Communication of Genetic Risk in Hereditary Breast and Ovarian Cancer and Lynch syndrome: Challenges and Prospects for Public Health and Clinical Practice

Inaugural dissertation

To be awarded the degree of Dr. sc. med.

presented at

the Faculty of Medicine

of the University of Basel

by

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From Como, Italy

Basel, 2022

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Basel, June 20th 2022

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ABSTRACT

In hereditary cancers, family communication of genetic information is essential to enable family members' independent decision making about genetic risk assessment and counselling. In Switzerland, as in many other countries, due to privacy law, communication of genetic test results to at-risk relatives is proband-mediated and currently it is the only way genetic information can be passed on. However, uptake of genetic services among at-risk relatives is less than 50%, suggesting poor family communication and inefficacy of proband-mediated approaches in disseminating genetic information. This PhD thesis aims to explore the challenges of communication of genetic risk in hereditary breast and ovarian cancer (HBOC) and Lynch Syndrome (LS), to identify prospects for public health and clinical practice and to propose a theoretical framework aiming to improve nursing practice around dissemination of genetic information. To reach the aim, three studies have been conducted: a cross-study comparison exploring genetic literacy using data collected from three sequential studies conducted in the U.S. and Switzerland over ≥10 years; a descriptive cross-sectional study using narrative data to clarify the process of communicating genetic risk to relatives; a descriptive study presenting an empirically-based framework to guide nursing practice for enhancing access to genetic services. The thesis demonstrates gaps in the dissemination of genetic information among at-risk relatives and confirms difficulties and a high level of complexity in the process of proband-mediated communication. It emphasises the need of interventions at the clinical and public health levels and suggests concrete actions to facilitate dissemination of genetic information and access to genetic services. To guide genomic nursing care, the thesis proposes the ACCESS model which focuses on promoting access to care, providing decisional support, supporting active coping, family risk communication and cascade screening, and ensuring ongoing surveillance.

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CHAPTER 1 - INTRODUCTION

Inherited cancer syndromes, as opposed to sporadic cancers that develop due to random somatic mutations, occur due to germline mutations that are transmitted from parents to offspring, conferring a variable risk of developing different and multiple early-onset cancers [1]. Germline pathogenic variants in *BRCA1* and *BRCA2* genes are associated with most hereditary breast and ovarian cancer (HBOC) cases, which account approximately for 5-10% and 15%-25% of all breast and ovarian cancer cases respectively [2]. Such pathogenic variants can be found in about 1 of 300-500 individuals in the general population. They confer a 69-72% and 17-44% cumulative risk of breast and ovarian cancer, respectively, by age 80 (12% and 1.3% lifetime risks in the general population) and an elevated risk of pancreatic and prostate cancers [3]. Lynch syndrome (LS) is another frequently occurring hereditary cancer condition, which accounts for about 2%-5% of colorectal and endometrial cancer cases, as well as several other malignancies. It is associated by inherited germline pathogenic variants in mismatch repair *(MMR)* genes and it is associated with 22-74% and 14-71% cumulative risk of colorectal and endometrial cancer, respectively, by age 70 (5.5% and 2.7% lifetime risks in general population) [4].

Germline pathogenic variants connected to most hereditary cancers, among which HBOC and LS, are transmitted in an autosomal dominant manner, which means that first-, second-, and third-degree relatives and first cousins of carriers have respectively 50%, 25% and 12.5% probability for inheriting the cancer predisposition [1]. Thus, in addition to carrier's individual cancer risk, it is also essential to manage the potential cancer risk for relatives through genetic services, i.e., counselling and testing. These are essential and recommended strategies to assess genetic risk and to support at-risk individuals in decision-making for effective cancer prevention and control interventions [5-6].

According to the Centers for Disease Control and Prevention (CDC) - Office for Public Health Genomics, HBOC, LS and familial hypercholesterolemia (FH) are Tier 1 genetic conditions, meaning that they are “actionable” and that there is a significant potential for positive impact on public health based on available evidence-based guidelines and recommendations [6]. In such conditions, clear steps at the individual, community, and public health level can be followed to improve health and prevent disease.

Cascade screening is among the most import public health interventions. It is the process of extending genomic services to first-, second-, and third-degree relatives of individuals who carry a germline pathogenic variant. Positive cascade test results can inform clinical management strategies to reduce morbidity and mortality, while negative results can help ameliorate distress and decrease unnecessary healthcare expenditures [6].

To enable independent decision making about genetic risk assessment and counselling and to enhance cascade screening, communication of genetic risk to members of families with hereditary cancers predisposition is essential [7-8]. However, the individual's autonomy and privacy regarding genetic information is protected, according to the Federal Act on Human Genetic Testing (HGTA), which is the legal regulation in Switzerland for clinical practice of genetic testing, as well as in many other countries worldwide. Thus communication of genetic test results to at-risk relatives is proband-mediated, meaning that it is the responsibility and duty of the proband (the individual identified with the pathogenic variant) to disseminate genetic information to their at-risk relatives [9-10]. Currently this is the primary way genetic information can be passed on to relatives with the proband’s responsibility to share genetic testing results and their implications for relatives and to advocate for cascade screening.

Empirical evidence shows that uptake of genetic services and cascade testing among at-risk relatives is less than 50%, suggesting poor family communication and inefficacy of

proband-mediated approaches in disseminating genetic information [11]. It is reported that about 20-40% of at-risk relatives, mainly second-degree and beyond, remain unaware of relevant genetic information and that frequently they are not well informed [12]. Probands mainly recognize their responsibility to inform relatives, and the majority have a sense of obligation towards relatives who need to know their risk and should be encouraged to get tested. However, this responsibility may be experienced as a burden and a dilemma [13-15]. The proband's decision and strategy around disclosure of genetic information are highly variable. A wide variety of barriers and factors related to the individual (i.e. mutation status, disease risk and severity; level of psychological adaptation; motivation) and the family (i.e. proximity and quality of the relationship; past experience with cancer; family rules and patterns) may affect them [7-8, 16-18]. Consequently, information to family may be deliberately withheld or there may be a failure to inform despite the intention to communicate or information may be inappropriate or delayed [19-20].

Genetic literacy facilitates seeking genetic evaluation and making informed decisions about genetic testing and cascade screening [21-22]. It refers to awareness about genetic risk factors, how they contribute to disease and understanding the chance of inheriting the genetic predisposition and developing the disease [21–24]. Genetic knowledge is especially important for individuals and families concerned with Tier 1 genetic conditions to enhance cascade screening. Indeed, it is recognized that when probands share information received during the consultation process, relatives' knowledge of cancer genetics, accuracy of risk perception and contacts with genetic services increase [25-26]. Thus, examining genetic literacy helps understand how genetic information is passed on from healthcare providers to probands and from probands to relatives.

Provider-mediated approaches to family information have been studied and adopted in some countries (i.e. provider direct contact, proband- or family- mediated contact with assistance from a healthcare provider, etc.) to face the issue of poor communication of genetic test results and increase accuracy and efficiency of information, [8, 11, 27]. They seem to be more effective than proband-mediated approaches but they have to consider probands' and relatives' preferences about contact modalities, feasibility, sustainability and legal implications, complying with local legislation [8, 11, 27]. However, proband involvement still remains a crucial issue even in more active approaches to inform at-risk relatives (e.g. informed consent to contact relatives, providing contact information, etc.) [8, 28]. Communication of genetic risk to family members is indeed extremely complex. It brings up a tension between the individual's right to privacy and autonomy on the one hand, and the dissemination of genetic information to family members and implication for public health on the other. Genetic information is indeed hybrid in nature: it belongs to the individuals, but also, to a certain extent, to their relatives. Respect for privacy and autonomy and in the meantime fairness and solidarity, arise thus a tension between individual interest and public health [10].

Nurses are at the forefront in genomic healthcare and can help in mitigate disparities in access to genetic information and in genomic healthcare. They are the most numerous and trusted of health professionals [29-30], have a long history of delivering holistic person- and family-centred care and are in a unique position in supporting individuals carrying germline pathogenic variants and their families. Many efforts have been done to integrate genomic competencies into nursing education and practice [31-32] but there is still a need for a unifying model to guide genomic nursing care and healthcare system policies.

The aim of this PhD project was thus to explore the challenges of communication of genetic risk in HBOC and LS, to identify prospects for public health and clinical practice and to propose a theoretical framework aiming to improve practice around familial communication and dissemination of genetic information to relatives.

Switzerland is a particularly suitable context for studying this phenomenon. Genetic risk communication is proband-mediated, some recommendations about supporting family communication to clinicians are given and the national healthcare system facilitates access to genetic services due to the national insurance system. Moreover, Switzerland is a country with limited social disparities and therefore, in principle, everyone has the social and cultural resources to access genetic services.

To reach the aim, three studies have been conducted:

1) A cross-study comparison explores genetic literacy both at the individual and the family level using data collected from three sequential studies conducted in the U.S. and Switzerland over ≥10 years. The purpose of the study is to examine genetic literacy among individuals who had genetic counselling for HBOC and how much of this information has been shared with their relatives. Specific aims are first to describe and compare genetic literacy between two groups of individuals, namely those who had genetic counselling for HBOC and their relatives who did not; and second to explore factors influencing genetic literacy both at the individual and at the family level.

2) A descriptive cross-sectional study using narrative data from three linguistic regions of Switzerland, clarifies the process of communicating genetic risk to relatives, based on the assumption that there is a communication chain along which information about genetic risk proceeds from healthcare providers to

carriers of pathogenic variants, and from carriers to relatives. The study's objectives are to explore how healthcare providers address family communication of genetic risk with probands; how probands decide to communicate genetic risk to relatives; how healthcare providers communication with probands may affect probands' decision to communicate genetic risk to relatives.

The study has been conducted in the framework of the CASCADE study, an open-ended cohort designed to elicit factors that enhance cascade genetic screening for HBOC and Lynch Syndrome (LS) in Switzerland (NCT03124212) [33].

3) Finally, a descriptive study presents an empirically-based framework, the ACCESS framework, to guide nursing practice for supporting disclosure of genetic information to relatives and, more in general, access to genetic services. The model was developed in a sequential, iterative process by an international group of nurse investigators from diverse healthcare systems and settings focusing on different genetic conditions.

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CHAPTER 2 – FIRST ARTICLE

Genetic Literacy And Communication Of Genetic Information In Families Concerned With Hereditary Breast And Ovarian Cancer: A Cross-Study Comparison In Two Countries And Within A Timeframe Of More Than 10 Years

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Published in: Cancers, 13(24), 6254. https://doi.org/10.3390/cancers13246254

Abstract: Examining genetic literacy in families concerned with hereditary breast and ovarian cancer (HBOC) helps understand how genetic information is passed on from individuals who had genetic counselling to their at-risk relatives. This cross-study comparison explored genetic literacy both at the individual and the family level using data collected from three sequential studies con-ducted in the U.S. and Switzerland over ≥10 years. Participants were primarily females, at-risk or confirmed carriers of HBOC-associated pathogenic variants, who had genetic counselling, and ≥1 of their relatives who did not. Fifteen items assessed genetic literacy. Among 1933 individuals from 518 families, 38.5% had genetic counselling and 61.5% did not. Although genetic literacy was higher among participants who had counselling, some risk factors were poorly

understood. At the individual level, genetic literacy was associated with having counselling, ≤5 years ago, higher education, and family history of cancer. At the family level, genetic literacy was associated with having counselling, higher education, and a cancer diagnosis. The findings suggest that specific genetic information should be emphasized during consultations, and that at-risk relatives feel less informed about inherited cancer risk, even if information is shared within families. There is a need to increase access to genetic information among at-risk individuals.

1. Introduction

Genetic literacy is the ability to understand and use genetic information for health-related decision-making [1, 2]. It refers to awareness about genetic risk factors, how they contribute to disease, understanding the chance of inheriting the genetic predisposition and developing the disease [1–4]. Genetic literacy facilitates seeking genetic evaluation and making informed decisions about genetic testing [1, 3, 5]. However, there are significant knowledge gaps in the general population, in stark contrast to the current levels of genetic and genomic discoveries and achievements in medicine and public health [1, 3, 6, 7]. Factors like age, race and ethnicity, education and socioeconomic status, and personal and family health history influence genetic literacy [3, 6, 8, 9], as well as access to specialized services [1, 10]. Finally, variations in genetic literacy have been reported for people living in different countries [7, 9].

Genetic literacy is especially important for families concerned with actionable (Tier 1) genetic conditions, such as hereditary breast and ovarian cancer (HBOC) [11]. HBOC is caused by germline autosomal dominant pathogenic variants; first-, second-, and third-degree relatives have a 50%, 25%, and 12.5% probability, respectively, of inheriting the

familial pathogenic variant [12]. In addition to managing the cancer risk of individuals carrying HBOC-associated pathogenic variants, it is also essential to address the potentially increased risk to relatives through cascade testing [11, 13]. Due to privacy laws in most countries, individuals carrying HBOC-associated variants have a key role in disseminating genetic information to relatives and in advocating for cascade testing [14, 15]. The proportion of relatives who initiate contact with genetic services and their knowledge of cancer genetics increases with genetic consultation [16, 17], and when counselled individuals share information received during the consultation process [18, 19].

