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PhD Course Coordinator: Prof. Claudio Ferri



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Constructivist approach in genetic counseling: medical, psychosocial and familiar implications into patient-centered approach

Eleonora Cilli

Tutor: Prof.ssa Dina Di Giacomo

Co-Tutor: Prof. Francesco Brancati

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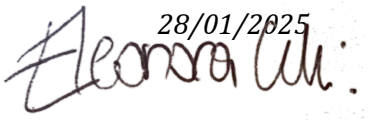
Constructivist approach in genetic counseling: medical, psychosocial and familiar implications into patient-centered approach

Eleonora Cilli

Declaration

I hereby declare that, the contents and organization of this dissertation constitute my own original work and does not compromise in any way the rights of third parties, including those relating to the security of personal data.

28/01/2025



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Abstract

Aim of the present Doctoral thesis entitled 'Constructivist approach in genetic counseling: medical, psychosocial and familiar implications into patient-centered approach' was to investigate the scientific landscape of the role of biopsychosocial approaches in the context of genetic counseling.
The thesis is articulated in 2 parts: theoretical and scientific sections.
The Theoretical Section exploited the research perspective in the genetic counseling pointing out the focus on how to put the discoveries from genetic research to use in healthcare. The aim was to describe the produced potential new ways of predicting risk, of diagnosis, and disease prevention and treatment. Particularly, the genetic counseling process was analyzed in its several aspects:

- providing information about test options
- assessing psychological well-being
- helping patients and families communicate about genetic risk
- facilitating adaptation to grief and loss, interpreting results
- assisting with decision-making and referrals

The application of the biopsychosocial model seems essential in the context of genetic counseling: health as the result of multiple interacting biological, psychological, and social factors, and recognizes that behavior can be explained in terms of multiple contexts or levels of organization that mutually influence each other.
Considering the genetic counseling might ask for individual adaptive dynamics, psychological distress seemed to be a matter of debate that was the starting point of experimental investigation of the thesis.
The Scientific Section was structured on three studies based on the primary endpoint to contribute to model the psychological and behavioral implications to boost the efficiency of genetic counseling by multidisciplinary approach. Aim of Scientific Section was to highlight the relevance of clinical setting based on a patient-centered approach, tailoring clinical practice on the integration of physical, mental, and social factors to patients' and relatives' wellbeing, to enhance healthcare and patient lives. Scope was to investigate the genetic counseling impact in the disclosure toward to health management and Quality of Life of patients.
During the PhD program n.3 studies have been conducted as follow:
Study 1. BRCA genetic result disclosure for women with breast cancer: influence of +/- predisposition genetic mutation (observational study design)
Study 2. Patient perspective in perceived comparative genetic mutation risk: an exploratory review (review study design)
Study 3. Perceived cancer risk and genetic counselling: a biopsychological perspective to boost lifestyle medicine (observational study design)
General objective of observational studies (n.1 and n.3 of the above list) was to examine a) the psychological impact of disclosure of BRCA genetic result, b) the emotional health of patients and, c) the role of cancer worry in the psychological dimensions of patients undergoing genetic testing.

THEORETICAL SECTION

CHAPTER 1. GENETIC CLINICAL PRACTICE AND EPIDEMIOLOGICAL DATA

1.1 Public Health Genomics

In the last few years there has been an increasing focus on how to put the very exciting discoveries from genetic research to use in healthcare. Research has produced potential new ways of predicting risk, of diagnosis, and disease prevention and treatment. The complex relationship between genes and environment, and their role in the development of chronic conditions such as cardiovascular disease, cancer and diabetes is slowly being understood. These conditions have a high impact on overall population health. Public health practice includes activities such as needs assessment, health promotion, disease prevention programs, and evaluation and routine collection of health data for monitoring and auditing. The integrations of genetics into this have become the area of concern of public health genomics. An international definition of public health genomics[1] is: "*The responsible and effective translation of genome-based knowledge for the benefit of population health*". Aim of the public health genomics is to combine the scientific knowledge from basic research with knowledge from public health and social sciences, ethics, and humanities to develop programs and policies to improve health. The health benefits of the Human Genome Project have been widely anticipated. Experts predict new era of individualized disease prevention based on testing for genetic susceptibilities[2], and safer, more effective use of drugs based on pharmacogenomic testing[3]. Genomic research is also predicted to improve disease classification and generate innovation therapies, targeted more precisely to the molecular mechanism

of disease[4]. Early breakthroughs support this promise. Genetic testing can identify women at high risk for breast and ovarian cancer who may benefits from interventions such as breast screening[5], also pharmacogenomic testing offers a potential means to increase the safety of the drugs. Despite these impressive early advances, serious reservations have been voiced about the occurrence and timing of a genomics revolution in medicine[6]. The relationship between DNA sequence and phenotype is far from simple, even for highly penetrant single gene condition. Also, an overemphasis on genetic contributors to disease may result in neglect of other factors, such as environmental exposures, social structure and lifestyle[6]. Even without genotype-specific interventions, some experts propose that knowledge of genetic risk can inform individuals about lifestyle changes most beneficial for them, letting them know what health risk to worry about[7]. The limited available data offer mixed results. Genetic tests identifying an increased risk for lung cancer do not appear to result in increased smoking cessation[8]. Conversely, genetic risk information may motivate participation in preventive screening: several studies have shown that the likelihood of participating in cancer screening is positively associated with having a family history of the disease[9]. False reassurance is a risk of this approach. When genetic risk is emphasized, a test showing the absence of genetic risk for a condition such as a cardiovascular disease, diabetes or cancer could send the message that there is no need to worry about that particular risk, yet the negative predictive value of such tests is likely to be very low[10].

The Public Health Genomics Enterprise. With these challenges in mind, an international expert workshop was convened in April 2005, in Bellagio, Italy. The workshop was attended by a multidisciplinary group of 18 experts from Canada, France, Germany, the United Kingdom and the United States[11]. Participants at the meeting developed a consensus on the structure needed for effective translation of genome-based science and technology into improved population health. Figure 1 shows this concept in visual form[10]: the functions and activities shown in *blue* represent the scope of the enterprise of public health genomics, which can be simply defined as the effective and responsible translation of genome-based knowledge and technologies for the benefit of population health. Initiatives in several countries have already begun this effort. *Yellow* represents the generation of knowledge through research; genome-based science and technology (highlighted in *red*) play a fundamental role. Any new development in modern genomics, or in molecular or cell biology, can legitimately be considered as a potential contributor to innovate approaches to achieving population health. *Green* represents all activities, people, institutions, and

views that make up society in its widest sense, comprising key stakeholders in the success of the translational process.

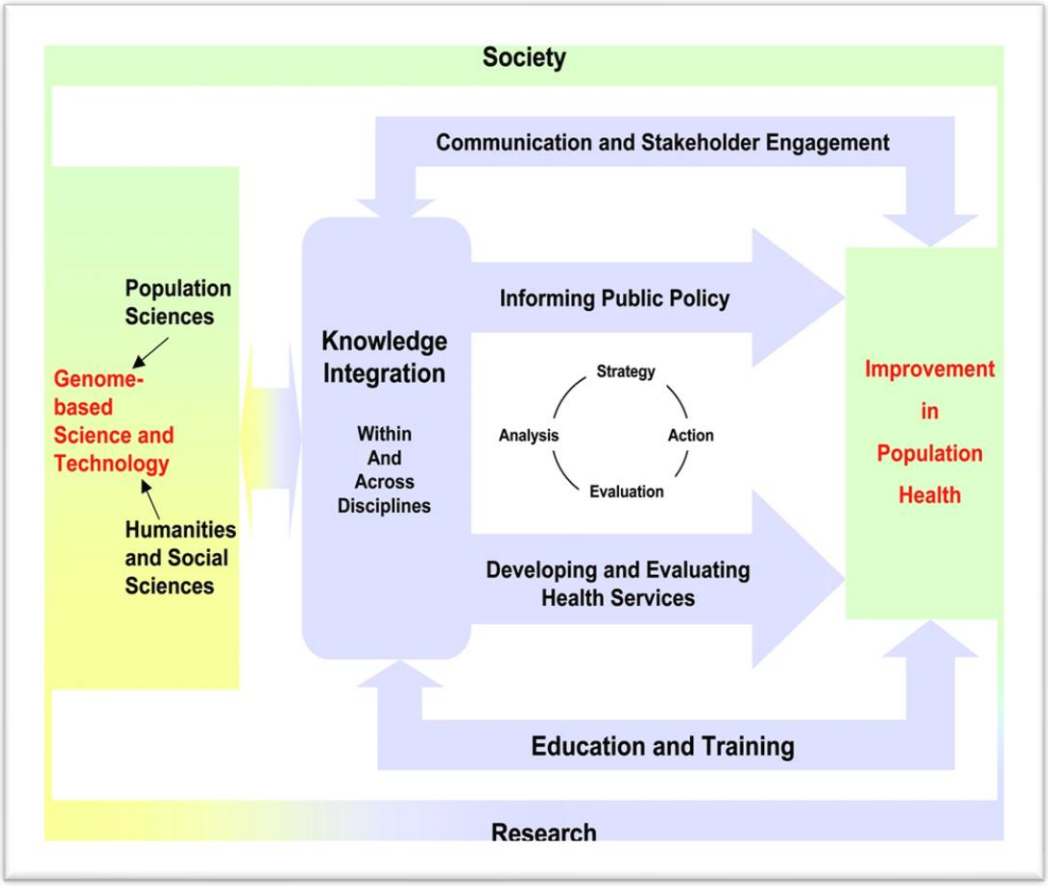


Figure 1 *– Components of the public health genomics enterprise.*

The central role of knowledge integration. Knowledge integration, both within and across disciplines, is the driving force of the public health genomics enterprise. It is defined as the process of selecting, storing, collating, analyzing, integrating, and disseminating information both within and across disciplines for the benefit of population health. It includes methodological development and is the means by which information is transformed into useful knowledge[10]. This integrated knowledge contributes to service development, education and training, informing public policy, communication and stakeholder engagement. Examples of where public health genomics could contribute include screening programs for genetic diseases. Much of the research in genetics to date has been in discovering disease-causing genes or genetic variation that is associated with disease.

This has led to more tests for diagnosis and prediction being made available. There is also of course the often-raised promise of personalized medicine and the developing market in tests for susceptibility, some of which are sold directly to the consumer[12].

Integration of knowledge across disciplines. Creating productive collaboration in a single discipline is only the first step in knowledge integration. Knowledge and insight from many disciplines will be needed to fully evaluate the potential for genome-based research to improve population health (Figure 1). Both medical and social outcomes of test use must be considered, and appropriate procedures must be implemented for practice guideline development, decision-making by healthcare payers, and population-based consultation and education. In addition, current ethical and regulatory frameworks need to be assessed for their appropriateness to new conceptual and technologic approaches based on genomic research.

1.1.1 Genomic screening

Early identification of genetic contributions to disease risk can lead to reduced morbidity and mortality with the implementation of screening and management recommendations[3]. Population genomic screening programs are one way the public can obtain information about their health through genetic information[13]. Typically, variants reported via population screening consist of those in actionable genes associated with autosomal dominant conditions[14,15]. Actionable genes are those with defined screening and/or medical management guidelines given a positive result or identified pathogenic variant. Multiple studies have shown unselected population screening can reveal genetic predispositions for disease in individuals that do not meet testing guidelines based on family and/or personal history[16,17]. Thus, population genomic screening can be utilized to identify genetic risk that may not have been identified via routine medical care[15,18]. Furthermore, studies have shown that individuals are highly motivated to pursue population genomic screening to gain information that would aid in understanding and maintaining personal health. This screening can also inform health concerns for other family members who share the same genetic information. Alternatively, many individuals are interested in population screening as a means of contributing to research that works toward promoting a healthier population. Given the myriad motivations for

population genomic screening understanding whether this screening provides a significant benefit is imperative[19]. Several population screening programs have reported implementation coordination and potential health impact. However, a paucity of data exists regarding medical outcomes and cost. It is unclear if individuals take actions based on screening results, particularly for those with medically actionable results[13]. When evaluating benefits and limitations of population genomic screening, current and log-term clinical outcomes as well as personal impacts on the individual and their close relatives should be considered. Data have shown no statistically significant long-term differences in level of depression, health-anxiety, distress, uncertainty, and overall quality of life before and after undergoing population screening for cancer predisposition[18]. Even so, additional considerations need to be addressed, including emotional impact, overinterpretation or under interpretation of disease risk by both patients and providers, ethical and social implications of sharing results, potential for added care costs given a positive result, challenges of inclusivity and testing of diverse population[20–22].

1.1.2 Motivation to learn genomic information

Historically, genetic testing has been offered to patients primarily when clear evidence of clinical utility exists. Clinical utility can be defined as instances in which genetic test results could inform medical recommendations or provide a means to achieve improved health outcomes[23]. Thus, clinical utility exists when there is the promise that the test results could influence one's health, but whether any individual's health is affected depends on the test result itself and the patient's response. In contrast to genetic testing, much of the genome sequence cannot yet be interpreted[24]. Nevertheless, genome sequencing is becoming more widely available in clinical and research contexts, and studies have shown that patients and research participants desire to learn their personal genomic information even when clinical utility is low or absent[25]. Although not currently widely available, population testing of low-risk individuals without a family history is being piloted and will increase in frequency and accessibility. Individuals enrolling in this kind of testing have a low likelihood of actionable results yet may still pursue testing[26]. Pursuing genome sequencing information resembles efforts to pursue any information about oneself, and thus, we consider how research on basic human motivations can be applied to understanding decision

making in the novel context of genome sequencing. Taber et al.[27] suggest that the concept of decision utility provides a useful framework to understand patients' and research participants' decision to undergo genome sequencing and to learn their results. Using a decision utility, Taber et al.[27] identified 10 common motivations (Table 1) for seeking personal information that may underlie decision to undergo genome sequencing and learn one's results.

Table 1 - Motivations to undergo genome sequencing

INDEX	DESCRIPTION
COGNITIVE MOTIVATIONS	**Driven by a desire to learn new information or to make sense of the world and oneself**
Availability motivation	People desire available and "knowable" information
Motivation to reduce uncertainty	People desire to minimize uncertainty and to obtain accuracy and predictability
Motivation to obtain information that increases perceived empowerment and self-efficacy	People desire to feel empowered and to experience self-efficacy, which can be increased by personally relevant information irrespective of its clinical utility
Self-knowledge motivation	People desire to learn about themselves
AFFECTIVE MOTIVATIONS	**Driven by a desire to experience positive affect and avoid negative affect**
Maxime current and future positive affect	People desire to increase or enhance positive emotion, such as happiness, hope, or relief, now and in the future
Minimize current and future negative affect	People desire to decrease or prevent negative emotion, such as sadness, disappointment, fear, worry, or regret, now and in the future
SOCIAL MOTIVATIONS	**Driven by a desire to connect with or relate to others**
Social connection	People desire to affiliate and connect with other people
Social norms	People tend to adhere to social norms indicating what others are doing or expect others to do
Social comparison	People tend to compare themselves to other people, allowing them to better understand the self or to feel better about the self
Prosocial motivation	People desire to engage in actions that improve the well-being of others

Understanding decision utility in the context of genome sequencing is becoming increasingly important considering rapid advances in genomics and functional genetics to disease risk and development of targeted treatments[28]. People may opt to learn genomic information when the test has clinical utility; that is, when it could provide information with implications for improving health outcomes that, in part, depend on development of evidence-based guidelines to inform health behaviors.

The ten salient motivations are based on behavioral science, including research on basic human motivations and the pursuit of health risk information. Importantly, the motivations should be relevant regardless of

the degree of clinical utility any test offers, if any. Motivations to undergo sequencing or testing are often clear when some degree of clinical utility is present: there is the possibility that one's test result could be used to improve one's health. The authors categorize the motivations as primarily cognitive, affective, or social, but they can overlap and operate simultaneously and sometimes synergistically. Each motivation is known to affect people's perceptions of the value of decision options (decision utility). Thus, these motivations underlie and feed into decision utility. These motivations may be independent of clinical utility but nonetheless generate value in the form of personal utility that can greatly influence choices[29]. Taber et al.[27] argue that the 10 motivations for the current framework help explain these perceptions of personal utility. Stemming from empirical research indicating that people are motivated to learn genomic information when the test has low or no clinical utility, frameworks of utilities of genomic information have been developed that typically highlight constructs such as perceived utilities[30,31]. The most notable example of perceived utility is personal utility – patient-endorsed benefits that are also referred to as non-clinical outcomes[32]. Personal utility has been defined as the individual's perceived value of genomic information that is distinct from its clinical value. This construct was delineated by Kohler et al.[33] in their systematic review. Examples of personal utility include concepts that are known antecedents and outcomes of the decision-making process in healthcare settings, such as informing future decisions about having children, mentally preparing for the future, and feeling more in control of one's life. The notion of personal utility describes why, when clinical utility and actionable results are unlikely, research participants and patients nonetheless seek out their genomic information[24,25,29]. Understanding motivations to undergo genome sequencing will also have a practical impact in that it will help researchers to recruit individuals to participate in genome sequencing research: researchers can highlight potential utilities that people may experience from learning the information. In addition, understanding the motivations will allow clinicians to walk people through the decision-making process, helping them make better decision about whether to learn the information. Helping the patient understand this influence and any potential clinical relevance of genome sequencing, while treating their utility perceptions respectfully, may help the patient to balance the perceived personal utility of the motivation with the potential clinical utility of the test[27].

