A Web-Based Platform Promoting Family Communication and Cascade Genetic Testing for Families with Hereditary Breast and Ovarian Cancer (DIALOGUE Study): Design, Development, and Testing

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Vasiliki Baroutsou

from Athens, Greece

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Approved by the Faculty of Medicine

On application of

First Supervisor	Prof. Dr. Maria C. Katapodi
Second Supervisor	Prof. Dr. Florina Ciorba
Further Advisor	Prof. Dr. Meghan Underhill
External Expert	Prof Dr. Alanna Kulchak Rahm

Basel, 08. August.2023

Prof. Dr. Primo Leo Schär

Dean

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List of Abbreviations

BRCA1	Breast Cancer 1 Gene
BRCA2	Breast Cancer 2 Gene
CI	Confidence Interval
EGFR	Epidermal Growth Factor Receptor
HCP	Health Care Provider
HBOC	Hereditary Breast and Ovarian Cancer
I^2	Statistical Index of Heterogeneity
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homologue
NLP	Natural Language Processing
ODSF	Ottawa Decision Support Framework
PRISMA	Guidelines for preferred reported items for systematic reviews and meta-analysis
SDG	Sustainable Development Goal
WHO	World Health Organization

Schriftliche Erklärung

Ich erkläre, dass ich die Dissertation ´´*A Web-Based Platform Promoting Family Communication and Cascade Genetic Testing for Families with Hereditary Breast and Ovarian Cancer (DIALOGUE Study): Design, Development, and Testing*´´

nur mit der darin angegebenen Hilfe verfasst und bei keiner anderen Universität und keiner anderen Fakultät der Universität Basel eingereicht habe.

Ich bin mir bewusst, dass eine unwahre Erklärung rechtliche Folgen haben kann.

Basel, 10. September 2023 

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Summary

The overall aim of this dissertation is to develop an eHealth intervention to promote family communication and cascade genetic testing among families concerned with Hereditary Breast and Ovarian Cancer (HBOC) syndrome. Within this context an international, multi-centre scientific project entitled "DIALOGUE" was designed that aims to develop (Phase A), and test the feasibility (Phase B) of an intervention within various genetic clinics across Switzerland and South Korea. This dissertation describes only the Phase A, the adaptation of an intervention, a web-based platform designed for families with HBOC to share genetic test results, including usability testing in a sample from Switzerland.

Chapter 1 provides a general introduction to the current field of hereditary cancer and cascade genetic testing, including the current state of eHealth technologies in science. The chapter also includes a short introduction to the prototype developed in the U.S.—as well as a description of the DIALOGUE study. In addition, the chapter summarises the main conceptual models, i.e. the Ottawa Decision Support Framework (ODSF) and the Medical Research Council (MRC) framework. These models are commonly implemented in the development and evaluation of complex interventions. The rational of this dissertation is guided by all of these elements.

Chapter 2 provides a detailed description of the dissertation's specific aims, including the three studies conducted. The articles presented in Chapter 3 describe the methodology and findings of the dissertation. Study I comprises a systematic literature review of previous studies, with a particular focus on HBOC and Lynch syndromes. The literature review identified and synthesised evidence from psychoeducational interventions designed to facilitate family communication of genetic testing results and/or cancer predisposition and to promote cascade genetic testing. A meta-analysis was also conducted to assess intervention efficacy in relation to these two research aims. Our findings highlight the need to develop new interventions and

approaches to family communication and cascade testing for cancer susceptibility. Study II describes the state-of-the-art text mining techniques used to detect and classify valuable information from interviews with study participants concerning determinants of open intrafamilial communication regarding genetic cancer risk. This study had two major aims: 1) to quantify openness of communication about HBOC cancer risk, and 2) to examine the role of sentiment in predicting openness of communication. Our findings showed that the overall expressed sentiment was associated with the communication of genetic risk among HBOC families. This analysis identified additional factors that affect openness to communicate genetic risk. These were defined as "high-risk" factors and integrated into the design and development of the intervention. Study III describes the development of the intervention, a web-based platform designed for families with HBOC to share genetic test results. The platform was developed in line with the quality criteria set by the MRC framework. Being web-based, the platform could be accessed via a laptop, smartphone or tablet. Usability testing was applied to evaluate the prototype intervention which received high ratings on a satisfaction scale. Chapter 4 synthesises and discusses the key findings of all the studies presented in the previous chapter, and addresses study limitations and implications for future research.

Zusammenfassung

Das übergeordnete Ziel dieser Dissertation war die Entwicklung einer eHealth-Intervention zur Förderung der familiären Kommunikation und der kaskadenartigen Durchführung von Gentests bei Familien, die vom erblichem Brust- und Eierstockkrebs (engl. Hereditary Breast and Ovarian Cancer, HBOC) betroffen sind. Die DIALOGUE-Studie ist ein internationales, multizentrisches Projekt zur Entwicklung (Phase A) und Prüfung der Machbarkeit (Phase B) einer Intervention in verschiedenen genetischen Kliniken in der Schweiz und Südkorea. In dieser Dissertation wird nur die Phase A beschrieben, d. h. die Anpassung (" adaptation ") der Intervention, einer webbasierten Plattform, die für Familien mit HBOC entwickelt wurde, um genetische Testergebnisse auszutauschen, einschließlich Tests zur Benutzerfreundlichkeit in einer Stichprobe aus der Schweiz. Kapitel 1 bietet eine allgemeine Einführung in das aktuelle Feld der genetischen Krebs- und Kaskadentests, einschließlich des aktuellen Stands der Wissenschaft in Bezug auf eHealth-Technologien. Dieses Kapitel enthält auch eine kurze Einführung in den Prototyp, der bereits in den USA entwickelt wurde, sowie eine Beschreibung der DIALOGUE-Studie. Darüber hinaus werden die wichtigsten konzeptionellen Modelle zusammengefasst, d. h. das Ottawa Decision Support Framework (ODSF) und das Medical Research Council (MRC) Framework, die üblicherweise bei der Entwicklung und Bewertung komplexer Interventionen eingesetzt werden. All dies führt zu den Überlegungen, die dieser Dissertation zugrunde liegen.

Kapitel 2 enthält eine detaillierte Beschreibung der spezifischen Ziele der Dissertation, einschließlich der drei durchgeführten Studien. Die in Kapitel 3 vorgestellten Artikel beschreiben die Methodik und die Ergebnisse der Dissertation. Studie I umfasst eine systematische Literaturanalyse früherer Studien zur Identifizierung und Synthese von Belegen für psychoedukative Interventionen, die darauf abzielen, die familiäre Kommunikation über die Ergebnisse genetischer Tests und/oder genetischer Kaskadentests zur Krebsprädisposition zu

erleichtern, wobei der Schwerpunkt auf HBOC- und Lynch-Syndromen liegt. Darüber hinaus wurde eine Meta-Analyse durchgeführt, um die Wirksamkeit der Interventionen für diese beiden Zielgrößen zu bewerten. Unsere Ergebnisse unterstreichen die Notwendigkeit der Entwicklung neuer Interventionen und neuer Ansätze für die Kommunikation in der Familie und für Kaskadentests auf Krebsanfälligkeit. Studie II beschreibt modernste Text-Mining-Techniken, die eingesetzt wurden, um wertvolle Informationen zu erkennen und zu klassifizieren, die die offene innerfamiliäre Kommunikation über das genetische Krebsrisiko aus Interviews mit Studienteilnehmern vorantreiben. Diese Studie hatte zwei Hauptziele: 1) Quantifizierung der Offenheit der Kommunikation über das HBOC-Krebsrisiko und 2) Untersuchung der Rolle von Gefühlen bei der Vorhersage der Offenheit der Kommunikation. Unsere Ergebnisse zeigten, dass die insgesamt geäußerte Stimmung mit der Kommunikation über das genetische Risiko in HBOC-Familien zusammenhing. Durch diese Analyse wurden zusätzliche Faktoren identifiziert, die als signifikante Anhaltspunkte für die Offenheit bei der Mitteilung des genetischen Risikos beitragen. Diese wurden als Hochrisikofaktoren definiert und in das Design und die Entwicklung der Intervention integriert.

Studie III beschreibt die Entwicklungsintervention, eine webbasierte Plattform, die für Familien mit HBOC entwickelt wurde, um genetische Testergebnisse auszutauschen. Die Entwicklung der Plattform erfolgte innerhalb der Qualitätskriterien des MRC-Rahmens. Die webbasierte Plattform war über Laptop, Smartphone oder Tablet zugänglich. Zur Bewertung des Prototyps wurde ein Usability-Test durchgeführt, der auf der Zufriedenheitsskala hohe Werte erzielte. Kapitel 4 fasst die wichtigsten Ergebnisse aller im vorangegangenen Kapitel vorgestellten Studien zusammen und erörtert sie, ebenso wie Einschränkungen und Implikationen für die zukünftige Forschung.

Chapter 1

Introduction

1.1. Cancer and Genetics

Globally, cancer is the second largest cause of death after cardiovascular disease, with almost 10 million deaths recorded in 2020 [1]. With 2.26 million cases detected worldwide in 2020, breast cancer is the most common cancer worldwide, followed by lung, colon, prostate and gastric cancers [1]. Cancer is a complex disease influenced by a combination of environmental and hereditary factors [2-5]. Environmental factors may be physical, i.e., ultraviolet light, ionising radiations, and thermal disruption, or chemical, i.e., chemotherapeutic drugs, industrial chemicals and smoking [6]. Researchers estimate that each cell contains around 30,000 different genes [7]. Within each cell, genes are located on chromosomes [8]. Somatic mutations are not found in every cell in the body and therefore they are not inherited. Cancer that occurs because of somatic mutations is called sporadic cancer [6]. In contrast, germline mutations occur in reproductive cells and thus are inherited. Approximately 5-10% of common cancers are associated with hereditary cancer syndromes [9].

1.1.1. Oncogenes, Tumor Suppressor Genes and DNA Repair Genes

Some of the most important genetic factors in cancer are mutations in oncogenes, tumor suppressor genes and DNA repair genes. Oncogenes are genes that are able to encode proteins responsible for promoting tumorigenesis. Proto-oncogenes, which are the normal functioning cellular counterparts of oncogenes, can be altered into oncogenes due to mutation or overexpression [10]. The first human oncogene was discovered in the early 1980s by Bishop and Varmus [11] and, a large number of oncogenes have subsequently been identified [12]. Oncogenes can be classified into numerous categories, including growth factors and their receptors, transcription factors, and signal transduction proteins [13]. Examples of oncogenes include HER2/Neu (also known as ErbB-2), which belongs to the epidermal growth factor receptor (EGFR) family and is amplified in 15% to 20% of breast cancers, leading to increased

expression of the protein gene product [14]. Also, the Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene is an oncogene that encrypts a small GTPase transductor protein and is frequently mutated in pancreatic ductal adenocarcinoma, colorectal cancer and non-small cell lung cancer [15].

Tumor suppressor genes encode proteins that regulate cell growth and prevent tumorigenesis. Mutations in these genes are characteristically spread across the exon–intron boundaries of exon boundaries and can result in the loss of their function, contributing to the development of cancer [16]. Tumor suppressor genes include variants in the Breast Cancer 1 (*BRCA1*) and Breast Cancer 2 (*BRCA2*) genes. This is associated with an increased risk of breast and ovarian cancer (including fallopian tube and primary peritoneal cancers) as well as other cancers, such as prostate cancer, pancreatic cancer, and melanoma [16].

DNA repair genes have evolved elaborate in the recognition and removal of DNA lesions and any defect in these pathways can lead to the accumulation of mutations. Many of these, such as *BRCA1, BRCA2, CHEK1, CHEK2, p53*, work as tumour suppressor genes [17-19]. Mutations in DNA repair genes can be inherited from either the parental or maternal side.

1.1.2. Hereditary Breast and Ovarian Cancer

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is an inherited genetic condition that predisposes individuals to developing breast, ovarian, endometrial and other types of cancer, accounting for about 5-10% of all breast cancer cases and about 2% of all ovarian cancer cases [20]. This condition is predominantly caused by mutations in tumour suppressor genes such as *BRCA1* and *BRCA2*, which normally help to prevent the development of cancer by repairing damaged DNA [16]. Each person inherits one copy of these genes from each of their parents, which are located on chromosome 17 for *BRCA1* and chromosome 13 for *BRCA2*. Hence, each person has two copies of each gene, one from the maternal side and one

from the paternal side, with a total of four copies. [20]. Cancer develops when a second alteration occurs that affects the normal copy of the gene, and *BRCA1* or *BRCA2* genes do not function correctly. However, it is not inevitable that a person will develop cancer. Furthermore, additional genes are associated with breast and ovarian cancer such as *ATM, BARD1, BRIP1, CDH1, CHEK2, MSH2, MSH6, MLH1, PMS2, EPCAM, NF1, PALB2, RAD51C, RAD51D,* and *STK11* [21-24]. Individuals with mutation in *BRCA1* and *BRCA2* genes have a significantly increased risk of developing breast and ovarian cancer, with lifetime risks of up to 72% and 69% respectively compared to the general population. More specifically, a woman's risk of developing breast cancer is increased to 45-72% compared to a lifetime risk of 13% for women in the general population [25]. Females also have an increased risk of ovarian cancer of between 39–58% and 13–29% [26] for *BRCA1* and *BRCA2* by age 70 years respectively, compared to a risk of less than 2% for the general population. Males with mutation in *BRCA1* and *BRCA2* genes also have an increased risk of developing breast cancer of up to 7% compared to a 0.1% risk for the general population (Table 1) [26]. Men with pathogenic *BRCA2* mutations have a higher risk of prostate cancer of about 40%. Males and females with HBOC syndrome may also have an increased risk of other types of cancer, including pancreatic cancer and melanoma [26].

Table 1. Overview of pathogenic variants in *BRCA1* and *BRCA2* genes linked to different types of cancer [2,3]

Cancer	**General Population Risk**	**Lifetime risk with 95% CI**	
		BRCA1	***BRCA2***
Breast (female)	12.9%	55%–72%	45%–69%
Ovarian	2.2%	39%–58%	13.3%–29.0%
Pancreatic	1.7%	1%–11%	0%–17%
Melanoma	2.1%	undefined	undefined
Prostate	12.6%	7%–26%	19%–61%
Breast (male)	0.1%	0.2%–1.2%	1.8%–7.1%

Many studies indicate that the prevalence of *BRCA1* or *BRCA2* mutations varies significantly according to ethnic groups and geographical location [27-30]. Mutations in

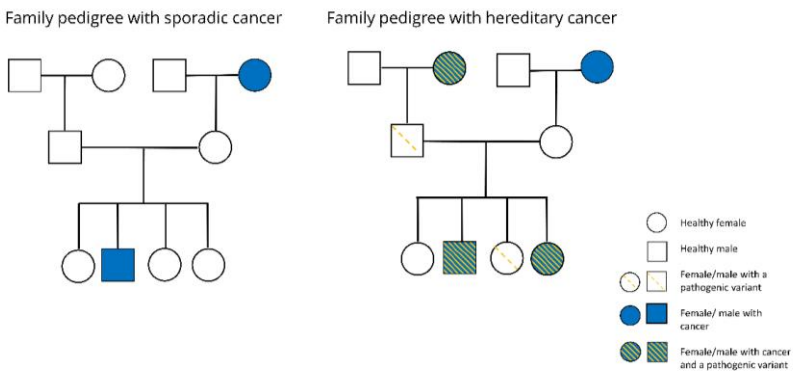
BRCA1 and *BRCA2* genes are often observed in certain ethnic groups such as Jewish Ashkenazi ancestry [31,32]. Individuals with this syndrome are more likely to develop cancer before the age when routine screening becomes available.

1.2. Genetic Counselling and Testing

1.2.1. Genetic Counselling

Genetic counselling is a consultation with a health care provider (HCP) who specialises in genetics and inheritance patterns. The goal of a genetic consultation is to establish the risk of carrying a pathogenic variant and the risk of getting cancer, to enable individuals and families to understand the risk of genetic conditions as well as the available testing, management and treatment options [33]. This involves the use of medical and family histories, genetic testing results and other diagnostic tools to identify the risk of genetic conditions and to provide guidance and support for decision-making. During genetic counselling, genetic specialists assess the risk for having a pathogenic variant and the likelihood of developing cancer based on medical and familial history [33]. Creating a family tree, i.e., pedigree, is an important part of the genetic counselling process, as it helps to visualise the family history and identify patterns of inheritance for genetic conditions. Family pedigrees are diagrams that show the relationships between family members, and can be used to trace the occurrence of a particular peculiarity or condition through multiple generations (Figure 1).

Figure 1. An example of a family pedigree concerning sporadic vs hereditary cancer



1.2.2. Cascade Genetic Testing

Genetic screening has been defined by the European Society of Human Genetics (ESHG) as "*any kind of test performed for the systematic early detection or exclusion of a genetic disease, the predisposition or resistance to such a disease, or to determine whether a person carries a gene variant which may produce disease in offspring*" [34]. Cascade genetic testing is the process of providing genetic counselling and testing to biologically at-risk relatives of individuals with a known pathogenic variant in order to determine if they also carry it [35,36]. This approach allows the identification of individuals at increased risk for certain hereditary conditions, and facilitates timely initiation of risk-management strategies such as surveillance, screenings and prophylactic surgeries. Cascade genetic testing is also particularly important for genetic disorders that are autosomal recessive, as carriers of a pathogenic variant can pass the mutation onto their offspring. Cascade testing such as prenatal diagnosis or preimplantation genetic diagnosis can inform family planning decisions [37].

Cascade genetic testing has been shown to be critical and cost-effective, as it allows the targeted testing of at-risk individuals rather than widespread population screening [38-42]. It is almost 100% reliable and cost-effective because it is now known which gene is responsible and where the exact mutation is located in that gene. This approach can also improve adherence to screening and risk-reducing interventions, as individuals who are aware of their increased risk may be more motivated to engage in risk management strategies [40]. Cascade genetic testing clearly has the potential to improve the efficiency of healthcare resource utilisation [42,43]. For instance, individuals who get tested negative for a familial pathogenic variant can be excluded from intensive screening and risk-reducing interventions without over treating relatives as the risk of developing cancer is not significantly higher than the general population [43].

1.3. Family Communication and Disclosure of Genetic Results

Disclosure of genetic results is subject to several ethical and legal concerns, mainly regarding privacy, confidentiality and moral responsibility [44-47]. According to the Swiss Federal Law on Human Genetic Testing, a proband has the right to know and the right to refuse information about their genetic status. Health care professionals convey the result of the test to the proband after obtaining his or her express consent [48]. However, they cannot disclose genetic test results to other biological relatives and are legally bound to respect the patient's right to confidentiality regarding their genetic information. In such cases, the proband often accepts the burden of disclosing their potential genetic risk to their biological relatives. Probands are usually supported in these efforts by their genetic counsellor who can assist with drafting a letter that can be sent to their relatives [49,50]. Although disclosure of genetic results has many benefits, it may have a psychological impact on probands and their relatives [51-58]. Family dynamics may make family communication surrounding genetic risk complex. Disclosure of genetic results may cause anxiety, worry, guilt, and depression. Empirical studies on family communication demonstrates that not all family members are informed of their inherited risk [59-63]. The most common reasons that individuals do not inform their biological relatives are the potential for family conflict caused by the genetic risk information, absence of close family relationships, or the belief that the relative does not need to know [64-67]. However, the duty to inform or the decision not to inform genetically at-risk relatives may also strain family relationships. Studies have shown that uptake of cascade testing and disclosure of genetic risk can also be improved through targeted educational interventions. In the last decades, several studies have introduced the importance of interventions to the uptake of cascade genetic testing [68-74].

1.4. Current Practice in Switzerland

Between 2013 to 2017, Switzerland had nearly 43,000 new cancer cases annually, with breast, prostate, and colorectal cancers contributing about 33% of all incident cases [75]. According to Kraemer et al study, the estimated prevalence of HBOC in Switzerland is around 1 in 500 individuals (0.2%) [76]. Similarly, the prevalence of Lynch Syndrome in Switzerland is not well established. However, it is estimated to be similar to other western countries, with a prevalence of 2% to 3% [77].

Swiss law contains specific provisions on genetic testing in humans. According to the Federal Law on Human Genetic Testing, genetic counselling is required before and after predictive genetic testing by medical genetic specialist who have a qualification in medical genetics (Swiss Society of Medical Genetics) or are members of the Network for Cancer Predisposition Testing and Counseling, of the Swiss Group for Clinical Cancer Research [48]. If the Swiss guidelines for offering genetic testing are met, the costs for targeted testing can be covered by health insurance. Usually, the assumption of costs is obtained before the test. Insurance companies and employers are not informed of the results of genetic testing [48,78]. Insurance companies can request results of genetic tests only in cases where individuals plan to take life insurance policies worth more than 400,000 Swiss francs [48].

1.5. eHealth Technologies

1.5.1. Application of eHealth Technologies

E-health encompasses a range of different practices and the use of different means, i.e., telemedicine, mobile health (mHealth), electronic medical records (EMRs) and health information exchange (HIE) [79]. E-Health has the potential to improve healthcare delivery by leveraging technology to improve access, efficiency and quality of healthcare. E-health technologies such as telemedicine enable patients to access healthcare services regardless of their location by increasing their accessibility and reducing the need for travel [80,81]. This is

particularly important for individuals with limited time or those who live in rural or remote areas with limited access to healthcare services. The use of EMRs and HIE systems enable healthcare providers to access and share patient´s information easily by minimising the probability of errors [82,83]. Furthermore, storing patient health information digitally allows unlimited access to it, which can be beneficial for public health surveillance. Recent examples of disease outbreaks have confirmed that digitalisation allows health experts to provide rapid responses and better management of public health crises [84-86]. Overall, it can lead to better care coordination and improved outcomes. MHealth-related solutions delivered via mobile devices, such as smartphones and tablets, have also been launched globally increasing accessibility, efficiency and personalisation [87,88].

In 2012, the European Commission has adopted the eHealth Action Plan 2012–2020 which identifies eHealth as a more personalised, targeted healthcare that can be more effective and efficient, while also facilitating equality and patient empowerment [89]. Similarly, the World Health Organization (WHO) underlines the important role of digital technologies in medicine with the Action Plan for the Global Strategy on Digital Health [90]. The Action Plan outlines the importance of proper use of digital health technologies to support the achievement of the health-related Sustainable Development Goals (SDG) and to access universal health coverage at all levels [90]. WHO defines e-Health as "*cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research*" [91].

In Switzerland, the use of telemedicine has received wide acceptance in several fields of medicine and has been broadly supported by almost all health insurance companies [92]. In 2017, the Swiss eHealth strategy which supports a national electronic health record system for the country, became effective in Switzerland [93].

1.5.2. The Current Landscape for Digital Health Solutions in Genomics

Genomic medicine is a multidisciplinary field that aims to improve human health through the application of genomic research findings to clinical care. E-Health has also found a ground in the field of genomics, incorporating tools to improve health literacy, empower patients' decision-making and facilitate patient-centered care delivery [68,94-96]. Digital interventions have gradually been adopted to support pre-test counselling, improve knowledge in genetics and reduce decisional conflict [94-96]. Other examples of digital health tools in genetics include family tree software, hereditary cancer risk assessment tools and computer-based facial dysmorphology analysis tools [97-102]. Extant evidence on patient experience suggests a relatively high level of acceptability of pre-test counseling tools from a range of contexts, with the majority of patients recommending and reporting high levels of satisfaction with these tools. However, most of the digital tools are focused on the pre-test phase and none cover the complete genetic testing trajectory from testing to cancer surveillance [103].

1.6. Frameworks to Guide Intervention Development

1.6.1. Ottawa Decision Support Framework

The Ottawa Decision Support Framework (ODSF) was developed to guide decision-support interventions aimed at preparing patients and HCPs for shared decision-making [104]. In particular, the ODSF is an evidence-based framework that conceptualises the support needed by patients, their families and their HCPs for health decisions that require consideration of extensive amounts of information. It guides HCPs in assessing a patient's decisional needs, while providing decision support interventions and evaluating the effects of these on decisional outcomes [105-107]. The ODSF comprises a variety of theories such as prospect theory, decision analysis, reasoned action, decisional conflict, social support and self-efficacy theory [104,108-112].

1.6.2. Medical Research Council Framework

The Medical Research Council (MRC) framework is a widely used approach to developing and evaluating complex interventions in healthcare research. It was first introduced in the 1990s and has since been refined and expanded [113-115]. The MRC framework consists of four stages: development, feasibility and piloting, evaluation and implementation. The first stage involves developing a clear understanding of the intervention's rationale and identifying its key components. This stage involves conducting a thorough review of the existing literature and engaging with stakeholders, such as patients and healthcare providers, to gather input and feedback. Also, introducing a theory or developing an appropriate theory can improve the intervention. Before implementing and evaluating the intervention, it is also possible to model an intervention and clarify any details about the design. Feasibility and piloting is the second stage of the framework and involves testing the feasibility and acceptability of the intervention. This stage helps to identify any practical issues or barriers that may need to be addressed before conducting a larger study. The third stage involves conducting a thorough evaluation of the intervention. The fourth stage involves disseminating the intervention and the results of the study. This stage may involve decision-makers and policy-makers to ensure that interventions and their results are accessible and comprehensible and implemented in a practical and effective way [113].

The MRC framework is a useful tool for healthcare researchers because it provides a structured approach to developing and evaluating complex interventions. By following the framework's guidelines, researchers can ensure that their interventions are developed and evaluated rigorously and systematically. This can improve the chances of success and increase the likelihood of the intervention being adopted into routine clinical practice.

1.7. Knowledge Gaps and Rational of the PhD Dissertation

HBOC syndrome is a multigenerational inherited disorder in which multiple members of a family may be affected. Studies [102] suggest that disclosure of genetic results and post-disclosure variables, such as emotional reactions by at-risk relatives for *BRCA1* and *BRCA2*, are significant to maximising genetic testing uptake. Notably, a study conducted by Zhao et al. [116] reveals that only a few effective interventions promoting family communication about inherited cancer risk exist, most of which are conducted with women. The study confirms that there is significant heterogeneity in approach.

Given the lack of well-developed digital health tools to assist individuals with genetic predisposition to cancer to effectively communicate genetic information to their relatives, there is an urgent need for the development and evaluation of interventions in a broader set of contexts. In Switzerland, no relevant digital health tools exist to support communication of genetic information among HBOC families. The purpose of this study was to create an effective and culturally sensitive digital health intervention that could enhance the communication processes among HBOC families and promote cancer predisposition cascade genetic testing.

1.8. Family Gene Toolkit

The Family Gene Toolkit is a web-based intervention designed to assist female carriers of pathogenic *BRCA1* and *BRCA2* variants in disclosing their genetic testing results to biological relatives while providing decisional support for cascade testing. The Family Gene Toolkit was tested within the U.S. population. It was delivered using two live webinars and a follow-up phone call. The webinars were facilitated by genetic counsellors and an oncology nurse and covered topics related to cancer genetics, counselling and testing, active coping strategies and effective communication of genetic testing results. The results of the intervention showed high acceptability, usefulness, participant satisfaction and efficacy [117]. However, the

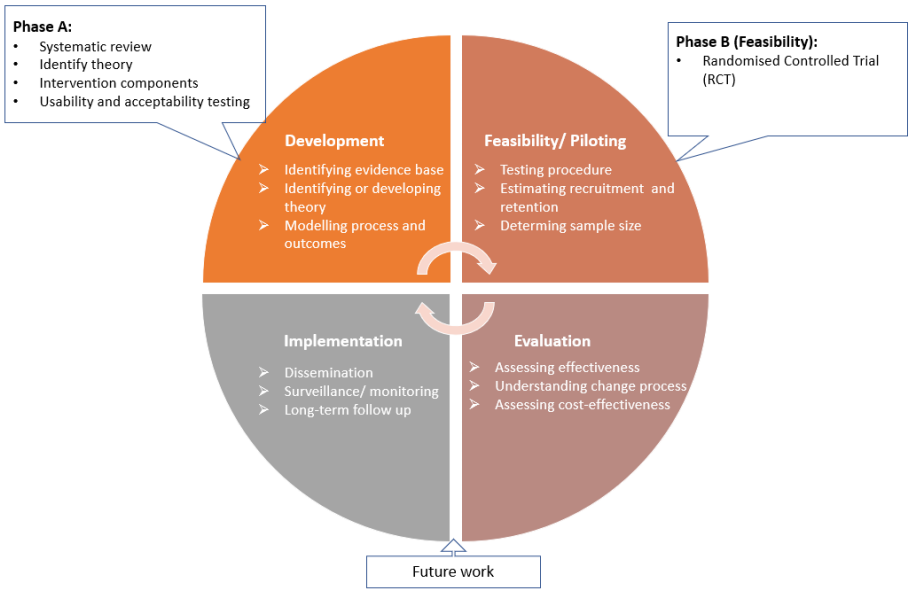
feasibility of up-scaling the delivery to clinical practice was challenged by several issues. Scheduling live webinar sessions in different time zones of probands and clinicians could limit the success of this approach. The provision of live sessions by HCPs was an expensive task and raised questions about its cost-effectiveness. There was also a lack of consensus about the optimal time frame for intervening, indicating variability in preferences due to personal life circumstances.

In summary, the Family Gene Toolkit was a sophisticated intervention for enhancing communication and providing decisional support in *BRCA1 and BRCA2* families. However, further adaptations are needed to address feasibility and cost-effectiveness issues and to create an improved version that can be implemented in clinical practice.

1.9. Positioning the DIALOGUE study

This dissertation is embedded within the DIALOGUE project, a project that was designed at the University of Basel in Switzerland in collaboration with Yonsei University in South Korea. The DIALOGUE is a multistep science project that currently involves several genetic clinics across Switzerland and South Korea in order to support communication of genetic test results in HBOC families [118]. The DIALOGUE project involves two phases: A) the development and testing of a web-based platform, including its usability and acceptability testing; and B) the feasibility of the intervention by evaluating the effectiveness of the digital health intervention on primary (communication of genetic test results to relatives and cascade genetic testing uptake) and secondary (psychological distress, genetic literacy, coping, and decision making) outcomes. Figure 2 presents the different steps of the DIALOGUE study. The DIALOGUE study is in line with the MRC framework developing and evaluating complex interventions guidance. In Chapter 3, the three studies present phase A which encompasses the development process. Each step, from the adaptation of the prototype to usability testing with real users, is described.

Figure 2. MRC framework for designing and evaluating complex interventions



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Chapter 2

Aims and Objectives of the PhD Dissertation

2.1. Aims and Objectives

The overall aim of this dissertation is to develop an eHealth intervention for families with BRCA mutation-associated HBOC syndrome to promote family communication and cascade genetic testing. In order to develop the intervention three studies were conducted. The specific aims of the three studies are:

- *Study I*: To identify interventions that were designed to facilitate disclosure of cancer genetic testing results and/or cascade genetic testing among blood relatives concerning inherited cancer predisposition.
- *Study II*: To identify important components that predict the level of openness of intrafamilial communication about genetic cancer risk associated with HBOC syndrome.
- *Study III*: To describe the development of a web-based platform designed for families with HBOC, and to evaluate the platform's acceptability, usability and participant satisfaction.

