in the context of genetic health service.

The original search was performed in October 2011. As an update for this thesis, the search was repeated in December 2018 within the same parameters, excluding the grey literature. Apart from our own studies, no new paers fitting the inclusion criteria were identified in the repeated search.

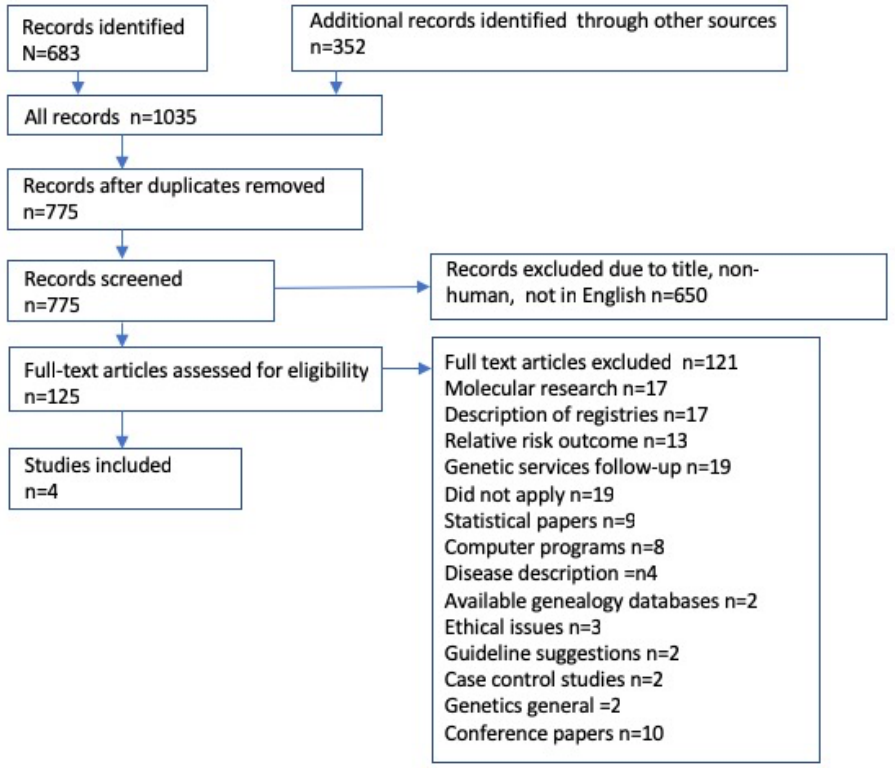

Figure 8 Selection of papers from the initial search in 2011. (Stefansdottir et.al., 2013)

The initial search retrieved 1035 titles. Of those, 260 were duplicates, and 650 were excluded by title only, being non-human or not in English. The remaining 125 titles were analysed further, and 121 were excluded (Figure 6). The four remaining papers were two original research papers, one Icelandic and one from Scotland. The two other papers were discussion papers (Cannon Albright, 2006; Tu & Mason, 2004). Table 6 shows the main outcome of the selected papers. The Icelandic paper described the use of the same genealogy database as was used in this study, but the paper from Scotland described cancer genetic risk assessment using database generated pedigrees in four major health care centres in Scotland.

The first paper; *"Organizing population data into complex family pedigrees: application of a second-order data linkage to State Birth Defects Registries"* was a discussion paper with no original data (Tu & Mason, 2004). The authors discussed the possibility of linking individuals using previously collected data in various national and regional databases in clinical health care. They acknowledged that such linking for research was limited to a first-order linkage, i.e., only linking the same individual to himself or herself in different databases. The authors suggested that being able to linking various data into pedigrees could significantly impact scientific genetic studies, and by additionally link environmental data as well, large-scale studies could be executed on gene-environment interactions.

In the second paper; *"Computerized genealogies linked to medical histories for research and clinical care – a national view",* (Cannon Albright, 2006), the author discussed the possibilities of connecting genealogy data and medical records, and how it could increase the power of clinical and scientific research. This was a proceedings paper from the Australasian Integrative Medicine Association (AIMA) annual symposium. It describes the two geographical areas where ample resources existed for making accurate genealogical data linked to medical data, Iceland and Utah, and how the computerisation of their data began 30 years earlier (the paper is from 2006). The author also describes the collection of genealogy data for Utah and neighbouring states, going back to the founder population, including millions of individuals. In the concluding sentence, the author mentioned that linked genealogy and medical data were not used anywhere to access the familial risk of disease.

In the third paper entitled *"Impact of a cancer registry-based genealogy service to support clinical genetics services,"* Brewster and colleagues described a survey looking at the effect of database-generated pedigrees on

cancer genetic risk assessment in four major centres in Scotland. The authors found that the pedigrees provided by the Scottish Cancer Registry were accurate and extensive and that using them changed the risk category in 41% of cases and the management in 23% of cases. They concluded that linking pedigrees to cancer registry could affect genetic counselling positively as the family history was more comprehensive (Brewster et al., 2004).

The fourth paper *"Systematic family screening for familial hypercholesterolemia in Iceland"* (Thorsson et al., 2003) described the use of the Icelandic genealogy database in clinical service. The authors compared two methods of screening for familial hypercholesterolemia, a conventional screening method and a novel approach using the genealogy database to find relatives for systematic family screening. The latter method, systematic screening identified 19% more relatives than the conventional type. The results indicated that using genealogy databases to identify family members in a systematic way, could increase the number of those found to be at risk.

In summary, there was very limited data in the literature describing the use of electronic genealogy and cancer registry data in generating pedigrees in genetic counselling.

Table 6 The four papers identified in the literature review, describing the use or potential use of genealogy databases in clinical genetic services, (Stefansdottir, 2013).

Authors	Title	Type of paper	Description	Results	Conclusion
Tu and Mason (2004)	Organising population data into complex family pedigrees: application of a second-order data linkage to State Birth Defects Registries	This paper is a discussion paper and includes no primary data	Discusses the possibility of using previously collected data in clinical health care. Also describes the best way of organising and collecting such data	Description of available data in diverse national and regional databases and how the data can be used	The power of data collected routinely into regional and national databases is underused in clinical health care
Cannon Albright (2006)	Computerized genealogies linked to medical histories for research and clinical care—a national view	Symposium proceedings. This is a discussion paper with no primary data collection or results	Discussion of the possibilities of combining genealogy data with medical histories	The use of linked genealogy databases and medical histories can enhance the power of research and make clinical care better	Genealogy data can contribute widely to the understanding of familial and genetic factors in human health and disease
Brewster (2004)	Impact of a cancer registry-based genealogy service to support clinical genetics services	Short research paper describing a survey	The paper describes the effect of database-generated pedigrees on cancer genetic risk assessment in four major centres in Scotland	The pedigrees provided by the Scottish Cancer Registry were accurate and extensive and often changed risk category (41 %) and management (23 %)	Linking of pedigrees to a cancer registry results in more comprehensive family history and can change cancer genetic counselling
Thorsson (2003)	Systematic family screening for familial hypercholesterolemia in Iceland	Research paper comparing two methods of screening	The paper describes a novel approach in screening for familial hypercholesterolemia and compares it with conventional method	The systematic family screening identified 19 % more individuals than the conventional one	The new method adds considerable to the conventional method of FH screening

4.2 Study II

This was a qualitative study with questions posted on a PHP Bulletin Board (phpBB) forum. The forum allowed the participants to discuss any of the topics among themselves as well as reply to the questions posted on the board. However, they did not use the opportunity to post comments despite encouragement from the board administrator. In general, participants were positive towards the use of EGP´s and did not oppose the use in genetic counselling. Participants had trust in both the service and the information. Obtaining consent for the EGP and explaining the reason for using it followed without complication.

No security breach or misuse of information was noted during the collection and use of the data. Table 7 lists the emerging themes and their components arising from the replies. In the quotes, participants were identified by age genetic status (PV positive or PV negative). All replies are listed in supplementary files as Supp. replies.

4.2.1 Reasons for attending GC

The reason most participants had come for genetic counselling was a family history of either breast cancer or knowledge of the Icelandic founder *BRCA2* PV within the family. It could be very close relatives like mothers and sisters:

> "I decided to get genetic counselling because my mother died at 49 after getting breast cancer and my sister's mother also when she was 69. The oncologist advised it. I did not have any ideas about the genetic counselling beforehand, but of course, I had thoughts about what to expect, that is, if it turned out to be genetic and such" (PV negative, 45).

The sense of duty to relatives diagnosed with breast cancer was present:

> "After my mother was diagnosed with *BRCA2* gene, I felt I had to go when it was offered. I had no idea that this service was available, but then I had never given it any thought (PV negative, 41).

Table 7. The main emerging categories, components and themes from the participants replies on the forum.

Themes	Categories	Components	Themes
Motivation	Family history		
	Experience of condition		
	Experience of mutation or testing	Awareness	
	Experience (self or family) of genetic counselling		
Information	Information	Sufficient	Would have liked more later
and trust	Trust		
	Electronic pedigrees		
	Genetic counselling		
	General		
	Data protection	Privacy issues	Worries
Impact of testing	Waiting time	Difficult or long	Normal
	Family communication	No change or positive	Little
	Decision making about future		
	Survival guilt	None	Little
	Lifestyle changes	Definitely	
Emotional response	Emotions	Negative	Relief
Electronic pedigrees	Knowledge	No prior knowledge of electronic pedigrees or genetic counselling	Prior knowledge of electronic pedigrees or genetic counselling
	Family attitude towards EGPs	Positive	Diverse

Modified from Stefansdottir et al., 2015)

Even though families were not large, the knowledge of cancers in relatives could encourage seeking genetic counselling:

> "After my breast cancer diagnosis, I talked to my doctor about how many in my family had had cancer. He felt that it was enough reason for me to go to GC. I had my sons, siblings and other relatives strongly in my mind, but my family which descends from my grandfather and grandmother is not large, and we are very close (carrier, 55).

Some had relatives that had already been for genetic counselling:

> "As there is a lot of breast cancer in my family and many of my relatives had gone for GC and given me information, I decided that it was sensible to go, not in the least because of my descendants (PV negative, 67).

Others had had the information letter forwarded from relatives:

> "I have an aunt who got breast cancer, and she had been asked to relay the information to us that we might carry the gene" (PV positive, 57).

4.2.2 Trust

Participants described their trust toward the genetic services, pedigree information, and cancer registry. Concern over family members' attitudes regarding the use of information from databases was limited:

> "I trust this information completely. I have no reason not to" (PV positive, 45).

> "I know professionals do this. Therefore, I trust the information 100% (PV positive, 33).

> "Yes. I think this is all done very professionally (PV negative, 36).

> "I have no reason not to trust it, but I do not have enough knowledge about what the danger might be if the information is wrong. It is important that information like these to be accessible to the individual asking for them but not for others. No such information used in research should have personal identification. The individuals themselves should be able to get their own information" (PV positive, 56).

4.2.3 Emotional response

Some were stressed because of the testing and others found relief in knowing the outcome:

> "I was very stressed because it is a lot of hassle to test positive for the BRCA gene" (PV negative, 36).

Others were happy to be able to have surveillance:

> "I did not find it terrible, but of course it was a shock but I somehow had expected this outcome. Maybe I am playing Pollyanna, but I think it is like this. My parents both died of cancer, and I have many siblings with a yes, others no just like expected. However, we can all expect to get cancers, but those

> of us who had yes can have surveillance the others do not so I regard myself lucky" (PV positive, 44).

Still, others had done a lot of thinking and decided to have the test:

> "When I finally decided to be tested I was very pleased about it. The waiting time was a bit difficult as I had imagined" (PV negative, 57).

Some found family support valuable:

> "I thought a lot about the results. I pondered about my children's reaction. They would have to decide, I thought, what they wanted to do when I told them about the risk of having the mutation. I found it useful to talk to my relatives that are people my age who are in the same risk group. We met a lot during this period; three newly diagnosed with cancer were in the group and therefore easy to talk about the problem. I found it a lot of hassle to attend to the strict surveillance program. However, it turned out just to be anxiety. It is not a problem any longer.

Participants had mixed emotions.

> So, the emotions were mixed, good/bad. Good to know, sad to have to think about it but then I got used to this, and I think it is good that my people know that I have this mutation" (PV positive, 55).

There was some concern about insurance companies:

> "Yes, I trust the service as much as possible. Still, it is vital to ensure that insurance companies will not be able to access the information" (PV positive, 36).

4.2.4 Impact of testing

Having genetic testing had a great impact on most people however well they prepared for the results:

> "The results did not come as a surprise but are you ever ready for such knowledge? I do not think so. I got a bit scared as I had had breast cancer shortly before. I was worried about getting breast cancer again because now I knew for sure that the risk

> was quite high. Nevertheless, I did not let the scare overtake me. I was just more convinced that I had done right and I just felt good about the decision" (PV positive, 55).

Many felt it was preferable to know their genetic status, although the results were not optimal:

> When I had the results that I had the mutated gene, and on top of that I was a carrier, I was definitely taken back. On the other hand, I felt it useful to know my status and really nothing else to do but agree with the facts (PV positive, 45).

The relief accompanying a negative result could also be difficult if others had a different outcome:

> "It was a relief, but at the same time, I felt bad because my sister had a positive result. I had bad conscious because I felt that I was the stronger one and should have been the one to have positive results instead of her (PV negative, 41).

However, some did not think very much about the outcome until it was delivered:

> "Did not think about it much at the time" (PV positive, 57).

4.2.5 Family communication

Family communication remained unchanged or increased from before the genetic counselling. Some had worries about children and support from family members.

> "Family communication has not changed much, although we talk a lot about this (BRCA) as more and more have been tested positive. After I had breast surgery, cancer was found in the other breast, and I had to have another surgery. I found that difficult, and to know that two of my daughters had *BRCA2* (PV positive, 54).

> "No communication within the family has not changed; people just talk about this on a positive note. Mostly we are aware of each other and who is positive (with mutation) and who is not and try to support each other. I asked everyone if they wanted to

> get the letter… and all did… Most of those have been to GC and also their children who are old enough (PV positive, 54).

4.2.6 Prior knowledge of EGP´s

Some of the participants had prior knowledge of the possibility of generating electronic pedigrees.

> "Yes, I knew about such electronic pedigrees, and I think it is for the good that it is possible to use it for such research" (PV negative, 67).

> "Yes, I did know that it was possible to make electronic pedigrees. I think it is self-evident to do so if data protection is in order" (PV negative, 64).

Although some participants did not know about the EGP´s beforehand, they found them beneficial as in the following two accounts:

> "No, I did not know about them (electronic pedigrees) before I came to you. It is great that it is possible to do this for those who want to know if they belong to a risk group or not" (PV positive, 54).

> "I did not know about the electronic pedigrees before GC. I find it great that it is possible as it gives lots of information" (PV positive, 33).

Others had realised that there had to be a way of accessing family information and had other questions as well:

> "No, I did not know about electronic pedigrees, but I realised that somehow it was possible to find out about the family connection regarding disorders. I find it great that it can be done as I think it can help with decisions if one is diagnosed with a serious disease. I would like to ask (probably obvious) are bio-samples available from everyone? (PV negative, 45).

4.2.7 Attitude towards electronic pedigrees

The overall attitude towards the EGP´s was positive:

> "I am not at all against using electronic pedigrees in the GC and I am not worried about my relatives' attitude as everyone is really positive towards it" (PV positive, 33).

It was positive although they did not know beforehand:

> "I did not know until after the first visit to X (GC) and Y (Medic) that it was possible to make electronic pedigrees. I find this possibility to be a good thing. I find it very positive that people have access to such information if they want" (PV positive, 45).

4.2.8 Overall experience

Participants in the study had received genetic counselling at Landspitali and were approached to participate in the study as such. Explaining to the participants/counsellees during genetic counselling how the EGPs were used for risk assessment and obtaining consent to generate them was a straight-forward process, with no complications. They generally assumed that genealogy information was already available, and that using such information was a regular part of the service.

Occasionally during genetic counselling and in the qualitative study, the following questions were asked:

a) if permission was needed from other relatives;

b) if it would be possible for them to see or obtain a copy of their own pedigrees;

c) if they would receive information about relatives unknown to them, and whether such details should be available in the pedigree information; and

d) whether all disorders in the family would be seen in the finished pedigree.

Replies to the participants regarding the above questions were as follows:

a) No, permission is not needed from other relatives to generate a pedigree;

b) No, it is not permitted to share pedigrees with those in genetic counselling as they may include sensitive information about other people than themselves;

c) No, information about unknown family members is not shared even if it happens to be in the pedigree. It is not the role of the genetics services to disclose such information;

d) No. Iceland has only one public disease registry that can be used to add information to pedigrees, the cancer registry. Therefore, no other diseases or health problems would be included in the finished electronic pedigree.

On the other hand, information disclosed by individuals themselves would be added as needed, to make the pedigree as comprehensive as possible.

4.3 Study III

The study was observational and descriptive. Results from testing one or both Icelandic founders BRCA PVs were available for 1352 individuals in 370 EGPs at the end of 2015.

The different pedigree sizes of the study families are shown in Table 8. Families with the Icelandic founder *BRCA2* PV variation were 56. The average number of individuals in a family was 514 individuals (range 40-2031). There were 314 families without a known BRCA PV, and the average number of individuals in those families was 497 (range 13-4197). Some overlap was found between the different categories of families. Where it was not possible to construct an EGP due to lack of knowledge of the biological family (in four cases), the proband was offered genetic testing for the founder *BRCA* PVs.

4.3.1 Workload in constructing the EGPs

Pedigrees were of different sizes and complexity. The estimated amount of work required for the construction of an average sized, a full set (eight) of EGPs for each proband was estimated to be up to three working hours, calculated by measuring all parts of the work needed for a medium sized pedigree.