1.2 Epidemiological data

Epidemiological research on rare disease (RD) is difficult due to their rarity, scattered distribution, and the influence of the socioeconomic status of different regions on the diagnosis ability of RD[34]. Accurate diagnosis and timely the undiagnosed, misdiagnosed, and unknown people affected by RD remains a top public health priority. Although approximately 3 out of 4 RDs have a genetic basis[35], the low prevalence of individual disease, their varying manifesting due to genetic interactions or interplay with the environment, and the lack of expertise makes diagnosis difficult. Traditional methods of epidemiological survey require considerable manpower and time, and are costly and unsuitable for RD. The World Health Organization (WHO) defines RDs as medical condition with specific pattern of clinical signs, symptoms, and findings that affects fewer than or equal to 1 in 2000 persons living in any World Health Organization - defined region (Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, Western Pacific) (Figure 2) of the world.

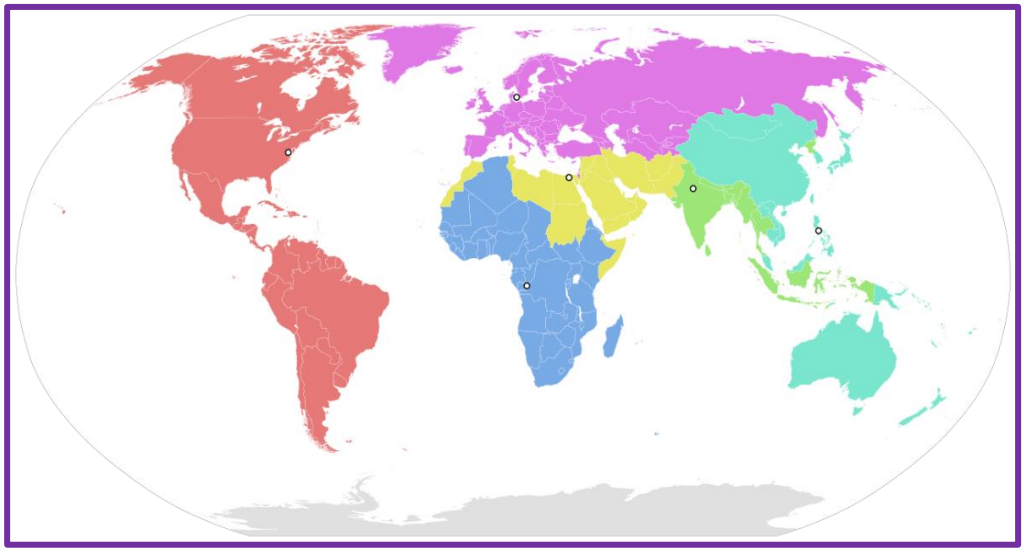


Figure 2 - Region of WHO

Also add that RDs include, but not limited to, rare genetic disease, rare cancers, rare infectious, rare poisonings, rare immune-related diseases, rare idiopathic disease, and rare undetermined conditions. While the frequency of most RDs ca be described by prevalence, some RDs, such as rare cancers and rare infectious diseases, can be more precisely describes by incidence[36]. The 6000-8000[37] RDs collectively affect an estimated 3-8% of the global population or over 350 million persons globally[35] (Figure 3).

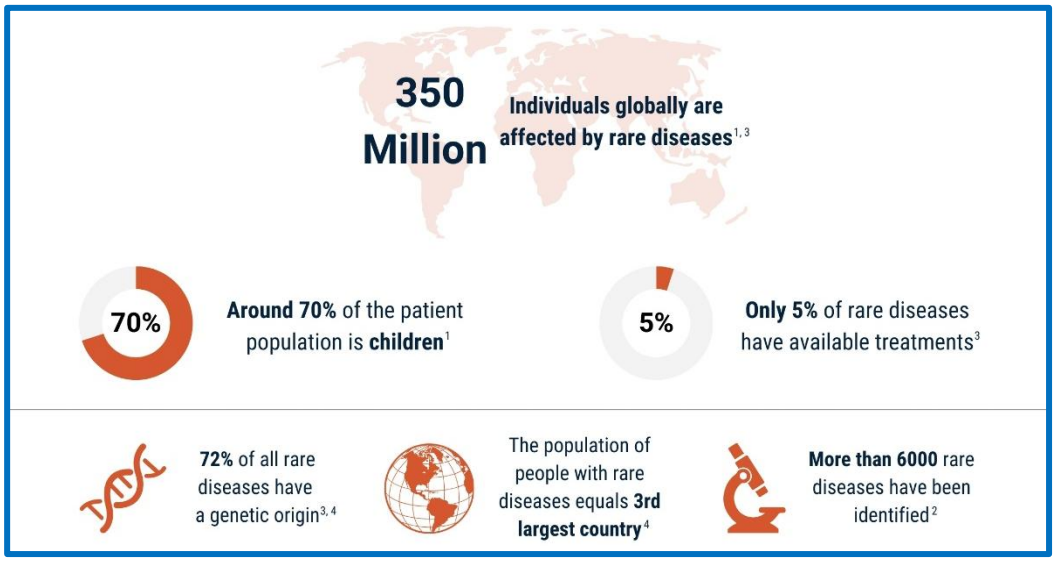


Figure 3 - RDs epidemiology

RDs are numerous, heterogeneous in nature, and geographically disparate. Few are preventable or curable, most are chronic and many result in early death[38]. While there is no universal definition of RDs[39], the concept of RDs in the current political and legislative framework is closely linked to a definition according to point prevalence, and existing definitions are explicitly or implicitly based on a prevalence threshold. The Council of Minister of the European Union (EU) has suggested that between 6% and 8% of the European population could be affected by a RD in the course of their lives[40]. In the EU, the definition of RDs was established in EU Regulation on orphan medicinal products (1999) as conditions whose prevalence is not more than 50 per 100.000[41]. The American Orphan Drug Act (1983) defined RDs as disorders affecting <200.000 persons in the country, translating to a prevalence of 86 per 100.000 at that time[42]. Other national definitions translate to prevalence ranging from 5 to 76 per 100.000[43–47]. The exact

number of RDs also lacks a consensual standardization, with frequently cited numbers varying from 5000 to 8000 RD[48]. The website Global Genes[49] maintains a list of RDs which includes 6537 disorders (2018), but a close review of this list reveals several duplicate entries. Point prevalence is the most appropriate indicator for RDs ad it provides a measurement of the population burden of disease and can thus inform focused service delivery targeted at the specific needs of RD patients, pharmacoeconomic evaluation of orphan drugs, appropriate health and social service commissioning, and facilitation of clinical trials. Estimating the global point prevalence of RDs is challenging foremost for the diversity of the data, which are derived from a variety of disparate information sources, including published case reports or systematic reviews, patients registries, expert opinion and other anecdotal evidence[50] (Figure 4).

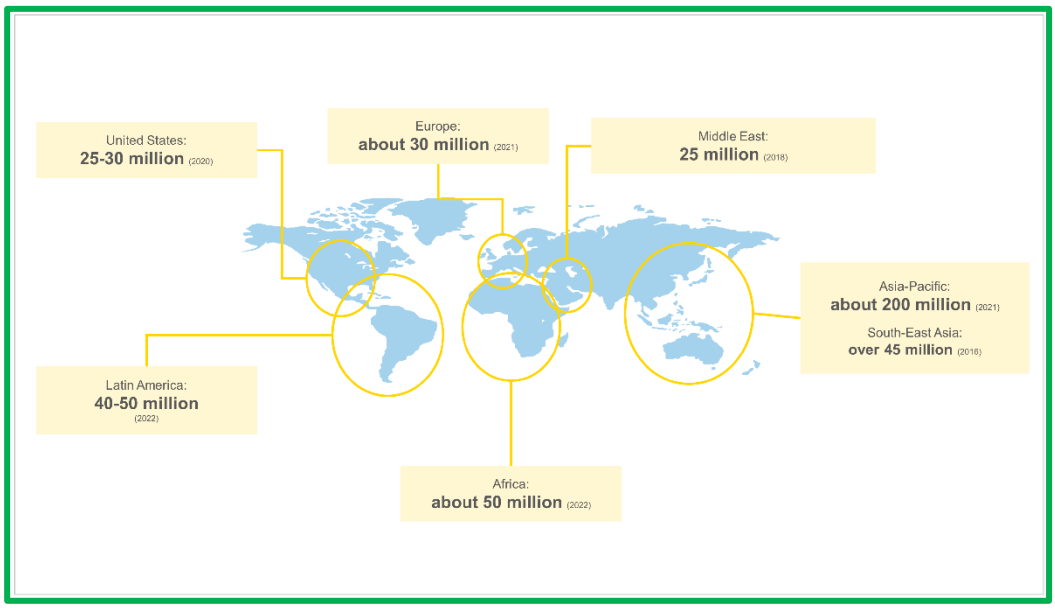


Figure 4 - Number of people affected by RDs across regions. The estimated values depend on data availability and local diagnostic and tracking capacity.

The nature of RDs raises further challenges because of the small number of cases, compounded by significant clinical heterogeneity. Some RDs vary in frequency across geographic area, due to population genetic diversity, environmental or society pressures, or survival issues in different regions[51,52]. Also, bibliometric data on RDs are scarce but some publications showed that the majority of publications for RDs are case reports, rarely reporting more than o case at once, and spread on numerous years and language[53]. Some characteristics of the disease themselves can also influence

the amount of publications[54]. The severity of the disease, often high in RD, can mitigate the prevalence effect[55]. Furthermore, previous bibliographic articles on RDs have reported that RDs publications stem rarely from international collaborations and are likely to be published in low impact journals. Therefore, the amount of literature on a RDs also depends on peer review process and editorial policies. In addition, for half of person with RDs, a definite diagnosis remains undiscovered. Thus, for this substantial number of patients and their families, physical, psychological, and social consequences represent a relevant burden to be sustained every day.[56] In 2008, the National Institute of Health (NIH) of USA launched the Undiagnosed Disease Program (UDP) to address a unmet need in the US healthcare system: the diagnosis of unsolved RDs cases[57]. In 2014, inspired by the USA UDP, the Undiagnosed Disease Network International (UDNI, http://www.udninternational.org/) was founded by five participants countries including Italy[58]. The National Centre for Rare Disease (NCRDs) – Italian National Institute of Health (ISS) (NCRDs-ISS) was the Italian representative in this network.

1.3 RDs patient registries

The RDs are scarcely represented in international classifications and therefore invisible in health information systems, contributing to their invisibility in society. RDs registries are initiated by many organizations, such as patients and their families, patients' advocacy groups, clinicians, national health systems, and biopharmaceutical product manufacturer, for many reasons. In RDs where patients are few, research agendas do not exist, standard case guidelines are absent, and patients' communities have not yet formed, patients' registries are an intuitive first step for stakeholders trying to understand the number of people affected their geographical distribution, and the basic demographic and clinical characteristics of disease. The scope of RDs patient registries may evolve over time, maturing from a community-building effort or a means for understanding of patient and disease characteristics, to a supportive mechanism for research funding[59]. It should be noted that RDs registries include not only disease that are inherently rare, but also common diseases that are in specific populations, such as breast cancer, common among women, is rare among men. The design of registries depends upon the maturity of the research plan around the disease, the availability and duration of funding, and to some

extent, the number of patients affected. The specific objectives of RD registries typically cluster into the following categories[60]:

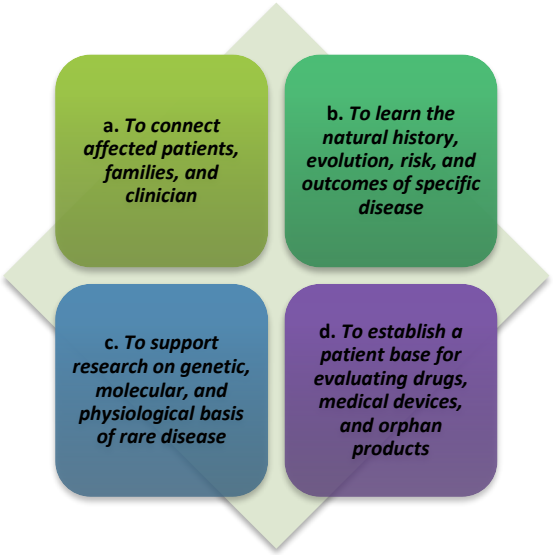


Figure 5 - Objectives of RD registries

a *To connect affected patients, families, and clinicians*: patients and families of affected individuals are often interested in knowing about others who share their disease. The need to connect is enhanced if the patient of family has difficulty in finding an expert to provide advice or the medical geneticists points out how little is known about the rare condition. Registries meeting provide an opportunity to talk and share personal experiences. Also, clinicians may want to connect with other colleagues to learn more about the disease and possible treatment options.

b *To learn the natural history, evolution, risk, and outcomes of specific disease*: natural history of disease registries are developed to better understand the burden of disease, elements of disease progression, disease genotypic, and phenotypic heterogeneity, and potential endpoints that may be used in therapeutic clinical development. In addition, the registries are also used to understand patient and caregiver quality of life, and the economic consequences of these diseases, as well as to understand the background risk of specific outcomes that usually cannot be found from other sources of data when disease is rare.

c *To support research on genetic, molecular, and physiological basis of rare disease*: clinical research depends on having a representative population for determining the timing and frequency of natural events and complications. RD registries benefit from a comprehensive database that is sufficient to address critical clinical questions, while at the same time not

being so all-inclusive that the data cannot be acquired and maintained with reasonable effort on the part of registry team.

d *To establish a patient base for evaluating drugs, medical devices, and orphan products*: stakeholders are interested in developing drugs, devices, and other therapies for RDs, and many RDs registries have been developed to support the drug development process.

Patient registries may emerge from suggestion, pressure, or advocacy of affected patients and/or families. Often, developing a treatment for RDs will provide information about pathophysiology that informs treatment development of a related disease. For instance, hospital information systems in many countries use the WHO's International Classification of Diseases (ICD) in its 10th version to record patient information. Only around five hundred RDs are listed in the ICD_10, and only half of these have their own specific code. As a results, clinical research on these disorders requires specific sources of information (disease registers) for epidemiological and research purposes, which are costly to set up and to maintain[61]. On the European level, RDs were identified by the 2nd EU Health Program as a healthcare priority with unmet needs, highlighting patient registries as the best way to pool data to achieve sufficient sample sizes for epidemiological and clinical research[60]. For RDs patient registries are thought to be key instruments to achieve a sufficient sample size for clinical research, to guide healthcare planning, and to foster the development and evaluation of diagnostic and therapeutic interventions. Patient registries significantly contribute to evidence-based personalized medicine in the field or RDs, since they can be used for multiple purposes, such as improvement of case definitions, revision of diseases classification, evaluation of indications to treat and risk stratification, as well safety, effectiveness, feasibility, limitations and benefits of diagnostic and therapeutic strategies under real-world conditions[60].



Figure 6 - Orphanet website

Orphanet (www.orpha.net) (Figure 6) is a 37-country network (included Italy), cofounded by the European Commission that aims to increase knowledge on RDs so as to improve the diagnosis, care, and treatment of people with RDs[62]. The database is a comprehensive, manually curated and expert-reviewed knowledge-based specific for RD. The catalogue is structured to provide a hierarchical

representation classified by medical domain, annotated with medical classification, age of onset, inheritance, genes, and a directory of health and research resources[61,63]. Oprhanet has built a representation of knowledge on RDs, which is constantly evolving to better serve its diverse population of users. This representation can be analyzed in its level of increasing complexity: lexical, nosologically classification, annotations and classes of objects integrated in a relational database, and semantic interoperability. According to the user's needs, data on RDs ca ne obtained at each one of these levels to be used for different purposes, either from the Orphanet website (www.orpha.net), which is continuously update, or from a dedicated download platform, OrphaData (www.orphadata.org), which is monthly updated. In April 2023, Oprhanet published a report of RD Registries, cohorts and database[64] about countries participating to the Orphanet Network funded by a member of International Rare Diseases Research Consortium (IRDiRC) and also taken into account, even if they are located in a country which is not part of the Orphanet Network. This report provides summarized data about RD registries, cohorts and databased with all the relative information, such as disorder list covered and corresponding codes, geographical location, geographical coverage, and other descriptions. The number of registries, cohorts and databases collected up to April 2023 is 827. The figure 7 and 8 show the global distribution of these activities and the number of registries, cohorts and databased by country.