Examining genetic literacy in the context of HBOC helps understand how genetic information is passed on from healthcare providers to index cases i.e., first in the family identified with a pathogenic variant, during genetic counselling, and from index cases to relatives. This is an essential step to support HBOC cascade testing. The purpose of this study is to explore genetic literacy among individuals who had genetic counselling for HBOC, i.e., whether they can recall information about genetic risk factors, modes of inheritance, and probability of developing an HBOC-associated cancer, and how much of this information has been shared with their relatives. Specific aims are first to describe and compare genetic literacy between two groups of individuals, namely those who had genetic counselling for HBOC and their relatives who did not; and second to explore factors influencing genetic literacy both at the individual and at the family level. To achieve these aims we examined data collected from three sequential studies conducted in the U.S. and Switzerland over a timeframe of more than 10 years. Pooling data across studies is feasible, since there are many similarities in the delivery and contents of genetic counselling in different countries [20].

2. Materials and Methods

This cross-study comparison used descriptive data from three family-based studies: a cross-sectional study conducted in 2007 in the US [21], baseline data from a randomized trial (RCT) conducted in 2012 in the US (NCT 01612338) [22], and baseline data from an ongoing cohort initiated in 2017 in Switzerland (NCT03124212) [23]. All studies were approved by the appropriate Institutional Review and Scientific Advisory Boards and Ethical Committees (HUM00011707 and HUM00055949, approved on 10.05.2007 and 14.10.2011 respectively, are exempt due to analysis of fully anonymized data; BASEC 2016-02052, approved on 06.02.2017, is ongoing). For this cross-study comparison we pooled participants and divided them into two distinct groups: individuals who had genetic counselling for HBOC, i.e., "exposed" to counsel-ling and one or more of their first-, or second-, or third-degree relatives who did not have counselling, i.e., "not exposed".

All three studies recruited individuals 18 years or older using the same procedures, identifying potentially eligible participants either from genetic clinics [21, 23] or from a state-wide cancer registry [22]. The 2007 US-based cross-sectional study identified females who had genetic counselling in a comprehensive cancer center with approximately 65% identified as carrying an HBOC-associated pathogenic variant [21]. The 2012 US-based RCT identified females diagnosed with breast cancer younger than 45 years old from a state-wide cancer registry, with 25% reportedly receiving genetic consultation at enrolment [22]. The Swiss-based cohort recruits both males and females who are confirmed carriers of an HBOC-associated pathogenic variant and who joined the cohort between January 2017 and January 2021 [23].

In all three studies, potentially eligible participants were mailed study materials from each recruitment site (genetic clinic or cancer registry). Those agreeing to participate returned

a signed consent form, revealing their name and address to the research team, and were asked to approach and pass on recruitment materials to relatives. Relatives who accepted participation also returned a signed consent, revealing their name, address, and degree of biological relation to the person who initiated the invitation. Inviting relatives was not a mandatory requirement for participating in the three studies, while each participant could invite one or more relatives. Details about recruitment of participants and relatives have been reported for each original study [21–23]. All studies mailed self-administered questionnaires, which were identical for those that had counselling and those who did not.

Genetic literacy was assessed with items used in all three studies, and was conceptualized as having two components, i.e., objective knowledge of cancer genetics and genetic affinity [9, 24]. Objective knowledge of cancer genetics included genetic risk factors, and probabilities of carrying a pathogenic variant and developing the disease. This information consists the "core knowledge" explained during genetic counselling. Objective knowledge was assessed with 13 items, asking participants to respond "True", "False", or "Do not Know" to statements related to this "core knowledge" [25]. Objective knowledge of cancer genetics was examined first through an overall score, calculated by summing the number of correct answers, and second by examining each knowledge item individually to reveal patterns of potentially not well-understood in-formation. Cronbach's α was greater than 0.85 in all three original studies and was 0.88 in the whole sample of the cross-study comparison. Genetic affinity, i.e., perceptions of being informed about cancer genetics and cancer risk, was assessed with two items asking: "How well informed do you feel about the probability of getting cancer?" ranging from 1 "Not at all informed" to 7 "Very Informed" and "How much do you know about the genetics of cancer?" ranging from 1 "Not at all" to 7 "A great deal". A genetic affinity score was calculated by summing responses in these two items.

Questionnaires also assessed demographics i.e., age, gender, race and ethnicity, marital status, education, employment, and clinical characteristics i.e., personal history of cancer "Yes" or "No"; family history of cancer "Yes" or "No"; years since personal cancer diagnosis "≤5 years" or ">5 years"; and years since genetic counselling "≤5 years" or ">5 years". We selected five years as a cut-off to assess the relevance of personal cancer diagnosis and years since genetic counselling since international guidelines consider this timeframe indicative of cancer survival [26].

Data analyses were performed in R version 4.0.4 [27]. Demographic and clinical characteristics were described by counselling status (counselled/not counselled) per study and for the total sample. Continuous variables were described using means and standard deviations (SD) and categorical variables with frequency of observations (n) and percentages (%). Differences between the two groups (counselled/not counselled) were examined on two primary outcomes i.e., objective knowledge of cancer genetics and genetic affinity, using t-test for means and chi-square or Fisher's exact test for counts. The two-sided significance level was set at 5% for all tests, and Bonferroni corrections were used to address multiple testing.

A linear mixed-effect model examined factors that may influence the sum scores of primary outcomes, i.e., demographics, personal and family history of cancer, time since cancer diagnosis and time since genetic counselling, recruitment from genetic clinics or the cancer registry, and country (US and Switzerland). The mixed model incorporated a study-specific random intercept which accommodated for including sub-jects from the same family unit (non-independent observations) within each study. All factors were considered as fixed effects. To address factors influencing primary out-comes within family units, we also conducted sensitivity analyses by adding a family unit-specific random intercept to the previous linear mixed-effect model. The sensitivity analyses

included only family units with more than one member enrolled in each of the three studies.

3. Results

The overall sample included a total of n = 1933 participants from n = 518 family units, with the majority (n = 1660, 85.9%) being from the US. Approximately 70% self-identified as White and 30% as belonging to minority racial or ethnic groups, i.e., Black or African American, American Indian or Alaskan Native, Arab or Arab American, Asian or Southeast Asian, Native Hawaiian or other Pacific Islander for the US-based samples; and African or Asian for the Swiss-based sample (Table 1). Given the small number of participants from minority racial and ethnic minority groups, we treated them as a single group in subsequent analyses.

Table 1. Demographics and clinical characteristics of the samples.

Characteristics	Total Sample *n* = 1933			Study 1 (2007) *n* = 370			Study 2 (2013) *n* = 1290			Study 3 (2017) *n* = 273		
	Counselled *n* = 745	Not Counselled *n* = 1188	*p*	Counselled *n* = 200	Not Counselled *n* = 170	*p*	Counselled *n* = 313	Not Counselled *n* = 977	*p*	Counselled *n* = 232	Not Counselled *n* = 41	*p*
Age (years)—mean (SD)	50.3 (10.3)	48.5 (11.0)	<0.001	50.6 (11.0)	48.7 (16.0)	0.53	48.7 (7.0)	48.3 (9.7)	0.53	52 (12.8)	51 (15.3)	0.70
Race and ethnicity—White (%)	78.4	69.5	<0.001	91.0	94.1	1	67.1	64.2	0.38	82.8	95.1	0.07
Married or Partnered—Yes (%)	86.7	93.9	<0.001	75.5	66.5	0.02	99.7	99.5	1	78.9	75.6	0.69
Education												
Elementary school (%)	10.3	20.9		8.5	14.1		15.7	22.7		4.7	4.9	
High degree school (%)	50.1	56.9	<0.0001	24.5	31.2	0.04	62.3	61.4	0.001	55.6	56.1	0.79
University/Post-graduate (%)	38.9	20.7		67.0	54.7		21.4	14.3		38.4	31.7	
Employed—Yes (%)	64.0	64.1	1	65.5	67.6	0.74	66.1	63.8	0.48	59.9	58.5	1
Cancer diagnosis—Yes (%)	69.5	50.6	<0.0001	53.5	11.8	<0.0001	89.7	59.2	<0.0001	56.0	7.3	<0.001
Family history of cancer—Yes (%)	80.8	85.4	0.01	67.5	71.2	0.51	88.5	87.2	0.61	81.9	100.0	<0.01

Among participants, 745 (38.5%) had genetic counselling and 1188 (61.5%) did not. In the overall sample and in each individual study separately, participants who had counselling were more likely to have a cancer diagnosis compared to those who did not

(69.5% vs. 50.6%, p < 0.0001). Those who had counselling were older, more likely to self-identify as White, married, and had higher education.

Knowledge of cancer genetics (total score) was overall higher in individuals who had counselling, with approximately 10 out of 13 items answered correctly (11, 9.5 and 9.5 items out of 13 in the three studies, respectively). The total score for individuals who did not have genetic counselling was 7.8 (Table 2).

Table 2. Objective knowledge of cancer genetics.

	Total Sample *n* = 1933			**Study 1 (2007) *n* = 370**			**Study 2 (2013) *n* = 1290**			**Study 3 (2019) *n* = 273**		
	Counselled *n* = 745	**Not Counselled *n* = 1188**		**Counselled *n* = 200**	**Not Counselled *n* = 170**		**Counselled *n* = 313**	**Not Counselled *n* = 977**		**Counselled *n* = 232**	**Not Counselled *n* = 41**	
	Correct (%)		***p***	**Correct (%)**		***p***	**Correct (%)**		***p***	**Correct (%)**		***p***
Cancer can be caused by a pathogenic variant passed on from one generation to the next	91.4	76.0	**<0.0001**	96.5	91.2	0.05	86.3	72.7	**<0.0001**	94.0	92.7	0.72
Families with a pathogenic variant in the BRCA1 or BRCA2 genes are likely to have cases of breast cancer in more than one generation	84.6	53.5	**<0.0001**	87.5	57.6	**<0.001**	77.6	51.4	**<0.0001**	91.4	87.8	0.55
A woman's risk for getting breast cancer is higher when she…												
…has a family history of ovarian cancer	74.6	51.1	**<0.0001**	80.5	69.4	0.01	65.5	47.5	**<0.0001**	81.9	61.0	0.004
…has a relative diagnosed with breast cancer younger than 50 years old	57.9	63.6	0.01	72.0	61.8	0.04	76.7	66.1	**<0.001**	20.3	12.2	0.31
…has a family history of breast cancer from the dad's side of the family	74.6	56.7	**<0.0001**	88.5	87.1	0.79	62.3	51.4	**<0.001**	79.3	58.5	<0.01
…has a family history of breast cancer from the mom's side of the family	87.8	77.3	**<0.001**	93.5	92.9	0.99	82.7	75.1	**<0.01**	89.7	63.4	**<0.001**
…has breast and ovarian cancer in the same side of the family	82.0	68.7	**<0.0001**	88.0	85.3	0.54	78.9	66.6	**<0.0001**	81.0	48.8	**<0.001**
…has a pathogenic variant in the BRCA1 or BRCA2 genes	88.1	53.7	**<0.0001**	89.0	76.5	**<0.01**	82.1	49.0	**<0.0001**	95.3	61.0	**<0.0001**
…is from Ashkenazi Jewish descent	38.3	13.5	**<0.0001**	62.5	33.5	**<0.001**	32.2	10.3	**<0.0001**	25.4	4.9	<0.01
…has a male relative who had breast cancer	65.1	47.8	**<0.0001**	73.0	65.9	0.17	60.1	44.7	**<0.0001**	65.1	46.3	0.03

…has a relative with breast cancer in both breasts	78.9	68.3	**<0.001**	86.0	85.3	0.96	75.1	65.9	**<0.01**	78.0	53.7	**0.001**
…has a relative who had both breast and ovarian cancer	82.6	71.5	**<0.001**	85.0	84.1	0.92	81.5	69.8	**<0.0001**	81.9	61.0	<0.01
…has multiple relatives with breast cancer	81.7	80.6	0.58	91.5	94.1	0.44	84.7	79.7	0.06	69.4	46.3	<0.01
Total correct answers (0–13)—mean (SD)	9.9 (3.2)	7.8 (3.8)	**<0.0001**	10.9 (2.9)	9.8 (2.9)	**<0.001**	9.5 (3.6)	7.5 (3.8)	**<0.0001**	9.5 (2.8)	7.0 (3.9)	**0.0002**

Bold: *p* value still significant after Bonferroni correction.

The items least identified as risk factors in the overall sample, even among individuals who had genetic counselling, were: "…is from Ashkenazi Jewish descent" (38.3% counselled and 13.5% not counselled), "having a relative diagnosed with breast cancer younger than 50 years old" (57.9% counselled and 63.6% not counselled ") and "…having a male relative with breast cancer" (65.1% counselled and 47.8% not counselled). All other items were answered correctly by more than 70% of participants who had counselling. "Having multiple relatives with breast cancer" was the one item identified as a genetic risk factor from more than 80% of all respondents (81.7% counselled and 80.6% not counselled).

Risk factors with the greatest discrepancies among individuals who had counsel-ling and those who did not were: "…a family history of ovarian cancer" (74.6% counselled and 51.1% not counselled); "…a family history of breast cancer from the dad's side of the family" (74.6% counselled and 56.7% not counselled); "…a pathogenic variant in the BRCA1 or BRCA2 genes" (88.1% counselled and 53.7% not counselled); and "…have cases of breast cancer in more than one generation" (84.6% counselled and 53.5% not counselled).

Individuals who had counselling reported higher genetic affinity and feeling more informed about the probability of getting cancer and about the genetics of cancer compared to those who did (Table 3). The total genetic affinity score was 7.3 out of 14 among those not counselled. There was a low-moderate correlation between knowledge

of cancer genetics and genetic affinity in the overall sample (r= 0.38) and in the three studies (r = 0.28; r = 0.32; and r = 0.50, respectively).