In *Study I*, a systematic literature review and a meta-analysis were conducted to explore the availability and efficacy of empirically tested interventions. A comprehensive search and screen procedures was conducted to identify interventions designed to facilitate family communication of genetic testing results and/or cascade genetic testing for HBOC and LS.

In *Study II*, narrative data from in-depth interviews were pre-processed in order to quantify openness of communication about HBOC cancer risk and to examine the role of sentiment in predicting openness of communication. Text mining was applied to analyse text data and extract features for building a statistical model.

In *Study III*, think-aloud interviews with real users have been conducted to refine the prototype and test the usability of the web-based platform. We developed the intervention in line with the quality criteria set by the ODSF, which is an evidence-based framework designed to support the development of intervention.

Chapter 3

List of Publications

This chapter summarises the main findings of the three publications based on the aims outlined in Chapter 2 and discusses the strengths and limitations of each publication in detail. The development of the web-based platform consisted of three key phases.

3.1. Study I: Interventions Facilitating Family Communication of Genetic Testing Results and Cascade Screening in Hereditary Breast/Ovarian Cancer or Lynch Syndrome: A Systematic Review and Meta-Analysis

Authors:

Vasiliki Baroutsou[1], Meghan L. Underhill-Blazey[2], Christian Appenzeller-Herzog[3] and Maria C. Katapodi[1]

[1] Department of Clinical Research, Faculty of Medicine, University of Basel, Basel, Switzerland

[2] School of Nursing, Wilmot Cancer Institute Hereditary Cancer Program, University of Rochester, Rochester, NY 14642, USA

[3] University Medical Library, University of Basel, Basel, Switzerland

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Systematic Review

Interventions Facilitating Family Communication of Genetic Testing Results and Cascade Screening in Hereditary Breast/Ovarian Cancer or Lynch Syndrome: A Systematic Review and Meta-Analysis

Vasiliki Baroutsou [1], Meghan L. Underhill-Blazey [2], Christian Appenzeller-Herzog [3] and Maria C. Katapodi [1,*]

[1] Department of Clinical Research, Faculty of Medicine, University of Basel, 4055 Basel, Switzerland; vasiliki.baroutsou@unibas.ch
[2] School of Nursing, Wilmot Cancer Institute Hereditary Cancer Program, University of Rochester, Rochester, NY 14642, USA; Meghan_Blazey@URMC.Rochester.edu
[3] University Medical Library, University of Basel, 4051 Basel, Switzerland; christian.appenzeller-herzog@unibas.ch
* Correspondence: maria.katapodi@unibas.ch; Tel.: +41-61-207-04-30

Simple Summary: In general, 5–20% of all cancers are due to pathogenic variants in cancer genes that are passed down in the family. It is recommended that blood relatives of individuals with such a pathogenic variant have genetic testing, to identify if they also carry the same variant. This information will help their healthcare providers to make individualized cancer screening and prevention plans. However, only around 30% of at-risk relatives have genetic testing, presumably due to a lack of communication about inherited cancer genes among family members. In this paper, we identified interventions that were designed to improve family communication about hereditary cancer and/or genetic testing among at-risk relatives for two common hereditary cancer syndromes. We analyzed the components of these interventions and synthesized outcomes with statistical methods. Although we identified 14 eligible studies, there are still many unanswered questions about clinical and research implications with diverse samples to be addressed in future studies.

Abstract: Evidence-based guidelines recommend cascade genetic testing of blood relatives of known Hereditary Breast and Ovarian Cancer (HBOC) or Lynch Syndrome (LS) cases, to inform individualized cancer screening and prevention plans. The study identified interventions designed to facilitate family communication of genetic testing results and/or cancer predisposition cascade genetic testing for HBOC and LS. We conducted a systematic review and meta-analysis of randomized trials that assessed intervention efficacy for these two outcomes. Additional outcomes were also recorded and synthesized when possible. Fourteen articles met the inclusion criteria and were included in the narrative synthesis and 13 in the meta-analysis. Lack of participant blinding was the most common risk of bias. Interventions targeted HBOC (n = 5); both HBOC and LS (n = 4); LS (n = 3); or ovarian cancer (n = 2). All protocols (n = 14) included a psychoeducational and/or counseling component. Additional components were decision aids (n = 4), building communication skills (n = 4), or motivational interviewing (n = 1). The overall effect size for family communication was small (g = 0.085) and not significant (p = 0.344), while for cascade testing, it was small (g = 0.169) but significant (p = 0.014). Interventions show promise for improving cancer predisposition cascade genetic testing for HBOC and LS. Future studies should employ family-based approaches and include racially diverse samples.

Keywords: Tier-1 genetic conditions; intervention efficacy; randomized controlled trials; psychoeducational interventions

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1. Introduction

Breast, colorectal, ovarian, and endometrial cancers constitute around 30% of newly diagnosed cancer cases [1,2]. In general, it is considered that approximately 5–10% of all breast and approximately 20% of ovarian cancer cases are due to an inherited pathogenic variant associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, with some estimates being higher for selected patients and families [3–7]. Lynch Syndrome (LS) accounts for 2–5% of colorectal and endometrial cancer cases and is associated with increased risk for several other malignancies, including pancreatic, gastric, ovarian, and small bowel cancer [8–10]. Individuals with HBOC or LS are more likely to develop cancer, usually before the age of 50, at which routine cancer screening applies [11].

Germline pathogenic variants associated with HBOC and LS are inherited in an autosomal dominant manner. First- and second-degree relatives and first cousins have 12.5–50% probability of inheriting the respective cancer predisposition. The availability of cancer genetic services (counselling and testing) for "actionable" hereditary cancer syndromes, such as HBOC and LS, is a significant milestone for effective cancer prevention and control [12,13]. When a pathogenic variant is identified, relatives can be tested with 100% accuracy. Intensive surveillance starting at a younger age, prophylactic surgery, and chemoprevention can lower the risk of primary and secondary cancers, reducing morbidity and mortality for those who carry the pathogenic variant and medical and insurance costs for those who test negative [14]. The Centers for Disease Control and Prevention (CDC), Office of Public Health Genomics, USA, issued evidence-based recommendations for genetic testing in affected individuals and unaffected relatives when there is a known family history of HBOC, personal history of *BRCA*-related cancers, and LS-related colorectal cancer [15,16]. Cascade genetic screening means identifying and testing blood relatives of mutation carriers to determine if they also carry the pathogenic variant and propose risk management options [13].

Despite calls to action for HBOC and LS cascade genetic testing, there are systemic barriers to its implementation. Privacy laws worldwide prohibit healthcare providers from revealing genetic information to anyone except the tested individual. The responsibility to share genetic test results lies almost exclusively with the mutation carrier, who has the right not to disclose this information [17,18]. This communication strategy has significant limitations in both ensuring contact with the appropriate people and the transmission of accurate information [19,20]. Potential benefits of genetic testing are not being effectively communicated through family networks, leading to more than 50% of at-risk individuals not using genetic services [21]. Nevertheless, a family-based approach in communicating hereditary cancer risk is advantageous because it is not limited only to those in contact with the healthcare system but may reach relatives through the social functions already existing within the family network [22]. Interventions that support mutation carriers during the disclosure of genetic test results can reduce their psychological distress and provide relatives with accurate and credible information about cascade genetic testing. Technology-enabled education is not inferior to face-to-face genetic consultations [23–25], while it increases access to services and cost-effectiveness [26–28].

In summary, interventions could facilitate communication and access to genetic information and services for families with hereditary predisposition to cancer. The purpose of this study was to identify and synthesize outcomes of psychoeducational interventions designed to facilitate family communication of genetic testing results and/or cancer predisposition cascade genetic testing, with a focus on HBOC and LS.

2. Materials and Methods

2.1. Literature Extraction

This systematic review is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [29]. The search strategy was designed to identify available randomized controlled trials (RCTs) that assessed the efficacy of interventions that included family communication of genetic testing results and/or cancer predisposition cascade genetic testing as a primary or a secondary outcome. Several criteria were used to select eligible studies: (1) the intervention had to involve mutation carriers, or blood relatives of known mutation carriers, or individuals with a strong family history indicative of HBOC or LS; (2) the intervention had to include a psychosocial, cognitive, or behavioral component; and (3) participants had to be randomly assigned to either the intervention or the control arm. The search strategies were developed by an information specialist (C.A.-H.) and peer-reviewed by a second information specialist (Dr. Hannah Ewald). The electronic databases Embase via Elsevier, Medline and PsycInfo via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using text word synonyms and database-specific subject headings for hereditary cancer, genetic counseling/screening, and interventions to promote family communication and/or genetic counseling/screening. For Embase, Medline, and PsycInfo, common RCT filters were applied [30,31] (last search June 15, 2020; Appendix A). References were exported to Endnote X9 [32] and de-duplicated using the Bramer method [33]. Queries were limited to studies published in the English language. Studies published in languages other than English were excluded due to time and resource limitations.

2.2. Screening, Inclusion, and Exclusion Criteria

Each research article was screened by title and abstract by at least two members of the research team (VB, MCK, MUB, and Dr. Tarsha Jones), who made an independent assessment among the full-text articles evaluated for eligibility. Disagreements were resolved through consensus. Papers with no original data, such as guidelines, study protocols, and reviews, were excluded. Only original articles assessing family communication and/or cancer predisposition cascade genetic testing for HBOC and LS were included. Studies involving patients with other types of cancer and/or other genetic conditions were excluded to reduce the heterogeneity of the studies analyzed. Full-text analysis was performed on 102 records selected during title and abstract screening.

2.3. Data Extraction

Data from eligible articles were extracted and were recorded using Covidence software [34]. We recorded the main author, year of publication, country of origin, study design, demographics of study population, and outcomes. Intervention content and components were also analyzed. In one case, specific intervention characteristics were obtained from an earlier publication that was identified from the reference list of the original article. When authors used more than one instrument to measure the same outcome, extracted data were reported from the most relevant instrument, which was determined by consensus after reviewing wording of each item. A similar procedure was followed when authors reported findings on multiple subscales of instruments, rather than on global scores. The Cochrane Risk of Bias (RoB) tool [35] was used to assess risk of bias in sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources. Based on the RoB tool, potential sources of bias were characterized as “low”, “high”, or “unclear” for each included study. Calculation of effect sizes was based on outcome data from the experimental and control arms of each study.

2.4. Statistical Analyses

Outcome data were synthesized using meta-analytic methods [36,37]. The standard mean difference, or the effect size between intervention and control groups, was calculated using Hedges' g unbiased approach, which is similar to Cohen's d statistic [38]. Calculation of effect sizes was based on means, standard deviations, difference in mean scores, odds ratios, p-values, and sample sizes of the groups. Data were statistically pooled by the standard meta-analytic approach, meaning that studies were weighted by the inverse of the sampling variance. For studies that did not report the coefficient of correlation (r) between pre- and post- intervention scores, we used Rosenthal's conservative estimate of $r = 0.7$ [39]. The random effects model was used as a conservative approach to account for different sources of variation among studies. The Q statistic was used to assess heterogeneity among studies. A significant Q value indicates lack of homogeneity of findings among studies [36,37]. Due to the small number of studies, we were not able to conduct moderation analyses and examine the effects of intervention characteristics on outcomes. We assessed for publication bias using the Egger's t-test with significance values based on one-tailed p-values [36,37]. Publication bias can occur because (i) journals are more likely to publish studies with positive results, (ii) authors are less likely to report negative or inconclusive outcomes in multi-outcome studies, or (iii) studies with smaller sample sizes need to detect larger effects to be published than studies with larger samples.

Comprehensive Meta-Analysis V.3© Software [40] was used for statistical analyses. Reported statistics conform to the PRISMA Statement [29]. Based on conventional standards, effect sizes of $g = 0.20$, 0.50, and 0.80 were considered small, medium, and large, respectively [38].

3. Results

Initial queries identified 2767 articles from all databases and search methods after removing duplicates (see Figure 1 for details). We identified 14 studies that met all inclusion criteria and were included in the narrative synthesis. However, the meta-analysis was based on data extracted from 13 RCTs published between 2002 and July 2019 that assessed family communication and/or cascade genetic testing for HBOC and/or LS among outcomes. Outcomes from one RCT were not included in the calculation of pooled effect sizes due to missing data [41]. Studies measured outcomes at various time points, ranging from one week to 14 months post-intervention. The median time for post-intervention assessments was three months. When studies assessed outcomes multiple times, we used data from the time point closer to three months. For outcomes assessed only once, we used data from that time point. Quality assessment indicated that lack of participant blinding was the most common source of bias among included studies (Table S1).

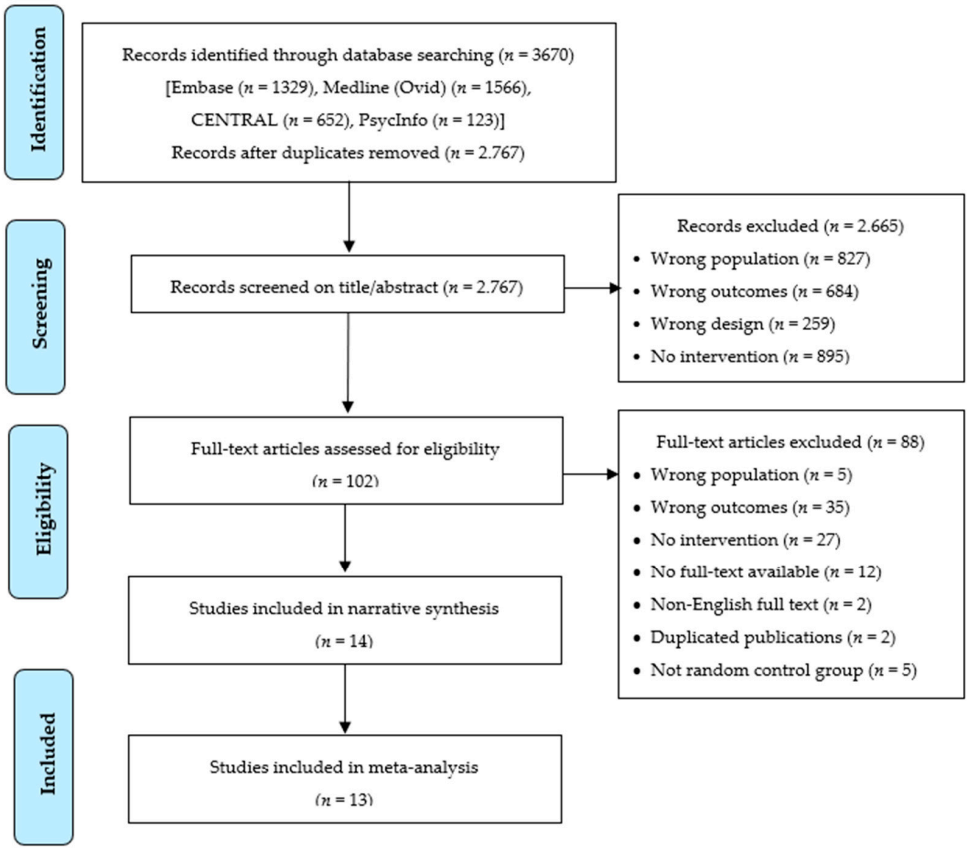

Figure 1. PRISMA flow diagram for study selection.

3.1. Characteristics and Content of Interventions

Most interventions targeted HBOC (n = 5) [41–45], followed by interventions that targeted multiple hereditary syndromes, including both HBOC and LS (n = 4) [46–49], colorectal cancer associated with LS (n = 3) [50–52], or ovarian cancer (n = 2) [53,54]. Characteristics and content of the identified studies are described in Table 1. All protocols (n = 14) included a psychoeducational and/or counseling component; n = 5 included skills building; n = 4 included a decision aid; and n = 1 focused on motivational interviewing. The psychoeducational components focused on genetics and hereditary cancer risk, prevention and risk management options, and impact on family and/or family communication. The counseling component was designed to enhance coping, problem solving, self-efficacy, and clarifying personal values. Less often, protocols included resources for participants accessing genetic services (n = 3) or additional training and resources for clinicians to enhance referral for genetic counseling (n = 1). Most interventions were theoretically driven (n = 9); Buckman's six-step strategy for "breaking bad news" was the most frequently mentioned theoretical approach, followed by the Ottawa Decision Support framework. Finally, most studies (n = 9) reported various outcomes related to intervention fidelity. Table 1 provides brief details about the content of controls and/or usual care of the identified RCTs.

Table 1. Characteristics of study interventions.

Author/Year	Syndrome/Outcomes *	Intervention	Control	Theoretical Framework	Mode of Delivery	Intervener	Dose	Duration	Fidelity
Bodurtha et al., 2014 [46], KinFact	Both/Communication	Booklet (27-page personalized information for family communication about cancer and cancer genetics)	Pamphlet—breast, colon cancer risks, screening, services	Health Belief Model; Buckman's 6-step strategy Breaking Bad News	Booklet/Pamphlet Face-to-face One-on-one	Trained Personnel	Once	20-min	NR~
Dekker et al., 2015 [50]	CRC **/Communication Cascade testing Knowledge	Website (CRC risk, risk calculators, decision aid) + Brochure (familial CRC risk, prevention) + 30-min Clinician education + Referral cards (criteria)	Usual care	NR	Website + Brochure	Self-administered	NR	NR	67% used website
Eijzenga et al., 2018 [47]	Both/Communication Knowledge Perceived risk	Standard genetic counseling + Phone call—motivational interviewing (enhance family communication, knowledge, motivation, self-efficacy, solutions)	Standard genetic counseling	Motivational interviewing	Telephone	Psychosocial Worker	Once	NR	33% random check interview recording
Hodgson et al., 2016 [48]	Multiple incl. HBOC + LSCascade testing	Enhanced genetic counseling over telephone with emphasis on family communication + Pedigree	Pedigree	NR	Telephone One-on-one	Genetic Counselors	2-3 times	12 months	NR
Katapodi et al., 2018 [42] Family Gene Toolkit	HBOC/ CommunicationKnowledge Perceived risk	Webinar (power point, live presentations about cancer genetics, risk, genetic counseling, coping, family communication) + Decision aid + Communication skills building + Phone call	Wait-listed control	Theory of Stress and Coping	Web-based + Telephone Face-to-face One-on-family + One-on-one	Genetic Counselor + Master's Oncology Nurse	2 webinars 45–60 min per webinar + 20 min phone call	3 weeks 110–140 min	71% completion rate

Table 1. *Cont.*

Author/Year	Syndrome/Outcomes *	Intervention	Control	Theoretical Framework	Mode of Delivery	Intervener	Dose	Duration	Fidelity
Loader et al., 2002 [51]	CRC/Cascade testing	Brochure (hereditary cancer, risk factors, prevention, genetic testing, family communication) + Invitation to counseling + Letter genetic counseling	Physician education (CRC risk, information about referrals to counseling)	NR	Brochure + Letter Face-to-face One-on-one	Mail, Self-administered	Once	NR	47% counseled
Lobb et al., 2002 [43]	HBOC/Anxiety Depression	Audio-recording of genetic consultation	Usual care	NR	Audiotapes	Self-administered	NR	NR	51% listened tape once
McInerney-Leo et al., 2004 *** [41]	HBOC	Family education + Problem Solving Training (expectations, concerns, feelings) for task- and emotional-focused coping and problem solving + Telephone interview	Family education + Client-centered counseling + Telephone interview	Cognitive–Behavioral Theory	Face-to-face or TelephoneOne-on-family + One-on-one	Trained Provider	Once	60 min	Standardized protocol
Montgomery et al., 2013 [44]	HBOC/Communication Depression	Counseling (risk factors, personal risk, pedigree) + Communication skills building (who, how, extent willing to know, share results, emotional responses, resources)	Wellness education (nutrition, exercise) + List of nutrition websites	Buckman's 6-step strategy Breaking Bad News + Theory of Planned Behavior	Face-to-face One-on-one	Genetic Counselor + Research Staff	NR	NR	NR
Niu et al., 2019 [52]	CRC/Communication Anxiety Depression	Genetic counseling + Clinical exome sequencing (21 to >50 actionable genes) + Additional genetic information	Counseling + Tumor testing OR panel testing + Review family history	NR	Telephone or Face-to-faceOne-on-one	Genetic Counselor or Geneticist	NR	NR	NR

Table 1. *Cont.*

Author/Year	Syndrome/Outcomes *	Intervention	Control	Theoretical Framework	Mode of Delivery	Intervener	Dose	Duration	Fidelity
Roshanai et al., 2009 [49]	Both/Communication Knowledge Anxiety DepressionPerceived risk	Genetic counseling + Extended meeting nurse specialist (pedigree, cancer risk, 6-step strategy for family communication) + Pamphlet + Videotape of counseling + Copies pedigree, medical records	Genetic counseling + Short meeting nurse specialist (intention inform relatives) + Videotape of counseling	Buckman's 6-step strategy Breaking Bad News	Clinical settingFace-to-face One-on-one	Genetic Counselor + Nurse Specialist	Once	NR	19-item survey counselees
Tiller et al., 2006 [53]	Ovarian Cancer/Knowledge Anxiety	Decision aid (booklet on risk factors, family history and risk, genetic testing, prevention) + Values clarification	General education pamphlet	Ottawa Decision Support Framework	Pamphlet	Self-administered	Once	NR	88% review booklet
Vogel et al., 2019 [54] mAGIC	Ovarian cancer/Communication Cascade testing Knowledge	Mobile app tailored messages (motivation, positive feedback, triggers) + Videos (genetic counseling, testing, personal health, cancer genetics, self-care, self-efficacy) + Training how to use mAGIC + Pamphlet (ovarian cancer risk, counseling, services)	Usual care + Pamphlet (hereditary cancer risk, counseling, services)	Health Belief Model + Fogg Behavioral Model of Mobile Persuasion	Mobile app + Pamphlet	Self-administered	Once per day10–15 min per day	7 days70–90 min	NR
Wakefield et al., 2008 [45]	HBOC/Cascade testing Knowledge	Decision aid (40-page booklet, hereditary cancer, testing, impact on individual and family) + Values clarification	Pamphlet (4-page education about HBOC genetic testing)	Ottawa Decision Support Framework	Brochure/Pamphlet	Self-administered	NR	NR	70% intervention read booklet

* Study outcomes included in the meta-analysis. Individual studies may have assessed additional outcomes that were not included because it was not possible to calculate effect sizes. ** CRC, Colorectal cancer. *** Intervention is not included in calculation of effect sizes due to missing data. ~ NR = Not Reported.

3.2. Intervention Mode of Delivery and Intervener

Few protocols (n = 2) targeted implicitly or explicitly more than one member from the same family. Most interventions (n = 8) required extensive counseling sessions with a healthcare provider, often specified as a genetic counselor/geneticist, Master's-prepared nurse, or psychosocial worker. Counseling involved mostly one-on-one sessions and was delivered entirely or partially over the telephone (n = 7). Interventions were developed either exclusively as booklets (n = 3) or included a paper handout as a complementary component (n = 4). Technology-enabled interventions were delivered either via the World Wide Web (n = 2), as a mobile app (n = 1), or included the audio recordings of the counseling sessions (n = 1).

3.3. Intervention Dose and Duration

The dose and duration of "received intervention" was not consistently reported among studies. Most protocols (n = 9) specified a dose of intervention that ranged from 1 to 7 contacts with participants, with an overall duration ranging from 20 to 140 min, over 7 days, 3 weeks, or 12 months.

3.4. Characteristics of Samples

Most studies were conducted in the US (n = 7), followed by Australia (n = 4), the Netherlands (n = 2), and Sweden (n = 1). Table 2 summarizes the sample characteristics of the 14 interventions included in the narrative synthesis. Sample sizes ranged from 24 to 490, with a total of 2968 participants across all studies. Recruitment in most studies (n = 8) was from outpatient settings. Enrollment rates varied from 23% to 96% of those approached, with an average enrollment of 71% across studies. Attrition ranged from 13% to 59%, with an average attrition of 27% across studies. Reasons for attrition were not consistently reported.

Most studies (n = 10) included over 50% female participants, the majority including 100% females (n = 7); few focused exclusively on ovarian cancer (n = 2); the remaining focused on HBOC (n = 5). A larger proportion of males was included in studies focusing on colorectal cancer and only one included a majority of male participants [50]. Race was not consistently reported, especially for studies conducted outside the US (n = 7). Studies that reported participants' race included only or primarily White individuals, and only one included 59% Black individuals [46]. The reported mean ages ranged from 33 to 61. Participants were mostly well-educated among the studies that reported educational level (n = 7).

Most studies (n = 11) included both affected and unaffected individuals. Four studies reported whether participants had a pathogenic variant associated with cancer; all others focused on personal and/or family history of cancer to describe risk.

Table 2. Sample characteristics.

Author/Year Country	Setting	Sample N	Cancer Type/Stage/PDx *	Carrier of PV ** or FH ***	Age Mean ± SD or Range	Sex	Race	Education% ≤ HS^	Enrollment	Attrition
Bodurtha et., al 2014 [46], USA	Outpatient	490	Stage/type NR: HBOC or CRC risk	75% FDR^{+} any cancer 10% FH breast or CRC	33.4 ± 11.9	100% female	59% Black 33% White 8% Other/Multiple	41% 16% missing	61%	42%
Dekker et al., 2015 [50], Netherlands	Hospital	384	100% CRC I: 86.4% Stage I–III C: 86.55 Stage I–III	I: 9% high risk C:13% high risk	I: 60 ± 8.2 C: 59 ± 7.5	I: 71% male C: 66% male	NR~	NR	55%	59%
Eijzenga et al., 2018 [47], Netherlands	Hospital	305	Stage/type NR; HBOC or CRC risk I: 70% PDx C: 73% PDx	I: 9% PV C: 12% PV	I: 53.1 ± 10.1 C: 54.4 ± 12.4	I: 75% female C:75% female	NR	I: 36%C: 30%	90%	21%
Hodgson et al., 2016 [48], Australia	Hospital and Genetic Clinic	95	Stage/type NR; HBOC and LS	I: 57.8% "actionable" groupC: 50.0% "actionable" group	I: 49.5 ± 14.9 C: 45.8 ± 13.9	I: 50% female C:48% female	NR	NR	57%	53%
Katapodi et al., 2018 [42], USA	Outpatient	24	Stage/type NR: HBOC 40% PDx Breast 10% PDx Ovarian 20% PDx Other	12 PV	41 ± 13	100% female	100% White	NR	23%	29%
Loader et al., 2002 [51], USA	Cancer Registry	101	100% PDxCRC; stage NR	100% ≥1 FDR or SDR^{++} CRC	Not Counseled: 57.3 ± 6.9 Counseled:59.2 ± 6.5	53% female	93% White	NR	71%	13%
Lobb et al., 2002 [43], Australia	Outpatient	193	Stage/type NR; HBOC I: 42% PDx C: 45% PDx	NR	I: 45 C: 44	100% female	NR	I: 47% C: 50%	88%	18%
McInerney-Leo et al., 2004 [41], USA	NR	262	Stage/type NR; HBOC families	26% PV 85% genetic testing	55% ≥ 40	65% female	Mostly White	NR	47%	19%

Table 2. *Cont.*

Author/Year Country	Setting	Sample N	Cancer Type/Stage/PDx *	Carrier of PV ** or FH ***	Age Mean ± SD or Range	Sex	Race	Education% ≤ HSˆ	Enrollment	Attrition
Montgomery et al., 2013 [44], USA	Outpatient	422	Stage/type NR; HBOC	NR	48.5 ± 11.0	100% female	95% White	77%	96%	41%
Niu et al., 2019 [52], USA	Outpatient	190	I: 33.68% CRC PDx C: 36.84% CRC PDx	NR	I: 53.4 ± 12.5 C: 51.8 ± 14.0	I: 46% female C:57% female	I: 81% White C: 84% White	NR	NR	26%
Roshanai et al., 2009 [49], Sweden	Outpatient	147	HBOC, CRC riskI: 38.36% PDxC: 35.14% PDx	I: 77% No PDx >20%risk 79% PDx >20% risk C:81% No PDx >20% risk 70% PDx >20% risk	56 (23-84)	I: 92% female C: 89% female	NR	NR	66%	15%
Tiller et al., 2006 [53], Australia	Outpatient	131	Ovarian cancer I: 51.5% PDx C: 52.4% PDx	I: 74.2% FH C: 71.4% FH	I: 45.8 C: 46.3	100% female	NR	I: 29% C:29%	92%	17%
Vogel et al., 2019 [54], USA	Outpatient	104	Ovarian cancer 100% PDx I: ≥74% Stage III C: ≥75% Stage III	NR	I: 60.9 ± 10.7 C: 61 ± 12	100% female	I: 91% White C: 88% White	I: 20.8% C: 18%	82%	13%
Wakefield et., al 2008 [45], Australia	Outpatient	120	Type NR; HBOC I:56.1% PDx C:65.1% PDx	100% FH HBOC—cancer	I: 45.8 (21–73) C: 49.6 (22–75)	100% female	NR	I: 26.3% C: 36.5%	94%	17%

* PDx = Personal cancer diagnosis. ** PV = Pathogenic variant. *** FH = Family history of cancer. ˆ %≤HS = Percentage of participants with education equal or less than high school. +FDR = First-degree relatives. ++SDR = Second-degree relatives. ~ NR = Not Reported.

3.5. Effect Sizes Obtained for Outcomes

Table 3 presents an overview of meta-analytic findings for outcomes assessed. Family communication was the most commonly assessed outcome (n = 8), followed by knowledge (n = 7), cascade genetic testing (n = 6), anxiety (n = 4), depression (n = 4), and perceived risk (n = 3). Primary studies assessed additional outcomes, i.e., decisional conflict, decisional regret, coping, distress, and self-efficacy. However, calculation of pooled effect sizes for these additional outcomes was not possible, either because there were less than three studies or due to missing data. The table provides the pooled effect sizes for assessed outcomes, 95% confidence intervals, assessment of heterogeneity across studies (Q statistic), and Egger's t-test for publication bias. Forest plots for each outcome are shown. Forest plots depict the effect sizes calculated for each study by outcome (■ symbol) as well as the overall effect size obtained for the outcome across studies (◆ symbol). Forest plots also indicate whether effects obtained in each study and across studies favor the control or the intervention.

Table 3. Pooled effect sizes of outcomes.

Outcomes	Number of Trials	Overall Sample N	Pooled Effect Size Hedges' g (95% CI)	Q for Heterogeneity	Egger's t-Test for Publication Bias
Family communication	8	2066	0.085 (−0.091 – 0.261)	15.50*	0.53
Cascade genetic testing	4	703	0.169 (0.034 – 0.305)*	0.93	−0.66
Knowledge	7	1215	0.244 (0.109 – 0.379)*	15.10 *	0.50
Anxiety	4	661	0.033 (−0.132 – 0.198)	6.14	−4.17*
Depression	4	952	0.183 (0.033 – 0.334)*	2.39	2.89
Risk perception	3	476	0.007 (−0.230 – 0.250)	1.69	0.97

* p-value ≤ 0.05.