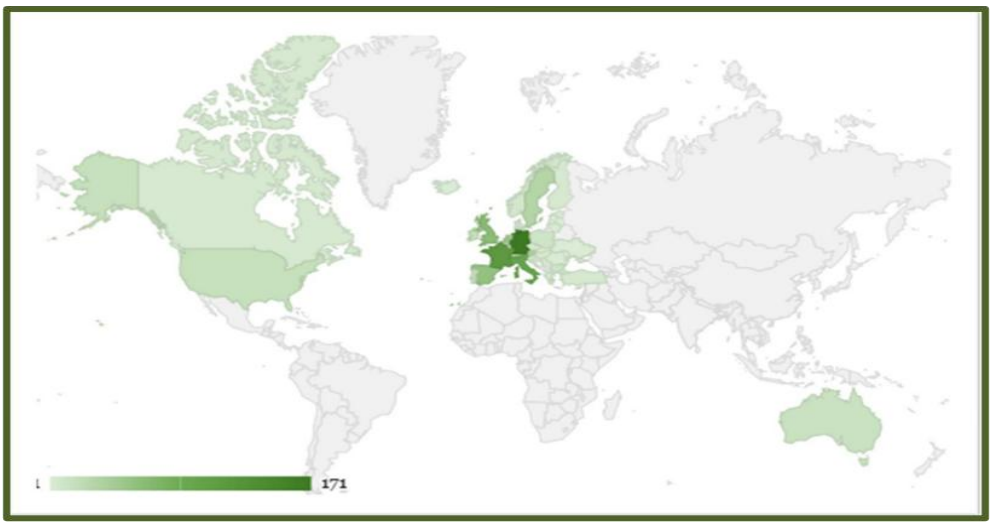


Figure 7 - Global distribution of registries, cohorts and database collected by Orphanet

The country with the highest number of registries, cohort and database is Germany (171) followed by France (117) and Italy (96).

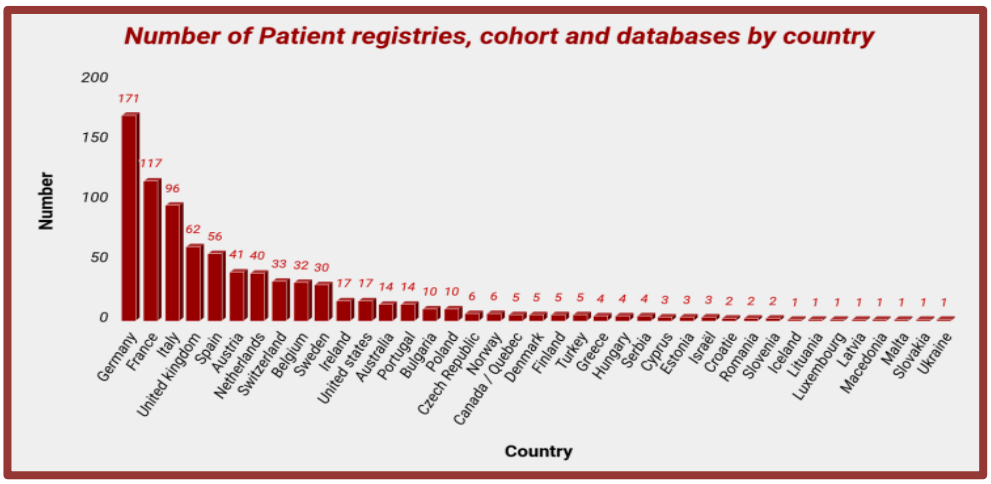


Figure 8 - Number of registries, cohorts and databases collected by Orphanet by Country

Figure 9 shows the geographical coverage of patient registries, cohorts and databases collected by Orphanet: most of these activities have a national coverage, while the proportion of patient registries, cohorts, and databases with a regional, European, or global coverage is very similar.

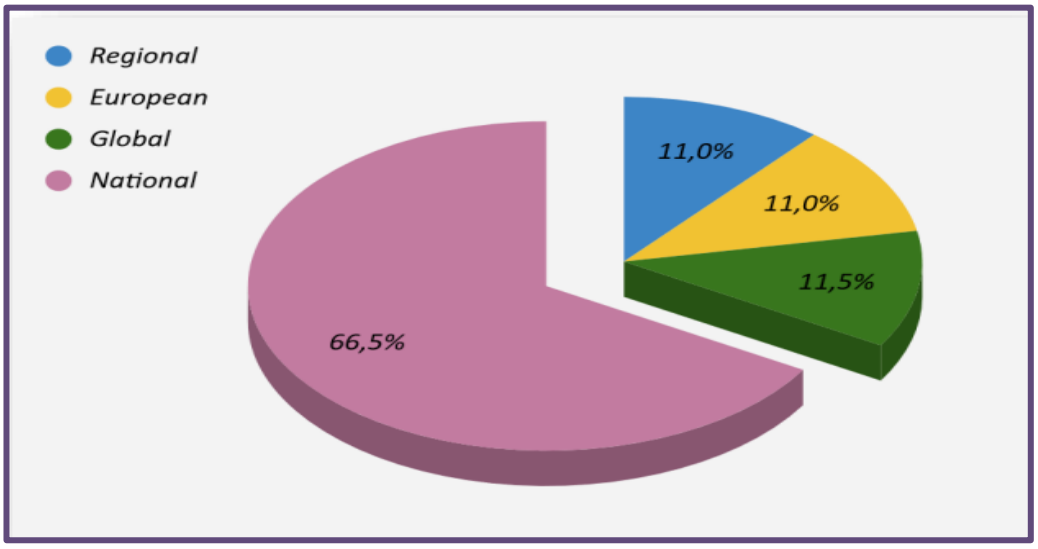


Figure 9 - Geo-coverage of patient registries, cohorts and databases

Finally, only 19% of patient registries, cohorts and databases are funded by an IRDiRC member. To support the development of registries and databases in the field of RDs for epidemiological purposes and to promote the interoperability of data in RDs registries, the European Commission co-founds the 24 European Reference Networks (ERNs) to develop their research capabilities, including the construction of patient registries. The development of these European patient registries aims to gather sufficient patient data to follow-up the natural course of diseases[64]. Existing literature suggests that RDs occur infrequently and there is a scarcity of information; however, difficulty in correct diagnosis and appropriate identification of patient with RDs is a global issue that precludes knowledge of these patients. The lack of information reflects the uncertainties in diagnostic criteria and even inadequacies in data gathering procedures. The increasing interest in RD patient registries will lead to development of many more patient registries. In the absence of a central health care system with all demographic and clinical data in one place, individual registries for different diseases are likely, each with a smaller and smaller set of patients.

Organizational collaboration and shared resources, plus engagement of the RD community, are needed to move research and knowledge forward. The proliferation of registries and the need for global multidisciplinary cooperation for RD research creates an urgent need for standards and best practices for these type of patient registries projects. The growth of Web-based patient communities and social media may also be increasingly integrated into registry data collection and conduct, as community building across geographical boundaries continues to become simpler[60]. Finally, the RD patient registries pave the way and improve the earlier and better therapeutic interventions in RD. Also, the RD patient registries extend: a) accuracy of diagnosis[65]; b) time and access from initial symptom(s) to accurate clinical and molecular diagnosis and subsequent therapy[66]; c) classification and further understanding of RDs; d) preventing and screening[67] (Figure 10).



Figure 10 - Diagnostic improvements

CHAPTER 2. GENETIC COUNSELING

2.1 Defining genetic counseling

The first episode of genetic counseling is said to have taken place in 1851, when a doctor discussed the risk of familiar cancer with a tailor who had a strong family history of disease. The doctor reported that seamstress looked sad, and when questioned she confessed that she felt her time on earth was limited, due to frequent occurrence of cancer in her family. She proved to be right, dying young of the condition. In 1931, Lancelot Hogben, a Professor of Social Science, proposed the establishment of dedicated units for the study of Human Genetics, staffed by a team's comprising geneticists, statisticians, doctors, psychologists, and ethnologists. Hogben had grasped the complexity of the subject of clinical genetics and its probable influence on individual human existence[12]. A current definition of genetic counseling was produced in 2006 by a Task Force appointed by US-based National Society of Genetic Counselors (NSGC)[68]: "*Genetic counseling is the process of helping people to understand and adapt to the medical, psychological, and familiar implications of genetic contributions to disease. This process integrates the following: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources, and research; counseling to promote informed choices and adaptation to the risk or condition.*"

This is more succinct definition that produced by the America Society for Human Genetics in 1975[69] but includes the same principles. Although over 30 years has passed since that was first written, it still accurately reflects the extent of services provided under the title "genetic counseling"[12]. Genetic diagnosis implies a process requiring at least three phases: information/preparation, laboratory, and psychological support. Work in the genetic field does not end run with the laboratory, as it entails a relational process between physician and patient, starting from the test execution proposal and ending in the communication of the results of the investigation carried out and providing the patient with genetic counseling. So, genetic counseling is therefore the basis of the assurance of diagnosis in the context of adequate information about the nature of the proposed genetic test, the nature of the disease, investigation timing and methods, the valence and significance to be attributed to the results and how to gain access to the collect data[70]. The NSGC definition of genetic counseling[68] integrates the following (Figure 11):

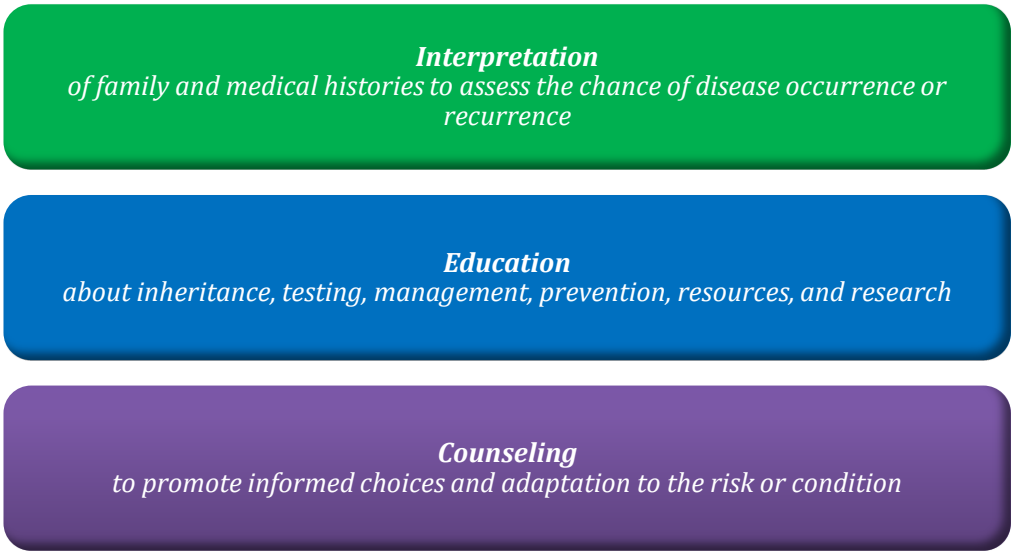


Figure 11 - NSGC definition of genetic counseling

Goals of the genetic counseling process may include providing information about test options, assessing psychological well-being, helping patients and families communicate about genetic risk, facilitating adaptation to grief and loss, interpreting results, assisting with decision-making and referrals, or some combination of these things[71]. Genomic testing can provide information about disease with differing prevention and treatment options. Ongoing research is generating evidence about which genetic findings are considered "actionable" according to criteria that consider the severity and likelihood of clinical outcome, and the effectiveness of available

interventions associated with findings in different genes. The concept of "actionable genetic information" can be interpreted broadly, to include results that impact patients' financial, family planning, and lifestyle choice or it can be interpreted narrowly, as a subset of results that point to effective medical intervention[72]. A key part of the person-centered genetic counseling process is to help patients explore what might change for them considering a test result. When the consequences of a genetic test result are contingent upon personal and contextual variables, we recognize that patient choice plays a critical role in determining how to act upon genetic information. However, when genetic information quite clearly has the potential to improve a patient's health through accessible, effective medical intervention, we agree with others that clinicians are bound by duties of beneficence to encourage patients to pursue an evidence-based course of action, taking care to remain within a well-defined scope of practice[73].

2.1.1 Genetic services

Genetic services in public health are provided in many countries by a variety of health professional. One model of care is based on the provision of clinical genetic services by a multi-disciplinary team. For example, in some European countries, genetic services are provided exclusively by medical or laboratory staff with very little input from other professions such as nursing. However, in an increasing number of countries, other professionals such as genetic counselors, genetic nurses, or psychologists are employed within the team. Most families are referred to the genetic services by either the family doctor or a specialist (e.g., pediatrician, neurologist, oncologist) caring for affected or at-risk person. The types of family referred for genetic services fall into four main groups:

- Families who are concerned about known or suspected genetic condition.
- Where there is concern about a child in the family who has learning delay and /or dysmorphic features.
- After the diagnosis of fetal abnormality or fetal loss during a pregnancy, or in the neonatal period, or recurrent spontaneous abortion.
- Family where there is a strong history of cancer.

Although the service for individual families varies according to need and the condition concerned, in general following aspects of care will be offered by the genetic service[12].

Medical Genetic services in Italy*.* Clinical Services of Medical Genetics in Italy target individuals or families who are affected, or at risk of being affected, by potentially hereditary diseases ensuring accurate genetic diagnosis and genetic counseling for reproductive and/or lifestyle choices. Clinical Services of Medical Genetics play a significant role in the surveillance and prevention of hereditary disease in the population.
Individual-oriented activities are: a) diagnosis, genetic counselling, treatment, and follow-up of people with genetic diseases; b) diagnosis, genetic counseling, treatment, and c) follow-up of families/people at risk of being affected by genetic disease. Also, genetic services conducted population-oriented activities, such as: a) targeted populations screening for specific disease (e.g. thalassemia); b) development of guidelines or protocols for specific disease and appropriate use of services; c) updating of specialist in other disciplines for the appropriate use of genetic services; d) health education to the population on topics of genetic interest; e) contribution to health planning.

These general concepts were taken up by "*Guidelines for Medical Genetic Activities of the State-Regions Conference*"[74], which defined genetic counseling as a complex process of communication, which aims to help patients and families to understand: medical information, the probable course of disease, and preventive, therapeutic and care interventions available; genetic component of the disease and the risk of transmitting it; the options available in coping with the risk; the most appropriate choices in relation to risk and families members; the best possible adaptation to the disease. Genetic services are provided exclusively by clinical geneticist, biology and laboratory staff specializing in clinical genetics with very little input from other professions such as nursing. The clinical geneticist is the key figure in genetic counseling: he is qualified to physician who has undergone specific training in medical genetics, and he works in a way integrated with other specialists.

2.1.2 Ethical practice

The ethical principles of relevance to genetic counseling[75] are reported in Figure 12.



Figure 12 - Ethical practice

Informed consent to the medical act constitutes the legitimate assumption of any healthcare provision and is therefore an essential element for the realization of an effective therapeutic alliance between the physician and the patient. The implementation of this principle implies a commitment on the part of the doctor about the type of information to be given and whether to inform the patient about his actual health conditions and finally to provide information about the diagnostic and therapeutic activities to be taken to restore or improve health conditions. The patient's decision-making process as a process based on the availability of adequate and complete information is problematic when genetic tests are the subject of the information[70].

2.2 Genetic counseling practice models

Historically, Kessler[76] described genetic counseling as composed of two practice models: a) teaching model and b) counseling model. These models have distinct goals that can be at cross purposes and must be integrated to achieve the goals of practice.

- The ***teaching model*** involves effective communication of information relevant to the patient, the counselor has more authority in the relationship and is looked to as an expert by the patient. In processing the information, the patient experiences psychological response. Many classic definitions of genetic counseling underscore the central importance of information-giving and education in genetic counseling; for example, it has been suggested that in most non-genetic doctor-patient encounters the central topic is treatment and cure, while in genetic counseling (where cure or treatment in the ordinary sense is rarely available), information-giving and education may be considered constituting the treatment itself[76]. The information that is transmitted is objectively very complex and difficult to understand. These components of genetic counseling make its information-giving and educational part central, leading to the possibility that communication aspects of care be more salient in determining client outcomes, compared to other types of medical consultations.