Table 3. Genetic affinity.

	Total Sample *n* = 1933			**Study 1 (2007) *n* = 370**			**Study 2 (2013) *n* = 1290**			**Study 3 (2019) *n* = 273**		
	Counselled *n* = 745	**Not Counselled *n* = 1188**		**Counselled *n* = 200**	**Not Counselled *n* = 170**		**Counselled *n* = 313**	**Not Counselled *n* = 977**		**Counselled *n* = 232**	**Not Counselled *n* = 41**	
	Mean (SD)		***p***	**Mean (SD)**		***p***	**Mean (SD)**		***p***	**Mean (SD)**		***p***
How informed do you feel about the chances of getting cancer? (1–7)	5.7 (1.3)	4.7 (1.8)	**<0.0001**	6.1 (1.2)	4.9 (1.4)	**<0.0001**	5.5 (1.6)	4.6 (1.8)	**<0.0001**	5.7 (1.1)	4.9 (1.8)	0.02
How much do you know about the genetics of cancer? (1–7)	4.6 (1.5)	3.0 (1.7)	**<0.0001**	5.0 (1.2)	3.8 (1.6)	**<0.0001**	4.4 (1.7)	2.8 (1.6)	**<0.0001**	4.4 (1.4)	3.6 (1.7)	<0.01
Sum score (2–14)	10.0 (2.9)	7.3 (3.3)	**<0.0001**	10.9 (2.4)	8.6 (2.8)	**<0.0001**	9.5 (3.4)	7.1 (3.3)	**<0.0001**	9.9 (2.3)	8.1 (3.6)	**0.003**

Bold: *p* value still significant after Bonferroni correction.

Regression analyses in the overall sample showed that at the individual level higher genetic literacy (knowledge of cancer genetics and genetic affinity) were associated with having had counselling, less or equal to five years ago, a higher education, and a family history of cancer (Table 4). Being younger and self-identified as White were associated with higher knowledge of cancer genetics, while having had cancer was associated with higher genetic affinity. Sensitivity analysis at the family level, i.e., considering whether participants were members of the same family unit, showed that counselling, higher education, and a cancer diagnosis were still associated with higher knowledge of cancer genetics and with higher genetic affinity (Table 5). Younger age and self-identified as White were associated with higher knowledge of cancer genetics among members of the same family unit. Variance partition coefficients in sensitivity analysis showed that only 7% and 6% of variance in knowledge of cancer genetics and genetic affinity, respectively, was contributed by family clustering.

Table 4. Fixed effects from linear mixed-effect models for factors influencing knowledge of cancer genetics and genetic affinity in the overall sample at the individual level.

	Knowledge of Cancer Genetics (*n* = 1895) *			**Genetic Affinity (*n* = 1895) ***		
	Estimate	**Standard Error**	***p***	**Estimate**	**Standard Error**	***p***
Age	−0.02	0.007	**<0.001**	−0.0004	0.007	0.95
Race and ethnicity (ref: White)	1.68	0.18	**<0.0001**	0.074	0.17	0.66
Education—(ref: Elementary school)	1.12	1.24	**<0.0001**	0.59	0.12	**<0.0001**
Employment (ref: No employment)	0.26	0.16	0.11	0.13	0.15	0.40
Cancer diagnosis (ref: No cancer)	0.21	0.21	0.33	0.59	0.21	**<0.01**
Genetic counselling (ref: No counselling)	0.80	0.27	**<0.01**	1.59	0.25	**<0.0001**
Family history of cancer (ref: No history)	1.45	0.25	**<0.0001**	0.50	0.23	**0.03**
Recruitment (ref: Clinic)	2.35	3.12	0.99	1.98	3.32	1.00
Country (ref: US)	2.82	3.13	0.99	1.38	3.32	1.00
≤5 years since cancer diagnosis (ref: Never diagnosed with cancer)	0.05	0.32	0.88	0.39	0.30	0.19
>5 years since cancer diagnosis (ref: Never diagnosed with cancer)	0.36	0.21	**0.09**	0.29	0.19	0.14
≤5 years since counselling (ref: Never counselled)	0.86	0.31	**<0.01**	0.34	0.29	0.21
>5 years since counselling (ref: Never counselled)	1.16	0.34	**<0.001**	0.68	0.32	**0.03**

* the number of participants is lower compared to the overall sample due to missing data. **Bold**: p value still significant after Bonferroni correction

Table 5. Fixed effects from linear mixed-effect model for factors influencing knowledge of cancer genetics and genetic affinity in members from the same family unit.

	Knowledge of Cancer Genetics (*n* = 1163) *			**Genetic Affinity (*n* = 1163) ***		
	Estimate	**Standard Error**	***p***	**Estimate**	**Standard Error**	***p***
Age	−0.03	0.008	**<0.0001**	<0.0001	0.007	0.99
Race and ethnicity (ref: White)	1.47	0.26	**<0.0001**	0.018	0.24	0.94
Education (ref: Elementary school)	0.98	0.15	**<0.0001**	0.54	0.14	**<0.0001**
Employment (ref: No employment)	0.27	0.20	0.18	−0.083	0.18	0.65
Cancer diagnosis (ref: No cancer)	0.72	0.27	**<0.01**	0.78	0.25	**0.002**
Genetic counselling (ref: No counselling)	0.84	0.32	**0.01**	1.63	0.30	**<0.0001**
Family history of cancer (ref: No history)	0.50	0.42	0.24	0.22	0.38	0.58
Recruitment (ref: Clinic)	1.81	1.80	0.24	1.86	2.21	0.40
Country (ref: US)	2.13	1.82	0.24	1.08	2.22	0.62

≤5 years since cancer diagnosis (ref: Never diagnosed with cancer)	−0.08	0.43	0.83	0.53	0.39	0.18
>5 years since cancer diagnosis (ref: Never diagnosed with cancer)	0.20	0.31	0.51	0.20	0.28	0.50
≤5 years since counselling (ref: Never counselled)	0.19	0.39	0.63	−0.03	0.35	0.93
>5 years since counselling (ref: Never counselled)	0.65	0.45	0.14	0.64	0.41	0.11

***** the number of participants is lower compared to the overall sample. Individuals were members of 518 family units. **Bold**: *p* value still significant after Bonferroni correction.

4. Discussion

This cross-study comparison used family-based data collected in the US and in Switzerland over a timeframe of more than 10 years to examine genetic literacy in individuals who had counselling for HBOC and their relatives who did not, and factors influencing genetic literacy both at the individual and at the family level. Genetic literacy was higher among participants who had counselling, compared to those who did not. Our findings support the role of genetic counseling in improving genetic literacy [1, 3, 18, 19, 28].

We identified specific risk factors and signs of HBOC that remain unclear, even to individuals who had a genetic consultation. Despite being important red flags for HBOC, early age of cancer onset, breast cancer in male relatives, and having Ashkenazi Jewish ancestry were not recognized as risk factors for most individuals. Genetic consultations provide personalized information and likely focus on individual risk factors. Thus, some of the above risk factors may not have been emphasized equally in all consultations, which may explain our findings. Nevertheless, HBOC cases need to be vigilant in identifying red flags in their family history since a new cancer diagnosis among relatives may provide important information that could change their own plans of managing hereditary cancer risk. Those who test negative (uninformative result) and those who do

not qualify for testing are encouraged to periodically contact the genetic testing center and re-evaluate their status. Given the lifelong consequences of carrying an HBOC-associated pathogenic variant, periodic "check-ins" with genetic specialists can clarify important information and reassess cancer risk management plans.

Important risk factors, such as having a family history of ovarian cancer and a family history of breast cancer from the paternal side of the family were less frequently identified among individuals who did not have genetic counselling. This finding further highlights gaps in the dissemination of genetic information to at-risk individuals that have been reported over a period of 20 years [6, 7, 29–31]. Individuals who are unsure about how and from whom HBOC-associated pathogenic variants can be inherited are more likely to overlook their hereditary cancer risk if affected relatives are on the paternal side of the family. One possible explanation for this persistent finding may be related to unbalanced presentations of HBOC from mass media [32, 33]. However, in light of the rapid evolution in cancer genetics, tracking changes in genetic literacy is extremely important. As knowledge continues to expand and educational materials are developed and made available to at-risk individuals and the lay public, the healthcare community needs to address these persistent knowledge gaps.

Consistent with studies that examined genetic literacy in the general population [3, 6, 8, 9], participants who were younger, self-identified as White, had higher education, and a personal and/or a family history of cancer were more likely to know about risk factors and to feel better informed about cancer genetics. It is difficult to disentangle the effects of counselling from the experiential knowledge gained from a personal and/or a family history of cancer on genetic literacy. Our data show that having a consultation less than five years ago was associated with both higher knowledge of cancer genetics and higher genetic affinity, while time since a personal cancer diagnosis did not influence genetic

literacy. These findings mean that the genetic consultation likely provides understandable and actionable information beyond the information that is discussed in the context of a personal cancer diagnosis [1, 3, 18, 19, 28].

Cascade testing for Tier 1 genetic conditions, such as HBOC, relies on assumptions of open family communication and effective dissemination of genetic information within members of family units. However, it is unclear if this communication strategy can ensure effective and accurate information transmission. We explored communication of genetic information within family units using sensitivity analysis, including only families with a member who received counseling and one or more at-risk relative who did not. By adding the random intercept term for each specific family unit into our modelling, unmeasured confounders, like level of family communication and information sharing between counselled and not counselled individuals, were controlled at that level. Interestingly, after adding family unit as a level in the analysis, genetic counselling was still significantly associated with knowledge of cancer genetics and with genetic affinity. Variance partition coefficients of sensitivity analyses showed that 6–7% of overall variation in objective knowledge and genetic affinity were explained by family clustering. If genetic information was openly and accurately shared from individuals who had counselling to their relatives, the variation in genetic literacy in members from different family units would have been observed more easily compared to the variation between members of random family units. This further implies that tailored educational interventions aiming to promote cascade testing should consider the characteristics of the family unit in addition to characteristics of the different individuals.

Using datasets from three studies could introduce a bias in the cross-study comparisons due to heterogeneity among the primary studies. In our case, the three primary studies had comparable aims and recruitment methods, which controlled for such bias and made

comparisons feasible. Since participants from minority ethnic and racial groups had significantly lower levels of genetic literacy, our findings point to the widening gap of disparities in healthcare brought upon the clinical application of genetics [34–36]. However, participants from different ethnic and racial minority groups were very heterogeneous among the US and the Swiss-based samples, and were recruited primarily from one study. Thus, our findings are likely not applicable to non-White/Caucasian individuals and families, but without any inference to specific ethnic and racial minority groups. The Swiss sample was smaller, which may have also influenced findings regarding the impact of country and year of study on genetic literacy. HBOC status could only be ascertained for clinic-based samples. Finally, for the sensitivity analyses, we removed individuals without any relatives, which may have led to insufficient sample size.

5. Conclusions

Our cross-study comparison demonstrated the need for increased access to genetic information among at-risk individuals and that the lay public needs more assistance from healthcare professionals to understand complex genetic information and use it to inform plans for cancer risk management [37, 38]. Our findings highlighted the role of counselling in improving genetic literacy and demonstrated persistent knowledge gaps and misconceptions, and that important red flags for HBOC remain poorly under-stood. Continued follow-up with genetic services could clarify and reinforce information that is overlooked or not well-understood. Addressing persistent knowledge gaps about aspects of HBOC, and racial and ethnic disparities in genetic care, should be priority public health goals. Efforts to improve family communication of genetic information should be enhanced with interventions at the clinical (support to carriers of pathogenic variants),

legal (healthcare providers ability to provide tailored assistance with family communication) and public health (policies to improve access to genetic services) levels [14, 39, 40].

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CHAPTER 3 – SECOND ARTICLE

Defining The Communication Chain Of Genetic Risk: An Analysis Of Narrative Data Exploring Proband-Provider And Proband-Family Communication In Hereditary Breast And Ovarian Cancer

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Published in: Journal of personalized medicine, 12(8), 1249. https://doi.org/10.3390/jpm12081249

Abstract: Low uptake of genetic services among members of families with hereditary breast and ovarian cancer (HBOC) suggests limitations of proband-mediated communication of genetic risk. The aim of this descriptive cross-sectional study is to explore from the probands' perspective, the communication chain, namely how genetic information proceeds from healthcare-providers to probands and from probands to relatives. Following Grounded Theory, we analysed narrative data collected with individual interviews and focus groups from a sample of 48 HBOC women from three linguistic regions of Switzerland.

In healthcare providers-probands communication, data highlight a three level-complexity in the way information about family communication is approached by the providers, received by the probands and followed-up by the health-care system. In the probands' decision-making regarding family communication, data show dynamic and often

contradictory logics interconnected with individual and family characteristics which lead to a high level of complexity in the arbitrating process.

The study confirms the difficulties of proband-mediated communication but highlights the active role that probands wish in the communication process to their relatives. This suggests the need to support probands in navigating the complexity of family communication rather than replacing them in their role as communicators. Concrete actions, both at the clinical and health-system level, are needed to improve proband-mediated communication.