Information from the ICR included the type of cancers and age at diagnosis. The ICR has data on most breast cancers back to 1911 (Snaedal, 1965) and other cancers back to 1954 when the ICR was established.

Table 8. Size of the EGPs for those attending the cancer genetic clinic, between 1.12.2006 and 31.12.2015 at Landspitali. Data only includes those who were alive in 1955 and those born before 1996.

	Icelandic founder *BRCA2* PV negative EGP´s*	**Icelandic founder *BRCA2* PV positive EGP´s****
Number of families	314	56
Average number in pedigrees	497	514
Female relatives in the family	46403	9432
Male relatives in the families	48470	9950
Females married into the families	18958	3835
Males married into the families	19805	3786
Max. number of individuals	4197	2031
Min. number of individuals	13	40
Genealogy information missing	1	3
*EGPs where no known BRCA PV was found.		
**EGPs where the Icelandic founder BRCA2 PV was found.		

Modified from Stefansdottir et al., 2018).

4.3.2 Types and numbers of cancers in the study families

At the end of 2015, 755 of the tested individuals were members of one or more of the 56 families with the Icelandic founder *BRCA2* PV. Of those, 340 were positive (45%) comprising 233 females and 107 males. Table 9 shows the number of *BRCA* related cancers in participants alive in 1955, born before 1996 and tested positive for the Icelandic founder *BRCA2 PV.* Of the females, 86 (37%) had breast cancer (average age 49 years - range 21-82), three of them had in-situ breast cancers eight years earlier at average and 11 (4.7%) two breast cancers. Ten (4.2%) of the females had ovarian cancer, earlier than average and nine (8.4%) males had prostate cancer. Seven males (6.5%) had breast cancer at the average age of 56 (range 46-70), and two of those had developed breast cancer twice. Two males with prostate cancers also had breast cancer.

Table 9. Number of subjects tested positive for the Icelandic founder *BRCA2* PV from 1.12.2006 and 31.12.2015 and their associated cancers diagnosed 1955-2015.

	Females	Males
	Number (%)	Number (%)
Positive individuals	233	107
Breast cancer	86 (37%)	7 (6.5%)
Two breast cancers	11 (4.7%)	2 (1.8%)
Prostate cancer	-	9 (8.4%)
Ovarian cancer	10 (4.2%)	-

Modified from Stefansdottir et al., 2018).

4.3.3 ROC analysis of the optimal size of pedigrees for risk assessment

The study group included 1352 individuals seeking HBOC genetic counselling at Landspitali, all having had genetic testing for the Icelandic founder *BRCA2* PV. Some had also had testing for the *BRCA1:G5193A* PV. Those positive for the *BRCA1* PV were subtracted (n=58), and from the remaining 1294, two sub-groups were formed by random selection (n=209). The first group included 104 women positive for the Icelandic founder *BRCA2* PV, and the second group had 105 negatives for the same PV. Related individuals to selected proband women were added incrementally to generate pedigrees with 1° to 6° relatedness. The average number of individuals in each degree of relatedness and the risk scores are shown in Table 10. The BOADICEA risk assessment program was unable to calculate risk for more than 275 individuals in one pedigree. This resulted in fewer families being included in the ROC analysis as the degree of relatedness got higher. However, this did not affect the calculation of 3 and 4° pedigrees as the highest number of individuals in 4° pedigrees was lower than 275. In contrast, some of the 5 and 6° pedigrees were not included due to their size. This may have affected the risk assessment for these categories of pedigrees. The lowest BOADICEA risk score for being a carrier for the Icelandic founder *BRCA2* PV was 0.1% for all pedigrees. The highest risk score was relatively low for the 1° or 39%. In contrast, the highest risk score was similar for 2-6° relative, ranging between 86-93%. The complete risk score table is in the supplementary files (Suppl. risk score).

Table 10. The number and range of individuals in the different degree of relatedness and BOADICEA risk score for the ROC curve analysis

Column1	Column2	Individuals	BOADICEA risk score (%)	Column3
Degree	Average no.	Range	Average	Range
1°	9	(3-22)	8	(0.1-39)
2°	26	(6-92)	12	(0.1-88)
3°	54	(9-220)	14	(0.1-86)
4°	103	(15-257)	15	(0.1-93)
5°	146	(15-498)	14	(0.1-88)
6°	166	(15-565)	11	(0.1-88)

Modified from Stefansdottir et al., 2018).

Figure 9, A and B, shows the efficiency of predicting whether the individual had the Icelandic founder *BRCA2* PV using pair wise comparison of ROC curves, adding increasing degrees of relatedness. C and D show the smaller and larger 3° and 4° pedigrees.

The 1° to 3° sample size was 209 individuals, 104 positive (49,76%) and 105 were negative (50,25%). Adding 2° relatives to the 1° relatives increased the C-statistic from 0.62 to 0.70 ($p < 0.0023$). The 95% CI was 0,291 to 0,134, the z statistics 3,046. The difference between areas was 0,815 and the Standard Error 0,0268. Adding 3° relatives increased the C-statistic to 0.77 ($p = <0.001$). The 95% CI was 0,0311 to 0,109, the z statistics 3,524. The difference between areas was 0,0701 and the Standard Error 0,0199.

Inclusion of 4° relatives, group size 206, (103 positive and 103 negative) did not significantly affect the C-statistic which decreased to 0.76 ($p=0.30$). The 95% CI was -0,00988 to 0,0318, the z statistic was 1,029. The difference between areas was 0,0109 and the Standard Error 0,0106. The lower number group in 3° pedigrees was converted into 4° relative pedigrees for further evaluation but there was no improvement in the C-statistic (0.718).

For further evaluation of the relationship between the pedigree size and efficiency of risk assessment, the 3° pedigrees were split into two groups, ranked based on number of individuals (Figure 9C). The lower number group (n =105, average no. of individuals 30, range = 9-46) had a C-statistic of 0.723 (0,626 to 0,807, SE 0,0505) but the higher number group (n=104, average no. of individuals 133, range = 46-220) had a C-statistic of 0.823 (0,736 to 0,890, SE 0,0419). The pair wise comparison of ROC curves showed that the 95% CI was

0,0294 to 0,228, the z statistics was 1,512. the difference between areas was 0,0993, p=0,1304 and the Standard Error 0,0656.

The 4° pedigrees group was also split in two groups, according to size. The lower number group (n =103, average no. of individuals 56, range = 15-87) had a C-statistic of 0.719 (0,622 to 0,804, SE 0,0509), but the higher number group (n=103, average no. of individuals 145, range 87-257) had a C-statistic of 0.815 (0,727 to 0,885, SE 0,0423). The pairwise comparison of ROC curves showed that the 95% CI was -0,0338 to 0,226. The z statistic was 1,449. The difference between areas was 0,0959, p=0,1474 and the Standard Error 0,0662.

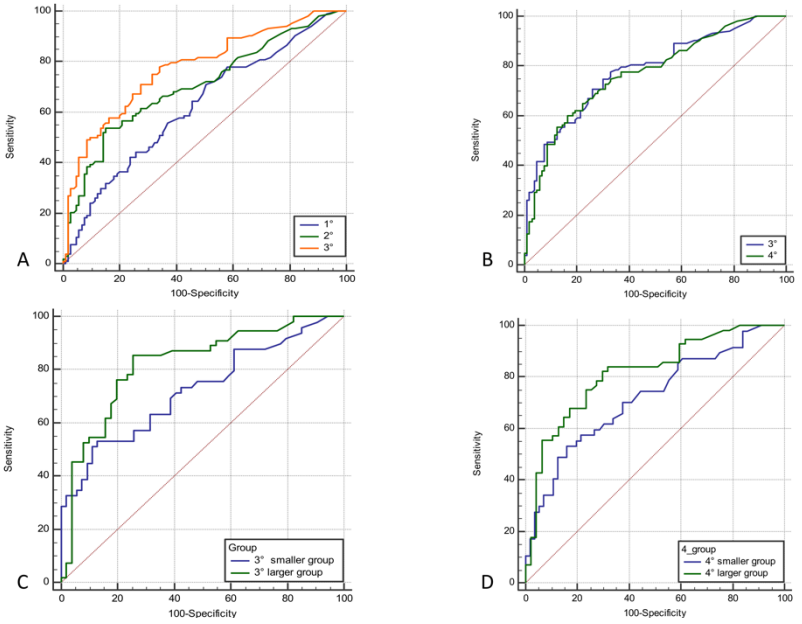

Figure 9. ROC curves demonstrating the effect of pedigree size on the efficiency of Boadicea risk calculations in predicting the presence of the Icelandic BRCA2 PV.

A. Pedigrees including 1°, 2° and 3° relatives. B. Pedigrees including 3° and 4° relatives. Increasing the size of the pedigree from 3° to 4° did not improve prediction. C. The smaller and larger 3° pedigrees. D. The smaller and larger 4° pedigrees. Pedigrees with 3° relatedness showed the best outcome. Comparison of pedigrees including 3°and 4° relatedness. (Stefansdottir et al., 2019)

Our conclusion, based on these results, was that the optimal size for risk assessment in HBOC genetic counselling, in this application was the 3° relatedness pedigree. There was no gain of efficiency by including the 4° relatives. In summary, the clinical experience of using EGPs was very favourable. They were convenient to use and gave better information than conventionally-made manual pedigrees. No adverse effects were noted.

5 Discussion

The main aim of this study was to evaluate the use of electronically generated pedigrees (EGPs) in HBOC genetic counselling risk assessment. The project was prepared and carried out in three different studies; as a systematic review, a qualitative study, and a quantitative study, to collectively gain knowledge and understanding of the various pertinent aspects.

The systematic literature review had the primary goal of mapping the current use of electronic genealogy databases in the genetic health service (Stefansdottir, 2013). There was limited evidence of the use of such databases found in GC, for generating pedigrees, reflecting the little use of this method outside of Iceland.

The qualitative study was done to illuminate the counsellees´ understanding and experience of having a genetic risk assessment for HBOC based on EGPs (Stefansdottir, V. et al., 2016). The results showed that participants agreed with the use of EGPs, and had trust both in the service providers and database information. There was some, albeit limited, concern regarding data security, especially about the potential for more restrictive insurance in the future. The concern was mainly that relatives, especially children or grandchildren of *BRCA* positive individuals would be denied health insurance if the information and genetic test results were accessible to third parties, such as insurance companies.

The final study described the clinical genetics services experience of using EGPs, including the optimal size of the EGPs for HBOC risk assessment. The results showed a positive clinical experience of using a genealogy database and cancer registry as the source of data for constructing EGPs. Further, pedigrees including 3° relatedness, were determined to be the optimal pedigree size.

5.1 Current use of electronic databases

The terms used in the literature search were chosen carefully and included the words usually found in connection with the topic. Using both single words and combined search terms increased the chance of finding relevant papers compared to using only single words.

The literature review did not show much evidence of the use of electronic databases to generate pedigrees in genetic health services. It identified only

four papers. A repeated literature search with the same search terms did not identify any new papers describing the clinical use of electronic databases in genetic counselling up to 2018. This outcome is intriguing, mainly due to great and growing interest in genealogy and genetic genealogy. The interest can be observed by the many available genealogy and genetic genealogy websites as well as within the news and social media discussion. Moreover, large genealogical and disorder databases are used for research as examples from, i.e. Utah, Scotland and the Scandinavian countries show (Ekbom, 2011; Cannon Albright et al., 2003;). Two research papers describing such use were among the four identified papers (Brewster et al., 2004; Cannon Albright, 2006;).

Consistent with this, no contacts have been made to inform me or my collegues about such use, despite the three studies presented in this thesis having all been published in international scientific journals and results from them introduced at international conferences. In addition, repeated questions by me to colleagues in other countries have not identified any such use. This further confirms that the use of electronic databases to construct pedigrees is either not, or only in a minimal way, used in clinical work outside of Iceland.

There are several reasons why electronic databases would not be used for the construction of pedigrees. One reason might be lack of awareness of the possibility of using genealogy databases in clinical work. However, with the assistance of family history coordinators, some genetic counselling services gradually build up their own databases with information from counsellees themselves, with confirmation of cancer diagnosis from cancer registries and medical records when applicable. A second reason is that population databases of sufficient quality may not be available. The third reason is that evidence about the EGPs improved risk assessment is lacking. The fourth reason is limited information on the relationship between the size of pedigree and its efficiency in predicting risk and that the size of the optimal cancer pedigree is too large for generating it with traditional handmade methods. The fifth reason is that laws or regulations restrict the use of such databases in the clinic, even if they are sometimes used in research settings. These reasons are discussed further below.

5.2 Availability of electronic genealogy databases

Genealogy databases linked to health care information are already widely available, as reviewed in the Introduction section. Among them are the UPDB, in Utah USA, the Icelandic deCODE database and the Veteran

database (Agarwala et al., 2003a; Cannon-Albright et al., 2013; Hakonarson et al., 2003). Increasingly, large genealogical databases have being created (Agarwala et al., 2003a). The most extensive examples to date are the Veterans Genealogy project with over 22 million records (Cannon-Albright et al., 2013) and the one described by Kaplanis et al., on genealogy data collected from the Internet. The pedigree derived from the collection comprises around 86 million individuals (Kaplanis et al., 2018). Another example of making genealogy database with clinical information would be one assessing EHR´s information, where next-of-kin is recorded. By this method, family information was collected from 7.4 million relationships and computer data on hereditability for 500 disease phenotypes. The phenotypes were diverse and were quantitative, as well as dichotomous (Polubriaginof et al., 2015). These and other similar data collections show that it is possible to use official data already available data to construct pedigrees that could be used in clinical settings if needed.

Genealogy databases for constructing EGPs should be widely available. Quality, however, may be of concern in some instances. The best solution appears to be if the database is connected to a national registry and managed with sufficient resources, including careful curation.

5.2.1 Genealogy genetics and cancer registries

In the Western countries at least, much of the available data, both personal and non-personal, are kept in electronic databases. Recent developments have shed light on the immense data collection by various service providers. This results, in part, from the new General Data Protection Regulation (GDPR) in Europe, ensure that service providers are held accountable for keeping data secure (Trunomi, 2018). Because of this, new and updated Terms of Service have been sent out to users of websites that collect data.

Recently, investigators have been able to use a commercial genealogy service, where DNA genetic variants and information were uploaded and available to view by other users, to identify individuals who have committed crimes. This was done by comparing a sample of the criminal´s DNA found at the crime scene to available information on websites (Arango, 2018; Bolan, 2018). It has led to concerns about the privacy and the possibility of the data being used for a different undisclosed purpose than was intended. Several direct-to-consumer (DTC) testing companies have agreed on assisting law enforcement in finding people (Daily Records, 2019). As shown above, it is relatively easy to construct enormous pedigrees only with information already

available on the Internet and the genetic data within the DTC databases will make it even easier.

Cancer registries are mostly electronic and according to the International Agency for Research on Cancer (IARC) there are over 700 population-based cancer registries (PBCR) worldwide (IARC, 2016). Their purpose is to collect information on every case of cancer within a geographically defined area, analyze the data and report, (Bray F, 2014; Tyczynski JE, 2003). The PBCR have a critical role in cancer surveillance, in planning cancer prevention and cancer research. They rely on multiple sources for obtaining cancer information. Among those are laboratories, hospitals and death certificates. Many, but not all, require mandatory cancer registration. The ICR is a part of the IARC and is curated in a similar way, guided by regulations on what needs to be included and how the data is presented and accessed (Alþingi, 2007; Sigurdardottir et al., 2012). This ensures the accurate and comprehensive information used in constructing EGPs.

The Nordic countries have excellent PBCRs and genealogy data. In Ireland and Scotland at least, genealogy records exist very far back (Collyer & De Mey, 1987; Scottish/Northern Irish, 2003). In these countries as well as in most European countries, cancer registries are comprehensive and have the potential along with genealogy databases to be used in constructing EGPs to be used in a similar way as we have described.

In accordance to the results from Study III, to be able to use a genealogy database in genetic health services in relation to cancer, it needs at a minimum to contain information about all those already listed in the cancer registry, and preferably their 3° relatives.

As most population-based cancer registries in the Western countries were established after 1950, individuals alive then should be in the database. Most of the cancer registries in the Western countries have comprehensive information, although registration is not compulsory in all countries (Pineros et al., 2017).

The Directorate of Health in Iceland holds vast information on population health, but the setup of data regarding other diseases than cancer does not allow for the integration of other disease information into pedigrees. In general, cancer registries appear to be the best-suited disease databases to use in constructing EGPs. It is preferable if the registration of cancers cases is mandatory to ensure the completeness of registration.

5.3 The efficiency of EGPs in risk assessment

Using data from electronic databases to rapidly assembly large EGPs for HBOC genetic counselling, adds considerably to the information received from the counsellee only, due to the large size of the pedigrees and amount of cancer information included as demonstrated in Study III. Studies have shown that collecting information for large pedigrees by conventional methods can be difficult and is time- and labour consuming (Lu et al., 2014). Our method lessens the counsellee's need to obtain information about relatives and health care professionals´ work in collecting various information, such as confirmation of cancer diagnosis, for the pedigree.