- The ***counseling model*** conceptualized the main goals of genetic counseling as promoting informed choices and facilitating

psychosocial adaptation to the hereditary risk or condition[68,76]. The counseling guide toward opportunities to gain personal insight, identify resources. Integrating these two models to address a patient's need is challenging but comprises a key professional skill in genetic counseling. Inherited illness has direct implications not only for the individuals presenting for genetic counseling but other family members as well and may therefore be construed as being particularly stressful. According to the counseling model, increasing the emotional well-being of clients and their family members is also considered a central part of genetic counseling, and thus genetic counseling has been likened to a psychotherapeutic process[77].

Use of one model without the other is insufficient to successfully meet the patient's needs as defined in traditional client-centered care. Kessler[76] advocates that genetic counselors base their practice on a combination of both models. Genetic counselors may then develop, and flexibility apply the skills required to implement either model, as required by an individual patient and/or the issue for which the patient sought genetic counseling. Research demonstrates that patients tend to express less concern and experience reduced anxiety when their expectations for reassurance and advice are met in the genetic counseling sessions. In contrast, meeting patients' expectations for information has not been associated with improved emotional outcomes. Higher counselor verbal dominance is also associated with higher anxiety levels and lower perceived needs fulfillment, highlighting the importance of client engagement and collaboration in the genetic counseling session. Patients also tend to have a greater improvement in depression levels when counselors use more empathic responses, and consistently rate higher satisfaction with practice models that emphasize counseling over teaching[78]. In addition, in a systematic review of interventions to improve risk communication in clinical genetics, Edwards et al.[79] found that supportive or emotional elements of counseling, such as addressing issues of loss, grief and relationship problems, provided greater benefits than purely informational or educational approaches. More recently the practice has been described as a psychotherapeutic based on the similarity of genetic counseling to the definition of psychotherapy[80]. Psychotherapeutic elements of genetic counseling have been recognized since the inception of the profession, as has its potential to evoke feelings of shame and guilt, especially when psychological concerns are not addressed. Recent comprehensive meta-analyses of hundreds of controlled studies have demonstrated that several facets of the therapy relationship have a robust and significant impact on therapy outcomes across a wide range of

approaches, clinical context, patients, and problems. These evidence-based facets include the appropriate expression of empathy, establishing an effective therapeutic alliance, collaboration, goal consensus, and positive regard, and they account for most of the explained variance in therapy outcomes[81]. While no studies have systematically assessed barriers to adopting a therapeutic model of practice in genetic counseling, several potential obstacles have been identified[82]. One view is that genetic counselors might feel underprepared in this realm of practice and feel more comfortable providing and education-based interventions. This suggest that there might be a gap within training programs regarding the development of adequate counseling ability[83]. Further exploration suggests that any lack of comfort with therapeutic skills among genetic counselors might arise from discrepancies between how genetic counseling is taught versus how it is practiced. Genetic counseling is implicitly conceptualized as a medical activity whose primary objective is to convey medical information about genetic diagnosis and its prognosis, treatments, recurrence risks, and reproductive options.

In connection with this, Shugar[84] conceptualized the **Genetic Counseling Adaptation Continuum (GCAC) Model** (Figure 13). Shugar started from the concept of adaptation at genetic condition and/or risk. The term adaptation is used extensively in the psychology and genetic counseling literature, and Biesecker et al.[77] defined as "*the dynamic and multidimensional process of coming to terms with the implications of a health threat and the outcomes of that process*". In the context of assessing patient adaptation in the genetic counseling, Shugar[84] proposed that Biesecker's definition[77] be refined to "*the process of coming to terms with the implications of a genetic diagnosis or risk*". The idea of adaptation being a process implies that one's state of adaptation lies on a continuum at any given point in time. The GCAC model conceptualizes a patient's adaptation to a genetic condition, risk, or the process of making an informed decision as being on a continuum, from a poorly adapted to well-adapted state.

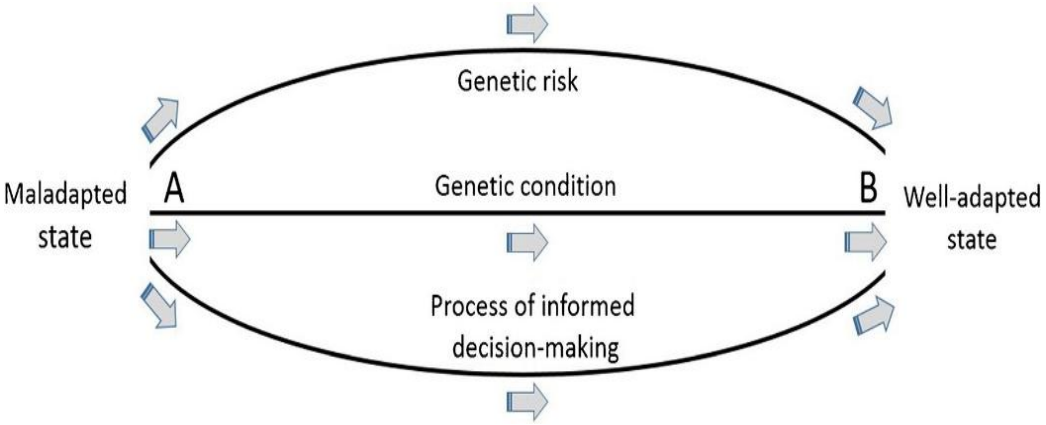


Figure 13 - Genetic Counseling Adaptation Continuum (GCAC)

The accompanying tool can be viewed as a visual-analog-like scale that helps assess a characteristic, such as adaptation, which cannot be directly measured, but rather lies across a continuum of values. In contrast to a validated scale that encourages the student to focus on measuring and scoring, this tool can be viewed as a "mental model" that the student integrates into their mind. The far-left hand side of the tool (A) represent a maladapted state in which the patient is struggling psychologically with a risk, a diagnosis or decision-making. The far-right hand side (B) represents a well-adapted state in which the patient has integrated the risk, diagnosis, or important decision into his life. In every genetic counseling session, one must ask oneself "*Is this individual, couple or family struggling to adapt to one or more of these three entities: the genetic diagnosis, the risk or the process of making an informed decision*?". Shugar[84] highlights the importance of psychosocial responses of patient to genetic counseling and the students practice a stepwise approach to help them obtain comprehensive answers to the above questions and formulate appropriate and effective psychosocial responses. The GCAC model is only one small component of a much larger teaching framework that must include the study and practice of discrete psychosocial, as well contextual, and situational skills, to achieve competency in genetic counseling. It should not be taught or used in isolation[85]. This model is also not designed to identify the patient who, often due to pre-existing mental health and/or extraordinary social challenges, requires assistance beyond the genetic counselor's skill set or scope of practice.

The ideal medical genetic diagnostic processes. Merker et al.[86] demonstrate that effective diagnostic communication of a RDs requires additional tasks beyond ascertaining the correct diagnosis and notifying the patient of it. The study highlights the essential role of effectiveness communication in the ideal biopsychosocial diagnostic process in medical genetics (Figure 14). Once a diagnosis is sufficiently established to direct medical management, patient should be educated in a meaningful way about the disorder and given psychosocial support within the contest of an emerging therapeutic alliance. These interlocking components of effective diagnostic communication are critical to minimize patients' psychological distress, support their ability to proactively engage in healthcare decision-making, and help them with appropriate treatments.

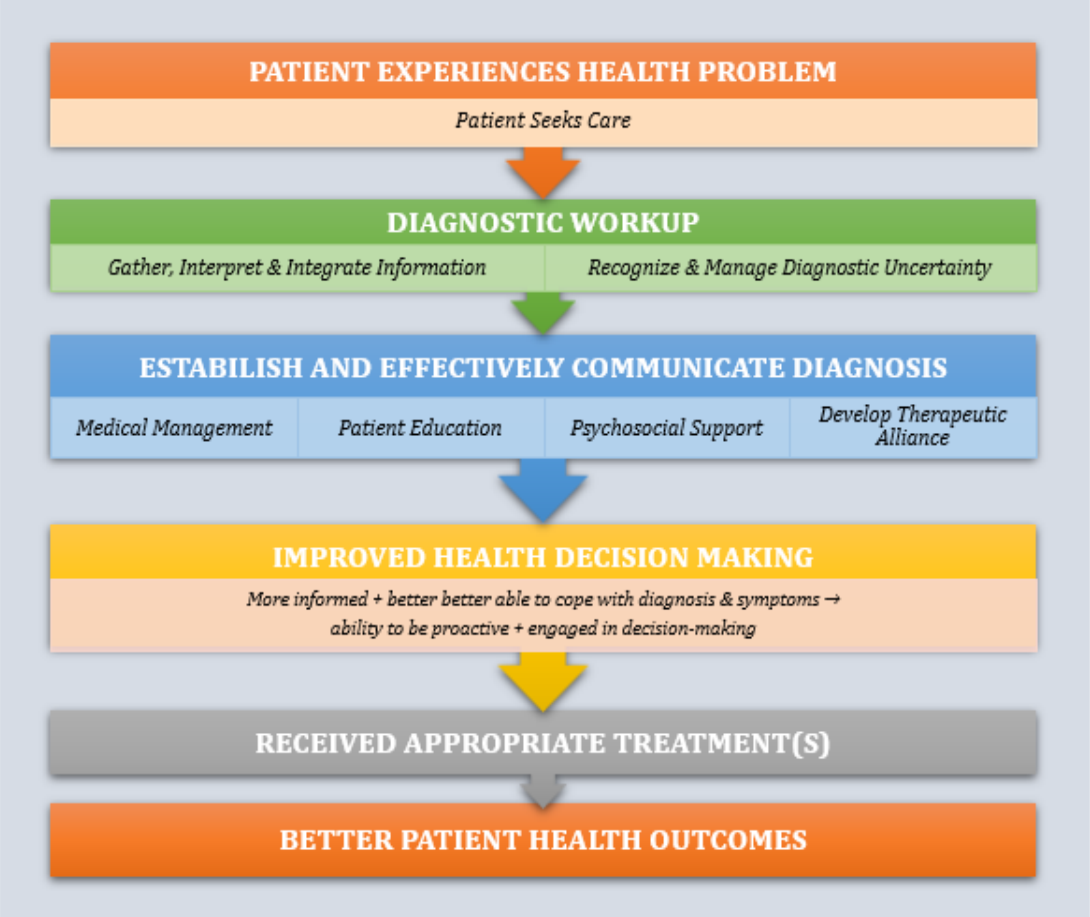


Figure 14 - The conceptual ideal diagnostic process

The components of effective diagnostic communication identified in the study line up with established models of patient-centered communication[87]. Research supports the importance of personalized information exchange and positive interpersonal relationship during genetic diagnosis and emphasizes the need for emotional support during RDs diagnosis[88,89]. Merker et al.[86] also show hot the concept of "therapeutic alliance", derived initially to describe patient-provider relationship during psychotherapy[90], applies to medical diagnosis or RDs. Psychological literature confirms the importance of trust, rapport, and collaboration on the development of therapeutic alliance[91] and empirical work corroborates that therapeutic alliance (particularly in early stages of the clinician-patient relationship) facilitates patients' collaborative and active participation in health decision-making[92,93]. Finally, some RD patients face particularly difficult diagnostic journey that may result in increased psychological distress and mistrust of clinicians[94–96]. These patients may require psychosocial support and special efforts to build a therapeutic alliance to counteract trauma from prior diagnostic experiences[97,98].

Genetic health literacy across the population is low, so people with rare, genetic disease will need education about genetic issues and may benefit from genetic counseling referrals. Psychological support from diagnosing providers, mental health professionals, and support groups, is likely beneficial across disorders as well[99]. RD's patients have been shown to experience psychosocial challenges at time of diagnosis and to have lower psychological functioning than the general population[100]. Finally, clinicians should provide appropriate education about the disorder's cause, symptoms and prognosis while monitoring patients' emotional state. Clinicians should evoke patients' individual concern, avoid jargon, and refer patients to relevant disease advocacy organizations – if they exist – for additional education and social support. If not personally equipped to direct medical management, clinicians should facilitate patients' connection to follow-up care so that patients do not feel alone. If the syndrome is genetic, consider referrals to medical genetics for education and counseling regarding the heritability, testing and family planning options. Referral to professional psychological care may help patients adjust to a diagnosis and cope with troublesome symptoms.

CHAPTER 3. BIOPSYCHOSOCIAL MODEL AND CLINICAL IMPLICATIONS

3.1 Introduction

The **biopsychosocial model (BPSM)** was proposed by George Engel in 1977 as improvement to the **biomedical model (BMM)**, necessary to account for psychological and social factors in health and disease as well as biological[101] (Figure 15).

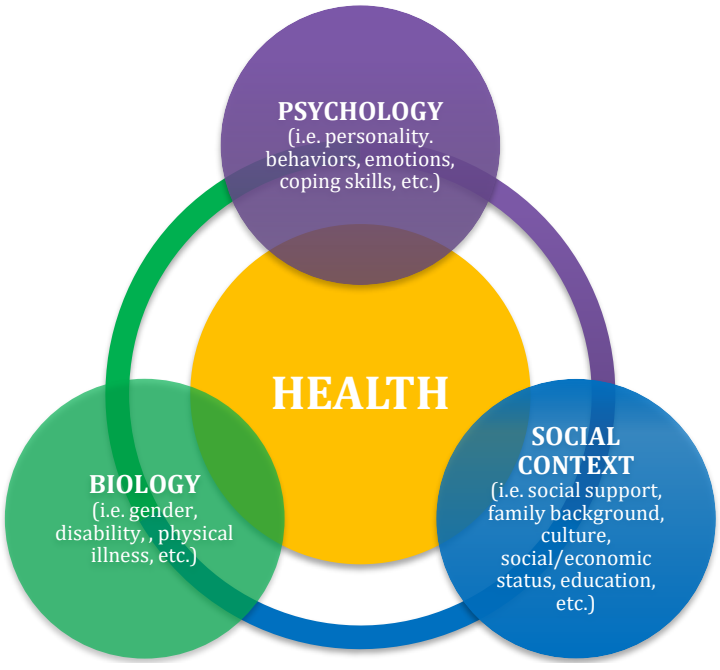


Figure 15 -BPS Model

This proposal remains critical in science and in service planning[102]. Engel's paper[101] implicates two foundational underpinnings of the BMM, the model for biomedicine as conceived at that time: one is that biology, as physiology, is reducible to physics and chemistry, and the other is the assumption of mind/body dualism. Dualism notoriously offers no scientific account of how immaterial mental processes can causally influence the material body, and there is no role for psychological causes in the scientific explanation of behavior unless they are somehow reducible to biological causes. The author implies that these two foundational underpinnings of the BMM will be abandoned. In the last few decades, biology, as physiology, has transformed itself in a revolution largely drive in fact by biomedicine. Biology with biomedicine is now closely integrated combination of two kinds of science: one is the physics and chemistry of energy exchanges and transformations quantified in enthalpy change equations, for example, but there is in addition new models of mechanism for the regulation and control of the physics and chemistry, and of other systems, maintaining functions, typically using feedback by information-transfer. The new "regulatory" paradigm, also known as the "information-processing" revolution, appeared clearly in molecular biology in the 1960s and 1970s, such as Jacob and Monod's ground-breaking work on genetic regulatory mechanisms in the synthesis of protein[103]. Von Bertalanffy[104] proposed the **general system theory**: negative entropy was achieved in open systems, in biology and in wider domains including the psychological and the social, and Engel refers to these theory as a key theoretical driver for the new BPSM, anticipating impacts on healthcare science and practice[101]. Engel supposed that the BMM assumed body/mind dualism and that this was an obstacle to accounting for psychological factors in health and disease. Post-dualism models can be characterized as having two working assumptions: one is that mental processes regulate behavior, and the other is that mental processing is a function of brain processing. The first point underpins cognitive psychology, while the second merges psychology with neuroscience. Both relate to the theoretical innovations in biology in the 1960s and 1970s: biology, psychology, and neuroscience all shared interests in new information-based models of the regulation of biological systems and behavior, the paradigm shift went across the life science.