1. Introduction

Communication of genetic risk among members of families with hereditary breast and ovarian cancer (HBOC) is essential to manage their potential cancer risk through genetic services. In Switzerland, as well as in many other countries, due to privacy laws, risk communication is proband-mediated, meaning that the individual identified with the pathogenic variant has the responsibility to share genetic test results and their implications to at-risk relatives, and advocate for cascade testing [1-2]. However, uptake of genetic services and cascade testing among at-risk relatives remains lower than 50%, suggesting that this approach has significant limitations in both ensuring contact with the appropriate individuals and the transmission of accurate information [3-5]. An extensive body of literature confirms that communication of genetic risk to relatives is a difficult and complex process, affected by interconnected individual and family characteristics e.g., disease risk and severity, level of psychological adaptation, motivation, proximity and quality of the relationship, family past experience with cancer, family rules and patterns, etc. [6-14]. Probands usually acknowledge their responsibility to inform relatives, but this

responsibility may be experienced as a burden and a dilemma with sentiments of guilt, fear, and frustration, which adds to probands' burden associate with a possible cancer diagnosis [15-16]. As a result, there may be a failure to inform relatives despite intentions to share genetic test results, the information may be inappropriate or delayed, or in some cases communicating information to the family may be deliberately withheld [17-19].

To address the issue of poor communication of genetic test results, thus alleviating probands' burden of notifying at-risk relatives and increasing the accuracy and efficiency of information-sharing, more active approaches are being considered, e.g., provider direct contact to relatives, proband- or family- mediated contact with assistance from a healthcare provider, etc. [3, 6, 20-22]. Provider-mediated approaches to inform at-risk relatives seem to be more effective [3, 6, 20, 23] but have to consider major ethical and legal implications, and to comply with local legislation and with probands' and relatives' preferences about contact modalities [2-3, 6, 21, 24]. Additionally, also in more active approaches to inform at-risk relatives, involvement of probands remains fundamental e.g., consent to contact relatives, providing contact information, etc. [6, 21].

Healthcare providers play an important role in supporting probands' communication even in proband-mediated approaches [18, 20, 25-26]. Although international guidelines recommend providing active support to probands for family communication [3, 20, 22, 25], in clinical practice, however, facilitating probands' discussions within families is complex, challenging, and still limited [3, 25, 27]. Concrete difficulties may contribute to this complexity, e.g., lack of information about distant relatives, lack of clarity on the side of the family that harbors the pathogenic variant, and ethical and professional dilemmas about respect for patients' autonomy and duty to warn [3, 25, 27]. Strategies used by providers to address family communication are mainly focused on information

content, often delivered without continuity, or delivered as part of research interventions rather than routine clinical practice [20].

In the context of the current debate about proband-mediated versus provider-mediated strategies for informing at-risk relatives, proband-mediated communication needs to be better understood. Thus, this study aims to clarify the process of communicating genetic risk to relatives, based on the assumption that this is an ongoing process, and that there is a communication chain along which information about genetic risk proceeds from healthcare providers to carriers of pathogenic variants, and from carriers to relatives.

Based on this hypothesis, the study's objectives are to explore:

1) how healthcare providers address family communication of genetic risk with probands

2) how probands decide to communicate genetic risk to relatives

3) how healthcare providers communication with probands may affect probands' decision to communicate genetic risk to relatives

Our study aims to understand, specifically from the probands' point of view, the way they manage the process of communicating genetic risk. This process begins the moment in which they receive the information about the pathogenic variant from their healthcare provider, to the moment in which they decide to transmit this information or not transmit it to relatives. Findings will thus help clarify the role of the proband and the role of the healthcare provider in proband-mediated communication.

2. Methods

This descriptive cross-sectional study used individual interviews and focus groups to collect narrative data from a sample of HBOC cases. Participants were recruited from the

CASCADE study, an open-ended cohort designed to elicit factors that enhance cascade genetic screening for HBOC and Lynch Syndrome (LS) in Switzerland (NCT03124212) [24]. Confirmed carriers of HBOC- or LS-associated pathogenic variants who are 18 years or older are recruited from cantonal hospitals and university centres in three linguistic regions of Switzerland. Details about eligibility criteria and recruitment procedures have been published [28]. The study, including the collection of narrative data, has been approved by appropriate ethics committees (BASEC 2016-02052).

Collection of narrative data took place between April 2019 and November 2021. Potential participants were identified among probands who were willing to provide narrative data. Initially, the research team planned to conduct a series of focus groups [29]. However, some participants expressed their preference towards individual interviews. Moreover, the organization of focus groups with compatible individuals was difficult due to the low numbers of participants in some centres, the geographical distance among centres from similar linguistic regions, and eventually the Covid-19 pandemic. Consequently, the research team decided on a pragmatic data collection, oriented by the emerging results (theoretical sampling) and in order to diversify the sample in terms of clinical history (affected by cancer or cancer-free), linguistic area (German, French, Italian), and age ($\leq$39, 40-49, 50-59, $\geq$ 60). Data collection included both focus groups and interviews that were conducted either face-to-face or online. The research team developed strategies to ensure data quality and comparability, paying attention to the advantages of each technique, as well as facing the challenges of online data collection on sensitive topics [30].

Interviews and focus groups were conducted by four members of the research team experienced in qualitative research and fluent in the language of conduction. The data collection guide was developed in English to support a common approach and then was

translated in German, French, and Italian. The data collection guide asked participants to reflect on how healthcare providers addressed disclosure of genetic risk to relatives; how they acted upon and experienced family communication (decision and disclosure or not disclosure); and how they perceived that communication with healthcare providers affected their own communication with relatives. Data collection and analysis were conducted simultaneously until data saturation occurred (iterativity). Throughout the period of data collection, the research team adapted the guide according to the mode of data collection (focus groups versus interviews, face-to-face versus online) and modified it according to emerging themes. Interviews and focus groups were audio- or video-recorded and transcribed verbatim. Pseudonyms were given to participants.

Data analyses were conducted by the four interviewers and two senior researchers based on premises of Grounded Theory [31]. Each interviewer was responsible for making a first analysis of their own collected data. The analysis started by reading the transcripts multiple times to familiarize with the content and to identify meaningful quotes. Data were continuously compared to form categories and to find relationships among concepts (analysis through constant comparison). Each interviewer inductively coded the data, linked the codes and grouped them into larger categories and concepts, and organized them into different topics. Prominent themes of each interview or focus group discussions were stressed and contrasted with those of other interviews or discussions. Regular meetings regarding emerging patterns were held to ensure analytical validity. Disagreements in interpretation were addressed through discussion and by making constant references to the transcripts in order to develop a reasonable representation of the studied phenomenon. A transversal analysis was proposed on a regular basis by one member of the research team, to develop a more general understanding of the studied phenomenon. Once data saturation was achieved [31], the research team consensually

developed a detailed codebook in English. Each researcher was then in charge of re-coding their own data following the codebook, identifying meaningful quotes, and translating them in English. Members of the research team provided feedback and checked the relevance and the validity of the developed argumentation and of the selected quotations.

3. Results

The following analyses are based on narrative data collected from 48 participants, of whom 20 participated in individual semi-structured interviews and the remaining 28 participated in 11 focus groups. Initial data collection for 7 interviews and 2 focus groups took place face-to-face, at participants' home or in a university room, while the remaining 13 interviews and 9 focus groups took place online.

Table 1 shows the socio-demographic and clinical characteristics of the sample.

Table 1: Socio-demographic and clinical characteristics of the sample

Characteristics	**N=48 (%)**
Gender	
Female	48 (100)
Age – mean (SD)	51.8 (10.9)
≤ 39	6 (12.5)
>39≤49	16 (33.3)
>49≤59	12 (25)
>59	14 (29.2)
Marital status	
Married/Partenered	37 (77.1)
Single	3 (6.25)
Divorced/Separated	6 (12.5)
Widowed	1 (2.1)
Education	
≤ High school/Technical school	14 (29.2)
Some college/Complete college	14 (29.2)
University/Post-graduate degree	19 (39.6)
Cancer diagnosis	
Yes	29 (60.4)
Years from genetic testing - mean (SD)	7.2 (5.1)

Linguistic region	
French	27 (56.3)
German	14 (29.2)
Italian	7 (14.6)

All participants were female, with mean age 51.8 years old, and on average 7 years post genetic testing. The majority were married or partnered and had at least some college education. Approximately two out of three participants had one or more previous cancer diagnoses, and provided an interview in French.

Communication between healthcare providers and probands: The challenge of discussing family communication

The first step of the communication chain, which is supposed to bring the genetic information from healthcare providers to relatives, takes place during the post-testing genetic consultation. At that moment probands become aware that they have been identified as carrying a pathogenic variant, that the genetic predisposition involves their relatives, and that there is a need to inform them. Participants' experiences highlighted how discussions about family communication with healthcare providers during genetic counselling were different and challenging. Data show variability and complexity at different levels of this phase, particularly in the way the need for family communication was broached by healthcare providers, was received by probands, and was followed-up by the healthcare system. Table 2 provides quotes identified in narrative data to support findings about communication between healthcare providers and probands.

Variability in the approach to family communication

Participants' experiences about how the need for family communication was addressed by healthcare providers were rather different and multifaceted. About half of the sample

perceived that the topic of family communication was approached in a rather superficial, hasty, and abstract manner. Accordingly, the discussion did not have any concrete effect and left them feeling "alone" in the duty to inform relatives. Details, such as information about whom to inform and whom not, were frequently missing and if they were addressed, the information was not always so clear (quotes 1 and 2). One participant mentioned that she would have preferred more incisive instructions, leaving no room for uncertainty or doubts, and a more active and direct role of healthcare providers in supporting her in the communication process (quote 3). Other experiences were more positive with the perception of a good and exhaustive discussion on family communication and a positive and helpful attitude from healthcare providers (quote 4). Concrete interventions, such as a letter received by some participants to distribute to all family members, were also considered very helpful to make communication easier and more effective (quote 5). This variability of experiences highlights that there was no common approach in addressing family communication. Thus, it appears that the discussion on family communication was guided by healthcare providers' individual sensitivity and interpretation of the situation.

Difficulty in receiving information about family communication

Often participants did not remember whether healthcare providers discussed about family communication during genetic counselling or they have a vague memory of it. This may be due to the amount of information given during the consultation and the particularity of the moment in which genetic counselling occurred. In some cases, participants recognize that their psychological state, due to the situation they were facing, influenced the level of attention and understanding during the counselling (quote 6). Genetic counselling frequently took place when priorities and needs were not focused on communicating genetic risk to others. In the case of women affected by cancer in particular, the

consultation tended to focus on management of the disease in light of its genetic nature. Healthcare providers and probands were thus somehow swayed away from the issue of family communication (quote 7). Even in the case of unaffected women, worries about the pathogenic variant and about decisions for risk management took precedence over the urgency to address the issue of family communication (quote 8). Therefore, both the particularity of the situation and participants' choices to give priority to other aspects during genetic counselling seem frequently to put the issue of family communication on "the back burner".

Inconsistency in the follow-up of the issue of family communication

Since priorities and needs may change along probands' trajectory of life and illness, the possibility to discuss again about communication of genetic risk with healthcare providers is crucial (quote 9). Given the amount of information provided during genetic counselling, the possibility of asking questions about issues which are not clear or are poorly remembered helps probands clarify their own doubts and provide more accurate information to relatives (quote 10). Participants highlighted how, over time, new needs and new questions arise due to changes in their own situation, however, they do not have the opportunity to discuss again the topic of family communication with healthcare providers (quote 11). In most cases, neither the genetic healthcare provider nor other providers (GP or specialist) addressed the topic of family communication after the post-testing consultation. In the rare events that this happened, there was no coordination among providers from different specialties (quote 12). Theoretically, participants had the possibility to contact the genetic healthcare provider at a later point, however, most women found it difficult to take this initiative. Some of them looked for information

elsewhere, with the risk to experience even more inconsistency in the way family communication was addressed (quote 13).