Large EGPs can reveal clusters of cancers or patterns of disorders in families, sometimes different from what was expected. As such, they could be used to monitor disease burden within societies and families with the possibility to intervene and help identify those who should be offered genetic testing. One of the articles identified in the literature review described how large pedigrees were used to find relatives of those with hypercholesteremia by tracing known carriers of a PV to common ancestors and finding the oldest offspring in each lineage. Their method added considerably to the existing method of finding those at risk (Thorsson et al., 2003). Another example is a paper by Palsdottir (2008), demonstrating clearly in a large pedigree that there was a drastic reduction in life expectancy among those who had the PV associated with Hereditary cystatin C amyloid angiopathy (Palsdottir et al., 2008). EGPs can affect surveillance plans by assessing the cancers within the larger family. Solomon et al., in 2015, published results from a study showing that extensive family histories are better in identifying those who should be referred for genetic counselling and testing (Benjamin Lev Solomon, 2015). This was supported by a study by Taylor et al., (2010) describing the use of the Utah Population Database with linkage to a state-wide cancer registry to determine the risk of colon cancer. The main outcome from their study was that positive family history in second and third-degree relatives increased the proband´s risk of getting colon cancer significantly, supporting the value of extended family history (Taylor et al., 2010). These studies, combined with the clinical experience from Iceland, support that large and comprehensive EGPs add considerably to the conventional manual method as well as being more accurate.

BRCA2 positive individuals are at increased risk for several cancers, among them pancreatic cancer (Mersch et al., 2015). The large EGPs have the potential to reveal pancreatic cancer in 3° or 4° relatives in *BRCA2*

families, thus changing the surveillance plan. Clear guidelines do not exist on surveillance for those at increased risk due to genetic status. The International Cancer of the Pancreas Screening (CAPS) Consortium has suggested that *BRCA2* positive individuals with at least one affected first-degree relative, or two affected relatives within second-degree, could be considered for surveillance for pancreatic cancer (Canto et al., 2013). In addition, at Landspitali, those with the Icelandic founder *BRCA2* PV and one 1° relative, two 2° relatives or three 3° relatives with pancreas cancer have been referred for surveillance. This is partly based on results from the study by Chiaro et al. (2015) in Sweden. In this study, 40 patients, with genetic risk for getting pancreatic cancer (three were *BRCA2* positive), were enrolled in a screening program using non-invasive magnetic resonance imaging (MRI) Using MRI, 40% of the high-risk patients were found to have lesions, some requiring operation, but most were benign (Del Chiaro et al., 2015).

5.3.1 The optimal size of pedigrees in cancer genetic counselling

We used the BOADICEA risk assessment tool for calculating the likelihood of having the Icelandic founder *BRCA2* PV. BOADICEA has been validated and is widely used in HBOC genetic services as well as in sutdies (Lee et al., 2014; MacInnis et al., 2013). As such, the program calculates the likelihood of having a PV in selected genes and the risk of getting breast and ovarian cancer based on family history. At the time of our study, the BRCA genes were the only ones used in the risk calculation, other genes were added later. The program has its limitations. One is that it cannot calculate families larger than 275 individuals. The decision to use *BRCA2* families only was due to the high frequency of the PV in Iceland and the fact that PV in the *BRCA1* gene is not common in Iceland.

To date, we are not aware of any studies evaluating the optimal size of the pedigree for risk assessment in cancer GC similar to the work in Study III. In this study, the genetic status of each proband was already known, and the risk calculations by BOADICEA could be verified. In a study by Moller (2007), a concern was raised about the general efficiency of the family history as a base for risk assessment regarding HBOC (Moller et al., 2007). There is, however, little information on how much this study reflected on the quality of the information in the pedigrees or if they were large enough.

Our calculations in Study III, strongly indicate that the 3° pedigree is the optimal size for risk assessment in HBOC genetic counselling. The results were not self-evident, but at the same time not surprising. Adding 4° relatives

did not improve the outcome from 3°pedigrees. To ensure that the outcome was less based on the number of individuals, rather than the relatedness in the pedigrees, we divided the 3 and 4° pedigrees into smaller and larger pedigrees, based on the number of people in each group and calculated the risk of having the Icelandic founder *BRCA2* PV. The number of individuals did not significantly change the outcome, indicating that the degrees of relatedness was the primary determinant of the outcome,

A significant result from this work is that the optimal size of cancer pedigree is 3° large. Such a pedigree is very difficult and impractical to generate using the conventional handmade technique. This should create a motive to use EGPs.

5.4 Ethical and legal restrictions

There are two key questions when discussing the ethical and legal aspects of constructing and using EGPs. The first one is whether one can gather information on relatives based on presumed consent. The second main ethical question relates to the obligation of communicating relevant information to relatives.

In genetic services, similar to other health care services, there are several stakeholders. Their rights and duties, harms and benefits must be considered carefully in genetic counselling. The primary stakeholder is the counsellee, whose rights it is to have the best possible service with minimal risk to autonomy, confidentiality and well-being. Second are the relatives of the counsellee, whose relevant rights are to confidentiality, privacy and autonomy. The third stakeholder is the counsellor whose interests include providing accurate information, risk assessment, and the best psychosocial care as possible, while ensuring privacy and confidentiality of all included. Last, there is the health care system, benefitting from the practical use of resources while providing quality care.

The genetic counselling sessions can be complicated with lots of information and discussion of ways of contacting relatives for information purposes as well as an outcome from genetic testing, psychosocial issues and confidentiality. The counsellee or patient has a right to confidentiality regarding health care information and results of genetic testing. At the same time, the genetic information and test results can prove to be a benefit to the counsellee relatives' well-being (Lucassen & Hall, 2012). The need for information sharing and confidentiality must be considered. This may be especially important in Iceland where the population is small as in Iceland.

5.5 Consent

A good and ethical practice, whether in healthcare or research, requires that valid consent is obtained from patients and participants. The consent must be simple enough to be understood by all in question, while including sufficient information to enable an informed choice. Genetic services differ from other healthcare services as the issues usually concern the family, rather than the counsellee or patient alone. Genetic germline tests which are often a part of the service, provide indirect information about relatives apart from the counsellee. Family health and genealogical history are collected to assess risk and clarify inheritance mode of the suspected or known disorder, most often from the counsellee or a family member. In Iceland, neither the initial handmade pedigrees nor the EGPs are a part of the counsellees medical records. They are kept separately in the genetics service files with limited access. The official medical records only contain information about the consent itself and general results on risk and diagnosis. This is due to the nature of the information within the pedigrees, i.e. the information about relatives. However, there is a clause in the initial consent form for generating the pedigree, on the update of the pedigree with new information emerging in the future.

To ensure that the consent for generating the pedigree is freely given, the counsellees are informed that it is not obligatory. They receive information on how the pedigree, once made, would be used for their and their families' benefit as a tool for risk assessment. This may put pressure on the counsellee to sign the consent, although this is standard practice in genetic counselling. Without family information, i.e. a pedigree, it is more difficult to assess the risk, unless there is a known PV in close relatives.

The most important ethical question about the EGPs is whether presumed consent is sufficient to gather information on relatives, either from the counsellees or databases. An absolute requirement would be that there is no added information risk and that autonomy is preserved.

5.6 GDPR and personal data

European regulations on data protection are key documents in discussing the legal framework for using cancer registries to generate EGP based on presumed consent. In 2011, the European Network of Cancer Registries (ENCR) and the IARC published "Guidelines on Confidentiality and ethics for population-based cancer registration and linked activities in Europe", version 3. (European Network of Cancer Registries Working Group on Confidentiality,

2011). In article 3.5, they discuss the use of cancer registry data and genetic counselling. It begins by addressing the fact that genetic counselling is not of public interest, but rather a service to families and individuals. Large EGPs can have several thousand individuals, and in cancer GC, they include information from the Nationwide ICR. The article continues to state that data from cancer registries can only be used on the basis of informed consent from each living individual in a pedigree. Still, information about deceased individuals can be released without consent. They state without argument, that the exceptions to using personal data without consent, as listed in the-then current Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals, with regard to the processing of personal data and on the free movement of such data, based on public interest or preventive medicine, do not apply. Thus, they decide to follow the UK precedent that consent is needed for the release of data on living persons for genetic counselling. However, they also mention the risk of inaccurate risk estimation in genetic counselling that might be an issue of public interest. In May 2018, the new EU General Data Protection Regulation (GDPR) replaced Directive 95/46/EC. Similar to the old Directive 95/46/EC, the GDPR explicitly prohibits the processing of personal data without consent unless specific conditions are met. The text in Article 9, paragraph 1 states:

> “Processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, and the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health or data concerning a natural person’s sex life or sexual orientation shall be prohibited."

However, in paragraph 2, there are listed several exceptions to the rule. The following two exception clauses are relevant to this discussion:

> h) "processing is necessary for the purposes of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems and services on the basis of Union or Member State law or pursuant to contract with a health professional and subject to the conditions and safeguards referred to in paragraph 3;"

> "i) processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health or ensuring high standards of quality and safety of health care and of medicinal products or medical devices, on the basis of Union or Member State law which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular professional secrecy."

In 2011, the GDPR had not been enacted, but as stated above, it does not forbid the use of data as these guidelines show. Participants in study II found the use of EGPs to be acceptable as a part of the services and the clinical experience supports that outcome. In some cases, participants expressed their belief that all the information needed to make the pedigrees were already available within the clinical services (Stefansdottir, V. et al., 2016). This has also been the experience in the clinic where counsellees have been surprised about the need to get information about them and their families from elsewhere than the hospital system. This can be partly because of the availability of genealogy information in Iceland, where genealogy is public and readily available for those interested and a favourite past-time activity. There is generally much trust regarding official information which is kept securely and used in a proper way for the inhabitants.

In Study II, most participants said that they trusted the service and how the information was used and supplied. Participants also found the method of using data from relatives acceptable and useful if the data was secure, the pedigrees were used for the purpose they were meant for, and there was no threat of discrimination from the use. As for autonomy, during my over 13 years of both academic and clinical experience of genetic counselling in Iceland, I have discussed the possible harms and benefits of using extensive family history in the clinic, with counsellees and professionals. No relative has been opposed to the use of his or her data for genetic counselling. Collectively, this experience shows that relatives very rarely, oppose to the use of their data being used for generating EGP with the objective of risk assessment of a relative given enough data protection. Infringement on autonomy has therefore been minimal.

My understanding, like the European Network Registries, is that the European regulations are not absolute when it comes to releasing information on individuals in cancer registries without consent. Rather, they are subject to interpretation depending on the situation. My thesis work demonstrates the

importance of using EGP and that the optimal size of pedigrees is impractical to construct without electronic databases. These results should influence the interpretation of GDPR and whether genetic counselling with EGPs is of sufficient public interest and with relevance for public health and preventive medicine. The GDPR permits state legislation to permit this use if felt necessary. However, it is important that the information is handled by competent professionals in GC and that specific measures are in place to protect the rights and interests of the persons in the EGP.

5.7 Presumed consent and EGPs

It is impractical not to use presumed consent on behalf of relatives to construct EGPs. In health care, it is traditional to document the family history, with a presumed consent of relatives included in the pedigree. This applies both for manually made pedigrees and those made with information derived from genealogy records. In the context of family history taking, the presumed consent infers the expectation that relatives would not object to the use of their information if asked for permission. Indirect benefits for the relatives, should they come for GC, is that there will be already available information about the family, with risk assessment and the genetic status of any tested relatives. It would be challenging to contact every member of each family to ensure his or her consent and even cause alarm as some might be distressed of learning in this manner that they had a possibility of health risks (Lucassen et al., 2006).

As for presumed consent for family information in health care, professionals exchange information about individuals and families when needed to provide for the best possible health care. The Joint Committee on Medical Genetics in the UK (2011), e.g. concluded that health professionals could share clinical information and family history given their duty of confidence (Royal College of Physicians, 2011). This practice is widely agreed upon as the information is used for the benefit of the counsellee and in many cases, other family members.

The consent for the construction and uses of pedigrees in GC can in some ways be compared to consent for participation in scientific health studies. The study consent can be narrow and apply only to the current study or for a predefined period (Grady et al., 2015). It can also be broad, (Hofmann, 2009), applying to a number of studies or dynamic where the consenter has the option to withdraw the consent at any time. It should be

able to cover follow up studies, that his or her data are being used in (Hansson et al., 2006; Ploug & Holm, 2015).

5.8 Ethical issues regarding this study

Important ethical issues include the use of EGPs in genetic counselling, consent, especially presumed consent of relatives, autonomy, justice, confidentiality, disclosure and non-disclosure. These issues have been addressed in light of GDPR, which were implemented after the study period. When performing a study upon one´s patients or counsellees, there is always the possibility of a conflict of interest. It must be clear that participation in the study is genuinely voluntarily and that the research is unrelated to the treatment. The researcher must make sure that these conditions are met. All active participation in Study II was built on informed consent. Study III was done on data already present, and no personal identification information was used.

5.9 Data privacy

EGPs are not shown to the counsellees as they contain information about others in the family. In genetic counselling, where various health and genealogy data are collected, the genetic counsellor must ensure that there is no significant new risk associated with the procedure, in addition to the sensitive information already in the health care system.

One of the findings from Study III was that no known data breach was identified by using EGPs. This is particularly important considering recent developments regarding data security such as data distribution to third parties and the GDPR. In Recital 54 of Article 9 in GDPR, states:

> "The processing of special categories of personal data may be necessary for reasons of public interest in the areas of public health without consent of the data subject. [2]Such processing should be subject to suitable and specific measures so as to protect the rights and freedoms of natural persons. [3]In that context, 'public health' should be interpreted as defined in Regulation (EC) No 1338/2008 of the European Parliament and of the Council (11), namely all elements related to health, namely health status, including morbidity and disability, the determinants having an effect on that health status, health care needs, resources allocated to health care, the provision of, and universal access to, health care as well as health care

> expenditure and financing, and the causes of mortality. [4]Such processing of data concerning health for reasons of public interest should not result in personal data being processed for other purposes by third parties such as employers or insurance and banking companies".

In light of the increase in genomic data, there is a need for more discussion about privacy and how data is collected and used in health care. A possible example of misuse could be an insurance company asking for medical records which include genetic test results. Genetic test results do not only apply to the person in question but also to relatives, making discrimination based on genetic information possible. Some of the participants in Study II, expressed worries over the possibility that data from the genetic services, the EGPs included, would be used by insurance companies. This in turn, could possibly result in higher premium cost or even in some cases, non-insurance for them and their descendants. To protect from such use, in addition to GDPR, the Genetic Information Non-discrimination Act, protecting individuals from genetic discrimination, (Akulenko et al. 1991) by federal law, in health insurance and employment (Department of Health and Human Services (HHS), 2009), exists in the USA. In Iceland, there are specific laws on the protection of personal data, with similar text as in the GDPR, (Alþingi, 2018).

There may be a need for specific regulation regarding who can access the pedigrees, to keep EGP data more secure. It must be considered whether and under what circumstances data can be transferred between services or even countries, given differences in rules and legislation. A decision should also be reached on whether and to what degree the pedigrees should become a part of a patient´s general medical record, taking the same arguments into account. There are pros and cons to that possibility; having access to the family history in a pedigree within the medical records could enable healthcare professionals to assess it quickly and therefore decide on testing based on pedigree information. As discussed above, a pattern of inherited disorders or early deaths or unusually common instance of a specific disease might be noticed in a pedigree. There has been some discussion about pedigrees used in genetic health care, how they should be kept and who should be able to access them apart from the professionals in each service. In a recent article, Scott and Trotter suggest that pedigrees with medical information should be kept as a part of electronic health records for easy access to possible familial diseases (Scott & Trotter, 2013). However, as discussed above, pedigrees include sensitive personal information not

only about the counsellee but relatives as well. Therefore, information about others would be included in the health records, which is not appropriate.

Health data, EGPs included, already have in place strict access regulation. At Landspitali, the work and setup have already been evaluated by the data manager, accepting the access regulation in place (Stefansdottir, unpublished data).

5.10 Trust

Trust towards genetic services and professionals is important as the very nature of genetic counselling is based on discussion, assistance and resolution of sensitive issues. Our results from Study II showed that participants generally trusted the service, the professionals, and the EGPs. However, this may in part be because participants had, necessarily, consented twice before participation; first to receive genetic counselling, and later in agreeing to participate in the study. However, differences in social and cultural context may make people less or more trusting. Ford et al., found that African-American women in urban health care did not trust the health care system and that Caucasian women who had not received genetic counselling did not trust the accuracy of the genetic testing (Ford et al., 2007). However, Riesgraf et al. found an overall favourable attitude towards genetic counselling in a rural community in the USA with 203 adult residents (Riesgraf et al., 2015). Icelanders are willing to participate in genetic studies and are very positive towards such studies (Rafnar et al., 2004). The positive experience of using EGPs in genetic counselling is consistent with this. As described elsewhere in this thesis, there is, in general, overall positive attitude to genealogy information being publicly available for all in Iceland.

5.10.1 Information sharing

Knowing one´s genetic risk is necessary for decision making, but some may not wish to know or like to control when andhow they receive the information. The counsellee is the one coming for genetic counselling and the one that receives the information about the potential risk to others should he or she be positive for a pathogenic variant. Therefore, the counsellee is customarily the one expected to inform relevant relatives who can then opt for genetic counselling. The right to know or not know is strong. At the same time, relatives need reliable information to be able to decide if they want genetic testing, they have a right to privacy and not to be disturbed by getting information they may not want. It is common practice to send information letters meant to be read by relatives. This method is not always applicable

due to various reasons such as not knowing their relatives, not being comfortable with contacting them, or not finding themselves able to explain the situation. In such cases, it is in some places possible, with permission from the counsellee, for the genetic services to contact relatives and inform them of the familial pathogenic variant. It is, however, already used in some situations, such as in familial hypercholesterolemia (Knowles et al., 2017). Another method could be to use health care portals such as Heilsuvera in Iceland (https://www.heilsuvera.is), where the information could be tied to genealogy data to identify and inform relatives. One possible implementation would be to inform 1° relatives, of those who have positive test results about the PV. If the proband agrees, this could possibly be enlarged to 2° relatives. This would work similarly to cascade screening, apart from the involvement of the counselee, as he or she would not need to inform relatives. However, as soon as an individual is informed and has positive testing results, he or she becomes the proband whose relatives will be contacted. Therefore, the connections would be like small interconnected clusters of people, increasing in numbers until the last person in the cluster tests positive. This method solves the problems regarding communicating genetic information about family members from other professionals or the counsellee (Lucassen et al., 2006). Using some form of cascade screening, whether it is done by contacting relatives directly or using a health portal, does, however, open the question of if there is a duty to inform relatives.