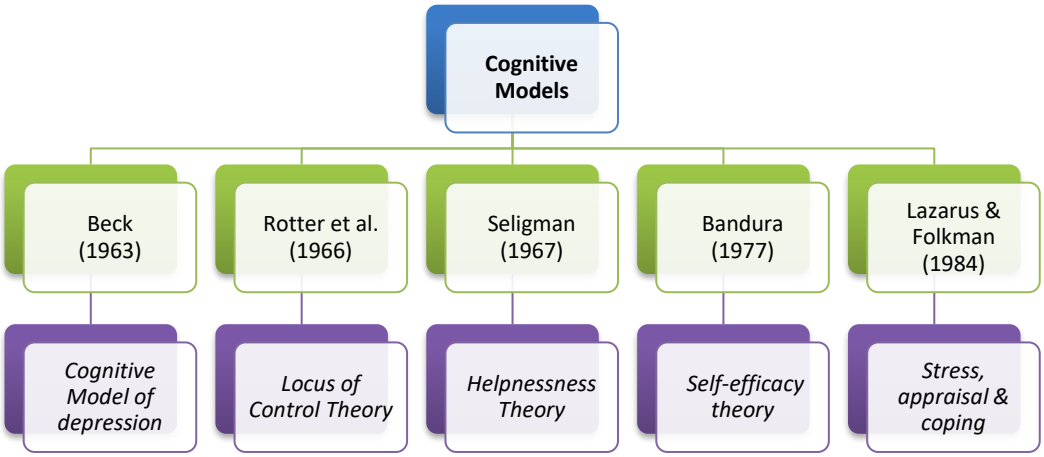


Figure 16 - Cognitive Models

Cognitive models in clinical psychology emphasized the causal role of personal beliefs in the regulation of affect and behavior (Figure 16), such as Beck's **cognitive model of depression**[105]. Around this period emerged a class of psychological models focused on the role of expectancies and beliefs about personal control over events or personal agency and their implications for well-being. Main examples are Rotter's **locus of control theory**[106], Seligman and colleagues' learned **helplessness theory** and associated model of depression[107], Bandura's **self-efficacy theory**[108], and Lazarus and Folkman's work on stress, appraisal, and coping[109]. The appearance of personal processes in the new psychological science, beliefs, about the world and our agency, personal goals, emotions, and behavior, has substantial relevance to the question whether a broader BPSM is needed in health science and healthcare. Engel gave a long list of important issues the BMM could not account for, and top of the list was "the person who has the illness"[101]. The second aspect of post-dualism models mentioned above is that psychological processing is regarded as a function of, or implemented by, brain processing, hence merging psychology with neuroscience. Cognitive (or cognitive-affective) neuroscience (as the merger can be called) has developed alongside cognitive psychology[110]. The new post-dualist constructs of mind and body accommodate crosstalk between neuroscience/psychology and biomedicine, in both directions. These interdisciplinary research programs, involving neuroscience, psychology, and biomedicine, were inconceivable in mind-body dualism[111].

Research designs relevant to the BPSM are those that examine the effects of psychological and social, as well as biological factors, on health outcomes[112]. BPSM compatible research studies were barely available when Engel proposed the new model in 1977: they began to appear at around the same time. The first clinical trials of psychology therapies appeared in the 1970s, heralding what has become a very large-scale research program of developing and evaluating psychological interventions for a wide range of health conditions and their complications. The early finding that cognitive therapy for depression was effective, and moreover, more effective than an antidepressant medication[113], reinforced the signal that the BMM was not enough, at least not for modeling and treating depression. At the same time, there was another majority anomaly for the BMM, the emerging findings of social epidemiology: social status affects a wide range of physical health and mental health outcomes[114]. The findings that are anomalous for the BMM but consistent with the BPSM are empirical data, related to specific influences on specific conditions at specific stages of disease. It is possible that a specific health condition at a particular stage may turn out to be primarily caused by only one kind of factor, biological, psychological, or social, and of course biomedical models of disease have had stunning successes in this way.

Such findings may be called a scientific explanatory reduction to biological processes[111]. To the extent that biology, neurology, and neuroscience are being broadly conceived to acknowledge the causal role psychosocial factors in some conditions, in etiology and course, and in prevention and intervention, these theoretical proposals are not reductionist and are compatible with a broad biopsychosocial framework. However, proposal to roll the psychosocial up into the biological appear to be a kind of reductionism, so far by-passing the need to theorize the acknowledged causal role of psychosocial factors or biopsychosocial causal mechanism. Psychological causation, implemented in brain processes, involves regulation of behavior functioning toward attaining or maintaining some state. Social factors can causally interact with psychological processes, to give an example by regulating task demands and available resources. Psychological and social causal processes are both causal in the sense of regulatory, as is one kind of causations in biology, the other being energy transformations and exchanges covered by physicochemical laws. As to dysfunction, this must involve disruption to regulation because physicochemical laws cannot be disrupted. Models in which regulation/dysregulation are prominent are now to be found not only in biomedicine, but also in clinical psychology and psychiatry[115].

The first example is a set of **models of chronic stress**, applied to epidemiological findings on the social determinants of health, aiming to explain pathways between unfavorable social status and unfavorable health outcomes[116,117]. The second example of a new causal explanatory biopsychosocial theory with wide application comprises **new models of pain perception**, implicating neurobiological–psychological processing as well as peripheral physiological or structural damage. The new models implicate the person's negative appraisals of the meaning of pain and expected adverse effects on their lives and task demands and associated Central Nervous System (CNS) pain-processing mechanisms[118,119]. "*Medically unexplained*" means biomedically unexplained, and biomedically oriented clinical typically no biopsychosocial management protocols in place; consequently needs are not met, and the patient journey can be potentially long and costly; to give an example, in general practice and medical clinics[120], cardiology[121], neurology[122], and surgery for some pain presentations[123]. It was advanced in genetics that introduced into biology theoretical ideas of a new kind of science involving coding, information-transfer, error, regulation, and control, additional to energy-transfer and exchanges covered by physical–chemical laws. Further, theories of genetics have always been thoroughly interactional across domains, in evolutionary theory, and recently in the new field of epigenetics, including in psychiatry[111]. The same theory-shift that transformed biology also transformed neuroscience and cognitive psychology, enabling a coherent biopsychology. As to the domain of social interactions, there is no shortage of research programs on its major importance to our biopsychology in phylogenesis[124] and ontogenesis[125].

3.2 Biopsychosocial conceptualization of health conditions

Some questions about illness are casual and some conceptual, though there is no hard and fast line between them. Causal questions are about identifying risks, pathways, and mechanism of disease, developing clinical therapeutics and treatment technologies. In condition of certainty, there is no need to spell out what illness means; all concerned know only too well, and they have other serious tasks to be getting on with. And if and when the need for a definition of illness or disease arises it is easy enough to give a simply by using some other term with similar meaning, such as abnormal structure or function, or disruption, disturbance, dysregulation, etc. The medical

textbook descriptions of signs, syndromes and diseases are full of such terms, and they can all be used to define each other well enough for most purposes[126]. The meaning of illness, and all the cognate to do with abnormality, becomes an issue in condition of uncertainty and dispute as to whether such and such a condition is an illness or not, in circumstances when it seems that no further observation or laboratory test would settle the matter clearly one way or the other. This uncertainty arises when criteria that normally go together, in the paradigm or prototypical kind of case, fall apart. Three key features of illness typically go together:

1 The person complains of distress or pain.

2 They are unable to do things they need to do, there is incapacity or activity limitation, loss of agency.

3 There is the assumption that these things are because something is not well with the person's body or mind. This implies that medical/psychological expertise is required, hopefully, to reduce the harm (the distress/pain and incapacity) and not create more.

The reference to pathologizing refers to a downside of the illness attribution. Also, the agency decreases. The adverse effects of illness on agency cue interpersonal responses to help, to provide resources including care and treatment. The social expectations are reduced and the attribution of causation of behavior, or of inactivity, is to the illness, not to the person as agent. However, pathologizing carries the risk of disqualification of the person from their full knock-on risk of being stigmatized and subjected to the many varieties of social exclusion[101,126]. The relative benefits and losses of being seen as ill depend on many general and individual factors. For sudden onset, the benefits are typically high and the costs of the above psychosocial sort relatively low. For log-term conditions, with no treatment may do as much harm as good, the balance shifts, costs may outweigh benefits, leading to a rejection of the illness label, in favor of "difference" and "diversity"[111] (Figure 17).



Figure 17 - The importance of biopsychosocial framework

3.2.1 Centrality of the person

In the BPSM, health conditions must be understood in terms of the person, specifically how it affects their agency, values and achievement of person goals. The centrality of the person was identified by Engel as a feature of the BPSM in his original paper[101]. There are some connections between the BPSM and the **Recovery model**[127,128]**.** The model focuses on chronic health conditions, on the centrality of the person's life and values, on achieving a good quality of life, on the need for good medical and nursing care, and on issues of access to social resources and opportunities. Many if not all aspects of the Recovery model can be applied as much to chronic physical health conditions as to mental health conditions, though so far this extension is its infancy[129].

The focus on chronic conditions has implications for a distinction often drawn in the literature between illness and disease: illness being the condition of the person, and hence involved in the personal and social world, and disease being a dysfunctional condition of a bodily organ or system, and not so involved[130]. It is much more important to know what sort of patient has a disease than what sort of a disease a patient has. This blurring of the difference between disease and illness is another aspect of the shift from the disease paradigm to focus on non-communicable conditions, which require a biopsychosocial approach[111,126]. Huber et al.[131] propose a conceptualization of health as *the ability to adapt and to self-manage*, discussing this in relation to physical health, mental health and social health. A concept of health along these lines makes personal agency fundamental, though in its broad biopsychosocial context, interacting with resources and opportunities. A person's sense of agency, whether they can do enough to

have a viable life, and with it whether they wish for life, as it is, or better, with treatment or with none, are all matters that depend on the person. The condition of the biological body matters, but insofar as it affects the person. It is of fundamental importance in healthcare that it is the person who feels ill and wants treatment, any or more, or feels well enough without it. We attend to the person, not the body part—and not to psychological signs and symptoms in isolation either[126,127,131].

3.3 Clinical implications

The clearest clinical implications of the BPSM, in contrast as always with the narrower BMM, is accommodation of psychological and social factors as well as biological factors relevant to clinical management and treatment. This is supported in the clinical trials literature, appearing mainly after Engel wrote his 1977 main paper. Large-scale clinical therapeutics research programs in the decades since have studied and shown the effectiveness of some psychological therapies for a large range of health conditions[132], of combination therapy, medication plus psychotherapy, for some conditions such as depression[133,134]. The details of exactly what helps what are always specific to details of treatment, conditions, and stage, but the overall picture that has emerged from the clinical trials literature is consistent with the broad biopsychosocial framework, in the precise sense that any narrower framework, envisaging treatments that are biological only, psychological only, or social only, omits some effective treatments for some health conditions at stages. Now that there is a substantial clinical trials literature, summarized and adapted in clinical guidelines, it is of major importance in clinical decision making[111]. A lot more is going on in clinical care than decisions as to what treatments to recommend, including personal, interpersonal, and institutional processes. Specific issues include the role of the person as patient – in determining what is wrong, whether anything is wrong, in collaborating on a treatment plan – the imperative of 'compassionate' care[135], and professional factors supporting good clinical care[136]. While persons, interpersonal relations, and institutions can be accommodated within the BPSM, the contrast with the BMM is, as always, clear. These matters are simply out of the scope of the narrower BMM: they are not in its ontology, and therefore, it has no idea of them at all, still less their causes and effects. There is of course a grand tradition of BMM in medical theorizing[137] and Engel argued against it, favoring rather a broadly scientific-investigatory approach to understanding and improving, for

example, receptive and expressive clinical communication skills, and institutional supports of clinical professional care[126]. The revitalized, cross-disciplinary BPSM proposed here can be used to theorize personal and institutional factors relevant to clinical care and highlight their role as critical and not merely discretionary considerations. For example, the fundamental importance of personal agency in psychology is consistent with the central role of the person as patient, and the fundamental importance of socio-political factors in regulating recognition and access to resources can help theorize and highlight interpersonal, institutional, and wider political processes that affect clinical care. The key added value of the BPSM, in contrast with BMM, is that it accommodates personal, interpersonal, and institutional factors in clinical care within the causal systems affecting health and disease[111].

3.4 Biopsychosocial approach and clinical psychology role in genetic counseling

Because of these premises, the application of the biopsychosocial model seems essential in the context of genetic counseling. This model interprets health as the result of multiple interacting biological, psychological, and social factors, and recognizes that behavior can be explained in terms of multiple contexts or levels of organization that mutually influence each other[101]. The medical geneticists usually explore the potential psychological consequences of DNA testing with the counselee and provides emotional support. Some medical geneticists may benefit from referral to a psychologist, as suggested by national and international guidelines[68,138]. Psychologists may offer psychotherapeutic counseling and may help with psychosocial issues. Until recently, psychologists with specific expertise in genetic counseling were frequently and intensively involved in the care of patients who received genetic counseling, for instance as standard procedure in genetic counseling in Belgium, Netherlands and in North America[139]. In September 1996, an International Meeting on "*Psychosocial aspects of genetic counseling*" pointed out the complexity of the consequences of a diagnosis of genetic disease, from the patients' point of view. The need for the other professionals such as psychologists, nurses or social workers was underlined in the meeting and also afterwards[140].

So, it was assumed that genetic counseling may be a psychologically difficult process, which may evoke psychopathological levels of distress in some counseling, although the operationalization and the level of distress seemed to be a matter of debate[141]. Recently, the support of a specialized psychologist is becoming a non-standard element in genetic counseling, especially regarding onco-genetics. Counselees may request and receive psychological help for a broad range of reasons, but this help is not automatically offered. This transformation in the psychosocial care for counselees may partially be attributed to the relatively small number of counselees showing long-term psychopathological levels of distress, and most of them seem to cope relatively adequately with the DNA test results[142]. Therefore, a medical geneticist may explicit explain to counselees for what kind of reasons they could be referred to a psychologist, for example, distress, difficult decision-making, family communication, difficulties in living with uncertainty, or creating their identity as (non)-mutation carrier. In this context, counselees may be asked the simple question of whether they would like to receive support for any of these reasons. Additionally, screening instruments may be used to identify counselees who may need to receive psychological help. In the Dutch context, when counselees asked for psychological help, they could receive help from a psychologist with specific expertise in genetic counseling. Clinical experience suggest that some psychological issues may be easier to understand and addressed by specialized psychological help, but more research is needed[139].
In the context of genetic counseling, the presence of the psychologist with specific expertise in genetic counseling is extremely useful.
In the interest of promoting better genetic translation in clinical and public health settings, there are at least five areas (reported in Figure 18) where the clinical psychologist can bring[138].

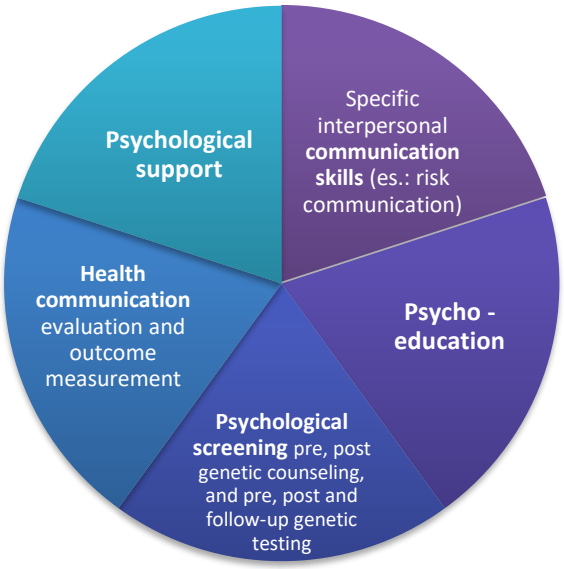


Figure 18 - Clinical psychologist skills in genetic counseling

In support of this, a 2022 study by Catapano et al. points out that in Europe there are only a limited number of master's degree programs that train genetic counsellors: there are some countries (e.g. France, Portugal, Romania, Spain and the United Kingdom) that recognize the profession of genetic counselor, while others do not (e.g. Austria, Italy, Belgium, Germany and Portugal). At the same time, the article highlights the importance of the multidisciplinary team within genetic counselling, and the psychologist is among the figures considered important[143] (Figure 19).

Importance of professional figures on the team. The mean and the standard deviation are reported on the right.

Role	Average	SD
Geneticist	6.82	0.76
Genetic counsellor	6.35	1.05
Biologist	5.66	1.61
Psychologist	5.54	1.43
Administrative	4.88	1.82
Nurse	4.81	1.74

Figure 19 - Importance of professional figures on the genetic team

The clinical psychologist in the context of genetic counseling must understand genetic counseling and its ethical implication; be able to effectively communicate relevant and objective information; ensure users' understanding of information emerging from genetic counseling and informed consent; and take charge of the individual and family through counseling and/or psychological support. Therefore, as a part of biopsychosocial approach based on a multidisciplinary team, the role of the clinical psychologist is twofold. First, clinical psychologists facilitate counseling and health education through communication and psychoeducation of the user about genetic risk. In particular, ensure the patients' understanding of the given genetic information, help patients express their own questions, guide the the patient in making the right decisions for themselves, discuss with the patient the potential effect on every-day life, discuss common psychological reactions and feelings, education of population, identify and help the patients in crisis, provide psychological support to the patient, literature research[143]. Second, supports the individual and family in the clinical pathway following genetic diagnosis with the goal of functional adaptation to the genetic condition and improved Quality of Life for the patients and families and ensures the scheduling of individualized psychological support for the patients who need and/or request it[144].