Table 2: Communication between healthcare providers and probands

Themes	Quotes	Supporting quotes
Variability in the approach to family communication	1	*"In the department they told me: "You have to communicate with your family….". But it was a bit abstract. I mean, I would have left from there and I might have done nothing too…" (Anna, 48 y.o., affected)*
	2	*"Actually the communication to the family was delegated to me. (…) Perhaps it was implied, they spoke more in the feminine, then for the offspring, they spoke in the masculine. (...) This thought made me think that there was no need to tell to my uncles. I understood so ... but then it is the perception.". (Carla, 48 y.o., affected)*
	3	*"No, that communication on her side (the genetic counsellor) was just too soft. And that applies to the family clarification as well, exactly the same. It shouldn't be "it would be best to inform your relatives", but: "We request you to clarify your family status." Clearly and unambiguously described. Not "you could". But: "Go there! Do it!" (Ms. P., 52 y.o, not affected)*
	4	*"(The physician) was absolutely available afterwards. I didn't feel the need to see him again. Anyway, he's a great person, I really found him to be totally adequate". (Katarina, 33 y.o., unaffected)*
	5	*"I received a letter from the hospital explaining what it was and that I could possibly have the gene mutation and that I should contact Dr…... And that's what we did, together with the sister. Afterwards we had all the genetic meetings with her. She (the physician) explained it very well. So, for me it was never the case that I was somehow all alone and badly informed." (Rose, 50 y.o, unaffected)*
Difficulty in the reception of information about family communication	6	"*The oncologist, I can't tell you right now if she's been talking to me about the mutation running in the family, I don't know. (…) When I was with her for the first time, I wasn't doing so well psychologically". (Antonia, 33 y.o., not affected).*
	7	*"Because of the speed with which everything happened, it (the topic of family communication) was touched on but not explored. It was said that there was a possibility to communicate to the boys and close family members, as there was heredity. This was*

		communicated. (…) It was probably enough at that moment. Because you're in a situation of turmoil (…) Maybe it would have been different, if illness happened afterwards". (Carla, 48 y.o., affected)
	8	*"So, for me the shock of finding out that I had this mutation was even greater than finding out to have a cancer. I did the test, and I got the results. It was terrible for me because it meant that I could have passed on this mutation to my daughter, and I felt guilt". (Luise, 45 y.o., unaffected)*
Inconsistency in the follow up of family communication	9	*"I'm really starting to get into it (communication to children) now. Before I was more about saving my own skin, that's done, for now anyway, and now I want to save my kids." (Mari, 42 y.o.,affected)*
	10	*"No, let's say they gave me a lot of information all at once at the beginning, so understanding and remembering everything was a bit of a struggle. (…) So, I remembered this thing, I told them (family members), but I didn't remember it specifically. Today I came, I spoke again about this thing here (with the physician) because I had not well understood it (...) I could resume some aspects that I had not understood, because it is not obvious on so many things to understand them all obviously". (Sabina, 52 y.o, unaffected).*
	11	*"He (the physician) did talk to me about all of this, but it was rather at the beginning. So sometimes I think it would have been necessary to take up the subject again later on. Because I was just informed by him once I had gotten the result, and I didn't really have any questions until later". (Gisela, 46 y.o., unaffected)*
	12	*"It was mainly the genetist who encouraged me to talk to the family. Then when I went back to my gynaecologist, he asked me if I had other family members, how they had taken it. Just out of interest. But...more than out of medical concern." (Christine, 47 y.o., unaffected)*
	13	*"I might have been able to go to him again, but somehow I looked for (information) then in other places" (Gisela, 46 y.o., unaffected)*

Probands' decision-making regarding family communication: Multiple logics of action

The second step in the communication chain involves patients' decision to communicate genetic information to relatives. This decision does not take place in a single moment and it is not linear. Different logics seem to come into play and guide the decision to

communicate or not, the way, and the time to do it. These principles of action help in understanding communication or lack of communication. They are linked with the proband's rationality, values, norms or beliefs; they may be more or less explicit, contradictory, and they may come into play simultaneously, making the decision process complex and difficult to interpret. Our data show four main logics of action as the base of the decision to communicate genetic information to relatives or not and the way to do it. Table 3 provides quotes identified in narrative data to support findings about probands' decision-making regarding family communication.

Responsibility

Discovering a pathogenic variant immediately allocates to the individual the burden of communication with relatives. Indeed, there is a sort of "normative" pressure that encourages the individual to consider communicating genetic risk to relatives. The majority of participants feel responsible of informing others and making them aware about their possible genetic risk. Communication of genetic information appears as a "due act", something necessary to do despite the difficulties it may imply (quotes 14 and 15). The sense of responsibility seems particularly prominent with close relatives, when there is emotional proximity. This leads to prompt and more insistent information, even if this is often more difficult due to the level of personal involvement (quotes 16 and 17). For some participants this sense of responsibility is also directed towards distant relatives, and even the general population to increase dissemination of genetic information among the lay public. For these persons transmission of genetic information is crucial due to their highly developed sense of civic duty (quotes 18 and 19). In many situations, the family and personal experiences reinforce this sense of responsibility. This is particularly the case when there is a sense of efficacy of the genetic testing or when there is personal or

family illness, which emphasise the importance of making others aware of the genetic risk as soon as possible, putting them under pressure to make a decision (quote 20). Healthcare professionals may also reinforce the sense of duty to inform relatives. In some cases, the healthcare provider convinced participants to take concrete actions in passing on the genetic information to relatives (quote 21).

Self-Preservation

Communicating the presence of a pathogenic variant to relatives inevitably implies a process of self-disclosure: individuals not only communicate that the variant is running in the family, but they also convey information that they do not necessarily would like to transmit, such as their clinical condition, and also their fears, wishes, emotional experiences, frailties, etc. It is extremely difficult, if not impossible, to control the flow of information when communicating genetic risk. It is thus possible that one tries to avoid possible discomfort and disadvantages arising from this communication process. Some do not feel comfortable talking about genetic risk, or even perceive this process as harmful for themselves. This was especially true for women affected by cancer, where being sick was considered a private issue and sharing was not anodyne (quotes 22 and 23). According to the logic of self-preservation, probands can decide to inform others about their possible genetic risk but only when they feel able and comfortable to do so. Some participants broached the topic of genetic risk with their relatives only after having finished cancer treatment and were more confident about their own illness (quote 24). This sense of self-preservation emerged particularly with distant relatives, when there is a geographical and emotional distance. Not knowing others' reactions or feeling that these reactions will be stressful and difficult to manage reinforce this logic (quote 25).

Protection of others

Receiving information about the possibility of carrying a pathogenic variant connected to cancer, is not a neutral event. Some probands may decide to protect relatives from possible negative effects of finding out about their potential cancer risk. This decision is based on the conviction that genetic risk information may create more problems than advantages to the relative, at least in particular moments. This is frequently due to the anticipation of the emotions and reactions of relatives, based on the interpretation of different factors, such as their personality traits, age, stage of life, or family dynamics. For instance, one may decide to postpone the transmission of genetic information because they consider their relative as particularly anxious or vulnerable (quotes 26 and 27) or because the relative goes through a difficult period of life. What is crucial, in this logic, is the interpretation of what might hurt the relatives and of how to protect them (quote 28). The logic of protection of others seems particularly present with close relatives, when possible reactions to genetic information are better known and the desire not to cause harm is especially prominent (quote 29).

Respect of autonomy

Most participants stated that they wanted to respect the views of their relatives about genetic risk and consequently their autonomy. The right of privacy and intimacy and the eventual diversity of opinions is recognized and respected, i.e., one acknowledges that there may be good reasons for choosing not to be open to receiving genetic information, based on the conviction that everybody is a unique individual, and as such must be acknowledged (quotes 30 and 31). The respect of relatives' autonomy may lead to lack of communication about the genetic risk when the relative showed no interest in this topic,

or doing it in a very superficial way and without going back to it later. This is true when one assumes that the relative has a high level of health literacy and thus, does not need further information (quote 32). The logic of respecting others' autonomy is supported by the value attributed to the free-will of the other and it is mitigated by the sense of efficacy of the genetic testing or by a personal or family history of illness. Awareness of the burdensome nature of cancer and at the same time of the opportunity offered by genetic testing for prevention, tend to make it difficult to accept relatives' choice not to afford the topic of genetic risk (quote 33).

Table 3: Probands' decision-making regarding family communication

Themes	**Quotes**	**Supporting quotes**
Responsibility	14	*«Communication is a due act, in the sense that (…) it is right and proper to talk about it. (…) I feel like I did the right thing. That I communicated. (…) in my opinion this (communication to relatives) is a right thing." (Sabina, 52 y.o, unaffected).*
	15	*"I did my part. I explained to them (my relatives) what had happened to me. What could possibly happen to them... Or not. I hope it never happens to them. But I thought it was important to communicate on the subject. (…) It has been a burden on me that. I mean it's not easy, to take the step, to do that, it's hyper personal anyway…" (Anna, 48 y.o, affected)*
	16	*"Genetic risk is part of my life and our life. For me what was very important was that my family knew about it. I have a sister who tested positive (...) she's much younger than me, she's 13 years younger, so she was tested a few years ago. So, for me it's very important that she knew that there was this risk". (Perla, 50 y.o., unaffected).*
	17	*"To the people you care about, you want to say it despite this difficulty... with a person that you know and that you care about, it is more difficult to do because emotionally you are more taken... (I felt bad) for my sisters because they have children, they have nieces and nephews, so the more people you care about, in my opinion, the more difficult it is to say it." (Sabina, 52 y.o, unaffected).*
	18	*"The responsibility in the family is so needed. That's not modern, nowadays people are no longer responsible for the cousins, grandparents, the widowed aunts, it's not like it used to be. This is something (genetic risk) that I have to actively tell people, and I think it's also something that should be emphasized by the authorities. This is a problem in our society." (Ms.P, 52 y.o., not affected)*

	19	*"I almost felt a little responsible for bringing this to the public. (…) Simply when I got into a conversation with someone, I actually communicated it openly because I think the more we know about it, the better. And yes, the way we were actually badly informed, that doesn't help anyone or anything." (Gisela, 46 y.o, unaffected)*
	20	*"This is what I said to myself, I have this thing that is not good, how can I make it useful? Communicating it as my mother did with me, it came to my mind afterwards, as an information to have. Then everyone has their own time, and maybe like me you do it in stages. But it's important to give the information so that everyone can decide what to do next. In a certain sense it's not pleasant, it's not easy, it's not nice, but it's useful information to know in order to make informed choices and not to say "if we had known about it before...." (Sonia, 34 y.o., unaffected).*
	21	*"I saw the psychologist to help me deal with the situation. And then she told me about it (communication), saying: "Now you have to communicate, you have to talk about it"…. And so, it was she who...convinced me to do it." (Anna, 48 y.o, affected).*
Self-preservation	22	*«It's not that I go to take all the relatives and "You know I had this..." , I hang out with a lot of people but nobody knows about my illness." (Bruna. 67 y.o., affected)*
	23	*"It was difficult to communicate that I was ill. (…) So only my sister knew and I only decided to tell my parents when I got home. Also because I spent 3-4 days crying all day long (…) It was clear that I was ill but I didn't... I didn't say it because I was mad as hell, honestly, I was mad at the world. I didn't want to say it out loud so it became reality even if it was reality. (…) The looks of pity as if I were going to die at any moment. I won't say... maybe because of those looks I never said it." (Fiona, 32 y.o., affected).*
	24	*"After my chemo (I wrote to my relatives). It was not possible before, I was so weak that it was not possible. But I did it maybe a year and a half after the cancer was discovered… When I started to get better…" (Anna, 48 y.o., affected)*
	25	*"So, it's difficult to talk to someone who you do not have any kind of contact with - because I know I had some distant relatives in Italy somewhere. And we didn't want to call them, since they are too far away. We made an effort to tell someone in the extended family who was closer to them, so that they could then transmit it. But really, with people who I barely know, I just do not feel comfortable to call them and confront them with something like that." (Gisela, 46 y.o., unaffected)*
Protection of others	26	*"I never talked to my sister, I don't even know how she reacted (to my situation). She is scared (about cancer).. She's really scared. She's always been afraid." (Clara, 48 y.o., affected)*
	27	*"I decided to inform only my cousins and not my uncles or aunts because of their age. I felt it would be "too much for them". For the same reason, I did not ask my parents to take the test. I didn't*

		want to put them in a difficult position, also in relation to possible feelings of guilt for having transmitted me the mutation." (Gaia, 42 y.o., affected).
	28	*"Yes, I just think my dad has closed the chapter on that (cancer), that's a story from the past that he's certainly carrying it with himself, but he didn't want it to be present anymore. It's probably wrong (of him), it's hard to describe, it's just a very extreme story from the past. And for me it is just, that for me the genetic defect is more acute/ present than for my father. But I think, as long as I'm healthy, it's okay for my dad the way it is. And with my brother I find it very difficult (to talk to him) because he has a lot of trouble to find grip under his feet". (Antonia, 33 y.o., not affected).*
	29	*"I think it makes a difference, because strangely enough I haven't talked about it so much with my sister, because I've always been afraid of scaring her, about me or whatever. With my partner or with my circle of friends I could talk about it again very well. They took it in a completely different way." (Rose, 50 y.o., unaffected).*
Respect of autonomy	30	*"Each case is, I think, different. And it has to do with your own experience. I think the only thing I would like to say is that I think each of us....must do what is right for the person who is." (Perla, 50 y.o., unaffected).*
	31	*"And in the end, everyone has to decide for themselves whether they want to know or not and what to do about it. So, I am ready to act or not. That's the thing, you have to think about it and make your mind up about it already before taking the test". (Daniela, 50 y.o., unaffected)*
	32	*"He is in the field (of medicine) and he is not married (…) I don't know if it is also related to the desire for children. If one knows that he can pass it on, one worries, if one has other plans, one does not. If one day he should have a daughter, he might change his mind. I had these stages, from something far away until it became too much, and I made decisions, it was indeed a path." (Sonia, 34 y.o., unaffected).*
	33	*"I struggle to understand and accept my cousins' decision to ignore what was said (about the genetic risk) and to do nothing about it." (Gaia, 42 y.o., affected)*

Proband-mediated communication: The complexity of the arbitrating process and the urgency of support

The principles of action that guide the decision of probands to communicate or not genetic information to relatives are multiple and dynamic. They can change depending on the relative, the situation, the time, the anticipated reaction to communication, etc.

Nonetheless, there are some possible interconnections between these logics and several individual and family characteristics, commonly known to influence family communication. These characteristics are the gender, the age and stage of life, and the socioeconomic and sociocultural context of the relative; probands' personal and family experiences with illness and genetic testing; personality traits of both the proband and the relative, their levels of health literacy and their geographical and affective distance; and family dynamics. In Table 4 we summarize the characteristics that, according to our data, most frequently influenced the different logics while Table 5 provides quotes to support findings about the complexity of the arbitrating process.

Table 4: Interconnection between logics and characteristics affecting family communication.