Family communication was conceptualized by primary studies most commonly as the number of relatives contacted/informed about the pathogenic variant, as well as frequency of contact and openness/ease of family communication. The Q statistic indicates significant heterogeneity among the eight studies that evaluated changes in family communication. The overall effect size was small and not significant, g = 0.085 (p = 0.344). (Figure 2). Among the eight studies, three assessed family communication as a secondary outcome [50,52,54]; removing these studies did not change the significance of the pooled effect size.

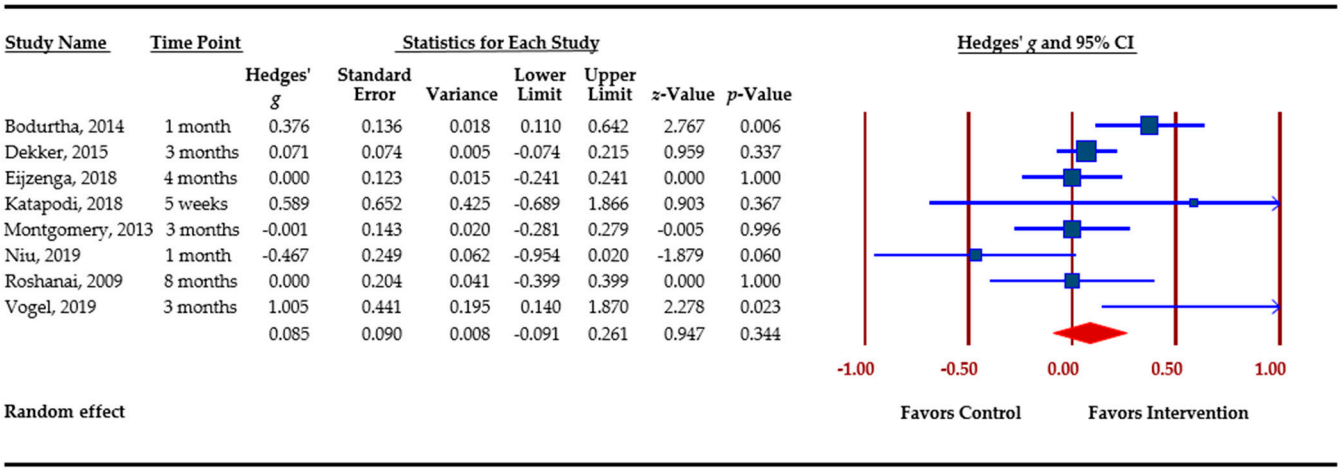

Figure 2. Family communication.

Cascade genetic testing was assessed by six primary studies as uptake of genetic testing by relatives and/or contact with genetic services and request for genetic consultation. The assessment was based on participants' self-reports, and/or less often on clinic records. The overall effect size was small and not significant, g = 0.086 (−0.075–0.247) (p = 0.295).

However, two of these studies [51,53] assessed cascade genetic testing as a secondary outcome. Removing these two studies changed the overall effect size, which remained small but significant, $g = 0.169$ ($p = 0.014$). (Figure 3). Effect sizes among primary studies ranged from 0.010 to 0.368.

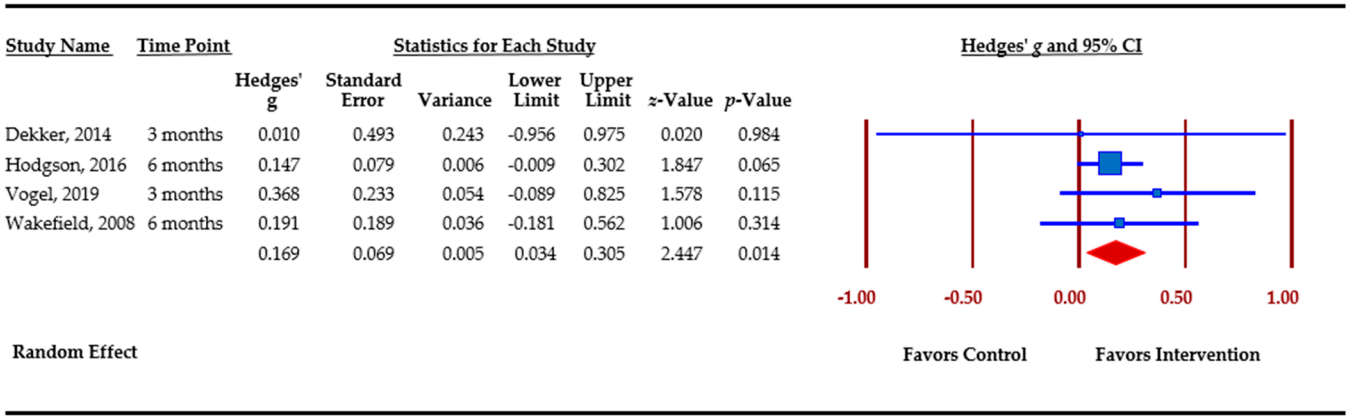

Figure 3. Cascade genetic testing.

Knowledge was conceptualized by primary studies as knowledge of heredity and cancer genetics, knowledge of risk factors and familial risk, and knowledge related to genetic testing. The Q statistic indicates significant heterogeneity among the seven studies that evaluated changes in knowledge. The overall effect size was small but significant, $g = 0.244$ ($p < 0.001$), favoring the intervention arm. Effect sizes among primary studies varied between −0.273 and 0.708 (Figure 4).

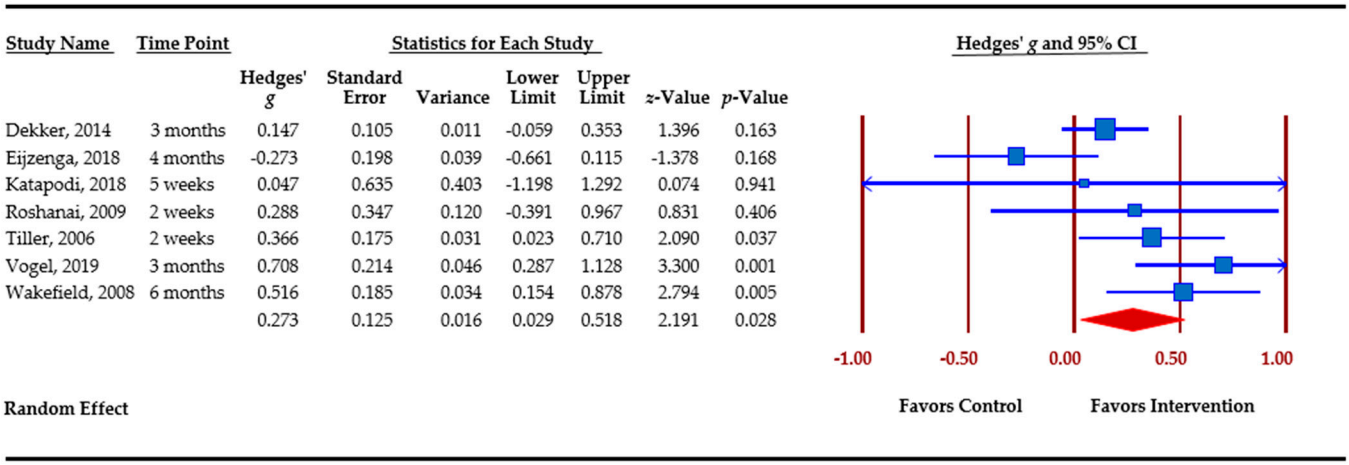

Figure 4. Knowledge.

Anxiety was assessed by primary studies with the Hospital Anxiety and Depression Scale (HADS) [55] and the Spielberger State Trait Anxiety Inventory (STAI) [56]. Egger's *t*-test indicates publication bias for the four studies that evaluated changes in anxiety. The overall effect size was small and not significant, $g = 0.033$ ($p = 0.695$). (Figure 5).

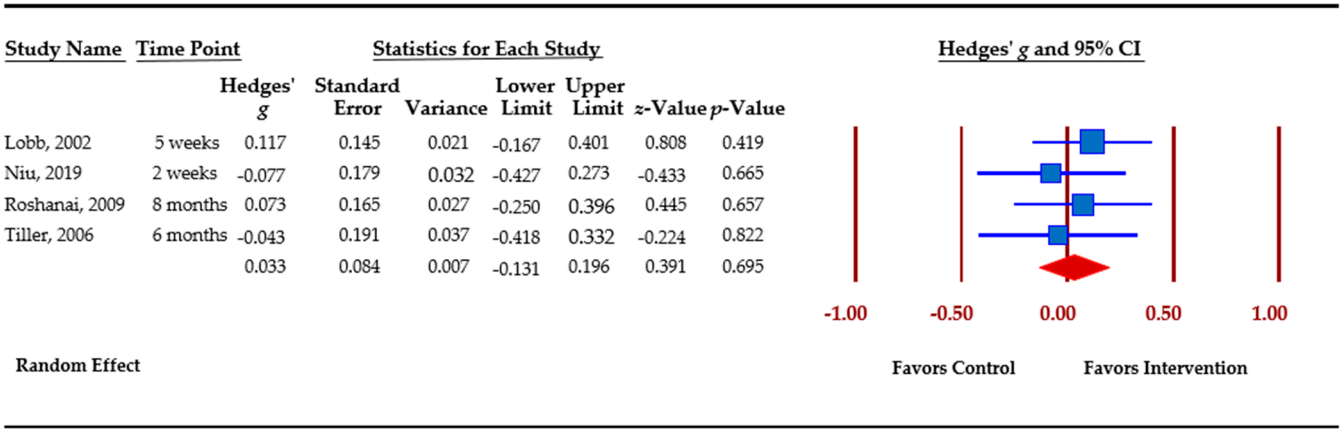

Figure 5. Anxiety.

Depression was assessed by primary studies using the Hospital Anxiety and Depression Scale (HADS) [55] and the Centers for Epidemiological Studies—Depression scale (CESD) [57]. Among the four studies that evaluated changes in depression, the overall effect size was small but significant, $g = 0.183$ ($p = 0.017$), favoring the intervention arm. Effect sizes among individual studies varied between 0.070 and 0.335 (Figure 6).

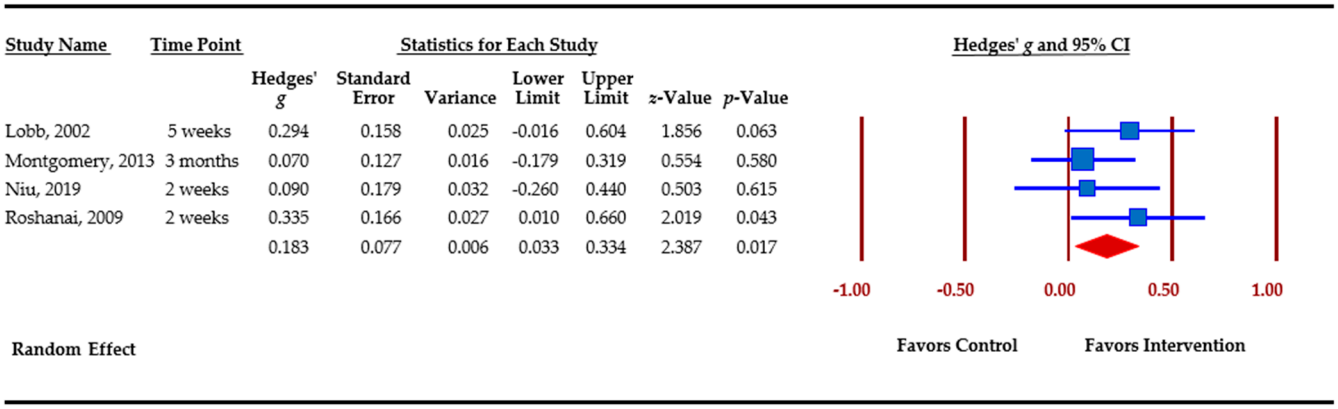

Figure 6. Depression.

Perceived risk for developing cancer was assessed in three studies. Changes in perceived risk were small and not significant, $g = 0.007$ ($p = 0.95$). (Figure 7).

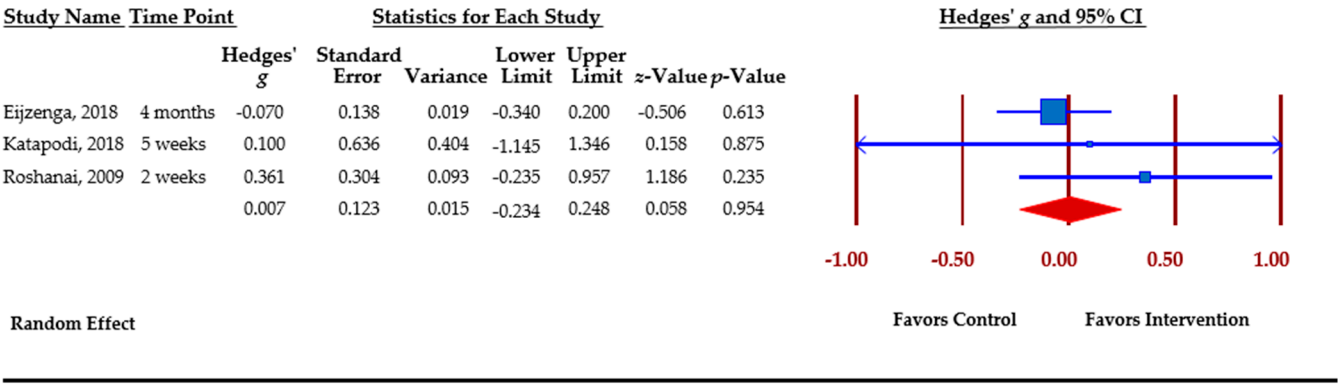

Figure 7. Perceived risk.

4. Discussion

The primary purpose of this paper was to identify interventions that were designed to facilitate family communication of cancer genetic testing results and/or cascade genetic testing among blood relatives, with a focus on HBOC and LS. To enhance the methodological rigor of our review, we focused exclusively on studies that tested intervention efficacy with an RCT design. Our systematic search identified 14 studies that met all inclusion criteria and were included in the narrative synthesis of this paper about intervention components, mode of delivery, and sample characteristics. Meta-analysis of outcomes was possible only for 13 studies, and not all of them had assessed family communication of test results and/or cascade genetic testing of relatives as a primary outcome. Our literature search identified serendipitously additional papers describing the development of relevant interventions [58–65]. However, none of them had been rigorously tested with an RCT, indicating that the scientific field is still in development. Our findings indicate that this is a growing field with significant heterogeneity of approaches, with few rigorously tested interventions that genetic professionals can emulate in cancer genetic practices.

The 14 identified interventions delivered to carriers of pathogenic variants and/or their blood relatives were comprehensive and addressed family communication, cascade testing of relatives, knowledge of cancer genetics, and psychosocial wellbeing as primary or secondary outcomes. We recorded three indicators of intervention quality. First, most studies included theory-driven intervention protocols, which decreases the likelihood of isolated or chance findings. However, there was considerable variability, with some studies mentioning the theory in passing or in generic terms, while others indicated specific theories and demonstrated how the theory was utilized in the selection of intervention content and choice of outcomes. Second, fewer studies instituted ways to examine intervention fidelity, i.e., the extent to which the protocol was delivered in a consistent manner. Investigators used protocol manuals, intervention logs, and/or tape-recorded sessions to assess or maintain intervention fidelity, indicating a growing understanding of the importance of adherence to standardized protocols. Third, there was considerable variability in intervention "dose" among protocols, both in the number of sessions (range 1 to 7 contacts) and duration of interventions (ranging from 20 to 140 min, delivered over 7 days to 12 months). Detailed information about intervention dose was not consistently reported. Intervention dose could be further evaluated or standardized within studies; otherwise, it is difficult to determine if, or how much of, the intervention "dose" affects outcomes.

The majority of protocols included one-on-one and face-to-face or telephone extensive counseling with a trained healthcare provider, often identified as a genetic counselor or Master's-prepared nurse. Moreover, few interventions were delivered via a web-based or mobile app platform. Given the shortfall of trained genetic health professionals, technology-based approaches are needed to extend the reach to individuals weighing genetic testing decisions and facilitating cascade genetic testing. Increased access to genetic information could be facilitated with web-based or mobile health technologies. The availability of internet access, rising levels of electronic literacy, and the growing number of patient portals/web-based approaches hold promise for expanding the reach of tailored, cost-effective genetic care [27,66]. Technology-enabled education and tele-genetics is equivalent to face-to-face consultations in presenting the benefits and drawbacks of genetic testing at half the cost of traditional consultations [24,66].

Content related to the implications of genetic test results for blood relatives and communication was included in most interventions. However, the overall effect size for this outcome was small and not significant. There was significant heterogeneity among protocols, ranging from booklets that carriers could pass on to untested relatives, to family-based communication training. Some studies assessed communication as a secondary outcome. Taken together, these findings suggest that although building communication skills and/or providing support for dissemination of genetic testing results is an essential component, little is known about the best approach to enhance this outcome [67]. From the 14 protocols included in the narrative synthesis, many included extensive meetings with a healthcare

provider, suggesting some individualization and tailoring of intervention content. However, most protocols targeted only carriers' communication skills and coping strategies, who are the transmitters of genetic information, and did not address communication and coping of relatives, who are the recipients. Communication of genetic test results is a two-way exchange between carriers and relatives and should be addressed as a family-based outcome, yet only two protocols included both a carrier and untested relatives. Enhancing communication of genetic testing results should be guided by family-based theoretical frameworks and tested with family-based designs [68–70].

When cascade genetic testing was the primary focus of interventions, the overall effect was small but significant. However, this finding should be interpreted with caution due to the small number of studies and the outcome based on self-reports. Invitation letters for genetic counseling, list of genetic resources, repeated contact with carriers over 12 months, and enhancing physician referrals were some of the techniques employed by the reviewed interventions. The current legal framework does not support healthcare professionals directly contacting blood relatives. However, removing this barrier does not guarantee successful cascading of blood relatives due to the resources needed to identify, contact, and counsel them. Additional measures, such as mailing of saliva kits [64] and family-based telephone or web-based counseling, hold promise to enhance cascade genetic testing and improve individual and population health outcomes.

Content related to cancer genetics, modes of inheritance, and risk factors was included in all interventions, resulting in a small but significant overall effect size and suggesting that this is an essential content area. This finding is consistent with an earlier review reporting that risk communication during genetic consultations increases genetic knowledge [71]. The significant heterogeneity observed for this outcome could be due to the different measures used to assess knowledge of cancer genetics, or due to the different syndromes and/or cancer types (e.g., colorectal or ovarian cancer) that were the focus of each intervention. Moreover, there is significant heterogeneity among counselees' preferences, with some preferring to receive detailed genetic information while others preferring "just the basics" [72,73], making streamlining lay genetic education difficult without a tailored approach.

Psychosocial outcomes, such as anxiety, depression, and perceived risk, as well as decisional conflict, regret, coping, and satisfaction were not assessed consistently among studies. Thus, we were unable to calculate pooled effect sizes for many of these outcomes. A significant number of interventions included decision aids, exercises for value clarification, and provided information on preventive and risk management options. These components likely enhance psychosocial adjustment to hereditary cancer risk and increase emotional wellbeing [71]. Although primary studies used validated instruments to assess these outcomes, meta-analysis findings regarding intervention efficacy, heterogeneity, and publication bias should be interpreted with caution due to the small number of primary studies and the heterogeneity of syndromes and/or cancer types. Risk communication in the clinical context resulted in general improvement for these outcomes [71].

Little is known about samples of racially, ethnically, and social diverse backgrounds. Only one study included a majority of Black participants, and only one study included a majority of male participants, indicating significant knowledge gaps regarding family communication and cascade genetic testing in males, especially in the context of HBOC. Future studies should also focus on LS, as it is the most common hereditary cancer condition known today, but remains largely undetected due to the different cancer types associated with LS and the lack of clear diagnostic criteria [74–77].

5. Limitations

We did not include studies published in languages other than English, unpublished studies, and abstracts from conference proceedings to ensure that findings were based on higher-quality, peer-reviewed studies. Excluding unpublished studies is likely to introduce an upward bias into the size of the effects found, which means that calculated effect sizes

are likely to be larger [37]. To address this limitation, we assessed the heterogeneity of findings with the Q statistic and publication bias with the Egger's *t*-test statistic. Publication bias appeared only in one outcome and may be related to the small number of studies. Our findings are comparable to a previous review assessing psychosocial outcomes of genetic counseling [62]. Finally, due to the small number of studies and the diverse outcomes, we were not able to conduct moderation analyses and examine the impact of similar types of interventions on outcomes (e.g., web-based vs. paper-based). The heterogeneity and attrition across studies also decrease our ability to discern the clinical utility of these interventions.

The time span of studies included in our meta-analysis covered a period of 17 years, during which there have been massive shifts in clinical practice and in public understanding of genetic testing. The introduction of panel testing has created new complexities in managing hereditary cancer risk associated with pathogenic variants of moderate penetrance, which may further contribute to existing barriers to family communication and cascade testing. GINA (Genetic Information Non-Discrimination Act), which was passed in the US in 2008 [78], may have lessened concerns about genetic discrimination, facilitating family communication and cascade genetic testing. However, this applies only to the seven studies conducted in the US, while the legal framework for protecting genetic information in other countries is not known. Discerning the influence of these two factors on family communication and cascade genetic testing is not possible under the scope of this study.

6. Conclusions

At the time of conducting this study, no similar reviews about family communication and/or cascade genetic testing for hereditary cancer syndromes have been published. Research has been mainly focused on helping healthcare professionals to facilitate family communication about genetic test results, and uptake of cascade testing has increased due to educational materials and technological resources and due to the active involvement of healthcare providers [79].

Although professional organizations call for the implementation of cascade testing for HBOC and LS, debate remains about the conflict between the need to protect the privacy of tested individuals and the rights of blood relatives to be notified about genetic information. Facilitating this process will contribute to the implementation of cascade genetic testing and significantly reduce the burden of cancer resulting from familial pathogenic variants. Technology- and theory-driven, rigorously-tested, psychoeducational interventions could play a significant role in this public health effort. Our study highlights the need for developing new interventions and new approaches in family communication and cascade testing for cancer susceptibility, laying the foundation for future work to address current knowledge gaps. Future studies could compare interventions assessing these outcomes regardless of the genetic condition, assuming similar "actionability" of genetic findings. Rigorous testing of promising interventions using an RCT design will propel the scientific field forward. In addition to individual- and family-level interventions, consideration should be given to health system and policy-level changes that might facilitate the communication of cancer genetic risk information and cascade testing.

Supplementary Materials: The following are available online at https://www.mdpi.com/2072-6694/13/4/925/s1, Table S1. Tabular representation of risk of bias in individual studies.

Author Contributions: Conceptualization, V.B., M.C.K.; methodology, V.B., M.C.K., M.L.U.-B., and C.A.-H.; software, V.B., M.C.K.; validation, V.B., M.L.U.-B., C.A.-H.; formal analysis, V.B., M.C.K.; investigation, V.B., M.L.U.-B., C.A.-H., M.C.K.; resources, M.C.K.; data curation, V.B.; writing—original draft preparation, V.B., M.C.K.; writing—review and editing, V.B., M.L.U.-B., C.A.-H., M.C.K.; visualization, V.B.; supervision M.C.K.; project administration V.B.; funding acquisition M.C.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Search Strategies

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('hereditary breast and ovarian cancer syndrome'/de OR 'hereditary nonpolyposis colorectal cancer'/de OR 'BRCA1 protein'/de OR 'BRCA2 protein'/de OR 'BRCA1 protein human'/de OR 'BRCA2 protein human'/de OR 'BRCA gene'/de OR 'BRCA2 gene'/de OR 'BRCA protein'/de OR 'MutL protein homolog 1′/de OR 'mlh1 gene'/de OR 'mlh1 protein human'/de OR 'DNA mismatch repair protein MSH2′/de OR 'msh2 gene'/de OR 'msh2 protein human'/de OR 'protein MSH6′/de OR 'mismatch repair protein PMS2′/de OR 'pms2 gene'/de OR 'pms2 protein human'/de OR 'epithelial cell adhesion molecule'/de OR 'epcam gene'/de OR 'epcam protein human'/de OR ('HBOC syndrome' OR (('hereditary nonpolyposis' OR 'hereditary non polyposis') NEXT/3 (cancer OR neoplasm*)) OR HNPCC OR 'Lynch syndrome' OR 'Lynch II syndrome' OR 'Muir Torre syndrome' OR BRCA* OR FANCD* OR ('Fanconi anaemia' NEXT/3 D1) OR (MutL NEXT/2 'homolog 1′) OR MLH1 OR hMLH1 OR 'MutS homolog 2′ OR MSH2 OR hMSH2 OR MSH6 OR 'post-meiotic segregation increased protein 2′ OR PMS2 OR 'epithelial cell adhesion molecule' OR EPCAM):ab,ti OR 'hereditary tumor syndrome'/de OR 'cancer risk'/de OR 'cancer susceptibility'/de OR 'oncogene'/de OR 'tumor suppressor gene'/de OR 'tumor gene'/de OR 'cancer genetics'/de OR (oncogene OR ((cancer* OR tumor* OR tumour*) NEAR/3 (syndrome OR risk OR predisposition OR susceptibility OR anticipation OR prognosis OR disorder OR gene*))):ab,ti OR (('genetic predisposition'/exp OR 'genetic risk'/de OR 'gene mutation'/de OR 'genetic disorder'/de OR 'single nucleotide polymorphism'/de OR 'family history'/de OR (hereditary OR inherit* OR inborn OR familial OR mutation* OR genetic* OR ((family OR genomic*) NEAR/3 (syndrome OR risk OR predisposition OR disposition OR susceptibility OR anticipation OR prognosis OR disorder OR condition* OR history)) OR 'single nucleotide polymorphism*' OR SNP OR SNPs):ab,ti) AND ('neoplasm'/exp OR (cancer* OR neoplas* OR tumor* OR tumour* OR carcinoma* OR carcinogenesis OR malignan*):ab,ti)))

and

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survey* OR 'compact disk' OR 'CD-I' OR 'CD-ROM' OR DVD OR ((mobile OR portable OR educational) NEXT/2 (app OR apps OR application*)) OR website* OR 'web site*' OR multimedia OR ((psychosocial OR social) NEXT (care OR support OR therapy OR intervention*)) OR telegenetic OR 'educational material*' OR 'tailored message*' OR 'message tailoring'):ab,ti)

and

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and

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and

(counseling/OR genetic counseling/OR Referral and Consultation/OR exp Remote Consultation/OR decision support systems, clinical/OR Decision Support Techniques/OR communication/OR persuasive communication/OR health education/OR patient education as topic/OR exp telecommunications/OR Interviews as Topic/OR online systems/OR "Surveys and Questionnaires"/OR computers/OR exp compact disks/OR mobile applications/OR multimedia/OR telemedicine/OR exp social support/OR (((family OR genetic OR genomic OR patient* OR intervention OR risk*) ADJ3 counsel*) OR preventive genetics OR consultation* OR teleconsultation* OR (decision ADJ2 (support* OR aid* OR framework OR computer-assisted)) OR communicat* OR disclos* OR persuasion OR ((medical OR health OR patient* OR cancer OR risk* OR program*) ADJ3 (information OR education)) OR internet OR world wide web OR web-based OR online OR social media OR facebook

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and

(exp genetic services/OR DNA mutational analysis/OR Sequence Analysis, DNA/OR family therapy/OR (((family OR genetic* OR genomic* OR cascade OR mutation*) ADJ3 (counsel* OR care OR testing OR screening OR analys* OR study OR studies OR discrimination OR diagnos*)) OR DNA sequencing OR preventive genetics OR ((family OR relative*) ADJ3 (communicat* OR intervention* OR inform*)) OR (informed ADJ (decision* OR choice*))).ab,ti.)

and

(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ti,ab. OR placebo.ti,ab. OR drug therapy.fs. OR randomly.ti,ab. OR trial.ti,ab. OR groups.ti,ab. NOT (exp animals/NOT exp humans/))

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(('HBOC syndrome' OR (('hereditary nonpolyposis' OR 'hereditary non polyposis') NEXT/3 (cancer OR neoplasm*)) OR HNPCC OR 'Lynch syndrome' OR 'Lynch II syndrome' OR 'Muir Torre syndrome' OR BRCA* OR FANCD* OR ('Fanconi anaemia' NEXT/3 D1) OR (MutL NEXT/2 'homolog 1') OR MLH1 OR hMLH1 OR 'MutS homolog 2' OR MSH2 OR hMSH2 OR MSH6 OR 'postmeiotic segregation increased protein 2' OR PMS2 OR 'epithelial cell adhesion molecule' OR EPCAM):ab,ti OR (oncogene OR ((cancer* OR tumor* OR tumour*) NEAR/3 (syndrome OR risk OR predisposition OR susceptibility OR anticipation OR prognosis OR disorder OR gene*))):ab,ti OR (((hereditary OR inherit* OR inborn OR familial OR mutation* OR genetic* OR ((family OR genomic*) NEAR/3 (syndrome OR risk OR predisposition OR disposition OR susceptibility OR anticipation OR prognosis OR disorder OR condition* OR history)) OR 'single nucleotide polymorphism*' OR SNP OR SNPs):ab,ti) AND ((cancer* OR neoplas* OR tumor* OR tumour* OR carcinoma* OR carcinogenesis OR malignan*):ab,ti))) AND ((((family OR genetic OR genomic OR patient* OR intervention OR risk*) NEAR/3 counsel*) OR 'preventive genetics' OR consultation* OR teleconsultation* OR (decision NEAR/2 (support* OR aid* OR framework OR computer-assisted)) OR communicat* OR disclos* OR persuasion OR ((medical OR health OR patient* OR cancer OR risk* OR program*) NEAR/3 (information OR education)) OR internet OR 'world wide web' OR web-based OR online OR 'social media' OR facebook OR twitter OR ((cell OR cellular OR mobile OR smart) NEXT phone*) OR cellphone* OR smartphone* OR mail OR (postal NEXT (delivery OR service)) OR letter* OR telehealth OR tele-health OR ehealth OR e-health OR 'digital health' OR mhealth OR telemedicine OR tele-medicine OR telephone* OR dataphone* OR videoconferenc* OR 'video conferenc*' OR webcast OR computer* OR questionnaire* OR survey* OR 'compact disk' OR 'CD-I' OR 'CD-ROM' OR DVD OR ((mobile OR portable OR educational) NEXT/2 (app OR apps OR application*)) OR website* OR 'web site*' OR multimedia OR ((psychosocial OR social) NEXT (care OR support OR therapy OR intervention*)) OR telegenetic OR 'educational material*' OR 'tailored message*' OR 'message tailoring'):ab,ti) AND ((((family OR genetic* OR genomic* OR cascade OR mutation*) NEAR/3 (counsel* OR care OR testing OR screening OR analys* OR study OR studies OR discrimination OR diagnos*)) OR 'DNA sequencing' OR 'preventive genetics' OR ((family OR relative*) NEAR/3 (communicat* OR intervention* OR inform*)) OR (informed NEXT (decision* OR choice*))):ab,ti)