In the context of genetic counseling and disease risk communication, effective communication should be encouraged with the aim to facilitating the adaptation of information based on the personological characteristics, cognitive reserve of the individual and family, while not neglecting the background of reference. A core component of genetic counseling scope of practice is applying counseling and psychotherapy skills to explore emotions and concerns, usually in the context of patient education and facilitating decision-making and adaptation to disease[76,80]. Psychologists are widely recognized as expert of assessment, diagnosis and treatment of mental health problems and disorders; clinical health psychologists develop and implement evidence-based clinical intervention, provide diagnostic and cognitive assessment across the lifespan, provide consultation to other specialists, and provide consultation and clinical skills training to other clinical staff[141]. It is well documented that interprofessional collaborative care can improve patient safety, quality of care, and provider satisfaction and retention; however, successful collaboration requires specific knowledge, skills, and attitudes that are best taught interprofessionally[145,146]. While both medical geneticists and clinical psychologists share patient-centered counseling and psychotherapeutic approaches and may refers patients to

each other, it is rare for trainees from medical geneticists and clinical psychologists to interact and learn together[147].

The common objectives in the context of genetic counseling of medical geneticists and clinical psychologists is described by Hartley & Holmqvist[147]:

- case formulations to help guide intervention and support training;
- recognize adaptive and maladaptive responses to life-altering information;
- describe the purposes of psychological assessment and identify appropriate referral questions;
- demonstrate skills related to recognizing and managing intense emotional responses that may arise during genetic counseling;
- demonstrate skills related to readiness assessment and managing ambivalence;
- recognize when a counseling approach needs to be modified based on patient and/or families characteristics;
- develop skills related to structured observation, case presentation, and reflective practice.

Also, the authors describe the genetic counseling toolkit useful for both medical geneticists and clinical psychologists (Figure 20: genetic counseling is represented in blue, and clinical psychology in red).

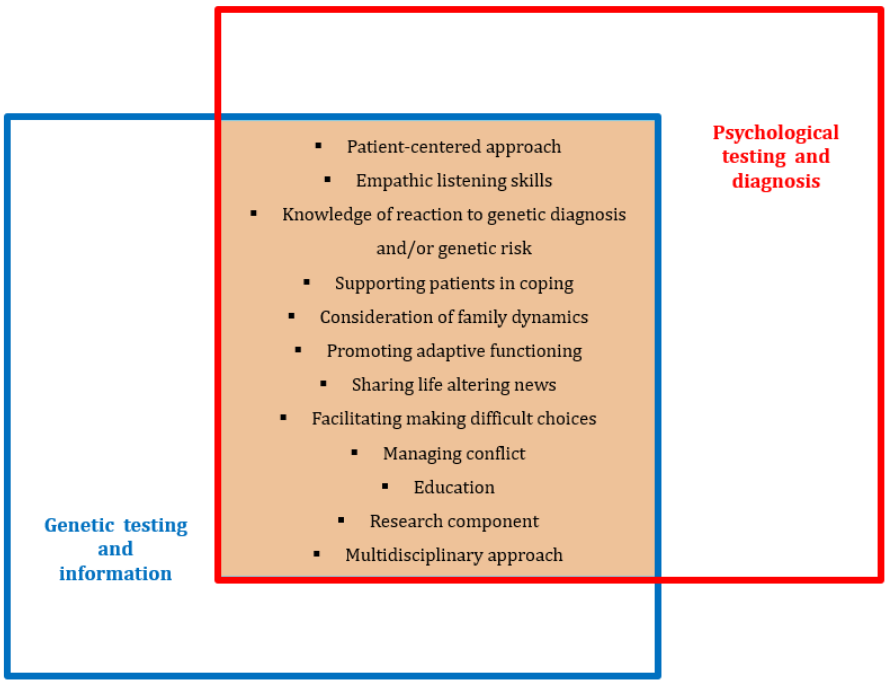


Figure 20 - Genetic counseling toolkit

CHAPTER 4. COMMUNICATION IN GENETIC COUNSELING

4.1 The role of communication into genetic counseling

During genetic counselling, communication cannot be directed only to the individual patient, as the genetic diagnosis and/or risk is a matter for the whole family. Although there are a vast number of genetic tests conducted in laboratory, the single most important tool and test in clinical genetics is the family history. Taking an accurate family history by family tree gives the medical geneticists a wealth of information about the likelihood of a genetic condition in the family, the probable inheritance pattern, and recurrence risks for family members. It also has an important function in providing context for any laboratory test results, so that can be correctly interpreted. Is important to explain why medical geneticists are drawing the family tree and how it will be used. Enable the patients to see what you are drawing. A basic family history should include three generations. To begin taking a family history, start by asking the patient about his/her health history and then ask about relatives. Questions should include general information such as names and birthdates, family's origin, health status, age at death and cause of death of each family members, and diagnosis of relatives[148]. Also, while taking the family history, the medical geneticists acquire a lot of information about the nature of relationship in the family and the social issues that have had an impact on the family.

The referral framework is the individualized care and patient-centered approach, because the medical can take family issues into account when discussing options and potential actions of care and/or prevention.

4.1.1 Brief summarize of theories of family communication

Several conceptual orientations could be applied in developing family genetic risk communication interventions:

- family system-oriented,
- dyadic-oriented,
- individual-oriented[149].

Family system-oriented theories (e.g. **Family System Perspective (FPS)** and **Family Communication Pattern Theory (FCPT)**), share the view that families operate as systems with unique patterns and process of communication, often referred to as a family communication climate[150]. These theories suggest that family relational structure facilitate or inhibit the flow of genetic risk information. Dyadic theorists characterize families as a collection of dyads with different relational patterns and levels of interpersonal influence. The **Communal Coping and Interdependence Theory** suggest that family risk communication occurs when inherited risk is perceived to represent a shared threat to specific dyadic relationship[151]. Thus, these theories suggest that interventions to capitalize on the relational communication could be most effective. Whether or not a proband shares inherited risk information with other relatives, rests on individual-level actions. The **Health Belief Model (HBM)**, **Social Cognitive Theory (SCT)**, and **Theory of Planned Behavior (TPB)** have relevance in this context[152–155]. The HBM holds that probands will communicate inherited risk information if they perceive blood relatives to be susceptible to the risk and that the benefits of informing relatives outweigh the barriers. SCT add to this notion of role of probands' confidence and knowledge, suggesting that low confidence to explain patterns of inherited risk and prevention option could inhibit communication flow. TPB emphasizes the importance of holding specific intentions to communicate as being critical to whether probands will communicate with at-risk relatives. Indeed, the theory holds that the more time-specific and goals- specific the communication intention is, the more likely it will be attempted[155]. Interventions aimed to improve communication would be expected to emphasize awareness of family

members' risk (e.g., perceptions that relatives are susceptibility), confidence (e.g., skills-building), and intentions (e.g., specifying how/when communication will occur to communicate[149].

4.1.2 Family communication in clinical practice

Identifying a genetic variant can be very impactful for the patients and for their families or caregivers. Willingness to share results with the family members was common among the population, regardless of result type, suggesting that event though individuals with negative results may feel that this information is not relevant for healthcare provider, it still has perceived value for family members[156]. Information regarding increased vulnerability for various outcomes based on genetic testing is typically provided by geneticists and genetic counselors, going over the results of the genetic testing with adult patients or the caregivers of younger patients. Family communication regarding genetic diagnosis is a complex process. This can be further complicated when genetic diagnosis is inherited from one or both caregivers or reproductive outcomes. There are the communication needs around illness, its management and morbidity, all of which can be stressful. But there is also a concomitant stressor because there is a need for intergenerational communication risks of inherited conditions and the implications this has for children, and their future health and reproductive decision[157]. Caregivers struggle with when and how to disclose this information to ensure a strong self-identity on the one hand, while minimizing potential stress and anxiety related to such disclosure[158]. While open communication appeared to empower families related to facilitate discussions, limited communication patterns may lead to more frustration related to family secrecy. When open communication existed, young people as they matured into adulthood were caution about their reproductive decisions and understood the possibility of genetic testing and its consequent effect on their choices and psychological health. In contrast, poor communication led to reproductive choices based on inaccurate information and emotionally driven decision-making[159]. When parents attempted to protect children by not discussing the genetic condition or the transgenerational risks, children picked up snatches of information but were often confused. Adult offspring recalling their childhood found out information from a variety of sources including television, other children, school, and mailings but this often resulted in

misconceptions. Children were unable to clarify their thoughts or interpretation due to secrecy and many felt obligated to protect their parents from having to answer difficult and emotionally taxing questions. Unaffected children thought health professionals were likely to be a good source of information or support but few had opportunity to access them[160]. In families where there was less open communication, the main concern of siblings if they were to have a child affected by a genetic condition was regarding the potential impact of this on the well-being of their other children[161]. Few studies explored the feelings and emotions involved in discussing genetic risk information for the patients. Adult patients expressed emotion of anxiety and worry to inform their families about the genetic condition. Most patients in all studies reported a complete lack of support or advice from health professionals about discussing genetic conditions with their children. Where health professionals did broach the subject, it was focused on disease management[162]. Children and young people growing up knowing the possible outcomes including their own risk found the information difficult to deal with initially but valued the honesty and openness, because it allowed them to discuss, share experiences and learn to cope with the condition. In families where there was more open communication, children were reported to be more emotionally and psychologically resilient, and were often pragmatic in response to genetic risks for themselves[163]. Guilt, fear, resentment and jealousy emerged as key features of studies, which included the retrospective perspective of now adult siblings. Often these feelings had not been discussed with parents. Several diverse types of guilt were expressed by unaffected siblings based on their feelings and behavior towards their ill sibling including guilt about feeling relieved that they were not affected, and guilt that they could leave the family home on reaching adulthood. Also, siblings of a child affected by a genetic condition often expressed feelings of embarrassment and discomfort. They tried to choose emotionally adept friends but often felt their own peers had insufficient knowledge or experiences to have insight into their feelings and feared being stigmatized if less sensitive individuals found out[164]. In a review, the authors concluded that patients need more help communicating genetic vulnerability to their families since this information can be empowering or threatening depending on this nature[162]. A large body of literature, spreading across several decades, has focused on clinical and personal implications of genetic disease, recognizing the need to support health professionals in encouraging communication and psychological adjustment[165]. According to Koerner et al.[166] in their recognition that family members are participant rather than mere bystanders in the counseling process with the implication that it is not

possible to talk to a person about genetics without talking about family. Understanding family communication is not important for health professionals in supporting disclosure to relatives at risk but the role of family is central for understanding the personal experience of genetic disease and genetic testing. Evidence suggests that sharing genetic test results tends to be limited to close family members[167]. Up to 50% of at-risk relatives are unaware of relevant genetic information, suggesting that the potential benefits of genetic testing are often not communicated effectively within families. Receiving genetic information has implications regarding the duty to warn and protect relatives and has often been linked to the concept of responsibility to share genetic testing results. However, this undertaking is not without potential drawbacks, as the implementation of preventive and risk-reducing measures has also raised question regarding their necessity, efficacy and expediency[168]. Communicating genetic risk to relatives is an intricate process influenced by a various factors, which can act as facilitators or barriers, reported in Figure 21[169–171].

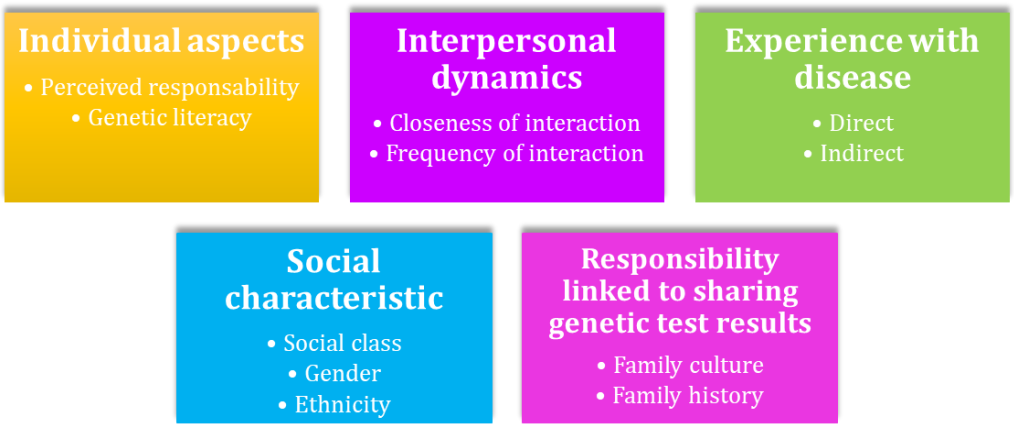


Figure 21 - Facilitators and barriers in genetic communication

Leefmann et al.[172] in a systematic review regarding the concept of genetic responsibility revealed vagueness and multiple meaning among different studies, underlining the rarity of reflection on culture variance. Aceti et al.[167] identified five different modes of responsibility to inform relatives about genetic test results, each one leading to different outcomes. These five modes are to be considered as ideal types.

1 *The Persuader mode* is centered on the belief of the duty of inform for relatives to commit to prevention and management of hereditary risk. The prevention awareness leads individuals who embrace the Persuader mode to accept relatives' right to know to have genetic testing and the chance to engage in risk management. They used a convincing tone and insistent recommendations, especially towards adult children but also towards their parents and more distant relatives. They expressed high levels of responsibility and a strong sense of duty towards relatives.

2 The second mode is *the Enabler mode*. Behind this mode, there was a high sense of duty to break the chain through enhancing relatives' reflection and enlightenment them. In the Enabler mode, individuals embraced the benefits of the right to know and focused on providing enough information so that relatives can make an informed decision, while they also respected private choice linked to sociocultural barriers. Therefore, they also respecting their right not to know. The Enabler mode focused on making relatives sufficiently aware to make an informed decision, and were interested in the process, not necessarily in the outcome of relatives' decision. Genetic information was presented as providing new choices for managing health.

3 *The Relayer mode* was represented by individuals who demonstrated feeling with the need to convey information about the pathogenic variant, without necessarily paying attention to the outcomes of this transmission. Their reasoning embraced the social norms of self-determination for relatives, and they considered relatives as independent actors. The information was transmitted with less emotional implications, sometimes in a more disengaged manner or with lightness and positivity to avoid creating fear, particularly among younger relatives and their own children. This disengaged manner can be generating indifference among relatives.

4 *The Delayer mode* that embraced the social norms of individual or family wellbeing. Choosing to delay the disclosure of genetic information for a good reason was related to their own or the relatives' life trajectory. Delaying the transmission of genetic information was often due to the desire to protect relatives who were in vulnerable periods in their lives or were facing significant life events. The duty to warn was often confronted with perception of bad timing for the disclosure. Some individuals were also seeking relational support to protect the family unit. However, the cost of withholding information is also high for the

Delayer mode, who may often experience loneliness and guilt, secretly carrying the weight of responsibility.

5 *The Decliner mode:* these individuals did not appear to feel a sense of responsibility towards relatives; thus, they were not informing them, at least for the time being. Their reasoning appears to center on their autonomy, conceived as a lack of connection to others or an emotional detachment, rather than the autonomy of relatives. These individuals exercised an autonomous choice regarding not wanting to share genetic information and their reasoning mitigated the senso of accountability. Another reason for omitting the sharing of genetic information was related to gender misconceptions or trivialization related to male transmission. However, participants appeared to make usually a conscious decision not to inform relatives about genetic test results, as they feel there is no need to share this information, and also after considering relatives' characteristics[167].

The five modes of responsibility to disclosure genetic information are dynamic, has multiple layers, is guided by various social norms, is supported by reasoning, and is associated with relational and contextual factors leading to different actions. The disclosure of genetic risk follows a communication chain, which is initiated by healthcare providers, reaches relatives through individuals with a pathogenic variant who had genetic consultation, and is governed by family dynamics and often contradictory logic of actions which compel carriers to engage in complex process[173]. Personal, professional, and/or familial affairs, such as a new partner of family events, appeared to play a significant role in the embraced responsibility mode. Balancing these aspects within one's social network was perceived by some individuals as a good reason to delay or omit disclosing genetic information. Consequently, a holistic approach to assisting with family disclosure of genetic results should also consider social events and life transitions, both of tested individuals and of untested relatives, to grasp how individual decisions for family communication evolve over time. Finally, healthcare providers may benefit from a three-step protocol, described in Figure 22, for discussing family sharing with patients[167].