There is an ongoing debate on the return of incidental and secondary findings from research and clinical testing, where how and if to return them. Thorogood et al. (2019) published an article about the return of individual results from WGS, where the different laws and regulations are listed, some recited here: In Spain, the laws require the return of health information overriding the consent of patients [25, art. 4.7]. In France, physicians are required to give genetic test results to relatives, if the counsellee/patient refuses to do so [20, art. R1131-20-2]. In Italy, the law authorises the disclosure of genetic results to relatives [22, art. 9]. (Thorogood et al., 2019). Large EGPs contain information about relatives that can in some ways be compared to genetic test results and as discussed later, could perhaps be used to inform relatives of genetic risk should and whether they come for genetic counselling and testing.

It must be kept in mind that relatives might have diverse reactions to the offer of genetic testing, offered without their prior knowledge of genetic risk within the family. Although not related to this research, the experience of web-based release information about *BRCA2* status shows that individuals,

who had no idea beforehand about their genetic risk, react differently to the information from those who have been prepared (Stefansdottir, V. unpublished results).

5.11 Awareness of genetic counselling in Iceland

Genetic counselling in Iceland was formally organised as a part of the medical genetics department in 2006 when I started working there after having finished the MSc genetic counselling program at Cardiff University. Earlier, medical doctors with training in genetics and an oncologist had offered genetic counselling. At the beginning of my work, I noticed the relatively little awareness and experience counsellees had of genetic counselling. This, in turn, initiated some of the questions in Study II. This has changed, and in the last few years, awareness of genetic counselling has increased rapidly. At the end of 2018, very few counsellees expressed no or very little knowledge about genetic counselling when asked in or before the clinical appointment (Stefansdottir, unpublished results). In Study II, most participants had sought genetic counselling due to a family history of cancer or after receiving information about positive genetic test results from relatives. In the same study, the majority said that they had prior knowledge of genetic counselling. In comparison, two recent studies, one in Canada and the other one in the USA, showed that less than half of participants had prior knowledge of genetic counselling. In the Canadian study, 1000 individuals were asked about their knowledge, and 69% of respondents had not heard of genetic counselling (Maio et al., 2013). Another study from the Midwest in the USA had a similar outcome where few of the respondents had knowledge about genetic counselling (Riesgraf et al., 2015).

Our results from Study II are interesting in the light of the short history of genetic counselling in Iceland compared to both Canada and the USA. However, most of the counsellees at Landspitali, which also were our participants in Study II, were in families with possible HBOC. They may have been following the discussion of inherited cancer in the Icelandic media more closely and therefore had a better knowledge of genetic health services than others in the society. Within the cancer GC service, knowledge about genetic counselling has been especially noted within families with HBOC (Stefansdottir, unpublished results), following Angelina Jolie´s letter to the Times in 2013. In this letter, she revealed her *BRCA* status and encouraged women to seek genetic testing (Angelina Jolie, 2013).

5.12 Family dynamics

Genetic information such as test results, affects not only the counsellee but also other family members. In the Icelandic genetic services model, the test results are given to the counselee, who then decides whom to share the information with and the responsibility to do so. In families with poor communication or where there is emotional distance, there is a greater risk of failure to share the information (Daly et al., 2016).

Family communication can be difficult, especially if the counselee has to inform relatives about the possibility of a genetic PV (Parker & Lucassen, 2003). When deciding who of the relatives should be contacted with genetic information, counsellees weigh many factors such as relatives´ coping skills, their stage of live and perceived vulnerability. For some families in Study II, the knowledge of having a common PV appeared to strengthen the family bonds. Family communication was either unchanged or improved following genetic counselling and participants encouraged other family members to get genetic counselling. Some of the counsellees have formed closed social media groups where they can share results and information with relatives whom they may not be in much contact with otherwise (Stefansdottir, unpublished results). We did not assess how many relatives each positive counsellee informed about the results. However, my empirical experience shows that in many cases, first and second-degree relatives contact the service within the first week after the first positive test results. All those who tested positive received an information letter to distribute among relatives. This letter is important and allows counsellees to inform relatives as well as helping them to find out how to seek genetic counselling if they like. As one participant in Study II said: “I asked everyone if they wanted to get the letter… and all did... Most of those have been to GC and also their children who are old enough”. Not everyone finds a way to inform relatives. In a study performed in 2013, some family members only disclosed information to a very few selected relatives or not at all (Lafreniere et al., 2013). The overall attitude towards testing, disclosure of results and family communication in families with the Icelandic founder *BRCA2* PV was positive in our study, and my clinical experience supports this.

5.13 Implications for clinical practice

Professional genetic service needs to have fast access to accurate and comprehensive pedigrees with relevant medical information for risk assessment and surveillance recommendations. Of note, the ASCO Expert

Statement (2014) stated that using digital health records could help collect and interpret family history in order to assess the cancer risk and that one of the goals should be the development of resources and electronic tools for integration of cancer genetics into the practice (Lu et al., 2014).

In Study II, we found that counsellees, in general, had a positive attitude towards the use of EGPs. This may prove to be a valuable insight for other genetic health care services contemplating the use of electronic pedigrees. In cost-sensitive healthcare, using the combination of a comprehensive genealogy database and high-quality cancer registries to construct EGPs if possible, seems to be an effective use of limited health resources. Using less time and workforce to collect information for pedigrees, should lead to shorter waiting time for the service.

As reviewed elsewhere in the Discussion section, the databases to support constructing EGPs should be available in several countries or could be made in many instances. The legal framework in Europe at least should not prohibit this use, or at least special law can be made to permit constructing EGPs. There do not seem to be any ethical issues that cannot be addressed. The approach described in this thesis, therefore, has the potential of being transferrable to other countries to facilitate GC in cancer genetics.

5.14 Strength and limitations of the study

A strength of this study was that the databases are population-based, accurate and include a whole nation. Such databases are not readily available elsewhere for clinical use, although extensive databases have been formed in some instances for use in scientific research. The study focussed mainly on one prevalent founder pathogenic variant with known prevalence in the population, so the risk assessment of having the Icelandic founder *BRCA2* PV could be verified. The risk assessment program BOADICEA was unable to calculate risks in larger pedigrees than 275, which initially was thought to be a limiting factor, but turned out not to be. The limits of the technology implemented, however, are certain to diminish over time.

Qualitative studies are a way of gathering non-numeriacal data in a a scientific way. They can enlighten why and how specific phenomenon may or has occurred and describe it. In light of the small cohort in Study II and mixed methods, the descriptive thematic analysis was chosen. It would have been possible to use constant comparison derived from grounded theory or a framework analysis and the findings might have been evaluated differently.

The approach of descriptive thematic analysis without a specific theory may have been a limiting factor. Thematic analysis method enables rich data to be collected and analysed without restrictive prior categories and has minimal organisational effects. It allows for searching for patterns across the entire data set, rather than within each interview or data for each participant separately

A limiting factor was that this study was conducted in a small country, with a relatively small study group with one type of inherited cancer in a society where most individuals have a similar culture. This setting may not be applicable elsewhere.

5.15 Reflective account

This PhD project was somewhat challenging as some of my former counsellees were also my study cohort. To be able to look at both the clinical and the academic side of genetic counselling has, in my mind, reinforced my knowledge of both areas. My clinical work has been and will be influenced and structured by the added knowledge obtained from the study, while the study benefitted from my experience with clinical work. In fact, I find that being a genetic counsellor for this patient group made it very difficult not to perform the study. However, juggling the responsibility of extensive clinical responsibilities at the same time as undertaking a PhD project certainly required me to prioritise clinical work over continued progress on the research project.

Genetic counselling is a profession that fundamentally is concerned with people and their genetic status. Working with people has always been of interest to me, especially if it is possible to assist with issues arising from genetic information. When I finished my MSc degree in genetic counselling and returned to Iceland to work, I had the vision of working primarily in the field of rare disorders and at-risk pregnancies. Hereditary cancers were low on my list of priorities, possibly because of my long-time fear of cancer. However, as soon as I began working in cancer genetic counselling, my interest in the families and the variation in family history and their penetrance increased and soon became a passion.

Early in the process of genetic counselling, the genetic services at Landspitali received permission to use the genealogy database in the clinic and the ability to obtain information from the cancer registry for better risk assessment. This enabled the generation of large pedigrees, and consequently, my interest in these families increased. I wanted to know more;

to understand how the Icelandic founder *BRCA2* PV segregated within families, know if other pathogenic variants could explain strong cancer family history, how the Icelandic founder *BRCA2* PV had spread in the country and what kind of cancers were in the families where the *BRCA* PV variants were found. One possible future study option was to assess the differences in penetrance between families. These are interesting topics for future study but not directly relevant to this thesis.

Performing a study on the main subject of one´s work is simultaneously easier and more complicated than using something completely unrelated. Genetic counselling is performed on a highly personal level, which impacts the process and the outcome. Everyone has a face and a name rather than existing as a record in an Excel file, as is often the case in scientific studies. The boundaries between work and study can become blurred, especially when the studies directly concern one´s counsellees. It is, however, imperative not to confuse the study with the clinical work.

6 Conclusions and further studies

In this thesis, I aimed to identify and analyse the work already published on the use of genealogical databases to generate pedigrees in genetic health care. The next part of the thesis was a qualitative study to examine the view of the user, the counsellee. In the last part, I looked at the experience and practicality of using EGPs in clinical services. The main findings in this work (Studies I-III) are that, although electronic databases are not used in cancer genetic counselling in general, in other countries, their use facilitates a more accurate and comprehensive family history.

From the results of the literature review (Study I), there was little evidence of the use of genealogy by others as a source for pedigrees in genetic health services although there seems to be an interest. In some cases, we found e.g. articles about the possibility of using electronic databases to either lessen the workload or make family history more accurate and comprehensive. A new systematic literature search could evaluate the impact of the search terms. New and added search terms would be “inheritance”, “familial”, Fhx, and “computer-based family history”. These terms were frequently used in the articles identified both in my searches.

In the qualitative part of the study (Study II), the main aim was to assess the counsellees´ experience where EGPs were used in HBOC genetic counselling. We found that participants in the study, who all had been to cancer genetic counselling prior to the study, were in general positive towards using EGP´s for risk assessment and trusted the service and information used for generating the pedigrees. These results concur with our 13 years of experience of using the EGPs in the genetic counselling service in Iceland, where counsellees have in many cases found it self-evident to use available genealogy and cancer registry.

We gained valuable insight into family dynamics and communication in families with high risk or confirmation of having a BRCA mutation. Replies to questions about the service gave us information about how to make it better. Our conclusion from this study was that counsellees received the use of EGPs well. The counsellees also valued the extensive information aiding risk assessment. The method of using online focus groups was unusual, and it could be interesting to repeat the study with different methods. To further assess the method, using participants of different age and gender and compare to a similar cohort as in this study would be interesting. Using three

different methods for comparison; a face-to-face focus group, online focus group and questionnaires could reveal a difference in outcome due to the method alone. Additionally, having different age groups in the study could shed light on different views of young people versus older ones. Another possible angle would be to contact individuals from the study and follow up on the questions asked to see if views or family dynamics have changed over time.

Of personal interest initially would be to collaborate with investigators in other countries, to better assess the attitude toward using EGPs elsewhere. It would be particularly interesting to set up a program using a genealogy database to generate pedigrees and study the effects in a country different from Iceland.

In the last of the three studies, we aimed to determine the practicality of using large EGP´s in HBOC genetic counselling. This included calculating the optimal size of a pedigree for risk assessment, balancing the cost of ascertainment. The optimal pedigree size included 3° relatives and adding 4° relatives did not add information to the risk assessment. The clinical experience supports the use of EGPs as we have not experienced any adverse effects of using them. It is impractical to try to do large pedigrees by hand and seeking all relevant information for them. In clinical work, the larger pedigrees enabled finding remote relatives who had also been tested. Larger pedigrees can also be used to determine if a counsellee has a distant relative with a *BRCA* PV, thus potentially changing the risk assessment of the individual.

This study only included HBOC cases. It would be informative to test EGPs for other types of common cancer syndromes, preferably syndromes where tumours are not mainly gender-specific. One ideal subject would be Lynch syndrome which is relatively common with a prevalence of about 1 in 500 (Steinke et al., 2013). In Iceland, it is estimated that 1 in 226 has a genetic predisposition to Lynch syndrome (Haraldsdottir et al., 2017). It is non-gender specific and increases the risk of many cancers. Such a study may shed light on several existing problems. Applying EGPs in studies of other genetic non-cancer syndromes would also be of interest in the hope that the results may reveal a pattern. However, in Iceland, at least, no equally comprehensive disorder databases other than the cancer registry are currently available, although groups of people with the same diagnosis could be found by using ICD numbers. Such registries might have to be set up prior to the conduction of any such studies and it would have to be highly curated.

It is challenging to determine the cost of generating pedigrees, but we attempted to calculate the workload in Iceland. We found the cost to be reasonable, taking into the account how much information the pedigrees include and when comparing to the work needed elsewhere to collect various information for risk assessment. Our results indicate that using EGPs is cost effective and work reducing. This could be interesting to pursue further by doing a comparison study with comprehensive questionnaires, between Iceland and other countries, assessing the actual workload.

Using EGPs in practice has been established in Iceland, where this approach has been used for over 13 years in the genetics clinic. It is efficient and without complications such as breach of data and mistrust on behalf of the counsellees. This thesis reflects the experience of the clinical service and enhances the belief that EGPs can be used in other countries where some or all the resources are readily available.

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Paper I

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REVIEW

The use of genealogy databases for risk assessment in genetic health service: a systematic review

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Abstract The use of electronic genealogical databases facilitates the construction of accurate and extensive pedigrees for potential use in genetic services. Genealogy databases can be linked to specific disease databases, such as cancer registries, in order to increase the accuracy of pedigrees used, and inform the genetic risk assessment. To review the published literature on the use of genealogy databases to construct pedigrees for risk assessment in genetic health service, a systematic literature search was undertaken using 12 combined search terms to identify all relevant published articles. Data sources**:** EbscoHost, PubMed, Web of Science, Ovid and the "grey literature", as well as the reference lists of identified studies. Of 1,035 titles identified, two papers described a study on the use of genealogy databases in cancer risk assessment and two were discussion papers. While authors of the four papers described the potential use of genealogy databases in clinical genetic services, such use has not been adequately investigated and further research is required.

Keywords Genealogy databases · Genetic service · Cancer registry · Risk assessment · Systematic review · Genealogy · Databases · Health services

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Introduction

Genealogical records, both private and public, exist in many forms and have often been kept for a long time. Examples of old genealogy records are from the Royal Family of Japan, the genealogy descriptions in the Holy Bible and in an Irish textbook written in 1649 describing the Irish settlement (Wikipedia 2011; Firbishigh 1649–1653?). Recently, genealogy data have been stored in an electronic format and are sometimes available online (General Register Office for Scotland 2007). As an example "The Scotland's People" database, holding approximately 50 million records, which is accessible to those paying a small fee (General Register Office for Scotland 2007). The Mormon Church in Utah maintains a large public genealogy database, "FamilySearch" (New FamilySearch 2007) and has supported genealogical research for decades. This database is widely accessible and includes information on living or deceased individuals. Members of the church are encouraged to supply information

about their family history, relationships, and other data (New FamilySearch 2007; Cannon Albright 2008). The Utah Population Database (UPDB; Cannon Albright 2008) is another large database holding genetic, demographic, epidemiological, and medical information on approximately 6.4 million people, mostly Utah Mormon pioneers and their descendants. This database was created for research only and has restricted access. In some cases, databases have been formed to enable genealogical studies to identify specific disease genes. One example is the Anabaptist Genealogy Database of Old Order Amish of Lancaster County (Agarwala et al. 1999).

The Scandinavian countries and some other countries have National Population Registries that are updated regularly (Population Registry Centre 2006; Ekbom 2011; CPR-kontoret (http://www.skra.is/pages/1003); Hagstofan 2007; Folkeregisteret 2007). The information documented is demographic, i.e. names, dates of birth and death, addresses, identification numbers and citizenship. Other databases containing personal information on a large number of people are disease registries and of those, the cancer registries are the most common. Available in most Western countries, population-based cancer registries provide a source of information on the occurrence and outcome of cancer in defined population groups (Ringborg et al. 2008). Another example of specific disease registries are the rare bleeding disorder registries (Peyvandi and Spreafico 2008).

Iceland has a number of population-based genealogy databases, due to a longstanding general interest in genealogy. The first census to cover a whole nation was conducted in Iceland in 1703 (Tulinius 2011). As the Icelandic population has been historically stable and detailed genealogy records have been kept for centuries, genealogical records in Iceland are highly reliable and comprehensive, making ancestral tracing relatively straightforward (Stefansson and Taylor 2006; Tulinius 2011). One large electronic database is the genealogy database of the Genetical Committee of the University of Iceland (GCU) available for research and clinical use (unpublished data/personal communication, 15). The GCU database was launched in the 1960s and is now run jointly by Landspitali–National University Hospital and the University of Iceland. This database was constructed using the records from the national census from 1910 onwards and has, since 1953, been updated with data from the National Registry. Information from old parish records on births, deaths and marriages were added to the database as well as available information on migration. The database holds accurate information on almost all Icelanders born after 1840 and a number of individuals born before that time. To link individuals, a "mother's record" has been created for each woman who has given birth, including her name and identification as well as the name and identification code for each of her children and the father of each child (Tulinius 2011). A large number of studies that have been based on the database have been published; among them, most of the Icelandic cancer family studies. Islendingabok, another recent and large Icelandic genealogy database, is run by deCODE Genetics (OoSPa 2004). It is privately owned and accessible with restrictions to all Icelanders with a unique Icelandic personal identification number (kennitala). Individuals are able to use the database for themselves; to find out how they are linked to other Icelanders and to trace their ancestry. Islendingabok is not used in clinics and has been used in research by deCode Genetics. The database has been used in numerous research projects such as in mapping of loci-affecting disease phenotypes and other genetic traits (Gulcher et al. 2001).