Logics	**Responsibility**	**Self-preservation**	**Protection of others**	**Respect of autonomy**
Individual and family factors	Emotional proximity	Geographical and emotional distance	Emotional proximity	Age/stage of life (of the relative)
	Personal/family experience of genetic testing/illness	Personal experience of illness	Age/stage of life (of the relative)	Health literacy (of the relative)
	Personality traits	Family dynamics	Family dynamics	Gender (of the relative)
	Gender (of the relative)	Personality traits	Personality traits (of the relative)	Emotional proximity/distance

The same characteristics may support different and contradictory logics, and this may disorient or even paralyse the proband. For instance, in emotional proximity, the sense of responsibility frequently conflicts with the logics of protection of others or respect of their autonomy. This is the case, some participants wanted their close relatives not to lose the opportunity for early cancer prevention but at the same time, they did not want to scare them or to force their choices. This ambiguity may be a difficult burden to afford (quotes 34 and 35). In cases of cancer affected probands, the sense of responsibility frequently

conflicts with the logic of self-preservation. Probands may feel the duty to inform relatives but at the same time also feel the burden that talking about themselves may entail. It is also possible that logics may support each other, thus strongly encouraging the proband to adopt specific communication behaviours (quote 36). In case of male relatives, our data show that the underestimation of the risk by both the proband and the relative, may both attenuate the sense of responsibility and reinforce the respect for the autonomy of others (quote 37). Logics frequently come into play simultaneously and continuously interact, leading to a high level of complexity and sometimes to a real "dilemma" that forces the proband to engage in a process of arbitration. Life situations keep changing and probands have to constantly navigate variable and complex dynamics alone with frequent difficulties and feelings of inadequacy (quotes 38 and 39). Finally, it is important to note that the difficulty of managing communication with each relative is compounded by the need to harmonise communication at the family level. The way one communicates with a close relative, for example, cannot but influence the decision to communicate to another close relative due to their existing relationships, which adds significant complexity to the management of communication.

Our data did not show a direct interconnection between the way healthcare providers addressed family communication and the logics adopted by probands. Only the logic of responsibility was reinforced with a forthright communication from healthcare providers. Nevertheless, a supportive and continuous communication or concrete interventions from healthcare providers helped (or could have helped) participants in dealing more easily with the difficulties arising from the arbitrating process (quotes 40 and 41).

Table 5: Arbitrating process

Themes	Quotes	Supporting quotes
Complexity of the arbitrating process	34	*"I'm not going to upset him (my son). I just.... it's so that I don't miss out on something and then...and then that's it."(Federica, 40 y.o., unaffected).*
	35	*"No, my daughter does not do any checks and does not want to do the test. (…) It's her choice, sometimes we tell her but nobody can force her, she does what she feels. (…) On the one hand as a mother maybe I would like that... but I live this well.... Maybe my daughter is a little less determined...". (Bruna, 67 y.o., affected)*
	36	*"I did not tell to my father because this will take on enormous proportions for him and me, it will add something to me". (Katarina, 33 y.o., unaffected)*
	37	*"I also realize with my brother that he really doesn't want to talk about it, because with men it's like this that the disease only comes to them when they're in their 50s and 60s. (…) But for him it's right at the moment that he doesn't know and he doesn't think about it." (Antonia, 33 y.o., not affected).*
	38	*"It was only two years ago that I had more to do with my cousins and that I realized that the two of them didn't know much and didn't have much information. And yes, I felt a bit guilty afterwards, because I thought I should have informed them a lot more." (Gisela, 46 y.o., unaffected)*
	39	*"So, I know that my cousin who...who started the whole thing (communication to relatives), she had a hard time with it. She had the impression that she...that she was dropping a bomb. She was not well for a while. Moreover, when she knew I was positive, she was afraid to see me. (…) She was afraid that I would be mad at her". (Federica, 40 y.o., unaffected)*
	40	*"I'm satisfied with what they told me... (The doctor) talked to me well…, she explained me well (…) I immediately sent the test results to my two sisters because of what Dr. G. told me to tell to my family and I also informed all the other family members". (Sabina, 52 y.o, unaffected)*
	41	*"When I was told the result, he told me that he had prepared a letter for the families, that I had to distribute. It explained what to do and that you had to approach. (…) I thought it was good, it was important, it gave importance, credit, I thought, to what was happening." (Christine, 47 y.o., unaffected)*

4. Discussion

The study focused on proband-mediated communication of genetic risk by exploring, from the probands' perspective, the communication chain, namely how genetic

information proceeds from healthcare providers to probands and from probands to relatives. We analysed two main steps of this chain: the communication between healthcare providers and probands, and probands' decisions about disseminating genetic information to relatives. Consistent to other studies [3, 17, 25, 27, 32], our results show that supporting proband-mediated communication of genetic information is complex, challenging for healthcare providers, and has limited application in clinical practice. Particularly, we identified three levels of complexity related to the way family communication is addressed by providers, with lack of standardization arising an issue of inequality in care delivering, the way information is received and interpreted by probands, with a difficulty due to the clinical situation and the participants' choices to give other priorities, and the way information is followed-up and supported by the healthcare system, with a fragmentation of the system and a lack of continuity and of coordination confirmed also by other studies [20, 25].

Regarding probands' decision to communicate or not genetic information to relatives, consistent with our data, individual and family characteristics influencing this decision-making process have been identified in the literature [6-14]. However, our study introduced a specific perspective of analysis, focusing on the rationale behind this decision-making process, and interpreted the role of these characteristics through the prism of the dynamic and often contradictory logics behind the communication decision. What emerges is a high level of complexity in the arbitrating process of family communication, which the proband has to continuously navigate through. Probands are usually alone in this process due to critical aspects identified in the first step of the communication chain.

Our study thus confirms the difficulties of proband-mediated communication, leading to poor communication around genetic information within the family, as highlighted in the

literature [17-18]. Above all, these difficulties may place a significant burden on probands, who risk experiencing disorientation or paralysis in the action to be taken.

The criticalities seen in the first and second steps of the communication chain could apparently suggest the opportunity of introducing provider-mediated forms of communication. More active and direct approaches adopted by healthcare providers, which were also embraced by some participants in our study, could potentially simplify and facilitate the process of communicating genetic information to relatives, enhance standardization, and promote equity by enabling access to reliable and accurate information for all relatives. However, our data, and data from an independent Swiss-based sample [33], suggest that probands do not want to be excluded from the process of communicating genetic information to their relatives. Survey data collected as part of the CASCADE study indicate that only one in three or fewer individuals with HBOC- or LS-associated pathogenic variants endorsed provider-mediated communication [24]. Other studies also show a preference for proband involvement in the family communication process [11, 18, 34]. If we consider the multiple logics of communication identified in this study, it is clear that these are understandable and legitimate rationales, as communication of genetic risk may have crucial consequences for the individual's life. Probands are therefore the only ones in the position to modulate the logics in a sustainable way.

These considerations suggest that provider-mediated communication should not be oriented in replacing the role of probands in the communication process, but rather in supporting them when navigating the different logics and the complexity of family communication, empowering them to reflexively construct their own decision from a range of available options. The concept of "relational autonomy" [35] may be of particular interest to highlight the nature of the support provided by healthcare providers

to probands in this particular context. Providers should help not only or not so much probands to make independent choices, but to make choices that make sense for them and that enable them to live their life in their own way, thus promoting their autonomy, where autonomy means self-governance [36]. Therefore, it may be necessary to help probands understand what is important for themselves, clarify the implications of the different choices, make priorities, and consider strategies to manage the competing logics. In a context in which patient centeredness is more and more valuable, thus, our data suggest the necessity to support probands rather than replacing them in their role as communicators.

Our study has some limitations. First, the analysis of the communication chain is based only on the perspective of probands and, for the sake of sample homogeneity, our participants were only women HBOC mutation carriers. It will be interesting in the future to get the perspective also of healthcare providers and of relatives to give a broader picture of the communication chain and of male probands to describe similarities and differences based on gender. Participants were on average 7 years post genetic testing. This may have affected memories of their own experiences but also allowed a more neutral and accomplished view. Moreover, the majority of participants had some college education and this may have somewhat conditioned the results. Finally, we also do not know if our findings may be extend to other hereditary cancer conditions, as found in other studies [37].

Despite these limitations, this study provides an in-depth insight in the communication process of genetic information within the family. This is due to the specific hypothesis that guided our research process, i.e., the existence of a communication chain with the proband at its center. Moreover, the large sample from three linguistic regions of

Switzerland and the involvement of several researchers in the data collection and analyses has enriched the interpretation process. These results may be extended to other countries with similar legal conditions (privacy laws) and social context (national healthcare system, family solidarity). Cultural differences, on the contrary, might influence the logics of communication and their interactions.

Some important concrete actions, both at the clinical and healthcare system level, are needed to improve the management of family communication of genetic cancer risk. The main leads suggested by the study include first of all improving healthcare providers – proband communication in quality, continuity, personalization and dedicated moments, through providers' education and standardization of procedures. The development of instruments for tailored communication (children, men, distant and close family, etc.) has to be accelerated to fill in the existing gap and facilitate the communication process [38].

Healthcare-providers have to help probands in understanding and governing their communication logics and in framing genetic communication as «useful news» more than as «bad news». It is essential to identify a "communication manager" that can help the proband to make sense of all the challenges, to find the right way to communicate with the different relatives, and to navigate the system over time. Promoting genetic literacy among the lay people and health-professionals is a fundamental prerequisite for fostering family communication and the implementation of cascade genetic testing.

Overall, our study suggests the need to adopt a patient-centered approach focused on the relationship and the dialogue, in a continuum of care. This empowers probands to manage family communication, by clarifying relevant issues, setting well-considered priorities, and developing strategies to reduce eventual contradictions among communication logics.

Author Contributions: Conceptualization: M.C.K., M.C.Z. and C.P.; methodology: M.C.Z. and C.P.; validation: C.P. and M.C.Z.; formal analysis: C.P.; M.A.; R.S.; A.K.G.; investigation: M.C.K.; M.C.Z. and C.P.; resources: N.B., P.O.C., R.G.G.; C.M. and M.R.; data curation: C.P.; writing—original draft preparation: C.P. and M.C.Z.; writing—review and editing: M.C.K., M.A.; R.S.; A.K.G.; N.B., M.C.Z., P.O.C., R.G.G., C.M. O.P., C.P. and M.R.; visualization: C.P.; supervision: M.C.K. and M.C.Z.; project administration: C.P., M.C.K., M.C.Z.; funding acquisition: M.C.K., N.B., M.C.Z.,P.O.C., R.G.G., C.M. and M.R.

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CHAPTER 4 – THIRD ARTICLE

Addressing disparities in genomic healthcare through the nursing workforce: The ACCESS framework

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Published in: Frontiers in genetics, 14, 1337366. https://doi.org/10.3389/fgene.2023.1337366

Abstract: Efforts are needed across disciplines to close disparities in genomic healthcare. Nurses are the most numerous trained healthcare professionals worldwide and can play a key role in addressing disparities across the continuum of care. ACCESS is an empirically-based theoretical framework to guide clinical practice in order to ameliorate disparities in genomic healthcare. The framework was developed by the International Nursing CASCADE Consortium based on evidence collected between 2005 and 2023 from individuals and families of various ethnic backgrounds, with diverse hereditary conditions, and in different healthcare systems, i.e., Israel, Korea, Switzerland, and several U.S. States. The components of the framework were validated against published scientific literature. ACCESS stands for Advocating, Coping, Communication, cascadE Screening, and Surveillance. Each component is demonstrated in concrete examples of clinical practice within the scope of the nursing profession related to genomic healthcare. Key outcomes include advocacy, active coping, intrafamilial communication, cascade screening, and lifelong surveillance. Advocacy entails timely identification of at-risk individuals, facilitating referrals to specialized services, and informed decision-making

for testing. Active coping enhances lifelong adaptation and management of disease risk. Effective intrafamilial communication of predisposition to hereditary disease supports cascade testing of unaffected at-risk relatives. Lifelong surveillance is essential for identifying recurrence, changes in health status, and disease trajectory for life-threatening and for life-altering conditions. ACCESS embeds genomics in already established professional nursing roles, and provides a standardized, systematic, situational, and unifying guide to nursing practice. When appropriately enacted it will contribute towards equitable access to genomic resources and services.

1. Introduction

While the 'genomic era' introduced a new understanding of health and illness, it is paralleled by significant disparities in accessing genomic services and benefiting from technological advances, raising concerns about growing disparities in healthcare (National Academies of Sciences Engineering and Medicine, 2018). Genomic disparities affect patients, at-risk individuals, and families and are particularly prominent for racial, ethnic, and gender minorities, and for children, medically underserved, and geographically dispersed groups. Barriers to genomic healthcare are multilevel and include health finance structures, societal and cultural norms, provider bias, and concerns of discrimination and misuse of genomic information. An important contributor to genomic disparities is the relative lack of genetic specialists (Baars M et al., 2005; Ormond et al. 2018).

Nurses are the most numerous and among the most trusted of health professionals with a global workforce of 27.9 million (World Health Organization, 2020) and provide services to various settings, from remote rural areas to highly specialized centers. Nurses can play

an important role in genomic healthcare after integrating genomic competences in nursing practice (Calzone et al., 2010). However, there is a need for a unifying model to guide nursing practice and surmount the growing genomic health disparities. To fill this gap, this Perspective presents ACCESS, an empirically-based theoretical framework that was developed by a panel of nurses from different countries and healthcare systems, studying different populations and genomic conditions.