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((HBOC syndrome OR ((hereditary nonpolyposis OR hereditary non polyposis) ADJ3 (cancer OR neoplasm*)) OR HNPCC OR Lynch syndrome OR Lynch II syndrome OR Muir Torre syndrome OR BRCA* OR FANCD* OR (Fanconi anaemia ADJ3 D1) OR (MutL ADJ2 homolog 1) OR MLH1 OR hMLH1 OR MutS homolog 2 OR MSH2 OR hMSH2 OR MSH6 OR postmeiotic segregation increased protein 2 OR PMS2 OR epithelial cell adhesion molecule OR EPCAM).ab,ti. OR (oncogene OR ((cancer* OR tumor* OR tumour*) ADJ3 (syndrome OR risk OR predisposition OR susceptibility OR anticipation OR prognosis OR disorder OR gene*))).ab,ti. OR (((Genetics/AND Predisposition/) OR mutations/OR Genetic Disorders/OR At Risk Populations/OR (hereditary OR inherit* OR inborn OR familial OR mutation* OR genetic* OR ((family OR genomic*) ADJ3 (syndrome OR risk OR predisposition OR disposition OR susceptibility OR anticipation OR prognosis OR disorder OR condition* OR history)) OR single nucleotide polymorphism* OR SNP OR SNPs).ab,ti.) AND (exp neoplasms/OR (cancer* OR neoplas* OR tumor* OR tumour* OR carcinoma* OR carcinogenesis OR malignan*).ab,ti.)))

and

(counseling/OR genetic counseling/OR Professional Consultation/OR decision support systems/OR exp interpersonal communication/OR persuasive communication/OR health education/OR Interviews/OR Questionnaires/OR internet/OR exp computers/OR mobile applications/OR multimedia/OR exp telemedicine/OR social support/OR (((family OR genetic OR genomic OR patient* OR intervention OR risk*) ADJ3 counsel*) OR preventive genetics OR consultation* OR teleconsultation* OR (decision ADJ2 (support* OR aid* OR framework OR computer-assisted)) OR communicat* OR disclos* OR persuasion OR ((medical OR health OR patient* OR cancer OR risk* OR program*) ADJ3 (information OR education)) OR internet OR world wide web OR web-based OR online OR social media OR facebook OR twitter OR ((cell OR cellular OR mobile OR smart) ADJ phone*) OR cellphone* OR smartphone* OR mail OR (postal ADJ (delivery OR service)) OR letter* OR telehealth OR tele-health OR ehealth OR e-health OR digital health OR mhealth OR telemedicine OR tele-medicine OR telephone* OR dataphone* OR videoconferenc* OR video conferenc* OR webcast OR computer* OR questionnaire* OR survey* OR compact disk OR CD-I OR CD-ROM OR DVD OR ((mobile OR portable OR educational) ADJ2 (app OR apps OR application*)) OR website* OR web site* OR multimedia OR ((psychosocial OR social) ADJ (care OR support OR therapy OR intervention*)) OR telegenetic OR educational material* OR tailored message* OR message tailoring).ab,ti.)

and

(genetic counseling/OR genetic testing/OR exp family therapy/OR (((family OR genetic* OR genomic* OR cascade OR mutation*) ADJ3 (counsel* OR care OR testing OR screening OR analys* OR study OR studies OR discrimination OR diagnos*)) OR DNA sequencing OR preventive genetics OR ((family OR relative*) ADJ3 (communicat* OR intervention* OR inform*)) OR (informed ADJ (decision* OR choice*))).ab,ti.)

and

((Randomized Controlled Trial OR Controlled Clinical Trial OR Pragmatic Clinical Trial OR Equivalence Trial OR Clinical Trial, Phase III).pt. OR Randomized Controlled Trial/OR exp Randomized Controlled Trials as Topic/OR "Randomized Controlled Trial (topic)"/OR Controlled Clinical Trial/OR exp Controlled Clinical Trials as Topic/OR "Controlled Clinical Trial (topic)"/OR Randomization/OR Random Allocation/OR Double-Blind Method/OR Double Blind Procedure/OR Double-Blind Studies/OR Single-Blind Method/OR Single Blind Procedure/OR Single-Blind Studies/OR Placebos/OR Placebo/OR Control Groups/OR Control Group/OR (random* OR sham OR placebo*).ti,ab,hw. OR ((singl* OR doubl*) ADJ (blind* OR dumm* OR mask*)).ti,ab,hw. OR ((tripl* OR trebl*) ADJ (blind* OR dumm* OR mask*)).ti,ab,hw. OR (control* ADJ3 (study OR studies OR trial* OR group*)).ti,ab. OR (Nonrandom* OR non random* OR non-random* OR quasi-random* OR quasirandom*).ti,ab,hw. OR allocated.ti,ab,hw. OR ((open label OR open-label) ADJ5 (study OR studies OR trial*)).ti,ab,hw. OR ((equivalence

OR superiORity OR non-inferiORity OR noninferiORity) ADJ3 (study OR studies OR trial*)).ti,ab,hw. OR (pragmatic study OR pragmatic studies).ti,ab,hw. OR ((pragmatic OR practical) ADJ3 trial*).ti,ab,hw. OR ((quasiexperimental OR quasi-experimental) ADJ3 (study OR studies OR trial*)).ti,ab,hw. OR (phase ADJ3 (III OR "3") ADJ3 (study OR studies OR trial*)).ti,hw.)

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Supplementary Materials: Interventions Facilitating Family Communication of Genetic Testing Results and Cascade Screening in Hereditary Breast/Ovarian Cancer or Lynch Syndrome: A Systematic Review and Meta-Analysis

Table S1. Tabular representation of risk of bias in individual studies.

Study (Author/Year)	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcomes Accessors	Incomplete Outcome	Selective Outcome Reporting	Other Sources of Bias
Bodurtha 2014 [46]	+	+	-	?	?	?	-
Dekker 2015 [50]	+	+	-	-	+	+	?
Eijzenga 2018 [47]	+	+	+	+	+	-	-
Hodgson 2016 [48]	+	+	-	-	+	+	-
Katapodi 2018 [42]	+	?	-	?	+	+	?
Loader 2002 [51]	?	?	-	?	+	-	+
Lobb 2002 [43]	+	+	-	?	?	?	-
Mc-Inerney-Leo 2004 [41]	?	+	-	-	?	+	?
Montgomery 2013 [44]	+	?	+	?	+	+	+
Niu 2019 [52]	?	?	-	?	?	+	?
Roshanai 2009 [49]	+	?	+	+	-	?	-
Tiller 2006 [53]	+	+	+	?	+	+	?
Vogel 2019 [54]	+	+	-	-	+	+	?
Wakefield 2008 [45]	?	+	?	?	?	+	+

+	Low risk of bias	-	High risk of bias	?	Unclear risk of bias

3.2. Study II: Predicting Openness of Communication in Families with Hereditary Breast and Ovarian Cancer Syndrome: Natural Language Processing Analysis

Authors:

Vasiliki Baroutsou[1], Rodrigo Cerqueira Gonzalez Pena[2], Reka Schweighoffer[1], Maria Caiata-Zufferey[3], Sue Kim[4], Sharlene Hesse-Biber[5], Florina M Ciorba[6], Gerhard Lauer[7], Maria Katapodi[1], CASCADE Consortium[8]

[1] Department of Clinical Research, University of Basel, Basel, Switzerland

[2] Center for Data Analytics, University of Basel, Basel, Switzerland

[3] Competence Centre for Healthcare Practices and Policies, Department of Business Economics, Health and Social Care, University of Applied Sciences and Arts of Southern Switzerland, Manno, Switzerland

[4] College of Nursing, Yonsei University, Seoul, Republic of Korea

[5] Department of Sociology, Boston College, Chestnut Hill, MA, United States

[6] Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland

[7] Gutenberg-Institut für Weltliteratur und schriftorientierte Medien, Abteilung Buchwissenschaft Johannes Gutenberg, Universität Mainz Philosophicum, Mainz, Germany

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Original Paper

Predicting Openness of Communication in Families With Hereditary Breast and Ovarian Cancer Syndrome: Natural Language Processing Analysis

Vasiliki Baroutsou[1], MSc; Rodrigo Cerqueira Gonzalez Pena[2], PhD; Reka Schweighoffer[1], PhD; Maria Caiata-Zufferey[3], PhD; Sue Kim[4], PhD; Sharlene Hesse-Biber[5], PhD; Florina M Ciorba[6], PhD; Gerhard Lauer[7], PhD; Maria Katapodi[1], PhD; CASCADE Consortium[8]

[1]Department of Clinical Research, University of Basel, Basel, Switzerland
[2]Center for Data Analytics, University of Basel, Basel, Switzerland
[3]Competence Centre for Healthcare Practices and Policies, Department of Business Economics, Health and Social Care, University of Applied Sciences and Arts of Southern Switzerland, Manno, Switzerland
[4]College of Nursing, Yonsei University, Seoul, Republic of Korea
[5]Department of Sociology, Boston College, Chestnut Hill, MA, United States
[6]Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland
[7]Gutenberg-Institut für Weltliteratur und schriftorientierte Medien, Abteilung Buchwissenschaft Johannes Gutenberg, Universität Mainz Philosophicum, Mainz, Germany
[8]See Acknowledgments

Corresponding Author:
Maria Katapodi, PhD
Department of Clinical Research
University of Basel
Missionstrasse 64
Basel, 4055
Switzerland
Phone: 41 612070430
Email: maria.katapodi@unibas.ch

Abstract

Background: In health care research, patient-reported opinions are a critical element of personalized medicine and contribute to optimal health care delivery. The importance of integrating natural language processing (NLP) methods to extract patient-reported opinions has been gradually acknowledged over the past years. One form of NLP is sentiment analysis, which extracts and analyses information by detecting feelings (thoughts, emotions, attitudes, etc) behind words. Sentiment analysis has become particularly popular following the rise of digital interactions. However, NLP and sentiment analysis in the context of intrafamilial communication for genetic cancer risk is still unexplored. Due to privacy laws, intrafamilial communication is the main avenue to inform at-risk relatives about the pathogenic variant and the possibility of increased cancer risk.

Objective: The study examined the role of sentiment in predicting openness of intrafamilial communication about genetic cancer risk associated with hereditary breast and ovarian cancer (HBOC) syndrome.

Methods: We used narratives derived from 53 in-depth interviews with individuals from families that harbor pathogenic variants associated with HBOC: first, to quantify openness of communication about cancer risk, and second, to examine the role of sentiment in predicting openness of communication. The interviews were conducted between 2019 and 2021 in Switzerland and South Korea using the same interview guide. We used NLP to extract and quantify textual features to construct a handcrafted lexicon about interpersonal communication of genetic testing results and cancer risk associated with HBOC. Moreover, we examined the role of sentiment in predicting openness of communication using a stepwise linear regression model. To test model accuracy, we used a split-validation set. We measured the performance of the training and testing model using area under the curve, sensitivity, specificity, and root mean square error.

Results: Higher "openness of communication" scores were associated with higher overall net sentiment score of the narrative, higher fear, being single, having nonacademic education, and higher informational support within the family. Our results

demonstrate that NLP was highly effective in analyzing unstructured texts from individuals of different cultural and linguistic backgrounds and could also reliably predict a measure of "openness of communication" (area under the curve=0.72) in the context of genetic cancer risk associated with HBOC.

Conclusions: Our study showed that NLP can facilitate assessment of openness of communication in individuals carrying a pathogenic variant associated with HBOC. Findings provided promising evidence that various features from narratives such as sentiment and fear are important predictors of interpersonal communication and self-disclosure in this context. Our approach is promising and can be expanded in the field of personalized medicine and technology-mediated communication.

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KEYWORDS

cascade testing; dictionary-based approach; family communication; hereditary breast and ovarian cancer; HBOC; sentiment analysis; text mining; natural language processing; cancer; hereditary

Introduction

Natural language processing (NLP) is a computer-assisted analytical approach for automatically evaluating and interpreting human language by extracting meaningful insights from textual data sets [1-3]. NLP has been broadly used in various fields in the recent past, for example, in financial and business marketing, education, and health care [4-8]. The typical applications of NLP include information extraction, sentiment and semantic analysis, text classification, and text summarization. Among the different NLP applications, sentiment analysis has become particularly popular in recent years following the rise of digital communication and social media [2,9]. Sentiment analysis aims to assess whether people's opinions, emotions, and attitudes toward a certain event or experience are positive, negative, or neutral [3,10,11] and generates valuable insights that lead to the improvement of a new service or product.

In health care–related studies, patient-reported insights are an essential component of personalized medicine and contribute to optimal health care delivery. Researchers have applied NLP to extract and analyze patient-reported insights from social media and for different topics, for example, social exchange patterns in web-based health platforms [12], needs of patients and caregivers in different disease entities [13], online support groups for patients with breast cancer [14], or awareness for Lynch syndrome (LS) [15]. A major limitation of this approach is that population characteristics (age, socioeconomic status, etc) are often unavailable, which limits the clinical applicability of findings and may create disparities either due to increased representation or lack thereof of certain population subgroups. Others have applied NLP to clinical notes originating from electronic medical records to describe patients' experiences with symptoms [16] or free-text data from patient surveys evaluating the quality of hospital services [17]. One limitation of this approach is the lack of depth in these data sources, either because they lack the patient's perspective or because the texts are limited in scope and volume. We identified only a few studies that applied NLP to unstructured narratives collected from in-depth interviews aiming to describe experiences with cancer ambulatory services [18] or to predict changes in substance use [19] and perceived loneliness among older adults [20].

NLP and sentiment analysis in the context of intrafamilial communication for genetic cancer risk is unexplored. Due to privacy laws, individuals carrying pathogenic variants in cancer-causing genes have a key role in disseminating information to relatives and in advocating for genetic testing [21]. This self-disclosure process is currently the main avenue to alert relatives to their own risk of carrying the pathogenic variant. Self-disclosure is a process of interpersonal communication by which one person reveals information about themselves to another person, or a small intimate group, for example, their family. The information exchange can be based on verbal and nonverbal cues and can be face to face or technology mediated. Most importantly, in addition to information exchange, self-disclosure can include thoughts, emotional experiences and feelings, aspirations, goals, fears, likes, and dislikes [22]. During self-disclosure, humans adjust and adapt their verbal and nonverbal communication, and messages are produced, interpreted, understood, or misunderstood [23,24]. Intrafamilial communication for genetic cancer risk may involve significant levels of uncertainty and potential conflicts since the meaning of self-disclosure about the cancer-causing variant can be shaped by opposing arguments and negative responses from others. Indeed, information exchange about genetic cancer risk may be easier with some family members or may present a particularly difficult moment with others [25,26].

Predicting openness of communication and examining the role of sentiment in intrafamilial communication of genetic cancer risk may be used to enrich message tailoring in technology-assisted interventions. In this study, we examined the role of sentiment in predicting openness of communication about genetic cancer risk associated with hereditary breast and ovarian cancer (HBOC) syndrome. HBOC is a hereditary cancer syndrome that affects both men and women and accounts for a significant number of different cancers, such as breast, ovarian, pancreatic, and prostate [27]. Sharing information about HBOC-causing pathogenic variants is a complex process of intrafamilial communication and a key element of public health interventions aiming to promote cascade testing of relatives and cancer prevention and control [28,29]. In this study, we used narrative data collected with in-depth interviews: first, to quantify openness of communication about HBOC cancer risk, and second, to examine the role of sentiment in predicting openness of communication.

Methods

Design, Population, Settings, and Procedures

This analysis is part of a larger ongoing study, the Swiss CASCADE cohort, which follows adult (aged ≥18 years) men and women from families that harbor pathogenic variants associated with HBOC or LS. The cohort includes individuals who had genetic testing, confirming either the presence or the absence of the familial pathogenic variant, and their untested relatives with unknown mutation status. Eligible participants may have had a cancer diagnosis, or they could be cancer-free at the time of enrolment in the study. Recruitment takes place at 8 different oncology and genetic testing centers in the German-, French-, and Italian-speaking regions of Switzerland. The study collects survey data designed to elicit factors that enhance cascade genetic testing and cancer surveillance for HBOC and LS. A subsample of participants has consented to provide narrative data regarding family communication of test results. For the purposes of this paper, we focused only on individuals who have had genetic testing for HBOC-associated pathogenic variants and accepted to provide narrative data.

Ethics Approval

The study protocol has been approved by the Ethics Committee of Northwest Switzerland (BASEC 2016-02052) and is publicly available (ClinicalTrials.gov NCT03124212) [30]. We also used available data from participants in the K-CASCADE study (ClinicalTrials.gov NCT04214210) in South Korea, which focuses on HBOC. K-CASCADE and the collaboration of the 2 studies has been approved by local ethics committees (Severance Hospital Institutional Review Board: 4-2020-0520). K-CASCADE is identical to the Swiss CASCADE in respect to scope, research design, participant eligibility criteria (except for age ≥19 years), and data collection methodology. Participants to K-CASCADE are recruited from 5 hospitals in South Korea [31].

Narrative Data

Narrative data included in this paper were collected from 44 individuals living in Switzerland and 9 in South Korea. The in-depth interviews were conducted between April 2019 and June 2021 either face to face or online (after April 2020 due to the COVID-19 pandemic) by trained research staff in German, French, Italian, English, and Korean using the same interview guide. Interview questions were designed to explore general communication patterns within family networks and specific experiences and barriers of family communication regarding genetic risk including discussions with health care providers. Examples of questions included in the interview guide are “What are some issues (barriers) that people might experience, related to sharing genetic risk information with family members?” and “Think of your own experience of (not) sharing genetic risk information with family members. What did you do and how did you decide about it?” Interviews were recorded, and all narrative data were transcribed verbatim in the original language in Microsoft Word and translated into English for this paper.

Survey Data

Survey data were collected on an ongoing basis, starting in fall 2017 and occurring approximately 18-24 months apart. Self-administered surveys assessed demographic and clinical characteristics [30]. The surveys also included investigator-developed items that have been associated with family communication and intention to inform relatives about genetic cancer risk. These items assess informational support among family members, preference for patient-mediated communication of genetic testing results, and perceived utility of genetic testing for relatives (Textbox 1). These items are scored on 7-point Likert-type scales ranging from 1 “Strongly Disagree” to 7 “Strongly Agree.” Respondents also completed the Informing Relatives Inventory (IRI), a 37-item scale assessing knowledge, motivation, and self-efficacy to disclose genetic cancer risk to relatives [32]. IRI items are also scored on a 7-point Likert-type scale, with higher overall score indicating greater intention to inform relatives about genetic cancer risk.

Textbox 1. Items from the CASCADE baseline survey used for this study.

Demographic characteristics

- Age
- Sex (female/male)
- Education level (elementary-, high school–, or technical school–graduate or academic degree)
- Marital status (married or living as married, single, divorced or separated, or widowed)
- Employment status (working full time, nonworking, or retired)

Clinical characteristics

- Cancer status (affected or never diagnosed with cancer)
- Genetic testing result (positive or negative for the familial pathogenic variant)

Family communication

- "In our family when I have a health problem there is great willingness to share information with each other"
- "I would prefer not to discuss about genetic testing results with anyone in my family"
- "If you have blood relatives, would it be useful for them to have genetic testing?"

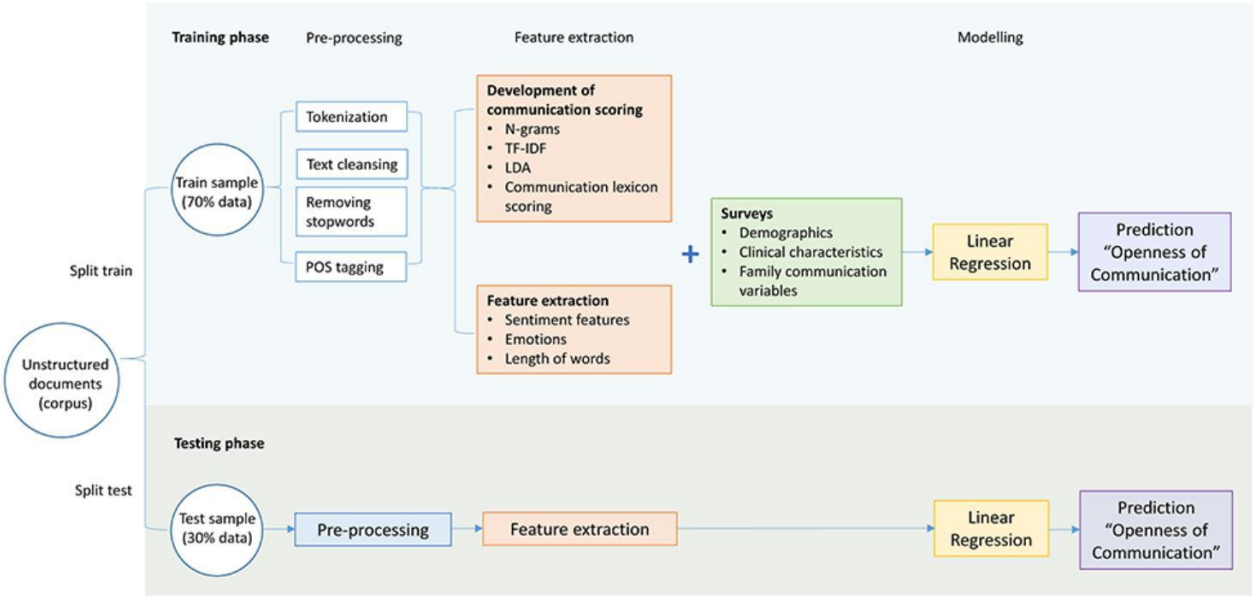
Data Analysis Overview

First, we examined narratives to assess "openness of communicating" genetic test results and cancer risk with relatives and with health care providers. Second, we categorized the text of each narrative as describing either a positive or negative sentiment toward experiences with genetic testing and health care services. Third, we examined whether demographic and clinical characteristics and sentiment, as expressed in the narrative, can predict "openness of communicating" genetic risk from tested individuals to relatives.

NLP Model Development

The ability of NLP to identify and predict different levels of "openness of communication" was evaluated following a multistep framework (Figure 1), which was divided into three phases: (1) preprocessing, (2) training, and (3) performance evaluation. All computations were performed in R software (version 3.6.3; R Foundation for Statistical Computing) [33]. We have made our analysis publicly available through the Zenodo open data repository [34].

Figure 1. Phases of developing the natural language processing (NLP) algorithm: (1) preprocessing, (2) training, and (3) performance evaluation. LDA: latent Dirichlet analysis; POS: part of speech; TF-IDF: term frequency–inverse document frequency.



Preprocessing Phase

To start data processing, we broke down each text into individual tokens. We then applied functions to remove stop words and special characters. All texts were converted to lower case. We also applied part-of-speech tagging to extract phrases from the text corpus, used a latent Dirichlet allocation model to generate the most appropriate topics, and computed the term frequency–inverse document frequency to indicate the significance of a word in the text corpus [35,36].

Creation of a Lexicon and a Score for "Openness of Communication"

To develop an "openness of communication" score, we built a lexicon containing words and phrases linked to communication (for example, "difficulties in communication" and "excellent communication") and classified them as positive or negative. After completing the preprocessing phase, we extracted N-grams from the text corpus. N-grams refer to single words (unigrams) or a combination of 2 or 3 words (bigrams or trigrams) associated with the outcome of interest, ie, "openness of communication." To further enrich the lexicon, we applied the same process in a US-based sample of 123 narratives related to experiences with HBOC genetic cancer risk. This database includes narrative data collected between January 2013 to September 2016 from women and men who are carriers of HBOC-associated variants [26]. The semistructured interviews inquired about experiences with genetic counseling, genetic testing, and family communication patterns. We enriched the lexicon with supplementary words related to communication identified in an online thesaurus [37]. The final lexicon we created contained 532 items (132 unigrams, 215 bigrams, and 185 trigrams). Two members of the research team independently created the scoring of N-grams in the lexicon as positive or negative without considering the context of the phrases in the interviews. Specifically, they evaluated each item on a 7-point scale on how favorable the items measure "openness of communication." Scoring values ranged from –3 (extremely strong negative word related to communication) to +3 (extremely strong positive word related to communication). In cases of disagreement, the final value was calculated by averaging the 2 values given by the 2 raters rounding to the greater nearest integer. The final "openness of communication" score assigned to the transcript of each narrative was developed by matching N-grams to the lexicon and summing up the corresponding scores. To ensure the robustness of the above scoring process, we calculated the Pearson correlation coefficient between the "openness of communication" scores we created with the IRI overall score. This correlation was examined only on Swiss data because Korean IRI scores were not available at the time of this analysis.

Sentiment Analysis and Attitude Toward Family Communication of Genetic Risk

To categorize the text of each narrative as describing either a positive or negative attitude toward genetic testing and health care services and to capture the overall emotional valence of the narrative, we used 3 common lexicons for text sentiment analysis: AFINN, Bing Liu, and the National Research Council Canada (NRC) Emotion Lexicon. The AFINN lexicon contains words with a score between –5 and +5, with negative and positive scores indicating negative and positive sentiments, respectively [38]. The Bing Liu lexicon classifies words into conveying a positive or a negative sentiment [1]. The NRC Emotion Lexicon estimates a sentiment score (positive and negative sentiment) based on 8 emotions. Positive emotions include anticipation, joy, surprise, and trust, whereas negative emotions include anger, disgust, fear, and sadness [39,40]. We also calculated an overall net sentiment expressed in each narrative, based on the difference between overall positive sentiment minus overall negative sentiment. An overall positive score meant that the individual expressed more positive sentiment in the narrative than negative, and vice versa.

Training Phase

For developing the model, the overall data set was split randomly, with 70% of data used in the training phase by using the "openness of communication" score as the dependent variable. To examine whether the demographic and clinical characteristics and sentiment features of each narrative predicted "openness of communication" scores, we used a linear regression model based on the following steps. Initially we performed a univariate analysis to identify those independent variables exhibiting more than 60% absolute correlation with one another. These variables were excluded to avoid multicollinearity. Then, we continued with a multivariate analysis using a stepwise linear regression to identify possible predictors of the dependent variable and remove nonsignificant independent variables. As an alternative model, we attempted to use an artificial neural network. We built a fully connected network with 1 hidden layer, 1 input and 1 output layer, and 5 neurons. Optimization was done through the Broyden-Fletcher-Goldfarb-Shanno method. Early stopping was utilized to avoid overfitting. However, we ended up discarding the artificial neural network from the analysis because it showed no improvement compared to the linear regression. Finally, the performance of the models was evaluated using the area under the curve (AUC), sensitivity, specificity, and root mean square error (RMSE).

Testing Phase

In this phase, we tested the model using the remaining 30% of the database (validation cohort). The performance of the models was evaluated using the same metrics as in the training phase, ie, AUC, sensitivity, specificity, and RMSE.

Results

Description of the Sample

Narrative and survey data from 53 individuals are included in this paper. Participants were aged 32-76 years. Most were female (47/53, 89%), married (41/53, 77%), and carriers of the familial pathogenic variant (51/53, 96%). Approximately 2 in 3 (32/53, 60%) had a prior diagnosis of cancer (Table 1). The Swiss and the Korean samples were not statistically different in respect to age (P=.71), prior cancer diagnosis (P=.38), educational level (P=.17), and employment status (P=.14).

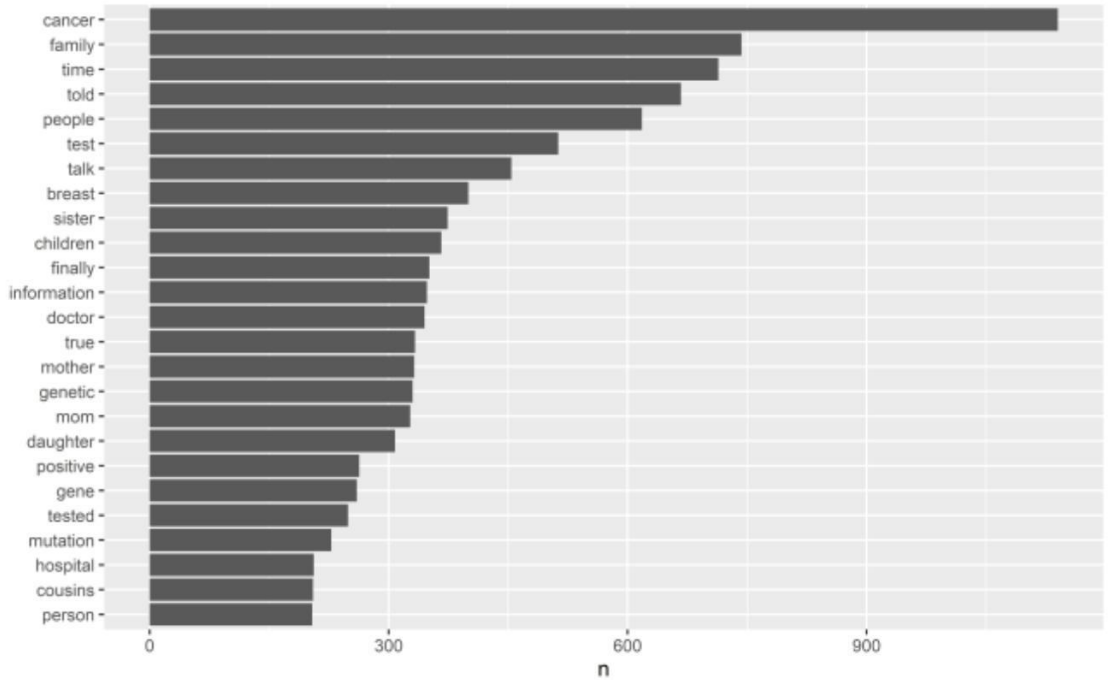
Table 1. Sociodemographic and clinical data of participants (N=53).

Characteristic	Value
Age (years), mean (SD)	53.3 (12.1)
Sex, n (%)	
Female	47 (89)
Education, n (%)	
Attended elementary/high school	5 (9)
High school graduate	14 (26)
Technical school graduate	13 (24)
University degree/postgraduate degree	21 (40)
Marital status, n (%)	
Married/living as married	41 (77)
Single	4 (8)
Divorced/separated/widowed	8 (15)
Employed full or part time (yes), n (%)	34 (64)
Cancer status, n (%)	
Previous cancer, one or more diagnoses	32 (60)
Never been diagnosed with cancer	21 (40)
Genetic test result, n (%)	
Positive for the familial pathogenic variant	51 (96)
Negative for the familial pathogenic variant	2 (4)

Description of the "Openness of Communication" Score and the Narrative Data

The average "openness of communication" score was 29.8 (SD 19.5; range –9 to 76), indicating an overall trend toward open communication. Narratives from these 53 individuals included 5837 unique unigrams, 4183 bigrams, and 654 trigrams. The most frequently appearing nontrivial words are shown in Figure 2. Based on the NRC Emotion Lexicon, the 10 most common positive words were "time," "true," "children," "talk," "finally," "information," "positive," "doctor," "understand," and "daughter". The 10 most common negative words were "cancer," "sick," "feel," "risk," "negative," "died," "difficult," "fear," "disease," and "bad."

Figure 2. The most frequent words identified in narratives.