The Icelandic National Registry (Þjóðskrá 2007) was established in 1953. It holds extensive information on all Icelanders (Íslands) and is accessible to all Icelanders in a restricted way. The population-based Cancer Registry is operated by the Icelandic Cancer Society (2010). In Iceland, cancer diagnosis recording is mandatory, making the registry comprehensive and accurate for its use in surveillance and research. Information regarding the accuracy and completeness of the Cancer Registry has not been published, but these parameters are thought to be up to 99 % (personal communication).

The pedigree is an essential tool for identifying individuals at risk of genetic diseases, to determine needs for genetic testing and for genetic counselling (Bennett et al. 1995). Genealogy databases have the potential to facilitate the construction of pedigrees. For instance, the clinical genetics service at Landspitali, the Cancer Registry and the GCU has collaborated in generating cancer pedigrees for genetic counselling since 2006 (personal communication). The accuracy of databases may however differ depending on how the data was collected and this may limit their clinical application. We were interested in identification and analysis of existing work on the use of genealogical databases in genetics healthcare. We did this by performing a systematic literature review (22) of the published literature in English. In this paper, we describe our results and discuss the possible reasons for the apparently very limited use of such databases.

Materials and methods

Data sources and searches

We conducted a systematic review following the method described by the Centre for Reviews and Dissemination (Dissemination CfRa 2009). We carried out a systematic search in October 2011 for papers in English on the use of genealogy databases in genetic health care. Four electronic

databases, PubMed, Web of Science, OVID and CINAHL EbscoHost were searched for papers published in peer-reviewed journals, theses, reference lists of relevant papers and articles in the "grey literature". The "grey literature", is "the term used for documents and ephemeral material issued in limited amounts outside the formal channels of publication and distribution" (Library HS Grey Literature 2011). The search was conducted using the following combined search terms:

- Genealogy database* AND genetic risk AND family history
- Genealogy database* AND clinical genetics
- Genealogy Database* AND medical AND family history
- Cancer registry AND genetic service
- Cancer registration AND clinical genetics AND genealogy
- Database* AND family history AND genetic risk assessment
- Genealogy database* AND cancer registry
- Database* AND genealogy AND genetics
- Genealogy AND database
- Genetic counsel* and clinical genetics AND genealogy
- Cancer genetic counsel* and genealogy.

The inclusion and exclusion criteria are described in Table 1.

Abstracts of the identified papers were reviewed for relevance by the authors VS and HS using the inclusion and exclusion criteria. In total, 1,035 titles were retrieved (Fig. 1). Of those, 260 were double publication, 598 were excluded on the basis of title alone. Of the remaining 125 papers, 121 were excluded after further examination, leaving four articles for inclusion in the review (Table 2).

Table 1 Inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Location	Any country	
Population	Human genealogy databases	Epidemiological studies
Language	English	Non-English
Time frame	January 1970–October 2010	
Type of paper	Research articles, conference papers, discussion papers, thesis	Magazine and newspaper articles, internet news
Main theme	Focused on the use of genealogy databases in genetic health services	Focused solely on use of genealogy databases for the purposes of genetic research rather than clinical service (e.g., mapping a gene)

Quality appraisal

The authors VS and HS used the quality appraisal tool for cohort studies designed by the Critical Appraisal Skills Program (Health SfP Critical Appraisal Skills Programme 2010) to evaluate the research-based paper (Brewster et al. 2004). The score was set at 93 %. The quality of the discussion-based papers was not formally appraised.

Data analysis

We constructed a table of the papers to record the salient features of each (Table 2). The papers were then thematically analysed (Clark 2003) for key codes, categories and themes within and across papers. As a meta-analysis was not possible, we present the findings in textual form under themes.

Findings

Description of selected papers

The search resulted in identification of two discussion papers from the USA (Cannon Albright 2006; Tu and Mason 2004) and two research papers, one from Scotland (Brewster et al. 2004) and the other one Icelandic (Thorsson et al. 2003). The Scottish research paper, described the use of a cancer registry-based service health care (Brewster et al. 2004). The Icelandic paper described how using a genealogy database in finding relatives for screening for familial hypercholesterolemia (FH) identified more patients than the conventional method. Overall, we found very little written evidence in the literature of the use of genealogy databases in genetic health service. However, none of the selected articles argued against such use. On the contrary, the main concept of the four articles was the recognised need for electronic genealogy databases and their possible linking to medical records or disease databases. The key outcomes of each paper are presented in Table 2. We present the findings under the themes (1) perceived value of electronic databases, (2) privacy issues and (3) future use of genealogy databases.

Perceived value of electronic databases

The perceived use of databases differed in the selected papers. While both the Scottish one and the Icelandic one (Brewster et al. 2004; Thorsson et al. 2003), described the use of a genealogy database in clinical service, Cannon Albright (2006) discussed the enormous possibilities of using such databases in both clinical service and research.

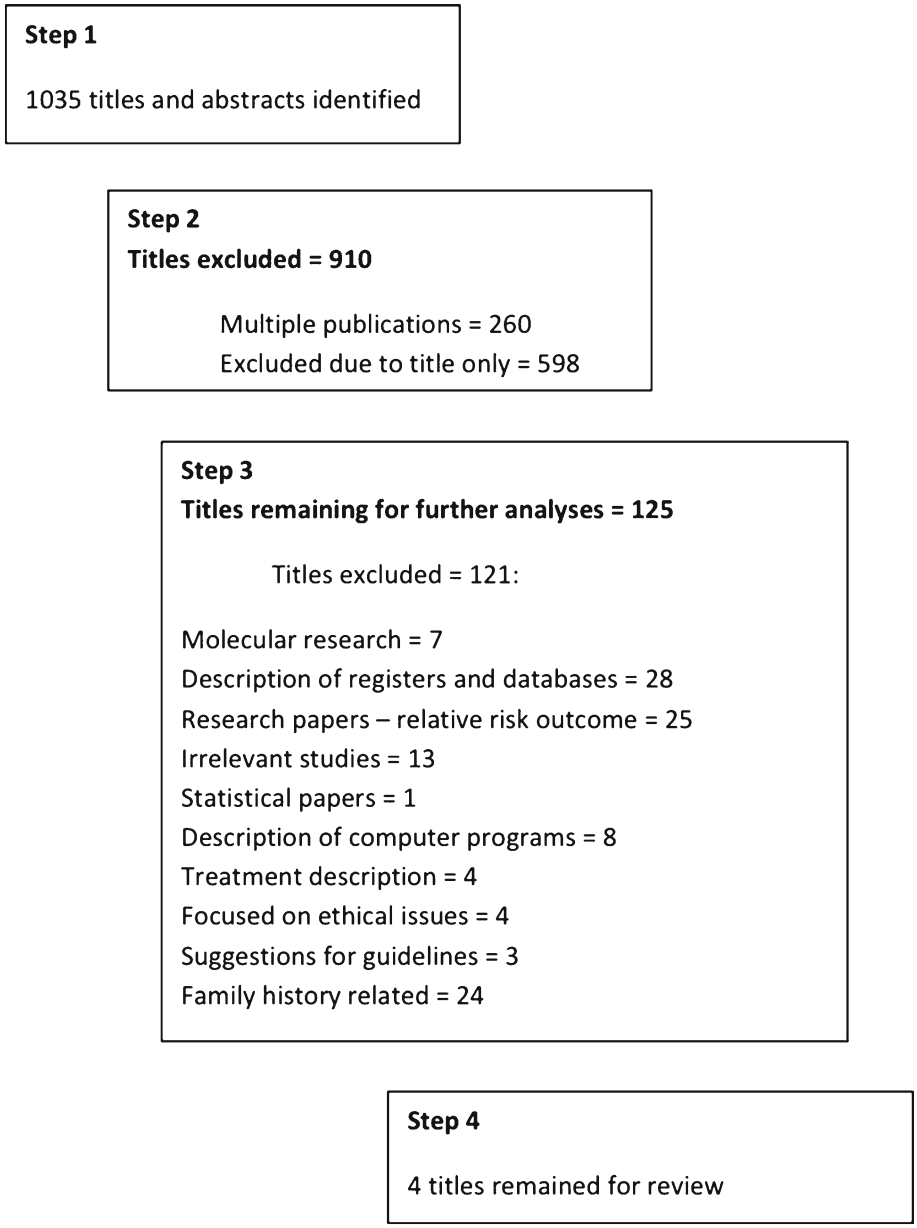

Fig. 1 Retrieval and selection of papers

Tu and Mason (2004) focused on the value of linking different databases to facilitate better surveillance in clinical care. Genealogy databases, linked to medical history or disease databases, could be used to guide medical decision making (Cannon Albright 2006), to identify individuals at risk (Thorsson et al. 2003), to make accurate risk assessment, for evaluation of cancer screening and treatment services (Brewster et al. 2004) and to follow up and coordinate service for individuals and whole families even if the family structure changes (Tu and Mason 2004; Thorsson et al. 2003). It was also described how the cancer registry-based genealogy service using the online public records of the General Register Office of Scotland (birth, death and marriage records) led to changes in the family history and enabled different risk categorisation and management for a number of counselees over a 12-month period (Brewster et al. 2004). Their article did not report on differences in accuracy when using the database as opposed to proband-generated pedigrees.

The tracing of FH probands to common ancestors, using a genealogy database, added considerably to the conventional method of FH cascade screening, where first-degree relatives are tested (Thorsson et al. 2003). The possibility of linking data from different databases, some already existing, by either of two methods was described (Tu and Mason 2004). The first method was a first-order linkage where information on a single individual could be linked together in different databases.

Table 2 Main outcome of selected papers

Authors	Title	Type of paper	Description	Results	Conclusion
Tu and Mason (2004)	Organising population data into complex family pedigrees: application of a second-order data linkage to State Birth Defects Registries	This paper is a discussion paper and includes no primary data	Discusses the possibility of using previously collected data in clinical health care. Also describes the best way of organising and collecting such data	Description of available data in diverse national and regional databases and how the data can be used	The power of data collected routinely into regional and national databases is underused in clinical health care
Cannon Albright (2006)	Computerized genealogies linked to medical histories for research and clinical care—a national view	Symposium proceedings. This is a discussion paper with no primary data collection or results	Discussion of the possibilities of combining genealogy data with medical histories	The use of linked genealogy databases and medical histories can enhance the power of research and make clinical care better	Genealogy data can contribute widely to the understanding of familial and genetic factors in human health and disease
Brewster 2004	Impact of a cancer registry-based genealogy service to support clinical genetics services	Short research paper describing a survey	The paper describes the effect of database-generated pedigrees on cancer genetic risk assessment in four major centres in Scotland	The pedigrees provided by the Scottish Cancer Registry were accurate and extensive and often changed risk category (41 %) and management (23 %)	Linking of pedigrees to a cancer registry results in more comprehensive family history and can change cancer genetic counselling
Thorsson . 2003	Systematic family screening for familial hypercholesterolemia in Iceland	Research paper comparing two methods of screening	The paper describes a novel approach in screening for familial hypercholesterolemia and compares it with conventional method	The systematic family screening identified 19 % more individuals than the conventional one	The new method adds considerable to the conventional method of FH screening

This is a similar method to the one many cancer registries use, with limited personal identification. The second method they called a second-order linkage. With this method, individuals can be organised into large family pedigrees within available databases if the appropriate fields are used. One way would be to create an individual ID for each person and include mothers and fathers identifier fields in the databases in question. This is a similar method to the one used in the Nordic countries for the National Population Registries and in the widely used Genealogical Data Communication data standard. Although the article focuses on birth defect registries, the formation and design of a family pedigree database is described. Similar is the possibility of linking genealogical resources such as the Veterans Administration data and the Social Security Death Index to the already available UPDB database, expanding their use (Cannon Albright 2006).

Authors agreed on the great impact that genealogy databases linked to disease registries, can have on research. Cannon Albright has described the UPDB and the Icelandic genealogy database as examples of such use (Cannon Albright 2006; Tu and Mason 2004).

Privacy issues

Cannon Albright (2006) discussed how the use of genealogy databases in clinical service required dealing with many issues, among them privacy and security issues concerning the data, as well as the liability implied in their use. Similarly, Tu and Mason recognised the potential concerns regarding privacy and confidentiality as it is possible that some could view such data linkage as intrusive (Tu and Mason 2004). They all stressed the importance of defining clear rules and procedures for the use of linking data. Brewster et al. mentioned the fundamental principles of the UK Data Protection Act 1988 (Brewster et al. 2004; Archives 1998).

Future use of genealogy databases

As for the future, Cannon Albright envisioned in her paper that a US genealogy database could be made by using already available data, such as the Veterans Administration Database and Social Security Death Index (Cannon Albright 2006). Tu and Mason pointed out the benefits that linked databases could have for applied public health service, using their suggested second-order linkage (Tu and Mason 2004). That method would probably be better than first-order linkage as name changing is frequent in the USA due to marriages. Also, families may move between states, making surveillance and paper follow-up difficult. Lastly, Brewster et al. claimed that the interaction between cancer registries and genetics clinics would likely increase in the future

(Brewster et al. 2004). They also stressed the benefit of such linking while Thorsson et al. discussed the limitation of using genealogy databases in clinical service caused by the lack of a comprehensive and accurate genealogy information in large multi-ethnic populations (Thorsson et al. 2003). Authors agreed on that suggestions for future genealogy databases used in clinical service will need to comply with strict requirements for privacy.

Discussion

This systematic review reports the results of a comprehensive search for papers describing the use genealogy databases in health care. Only four papers were identified, of which two described the actual existing use a genealogy database. The other two were discussion papers describing potential use. Presently, we are only aware of the use of genealogy databases in health care in Iceland and cancer genetics service in Scotland (Brewster et al. 2004; Thorsson et al. 2003). Thus the use of genealogy databases in health care appears very limited. However, it is possible that there is an ongoing use of databases that we are not aware of since reports may not have been published. Such use is unlikely to be common without us being aware of it from experience or through literature search. As an example of non-published use, except in a conference abstract form (Jonsson 2009) in Iceland, the GCU genealogy database is used by the cancer genetic counselling service. Files from the Icelandic Cancer Registry and the GCU database are linked to generate cancer pedigrees allowing for the construction of three to five generation pedigrees with cancer diagnosis. Similarly to the suggestion made by Tu and Mason, the linking used in the GCU database is made with a specific ID number issued to all Icelanders (Tu and Mason 2004). With this method, it is possible to make large family trees and to link almost all Icelanders. The GCU database is also used to generate pedigrees for other clinical use and to trace relationships between individuals. The FH familial screening method described by Thorsson et al. is a good example of such use (Thorsson et al. 2003).

Although we searched with many combinations of keywords and in comprehensive databases, the search may not have identified all papers. For example, the article by Thorsson et al. was not found by the search and only identified through a personal communication (Thorsson et al. 2003).

Genealogy databases of the size and quality suitable for clinical use are rare. However, this is likely to change. Family-based genealogy databases are becoming more common reflecting a growing interest in family history and user friendly computer programs. Such databases can now be generated with a modest effort by knowledgeable individuals. Large genealogy databases can be created with a reasonable effort, as the examples from Iceland and Utah show. Data from various existing demographic and family-based genealogy databases can be used to facilitate the creation of larger databases. There are existing databases that could potentially be used for health care with some modification and added information where needed. One is the Swedish Multi-generation Register (Ekbom 2011) and another one is the large UPDB in Utah which includes several million individuals coming from different countries (Cannon Albright et al. 2005). Some other large public genealogy databases exist and could potentially be linked with clinical information, given that the accuracy and reliability is acceptable. As for disease databases, cancer registries are well suited for such linking due to their size, formation and amount of information collected.

Our findings of limited publication may reflect legal or regulative restrictions based on perceived autonomy or information risk as well as worry about perceived risk for invasion of privacy. This is interesting as census microdata (Minnesota 2011) as well as large genealogy databases are freely available on the internet, making genealogy information public. Cannon Albright has suggested that the use of resources to assess an individual's risk of a disease requires different methods than for scientific research (Cannon Albright 2006). The quality of the available genealogical data must be very good and a medical history with diagnosis must be accessible and available for linking. Care must be taken to ensure privacy and to restrict the information to those who need it for the benefit of the family in question. It is debatable to what degree privacy is more endangered when linked databases are used by genetic professionals to form familial genetic risk assessment, as contrasted by the usual way by using the information received from the counselee. Of interest in this regard is the accepted practice of sharing genetic family trees between health services, apparently without risking privacy or needing specific consent of all family members. Genetic professionals are using family histories in their work, most often received only from counselees. The family information supplied by the counselee is often not fully accurate potentially causing risk misclassification (Janssens et al. 2012; Bensen et al. 1999). In some cases, there is information available about both affected and unaffected members of the family, either from previous communication or from Cancer Registry files. Cancer registries are generally accurate and comprehensive. In contrast, the disease information reported by health professionals on relatives is often incomplete. Linking information from cancer registries to genealogy databases should improve the efficiency of cancer genetics clinics (unpublished data; Reis et al. 2006; Gregory et al. 2007).