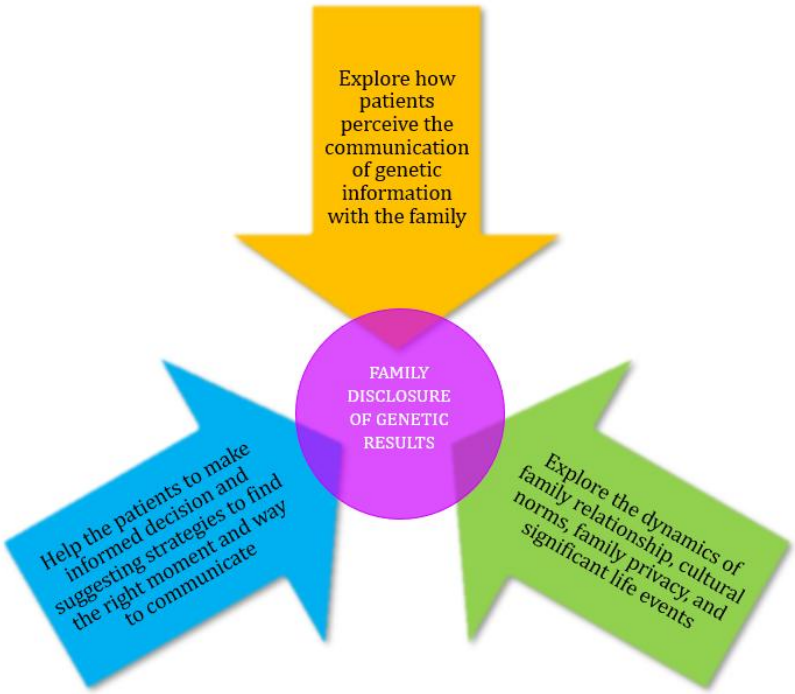


Figure 22 - Three-step protocol for discussing family sharing with patients

In conclusion, the literature considers psychological support necessary in families with genetic conditions and/or risk. Psychological support in genetic context is a broad term that can refer to reading materials (online/booklets), support groups, family organizations, conferences, psycho-education programs, or individual psychological support/psychotherapy. Perlman et al.[156] could not identify any published quantitative study addressing how often these psychological supports are provided to families when they receive genetic diagnosis or information about the risks. In several of the studies reviewed by Perlman et al.[156], families indicated that internet has become a major source of information about both common or rare pathogenic genetic variants[174–176]. Previous studies in various medical fields indicated that such information can be partial, inaccurate, or conflictual with possible lower utilization of internet-based resources in families of lower socioeconomic status[177].

4.2 Risk communication

Effectively communicating health risk information is a challenge across medical disciplines, and there are some challenges that are common to genomics. Common challenges include the need to communicate probability of risk and interact with an individual's behavior or his/her environment[178]. The genetic and environmental combination may lead to varying risks for both rare and common diseases across the population, requiring communicators to convey uncertainty around numerical risk estimates[179]. Traditionally, counseling on the genetic risk was mostly centered around controls and prevention of the illness including: collection of medical and family data, analysis of familiarity, estimation of risk, communication of condition of risk, education to the adoption of measures for control and prevention of disease[180]. If we agree on the importance of a global approach to this problem, psychosocial support, which is often considered a parallel intervention, becomes a component of genetic counseling: the focal point of the intervention becomes the person, and not only the problem, and the purpose becomes not only to resolve a difficult situation but to help people to use their own resources to better cope with situations[181]. Srinivasan et al. [182] in a systematic review identified barriers and facilitators for the risk communication in genetic context (Figure 23).

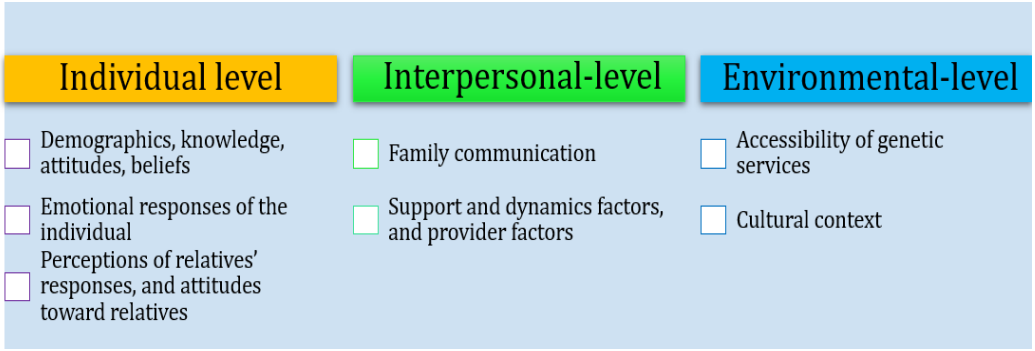


Figure 23 - Barriers and facilitators for the risk communication

Many authors in the fields recommend that psychological support and counseling should occur alongside delivering genetic test results to focus on support issues such as considering risk management options or support for parents sharing genetic results with children[173,183]. In fact, extensive literature indicates that communication of genetic risk at patients and their relatives is a difficult and complex process, compounded by a wide variety of interconnected factors that can act as facilitators or barriers[173]. Additionally,

in relation to cancer genetics patients, for example, the NICE Guidelines in 2013 stated that patients considering risk-reducing surgery should be managed by a multidisciplinary team, including psychological assessment and counseling[184]. Also, psychological support can facilitate family communication and promote better coping and adaptation to living with an inherited genetic condition and/or risk for families. Attentions to psychological needs is therefore key component of satisfaction with genetic counseling services[185].

4.3 Cognitive Behavior Theory and genetic counseling

Clinical psychology and psychotherapy have been major influencer on the profession of genetic counseling although there is a recognition that genetic counselors are not psychotherapeutic practitioners, and there are different ideas about how closely these different careers should be aligned[80]. Austin and colleagues[80] have argued that genetic counseling falls under the umbrella of psychotherapies broadly defined. Psychotherapy is the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable[186]. This describes genetic counseling. The National Society of Genetic Counselors (NSGC) definition of genetic counseling as the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease: this is absolutely compatible with the definition of psychotherapy[68,141]. The Accreditation Council of Genetic Counseling (ACGC) practice-based competencies include: employing active listening and interviewing skills to identify, assess and empathically respond to stated and emerging concerns, using a range of genetic counseling skills and models to facilitate informed decision-making and adaptation to genetic risks or conditions, and promoting patient-centered, informed, non-coercive and value-based decision-making[187]. Core genetic counseling skills are psychotherapeutically oriented. Some reasons for conceptualizing genetic counseling as a type of psychotherapy are the therapeutic alliance, mutual engagement, and interaction. In the desire to help people integrate, process, and use information in a way that helps them and their families, the key role of genetic presides. In choosing a psychotherapeutic approach the counselor need not do so at the expense of genetic information. The integrations of both

is essential to what constitutes genetic counseling[141].
One psychological orientation that supports these counseling goals is **Cognitive Behavior Therapy (CBT)**: the guiding principle is that there are inherent relationship among our thoughts, behaviors and emotions (Figure 24)[188].

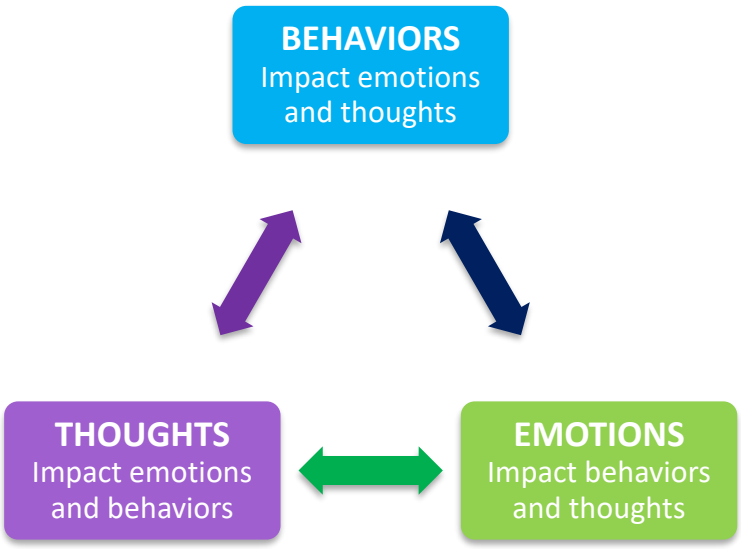


Figure 24 - CBT Diagram

Most CBT-based therapies focus on cognition as the point of intervention, to effect change in emotions and/or behavior. One of the key tasks of a genetic counselor is to provide genetic/scientific information to the patient, and session planning may be driven by what information needs to be provided. But Biesecker et al.[186] purport that the target is not knowledge, just cognition. This is particularly important when considering application of CBT to genetic counseling, with its inherent intertwining of medical education and psychotherapeutic counseling. CBT guides the practitioner to focus not on what patient knows about genetic condition or risk, but what thinks and believes, as it is thoughts that shape emotional experiences. The importance of patient understanding is recognized withing genetic counseling, as shown by a commitment to give people information in ways that can understand and that is relatable to their situation. During genetic counseling are not routinely working to helping people to process information and facilitate cognitive assimilation[189]. One of the key psychological drivers for genetic counseling is the potential for the patient

empowerment[190]. But both the process of becoming empowered and acting with empowerment require cognition[191]. This is acknowledged in the breakdown of what is meant by empowerment within genetic counseling which includes cognitive factors such as knowledge and understanding[190]. Ellington et al.[192] found that while genetic counseling did intervene to promote cognitive processing, it engaged in significantly more facilitation of emotion versus facilitation of cognitive activity statements. So, the biomedical informational dialogue dominates in genetic counseling session. CBT takes cognition as the focus of intervention and the topic of conversation within therapy. Also, CBT is the counseling approach with the most empirical support for neglected cognitive aspects of genetic counseling, for example, adaptation, assimilation, and cognitive restructuring[186]. Therefore, David et al.[193] proposed the adoption of evidence-based system of psychological intervention CBT could be added to the genetic counseling paradigm in helping patients deal with specific difficult life situation and emotional distress associated with them (Figure 25)[147].

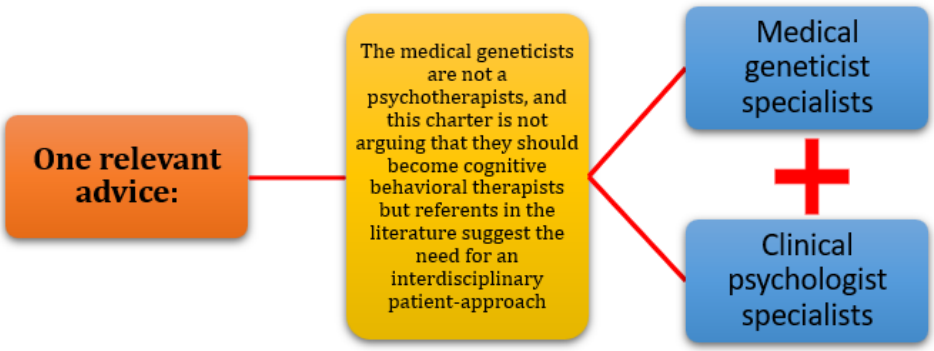


Figure 25 - One relevant advice

4.3.1 Psychoeducational paradigm for genetic counseling

The relevance of psychological understanding in genetic counseling was emphasized by Kallman[194]: he pointed out that a counselor cannot assume that a patient will be realistic about his/her genetic circumstances. The author expressed concerns that pitting intellect against emotion in presentation of genetic information might result in psychological injury and emphasized the importance of genetic counseling in addressing the client's fears, hopes, defenses, and rationalizations to help the client view the situation as it is, rather than as the client might hope that it is. In 1972, Hecht and Holmes[195] reiterated the importance of the mental health component in genetic counseling. Falek[196] also identified genetic counseling goals: to provide the family, in a personalized approach, information about recurrence risks with a long-term goal of facilitating rational decision-making. These goals were accompanied by an acknowledgement of the emotional impact of these issues and the need for genetics health providers to "*deal with them*".

Emery[197] claimed that by 1984 there had been an evolution as "content-oriented" to "person-oriented" genetic counseling. He based his claim on the acknowledgement in the literature that genetic information often has profound psychological effects, which may have long-term consequences that can extend to relatives. He asserted that a qualified genetic counselor had to be aware of the client's fears, hopes, defenses, and rationalizations to help the patient deal in realist manner. A psychological goal of genetic counseling aims to help clients cope with such feelings and adapt to their circumstances[83]. Genetic counseling should strive to achieve the psychoeducational goals of genetic counseling that emphasize assisting clients in their adaptation to genetic risk and/or a genetic condition. Genetic counseling is a dynamic psychoeducational process centered on genetic information. Within a therapeutic relationship established between clinicians and patients, patients are helped to personalize technical and probabilistic genetic information, to promote self-determination, and to enhance their ability to adapt over time. The goal is to facilitate clients' ability to use genetic information in a personally meaningful way that minimizes psychological distress and increases personal control[196].
The primary goals of genetic counseling within this definition resemble those of other psychological counseling interactions:

- promoting understanding,
- achieving informed consent,
- facilitating decision-making,

- reducing psychological distress,
- restoring feelings of personal control,
- advancing adaptation to stress-inducing events[140].

In most cases that present to pediatric or adult genetics clinic, few immediate decisions face the patients. In most of the cases, a family member is already affected with a condition and the patients are seeking to understand the diagnosis, prognosis, and recurrence risks. Genetic counseling thus focuses on understanding, accepting, and adapting to a genetic diagnosis and/or risk, and their impact on the individual and family. Taylor[198] identified three central components to adjusting to health-threatening information or events:

a search for understanding (including search for a cause),

b search for mastery,

c the restoration of self-esteem.

In these ways genetic counseling can facilitate the process of patients adaptation[140].

SCIENTIFIC SECTION
GENETIC COUNSELING AND PSYCOLOGICAL DETERMINANTS

Abridgment

In the Scientific Section reported three studies:

- n. 1 *explorative review*
    - *a)* **Capitol 5** Patient perspective in perceived comparative genetic mutation risk: an exploratory review
- n.2 *original articles*
    - *b)* **Capitol 6** BRCA genetic result disclosure for women with breast cancer: influence of +/- predisposition genetic mutation (IRB/UNIVAQ ID 123775/2020)
    - *c)* **Capitol 7** Perceived cancer risk and genetic counselling: a biopsychological perspective to boost lifestyle medicine (IRB/UNIVAQ ID 47/2022)

The objectives of the explorative study were to review the literature on genetic risk management, whereas the original articles wanted to examine the psychological impact of BRCA genetic result post-disclosure, the emotional health of patients and the role of cancer worry in the psychological dimensions of patients undergoing genetic testing.
The aim of Scientific Section was to highlight the relevance of setting based on a patient-centered approach, tailoring clinical practice on the integration of physical, mental, and social factors to patients' and relatives' wellbeing, to enhance healthcare and patient lives. We wanted to investigate the genetic counseling impact in the disclosure toward to health management and Quality of Life of patients.

CHAPTER 5. PATIENT PERSPECTIVE IN PERCEIVED COMPARATIVE GENETIC MUTATION RISK: AN EXPLORATORY REVIEW[1]

5.1 Introduction

Genetic predispositions for disease represent a complex medical setting pointing out wide human outcomes[199,200]. In a clinical setting, genetic risk information is based on scientific evidence about the nature of individuals' genetic conditions[201], and the genetic counselling assists patients in understanding the genetic ethology of disease, assessing risk for genetic disease, and providing support to those who are encountering a genetic disorder in themselves or family member[202]. More, genetic counselling is the process by which patients or relatives at risk of developing a disorder with a potential hereditary component are advised of the consequences of the disorder, the probability of developing or transmitting it, and the ways in which the risk may be prevented, avoided, or ameliorated. Genetic counselling is based on medical process oriented to 3 factors[203] as reported into Figure 26. According to that, genetic counselling could represent a fundamental for quality of life of patients understanding the

[1] Cilli E, Guerra F, Ranieri J, Brancati F, Di Giacomo D. Patient perspective in perceived comparative genetic mutation risk: An exploratory review. Clin Genet. 2024 Feb 10. doi: 10.1111/cge.14489IF: 3.5 Q2. Epub ahead of print. PMID: 38339844

nature of diagnosticated disease or the risk for developing of hereditary diseases [83]. However, it is well known that individuals have difficulties in understanding and making sense of this information in their own lives. When working with any group of patients in a healthcare setting, the psychological needs of the patients must be considered as a part of the total package of care for that individual. When the patient is facing genetic issues, the situation may be more complex because of the effect of the condition on more than one family member, through many generations.