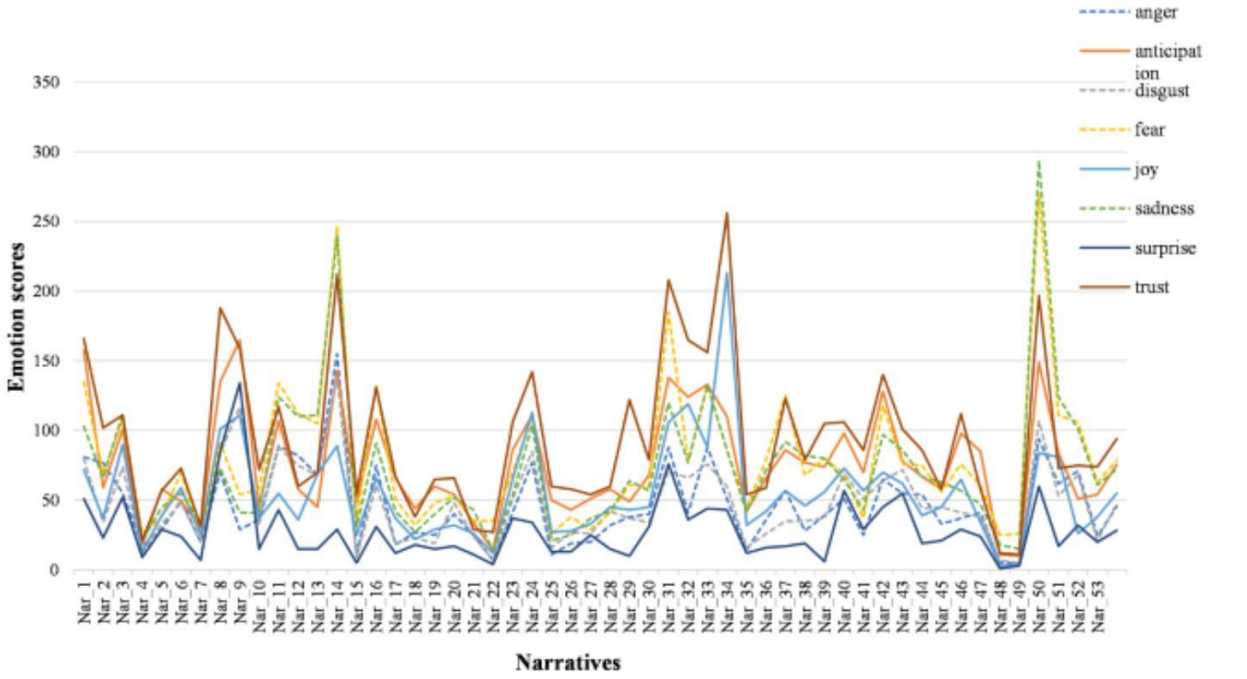
Validating the Relationship of "Openness of Communication" scores with IRI

The correlation coefficient between the "openness of communication" score and IRI in the Swiss data was r=0.46, indicating a moderate positive correlation.

Attitude Toward Genetic Testing and Health Care Services

Attitude toward genetic testing and health care services varied among participants, but it was overall positive. "Trust" appeared as the strongest positive emotion, whereas "fear" and "sadness" appeared as the strongest negative emotions in the text corpus based on the NRC Emotion Lexicon. The least perceived emotions were "surprise" and "anger." Figure 3 describes the frequencies of words identified in the corpus for each emotion.

Figure 3. Frequencies of words identified for each emotion (anger, anticipation, disgust, fear, joy, sadness, surprise, and trust) based on the National Research Council Canada Emotion Lexicon.



Prediction of "Openness of Communication" Score

The R^2 for the overall model was 0.87 (adjusted R^2=0.85; P<.001). A stepwise linear regression identified 5 significant predictors of "openness of communication" score, ie, the overall net sentiment of the narrative and fear, which were obtained based on the NRC Emotion Lexicon; informational support among family members; educational level; and being single (Table 2). Specifically, findings showed that both the higher overall net sentiment score of the narrative (P=.007) and also greater fear (P=1.97 × 10^{-5}) were strongly associated with higher "openness of communication" scores. There was a positive correlation between "openness of communication" score and the statement "In our family when I have a health problem there is great willingness to share information with each other" (P=.005). Participants with nonacademic education were also more likely to communicate genetic risk with their relatives (P=.02). Lastly, there was a positive correlation between being single and "openness of communication" scores (P=.047).

Table 2. Results of the linear regression analysis predicting "openness of communication."

Variables	Estimate	SE	*t* test[a] (*df*)	*P* value
Being single	19.782	9.574	2.066 (1)	.047[b]
Academic education	–10.387	4.256	–2.44 (1)	.02[b]
Fear	0.204	0.041	4.954 (1)	1.97 × 10–5[c]
Informational support	11.392	3.790	3.006 (1)	.005[d]
Net sentiment score of the narrative	0.260	0.091	2.861 (1)	.007[d]

[a]2-tailed *t* test.

[b]Significance level: *P*<.05.

[c]Significance level: *P*<.001.

[d]Significance level: *P*<.01.

Model Performance

The predictive accuracy of the model using a stepwise linear regression for the training and testing data sets reached 0.85 (AUC=0.92, specificity=0.86, and sensitivity=0.82) and 0.72 (AUC=0.69, specificity=0.62, and sensitivity=0.83), respectively. Figure 4 presents the receiver operating characteristic curves that visualize the accuracy improvement between the training and testing data sets applying linear regression.

The predicted values are plotted against the target values and are shown on a scatter plot for the linear regression model (Figure 5). The linear regression model achieved RMSEs of 11.76 (training data set) and 16.04 (testing data set). In this case, our model performs more accurately when it yields lower values of RSME.

Figure 4. Receiver operating characteristic (ROC) curves of the training (A) and testing (B) model predicting "openness of communication" applying linear regression. AUC: area under the curve.

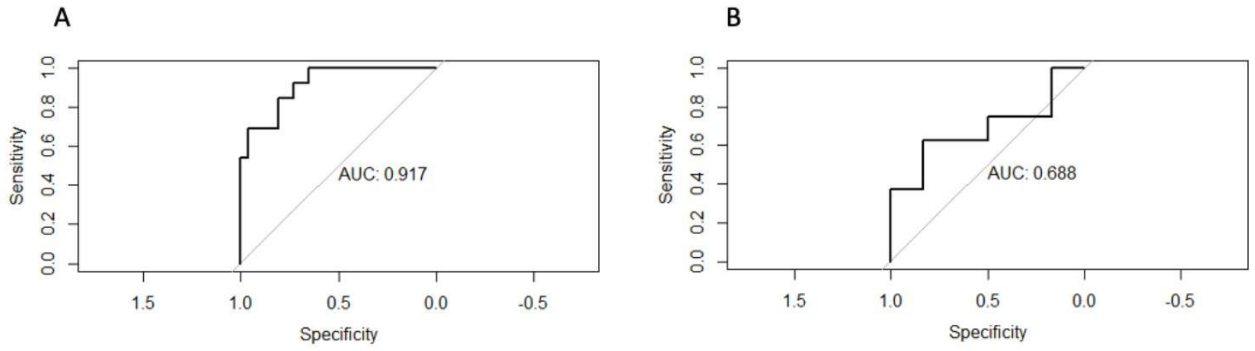
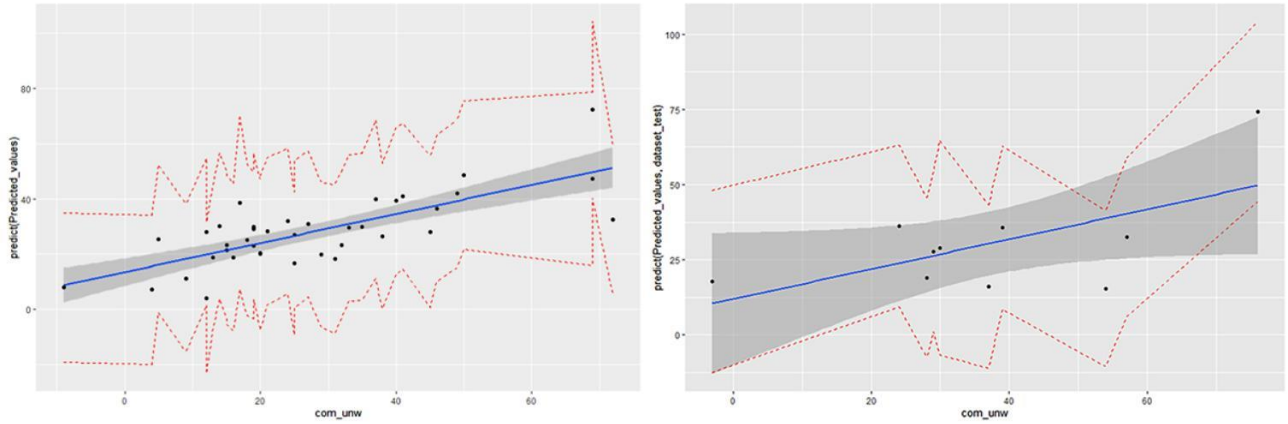


Figure 5. Scatter plot of predicted values against target values with 95% confidence and prediction intervals for the training (A) and testing (B) data sets applying linear regression.



Discussion

Principal Findings

We analyzed 53 narratives regarding intrafamilial communication of genetic cancer risk associated with HBOC. NLP enabled the analysis of unstructured narratives from different languages and identified the most frequently used words or combination of words describing openness in family communication of genetic cancer risk. This was the first study in which we applied NLP and sentiment analysis to better understand factors driving open intrafamilial communication regarding genetic cancer risk. Our findings showed that sentiment plays a crucial role and that emotions are a pervasive feature that predict intrafamilial communication in this particular population. Sentiment analysis performed on all interviews provided scores demonstrating positive or negative emotional valence, which were highly predictive of the direction of intrafamilial communication in this context. The higher overall net sentiment scores predicted greater openness in intrafamilial communication, whereas the lower overall net sentiment scores predicted closed or absent communication. This finding provides insights consistent with social penetration theory related to self-disclosure of carrying a cancer-causing genetic variant [41,42]. The depth of self-disclosure, ie, the degree to which the individual reveals personal and private information involving unusual traits and painful memories, reflects the degree of intimacy of a relationship. In the context of HBOC intrafamilial communication, self-disclosure of personal genetic information may be opposed by the desire to retain privacy and to avoid creating uncertainty and unpredictability in interpersonal relationships. Anticipating future negative emotions, such as regret or conflict, categorizes genetic risk information as a considerable emotional threat [43]. This finding was captured in our analysis as the overall net sentiment of each narrative, and its predictive value was confirmed based on the performance of our models. Taken together, findings indicate that sentiment can be used to frame genetic cancer risk as an opportunity for proactive risk reduction and for enhancing technology-mediated HBOC intrafamilial communication.

Our linear regression model explained more than 80% of the variance in openness of communication and achieved good performance in both the training and the testing samples. Our findings show that NLP was highly accurate in analyzing unstructured narratives from individuals of different cultural and linguistic backgrounds (Swiss German, French, Italian, English, and Korean) and in quantifying openness of communication in intrafamilial discussions about genetic cancer risk. The "openness of communication" scores were also validated against IRI. IRI was developed on the premise that increased genetic knowledge, positive motivation, and increased self-efficacy are prerequisites of increased intention to inform relatives about genetic risk. Although "intention to inform relatives" is closely related to "openness of communicating genetic risk," the 2 concepts are not identical, which was also confirmed in our data with a moderate positive correlation between the 2 scores. An individual may have high intention to inform relatives about their genetic risk despite difficulties in communication within their family.

Creating a new lexicon for openness in communication enriched with terms from different sources contributes to the innovation of our approach and the generalizability and applicability of our findings. Our lexicon can be further used and expanded in future projects, providing a solid foundation for the use of NLP in the growing field of research in interpersonal communication, focusing on family communication and health care and technology-mediated communication [44]. Sentiment analysis can be further utilized in the era of precision medicine and precision public health for message tailoring and message framing. Extracting sentiment polarities can be highly informative in improving consumer experiences when using digital health platforms in promoting precision public health campaigns. For example, trust in the health care system has been associated with use of cancer surveillance, whereas conflicting messages from providers create a sense of disorientation and mistrust [45-48].

Our findings also indicated a greater likelihood of open intrafamilial communication in those who were single, had a nonacademic education, and higher informational support within their family network. These findings should be interpreted with caution and should be replicated with analyses of narratives from larger, and possibly more diverse, samples.

Strengths and Limitations

Studies in different domains have also considered sentiment for analyzing textual communication in social media such as Twitter or Facebook [5,9,11]. However, one significant strength of our approach was that narrative data were combined with the demographic and clinical characteristics of participants, which can increase the applicability of findings. Another important strength was the use of several sentiment lexicons to select the most suitable for this context. Sentiment scores originating from the NRC Emotion Lexicon were the most appropriate to predict "openness of communication," whereas the other 2 sentiment lexicons (AFINN and Bing Liu) were highly correlated, resulting in a predictive algorithm of lesser importance. Studies have shown that the selection of inappropriate lexicons may impact prediction performance [39,40]. Finally, NLP can automate parts of text analysis and can be used as an assisting tool to help researchers navigate through large volumes of text data.

One limitation of our study was the small sample size and the size of the available corpus, which did not allow us to include possible significant covariates and to fully explore the potential of the NLP methodology, including sentence structure and length of words. Despite this limitation, the results of our study can be used as indicators of various narrative features, such as overall sentiment and fear, which can be important predictors of interpersonal communication and self-disclosure in this specific population. Important features of NLP analysis, such as sentence structure and length of words, can be investigated with a larger number of narratives and larger number of corpora. The analytical approach we describe in this paper can be further improved by using larger samples. Further development of a robust model will advance a more precise assessment and reach higher accuracy.

Conclusions

We demonstrate how various features from narratives can be used to predict "openness of communication" in individuals carrying a pathogenic variant connected to HBOC. Although our methodology requires further exploration and our findings require replication with larger samples, this is an important first step to understand how individuals and the public may react in discourses involving communication of genetic cancer risk. Overall, this experimental analysis provides evidence that our approach is promising and can be further used in the field of technology-mediated communication and precision public health.

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Authors' Contributions

VB, RCGP, GL, and MCK contributed to conceptualization. VB, RCGP, RS, and MCK contributed to methodology. VB contributed to formal analysis and visualization. VB and MCK contributed to writing—original draft preparation. VB, RCGP, SK, RS, SHB, MCZ, GL, FC, and MCK contributed to writing—review and editing. MCK contributed to supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the curve
HBOC: hereditary breast and ovarian cancer
IRI: Informing Relatives Inventory
LS: Lynch syndrome
NLP: natural language processing
NRC: National Research Council Canada
RMSE: root mean square error

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3.3. Study III: Acceptability and Usability of the Family Gene Toolkit for Swiss and Korean Families Harboring BRCA1/BRAC2 Pathogenic Variants: A Web-Based Platform for Cascade Genetic Testing

Authors:

Vasiliki Baroutsou [1], Vu Duong [1], Alice Signorini [1], Ramon Saccilotto [1], Florina M. Ciorba [2], Nicole Bürki [3], Maria Caiata-Zufferey [4], Jai Min Ryu [5], Sung-Won Kim [6], Myong Cheol Lim [7], Christian Monnerat [8], Ursina Zürrer-Härdi [9], Jisun Kim [10], Karl Heinimann [11,12], Rossella Graffeo [13], Ji Soo Park [14], Manuela Rabaglio [15], Pierre Olivier Chappuis [16,17], Sue Kim [18] and Maria C. Katapodi [1,*] on behalf of the CASCADE and K-CASCADE Consortia

1 Department of Clinical Research, Faculty of Medicine, University of Basel, Basel, Switzerland
2 Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland
3 Women's Clinic, University Hospital Basel, Basel, Switzerland
4 Department of Business Economics, Health and Social Care, University of Applied Sciences and Arts of Southern Switzerland, Manno, Switzerland
5 Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
6 Department of Breast Surgery, Breast Care Center, Dairim St Mary's Hospital, Seoul, Republic of Korea
7 Division of Tumor Immunology, Center for Gynecologic Cancer Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea
8 Department of Medical Oncology, Hospital of Jura, Delemont, Switzerland
9 Department of Medical Oncology, Cantonal Hospital Winterthur, 8400 Winterthur, Switzerland
10 Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
11 Institute for Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland
12 Research Group Human Genomics, Department of Biomedicine, University of Basel, Basel, Switzerland
13 Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland
14 Hereditary Cancer Clinic, Cancer Prevention Center, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
15 Department of Medical Oncology, Inselspital, Bern University Hospital, Bern, Switzerland
16 Unit of Oncogenetics, Division of Precision Oncology, University Hospitals of Geneva, Geneva, Switzerland
17 Division of Genetic Medicine, University Hospitals of Geneva, Geneva, Switzerland
18 College of Nursing, Yonsei University, Seoul 03722, Republic of Korea

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Article

Acceptability and Usability of the Family Gene Toolkit for Swiss and Korean Families Harboring *BRCA1/BRAC2* Pathogenic Variants: A Web-Based Platform for Cascade Genetic Testing

Vasiliki Baroutsou [1], Vu Duong [1], Alice Signorini [1], Ramon Saccilotto [1], Florina M. Ciorba [2], Nicole Bürki [3], Maria Caiata-Zufferey [4], Jai Min Ryu [5], Sung-Won Kim [6], Myong Cheol Lim [7], Christian Monnerat [8], Ursina Zürrer-Härdi [9], Jisun Kim [10], Karl Heinimann [11,12], Rossella Graffeo [13], Ji Soo Park [14], Manuela Rabaglio [15], Pierre Olivier Chappuis [16,17], Sue Kim [18], Maria C. Katapodi [1,*] and on behalf of the CASCADE and K-CASCADE Consortia [†]

1 Department of Clinical Research, Faculty of Medicine, University of Basel, 4055 Basel, Switzerland; vasiliki.baroutsou@unibas.ch (V.B.); vu.duong@usb.ch (V.D.); alice.signorini@stud.unibas.ch (A.S.); ramon.saccilotto@usb.ch (R.S.)
2 Department of Mathematics and Computer Science, University of Basel, 4051 Basel, Switzerland; florina.ciorba@unibas.ch
3 Women's Clinic, University Hospital Basel, 4031 Basel, Switzerland; n.buerki@hin.ch
4 Department of Business Economics, Health and Social Care, University of Applied Sciences and Arts of Southern Switzerland, 6928 Manno, Switzerland; maria.caiata@supsi.ch
5 Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea; jaimin.ryu@samsung.com
6 Department of Breast Surgery, Breast Care Center, Dairim St Mary's Hospital, Seoul 07442, Republic of Korea; brcakorea@gmail.com
7 Division of Tumor Immunology, Center for Gynecologic Cancer Research Institute and Hospital, National Cancer Center, Goyang 10408, Republic of Korea; mclim@ncc.re.kr
8 Department of Medical Oncology, Hospital of Jura, 2800 Delemont, Switzerland; christian.monnerat@h-ju.ch
9 Department of Medical Oncology, Cantonal Hospital Winterthur, 8400 Winterthur, Switzerland; ursina.zuerrer@ksw.ch
10 Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Republic of Korea; jisunkim@amc.seoul.kr
11 Institute for Medical Genetics and Pathology, University Hospital Basel, 4031 Basel, Switzerland; karl.heinimann@usb.ch
12 Research Group Human Genomics, Department of Biomedicine, University of Basel, 4031 Basel, Switzerland
13 Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale (EOC), 6500 Bellinzona, Switzerland; rossella.graffeogalbiati@eoc.ch
14 Hereditary Cancer Clinic, Cancer Prevention Center, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03772, Republic of Korea; pmjisu@yuhs.ac
15 Department of Medical Oncology, Inselspital, Bern University Hospital, 3010 Bern, Switzerland; manuela.rabaglio@insel.ch
16 Unit of Oncogenetics, Division of Precision Oncology, University Hospitals of Geneva, 1205 Geneva, Switzerland; pierre.chappuis@hcuge.ch
17 Division of Genetic Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland
18 College of Nursing, Yonsei University, Seoul 03722, Republic of Korea; suekim@yuhs.ac
* Correspondence: maria.katapodi@unibas.ch
† Membership of the CASCADE and K-CASCADE consortia is provided in the Acknowledgments.

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Simple Summary: The study adapted an existing Web-based intervention, the Family Gene Toolkit, for Swiss and Korean families that harbor the genetic changes associated with hereditary breast and ovarian cancer syndrome. The Family Gene Toolkit encourages family communication of genetic testing results and cascade genetic testing among at-risk relatives. Feedback from 68 women with genetic changes and 31 clinicians informed the culturally sensitive adaptation of the content. The Information Technology team developed the web application that will host the intervention. Finally, a new sample of 18 women from families with hereditary breast and ovarian cancer reviewed and

evaluated the adapted content and the functions of the web application. Findings support that overall, the adapted Family Gene Toolkit is well-designed, has useful information for these families, and provides interactive content and illustrative stories. The research team will test if it can increase rates of cascade testing among at-risk relatives in a subsequent randomized trial.

Abstract: The study adapted the Family Gene Toolkit and developed a customized web application for Swiss and Korean families harboring *BRCA1* or *BRCA2* pathogenic variants to support family communication of genetic testing results and promote cascade genetic testing among at-risk relatives. In the first step, narrative data from 68 women with *BRCA1/BRCA2* pathogenic variants and clinician feedback informed a culturally sensitive adaptation of the content consistent with current risk management guidelines. In the second step, the Information Technology team developed the functions and the interface of the web application that will host the intervention. In the third step, a new sample of 18 women from families harboring *BRCA1/BRCA2* pathogenic variants tested the acceptability and usability of the intervention using "think-aloud" interviews and a questionnaire. Participants expressed high levels of satisfaction with the intervention. They provided positive feedback for the information regarding active coping, strategies to enhance family communication, interactive elements, and illustrative stories. They reported that the information was useful and the web application was easy to navigate. Findings suggest that the Family Gene Toolkit is well-designed and can increase rates of cascade testing among at-risk relatives. Its efficacy will be tested in a subsequent randomized trial.

Keywords: active coping; decisional support; family communication; genetic counseling; HBOC; psychoeducational intervention; Tier 1 genetic condition

1. Introduction

Clinical practice guidelines recommend testing individuals diagnosed with cancer to identify carriers of germline pathogenic variants [1]. Upon identifying a germline pathogenic variant, offering cascade genetic testing to cancer-free relatives promotes primary and secondary cancer prevention. Cascade testing for Hereditary Breast and Ovarian Cancer syndrome (HBOC) has been described by the Centers for Disease Control and Prevention (CDC) as a Tier 1 genetic application [2]. HBOC is diagnosed in about 5–10% and about 20% of all breast and ovarian cancer cases, respectively, with some estimates being higher for selected patients and families [3]. HBOC is also implicated in prostate, pancreatic, and skin cancer, as well as in other malignancies [4].

Despite calls to action for cascade testing of biological relatives of HBOC cases, there are barriers to its implementation. Privacy laws worldwide prohibit healthcare providers from reaching at-risk relatives without the explicit consent of the tested individual [5]. The responsibility to share genetic test results lies exclusively with the individual carrying the pathogenic variant, who may simultaneously be struggling with a cancer diagnosis [6–8]. This communication strategy has significant limitations in ensuring contact with at-risk relatives and the transmission of accurate information [9,10], leaving approximately 50% of them unaware of their potential cancer risk [11]. This created the challenge of reaching relatives who are not in contact with the healthcare system through family networks [12–15]. Genetic specialists responded by writing family letters that can be distributed by the tested individual or sent directly to at-risk relatives. However, family letters have been implemented inconsistently due to increased clinician burden, and studies have shown mixed results [16,17].

Interventions supporting individuals with HBOC-associated variants during the disclosure of genetic test results have the potential to reduce their psychological distress. Additionally, such interventions can serve to provide relatives with accurate and dependable information about cascade testing. They also need to minimize the efforts of genetic specialists while abiding by existing legal frameworks regarding the privacy and

confidentiality of genomic information. Given the explosion of health communication technologies [18], novel approaches are needed. Technology-enabled health communication is equally effective in disseminating accurate information, is cost-effective, and can increase access to services [19–21]. Leveraging digital health communication is also consistent with consumer behavior since about 20% of families use social media to share genetic testing results [22], and more than 80% of individuals use the World Wide Web to acquire health-related information [23–25]. However, there are only a handful of trials regarding family communication of genetic testing results and/or cascade genetic testing [26]. Few studies involving digital communication technologies, such as chatbots or other digital media, describe pilot testing in non-randomized trials and/or without comparisons to a control group [27–33].

We developed a web-based family intervention, the Family Gene Toolkit, to encourage disclosure of genetic testing results from individuals with *BRCA1* or *BRCA2* pathogenic variants and support cascade testing among at-risk relatives [34]. The prototype was based on the theory of stress and coping [35] and adapted to the needs of HBOC families, i.e., individual and family adaptation to genetic illness [36,37] and decision-making [38]. The prototype addressed genetic predisposition to cancer and the accuracy of genetic testing. A decisional support tool included patient testimonials about accepting or refusing genetic testing based on the International Patient Decision Aids Standards criteria [39]. The prototype was delivered by a certified genetic counselor and a master's prepared oncology nurse using two live webinars (PowerPoint presentations with live audio) and one brief follow-up phone call [34]. Live webinars enabled real-time interaction among family members and expert clinicians and lasted approximately 60 min. The first webinar was facilitated by the genetic counselor and provided information about cancer genetics, counseling, and testing. The second webinar was offered a week later by the oncology nurse and provided information on active coping strategies and the effective communication of genetic testing results. Two weeks following the second webinar, each participant received a 15-min phone call from the genetic counselor and the nurse to address individual concerns.

The Family Gene Toolkit prototype was tested with U.S.-based participants. Acceptability and usability were tested with focus groups, while feasibility and efficacy were tested in a pilot study using a randomly assigned wait-listed control group. Results provided proof of concept for the high acceptability, usefulness, participant satisfaction, and efficacy of the intervention [34]. However, findings also highlighted issues that would impede the upscale of implementation. Scheduling live webinars to accommodate the lifestyle and different time zones of family members and clinicians was interfering with the success of the approach. The involvement of two master's prepared clinicians made for an expensive intervention and raised questions about its cost-effectiveness. There was also a lack of consensus about the optimal time frame for intervening, indicating variability in preferences due to competing priorities, e.g., cancer treatment or relatives' life trajectories. Live webinars precluded the possibility of tailoring the timing of delivering the intervention to individual circumstances and preferences.

The purpose of this study was to describe the adaptation of the Family Gene Toolkit prototype for upscaling its implementation in clinical practice. Adapting and expanding an existing prototype, rather than developing a new intervention, takes advantage of previous valid experiences without duplicating efforts. The adapted Family Gene Toolkit also addresses the changing informational requirements of international audiences, specifically Swiss and Korean families. Although Swiss and Korean populations are ancestrally different, the prevalence of *BRCA* pathogenic variants is comparable between the two countries, along with a growing interest and concern about HBOC in Korea [40–42]. The culturally sensitive adaptation of digital health communication interventions is extremely timely and relevant, given the expansion of genetic technologies, the falling costs of testing, and the increased pressure for integrating genetic knowledge into practice.

2. Materials and Methods

The adaptation of the Family Gene Toolkit prototype followed a three-step process (Figure 1). In step 1, we updated and adapted the prototype based on newer evidence regarding cancer risks associated with *BRCA1*/*BRCA2* pathogenic variants and feedback from expert clinicians, researchers, and individuals from *BRCA1*/*BRAC2*-harboring families. In step 2, we designed and programmed the functions of the web application that will host the Family Gene Toolkit. In step 3, we tested the acceptability and usability of the new Family Gene Toolkit. The study protocol has been approved by appropriate Ethics Committees (BASEC 2016-02052 and SEVIRB 2020-0833-006) and is publicly available (NCT04214210; KCT0005643).

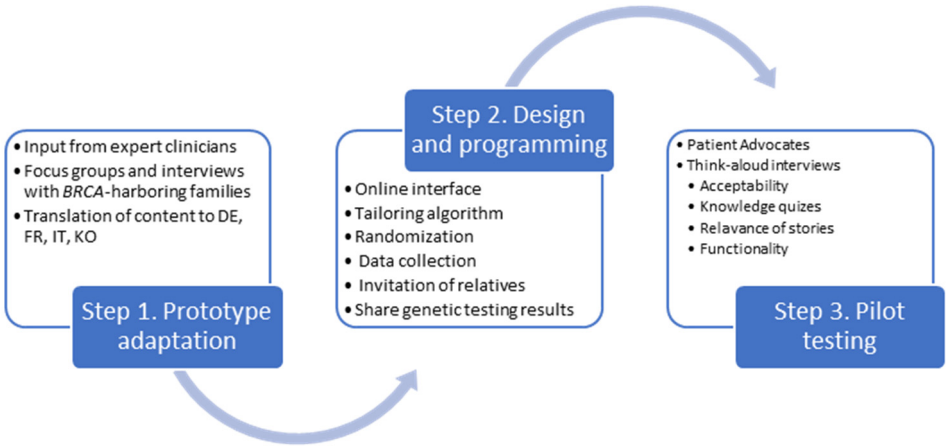

Figure 1. The steps of adaptation and pilot testing of the Family Gene Toolkit.

2.1. Step 1. Adaptation of the Prototype

The cultural adaptation of the Family Gene Toolkit involved collecting narrative data through focus groups and in-depth interviews. This process included individuals from families harboring *BRCA1* or *BRCA2* pathogenic variants and took into account Swiss and Korean legislation, health insurance policies, and cultural values. Narratives evolved around cancer risk and genetic testing, risk management, and family communication [8], and informed culturally appropriate message framing, identified tailoring elements, and illustrative stories. The adapted content was translated from English to German, French, Italian, and Korean, following the established methods for the translation of health-related messages [43].

The adapted Family Gene Toolkit was reviewed by clinicians involved in genetic counseling in Switzerland and Korea and experts in health communication, nursing, psychology, and sociology. Clinicians and experts were identified through the Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) Network for Cancer Predisposition Testing and Counseling, through the Oncoplastic Breast Consortium [44], and through the CASCADE (NCT03124212) [45] and the K-CASCADE (KCT0005643) [46] consortia. Experts met in small groups and evaluated the alignment of the content with the current guidelines regarding the management of *BRCA1* and *BRCA2*-associated cancer risks, the consistency of the translated medical and genetic terms with terminology used in clinical practice, the appropriateness and relevance of messages and illustrative stories, and the appearance, organization, and clarity of the slideshow.

2.2. Design and Programming

The interface of the adapted Family Gene Toolkit was based on design principles for navigability and user experience of web applications [47–49]. To design the main content of the Family Gene Toolkit, we used a readily available e-learning product (www.articulate.com accessed on 5 September 2023) that offers software solutions to create an interface accessible from a computer, tablet, and smartphone. This was integrated with a customized

system to manage user accounts, provide localization into various languages, allow users to invite relatives to the system, and track user activities for research purposes.