Genealogy databases have great potential for risk assessment in genetic health care but their use apparently very limited. Further studies are needed to address the benefits and drawbacks including requirements for data accuracy.

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ORIGINAL ARTICLE

Counsellee's experience of cancer genetic counselling with pedigrees that automatically incorporate genealogical and cancer database information

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Abstract While pedigree drawing software is often utilised in genetic services, the use of genealogical databases in genetic counselling is unusual. This is mainly because of the unavailability of such databases in most countries. Electronically generated pedigrees used for cancer genetic counselling in Iceland create pedigrees that automatically incorporate information from a large, comprehensive genealogy database and nationwide cancer registry. The aim of this descriptive qualitative study was to explore counsellees' experiences of genetic services, including family history taking, using these electronically generated pedigrees. Four online focus groups with 19 participants were formed, using an asynchronous posting method. Participants were encouraged to discuss their responses to questions posted on the website by the researcher. The main themes arising were motivation, information and trust, impact of testing and emotional responses. Most of the participants expressed trust in the method of using electronically generated pedigrees, although some voiced worries about information safety. Many experienced worry and anxiety while waiting for results of genetic testing, but limited survival guilt was noted. Family communication was either unchanged or improved following genetic counselling. The use of electronically generated pedigrees was well received by participants, and they trusted the information obtained via the databases. Age did not seem to influence responses. These results may be indicative of the particular culture in Iceland, where genealogical information is well known and freely shared. Further studies are needed to determine whether use of similar approaches to genealogical information gathering may be acceptable elsewhere.

Keywords Electronic pedigrees · Genetic counselling · Genealogy database · Risk assessment · Cancer genetics · Patient satisfaction

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Introduction

Recording the family health history to gain insight into possible inheritance patterns for a specific disorder has been a major tool in medical genetics for many decades (Bennett 2009). This process includes obtaining accurate information about family members, preferably for at least three generations (Eccles 2004). The family history information includes number of individuals, current ages or ages of death of relatives, as well as relevant health information. The information gathering may be done face-to-face, by telephone or via a written questionnaire (Bennett 2012). In the course of taking a pedigree, medical information on relatives is often provided by a family member without the explicit consent of the person concerned.

Genetic counsellors increasingly use electronic recording methods in their work. In 2013, a study of how genetic counsellors use electronic family history tools found that over 70 % had used such tools to record family histories. The same study found that the majority of genetic counsellors felt that linking

electronic medical records to a family history tool would be time saving (Widmer et al. 2013). This has been supported by other studies concluding that time and effort could be saved by enabling counsellees to record their family history by electronic methods (Guttmacher et al. 2004, Hulse et al. 2011). One context in which accurate family history is particularly important is in the field of cancer genetics, where counselling can benefit both the counsellee and his or her family by identifying those at risk, providing options for surveillance and preventive treatment (Brewster et al. 2004, Stefansdottir et al., 2013a, Nelson et al. 2014).

While staff of many genetic services uses pedigree-drawing software, the electronically generated pedigrees used for genetic counselling in Iceland differ, as they automatically incorporate information from a large, comprehensive genealogy database and the nation-wide cancer registry. This ability to link cancer and genealogical registries to the pedigree can be used to generate relevant information for the family history, which in turn can be used in cancer genetic counselling (Stefansdottir et al., 2013b). In order to do this, counsellees consent to have their family tree generated from the genealogy database of the Genetical Committee of the University of Iceland, which holds accurate genealogy information about Icelanders back to at least 1840 (Tulinius 2011). The history of cancer(s) is then added, using the population-based Cancer Registry operated by the Icelandic Cancer Society (http://www.krabbameinsskra.is). By this method, comprehensive, electronically generated pedigrees (EGP) are made, enabling very accurate family history for risk assessment and calculations (Stefansdottir et al., 2013a, Lee et al. 2014). However, like other methods of family history taking, this may also help to identify individuals who may be at increased risk of having a mutation in either the *BRCA1* or *BRCA2* gene, (hereafter referred to as BRCA mutations) or other inherited cancer predisposition. Specific founder mutations in BRCA genes are present in the Icelandic population. The *BRCA2* c.771_775del5 mutation (formerly known as BRCA2:999del5) is carried by appr. 0.6 % of the Icelandic population (Thorlacius et al. 1997) while the:5193G> A is rare and the population frequency has not been determined. Although only 5–10 % of breast cancers can be explained by inherited mutations in the BRCA genes, the risk of mutation carriers developing breast or ovarian cancer is considerably raised compared to women in the general population (Janavicius 2010) and early clinical surveillance is advised. Therefore, cancer genetic counselling can benefit both the counsellee and his or her family. Some family members may be aware of their risk, but for others, this may occur without their knowledge. Counsellees are therefore not shown the family EGP to protect the privacy of other family members.

Using family history to assess risk of hereditary cancers is a widely used method and an important part of genetic health services. We were, however, unable to indentify published literature on the counsellees' experience of having a family history taken, with or without the use of EGPs. The aim of this study was to gain insight into the counsellees' experience of cancer genetic counselling where EGPs were used to document accurate family history and make a risk assessment. In this study, EGPs were created using information from two databases: a comprehensive genealogy database and a nation-wide population cancer registry.

Methods

A qualitative descriptive approach (Sandelowski 2000) was used to ascertain the views of the counsellees. Focus groups are generally used to collect data through exploration of a topic with a number of participants, where one or more group facilitators moderate the focus group (Kevern and Webb 2001). Using online focus groups is an adaption of the conventional face-to-face group methods in qualitative research (Hansen and Hansen 2006), where all text is available after replies have been made. On the other hand, online focus groups lack the human presence of face-to-face group sessions (Schneider et al. 2002). Some participants find it easier to participate if they do not have to travel or be at a specific place on a specific time (Chen and Hinton 1999). In addition, the visual anonymity of the Internet makes it sometimes easier to give personal information without being identified (Montoya-Weiss et al. 1998), thus giving participants the chance of revealing only what they want about themselves. Online focus group studies can be done in two different ways. We used an asynchronously method, where the participants log on in their own time to read contributions from others and then post contributions themselves (Tates et al. 2009, Zwaanswijk and van Dulmen 2014). The other way is synchronously, where participants log on at the same time and exchange written sentences on the chosen forum (Fox et al. 2007). The choice of method must be made according to the topic and availability of participants.

Participants

The participants were individuals from families identified as having a *BRCA* mutation and had attended for cancer genetic counselling between 01.01.2007 and 31.12.2012. In all, there were 158 eligible females and 67 eligible males. All participants had been tested for one of the two known Icelandic founder mutations: the *BRCA1:5193G- > A*, and the *BRCA2* c.771_775del5 mutation, the majority for the BRCA2 mutation. An invitation letter was sent to eligible participants describing the study objectives and requesting participation. We aimed to recruit between six and 10 individuals to each focus group, with variation in terms of age, gender and genetic status. We believed saturation was reached after the first two

focus groups, but continued to recruit to test this. As all participants in the first three groups were women, a decision was made to purposively invite only males to the 4th group.

In all, 26 returned consent forms by either email or post and 19 remained as participants, 17 females and two males. The average age of those invited (n = 225) was 50.4 (range 23–86 years), while the average age of participants was 52.2 (range 33–69 years). Group 1 had three women, groups 2 and 3 seven women in each and group 4 had two males. Eleven participants were mutation positive and eight were mutation negative.

Forum

The Phpbb forum https://www.phpbb.com/, a free flat-forum bulletin board was chosen for the study. The forum was hosted on the Icelandic Human Genetics Society site, www.mannis.is. To ensure privacy, the board was closed from others than the participants. The Internet Protocol (IP) numbers and email addresses of participants were concealed. Users chose their own user names and passwords when registering. When each group finished, the board was taken down and all communications completely deleted.

Questions

Groups 1 and 2 received the same ten questions, posted on the board one at a time. A reminder was sent by email to the group each time a new question had been posted. In the reminder and on the board, participants were encouraged to post their own questions and comments. A second reminder was sent when a week had passed without replies. When the first two groups were completed, a decision was made to make small changes to the questions, as is usual in qualitative studies where data collection is influenced by concurrent data analysis (Green et al. 2007). Therefore, groups 3 and 4 received 15 questions. Although the content had not been changed, complex questions were presented as several simpler questions. Based on the experience of limited response from the first two groups, for group 3, the first seven questions were put on the board all at once, followed later by the last eight questions. These changes resulted in better return of replies. The questions are listed in a supplemental file.

Data analysis

We followed the approach used by Braun and Clarke (2006) for thematic analysis of data. All comments were initially independently coded, by two of the authors (VS and HS) by hand using descriptive coding. The codes were sorted into categories and themes and discussed by both researchers until a consensus was reached.

Results

Emerging themes arising from the results were motivation for testing, informational need for testing, impact of testing, emotional response to testing and EGP (Table 1). One main outcome was that participants did not oppose the use of, and most trusted, the information from the electronic databases from which the EGPs were sourced. There was some concern about data privacy; however, concern about other family members' attitudes to use information from databases was limited and family communication remained the same or increased.

Theme 1: *motivation.*

The strongest motivation for seeking genetic counselling was knowledge of the family history of breast cancer:

"*I decided to ask for genetic counselling as my mother died at 49 because of breast cancer and my mother's sister at 69*," (*female age 45*, *mutation negative*).

Some had knowledge about the mutation in the family:

"*I have an aunt who got breast cancer and she had been asked to relay the information to us that we might carry the gene*," (*female age 57*, *mutation positive*).

Few of the participants had information on genetic counselling from their relatives. For some, the idea of better cancer surveillance was one of the triggers:

"*I had heard about genetic counselling and found it to be of interest mainly because of the surveillance available to BRCA carriers*," (*female age 55*, *mutation positive*).

Theme 2: *electronic pedigrees.*

While many knew about the use of pedigrees, some did not but were nevertheless impressed by the possibilities offered:

"*I had no idea. This is a very cool tool both for families and professionals*," (*female age 36*, *mutation negative*).

Some were already aware of the use of EGPs:

"*I knew about it. This gene is common in my family and my pedigree has been mapped*," (*female age 56. mutation positive*).

Theme 3: *information and trust.*

The majority trusted that the information from the databases was correct and that the professionals could be trusted with the information:

"*Yes I trust the service as much as possible. Still*, *it is vital to ensure that insurance companies will not be able to access the information*" (*male age 46*, *mutation positive*).

However, some voiced concern over the amount of data available and were worried that it—especially the mutation results—could be used against them or their descendants later on:

"*I had not thought much about it*, *but knew that something like this had to exist. Of course it is fabulous that this can be mapped*, *but then it is a question of how long it will be so. Will my children or their children be able to buy life insurance or will it be like*: "*no*, *you belong to this family and therefore we*

Table 1 Main themes and categories, arising from analysis

Themes	Categories
1. Motivation	Family history
	Experience of condition
	Family experience of mutation or testing
	Awareness
	Experience (self or family) of genetic counselling
2. Electronic pedigrees (EGP)	Knowledge
	• Prior knowledge of EGPs or genetic counselling
	• No prior knowledge of EGPs or genetic counselling
	Family attitude—no worries
	Requirement
	Positive attitude towards EGPs
	Diverse attitude towards EGPs
3. Information and trust	Information
	• Sufficient
	• Would have liked more later
	Trust
	• EGPs
	• Genetic counselling
	• General
	Data protection/privacy issues/worries
	Insurance worries
4. Emotional response	Emotions
	• Negative
	• Relief
	• Positive
	• Verification
5. Impact of testing (not covered in the article)	Waiting time
	• Difficult or long
	Family communication
	• No change or positive
	• Little
	• Other
	Decision making about future
	Survival guilt
	• None
	• Little
	• Definitely
	Lifestyle changes

will not insure you, and so on?" (*female age 44, mutation positive*).

Others shared this opinion:

"*It is important that information like this is available for the individual himself, asking for them, but not for others. No such information used in research should be identifiable. On the other hand, the individuals themselves should be able to get them*," (*female age 56, mutation positive*).

Information about data privacy was mentioned by participants:

"*I have to agree with those who question what happens to the information* (*genetic*). *If doing this will result in institutes being able to access the information and use it against individuals or their family in any way, then I am not sure about how good this is. I think it will always be a question of information privacy*," (*female age 45, mutation negative*).

Some of those who broadly supported the idea of using EGPs were concerned about protection of privacy:

"*Yes I knew that it was possible to make such pedigrees. I think it is good if privacy issues are taken care of*," (*female age 64*, *mutation negative*).

Experience of genetic counselling

The last question was about the quality of the service. The majority of comments were positive. "*When we came before the testing and also when the results were ready*, *I found the information to be good*," (*female age 34*, *mutation positive*).

"*I found the whole procedure nice. The interviews were of good quality. From the beginning I felt secure and that they were really good people*" (*female age 55*, *mutation positive*).

However, some talked about the possibility of improving the follow-up:

"*I got warm welcome and good information. However*, *when the results had been given*, *I felt that the overall management could have been better. But I know I should have asked for further counselling*," (*female age 45*, *mutation positive*).

This was in agreement with others:

"*If there was something*, *it might be that the whole procedure was sort of mapped beforehand so that you would always know what was happening*," (*female age 56*, *mutation positive*).

Discussion

It is estimated that over 96 % of all Icelanders have access to the Internet (Iceland 2016). This was the basis of using an online focus group for the study instead of the more conventional face-to-face method. To our knowledge, this method has not been used before in similar studies in Iceland. The asynchronously method enables participants to connect and comment on their own time instead of logging on at specific times but at the same time does not encourage discussion between participants. As for the ratio of males to females, it reflects the clinical situation in breast and ovarian cancer genetic counselling clinics.

The family history taking is an important part of genetic counselling as risk assessment is based on the outcome. The outcome of genetic counselling in families with cancer history has been studied (Codori et al. 2005), but to our surprise, we did not find previous studies on the counsellees' experiences of the procedure of family history taking itself.

Trust is an important part of health services. Our participants expressed trust in our method of using EGPs although some mentioned data privacy in the context. This may have been confirmed by our policy not to share the EGP with the counsellee or other family members in case they hold sensitive information not known to others in the family. However, some participants voiced worries about the possibility that insurance companies or others might use the information "against" the participant or family. The nature of insurance companies demands that all relevant health information is provided, and as genetic testing is increasingly a part of health services, results from them may be included (Joly et al. 2003). However, few had any concerns for the attitudes of other family members regarding giving and accessing genealogy and cancer information about the family. This may have to do with the general attitude towards genealogical information in Iceland, where genealogical and other personal information is freely exchanged and discussed.

Those who seek genetic counselling usually do so on the basis of family history or their own medical history. It is the job of professionals to evaluate the family history and make decisions about genetic testing based on the level of risk of the person having a particular condition or mutation. A family history of breast or ovarian cancer was the most common reason to seek genetic testing, followed by a family experience of genetic counselling and/or prior testing of other family members.

Good information and support enhance the counsellee's ability to communicate to family members about the testing and the outcome (Lafreniere et al. 2013). Family communication is an important way of disseminating information about genetic testing and many individuals share test results, at least with first-degree relatives (Finlay et al. 2008). One of the roles of a genetic counsellor is to help individuals and families understand complex genetic information and share it with the family (Genetic Alliance 2009). Those receiving additional information are more satisfied, especially if this leads to better understanding (Roshanai et al. 2009). This may indicate that the opportunity for a follow-up session to reinforce and expand on the information given could be valued and useful to counselees. As can be expected, when more family members learn about the family mutation, the number of people with some knowledge prior to genetic counselling grows. This can help when giving complicated information to the counsellee, as other family members may have already shared their knowledge and experience. However, the counselee's prior knowledge does not mean that the counsellor should give less information or shorten the process.

Many of our participants found that family communication had either not changed or was positively affected during the process of genetic counselling. Having the mutation in common seemed to strengthen the bonds in some families. This has been supported elsewhere (Forrest et al. 2008) and genetic counsellors are well aware of the importance of addressing the family communication with counselees (Mendes 2015).

To our knowledge, the use of EGPs, which utilise information from genealogy databases with linkage to disease databases, to assist the genetic professional are not used in genetic

health services elsewhere than in Iceland, but should perhaps be promoted as means of easier, better and more accurate information for the genetic counsellor. It may be argued that in a country like Iceland where much genealogy information is already available and easily found, the attitude may be different from other countries. However, it has been suggested that national and regional databases hold valuable information and are an under-used and neglected source of information (Bain et al. 1997). In any genetic health service in the world, family history taking is an integral part as well as in many medical services. There, abundant information about families can be found - often without most of the family members being aware of it. This situation is therefore not unique and trust may be in part due to the knowledge that all health records should be confidential. Also, various large genealogy databases exist on the Internet where they can be easily accessed.

While EGPs in this form are not used elsewhere, we suggest that the experience from this study and others (Stefansdottir et al., 2013a, b) can be used to facilitate ways of using existing secure databases as means to improve risk assessment. This could especially apply where electronic databases are available, such as in the Nordic countries where comprehensive information is available in both national and cancer registries (Stefansdottir et al., 2013a, b, Bauer 2014).

Strength and limitations of the study

All participants in our study had been counselled at the same place by members of the same genetics team. Over the period where participants had received genetic counselling, the service evolved and this may have had an impact on differences in experience. While one of the limitations of the study was a relatively low response rate, we felt that saturation of themes was achieved. It may reflect the lack of familiarity with use of an online forum or reluctance to revisit a difficult period in the life of the participant. With increasing use of social media, this is likely to change. The ratio of males to females reflects the clinical situation in breast and ovarian cancer clinics.