2. Methods

ACCESS is based on a structured, rigorous process synthesizing empirical evidence with diverse populations in terms of gender, race and ethnicity, geography, and healthcare systems. It utilizes findings from more than sixty peer-reviewed publications of the investigators involved in the development of the framework over the past 18 years (2005 – 2023) on 'common', life-threatening conditions, e.g., hereditary breast and ovarian cancer (HBOC), and on rare, life-altering conditions, e.g., Kallmann syndrome (Supplementary Table 1). The development of ACCESS involved a sequential process with iterative refinement. The framework is based on the critical assumption that nursing employs a person- and family- centered approach to care. Investigators reflected on broad themes running through their studies and identified desired outcomes for reducing disparities and improving genomic healthcare. Findings were examined for similarities across populations, countries, and healthcare systems, and were organized according to the continuum of care. As a validation step, and a safeguard against potential bias, we juxtaposed our findings against studies focusing on genomic disparities that were identified by a systematic scoping review and a policy document analysis that examined the current state of genomics in nursing (Puddester et al., 2023; Thomas et al., 2023).

3. Results

ACCESS stands for Advocating, Coping, Communication, cascadE Screening, and Surveillance and provides a standardized, systematic, situational, and unifying guide to enable practicing nurses contribute towards decreasing disparities in genomic healthcare (Figure 1).

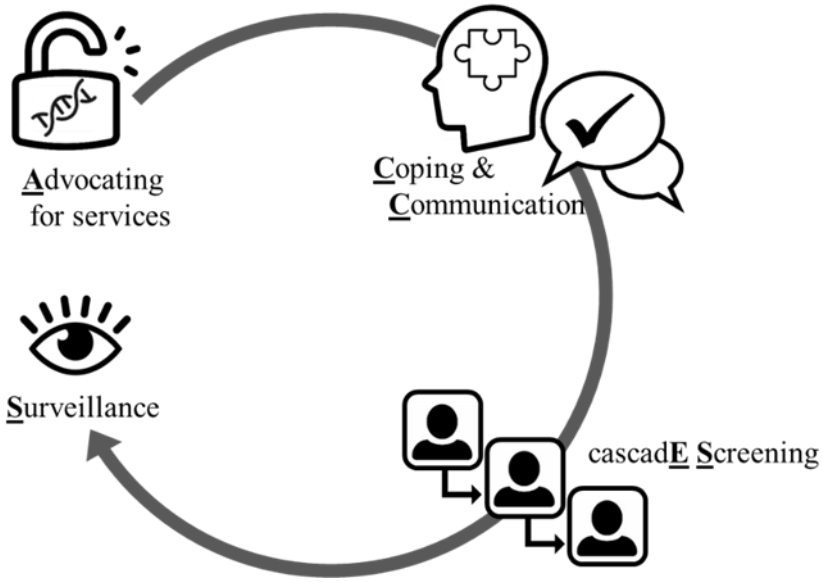

Figure 1. Schematic of the ACCESS framework. ACCESS proceeds from advocating for equitable access to care, to providing decisional support, to supporting active coping that precedes intra-familial communication of risk and cascade screening of relatives, and is followed by ongoing surveillance. Image credits: thenounproject.com

3.1 Advocating for access to services

Advocacy involves timely identification of at-risk individuals, facilitating access to reliable services, and promoting informed decision-making for testing as a prerequisite to decisions aligned with individual values and preferences. Advocating for access to services involves nurses, especially in primary care, taking a detailed medical history and

a three-generation family history to identify at-risk individuals and refer them to specialized services. Addressing out-of-pocket costs and insurance barriers remove roadblocks to genomic services, especially for those who are less likely to have genetic testing due to financial barriers. In countries with national or mandatory insurance coverage (e.g., Switzerland, Korea, Israel), variations in insurance coverage may create disparities in accessing testing or potentially lifesaving risk-reducing surgeries (Barnoy et al., 2023).

Health literacy barriers among underserved, low income, and less educated communities hinders integration of genomic information in health decision-making. Nurses can reach individuals with limited health literacy and numeracy and increase access to genomic healthcare by using professional competencies in patient education and outreach, along with culturally and linguistically appropriate education materials. Effective strategies include limiting the amount of information delivered in one counseling session, using lay language and understandable and actionable terms, assessing patient comprehension, employing "teach-back" strategies, and employing digital health technologies (Barr et al., 2018).

3.2 Active coping and family communication

A family-based approach to communicating risk for genomic diseases can leverage bonds within a family network and can reach individuals with irregular interactions with healthcare providers. However, it is not uncommon for individuals with disease-causing variants to conceal genomic information from first-degree relatives as well as from more distant or estranged relatives (Srinivasan et al., 2020). Family communication involves

navigating and managing complex and potentially conflicting individual and family needs. The process is most effective when individuals engage in active coping strategies (e.g., seek expert advice and support) as opposed to avoidant coping. Active coping precedes management of disease risk, while intra-familial communication is essential for subsequent cascade testing of relatives. This is especially important under the current regulatory milieu that precludes direct contact between healthcare providers and at-risk relatives without the consent of the tested individual (Henrikson et al., 2020). Individuals with disease-causing variants need support to initiate disclosure of testing results to relatives, and relatives' active coping response will lead to seeking reliable information and support from healthcare professionals, and to an informed decision regarding initiating or forging cascade testing. Nurses can support and empower individuals with disease-causing variants by adopting a patient-centered, tailored approach that fosters therapeutic relationships and open dialogue, considering the realm of the individual, family, and healthcare system.

3.3 Cascade genetic screening

Using genetic testing to identify asymptomatic individuals with disease-causing pathogenic/likely pathogenic (P/LP) variants is an important genomic public health intervention. Cascade screening refers to the process of extending genomic services to biological relatives of individuals harboring disease-causing P/LP variant(s) to inform risk management of relatives, while decreasing unnecessary healthcare expenditures for relatives that test negative. The U.S. Centers for Disease Control and Prevention, Office of Public Health Genomics classifies HBOC, Lynch syndrome (LS), and familial hypercholesterolemia (FH) as 'Tier-1' genetic conditions (Khoury and Dotson, 2021). Tier 1 conditions are identified through genetic testing, and are actionable, meaning that

implementing evidence-based guidelines can result in improved, measurable public health outcomes. Cascade screening involves asymptomatic individuals being educated about and considering testing for the P/LP variant in the family. Cascade screening enables asymptomatic individuals to access specialized services, receive accurate information, and initiate appropriate risk management.

Post-testing consultation usually includes a discussion about cascade screening yet, this aspect typically represents a relatively small portion of the patient encounter. Cascade screening may be more likely when healthcare providers have direct contact with relatives (Frey et al., 2022). However, approximately 70% of countries worldwide have in place legislation regarding privacy and protection of personal information, including genomic information (United Nations Conference on Trade and Development, 2021). Such legislation precludes healthcare providers from directly contacting at-risk relatives. Nurse-led, pre- and/or post-genetic testing consultations focused on enhancing active coping and family communication can also facilitate disclosure of genomic information and catalyze cascade genetic screening. A nurse-led cascade screening program for FH in Western Australia demonstrated cost-effectiveness and reduced incident of cardiovascular disease by 25-50% over 10 years (Ademi et al., 2014). A cascade genetic screening program for FH in the Netherlands, facilitated by specialized nurses who carried out home visits for consent, pre-testing counseling, blood sampling for genetic testing, and collection of personal and family data, yielded a participation rate of 90% within the first 5 years, and identified approximately 3% of the FH population in the Netherlands (Umans-Eckenhausen et al., 2001). Within 20 years, the program has identified and treated an estimated 42% of the total FH population in the Netherlands (Besseling et al., 2015).

3.4 Ongoing surveillance

After receiving a genomic diagnosis, individuals face multiple health- and life-altering decisions that relate to risk-reducing and screening behaviors, reproduction, interpersonal relationships, occupation, and career. Continuity of care and long-term patient-provider relationships are the basis for assessing psychosocial adaptation to living with a genetic diagnosis. For individuals harboring P/LP variants in genes underlying life-threatening conditions (e.g., HBOC), ongoing surveillance with biomarkers and serial imaging is critical for managing risk and detecting cancer (re)occurrence. For rare, non-life-threatening diseases (e.g., Kallmann syndrome), ongoing surveillance is essential for monitoring disease progression and for comprehensive chronic care. The therapeutic relationship that grows from continuity of care helps identify patients' challenges and creates opportunities to intervene with education and counseling or appropriate referrals (e.g., reproductive specialists), thus, supporting comprehensive, coordinated, inter-professional care.

3.5 Applying the ACCESS framework to nursing practice

ACCESS provides a standardized, systematic, situational, and unifying guide to nursing practice that enables practicing nurses to help close disparities in genomic healthcare. ACCESS embeds genomics in already established professional nursing roles, which when appropriately enacted, enable equitable access to genomic resources and services. Table 1 provides concrete examples of nursing practice relating to each of the components.

Table 1. Examples of applying the ACCESS framework to nursing practice

"A" *Advocacy*

- Enhance access: provide documentation to facilitate insurance coverage for genetic counselling and testing and to address other economic barriers e.g., coverage for subsequent treatment.
- Decisional support: use active listening techniques to reflect back values and preferences for genetic testing decisions.
- Genetic literacy and numeracy: elicit and evaluate understanding of and attitudes towards genomic healthcare with tailored and linguistically appropriate education materials.
- Identification: identify "red flags" indicating a genomic condition in personal or family health history. Apply the "too"/"two" rule i.e., recognizing that genomic conditions may produce extreme phenotypes ("too") or may cause disease in bilateral organs ("two"). Taking and documenting a 3-generation family history using standard nomenclature; identifying those who could benefit from genomic services.
- Referrals: Provide information and anticipatory guidance about genetic counselling and make referrals to such services.

"C" *Coping*

- Addressing unique needs of caregivers: evaluate levels of distress and cancer worry and develop supportive care resources.
- Individualized approach: tailor approach to respond to client's priority concerns and informational needs. Use "teach back" to assess and ensure comprehension.
- Narrative nudges: highlight aspects of patient narratives that shift the perspective towards "living with" a diagnosis rather than being "defined by" a diagnosis.
- Reframing, emotional support, and stress reducing interventions: use active listening and therapeutic communication to reframe fears and concerns as opportunities to improve health and support relatives, organize personal exchanges with other affected persons.
- Therapeutic listening: use a strengths-based approach to foster confidence in coping with challenging situations and health threats.
- Uncertainty management: assess for sources of and responses to uncertainty, offer psychosocial and educational support.

"C" Communication of risk

- Coaching: provide tailored coaching with modeling and opportunities to build self-efficacy.
- Cultural norms: assess cultural norms and patterns of familial communication.

- Supporting and empowering: Inquire about people who can initiate and maintain family communication about hereditary conditions. Support in informing biological relatives with letters and build communication strategies for direct information.
- Therapeutic education: provide information, supporting documents, anticipatory guidance on possible emotional reactions, and reinforcement to build self-efficacy for family discussions.

"ES" ***CascadE Screening***

- Nurse-led interventions: implement rigorous evidence-based interventions that enhance uptake of cascade genetic screening among relatives.
- Referral sources: provide information on costs of genetic counselling and testing, and insurance coverage to relatives.
- Resource materials: have materials and resources at hand regarding disease management, prophylaxis, expert care that can be passed on to relatives.

"S" ***Surveillance***

- Continuity and long-term care: assist navigating through lifelong challenges and life-altering decisions (i.e., risk-reducing surgery, fertility preservation). Provide long-term support in specialized clinics.
- Disease recurrence: follow established, evidence-based ongoing disease-specific surveillance activities (i.e., imaging, blood tests, biomarkers, etc.).
- Lifestyle, stress reduction, and health promoting behavioral counseling: enhance health promoting and risk-reducing behaviors. Recognize and address patient experience about risk-reducing surgery, support living with side effects.
- Therapeutic relationship: use trust in the therapeutic relationship to provide ongoing coping reinforcement, emotional support, and strengths-based encouragement tailored to the individual, familial, and cultural norms.
- Referrals for additional services: assess for changing needs and refer for additional services (e.g., psychologists, reproductive specialists, etc.), providing comprehensive, coordinated and inter-professional care.

4. Discussion

Evidence of growing genomic health disparities and implications for individuals, families, and communities present an urgent call for action. A number of barriers must be overcome to ameliorate genomic disparities and harness the full potential of genomics for improving prevention, screening, diagnosis, and treatment for individuals, families, and communities. Nursing has a long history of promoting self-care and delivering holistic person-, family-, and community-centered care, that is built on sound assessment, effective communication, and therapeutic education (Fee and Bu, 2010). To keep pace with the growing integration of genomics into healthcare delivery, nurses at all levels of practice must apply relevant competencies in practice. Nurses are the most numerous of trained healthcare professionals (World Health Organization, 2020), involved in interprofessional care delivered in ambulatory and community-based facilities, hospitals, and integrated healthcare systems. Nurses provide care in a variety of settings ranging from remote, rural, and medically underserved communities to urban and tertiary care settings. Most importantly, nurses and nursing practice worldwide are governed by the International Council of Nurses Code of Ethics, which is concerned with issues of privacy, confidentiality, advocacy, equity, and responsibility (International Council of Nurses, 2021). Specifically, article 1.3 clarifies that nurses ensure that the individual and family receive understandable, accurate, sufficient and timely information on which to base care and treatment. Articles 1.4 and 1.5 hold nurses accountable towards confidentiality of personal information and respect for privacy of individuals needing care. Finally, articles 1.6 and 1.7 1.6 hold nurses responsible for initiating and supporting actions that meet the health and social needs of all people, and advocate and promote equity and social justice in accessing healthcare and other social and economic services. As such, nurses worldwide are uniquely positioned to play a key role in bridging

disparities in genomic healthcare. Nursing actions include safeguarding individual rights to privacy and confidentiality, advocating for equitable access to genomic services, as well as monitoring and calling out health practices and policies that contribute to widening healthcare disparities or to discriminatory practices related to genomic information.