2.3. Acceptability and Usability Testing

The final version of the Family Gene Toolkit underwent acceptability (favorable attitude toward and satisfaction with the intervention) and usability testing (testing for functional errors) through an iterative process. Acceptability and usability testing was conducted with patient advocates in each country and new members from families harboring *BRCA1/BRCA2* pathogenic variants recruited from the CASCADE and K-CASCADE consortia. Acceptability was tested using "think-aloud" interviews, an established method for participants to voice their thoughts, feelings, and opinions while they are completing each task of the web application [50]. During the "think-aloud" interviews, participants provided verbal feedback on various aspects of the Family Gene Toolkit. This included assessing its usefulness and the reading level and comprehension of messages from the lay public, evaluating the effectiveness of visual illustrations and narratives in conveying key concepts, and offering suggestions for improving the context, layout, pictures, and color scheme. "Think-aloud" interviews were conducted in five languages (German, French, Italian, Korean, and English).

Usability testing is an established technique aiming to systematically test the navigability of a tool prior to its distribution [51,52]. Usability testing assessed two main aspects. First, the ability of participants to use all functions and features of the web application. Second, the ease and user-friendliness of navigation across various devices, including laptops, tablets, and smartphones. This evaluation included opening the platform, navigating through each module, and interacting with its components. Participant feedback was elicited either in person or in virtual sessions via Zoom. Sessions were recorded, and team members took notes for each step. Feedback from each cycle informed the modifications that were tested in the subsequent cycle.

The acceptability and usability of the Family Gene Toolkit were also assessed with a 14-item Likert scale (1 = low to 7 = high). After completing the "think-aloud" protocol, participants were asked to rate their overall satisfaction with the application. Satisfaction included aspects such as the helpfulness and clarity of the content, expressing whether they desired additional information in specific content areas, evaluating the user-friendliness of navigation, and sharing their thoughts on the format and appearance of the slideshow. We used descriptive statistics, such as medians and interquartile range (IQR), to describe participants' demographic characteristics and summarize the acceptability and usability data. All computations were performed in R software, version 3.6.3 [53]. Narrative data from the "think aloud" interviews were analyzed using content analysis [54] from two members of the research team in each country.

3. Results

3.1. Adaptation of the Prototype

Insights for culturally sensitive message framing, tailoring, and illustrative stories were gained from 68 women (46 Swiss and 22 Korean) harboring *BRCA1/BRCA2* pathogenic variants who provided narrative data. Most women in both countries were well-educated, married or in a relationship, and had at least one previous cancer diagnosis. The only difference was that Swiss women were more likely to be employed outside the household (Table 1). Participants emphasized the significance of including certain elements in the web-based platform. For example, they highlighted the importance of information about cancer risk for both sexes and suggested a comprehensive explanation of the genetic counseling and testing process that would address common concerns that people might have. They also stressed the importance of incorporating information about prophylactic surgeries, such as mastectomy and salpingo-oophorectomy, into the platform, as these details are often overlooked in genetic counseling sessions. In addition, the inclusion of testimonials

and personal stories would greatly enhance the platform by creating a sense of community and providing reassurance to users.

Feedback was also elicited from 31 clinicians and experts (24 Swiss and 7 Korean) representing different linguistic regions (n = 11 German-, n = 8 French-, n = 5 Italian-, and n = 7 Korean-speaking). Feedback was elicited in two rounds of 4 mini focus groups (a total of 8 focus groups) in Switzerland and 7 individual interviews in Korea. Teams in each country met independently and together to finalize the culturally sensitive adaptation of the content, message-framing, and illustrative stories. This iterative process took place from January 2022 to April 2023. The adapted content was first developed in English at an eighth-grade reading level and was translated into German, French, Italian, and Korean. Clinicians and researchers provided feedback at least twice during the adaptation process, both for the English and translated versions.

Table 1. Characteristics of the 68 women who provided narrative data for culturally sensitive content adaptation and message framing.

Characteristic	Swiss Sample N = 46	Korean Sample N = 22
Age (mean, range)	50 (32–72)	42 (27–68)
Linguistic region	(n, %)	(n, %)
French-speaking	25 (54%)	Not applicable
German-speaking	14 (31%)	
Italian-speaking	7 (15%)	
Education		
Compulsory/High school/Technical school	28 (61%)	7 (32%)
University/Post-graduate degree	18 (39%)	15 (68%)
Employment		
Yes	36 (78%)	8 (36%)
No	10 (22%)	14 (64%)
Marital status		
Married/Partnered	35 (76%)	15 (68%)
Divorced/Separated/Widowed	7 (15%)	1 (5%)
Single	4 (9%)	6 (27%)
Previous cancer diagnosis		
Yes (breast, ovarian, other)	29 (63%)	17 (77%)
No	17 (37%)	5 (23%)

The adapted Family Gene Toolkit included the original four modules and a newly developed fifth module addressing cancer risk management. The modules and the interface were supplemented with multiple interaction options to enhance user engagement, i.e., quizzes and assessments, illustrative stories, and resources to connect with psychologists, family therapists, nutritionists, and specialists for smoking cessation. Pictures were carefully selected for each country to enhance the displayed messages and increase relatedness based on age, sex, and race (Figure 2 and Supplementary Materials). The content was adapted as follows:

Genetics and cancer: This module provides basic information about the risk of developing HBOC-associated cancers with and without the contribution of *BRCA1* or *BRCA2* pathogenic variants and the modes of inheritance of these variants. The content was updated to emphasize the association of *BRCA1*/*BRCA2* variants with prostate, pancreatic, and possibly other types of cancer [4]. A link to available genetic services and a quiz were added to increase user interaction.

Genetic counseling and testing: This module is intended only for relatives who did not have genetic testing. It describes the genetic counseling process and provides updated information regarding panel and targeted testing, country-specific laws for the protection of

genetic information and associated costs, and illustrative stories about the advantages and disadvantages of genetic testing. It enables interactive pedigree visualization and includes a knowledge quiz, a link to available genetic services, and a list of questions relevant to the pre- and post-testing consultations.

Coping with cancer risk: This module explains the difference between active coping and avoidance and focuses on the importance of active coping and family support in HBOC. Testimonials from individuals with *BRCA1* or *BRCA2* pathogenic variants are used to demonstrate active coping with lifelong personal and family challenges associated with HBOC. The module was updated with links to genetic services in each country, while information on accessing psychological services and support groups increase user interaction.

Family communication: This module is intended only for individuals with *BRCA1* or *BRCA2* pathogenic variants. It explains the legal framework regarding the family-mediated communication of test results in each country, describes common issues that arise during this process, and provides practical tips to avoid family conflicts. Communication skills are enhanced with a prescriptive approach to the disclosure of testing results. The module was updated with culturally sensitive testimonials from individuals with *BRCA1* or *BRCA2* pathogenic variants. Links to the available genetic and psychological services in each country increase user interaction.

Cancer risk management: This module offers generic information on how testing results can inform prevention and screening for cancers known to be associated with *BRCA1*/*BRCA2*-associated HBOC. It also provides information exclusively for women, i.e., risk-reducing surgeries, breast reconstruction, esthetic flat closure, and risks and benefits of anti-hormonal treatment and oral contraceptives. The content includes country-specific information on a balanced diet, recommended levels of physical activity and alcohol consumption, and encourages smoking cessation. A quiz and links to available nutritional and smoking cessation services increase user interaction.

3.2. Design and Programming

The Information Technology (IT) Services team from the Department of Clinical Research at the University Hospital of Basel, Switzerland, developed a custom web application to facilitate the following processes:

- Enable secure, password-protected log-in for potential participants, assess eligibility, and provide a web-based consent form;
- Deliver a baseline questionnaire to collect information used for message tailoring and for evaluating outcomes;
- Facilitate the invitation of at-risk relatives to the web application via email and SMS messaging;
- Randomize participants either to the Family Gene Toolkit or a comparator website. At-risk relatives will be automatically assigned to the same group as the person who invited them to the study;
- Deliver the Family Gene Toolkit or the comparator, a non-interactive generic website that provides basic information related to HBOC;
- Deliver an evaluation questionnaire to assess satisfaction with the content of the Family Gene Toolkit and the comparator and with the technical aspects of navigating the web application;
- Deliver a follow-up questionnaire that will be used for evaluating primary and secondary outcomes related to family communication of testing results and cascade testing of relatives.

The function of the web application that facilitates cascade testing of at-risk relatives is the ability to send SMS and email messages to at-risk relatives and links to available genetic and other healthcare services. The web application will track the number of invitations sent to relatives, the proportion of at-risk relatives who receive an invitation over the number of relatives potentially eligible for cascade testing, and the number of invitations

that have been accepted by invited relatives. The web application will track access and use various indicators of "intervention dose", e.g., time spent on each session and engagement with interactive content. Instructions are provided on the main menu page, and users are directed through the content with "next ", "previous", and "home" buttons. All collected data will be securely stored and routinely backed up in protected servers of the University Hospital, Basel, Switzerland.

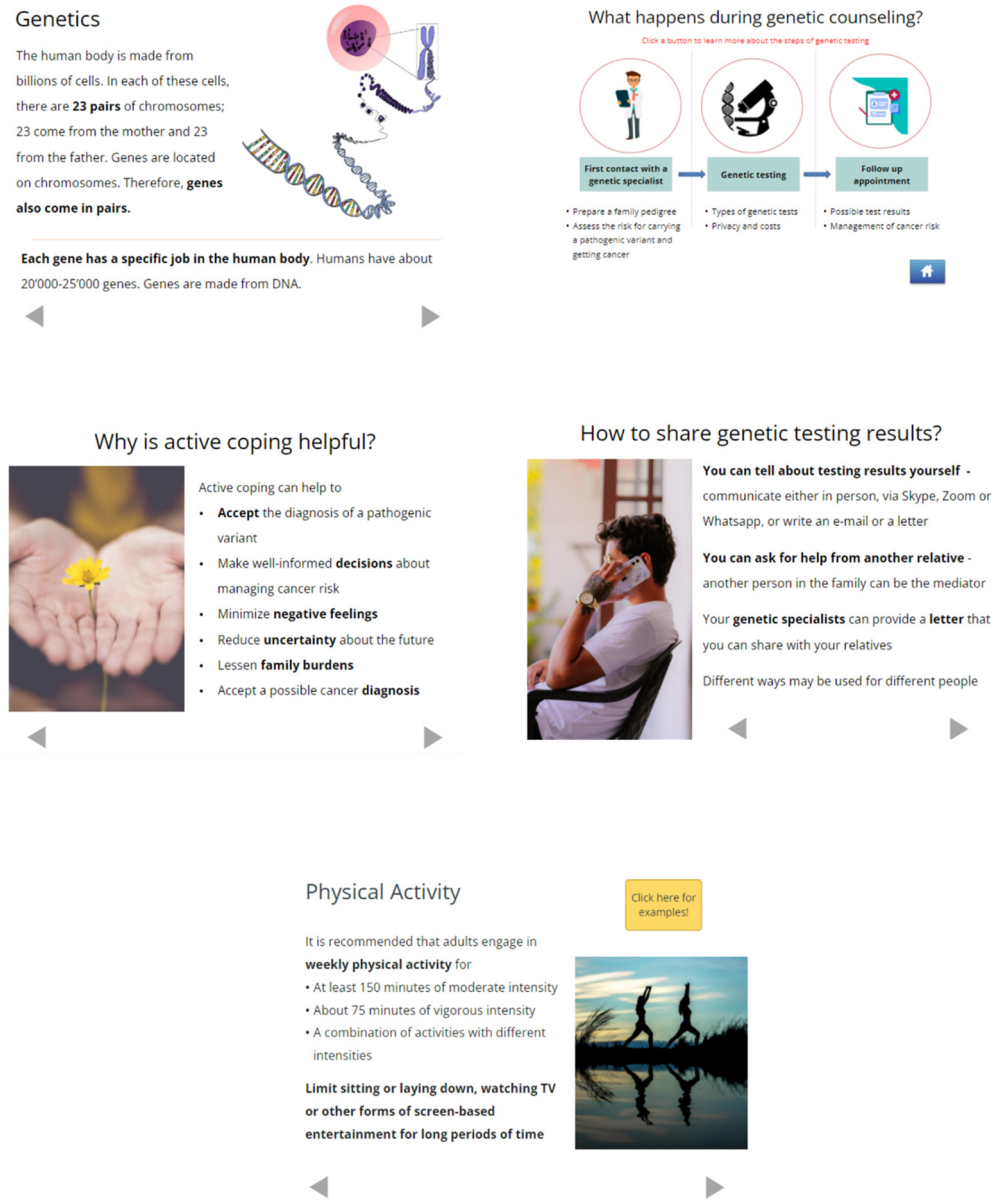

Figure 2. Examples from the five modules of the Family Gene Toolkit.

3.3. Acceptability and Usability Testing

Acceptability and usability testing of the adapted Family Gene Toolkit was tested with 18 women (13 Swiss and 5 Korean) who participated in the "think-aloud" interviews. The sample included mostly well-educated women who were employed outside their households. There was one untested relative, while the remaining 17 women had genetic testing and were identified as carriers of a *BRCA1* or *BRCA2* pathogenic variant (Table 2).

Participants in the 'think aloud' interviews in both countries engaged with the entire content of the Family Gene Toolkit and provided favorable feedback for the navigation. They clicked at least once on the links with the list of available genetic specialists while

navigating each module. They also clicked on the links with the list of psychological and nutritional services and patient support groups. Most participants provided positive feedback for the testimonials in their respective language that illustrated active coping and the challenges of communicating testing results. They referred to the module for family communication as 'fresh and helpful'. Participants also appreciated the engagement with quizzes and found the comprehensive explanation of the correct answer useful. The newly developed module on cancer risk management was highly appreciated, especially the information about the various types of breast reconstruction after mastectomy, which was referred to as 'empowering'. Almost all participants rated the content as highly acceptable (Table 3). They perceived that the length of each module and the amount of information was well-balanced and that the information was useful and easy to understand and made them think of ways to help their family.

Usability testing showed that navigating through the entire content of the Family Gene Toolkit took, on average, 55 min (range: 25–110). Completing the baseline questionnaire took approximately 15 min, and the evaluation questionnaire took approximately 3 min. Most participants (78%) stated that they would have liked to see the Family Gene Toolkit before or at the time they had genetic testing. An area for further improvement expressed by about 33% of participants included the possibility of a personalized risk assessment for various cancers rather than a range of risks. Table 4 presents illustrative quotes that convey satisfaction with the web application and suggestions for improvement.

Table 2. Characteristics of the 18 women who participated in the "think-aloud" interviews for acceptability and usability.

Characteristic	*N* = 18
Age (mean, range)	51 (28–70)
Linguistic region	
French-speaking	7 (39%)
German-speaking	5 (28%)
Italian-speaking	1 (6%)
Korean-speaking	5 (28%)
Education	
Compulsory/High school/Technical school	10 (56%)
University/Post-graduate degree	8 (44%)
Employment	
Yes	12 (67%)
No	6 (33%)
Marital status	
Married/Partnered	13 (72%)
Divorced/Separated/Widowed	2 (12%)
Single	3 (16%)
Previous cancer diagnosis	
Yes (breast, ovarian, other)	12 (67%)
No	6 (33%)

Table 3. Acceptability of the Family Gene Toolkit.

Question	Median (IQR) *
The Family Gene Toolkit had helpful information for...	
risk factors for hereditary breast and ovarian cancer syndrome	7 (1)
the genetic counseling and genetic testing process	7 (1)
how to find genetic services	7 (1)
cancer screening for people at higher risk	7 (1)
tips for family communication of genetic testing results	7 (0)
tips for family support in genetic cancer syndromes	7 (0)

Table 3. *Cont.*

Question	Median (IQR) *
The Family Gene Toolkit...	
was easy to understand	7 (1)
took too much time to review	3 (4)
made me nervous	1 (1)
was important to me	7 (1)
made me think about ways to help my family	6 (2)
was not useful to me	1 (1)
I would suggest this study to other people	7 (1)
The study was important	7 (1)

Note: * Likert point scale (1: Strongly Disagree; 2: Disagree; 3: Somewhat Disagree; 4: Neutral; 5: Somewhat Agree; 6: Agree; 7: Strongly Agree).

Table 4. Quotes demonstrating overall satisfaction with the Family Gene Toolkit.

Topic	Question	Quotes from "Think Aloud" Interviews
Content	How did you like the content of the Family Gene Toolkit?	*"I'd like to show it to my son...there is a lot of information about men."*
		"I had no idea that there are medications that could reduce cancer risk."
		"I found the quiz really helpful; it helps the information to stick in my mind."
Missing information	Is there any information that you needed but it was not addressed?	*"I would like to find more information about my personal cancer risk. And a specific risk estimate....That would be more helpful for me."*
Timing of intervention	When do you think is the best time to deliver this information?	*"I wish I had this intervention before I even started thinking about genetic testing and dealing with my cancer risk."*
		"I think this intervention would be more helpful when someone is just being diagnosed with the mutation."
Navigation	How easy or difficult was it to navigate the web application?	*"I expected that clicking on the arrow would take me back to the main menu, but it didn't. It was not clear to me what this 'home' button was."*
		"The quizzes are very nice, but I would also like to have a detailed explanation when I selected the correct answer." (This comment was addressed in subsequent interviews.)
		"It was not clear that I could find more links and see more stories when I clicked on words that were blue and bold."
Overall satisfaction	Overall, what do you think about the information covered in the Family Gene Toolkit?	*"The intervention is very well-done, with clear and comprehensive information, and made me feel that I want to read more."*
		"It contains everything and exhausted all the information."
		"Overall, I think the intervention is nice, has beautiful pictures, and is user-friendly. I had no trouble navigating through and finding what I needed."
	Overall, was there something that you did not like?	*"The intervention was very informative and well-structured, but I feel that this is very long."*
		"I think it would be stressful for some people to get this information. Maybe the intervention needs some more positive content."
		"I felt burdoned to tell my relatives. To me, it was hard to share results with my family members."

Italics present excerpts from narrative data demonstrating participants' perceptions about the Family Gene Toolkit.

4. Discussion

This study presents the adaptation of the Family Gene Toolkit and results from acceptability and usability testing with members from Swiss and Korean families harboring

BRCA1 or *BRCA2* pathogenic variants. An essential component of the adaptation process was the engagement and collaboration of multiple stakeholders, i.e., clinicians, content experts, patient advocates, and members of families harboring *BRCA1*/*BRCA2* pathogenic variants from Switzerland and Korea. The two teams worked together to create tailored and culturally sensitive messages and an interactive, user-engaging interface.

The adapted Family Gene Toolkit will be delivered via a website in an asynchronous communication pattern. While real-time interaction between family members and clinicians may be lacking, along with the chance for immediate feedback, asynchronous communication offers maximum flexibility and can support implementation upscaling. It allows tailoring the delivery time to the circumstances and preferences of individuals with pathogenic variants and at-risk relatives and the possibility of reviewing the content multiple times. Another advantage is the ability to reach a wider audience across all time zones. Given the linguistic and cultural diversity of Swiss-based families (62% German, 23% French, 8% Italian, 1% Romansh, and 23% of other ethnic and racial origin) [55], it is expected that the Family Gene Toolkit will be accessed by many families in German, French, Italian, and English-speaking countries. Korean-speaking families worldwide may also benefit from the intervention since the Korean diaspora accounts for more than 14% of the Korean population [56].

The tailoring algorithm is based on genetic testing status, with different content delivered to carriers of *BRCA1*/*BRCA2* pathogenic variants and untested relatives. The Family Gene Toolkit can be accessed outside of a clinical setting as an additional product to assist initial and follow-up discussions with genetic specialists during the continuum of genetic care. Individuals with pathogenic variants can review information about cancer genetics, which may have been overwhelming during genetic consultation [8]. They can also review the steps for effective communication and use the communication guide to create a tailored algorithm for disseminating testing results to at-risk relatives. Although the web application does not necessarily foster interaction among family members, the prescriptive approach increases awareness about maintaining healthy boundaries in family communication, which can promote positive family dynamics [57].

Similarly, untested relatives are introduced to complex information. They become aware of the possible risks and advantages of genetic testing, and they can also compile a list of questions before consulting a specialist. This proactive approach aids in addressing misunderstandings and encourages well-informed decision-making. The web application can help relatives process this information without the perceived pressures of a clinical setting. Information about available genetic specialists is expected to increase self-efficacy and remove barriers related to accessibility of services [58,59].

All participants receive information about active coping strategies. These strategies are linked to various positive outcomes, such as enhanced mental well-being, increased feelings of empowerment and control, and greater resilience when dealing with challenges [60,61]. The Family Gene Toolkit is also designed to enhance participants' self-reflections on how their own values and practices impact their families and social environment. Reflexivity about one's practices is crucial for promoting the capacity to make choices according to one's values in the context of one's intimate family and social life [62,63]. All participants are provided with information concerning lifestyle adjustments and cancer risk management. This includes details about medication, risk-reducing surgeries, early detection through screening, and options for breast reconstruction. This newly developed module is among the few interventions designed to address the informational needs of individuals with *BRCA1*/*BRCA2* pathogenic variants and their untested relatives across the continuum of care [9].

Accessibility and usability testing showed that the adapted Family Gene Toolkit is a well-designed, well-functioning, and scalable tool. All users indicated that the web application provided useful information they wished they had when first confronted with their genetic testing results and increased susceptibility to cancer. The use of testimonials helped participants relate to the content based on their life trajectory, medical history, and

family dynamics. One possible improvement is the ability to provide individualized predictions for various cancer risks rather than a range of risks. Another possible improvement is to integrate large language models (such as Generative Pretrained Transformers) into the Family Gene Toolkit to guide the tailoring algorithm and increase the usability of the web-based platform through natural language processing [64].

One limitation is that the current version of the Family Gene Toolkit is limited to individuals with *BRCA1/BRCA2* pathogenic variants and does not cover other genes associated with HBOC. While our sample size was sufficient for acceptability and usability testing, further testing in a randomized trial with a parallel control group (RCT) and a larger sample will provide evidence of its efficacy in increasing rates of cascade testing among at-risk relatives. The RCT will also inform deep message tailoring, for example, whether participants choose to view some content based on their own coping style. It is also envisioned that data collected from the RCT will help determine a further need to add narration. At this stage, the team decided against this option because integrating speech technologies using the web speech API is time-consuming and costly due to continuous updates and limited browser support [65]. Moreover, privacy considerations must be considered if APIs send data from medically-focused websites to central servers for translation. Another limitation is that most participants were well-educated, implying that they were at least moderately skilled in using a web application. This may have contributed to positive usability ratings. The sample also included exclusively females since no males expressed willingness to test the web application. The RCT will also provide insights on how to engage males with HBOC-associated genetic testing and reduce the gender-based disparity for this syndrome [66].

5. Conclusions

Given the constantly changing landscape of cancer genomics and the lack of genetic specialists, there is a clear need for digital tools designed to support the communication of genetic testing results and facilitate cascade testing of at-risk relatives. Web applications can significantly contribute to ease and convenient access to health-related information, supporting the genetic counseling process and patient satisfaction in the continuum of genetic care [26,67]. In Switzerland, only 25% of patients with breast cancer and a strong family history have received genetic counseling for HBOC-associated variants [68]. In Korea, genetic counseling is not yet mandated, although it is offered in many tertiary hospitals. The Family Gene Toolkit can provide valuable assistance to families in order to cope with and manage their cancer risk, communicate effectively about pathogenic variants, and increase rates of cascade testing among at-risk relatives.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers15184485/s1.

Author Contributions: Conceptualization, V.B., S.K. and M.C.K.; Methodology, V.B., S.K. and M.C.K.; Software, V.B., V.D., A.S., R.S., S.K. and M.C.K.; Validation, V.B., N.B., M.C.-Z., C.M., K.H., R.G., M.R., P.O.C., S.K. and M.C.K.; Formal analysis, V.B. and S.K.; Investigation, V.B., A.S., U.Z.-H., S.K. and M.C.K.; Resources, M.C.K.; Data curation, V.B.; Writing—original draft, V.B.; Writing—review and editing, V.B., V.D., A.S., R.S., F.M.C., N.B., M.C.-Z., J.M.R., S.-W.K., M.C.L., C.M., U.Z.-H., J.K., K.H., R.G., J.S.P., M.R., P.O.C., S.K., M.C.K. and CASCADE and K-CASCADE Consortia; Visualization, V.B.; Supervision, M.C.K.; Project administration, M.C.K.; Funding acquisition, M.C.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by appropriate Ethics Committees in Switzerland (BASEC 2016-02052) and in Korea (YUHS 4-2020-0520).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The CASCADE and K-CASCADE Consortia are open to collaborations with national and international researchers. We invite interested parties to contact the study team through website (https://swisscascade.ch/en/contact-2/, accessed on 5 September 2023) to discuss project ideas, data access, and the submission of research concepts to the Scientific Board. Templates for data requests and further information on the study are available (https://swisscascade.ch/en/research-projectdata-request/, accessed on 5 September 2023).

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Conflicts of Interest: The authors declare no conflict of interest.

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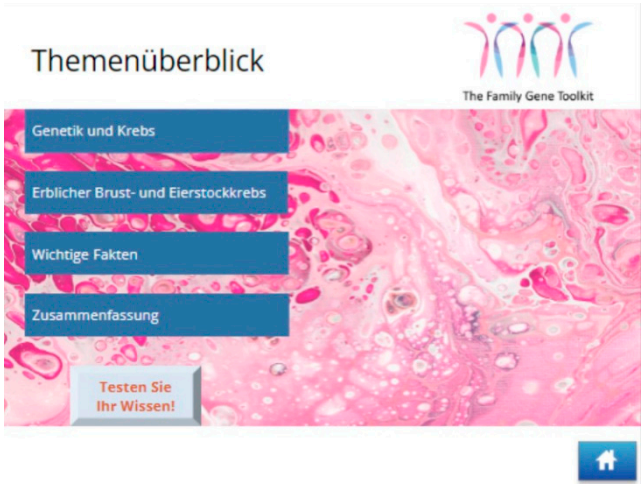
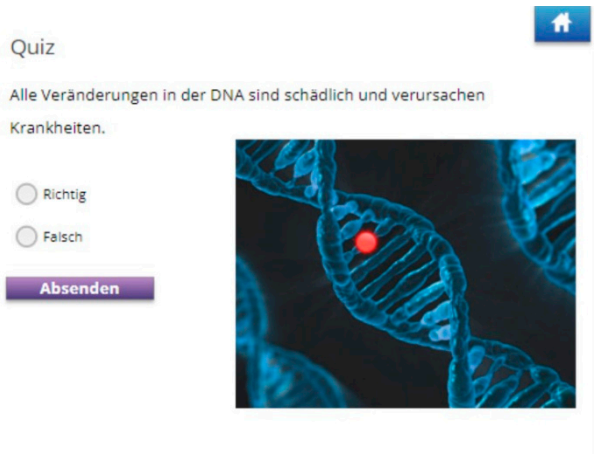
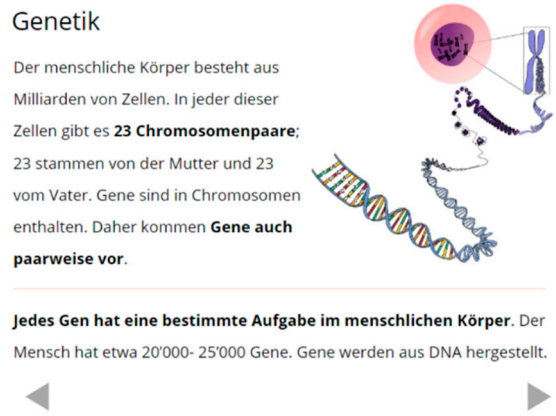
Examples of the interface and context of the web-based platform

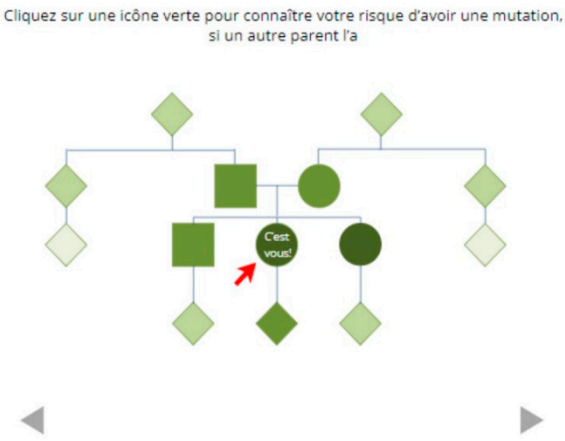
I. German version

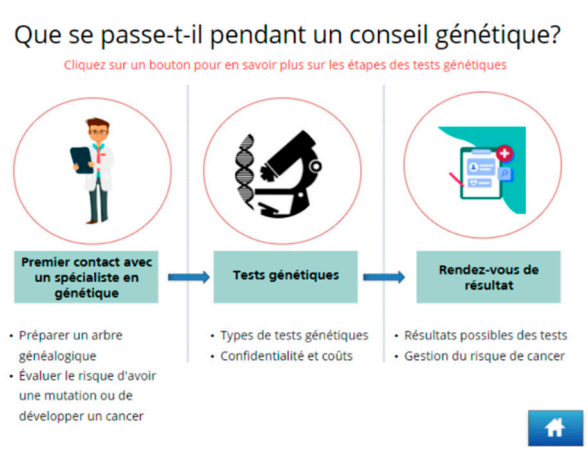




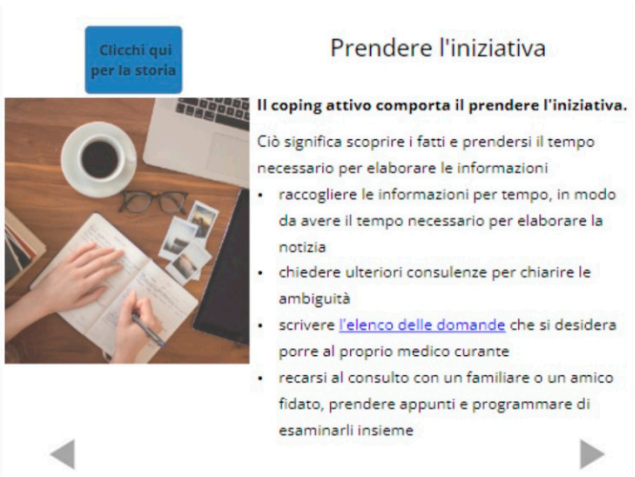


II. French version

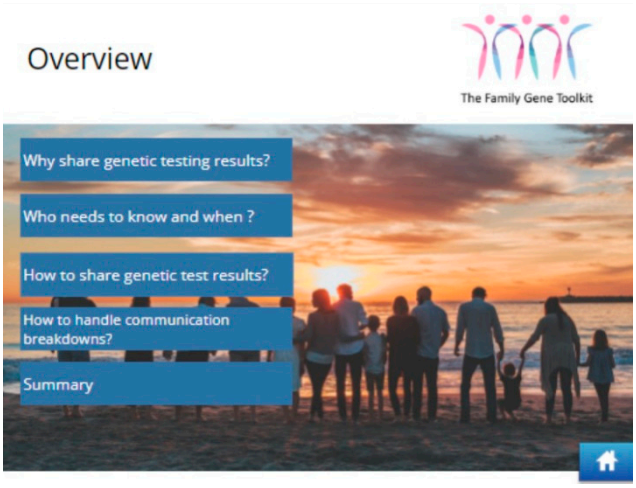


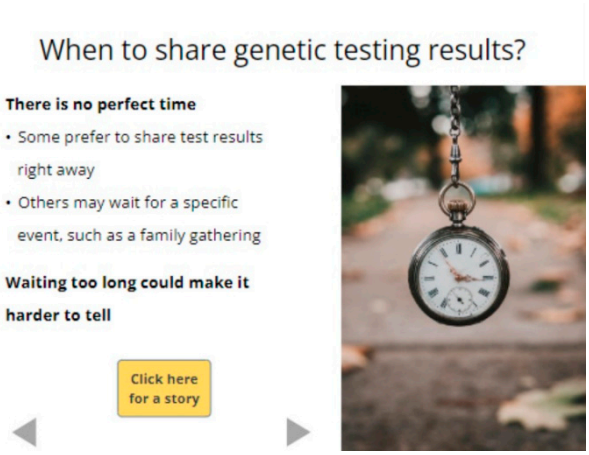


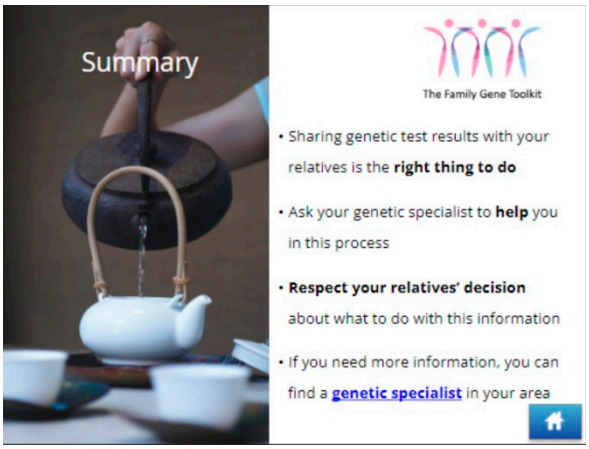
III. Italian version



IV. English version







V. Korean version

퀴즈

선별검사(암 조기 검진)를 받는 것과 위험감소를 위한 치료를 받는 것은 *BRCA1* 또는 *BRCA2* 병인성 변이가 있는 모든 남성과 여성에게 적용된[

- ○ 참
- ◉ 거짓

제출하기

정답

선별검사를 받는 것과 위험 감소를 위한 치료를 받는 것은 모든 남성과 여성에게 적용되는 것은 아닙니다. 선별검사는 특정 병인성 변이, 성별, 그리고 다른 건강 상태에 따라 달라집니다. 또한 개인적인 상황, 선호도, 가치관에 따라 달라질 수 있습니다. 유전학 전문가는 다른 선택지를 제시할 수도 있고, 개인별 가장 좋은 선택지가 무엇인지 결정하도록 도울 수 있습니다.