Conclusions and implication for practice

The use of EGPs enables the genetic counsellor to make a faster and more comprehensive risk assessment. While our participants did not oppose the use of the EGP in genetic counselling and gave mainly positive feedback, further studies are needed to determine to what degree this can change clinical management. It is possible that some of our results were culture dependant, as the knowledge of genealogy is high in Iceland. However, similar to other nations, Icelanders are also concerned about data privacy. Our results indicate general patient support for wider use of electronic databases in genetic counselling, although we are aware of the importance of careful planning and evaluation to ensure that systems are fit for purpose and practice.

For genetic counselling practice more generally, it is crucial that counsellors appreciate client concerns about protection of data, as this has implications for the trust relationship between clients and counsellors, with an ultimate impact on the way in which clients view the information provided to them (Skirton 2001). Stringent systems of consent to access personal information, offering support for discussion with relatives and protection of confidential information, are already key components of service in many genetic counselling settings (Committee on Health Research and the Privacy of Health Information 2009). However, while genetic health professionals may understand this, it is important that clients are also made aware of the arrangements to access and protect their data. This will enable maximum use of genealogical and disease history information for patient benefit, while enhancing patient confidence in the process.

Compliance with ethical standards This study was approved by the National Bioethics Committee no 15–038: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Informed consent Informed consent was obtained from all participants included in the study.

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Paper III

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ORIGINAL ARTICLE

Electronically ascertained extended pedigrees in breast cancer genetic counseling

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Abstract

A comprehensive pedigree, usually provided by the counselee and verified by medical records, is essential for risk assessment in cancer genetic counseling. Collecting the relevant information is time-consuming and sometimes impossible. We studied the use of electronically ascertained pedigrees (EGP). The study group comprised women (n = 1352) receiving HBOC genetic counseling between December 2006 and December 2016 at Landspitali in Iceland. EGP's were ascertained using information from the population-based Genealogy Database and Icelandic Cancer Registry. The likelihood of being positive for the Icelandic founder *BRCA2* pathogenic variant NM_000059.3:*c.767_771delCAAAT* was calculated using the risk assessment program Boadicea. We used this unique data to estimate the optimal size of pedigrees, e.g., those that best balance the accuracy of risk assessment using Boadicea and cost of ascertainment. Sub-groups of randomly selected 104 positive and 105 negative women for the founder *BRCA2* PV were formed and Receiver Operating Characteristics curves compared for efficiency of PV prediction with a Boadicea score. The optimal pedigree size included 3° relatives or up to five generations with an average no. of 53.8 individuals (range 9–220) (AUC 0.801). Adding 4° relatives did not improve the outcome. Pedigrees including 3° relatives are difficult and sometimes impossible to generate with conventional methods. Pedigrees ascertained with data from pre-existing genealogy databases and cancer registries can save effort and contain more information than traditional pedigrees. Genetic services should consider generating EGP's which requires access to an accurate genealogy database and cancer registry. Local data protection laws and regulations have to be addressed.

Keywords Cancer genetic counseling · BRCA2 · Electronically generated pedigrees · Breast cancer · Genealogy database

Introduction

Family history is an important tool to assess risk in cancer genetic counseling, but recommendations differ regarding the size of pedigrees. Most guidelines call for a three-generation or third-degree family history for assessment of hereditary cancers [1]. Concern has been raised about the efficacy of family history in predicting risk assessment in hereditary breast and ovarian cancers (HBOC) [2], but to what degree this reflects too small or inaccurate pedigrees has not been determined.

Solomon et al. found that 19% of high-risk colon cancer and 72% of high-risk breast cancer candidates would have been excluded from testing without extended family history [3]. However, it can be difficult to obtain an accurate cancer family history from a patient, especially when the family is large [4, 5]. Barriers to identifying a clear pattern of inheritance from family history include a small family [6],

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limited knowledge of relatives with cancer, misinformation, unwillingness to talk about other family members and lack of communication within the family [7, 8]. People tend to know more about cancers in their closest relatives [8–11]. In addition, health care providers do not always obtain adequate cancer family history [12]. Wood et al. did a pilot test on the quality of cancer family history for 10,466 patients from over 200 practices participating in QOPI (practice-based quality assessment and improvement program). Their result showed that 79.8% of patients with either breast or colorectal cancer had their first-degree family history recorded and 64.6% their second-degree history. Complete family history, with diagnosis and age of diagnosis for first- and second-degree relatives was present for 32.9% of breast cancer patients and 22% of colorectal cancer patients [13]. Obtaining comprehensive cancer family history with conventional methods remains problematic, and alternative approaches should be considered.

Breast cancer and the BRCA genes

The lifetime risk of breast cancer is close to 1 in 8 among women in Western countries [14, 15]. During 2010–2014, on average, 202 women were diagnosed with breast cancer in Iceland each year, at the average age of 61 years [16]. The incidence is similar to other Western countries. Registration of cancers is mandatory in Iceland and the other Nordic countries [17] resulting in comprehensive and accurate registries.

Pathogenic variants (PV's) in the five high-risk genes; *BRCA1, BRCA2, CHEK2, TP53*, and *PTEN* are collectively thought to account for 5–10% of all breast and ovarian cancer cases and the *BRCA* genes for the majority of HBOC [18]. The Icelandic population has one prevalent *BRCA2* founder PV *NM_000059.3:c.767_771delCAAAT* with an estimated population carrier frequency of 0.8% [19]. At the beginning of this study, one Icelandic founder PV was known in the *BRCA1* gene, NM_007294.3:c.5074G > A, with unknown but very low population frequency. Recently, other rare *BRCA* PV's have been found in the Icelandic population, mainly family specific. It has been estimated that 7–8% of Icelandic women with breast cancer had the *BRCA2* founder PV [20]. However, this may be an overestimate and has not been confirmed recently in a larger study of unselected patients.

The risk of HBOC varies depending on family history and the nature of the PV [21]. A recent study showed that the estimated cumulative breast and ovarian cancer risk by age 80, in women with a *BRCA2* PV, is 69% and 17%, respectively [22]. Estimates of breast cancer penetrance in Iceland due to the founder *BRCA2* PV were lower when including many decades of diagnosis, or 17% and 37% by age 50 and 70 years, respectively [20]. In contrast, in women diagnosed after the year 2000, the estimated risk was 72% (95% CI 45.9–100.0) before age 70 years [23].

Genealogy database

In the 1960s, large and extensive multi-generation Icelandic Genealogy Database was set up in Iceland as part of a large research project [24]. It comprises data from all living Icelanders and their ancestors and is largely complete and accurate since the mid nineteenth century [24]. The database is used in scientific and private research (by genealogists, clergy, inheritance lawyers), as well as in genetic health services [25].

Genetic counseling in Iceland

Iceland has one clinical genetics clinic at Landspitali—The National University Hospital [25]. Uniquely, the clinical genetics service at Landspitali has permission to use information from the Icelandic Genealogy Database and the population-based, high-quality, Icelandic Cancer Registry [26, 27] to construct electronically ascertained pedigrees (EGP's) [25]. Explicit consent for generating a pedigree is required from the counselee who does not get access to the pedigree, but receives only the final personal risk assessment. This approach enables construction of extensive pedigrees with information on exact diagnosis, age at diagnosis, and tumor type. These extended pedigrees ascertained from electronic databases can augment pedigree information provided by the counselee. Using this approach allows for more accurate risk assessment and better surveillance recommendations than with conventionally made pedigrees. General methods to calculate risk in pedigrees have been developed and used [28, 29]. In the Icelandic Genetics Clinic, we use the Boadicea risk assessment model which has been validated and is commonly used in HBOC genetic counseling [30]. In this study, we took advantage of the unique situation in Iceland where inherited breast cancer risk is to large extent due to one founder *BRCA2* PV.

Study aims

We determined the practicality of using large EGP's in cancer genetic counseling. Secondly, we made use of this unique dataset of large and accurate pedigrees to determine the optimal degree of relatives to include balancing the accuracy of risk assessment using Boadicea, and cost of ascertainment.

Methods

Study population

The study population comprised all individuals of Icelandic origin, tested for the two Icelandic founder *BRCA* PV's

relating to HBOC in genetic counseling at Landspitali, between December 2006 and December 2015 (n = 1352). The group was organized into carriers and non-carriers of the founder *BRCA2* PV. From both groups, randomly selected women were added into sub-groups by the RAND function in Excel. The sub-groups comprised 209 women, 104 positive and 105 negative for the founder *BRCA2* PV. ROC analyses was used to assess the effect of family size on predicting the presence of the founder *BRCA2* PV with a Boadicea score (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) [31].

Data analysis

The pedigree software ClinicalPedigree™ was used to ascertaine the pedigrees [32]. Excel software was used for statistical analysis. Boadicea was used to estimate the likelihood of having a *BRCA2* PV, using Icelandic allele frequency 0.3 for the founder *BRCA2* PV, search sensitivity 0.8 and cancer incidence rates for Iceland. The MedCalc™ Receiver Operating Characteristic (ROC) Curve Analysis and C-statistics based on pair-wise comparison were used to evaluate the effect of increasing pedigree size on the risk estimates [33], and 95% CIs were obtained based on exact binomial function. Statistical tests were two-sided at the significance level of 0.05 [34]. For calculating the statistical significance of the difference between the ROC curves, based on a number of individuals, we used VassarStats for ROC curve analysis (http://vassarstats.net/roc_comp.html) [35].

Electronically ascertained pedigrees

For ascertainment of the EGP's, genealogical information was obtained from the Genealogy Database [24] and relevant information on cancer in relatives added by record linkage with the ICR. A full EGP set for each person comprised eight pedigrees, each containing all descendants from one of the great-grandparents of the proband. Some individuals appeared in more than one EGP. Counselees were not shown the pedigrees.

Ethical approval for the study was obtained from the National Bioethics Committee (no. 11–147). No personal information based on EGP's was disclosed.

Results

Between December 2006 and end of December 2015, 1352 individuals, in 370 EGP's had been tested for one or both of the Icelandic founder *BRCA* PVs. In 314 EGPs, no *BRCA* PV had been found, whereas in 56 EGPs the founder *BRCA2* PV had been found (Table 1), with the largest EGPs comprising 4197 and 2031 individuals, respectively. Of the 1352 individuals tested, 340 tested positive for the founder *BRCA2* PV, 233 females and 107 males (Table 2). There was some overlap of individuals in EGPs within the two categories. In four cases, it was not possible to construct an EGP due to unknown paternity/maternity or adoption. In those cases, the counsellee was offered genetic testing for the two founder *BRCA* PV's.

Work required in constructing EGP's

The estimated amount of all work creating the EGP's for each proband, with all relevant cancer information and at least 4° relatives, took up to three working hours depending on the size of the pedigrees. Each probands family was traced back to great-grandparents, resulting in eight pedigrees for each counsellee. Pedigrees include the date of birth and death, age at diagnosis, type of cancers back to 1954 (the first year of the ICR) and breast cancer back to 1911 due to the collection of comprehensive countrywide data

Table 1 Size of the EGPs attending the cancer genetic clinic, between 1.12.2006 and 31.12.2015 at Landspitali

	EGP's where no known BRCA PV was found	EGP's where the *BRCA2 NM_000059.3:c.767_771delCAAAT* was found
Number of EGP's	314	56
Average number of individuals in EGPs	497	514
Female relatives	46,403	9432
Male relatives	48,470	9950
Females married into the families	18,958	3835
Males married into the families	19,805	3786
Max. number of individuals	4197	2031
Min. number of individuals	13	40
Counsellees without genealogy information	1	3

Data only includes those alive in 1955 and born before 1996

Table 2 Number of subjects tested positive for the Icelandic BRCA2:c.771_775delTCAAA from 1.12.2006 and 31.12.2015 and their associated cancers diagnosed 1955–2015

	Females, number (%)	Males, number (%)
Positive individuals	233	107
Breast cancer	86 (37%)	7 (6.5%)
Two breast cancers	11 (4.7%)	2 (1.8%)
Prostate cancer	–	9 (8.4%)
Ovarian cancer	10 (4.2%)	–

on all breast cancer diagnosed in 1911–1954, for a doctoral thesis [36].

Experience of using the EGP's in genetic counseling

Obtaining consent and explaining the use of EGPs for risk assessment was a straightforward process without complications. No known security breach or misuse of the information occurred. Questions occasionally asked by counsellees included (1) whether permission was needed from other relatives, (2) whether the counselee could see/own the EPG, (3) whether possible former unknown family members would be revealed to them and (4) whether all disorders in the family was recorded. All the answers were negative.

Genetic services collect various types of information on counsellees and relatives. Relatives of counselees may not always know the nature of information obtained or available in the clinic. In some cases, the extended family history acquired using the EGP's revealed a distant relative with a known PV. In a number of cases, this resulted in an offer of genetic testing where it might not have been offered without the extended information.

The optimal size of pedigrees for risk assessment

ROC analysis based on the Boadicea score was used to assess the association between the size of the pedigree and the efficiency of risk assessment for *BRCA2* PV in HBOC cancer genetic counseling To test this effect, we randomly selected individuals from the study group, into two subgroups comprised 209 women, 104 positive and 105 negative for the *BRCA2* PV. Model pedigrees were ascertained for those women, where we incrementally added individuals more distantly related to the proband. Table 3 shows the average number of individuals, and range, for each degree of relatedness. The 6° pedigrees were not included in ROC analysis as Boadicea™ could only calculate up to max 275 individuals.

Table 3 also shows the average score and range of results from risk calculations for being a carrier for the founder *BRCA2* PV with Boadicea, according to a different degree of relatedness. The lowest score was 0.1% in all degrees of relatedness, and the highest risk was 93% in a pedigree with 4° of relatedness. ROC analysis on the efficiency of predicting whether the proband had the founder *BRCA2* PV according to inclusion of increasing degrees of relatedness can be seen in Figs. 1 and 2. Adding 2° relatives to the 1° degree relatives increased the C-statistic from 0.62 to 0.70 ($p < 0.001$), and adding 3° relatives increased the C-statistic from 0.70 to 0.77 ($p < 0.001$) (Fig. 1). In contrast, the inclusion of 4° relatives did not significantly affect the C-statistic which decreased to 0.76 ($p = 0.33$) (Fig. 2). To further evaluate the relationship between the size of the pedigree

Table 3 The number and range of individuals and Boadicea risk scores in pedigrees including different degrees of relatedness for ROC curve analysis

Degree	Average no.	Individuals	Boadicea risk score (%)	
		Range	Average	Range
1°	9	(3–22)	8	(0.1–39)
2°	26	(6–92)	12	(0.1–88)
3°	54	(9–220)	14	(0.1–86)
4°	103	(15–257)	15	(0.1–93)
5°	146	(15–498)	14	(0.1–88)
6°	166	(15–565)	11	(0.1–88)

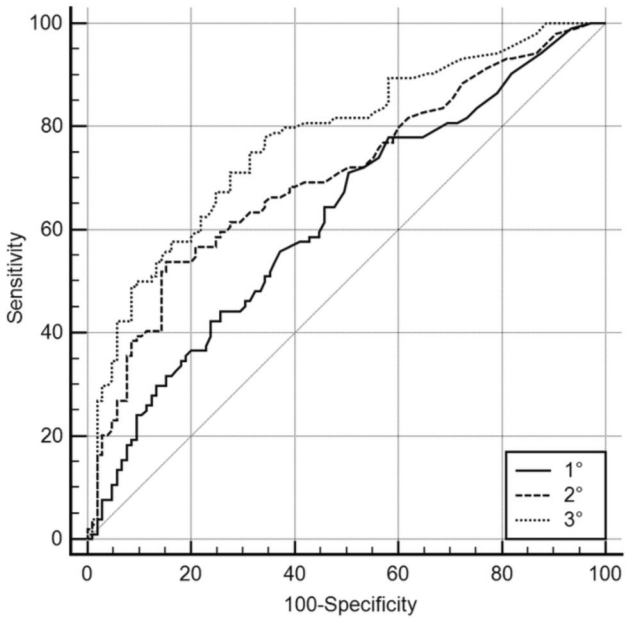

Fig. 1 ROC curves demonstrating the effect of pedigree size on the efficiency of Boadicea risk calculations in predicting the presence of the *BRCA2* NM_000059.3:c.767_771delCAAAT1A. Pedigrees with 1°, 2° and 3° relatives. Pedigrees with 3° relatedness showed the best outcome

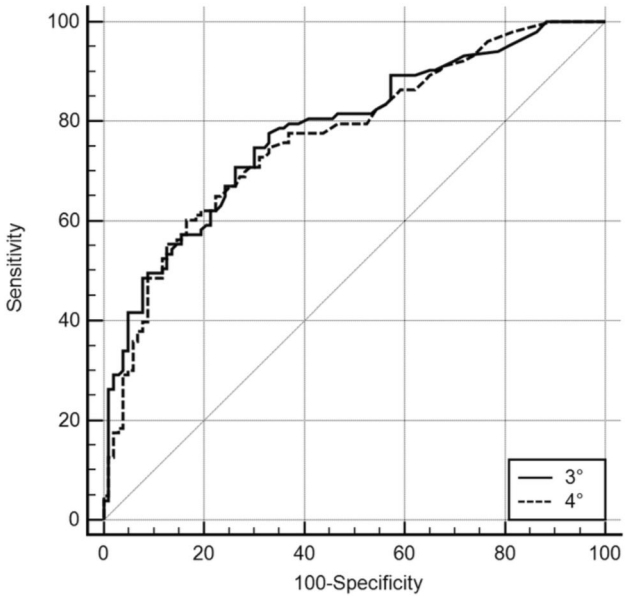

Fig. 2 Comparison of pedigrees including 3°and 4° relatedness. Increasing the size of the pedigree did not improve prediction

and efficiency of risk assessment, we divided the 3° pedigrees into two groups ranked by the number of individuals in each pedigree. The lower number group (n = 105, average no. of individuals 30, range 9–46) had a C-statistic of 0.718, but the higher number group (n = 104, average no. of individuals 133, range 46–220) had a C-statistic of 0.822. We also divided the 4° pedigrees in two according to size. The lower number group (n = 103, average no. of individuals 56, range 15–87) had a C-statistic of 0.719, but the higher number group (n = 103, average no. of individuals 145, range 87–257) had a C-statistic of 0.815. The C-statistics for 3° and 4° relative pedigrees were very similar and not significantly different. We converted the lower number group in 3° pedigrees into 4° relative pedigrees, but there was no improvement in the C-statistic (0.718).