We posit that ACCESS is a novel, simple, yet, practical framework that can be part of a multi-level approach to increase integration of genomic care into nursing practice. Importantly, the framework is not disease-specific, but rather it is flexible and relevant for a broad range of conditions and healthcare systems. Although ACCESS was initiated by and builds on work of an international nursing consortium, it is applicable to other disciplines involved in genomic healthcare, ranging from direct care provision at the bedside to health policy. The universal shortage of genomic specialists requires that healthcare providers and policy makers seek for novel, sustainable solutions regarding widespread implementation of germline testing, and streamlining of educational efforts regarding its implications, especially for prevention and targeted therapeutics (Al-Sukhun et al., 2023; Brown et al., 2023; Moyo et al., 2023). Implementation of a systematic guide, like the ACCESS framework, and partnering with the nursing workforce who is a major stakeholder in promoting health equity, may facilitate initiatives such as the Rare Genomes Project (RGP) (Serrano et al., 2023) and the Genomic Answers for Kids (GA4K) (Kane et al., 2023) reduce barriers and inequalities for underrepresented patients with rare genomic disorders and for children, respectively. Disparities are a global concern of patients and families, communities, providers, health systems, and public health agencies and are among the most anticipated challenges for healthcare policy for the next decade (Dolan et al., 2023; Hull et al., 2023; Phillips et al., 2023). Ameliorating

healthcare disparities, including genomic disparities, requires a unifying, comprehensive, and multilevel approach that can be embraced by and enacted upon across disciplines (e.g., bioethics, genetic counseling, medical genetics, medicine, nursing, social work, etc.). The components of ACCESS can be integrated both into education and practice as a standardized and systematic guide that can help create and maintain a pipeline of trained healthcare professionals who are vigilant about genomic disparities and engage in actions that equitably improve health and wellbeing for patients, families, and communities.

One potential limitation is that the ACCESS framework is that it is based on empirical evidence from studies conducted by the members of our consortium and not on a systematic literature search. Although members of our consortium conducted their studies worldwide, in a variety of settings, and with diverse patient populations, we cannot preclude the possibility of bias. However, the components of the ACCESS framework are consistent with conclusions of a recently published scoping review that examined health disparities and the current state of genomics in nursing (Thomas et al., 2023) and with other primary studies and systematic reviews referenced in this Perspective. Nevertheless, we propose that future studies should focus on implementation of the framework and evaluation of its effectiveness with rigorous research designs.

Author Contributions

Conceptualization, A.A.D, M.C.K. and C.P.; methodology, A.A.D, M.C.K. and C.P.; validation, A.A.D, M.C.K. and C.P.; formal analysis, A.A.D, C.P.,C S.B., E.D., M.F., T.J., S.K., M.L U-B., M.K.U., and M.C.K.; investigation, A.A.D and M.C.K.; resources, A.A.D, C.P., S.B., E.D., M.F., T.J., S.K., M.L U-B., M.K.U., and M.C.K; data curation,

A.A.D, M.C.K. and C.P.; writing—original draft preparation, A.A.D, M.C.K. and C.P.; writing—review and editing, A.A.D, C.P., S.B., E.D., M.F., T.J., S.K., M.L U-B., M.K.U., and M.C.K.; supervision, A.A.D. and M.C.K.; project administration, A.A.D. and M.C.K. All authors have read and agreed to the published version of the manuscript.

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CHAPTER 5 - DISCUSSION

Three sequential studies have been conducted using quantitative and narrative data to examine the challenges of communication of genetic risk in HBOC and LS and to identify prospects for improving dissemination of genetic information and genomic healthcare at both public health and clinical practice levels. The hypothesis of the existence of a communication chain along which information about genetic risk proceeds from healthcare providers to probands and from probands to relatives, guided the whole research project.

A cross-study comparison has been conducted using family-based data collected in the US and in Switzerland over a timeframe of more than 10 years with 1933 individuals. The study examines genetic literacy in the context of HBOC, both at the individual and the family level, to understand how genetic information is passed on from healthcare providers to probands and from them to at-risk relatives. Results support the role of genetic counselling in improving genetic literacy [1-4] but also demonstrates persistent knowledge gaps also in individuals who have genetic consultations, suggesting that specific genetic information should be emphasized during consultations and highlighting the importance of continued follow-up with genetic services. This is important for individuals carrying a pathogenic variant to clarify and reinforce information and reassess cancer risk management plans [5-6]. The study also highlights gaps in the dissemination of genetic information among the lay public, among at-risk individuals and within family units, suggesting that at-risk relatives are poorly informed about inherited cancer risk and that family communication does not work very well. The study emphasises efforts to improve family communication of genetic information to be enhanced with interventions at the clinical (support to carriers of pathogenic variants), legal (healthcare providers

ability to provide tailored assistance with family communication) and public health (policies to improve access to genetic services) levels [5-8].

A descriptive cross-sectional study using narrative data collected from 48 HBOC women in three linguistic regions of Switzerland, provides an in-depth insight in proband-mediated communication of genetic information. The study examines from the probands' point of view, the way they manage the process of communicating genetic risk from the moment in which they receive the information about the pathogenic variant from the healthcare provider, to the moment in which they decide to transmit this information or not transmit it to relatives. Results confirm difficulties and a high level of complexity both in the communication between healthcare providers and probands about family communication and in the proband's decision-making process about disseminating genetic information to relatives [4, 9-10]. The study identifies dynamic and often contradictory logics which are linked with the proband's rationality and values and are behind the communication decision. Probands have continuously to navigate through the complexity of the arbitrating process of family communication and they are usually alone in this process. Importantly, the study also showed that probands do not want to be excluded from the process of communicating genetic information to their relatives by the introduction of provider-mediated communication strategies. Consequently, health-providers' role should not be oriented in replacing probands' role in the communication process, but rather in supporting them when navigating the complexity of family communication. These results call up the concept of "relational autonomy", according to which autonomy in decision-making can never be exercised in total independence since individuals are always socially influenced in their choices and their decisions [11-12].

Finally, a descriptive study presents the ACCESS framework, an empirically-based framework, to guide nursing practice for supporting disclosure of genetic information to relatives and, more in general, access to genetic services. The model was developed in a sequential, iterative process by an international group of nurse investigators from diverse healthcare systems and settings focusing on different genetic conditions. ACCESS includes unlocking access to care, providing decisional support, supporting active coping, family communication of risk and cascade screening of relatives, followed by ongoing surveillance. The framework is a simple and practical guide for nurses to address genomic health disparities and a natural extension of basic aspects of nursing, including advocacy and a person-centred approach emphasizing assessment, therapeutic relationship, active coping, and effective communication. Cascade genetic screening and ongoing surveillance represent timely opportunities for nursing to propel genomic healthcare and improve health and wellbeing outcomes for all.

The three studies conducted within this PhD work importantly emphasise the need for concrete efforts at the clinical and public health levels, to improve dissemination of genetic information through intrafamilial communication, and suggest specific actions that can be taken. Special emphasis is placed on nursing practice while also valuing an interprofessional approach. Promoting genetic literacy among the lay people and health-professionals, is a fundamental prerequisite for fostering family communication and the implementation of cascade genetic testing among at-risk relatives [1-2]. Addressing persistent knowledge gaps about genetics should be priority at the public health level and in clinical practice. Related to family communication of genetic risk, actions need to be taken to improve healthcare providers – proband communication in terms of quality, continuity, personalization and dedicated moments, through providers' education and

standardization of procedures. The development of instruments for tailored communication has to be accelerated to fill in the existing gap and facilitate the communication process [7]. According to our results, healthcare-providers have to help probands in understanding and governing their communication logics, in framing genetic communication as «useful news» more than as «bad news» and in dealing with the "relational autonomy" dimension embedded in communication of genetic risk [11-12]. Particularly, nurses could fill the role of "communication manager" that can help the proband to make sense of all the challenges, to find the right way to communicate with the different relatives, and to navigate the system over time. They are in a favourite position to promote a patient-centered approach focused on the relationship and the dialogue, in a continuum of care.

Finally, the ACCESS framework proposes a model to guide genomic nursing care and a large number of concrete and systematic nursing actions that can improve health and wellbeing for patients and families along the individuals' lifespan, providing quality, continuity and tailored genetic care. Evidence of growing genomic health disparities and negative family implications represent urgent calls to action for healthcare professionals and the discipline of nursing, seeking ways to incorporate genomics in professional roles, and advocate for equitable access to genomic resources and services for patients and families [13].

Limitations of the PhD thesis include a lack of the perspective of healthcare providers with respect to both the challenges of communication of genetic risk and prospects for clinical practice. Health professionals' point of view would have provided a broader picture of the elements at play and possible strategies for improvement. Moreover, the

work only presents a number of critical elements and possible solutions but does not go into and explore their applicability and effectiveness.

Despite these limitations, this work provides an in-depth insight in the communication process of genetic information within the family, highlighting critical elements in the area of communication of genetic risk to family members and identifying strategies and interventions that could be implemented to overcome them. Future studies should examine the effects of different interventions (e.g. digital health platform) on dissemination of genetic information and on increasing genetic literacy. Further studies should also examine implementation in practice and effects of the ACCESS framework. This is a novel framework that easily can be integrated into clinical practice as a rational and active means for ameliorating genomic health disparities.

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ADDITIONAL MANUSCRIPTS

Manuscript IV

Nikolaidis C, Ming C, Pedrazzani C, van der Horst T, Kaiser-Grolimund A, Ademi Z, Bührer-Landolt R, Bürki N, Caiata-Zufferey M, Champion V, Chappuis P, O, Kohler C, Erlanger T, E, Graffeo R, Hampel H, Heinimann K, Heinzelmann-Schwarz V, Kurzeder C, Monnerat C, Northouse L, L, Pagani O, Probst-Hensch N, Rabaglio M, Schoenau E, Sijbrands E, J, G, Taborelli M, Urech C, Viassolo V, Wieser S, Katapodi M, C: Challenges and Opportunities for Cancer Predisposition Cascade Screening for Hereditary Breast and Ovarian Cancer and Lynch Syndrome in Switzerland: Findings from an International Workshop. Public Health Genomics 2018;21:121-132. doi: 10.1159/000496495

Manuscript V

Kim S, Aceti M, Baroutsou V, Bürki N, Caiata-Zufferey M, Cattaneo M, Chappuis PO, Ciorba FM, Graffeo-Galbiati R, Heinzelmann-Schwarz V, Jeong J, Jung MM, Kim SW, Kim J, Lim MC, Ming C, Monnerat C, Park HS, Park SH, Pedrazzani C, Rabaglio M, Ryu JM, Saccilotto R, Wieser S, Zürrer-Härdi U, Katapodi MC. 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. JMIR Res Protoc. 2021;10(6):e26264. doi: 10.2196/26264. PMID: 34114954; PMCID: PMC8235289.

CONTRIBUTION

The thesis was conceptualized by Prof. Dr. Maria C. Katapodi and myself. My specific contributions to the studies that constitute the thesis are specified in each single article. I contributed to the design of the three reported studies and to data collection and analyses, I conducted results interpretation, writing and critical revision of the manuscripts. The third study has been conducted in close collaboration with Dr. Andrew A. Dwyer, who wrote the article with equal contribution, as well as Prof. Maria C. Katapodi. The development of the ACCESS model took place also with the contribution of several other members of the International Nursing CASCADE Consortium (prof. Sivia Barnoy, Dr. Meghan L. Blazey-Underhill, Dr. Efrat Dagan, Dr. Tarsha Jones, prof. Sue Kim). For manuscripts IV and V I contributed to writing and critical revision of the manuscripts.

ACKNOWLEDGEMENTS

I would like to thank all those who made this thesis possible. Firstly, I would like to express my deep gratitude to prof. Dr. Maria C. Katapodi, my first advisor. During these four years of doctoral training, she always guided and supported me with great competence and professionality. Her persistent help, confident guidance and great comprehension have been of great value to me.

I would also like to express my appreciation to the other PhD committee members. Dr. Nicole Bürki, my second supervisor, always sustained this project with great interest providing me with valid and helpful suggestions and inputs. I am also extremely grateful to prof. Dr. Maria Caiata-Zufferey who gave me persistent and great support with her constant presence during these four years. Her contributions in developing the narrative part of this project were particularly of great value to me.

I would also like to gratefully thank all my colleagues at the University of Basel, Andrea Kaiser-Grolimund, Angela Duarte, Chang Ming, Islam Salikhanov, Mahesh Sarki, Marion Rudaz, Monica Aceti, Reka Schweighoffer, Sunyoung Park, Vicky Baroutsou and Yu-Yin Alleman. I thank all the members of the Cascade Consortium, particularly the colleagues at the Servizio di Genetica Medica EOC, Monica Taborelli, Olivia Pagani and Rossella Graffeo, and the colleagues with whom I collaborated internationally for this work, Andrew A. Dwyer, Efrat Dagan, Sivia Barnoy, Meghan L. Blazey-Underhill, Tarsha Jones, Sue Kim.

My sincere thanks to the University of Basel for the inspiring environment it offered me and the University of Applied Science and Arts of Southern Switzerland for sustaining and encouraging me over these years. I also thank the SSPH+ PhD program for supporting my studies and offering high-quality courses together with PPHS.

Finally, I would enormously like to thank my whole family, especially my children, for the time I had to dedicate to my studies.