계속하기

요약

The Family Gene Toolkit

의학적 지침(조기 발견, 위험 감소 예방적 수술, 약물 복용)과 건강한 생활 양식의 **조합**은 궁극적으로 **암 위험을 줄일 수 있습니다.**

신체활동

예를 보려면, 여기를 **클릭** 하십시오.

성인은 **주1회 신체활동(운동)**에 참여할 것을 권장합니다.

- *BRCA* 보인자에서 적당한 운동은 유방암의 위험 감소
- 일주일에 적어도 3번 이상 , 하루에 30분 이상 땀이 날 정도의 운동은 유방암 위험 감소

장시간 앉아 있거나 누워 있는 것, TV 또는 스마트폰 등 화면 기반 엔터테인먼트를 보는 것을 제한합니다.

Chapter 4

Discussion

4.1 Summary of Main Results

Digital interventions have the potential to support both physicians and patients to improve healthcare outcomes and enhance health-related decisions in clinical settings [1]. People usually seek or obtain health information from multiple sources, for example medical doctors, insurance companies, media, educational materials and the Internet [2-5]. In the era of digital health technologies, innovative approaches that leverage web interventions are needed. Leveraging digital health communication technologies aligns with consumer behaviour, as a significant number of people use social media to share genetic testing results and seek health-related information via digital media. In addition, Internet sources provide a fast and easy way to source health information. Nonetheless, incorrect information and fake news from internet sources may mislead patients [6-9]. Studies have shown that people who are exposed to confusing or unreliable information may be more prone to panic, depression, stress and anxiety [10-12]. The need for reliable information remains an important aspect in decision-making, and arguably patients would not be misled if comprehensible and accurate information were more accessible [13-15]. The web-based platform developed aims to fulfill this information need, by providing reliable and developed information about HBOC syndrome.

Patients can contribute significantly to their healthcare not only by preventing disease or harm and managing chronic conditions but also by collaborating with HCPs to select appropriate treatments for serious illnesses [16-18]. In the last decade, Switzerland has made significant progress in promoting evidence-based decision-making and patient involvement in healthcare decisions [19]. In particular, the Health2020 report emphasised the importance of patient involvement and autonomy in healthcare. In parallel, the Swiss Medical Association's has highlighted decision-making as the ideal model and has stressed the critical role of patient preferences in medical interventions and clinical guidelines [20]. Although carriers of

pathogenic variants would benefit from such interventions, no such tools have yet been developed, implemented and tested within clinical genetic settings in Switzerland. Therefore, the aim of this dissertation is to develop and test an educational/communication skill-building intervention, for *BRCA1* and *BRCA2* mutation carriers and their families that provides reliable information about HBOC syndrome and prepares probands to communicate their genetic test results to their relatives.

The first step of the intervention adaptation and development comprised undertaking a review of the extant literature to identify up-to-date evidence [21]. In Chapter 3 of this dissertation, *Study I* presents the results of a systematic review with meta-analysis designed to identify interventions for improving cascade genetic testing and family communication. The results of *Study I* confirmed that there is limited evidence regarding the effects of interventions on cascade genetic testing and communication of genetic results. There is therefore a critical need to develop new interventions to promote family communication and cascade genetic testing. *Study II* was conducted as an in-depth analysis in order to identify different features associated with the ability to effectively communicate genetic risk within the family. This analysis aims to detect early warning indicators of difficulties with communication by identifying patterns associated with open communication or challenges to communication. Early recognition of warning indicators could identify an "at risk" population who experience challenges with communicating genetic risk and may benefit from a support tool.

The second step was to identify an appropriate theory for designing the intervention in order to increase generalisability [21,22]. To identify an appropriate theory, it was essential to be able to define the logic behind an intervention and answer the question of "why this intervention should work" [22]. Lazarus and Folkman's transactional model of stress and coping was chosen as an appropriate theory to develop the current intervention. This is a framework designed to support people to manage stressful situations, using objective

judgement and coping strategies to reduce stress and create appropriate behaviours [23]. The findings from *Study I* and *II* were then mapped together following the ODSF in order to develop a prototype.

The final step in the adaptation and development of the intervention was first to create a prototype and then simulate it with real users. *Study III* describes the adaptation of the platform based on the previous version, the Family Gene Toolkit, and the pilot testing of the prototype in a research setting, by measuring the usability and acceptability of this approach.

4.1.1. Need for a Tool to Improve Cascade Genetic Testing and Family Communication

As described in *Study I,* we conducted a literature review and a meta-analysis to explore the effectiveness of innovative interventions in facilitating intrafamilial communication of genetic testing results and/or cancer predisposition cascade genetic testing, with a focus on HBOC and LS. This systematic review revealed that there is limited evidence of effective interventions to improve intrafamilial communication in genetic clinical settings. The review focused on studies that tested intervention efficacy within randomised controlled trial (RCT) design. In particular, the fourteen articles included in this review described interventions (i.e., psychoeducational and/or counseling component, skills building and decision aids) targeted towards hereditary cancer syndromes either through digital tools such as mobile apps and web-based platforms or non-use of digital technology (e.g., booklets, letters). The interventions focused on multiple components such as knowledge of cancer genetics (e.g., cancer risk, prevention, management options), family communication, cascade testing, coping with cancer risk, problem-solving, self-efficacy and clarifying personal values. Most studies included theory-driven intervention protocols, but there was considerable variability in the extent to which theories were utilized in the selection of intervention content and choice of outcomes.

The literature review revealed that although relevant interventions have been developed, there is limited evidence of interventions tested in a RCT. This may in part explain why few

interventions have been effective. Our findings from the literature review were consistent with the study of Zhao et al. which concluded that participants who used web-based interventions were more likely to gather and share genetic cancer information with relatives compared with a non-intervention control group [24]. The authors also emphasised the significance of creating family communication interventions that are grounded in multi-level theories of family processes. A further significant finding from the literature review was a lack of integrating specific components of coping, such as coping with relatives' cancer risk, in the reported interventions. However, several studies have already identified the importance of coping strategies for people with an inherited cancer risk [25-29] but with other inherited diseases [30,31]. Also, communication of genetic test results is a two-way exchange between carriers and untested relatives. This was acknowledged and addressed in only two studies.

In summary, the findings of the literature review and meta-analysis indicated the importance of interventions that promote intrafamilial communication of genetic test results and confirmed the lack of effective web-based technologies.

4.1.2. Factors Affecting the Level of Family Communication to Cancer Risk

Study II suggests that additional parameters related specifically to openness of communication may be highly significant. Various studies recognise the importance of intrafamilial communication [32-36], but indicate that informing relatives about genetic risk can be emotionally burdensome [37]. Some studies highlight the difficulties talking to family members about their genetic risks, which may generate confusion and misunderstandings within the family [35,38]. Our study identified early indicators of openness or challenges to intrafamilial communication regarding genetic cancer risk. We used state-of-the-art text mining techniques to analyse textual information from a population of carriers of pathogenic *BRCA1* and *BRCA2* variants. In particular, Natural Language Processing (NLP) was implemented for the extraction of narrative data from interviews describing experiences of family

communication and their challenges. In general, identifying the presence of sentiment can be a starting point for identifying people's needs when coping with a demanding situation. Negative and positive sentiment does not necessarily indicate a "bad" or a "good" outcome, respectively. As indicated by studies of Sinner et al. and Gaspar et al. studies [39,40], negative sentiment can be part of the adaptive process of coping with a threat. In our study, we were able to identify individuals with a significant increase or decrease in negative/positive sentiment and found that sentiment was a significant factor strongly associated with openness of communication. Disclosing genetic testing results involves self-disclosure as information about genetic cancer risk being shared is personal and specific to the individual. When individuals disclose personal information about themselves, it can have an impact on their emotional state and the emotional state of recipients [32,34-36,41]. This is where the concept of sentiment comes into play. Sentiment refers to the emotions, feelings, or opinions expressed by an individual or group in response to a particular situation [41]. In addition to personal emotions, self-disclosure can also affect the social dynamics of a relationship. For example, if someone discloses a negative genetic test result, it may create distance or tension if other family members feel differently about genetic testing or the disease in question.

Additional characteristics such as marital status (being single) and educational level (non-academic education) were also factors that indicated a higher probability of open intrafamilial communication. This finding contrasts with other studies that report that lower education levels are associated with a lower probability of discussing testing with family members [42,43]. However, these studies have not explored the level of communication (e.g., openness of communication) and used a different methodology to analyse data.

The findings of *Study II* revealed that our measures of sentiment and narrative consensus correlated well. Given that no specific set of indicators can provide a perfect guide to identifying risk profiles, this study offers a preliminary step to recognising patterns associated with

openness of communication. All the significant features extracted from narratives could be used as early warning indicators and applied in clinical settings. Detection of factors affecting the openness of communication is an important aspect of genetic consultation that should be addressed at an early stage. In this way, genetic experts could identify patients at "risk" of a reduced ability to communicate genetic cancer risk and therefore invest increased efforts to offer support or alert patients to the importance of family communication.

Overall, our methodology allowed us to examine different aspects of intrafamilial communication in depth, which was necessary for designing the intervention. However, the results of this study cannot easily be generalised beyond our study sample, as they largely reflect the experiences of the interview participants. Furthermore, a selection bias for participation may have occurred. The sampling was small and limited by the response of participants to provide narrative data. To create reliable models, it would be necessary to replicate these findings with analyses of narratives from larger samples in the future.

4.1.3. Design and Intervention Model Development

The findings from *Study I* and *Study II* provided useful insights and were therefore mapped together and adopted in the intervention development. The use of interventions with an existing evidence base is more efficient than creating a new intervention [44]. Using well-established interventions makes use of experience and is culturally sensitive to the growing importance of genetic technologies in healthcare. This approach saves time and avoids duplicating efforts [44]. In this particular project, the intervention's content was adopted based on a previous intervention, the Family Gene Toolkit, which was developed by Katapodi and colleagues [45]. Although the results of that intervention showed high acceptability, usefulness, participant satisfaction, and efficacy of the intervention in addressing gaps in the healthcare system, several factors may affect the feasibility of upscaling delivery to clinical practice. For instance, the mode of delivery through live webinars with genetic specialists in real time made

the intervention expensive and raised concerns about cost-effectiveness. The optimal time frame for intervention also lacked consensus due to personal circumstances, and live webinars made it difficult to tailor the intervention to individual preferences [45].

The MRC framework recommends an iterative development and testing of complex interventions through multiple stages: development, feasibility, evaluation and implementation. Hence, a combination of both the MRC framework and the OSDF principles formed the theoretical approach to our development work. The present dissertation outlines the design of the intervention, which is the first stage described in the MRC framework. The next stages which include the feasibility, evaluation and implementation processes, are not included in this dissertation.

The process of design was iterative and parallel, rather than linear or cyclical. To ensure that the design features and content of the intervention were theoretically grounded in the principles of MRC framework, our intervention was iteratively developed with the involvement of patients and HCPs in genetic services. A study conducted by Coulter et al. reports that only approximately half of the developed interventions have been tested by patients and even fewer have been tested by clinicians who were not involved in the development process (‘alpha’ testing stage) [46]. Within the development process, we focused on meeting the needs of patient and HCPs. *Study III* describes the process of adapting the prototype Family Gene Toolkit to address upscaling its implementation in clinical practice, including details about the context, operating system and its functionality to create a state-of-the-art web-based platform.

4.1.3.1. Engaging HCPs in the Development Intervention

The involvement of HCPs in terms of adaptation to the nature, quality, and transferability of previous intervention is critical to identifying remaining uncertainties, and hence what kinds of additional evidence are required in the new context. In this project, a multidisciplinary healthcare team (physicians, genetic experts, nurses, oncoplastic surgeons,

sociologists and psychologists) working in genetic settings was involved in the design of the technology. The team was first asked to review the Family Gene Toolkit and to provide constructive feedback before commencing adaptation for the new intervention. HCPs subsequently reviewed a preliminary version of the new design, including its functionality and provided feedback and suggestions for improvement. They also provided feedback at the end of the adaptation process.

The engagement of HCPs in the design or development process has the potential to improve the quality of digital health products and services [47]. However, the effectiveness of these engagement strategies was not the focus of this dissertation and therefore was not examined in the development of the intervention.

4.1.3.2. Engaging Patients in the Development Intervention

Patients engagement is increasingly recognised as a critical component in delivery of health services and a keystone of quality care [48]. Traditionally, patient engagement has centered on the relationship between patients and providers to guide care decisions or self-care management. However, there are increasing efforts to involve patients in broader ways, such as integrating patient experiences to improve or redesign service delivery [49-52]. This recognition of the value of patient engagement is due to acknowledgement of the rights and expertise of health service consumers, who contribute significantly to designing and delivering services [53]. Hence, we specifically focused on engaging patients in the adaptation process by gathering feedback to understand their experiences and needs.

In *Study III*, usability and acceptability feedback from thirteen individuals (either mutation carriers or relatives) suggest that the content presented in the web-based platform was both sufficient and relevant (Figure 3). In particular, patients were asked to think aloud while navigating through the adapted web-based platform. Navigation features allow the user to move

back and forth within the provided information, thereby allowing users to revisit information when necessary.

Figure 3. Probands and relative's engagement in development intervention

All of the participants suggested that the intervention's content was valid and comprehensible, and the majority of participants stated that the content provided new information about HBOC. Thus, the intervention has the potential to improve users' health literacy. Moreover, the platform enabled patients to regulate the modules that they wished to access each time, giving them the freedom to review previous sections at their own peace. During the usability testing, this navigation feature was particularly beneficial, as participants felt empowered to regulate which sections they wanted to access. Additionally, the intervention was tailored based on their own testing status (either having or not having genetic testing). Hence, the section describing the genetic counselling/testing process was removed for participants who had already been tested. Tested participants found this option very convenient as they felt that these kinds of details would not be valuable for them, as they already understood the process of genetic counselling.

As the intervention is partly designed to promote cascade genetic testing, we have also included relevant contact resources within genetic counselling services for participants who are seeking to identify genetic experts across Switzerland. Additionally, testimonials from individuals with pathogenic *BRCA1* or *BRCA2* variants were incorporated to demonstrate active strategies for coping with the lifelong personal and family challenges associated with HBOC.

Based on several studies, features such as testimonials were recognised as options that may support the decision-making process [54]. However, these may be useful only for particular patient groups due to individual bias in decision-making [55-57]. In the development process, patients reviewed this information and allowed the contact details of genetic experts and testimonials to be included in the platform.

Participants highlighted that having information about both sexes, especially for those who had children of both sexes, was a crucial aspect for their families. Therefore, we did not tailor the intervention according to gender. This issue and all other modifications proposed by the participants must be considered in the upcoming phases of intervention re-development. Engagement of patients in the development of this intervention was critical to improving satisfaction with the intervention.

4.2. Strengths and Limitations of the PhD Dissertation

The strengths and limitations of all studies have been previously discussed within their respective chapters. The next section will address the principal strengths and limitations of this dissertation which constitutes an integral part of phase A of the DIALOGUE project. Research literature indicates that successful implementation of complex eHealth interventions in clinical practice is hindered by a lack of adaptability to context-specific conditions and theoretical frameworks. A further limitation is the absence of a user-centered design approach, which is caused by a failure to engage patients in the research development process [58-60]. To address these limitations, this dissertation combined methods from implementation-, behavioural-, and computer science to develop a user-friendly eHealth intervention. Both qualitative and quantitative approaches to data collection were used within the three research projects to design and develop the pilot intervention. Each study was first analysed and discussed separately. The studies were then considered in relation to each other. This combination of methods enabled

different types of data and viewpoints to be considered carefully in relation to the complex research topic of this dissertation.

The intervention was able to deliver interactive functions that enabled user participation (e.g., risk assessment tool of being mutation carrier, quizzes and communication training tool). The interactive nature of these functions may have a stronger effect on outcomes than passive psycho-educational interventions. The intervention may also improve the accessibility of genetic services, as it can be used from the comfort of home or in remote locations. This is particularly beneficial for patients living in underserved areas or for those with mobility issues. In the same vein, it may also benefit HCPs by delivering services more efficiently. Genetic counsellors could provide a platform such as this to patients to help prepare for consultation. Equally, it could be less time-consuming for HCPs, as patients acquire basic knowledge from the intervention before meeting with a genetic expert and hence could ask more specific questions during a consultation. While this may not reduce the length of time clinicians spend with patients, it could improve patient experience and facilitate their preferences.

Although the three studies produced significant findings, it would be necessary to examine the effectiveness of the intervention by conducting an RCT. Furthermore, the functions provided by the platform were limited. The development of the intervention included shallow tailoring for specific elements such genetic testing status (tested vs. non-tested), deep tailoring involving more personalised elements which was not possible due to the small sample size. This platform will only be used as an educational intervention that provide general information. However, specific elements of the web-based platform such as information regarding the most appropriate surveillance for specific risk groups (e.g., cancer risk, Ashkenazy ancestry, surveillance for pancreatic cancer and melanoma, etc) will need to be expanded accordingly.

4.3. Future Research and Recommendations for Improvement

As the studies in the present dissertation are pioneering work, this dissertation describes the initial 'adaptation' stage of an intervention delivered in a sophisticated online format. The usefulness of the intervention was confirmed by the usability study. However, to create an e-health solution that promotes family communication and encourages cascade genetic testing, this intervention will require further development. In the next phase, we will need to evaluate the effectiveness of the intervention in the clinical setting with patients and clinicians in terms of an implementation strategy. It will be necessary to study the effectiveness of this intervention and its impact on patient-related outcomes such as genetic testing uptake of untested relatives. When the online intervention has been fully developed and finalised, it would be tested in a RCT.

The intervention has the potential to be developed for patients with different inherited diseases including other gene-related types of cancer (Lynch syndrome, Li-Fraumeni, etc.), Huntington disease, cardiovascular diseases, and many others. Adaptations would be required according to context but the design process as a whole could be used as the main guide. We would also try to expand the use of this intervention across national borders, as family member do not always reside in the same country. To achieve this, a multicentre study incorporating different nations would be of great importance. Best medical and legal practices of different countries with comparable healthcare systems, for example Germany, Austria, France and Italy, might be applicable to this context.

Finally, financial support would be critically important to enable updating according to context and maintain the intervention in the daily practice of genetic experts. Maintenance and revision of relevant context require ongoing financial resources.

4.4. Contributions by the PhD student

During my PhD, I had the opportunity to be part of the Swiss CASCADE Consortium team and contributed to ethics amendments, grants submissions, data management, database updates, and data analysis.

For *Study I*, I performed a systematic review of the literature and a meta-analysis of 3,670 studies, conducted a systematic assessment of data quality, extracted outcomes and performed data synthesis in a meta-analysis. Conducting a systematic review and meta-analysis has increased my critical thinking skills and I gained a comprehensive understanding of the literature on the available RCTs on cascade genetic testing and disclosure of genetic cancer risk. The process of conducting a systematic review and meta-analysis helped me to identify gaps in the research and suggest potential areas for future investigation. For this study, I worked closely with a librarian to design the search strategy, identified, selected and critically appraised relevant studies. In terms of the meta-analysis, I conducted the statistical analysis, interpreted the statistical results and wrote the manuscript.

Study II allowed me to investigate human emotions and proband's experiences regarding intrafamilial communication of cancer genetic risk. For *Study II*, I contributed to the planning and design of the study. I performed the data management of narrative data required analysis and also undertook the data cleaning to remove irrelevant or noisy data. I created a lexicon that assigned communication scores to words based on their positive or negative connotations. Analysing the communication and sentiment scores was of great importance to identify patterns and trends in the data regarding open communication. I performed the entire statistical analysis and drafted the manuscript.

With the support of my primary supervisor, I was involved in the design and development of the web-based platform as described in *Study III*. I recruited study participants from three linguistic regions (German-, French- and Italian speaking areas) and conducted

usability and acceptability testing. For the development of the intervention, I used a readily available e-learning product (www.articulate.com) to create an interface of all five modules that were accessible from computer, tablet, and smartphone devices. I was also involved in the drafting of the manuscript related to the study protocol and ethical approval of the DIALOGUE study. I also helped in the setup of the electronic database in collaboration with IT developers of the Clinical Trial Unit in Basel. I interviewed participants using think aloud, performed the entire statistical analysis and drafted a first version of the manuscript.

4.5. Conclusion

Overall, e-Health has significantly enhanced the provision of genetic services, increasing accessibility, efficiency and personalisation. Using e-Health could enable HCPs to offer better care and support to their patients, while empowering patients to take an active role in decision-making. We designed and developed an intervention to support carriers concerning pathogenic BRCA1 and BRCA2 variants to communicate genetic cancer risk to their relatives. This educational intervention is also centered on mutation carrier´s relatives and could contribute to decision-making by providing them with all the necessary information to weigh the pros and cons of their options in terms of cascade genetic testing. In general, this intervention provides reliable educational resources, which could empower patients to make informed decisions about their health and take an active role in management of cancer risk. Ultimately, the intervention could enable patients to make a decision that aligns with their personal objectives and values.

4.5. Reference

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Appendix

A) List of Additional Manuscript

Using a Tailored Digital Health Intervention for Family Communication and Cascade Genetic Testing in Swiss and Korean Families with Hereditary Breast and Ovarian Cancer: Protocol for the DIALOGUE Study

Authors:

Sue Kim[1], Monica Aceti[2], Vasiliki Baroutsou[2], Nicole Bürki[3], Maria Caiata-Zufferey[4], Marco Cattaneo[2], Pierre O Chappuis[5], Florina M Ciorba[6], Rossella Graffeo-Galbiati[7], Viola Heinzelmann-Schwarz[3], Joon Jeong[8], MiSook M Jung[9], Sung-Won Kim[10], Jisun Kim[11], Myong Cheol Lim[12], Chang Ming[2], Christian Monnerat[13], Hyung Seok Park[8], Sang Hyung Park[14], Carla A Pedrazzani[2], Manuela Rabaglio[15], Jai Min Ryu[16], Ramon Saccilotto[2], Simon Wieser[17], Ursina Zürrer-Härdi[18], Maria C Katapodi[2]

[1]Mo-Im Kim Nursing Research Institute, College of Nursing, Yonsei University, Republic of Korea

[2]Department of Clinical Research, University of Basel, Switzerland

[3]Women's Clinic and Gynecological Oncology, University Hospital Basel, University of Basel, Switzerland

[4]La Scuola Universitaria Professionale della Svizzera Italiana (SUPSI), Switzerland

[5]Unit of Oncogenetics, Division of Oncology, Division of Genetic Medicine, Geneva University Hospitals, Geneva

[6]Department of Mathematics and Computer Science, University of Basel, Switzerland

[7]Oncology Institute of Southern Switzerland (IOSI), Switzerland

[8]Department of Surgery, Gangnam Severance Hospital, College of Medicine, Yonsei University, Republic of Korea

[9]College of Nursing, Chungnam National University, Republic of Korea

[10]Dairim St Mary's Hospital, Republic of Korea

[11]Department of Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Republic of Korea

[12]Division of Tumor Immunology, Center for Gynecologic Cancer Research Institute and Hospital, National Cancer Center, Republic of Korea

[13]Oncology Department, Jura Hospital, Switzerland

[14]Department of Computer Science, Yonsei University, Republic of Korea

[15]University Clinic for Medical Oncology, Inselspital Bern, Switzerland

[16]Department of Surgery, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Republic of Korea

[17]School of Management and Law, Winterthur Institute of Health Economics, Zurich University of Applied Sciences, Switzerland

[18]Medical Oncology and Hematology, Kantonsspital Winterthur, Switzerland

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Protocol

Using a Tailored Digital Health Intervention for Family Communication and Cascade Genetic Testing in Swiss and Korean Families With Hereditary Breast and Ovarian Cancer: Protocol for the DIALOGUE Study

Sue Kim[1], PhD; Monica Aceti[2], PhD; Vasiliki Baroutsou[2], MSc; Nicole Bürki[3], MD, PhD; Maria Caiata-Zufferey[4], PhD; Marco Cattaneo[2], PhD; Pierre O Chappuis[5], MD; Florina M Ciorba[6], PhD; Rossella Graffeo-Galbiati[7], MD; Viola Heinzelmann-Schwarz[3], MD; Joon Jeong[8], MD, PhD; MiSook M Jung[9], PhD; Sung-Won Kim[10], MD, PhD, FACS; Jisun Kim[11], MD, PhD; Myong Cheol Lim[12], MD, PhD; Chang Ming[2], MSc, PhD; Christian Monnerat[13], MD; Hyung Seok Park[8], MD, PhD; Sang Hyung Park[14], PhD; Carla A Pedrazzani[2], MSN; Manuela Rabaglio[15], MD; Jai Min Ryu[16], MD, PhD; Ramon Saccilotto[2], MD; Simon Wieser[17], PhD; Ursina Zürrer-Härdi[18], MD; Maria C Katapodi[2], PhD

[1]Mo-Im Kim Nursing Research Institute, College of Nursing, Yonsei University, Seoul, Republic of Korea
[2]Department of Clinical Research, University of Basel, Basel, Switzerland
[3]Women's Clinic and Gynecological Oncology, University Hospital Basel, University of Basel, Basel, Switzerland
[4]La Scuola Universitaria Professionale della Svizzera Italiana (SUPSI), Manno, Switzerland
[5]Unit of Oncogenetics, Division of Oncology, Division of Genetic Medicine, Geneva University Hospitals, Geneva, Switzerland
[6]Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland
[7]Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland
[8]Department of Surgery, Gangnam Severance Hospital, College of Medicine, Yonsei University, Seoul, Republic of Korea
[9]College of Nursing, Chungnam National University, Deajeon, Republic of Korea
[10]Dairim St Mary's Hospital, Seoul, Republic of Korea
[11]Department of Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Republic of Korea
[12]Division of Tumor Immunology, Center for Gynecologic Cancer Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea
[13]Oncology Department, Jura Hospital, Delemont, Switzerland
[14]Department of Computer Science, Yonsei University, Seoul, Republic of Korea
[15]University Clinic for Medical Oncology, Inselspital, Bern, Switzerland
[16]Department of Surgery, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, Republic of Korea
[17]School of Management and Law, Winterthur Institute of Health Economics, Zurich University of Applied Sciences, Winterthur, Switzerland
[18]Medical Oncology and Hematology, Kantonsspital Winterthur, Winterthur, Switzerland

Corresponding Author:
Maria C Katapodi, PhD
Department of Clinical Research
University of Basel
Missionstrasse 64
Basel, 4055
Switzerland
Phone: 41 61 207 0430
Fax: 41 61 207 6155
Email: maria.katapodi@unibas.ch

Abstract

Background: In hereditary breast and ovarian cancer (HBOC), family communication of genetic test results is essential for cascade genetic screening, that is, identifying and testing blood relatives of known mutation carriers to determine whether they also carry the pathogenic variant, and to propose preventive and clinical management options. However, up to 50% of blood

relatives are unaware of relevant genetic information, suggesting that potential benefits of genetic testing are not communicated effectively within family networks. Technology can facilitate communication and genetic education within HBOC families.

Objective: The aims of this study are to develop the K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing) cohort in Korea by expanding an infrastructure developed by the CASCADE (Cancer Predisposition Cascade Genetic Testing) Consortium in Switzerland; develop a digital health intervention to support the communication of cancer predisposition for Swiss and Korean HBOC families, based on linguistic and cultural adaptation of the Family Gene Toolkit; evaluate its efficacy on primary (family communication of genetic results and cascade testing) and secondary (psychological distress, genetic literacy, active coping, and decision making) outcomes; and explore its translatability using the reach, effectiveness, adoption, implementation, and maintenance framework.

Methods: The digital health intervention will be available in French, German, Italian, Korean, and English and can be accessed via the web, mobile phone, or tablet (ie, device-agnostic). K-CASCADE cohort of Korean HBOC mutation carriers and relatives will be based on the CASCADE infrastructure. Narrative data collected through individual interviews or mini focus groups from 20 to 24 HBOC family members per linguistic region and 6-10 health care providers involved in genetic services will identify the local cultures and context, and inform the content of the tailored messages. The efficacy of the digital health intervention against a comparison website will be assessed in a randomized trial with 104 HBOC mutation carriers (52 in each study arm). The translatability of the digital health intervention will be assessed using survey data collected from HBOC families and health care providers.

Results: Funding was received in October 2019. It is projected that data collection will be completed by January 2023 and results will be published in fall 2023.