From these results, we concluded that in this application, there was no gain of efficiency by including the 4° relatives.

Discussion

Family history with detailed demographic and medical information is an essential tool for risk assessment in genetic counseling, but constructing accurate and large enough pedigrees is work- and time-consuming. We demonstrate the feasibility of using EGP's and the advantage of using them instead of conventionally made pedigrees. Further, by comparing different pedigrees with different degree of relatedness with ROC curves, we show that 3° relatedness is the optimal size risk assessment in cancer genetic counseling due to the risk of having a pathogenic variant in *BRCA2*. To our knowledge, this study is the best objective estimate of the optimal pedigree size with respect to accuracy of cancer risk assessment. Giving the referral indication, HBOC, other cancer syndromes were only suspected in rare cases when assessing the EGPs. Results from other than the two *BRCA* genes were not included. We suggest that the same approach could be used for other inherited cancer syndromes, although the optimal size of pedigrees will likely depend on both the incidence of the relevant cancers and the gene penetrance. Presumably, large pedigrees will also be found advantageous where inherited cancer syndromes comprise common cancers with incomplete penetrance. The benefit of using extended family history for risk assessment is supported further by other research studies where large genealogy databases and information from cancer registries identified distant relatives in colorectal and breast cancer families within a familial cluster of cancer [3, 37].

Work effort in creating the pedigrees

The actual workload or cost of obtaining conventional 2–3 generation cancer family history, in the genetics clinic, is difficult to evaluate as it differs considerably between cases and services. However, sending out family history forms and recording information as well as collecting various tumor and health records from different healthcare institutions, after obtaining informed consent, involves considerable work. Therefore, we estimate that constructiong the EGP's, which eliminates most of this work by doing record linkage between electronic databases, saves considerable work and money and is an important consideration in resource allocation. However, the work involved in ascertaining the pedigrees could be significantly reduced, if approved by data protection authorities, with a more purposeful, integrated electronic data system. This method allows the counselor more time to review pedigrees, make a risk assessment and organize relevant testing and surveillance according to the family history.

Factors related to the Icelandic population

This study builds on our previous work; a systematic literature review on the use of electronic genealogy databases in genetic health services [38] and a qualitative study exploring counselees' experiences of genetic services using EGP's [39]. Our former study shows that counsellees in general trust the use of EGP's [39]. This trust can perhaps be explained partly by the fact that Icelanders are used to having good access to genealogy data, both in books and online [40] and genealogy is a major interest in the population. Demographic information is readily accessible, and importantly, record linkage is very accurate in Iceland due

to the unique 10-digit personal identification number that is assigned to all newborns and residents. Icelanders are generally ready to participate in genetic studies, even knowing that their samples would be connected to various databases [41]. Therefore, the idea of constructing EGPs with information from electronic databases may be more generally acceptable to Icelanders than citizens of other nations.

Presumed consent

In genetic health services, the counselee gives information about other family members, usually without their explicit consent, i.e., the consent is presumed. The information is used for risk assessment on the assumption that there is a minimum risk of harm and that the assessment could benefit the counselee and indirectly other family members. Genetic health professionals sometimes obtain relevant health information from preexisting databases for the sole purposes of genetic risk assessment. As an example, The Joint Committee on Medical Genetics in the UK (2011) concluded that health professionals could share clinical information and family history given their duty of confidence [42]. Large databases with comprehensive information based on presumed consent are the foundation of genetic population studies [19, 43–47]. We argue that if it is ethically acceptable to use extensive data on genealogy and disease in research, it should be satisfactory for clinical use as well.

Generating EPG's in other counseling practices

In cost-sensitive healthcare, using EGPs when feasible seems to be the most effective use of resources and provide the best results in cancer genetic counseling. High-quality cancer registries and genealogy databases are necessary to create EGPs in cancer genetic counselling. *In the Nordic countries, both genealogy databases and comprehensive cancer registries are available and could be used similarly as in Iceland. Similarly, Scotland and Ireland have excellent genealogy records and cancer registries* [48, 49]. However, the use of the available data and pedigrees must be legally permissible.

There are 535 listed members in the International Association of Cancer Registries [50]. Registries differ in how comprehensive they are and whether registering individual cases is mandatory. The Nordic countries e.g., have high-quality, compulsory cancer registries and unique personal identification numbers that allow accurate record linkage, and thus have the required conditions for accurate EGP's [51]. Various registries of specific hereditary cancers are available in many countries.

Genealogy databases [52] are becoming increasingly easy to create, e.g. the Veterans Genealogy project with over 22 million records [47]. Additionally, Kaplanis et al., have shown how easy it is to collect millions of profiles from online data to generate population scale pedigrees [53]. Of note, electronic information-sharing, sometimes via social media, has become common in our cultural environment [54]. These developments plus electronic two-way personal medical records between health worker and a patient will facilitate generation of genealogy databases. This also facilitates obtaining accurate cancer information on relatives based on either presumed or informed consent.

Pedigrees and next generation sequencing (NGS)

Next generation sequencing identifies pathogenic variants and variants with unknown significance [55], facilitating accurate genetic counseling. As the effect of the pathogenic variants can be family-dependent, pedigrees can be important when evaluating penetrance, impact and segregation of a PV in the family. Pedigrees are also important in evaluating VUS by examining how well a cancer spectrum in a pedigree fits with cancers known to be associated with pathogenic variants in the particular gene. High-quality pedigrees will, therefore, continue to be very relevant with an increased adaptation of NGS [56].

Implications for practice

In the genetics clinic, the optimal situation is to have access to large and accurate pedigrees constructed with minimum cost. In this study, we show that cancer pedigrees can be ascertained based on data in preexisting genealogy databases and cancer registry. We also show that the efficiency of risk estimates based on pedigrees are mainly dependent on the degree of relatedness. Importantly, the efficiency of risk assessment was improved up to 3° relatedness. Construction of 3° pedigrees with traditional methods is very difficult and time-consuming, and it may be nearly impossible if little or no knowledge is available on relatives. Genetic services are therefore advised to consider if they can generate EGPs locally using available data. Adaption of our, or similar electronic methods, to construct EGP will require careful consideration of the local legal and regulatory environment. Data Protection Laws and regulations may in many cases need to be modified before EGP's can be used in genetic counseling.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Supplementary material

Questions for group 1 and 2 in Study II

1. Why did you go for genetic counselling and what were your ideas about it beforehand?
2. I would like you to ponder about the EGP´s we use for the risk assessment, made with the information from the genealogy database and Cancer Registry. Did you know anything about them beforehand – if it was possible to make them? What were your thoughts about the capability to make such extensive pedigrees?
3. Did you have anything against using EGP´s in the genetic counselling and were you worried about other family member's issues or attitude regarding the extensive information in the pedigree?
4. Do you trust the information in the EGP? Any thoughts?
5. What did you think about also having to give your information for a handmade pedigree?
6. When you had to make decision about the genetic testing, how did you feel about your decision? Describe your feelings during the waiting period.
7. Can you describe your emotions right after and for the first few days after you got the results? What about later?
8. Has the family dynamics and communication changed after the genetic counselling. In what way?
9. Do you think that anyone in your family is suffering from survival guilt? (Survival guilt can be described as when one feels "guilty" when not having a mutation, when others in the family have it).
10. Question 10: This question is a bit complicated and long: What do you think has been well done during the genetic counselling? What do you think can be done better? A) Information before the testing, b) information after the testing, c) anything else? Also, is there anything else you want to share?

Questions for group 3 and 4 in Study II

1. Why did you come for genetic counselling?
2. What ideas had you about the genetic counselling prior to your visit?
3. Did you know anything about EGP´s prior to genetic counselling?
4. Can you tell us about your thoughts when you knew that it was possible to get the extensive information from the electronic databases?
5. Were you against using EGP´s in the genetic counselling?
6. Did you worry about others in the family because of the use of the EGP and the information they contained?
7. What did you think about also having to give your information for a handmade pedigree? (This is only for those who had no relatives that have come before to genetic counselling).
8. Do you trust the information in the EGP? Any thoughts?
9. When you had to make decision about the genetic testing, how did you feel about your decision?
10. The waiting period for the results – can you say something about that?
11. Can you describe your emotions right after and for the first few days after you got the results? What about later?
12. Has the family dynamics and communication changed after the genetic counselling. In what way?
13. Do you think that anyone in your family is suffering from survival guilt? (Survival guilt can be described as when one feels “guilty” when not having a mutation, when others in the family have it).
14. What do you think the genetic counselling has done well?
15. What do you think we can do better?

    a) Information before the genetic testing

    b) Information after the genetic testing

    c) Anything else you want to add?

Introduction letter for participation in Study II

Kynningarbréf fyrir þátttöku í vísindarannsókninni:

Upplifun ráðþega og fjölskyldna þeirra þegar notuð eru rafræn ættartré í krabbameinserfðaráðgjöf

Kæri viðtakandi

Tilefni þessa bréfs er að biðja þig um taka þátt í vísindarannsókn sem hefur að markmiði að kanna langtímaáhrif erfðaráðgjafar vegna krabbameina á einstaklinga og fjölskyldur þeirra.

Ástæða þess að leitað er til þín varðandi þessa rannsókn er sú að þú hefur komið í erfðaráðgjöf vegna krabbameina á Landspítala en allir sem komu í erfðaráðgjöf á skilgreindu og fyrirfram ákveðnu tímabili fá samskonar bréf.

Rannsóknin er hluti af doktorsverkefni Vigdísar Stefánsdóttur erfðaráðgjafa. Ábyrgðaraðili er Jón Jóhannes Jónsson, yfirlæknir erfða- og sameindalæknisfræðideildar LSH. Símanúmer hans er 543 5032 og 824 5917. Tölvufang hans er jonjj@landspitali.is. Erfða- og sameindalæknisfræðideild er í K-byggingu Landspítala við Hringbraut. Aðrir sem að rannsókninni standa eru nefndarmenn í doktorsnefnd Vigdísar: Óskar Þór Jóhannsson sérfræðingur í krabbameinslækningum á Landspítala, Laufey Tryggvadóttir framkvæmdastjóri Krabbameinsskrár, Hrafn Tulinius prófessor emeritus við Háskóla Íslands og Heather Skirton prófessor við Plymouth háskóla.

Tilgangur og markmið rannsóknarinar eru tvíþætt. Annars vegar sá að kanna hvernig einstaklingar og fjölskyldur upplifa krabbameinserfðaráðgjöf þar sem notuð eru rafræn ættartré og gerðar erfðarannsóknir og hins vegar að leita leiða til þess að bæta þjónustu erfðaráðgjafaeiningar erfða- og sameindalæknisfræðideildar LSH.

Í þátttöku felst eftirfarandi:

- Að senda okkur undirritað meðfylgjandi upplýst samþykki þar sem fram kemur heiti sem þú velur þér á spjallborðinu.
    - EÐA svara í tölvupósti (vigdisst@landspitali.is) og samþykkja þátttöku.

- Að taka þátt í umræðum og svara spurningum á netinu. Útbúið verður spjallborð á netinu sem þátttakendur skrá sig inn á með lykilorði. Þeir sem taka þátt gera það án þess að þeirra rétta nafn komi fram eða að þeir fái að vita nöfn annarra þátttakenda.

- Að taka þátt í umræðum og svara 20 spurningum.

- Á umræðuborðið verða settar fram spurningar sem þátttakendur svara ýmist hver fyrir sig eða í umræðum sín á milli.

- Tímalengdin er að mestu á valdi þátttakenda sjálfra.

Þátttökuskilyrði fyrir rannsókninni eru:

a) Að hafa leitað til LSH vegna erfðaráðgjafar krabbameina á rannsóknartímabilinu.

b) Að geta lesið og skilið íslensku.

c) Að vera orðin 18 ára og sjálfráða.

Útilokunarskilyrði eru:

Engin.

Réttur þinn sem þátttakanda

Þér er ekki skylt að taka þátt í þessari rannsókn og þú getur hætt þátttöku hvenær sem er án útskýringa. Ákveðir þú að hætta þátttöku verður gögnunum sem þú hefur skráð á spjallborðið eytt. Hafnir þú þátttöku mun það ekki hafa áhrif á þjónustu sem veitt er af heilbrigðiskerfinu. Heimilt er að sleppa spurningum ef þú telur þær ekki eiga við þig eða vilt ekki svara þeim. Æskilegt er þó að sem flestum spurningum sé svarað eins nákvæmlega og unnt er til þess að niðurstöður verði sem bestar.

Meðferð gagna

Rannsóknaraðilar skuldbinda sig til að gæta fyllsta trúnaðar varðandi þær upplýsingar sem verður aflað. Farið verður að íslenskum lögum í hvívetna varðandi persónuvernd, vinnslu og eyðingu frumgagna. Einungis rannsóknaraðilar munu hafa aðgang að svörum einstaklinga á spjallborði en umræður veða sýnilegar öllum þátttakendum. Gögn verða geymd án persónuauðkenna. Niðurstöður rannsóknarinnar verða ekki tengdar við nöfn þátttakenda. Eftir því sem best er vitað er þetta í fyrsta sinn sem svona rannsókn er gerð á neti á Íslandi. Spjallborðið er einungis sýnilegt þeim sem boðið er til þess og ekki er hægt að rekja IP tölur þáttakenda.

Áhætta og ávinningur

Ávinningur þátttakenda er enginn. Áhætta þáttakenda er talin lítil en mögulegt er þó að sumum finnist erfitt tilfinningalega að ræða um erfðaráðgjöf, erfðarannsóknir og áhrif þeirra. Þeim sem þess óska býðst aðstoð sálfræðings og erfðaráðgjafa.

Þátttakendur eru ekki sérstaklega tryggðir vegna rannsóknarinnar.

Niðurstöður og birting rannsóknargagna

Niðurstöður rannsóknarinnar verða birtar í doktorsrannsókn Vigdísar en einnig í ritrýndum vísindatímaritum. Engar persónugreinanlegar upplýsingar verða í birtum gögnum.

Rannsóknin er unnin með samþykki Vísindasiðanefndar og tilkynning hefur verið send til Persónuverndar.

Ef þú hefur spurningar um rétt þinn sem þátttakandi í vísindarannsókn eða vilt hætta þátttöku í rannsókninni, getur þú snúið þér til Vísindasiðanefndar, Hafnarhúsi, Tryggvagötu 17, 101 Reykjavík. Sími: 551-7100, fax: 551-1444.

Með fyrirfram þökk fyrir þátttökuna.

_____

Jón Jóhannes Jónsson

Ábyrgðarmaður rannsóknar

The risk score table.

		Numer of individuals in different degrees						Likelihood of having the *BRCA2* PV					
Mut stat	Family size	1°	2°	3°	4°	5°	6°	1°	2°	3°	4°	5°	6°
0	148	9	27	56	84	87	87	0,1	0,2	1,3	1,3	1,3	1,3
1	137	11	43	67	102	137	137	56,2	64,9	70,5	70,3	70,4	
1	297	10	19	50	116	192	247	2	2,3	6,7	3,9	3,8	3,8
0	432	12	37	51	64	86	115	3,3	2,4	2,2	2,1	2,1	2,1
1	617	9	21	32	67	152	313	43,1	62,9	54,2	35,2	32,7	
1	70	10	34	57	70			4	44,8	60,3	60,3		
1	397	12	60	147	223			35,7	56,2	67,9	66,4		
0	445	4	10	36	97	256		0,2	7,6	9,5	6,2	5,7	
0	1046	3	8	21	43	88	145	0,3	1,7	1,5	1,4	1,4	1,4
1	197	4	10	21	48	75	119	0,7	37,2	36,4	36,7	37,1	35,9
1	463	10	20	29	57	166		16,3	24,1	32,8	44	43,8	
0	345	5	10	29	53	104	193	0,2	0,5	0,5	0,4	0,4	0,4
0	427	10	32	84	213	403	290	19,6	4,4	2,8	2,7	2,8	
1	229	7	19	61	107	200	119	2,2	3,6	4,1	2	1,9	
0	100	10	21	45	73	91	93	4,1	2,3	2,1	2,4	2,4	2,4
1	184	8	22	37	64	101	167	2,9	17,1	45,7	56,5	58,3	
0	419	9	23	55	114	195		0,3	2,3	5,9	2,4	2,9	
1	554	5	9	16	30	57	121	1	3	3,6	3,5	2,6	2,2
1	312	9	13	28	54	115	202	0,3	0,8	5,2	5,2	6,2	6,2
0	885	8	12	25	65	195		8,2	7,5	6,7	49,3	52,8	
0	567	19	64	109	202	275	280	1,8	1,5	1,5	1,5	1,5	
0	1966	9	15	26	89	257		7,3	6,4	5,8	5,2	5	
0	149	4	15	27	48	75	131	0,1	1,4	4,9	5,1	4,8	4,8
1	161	12	49	100				63,1	46,6	47,2			
1	338	6	13	55	117	239		7,1	22,5	13,5	31,8	26	
1	463	7	12	34	95	224	311	14,2	27	49,9	37,9	74,8	