Conclusions: This study addresses the continuum of translational research, from developing an international research infrastructure and adapting an existing digital health intervention to testing its efficacy in a randomized controlled trial and exploring its translatability using an established framework. Adapting existing interventions, rather than developing new ones, takes advantage of previous valid experiences without duplicating efforts. Culturally sensitive web-based interventions that enhance family communication and understanding of genetic cancer risk are timely. This collaboration creates a research infrastructure between Switzerland and Korea that can be scaled up to cover other hereditary cancer syndromes.

Trial Registration: ClinicalTrials.gov NCT04214210; https://clinicaltrials.gov/ct2/show/NCT04214210 and CRiS KCT0005643; https://cris.nih.go.kr/cris/

International Registered Report Identifier (IRRID): PRR1-10.2196/26264

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KEYWORDS

HBOC; proportion of informed at-risk relatives; coping; communicating; decisional conflict; cultural and linguistic adaptation; implementation; RE-AIM; mobile phone

Introduction

Background

In 2018, there were approximately 2.1 million breast cancer diagnoses and more than 600,000 associated deaths worldwide [1,2]. The worldwide average breast cancer incidence is 74.2 per 100,000 women [3], with approximately 25% of cases occurring in women younger than 50 years and in women with a family history of cancer [4,5]. Approximately 5%-10% of breast cancer and 20% of ovarian cancer cases occur due to germline pathogenic variants associated with hereditary breast and ovarian cancer (HBOC) syndrome, most commonly observed in the *BRCA-1* and *BRCA-2* genes (hereafter *BRCA*). The prevalence of germline pathogenic variants differs among ethnic groups [6]; however, Switzerland and Korea have a similar prevalence ranging from 23% to 26% [7,8].

The availability of genetic services (counseling and testing) for actionable hereditary cancer syndromes such as HBOC enables population-level cancer prevention [9]. Blood relatives of HBOC cases have a 12.5%-50% probability of inheriting the same pathogenic variant and can be tested with 100% accuracy. Chemoprevention, prophylactic surgery, and intensive surveillance can lower cancer risks for relatives who test positive, whereas those who test negative are excluded from these interventions [10-12]. The Centers for Disease Control and Prevention Office for Public Health Genomics recommend genetic testing in cancer-free individuals with a known HBOC family history and in patients with cancer who have strong indications of HBOC syndrome (eg, ovarian cancer) [13]. Cascade genetic screening is a systematic effort to identify and test all blood relatives of HBOC cases to determine whether they also carry the same pathogenic variant [10]. The CASCADE (Cancer Predisposition Cascade Genetic Testing) Consortium in Switzerland promotes cascade genetic screening for HBOC [14,15], whereas the Korean Hereditary Breast Cancer (KOHBRA) network identifies the prevalence of HBOC-associated pathogenic variants in the Korean population [16,17].

Despite calls to action for HBOC cascade genetic testing, there are systemic barriers to its implementation. Privacy laws worldwide, including Switzerland and Korea, restrict health care providers from revealing genetic information to anyone except the tested individual, who has the right not to disclose this information, despite implications for relatives' health

[18-20]. The potential benefits of genetic testing are not being effectively communicated through family networks, leading to more than 50% of at-risk individuals not using genetic services and not receiving important information from a credible source [21-23]. Second-degree and male relatives, those living further away, and those with an estranged relationship with the mutation carrier are most likely not to be informed about genetic testing [24,25]. Despite these difficulties, a family-based approach in communicating hereditary cancer risk is advantageous because it may reach relatives through the social bonds and functions already existing within the family network, and it is not limited to those in contact with the health care system [26].

Interventions that support mutation carriers during the disclosure of genetic test results can reduce psychological distress and provide relatives with accurate and credible information about cascade genetic testing. Technology-enabled education is not inferior to face-to-face genetic consultations [27,28], but it increases access to services and cost-effectiveness [29-32]. The Family Gene Toolkit [33] is a web-based intervention designed to increase prerequisites for HBOC cascade testing, that is, active coping, open family communication, and informed decision making. The prototype Family Gene Toolkit was tested in the United States for acceptability and patient satisfaction with excellent results, confirming its value for these families. However, it is not available in other linguistic and cultural contexts. Adapting existing interventions, rather than developing new ones, takes advantage of the previous valid experiences without duplicating efforts.

In summary, HBOC cascade genetic testing, meaning the identification and testing of blood relatives, provides risk management options for those with a germline pathogenic variant and excludes confirmed noncarriers (ie, negative testing when there is a known pathogenic variant in the family) from intensive surveillance and risk-reducing measures. Due to privacy laws, mutation carriers have the sole responsibility to inform blood relatives about genetic test results and advocate for genetic services. Digital health platforms can support mutation carriers during the disclosure process and provide relatives with accurate and credible information.

Objectives

The DIALOGUE study will build a bilateral research infrastructure to support collaboration and multidisciplinary initiatives around HBOC in Switzerland and Korea. The specific aims are to develop the K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing) cohort in Korea by expanding an existing research infrastructure developed by the CASCADE Consortium in Switzerland; develop a digital health intervention to support open communication and cascade genetic testing in HBOC families, based on the linguistic and cultural adaptation of the Family Gene Toolkit; evaluate the efficacy of the digital health intervention on primary (communication of genetic test results to relatives and cascade genetic testing) and secondary (psychological distress, genetic literacy, coping, and decision making) outcomes; and explore the translatability of the platform using the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework.

Methods

Design

The DIALOGUE study will use a cohort design to establish the K-CASCADE in Korea and a randomized controlled trial (RCT) design to test the effects of digital health intervention in the Swiss and Korean contexts. The study will measure clinical and process outcomes in real-world conditions, including different settings, participants, and resources [34,35].

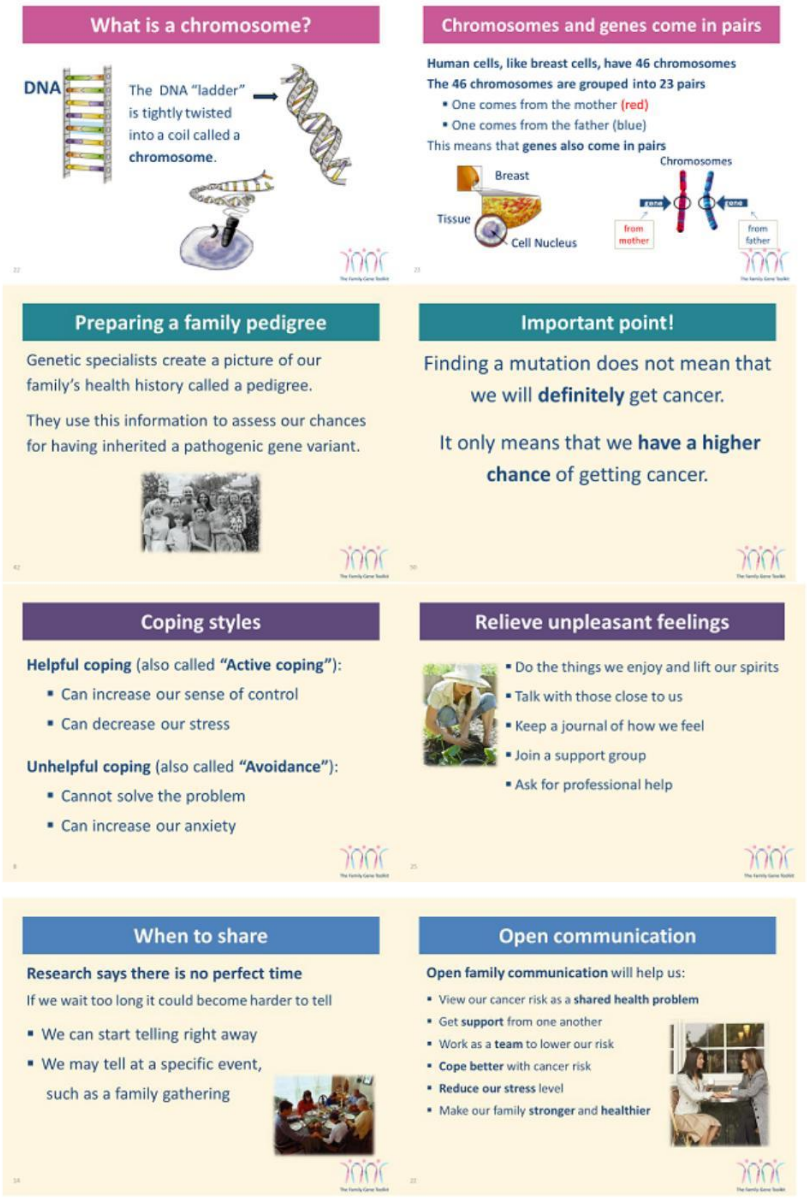
Aim 1: Develop the K-CASCADE Cohort

The K-CASCADE cohort will identify and survey mutation carriers and blood relatives as its archetype, the Swiss CASCADE cohort, using similar design, assessments, and procedures for sample identification and data collection [14]. Adult Korean men and women with *BRCA* pathogenic variants will be invited to the K-CASCADE cohort. They will also be asked to invite their first- and second-degree relatives and their first cousins for cascade genetic screening. Similar to the Swiss CASCADE, it is envisioned that the K-CASCADE cohort will include known mutation carriers, untested relatives with unknown mutation status, and relatives who tested negative for the pathogenic variant.

Aim 2: Adapt the Digital Health Intervention

The content of the Family Gene Toolkit is driven by theory [36] and supported by empirical findings [37-41]. It is designed to address challenges related to the quantity and complexity of genetic information mutation carriers are asked to communicate with family members [42,43]. Understanding HBOC (eg, probability of mutation, prognosis, prevention, and treatment) and the accuracy of genetic testing are important for decision making. Inherited cancer risk requires ongoing management and, thus, active coping with health challenges. Mutation carriers'personal values and communication skills are important for the disclosure of genetic cancer risk. The Family Gene Toolkit embraced the above challenges and included 4 modules designed to increase knowledge of cancer genetics (module 1), provide decisional support for genetic testing to untested relatives (module 2), increase active coping with common challenges faced by HBOC families (module 3), and provide skills-building communication training (module 4; Figure 1). The adapted Family Gene Toolkit will include the 4 original modules and a fifth module about the management of cancer risk based on recommendations from the National Comprehensive Cancer Network [44].

Figure 1. Examples from the Family Gene Toolkit.



The research team will create tailored messages based on the linguistic and cultural adaptations of the modules. Tailoring is a process that *fits* the message to meet one's personal needs and characteristics, rather than targeting group criteria [45,46]. Tailored messages improve whether and how one listens to a message and its impact on behavior change. Shallow tailoring involves elements of appearance (eg, female or male mutation carriers), whereas deep tailoring involves more complex elements of relevance (eg, coping style). Adaptation of the Family Gene Toolkit involves elements of both shallow and deep tailoring based on preintervention assessments of participants' characteristics such as sex, affected with cancer versus cancer-free, and tendency to rely more on a specific coping style. The research team will use readily available e-learning products with different tailored messages, multiple interactions and assessments, and a device-agnostic interface for the adaptation of the Family Gene Toolkit. Messages will be developed in English and translated at the eighth-grade reading level while considering Swiss and Korean legislation, health insurance policy, cultural values, and national languages. Swiss and Korean stakeholders will review the content of the adapted Family Gene Toolkit and identify the required modifications by providing feedback on word choices, sensitivity of messages, and appearance. Mini focus groups and individual interviews with clinicians involved in genetic consultations will evaluate the prototype of each module and the tailoring elements. Focus groups with Swiss and Korean HBOC mutation carriers and relatives will provide suggestions to enhance the comprehensibility, usefulness, acceptability, and feasibility of the intervention. Feedback from clinicians and HBOC families will help in further refining each module and the tailored messages.

Assessing the usability of the adapted Family Gene Toolkit involves task-oriented assignments about the most important functions and features of the website as well as the ease and user-friendliness of navigation. Participants will *think aloud* while navigating each module and complete each task [47].

They will also evaluate the tailored messages for readability and comprehension.

Swiss and Korean participants will complete the 5 modules at their own pace, but within a timeframe of 4 weeks after they first engage with the platform. The 4-week interval enables information assimilation and adequate time to reflect and act based on tailored messages while providing a controlled learning environment. Feedback will be based on baseline responses, including tailored advice about improvements that can be made.

Consistent with testing real-world alternatives [48], the DIALOGUE study will provide a comparison website with targeted (generic) information. The comparison website will mimic the structure and functions of an existing website [49]. The adapted Family Gene Toolkit and the comparison website will be technically implemented in the same system that will collect baseline and follow-up data, randomize participants, deliver the intervention and the comparison website, track access and use of the platform, and provide a user-friendly experience to participants.

Aim 3: Evaluate Intervention Efficacy on Primary and Secondary Outcomes

A cluster RCT will evaluate the magnitude of intervention effects as compared with the comparison website. Randomization will occur at the family level, that is, after baseline data collection, the digital health intervention will randomly assign mutation carriers to either intervention arm, stratifying for country. Invited relatives will be automatically directed to the same arm as the mutation carrier. All study participants will complete a survey at baseline (T_1) before the intervention and again at 2 months (T_2) and 6 months (T_3) after the intervention. The 2- and 6-month follow-up time points will assess the short-term and long-term effects in line with our previous studies [33,50].

Aim 4: Explore Intervention Translatability

The implementation and dissemination of the adapted Family Gene Toolkit will be evaluated based on the constructs of the RE-AIM framework [51] at the individual and organizational levels.

Settings

The DIALOGUE study involves oncology and genetic testing centers of the Swiss CASCADE Consortium from 3 linguistic regions of Switzerland (German-, French-, and Italian-speaking) and similar settings in Korea, eg, Severance Hospital, Seoul, and the National Cancer Center, Goyang. Settings ensure diversity in hospital characteristics (eg, general or advanced level) and geographic location to increase sample representativeness and generalizability.

Sample and Sample Size

The DIALOGUE study targets individuals who have been identified through genetic testing as carrying a *BRCA* pathogenic variant (proband) and their blood relatives. Textbox 1 describes the inclusion criteria for the probands and relatives. Eligible probands will be females and males (expected female-to-male ratio=4:1) and their first- and second-degree relatives (parents, siblings, offspring, aunts, uncles, nieces, nephews, and grandparents) and their first cousins. Participants may have a cancer diagnosis (expected breast-to-ovarian cancer ratio=5:1) or they may be cancer-free. Individuals who tested positive for a variant of uncertain significance and mutation carriers without any blood relatives, spouses, and partners are excluded because cascade genetic testing does not apply to them. We also exclude individuals who tested positive for a non-*BRCA* pathogenic variant because of the current variation in the implementation of panel testing among the different sites, which will likely influence the recruitment of participants with non-*BRCA* mutations. The study will only include adults because hereditary cancer risk assessment is not recommended for children. The study will also exclude vulnerable participants, such as critically ill patients and those living in nursing homes, to avoid increasing the subject burden and provide surveillance recommendations to participants who are not able to follow through the program.

Recruitment and Procedures

K-CASCADE Cohort

The opportunity to participate in the K-CASCADE cohort will be advertised through the KOHBRA network, the Ovarian Cancer and Genetics study group, and other clinical sites. Recruitment procedures for Korean probands and relatives will follow steps and procedures similar to those outlined for the Swiss CASCADE cohort [14]. In short, index cases (first person in the family with the pathogenic variant) identified in participating centers will be invited to participate in the study by collaborating clinicians and through patient advertisements posted in the clinics. Potential participants will also be able to view information on the study website. Individuals carrying a *BRCA* pathogenic variant, and if they have at least one eligible relative based on pedigree data, will meet study recruiters to ask questions and provide written consent. To alleviate ethical concerns associated with contacting blood relatives without their explicit consent, the K-CASCADE cohort will approach them through probands, targeting only relatives the proband is willing to contact. This recruitment method is used by the Swiss CASCADE cohort and in previous family-based studies with very good recruitment outcomes [39,54]. Relatives agreeing to participate will also provide written consent. In the consent form, probands and relatives will indicate their willingness to invite additional relatives to the K-CASCADE, be contacted once a year for 5 years and provide updated information about their health, participate in a focus group or individual interview for the adaptation of the Family Gene Toolkit in Korean, and participate in an RCT for testing the effects of the adapted Family Gene Toolkit. Probands and relatives may participate in all or some of the study steps previously described.

Probands and relatives will provide baseline assessments via a URL link to the digital health intervention and a unique passcode. A second prompt will be sent 2 weeks later. If there is no response to the second contact, study recruiters will contact the participants by phone. Relatives will also provide written consent, and they will receive a URL with a unique passcode. The Swiss CASCADE platform will facilitate data collection in both countries to maintain the consistency and accuracy of data entry, data management, and analyses. Korean respondents will log on as K-CASCADE participants to provide survey data.

Intervention Adaptation

Participants will be recruited through the Swiss CASCADE cohort and through flyers posted in the affiliated Korean institutions and clinics. After obtaining consent, focus groups or individual interviews will be organized at an easily accessible site and in participants' language. Focus groups will be coded by 2 members of the team in each country and linguistic region and will be audiotaped with participants' explicit consent. Participants will be asked to *think aloud* while viewing electronic mockups of the intervention and while navigating a final version of the digital health intervention. The latter sessions will be videotaped.

Clinicians involved in genetic consultations will be identified through the CASCADE Consortium in Switzerland; through the Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung, Network for Cancer Predisposition Testing and Counseling in Switzerland; and through the KOHBRA network in Korea. They will be recruited via email and/or invitation letters and will also provide consent. Semistructured exploratory questions will elicit their opinions on structural barriers to HBOC cascade genetic testing. At a later stage, they will also view a nearly final version of the digital health intervention and will provide feedback. Sessions will be audiotaped and videotaped with clinicians' consent.

Intervention Efficacy

After they complete the baseline questionnaires (T_1), probands (index case) in both countries who agree to participate in an RCT and test the effects of the adapted Family Gene Toolkit will be emailed a unique URL link and passcode allowing them access to the digital health intervention. Furthermore, they will be able to log in and review the intervention modules multiple times using the same URL link and passcode. The system will randomize participants in a 1:1 ratio to either the digital health intervention or the comparison website. Stratification by country (Switzerland vs Korea) will be facilitated with different URL links for participants from each country. Participants will receive weekly email or text alerts, encouraging them to visit the website and complete viewing of the contents of the digital health intervention within 4 weeks. They will also receive email or text alerts to complete a knowledge quiz, an exercise for value clarification related to genetic testing, and a family communication rubric that will be included in the content of the different modules. Participants randomized to the comparison website will receive 1 email alert 2 weeks after they engage with the website. Relatives will be allocated to the same study arm as the respective proband and will also receive a URL link and a unique passcode. Relatives will first be asked to complete a consent form and then to complete the baseline survey, after which they will have access to either the adapted Family Gene Toolkit or the comparison.

Primary and secondary outcomes will be assessed at 2 months (T_2) and 6 months (T_3) after the intervention. We selected the 2- and 6-month follow-up time points to measure the short-term and long-term intervention effects, in line with our previous studies [33,50]. To minimize the attrition rate, if a response has not been received within 2 weeks from the time participants receive the URL link to the follow-up survey, then the study personnel will make 3 attempts to contact them by email or phone and encourage them to complete the survey.

Measures and Outcomes

K-CASCADE

The core questions of the Swiss CASCADE cohort [14] constitute the basic measurements for the K-CASCADE. Instruments are purchased (if not available for free) and will be translated into Korean (if not available) following the World Health Organization's translation guidelines. The baseline survey covers cancer diagnoses and surveillance, use of and experience with genetic testing (for testers and nontesters), communication with health care providers, and satisfaction with cancer genetic services. It assesses information about prophylactic surgeries; epidemiological data about personal,

reproductive, and family history of breast and ovarian cancer; and modifiable lifestyle risk factors (smoking, drinking, physical activity, etc). The baseline survey also assesses demographic characteristics and psychosocial variables, for example, the fear of cancer recurrence and self-efficacy to use services, which constitute the basis for creating the tailored messages provided by the adapted Family Gene Toolkit. These instruments are listed in Table 1. The Korean survey will be pilot tested with 10 study participants for comprehension and accuracy.

Table 1. Demographics and psychosocial characteristics.

Variables	Instruments	Cronbach α	Test-retest reliability	Assessment	
				Baseline	Follow-up
Demographics, personal, and family cancer history	Self-report [55]	—[a]	—	✓[b]	
Tailoring variables					
Degree of relationship between proband-relatives (eg, first degree)	Self-report	N/A[c]	N/A	✓	
Fear of cancer recurrence (for patients)	Concerns About Recurrence Scale [56], 4 items, 7-point Likert scale	.93	0.91	✓	
Self-efficacy dealing with cancer (for patients)	Self-efficacy–HBOC[d]-related cancer [57], 14 items, 7-point Likert scale	.80	0.71	✓	
Self-efficacy using genetic services	1 item, 7-point Likert scale	N/A	N/A	✓	
Family support	Family Support in Illness [58], 10 items, 7-point Likert scale	.86	0.83	✓	
Family hardiness	Family Hardness Index [59], 20 items, 7-point Likert scale	.90	0.82	✓	
Satisfaction with genetic counseling (for tested individuals)	Multidimensional Impact of Cancer Risk Assessment [60], 19 items, 7-point Likert scale	.81	—	✓	
Barriers and facilitators for genetic services	Barriers and facilitators for genetic services [61], 11 items, multiple choice	N/A	N/A	✓	

[a]Not available.

[b]The variable will be assessed at the specific time frame.

[c]N/A: not applicable.

[d]HBOC: hereditary breast and ovarian cancer.

Intervention Adaptation

A trained moderator will ask focus group participants to answer semistructured exploratory questions designed to elicit their opinions on the most pressing issues for family communication, using appropriate probe questions to explore potential cultural interpretations. The interview guide explores issues around family communication that took place during the genetic consultation, decision making related to the disclosure of test results to relatives, and attitudes toward using digital health platforms. Participants will also rate their satisfaction with the content, format, and appearance of the website. Assessing intervention feasibility also involves assessing the number of modules accessed, time spent on each module, and the utilization of links, which are automatically recorded on the website.

Intervention Efficacy

Data to evaluate the magnitude of intervention effects will be assessed using the instruments listed in Table 2. These have strong psychometric properties and have been used in previous studies on patients with cancer. Most of these instruments have been translated into and validated in German, French, and Italian and will be translated into and validated in Korean. Primary and secondary outcomes are assessed at the 2-month and 6-month follow-up surveys. Satisfaction with the intervention and acceptability will be assessed at the 2-month follow-up with questions about intervention usefulness, ease of use, clarity, appropriate length, level of detail, relevance, and interest with a 7-item survey (Likert scale ranging from 1=low to 7=high) [62,63].

Table 2. Instruments to assess primary and secondary outcomes.

Concepts	Instruments	Cronbach α	Test-retest reliability	Assessment	
				Baseline	Follow-up
Primary outcomes					
Proportion of informed relatives	Website data	N/A[a]	N/A	✓[b]	✓
Intention to inform relatives	Informing Relatives Inventory [64], 68 items, 7-point Likert scale	.86	—[c]	✓	✓
Intention for genetic testing (untested relatives)	1 item, 7-point Likert scale	N/A	N/A	✓	✓
Secondary outcomes					
Psychological distress	Profile of Mood States [65], 37 items, 7-point Likert scale	.86	—	✓	✓
Genetic literacy—genetic affinity	Risk Factor Knowledge Index [39], 17 items, true, false, and do not know	.89	0.85	✓	✓
Genetic literacy—cancer genetics	Breast Cancer Genetics Index [66], 12 items, true, false, and do not know	.82	0.81	✓	✓
Coping with stressful events	Brief Cope [67], 25 items, 7-point Likert scale	.81	0.78	✓	✓
Decision making—untested individuals	Decisional Conflict Scale-HBOC[d] Genetic Testing [68], 16 items, 7-point Likert scale	.96	—	✓	✓
Decision making—tested individuals	Decisional Regret-Genetic Testing [69], 5 items, 7-point Likert scale	.87	—	✓	✓
Intervention evaluation					
Acceptability, detail, usefulness, relevance, and satisfaction	Intervention Evaluation [62,70], 16 items, 7-point Likert scale	—	—		✓

[a]N/A: not applicable.
[b]The variable will be assessed at the specific time frame.
[c]Not available.

[d]HBOC: hereditary breast and ovarian cancer.

Intervention Translatability

Textbox 2 outlines RE-AIM outcomes to be assessed, which will help in evaluating the potential for a broader implementation and dissemination of the digital health intervention.

Textbox 2. Reach, effectiveness, adoption, implementation, and maintenance outcomes assessed in the study.

Reach (individual)

- Response rate of mutation carriers and relatives
- Number of probands and relatives accessing the website
- Demographic, linguistic characteristics, and region
- Response rate to K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing)

Effectiveness (individual)

- Assess the number of times participants accessed each module
- Assess the number of relative invites initiated through the website
- Evaluate the acceptability, interest, usefulness, level of detail, relevance, and satisfaction follow-up survey

Adoption (setting, staff, and organization)

- Number of clinicians and new settings willing to participate in the study
- Diversity (geographic, linguistic, etc) in participating settings

Implementation (setting, staff, and organization)

- Monitor referrals of mutation carriers from different clinical sites
- Evaluate the cost for adapting modules for other hereditary cancer syndromes (eg, Lynch syndrome)

Maintenance (individual and setting)

- Assess resources needed to maintain the website
- Assess the number of visits per month per year

Data Management and Data Analyses

K-CASCADE Cohort

Korean participants' data entered in the Swiss CASCADE platform will be available for descriptive and comparative analyses, using epidemiological and psychosocial data along with coded and nonidentified clinical data. Existing clinical data from Severance Hospital, stored in the Clinical Research Analysis Portal, will also be accessed for participants who provide additional consent. At year 4, the accrued data from Korean women will be used in conjunction with clinical data for comparative analyses with the Swiss CASCADE cohort.

Intervention Adaptation

The mini focus groups or interviews with HBOC families and clinicians will be audiorecorded with participants' consent and transcribed verbatim, using codes to protect individual identification. Transcripts will be reviewed by the research team, and content will be analyzed using an iterative process of reading transcripts, coding, and comparing the data to identify salient themes. Two members of the research team in each country will also review the videotapes obtained from usability testing and the *think aloud* protocol. They will confirm that there are no functional errors on the website, color schemes and graphical images are well received, participants can navigate through various sections of the website with ease, the layout accurately conveys information, and the program works as expected. Data regarding acceptability will be analyzed using descriptive statistics.

Intervention Efficacy

The efficacy cluster RCT will use pre- and postintervention data from baseline (T_1) and follow-up (T_2 and T_3) surveys. Data values will be checked for validity (within the appropriate range) using histograms and box plots and corrected whenever possible. Many items are a part of multi-item scales and are anticipated to correlate with each other. Scales will be tested for internal consistency reliability with Swiss and Korean participants using principal component analysis and Cronbach α coefficients. Scales with Cronbach α values of .71 and higher will be used. Multiple imputation or other techniques will address missing data if they exceed 5% of observations and if they are less than 25% for each specific scale. Data from participants who withdraw will be kept to ensure internal validity.

Primary outcomes will be calculated with the Wilcoxon-Mann-Whitney test to compare the proportions of informed relatives per study arm. Other primary and secondary outcomes and metadata from the automatic recording of website activity will be analyzed using descriptive statistics. Descriptive analyses will include calculating the means and frequencies of key variables and subject descriptors (eg, genetic testing). This will include tabulating counts and frequencies of variables, including demographics and personal cancer history. Bivariate analyses (using the chi-square test for differences in proportions and *t* test for differences in means) will assess the associations between demographic factors and clinical characteristics. The following comparisons will be made: between probands and relatives, between men and women, between patients with cancer and cancer-free individuals, between participants with

children and those with no children, between different age groups, and between patients with different cancer diagnoses. A detailed methodology for summaries and statistical analyses will be documented in a statistical analysis plan. This plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel. All analyses will be conducted using the statistical software R [71], using *two-sided* statistical tests and confidence intervals with confidence levels α=5% and (100%−α)=95%, respectively. Deviations from planned analyses are not foreseen. The study statistician will review and approve any deviations from the original statistical plan.

Intervention Translatability

Data exploring the RE-AIM of the digital health intervention will be analyzed using qualitative and quantitative methods. Narrative data obtained from mini-interviews will be audiorecorded, transcribed verbatim, and analyzed for common themes. Descriptive analyses will include calculating the means and frequencies of the key variables and subject descriptors. Bivariate analyses (chi-square test for differences in proportions and *t* test for differences in means) will compare key variables between participants and nonparticipants.

Results

The DIALOGUE study, including the development of the K-CASCADE cohort in Korea, was funded in October 2019. It is projected that data collection will be completed by January 2023, and results will be published in fall 2023.

Discussion

Principal Findings

The need to enhance family communication around HBOC has been documented in the literature since mid-2000 [72-74], followed approximately 10 years later by scientific calls to enhance cancer predisposition cascade genetic testing [75-77]. The DIALOGUE study is a resource-effective international research platform that proposes building a tailored, interactive website to reach a large number of HBOC families and enhance cancer predisposition cascade genetic screening, presumably requiring only a fraction of the cost and required clinician time compared with previous approaches. Developing the K-CASCADE cohort will link together the expertise of an eminent network of HBOC scholars and clinicians that will benefit both countries and serve as a model for potential expansion to other countries and in other language contexts. The cross-cultural adaptation of the Family Gene Toolkit will help explore the similarities and differences in communication practices among HBOC families in the Swiss and Korean contexts, potentially providing important information about the Korean and Swiss contexts that affect HBOC discourse [78]. This comparison will also reveal context-specific characteristics regarding the influence of the health care system, insurance coverage, and socioeconomic aspects on the application of genetic knowledge that can provide useful information for adapting other digital health solutions within the Swiss and Korean contexts. The goal of the adapted Family Gene Toolkit is to attend to the needs of diverse families, including the function of different members, and cultural and linguistic backgrounds. It is thus important to consider digital health technologies as sociocultural products with a need for an adaptation to specific local contexts and a critical reflection about how they may affect local perceptions of illness [78]. The final product will likely be more cost-effective and will expedite scaling-up, dissemination, and implementation, given the existing strong clinical partnerships within each country.

Conclusions

The adaptation and implementation of culturally sensitive, digitally based health interventions that enhance the understanding of genetic cancer risk are extremely timely and relevant, given the expansion of genetic testing technology, the falling costs of genetic testing, and the increased pressure for the integration of genetic knowledge in routine clinical care. Genetic testing for hereditary susceptibility to disease has received increasing attention among the health care community and at the individual, familial, and international levels. The DIALOGUE study will contribute to the development of high-quality comprehensive support systems that enhance the counseling process and facilitate informed decision making by minimizing conflict and distress and making resources available in culturally appropriate ways. Ultimately, the study contributes to a broader dissemination of genetic information and helps in expanding the public health understanding of the impact of new technologies on risk stratification and disease management.

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Conflicts of Interest

None declared.

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Abbreviations

CASCADE: Cancer Predisposition Cascade Genetic Testing
HBOC: hereditary breast and ovarian cancer
K-CASCADE: Korean–Cancer Predisposition Cascade Genetic Testing
KOHBRA: Korean Hereditary Breast Cancer
RCT: randomized controlled trial
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

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