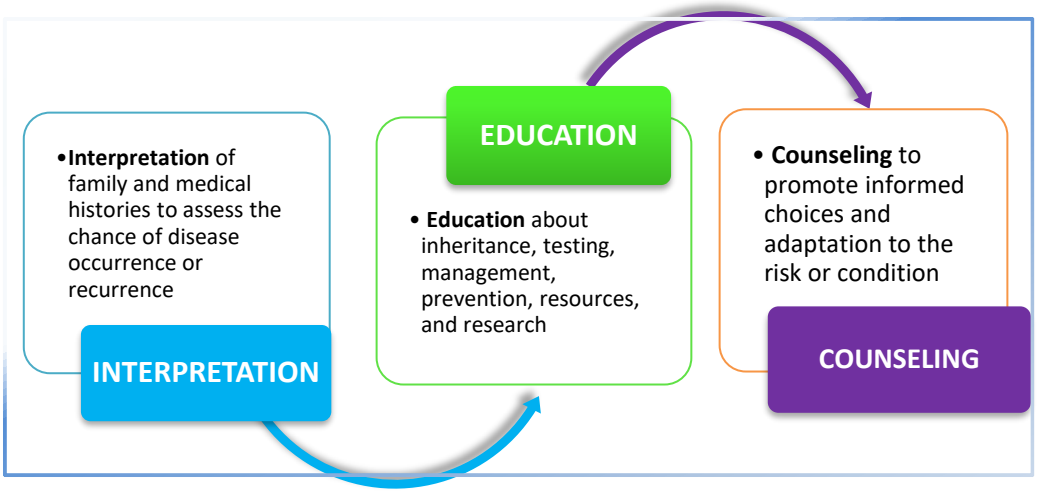


Figure 26 - Medical process for clinical information for the patient

There may be guilt at having passed a condition onto the children, blame toward sections of the family, or secrecy to try to hide the condition. Because being affected or at risk of a genetic condition cause grief in many forms, clients may be in a state of perpetual mourning. For patients who experience this type of psychological pressure, counselling may provide an outlet for emotions that are hidden from the family[12]. Person-centred counselling was develop through the work of Carl Rogers[204], based on his belief that each person has the ability to solve their own problems and work through difficult situations using their own resources, providing that they have support from another person. The person-centred counsellor is not “an expert”, who can solve the patient’s problems, but rather a supporter whose role is to reinforce the patient’s self-belief and enable the patient to explore the situation in a safe emotional environment.

The relationship the patient develops with the genetic counsellor is of importance to the therapeutic work. In providing an environment where the

individual feels valued and is encouraged to express the feelings. Genetic counsellor, therefore, need to be fully in command of the psychological impact of their communication. An in-depth understanding of empathy enables the counsellor to help the individual contain anxiety and process grief, and so facilitate decision-making or help with the effects of having a test result[205]. Accordingly, the emerging need for medical setting as well for patient outcomes is to investigate whether any methodologies in psychological research may shed light on how individuals perceive genetic risk information within their specific contexts of family history, personal relationships, lifestyles, and future. Some studies have been conducted regarding the psychological outcome of genetic counselling: we wanted to deal with the topic examining the methods and results of protocol research and, trying to draw the patient perspective for future research to figure out efficient psychological strategies in genetic counselling.

5.2 Review study

We conducted an explorative review to map literature about the impact of genetic counselling in patient perspective. The framework outlined by Arksey and O'Malley [206] in their methodological paper was adopted. Aim of the review was to investigate the impact of genetic counselling on involved individuals conducting an explorative review on scientific literature (Figure 27).

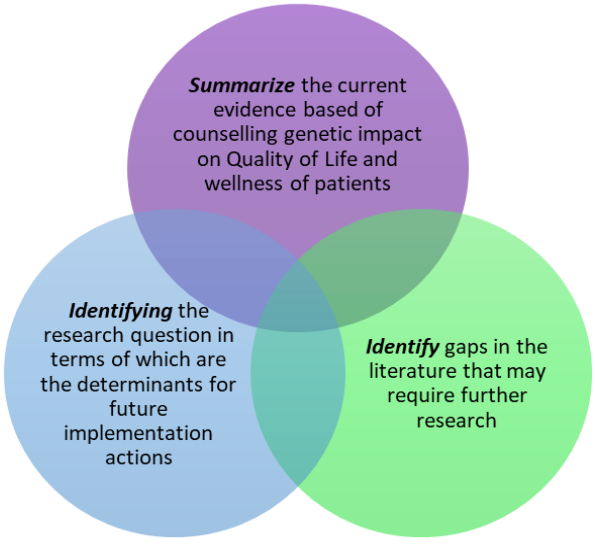


Figure 27 - The research objectives

5.2.1 Search strategy

We performed a systematic search of MEDLINE via PubMed and Web of Science in August 2023 with the terms 'genetic counselling' and 'psychological screening' or 'psychological outcomes' or 'psychological interventions' published from May 2012 to August 2023 (Table 2).

Table 2 - Data extraction procedure

FIRST EXTRACTION	
1° Keyword: "Genetic Counseling" and "Psychological Screening"	
via PUBMED	15
via WEB OF SCIENCE	50
TOT	65
Records Duplicate removed	4
Records excluded, with reason: **- Protocol study.** **- No free-full text.**	24
1° keyword included	***37***
2° Keyword: *"Genetic Counseling"* and *"Psychological Outcome"*	
via PUBMED	36
via WEB OF SCIENCE	85
TOT	121
Records Duplicate removed	5
Records excluded, with reason: **- Protocol study.** **- No free-full text.**	31
2° keyword included	***85***
3° Keyword: *"Genetic Counseling"* and *"Psychological Interventions"*	
via PUBMED	28
via WEB OF SCIENCE	36
TOT	64
Records Duplicate removed	2
Records excluded, with reason: **- Protocol study.** **- No free-full text.**	20
3° keyword included	**42**
TOTAL RECORD INCLUDED	***164***
SECOND EXTRACTION	
Duplicate removed	15
Record excluded, with reason: **- Protocol study.** **- Qualitative study design.** **- No psychological topic.** **- No genetic testing.**	147
RECORD INCLUDED	***17***

5.2.2 Inclusion and exclusion criteria

To be considered eligible, titles and abstracts of retrieved studies had to refer to patients with diagnosis of disease related to genetic mutation. Inclusion and exclusion criteria were reported in Figure 28.

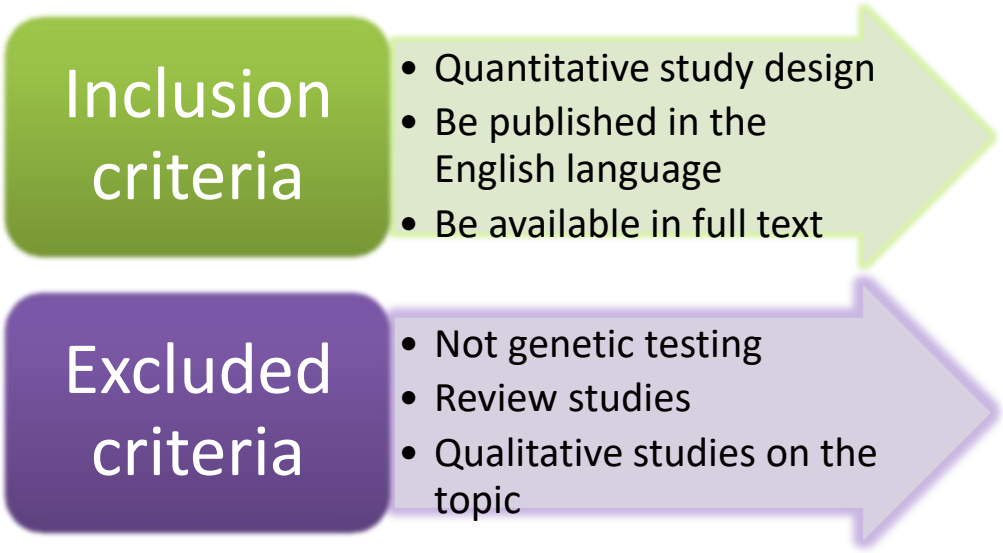


Figure 28 - Inclusion and exclusion criteria

5.2.3 Article selection and data extraction procedure

Two reviewers screened all titles, abstracts, and full texts independently and solved disagreements by consensus or consultation with a third reviewer. Then the following information was extracted from each paper:

a general information: authors, publication year, and country;
b study characteristic: study design, sample size, statistical analysis, range age, diagnosis of disease, and genetic test;
c data related to the research question of the review: study aim, psychological testing time, psychological measures, and outcomes (Figure 29).

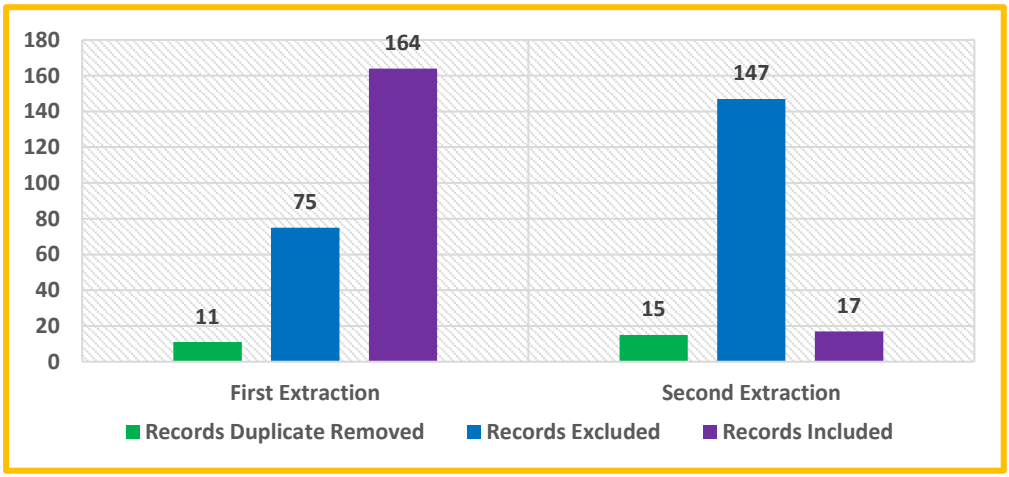


Figure 29 - Data extraction procedure

5.2.4 Data analysis

We conducted a descriptive analysis of the characteristics of the included literature. We described the source where we found the article, publication year, study design, and topic of article/study on psychological testing time, psychological measures, and outcomes to improve the empowerment of people undergoing genetic counselling and/or genetic testing, to examine existing research gaps. We categorized the literature into clinical studies, including randomized controlled trials and observational studies. We conducted this exploring review in accordance with the PRISMA flowchart [207].

5.3 Results

The literature search of PubMed and Web of Science provided a total of n. 250 papers. After removing duplicates (n. 26), n. 224 references were identified for screening. Based on the inclusion/exclusion criteria, two reviewers screened for eligibility all titles and abstract and successfully resolved disagreements by consensus. N. 17 full text were assessed for eligibility and n. 207 articles were excluded and reasons for exclusion were: a) protocol study; b) qualitative study design; c) no psychological topic; d)

no genetic testing; e) no free full text. Figure 30 shows all details about the studies search and selection process. Finally, sixteen studies were included.

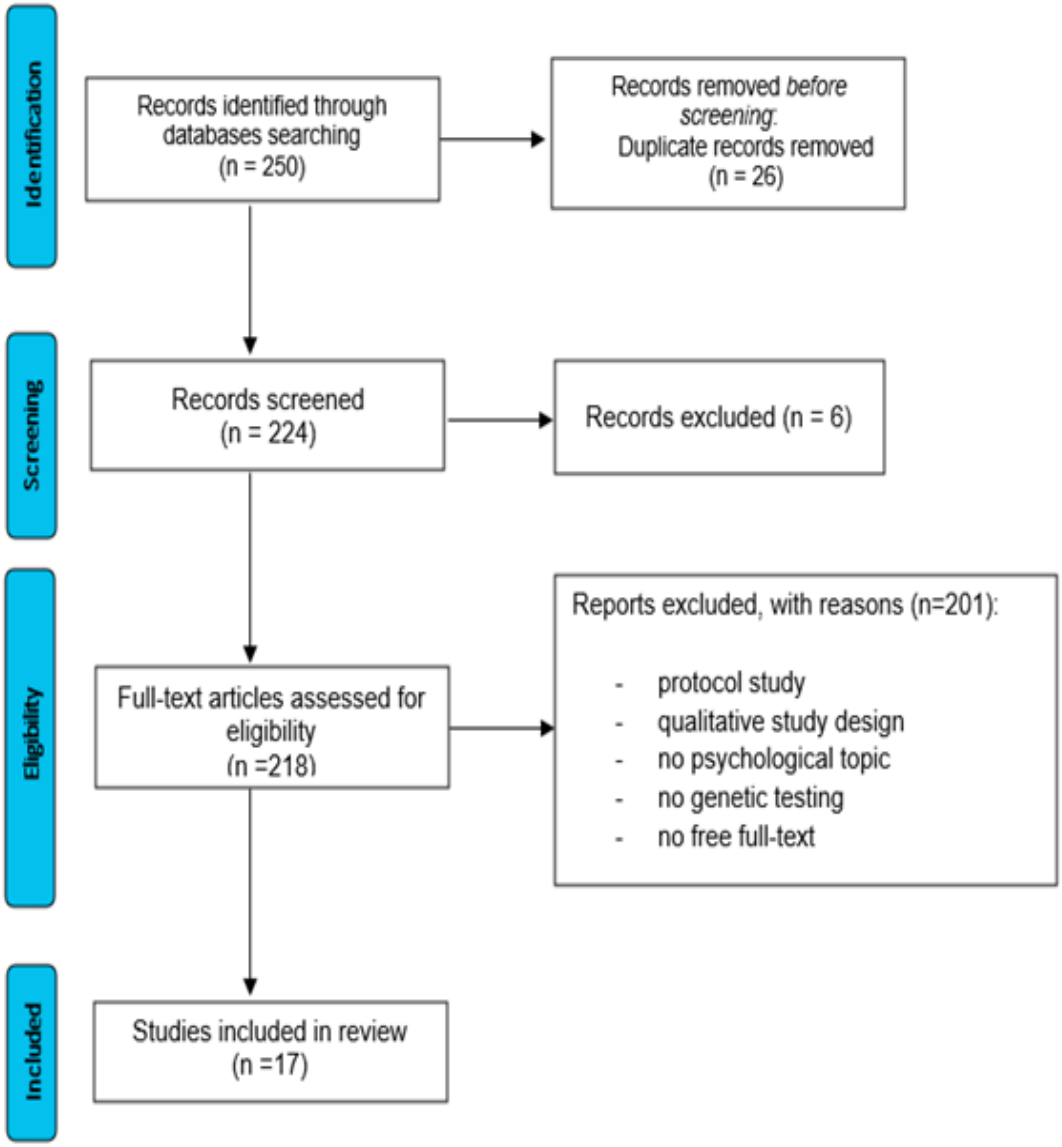


Figure 30 *- PRISMA Flowchart of selection process for the exploring review.*

5.3.1 Characteristics of included articles

Articles included in the study were n. 2 randomized controlled trials (RCT), and n. 15 observational study (OB). Summarizing general information about the publisher of the included studies, we identified for each included paper: a) source title; b) subject area; c) first author's country; and d) publication year. All papers were published in peer-reviewed journals from 2012 to

2023. Concerning publication year, the research interest was growing along years. The journal's subject area (SJR Ranking) with the highest number of published studies were on Journal 'Genetics in Medicine' by n.3 papers (17%): this platform was focusing on enhance the knowledge, understanding, and practice of medical genetics and genomic through publications in clinical and laboratory genetic and genomics, including ethical, legal, and social issues as well as public health; then, the 'Journal of Genetic Counseling' published n.3 papers (17%), focusing on the critical questions that arise at the interface between rapidly advancing technological developments and the concerns of individuals and communities at genetic risk. Others journal platforms were Alzheimer Research & Therapy (6%); Annals of Surgical Oncology (6%); Cancer (6%); Cancer Epidemiology, Biomarkers & Prevention (6%); European Journal of Paediatric Neurology (6%); JGH Open (6%); Journal of Community Genetics (6%); Acta Oncologica (6%); Public Health Genomics (6%).

5.3.2 Type of article

As reported in Figure 31, Platforms of screened publications are focused on medical genetics (29%), oncology (24%), genetic counselling (18%), and psycho-oncology topics (11%).

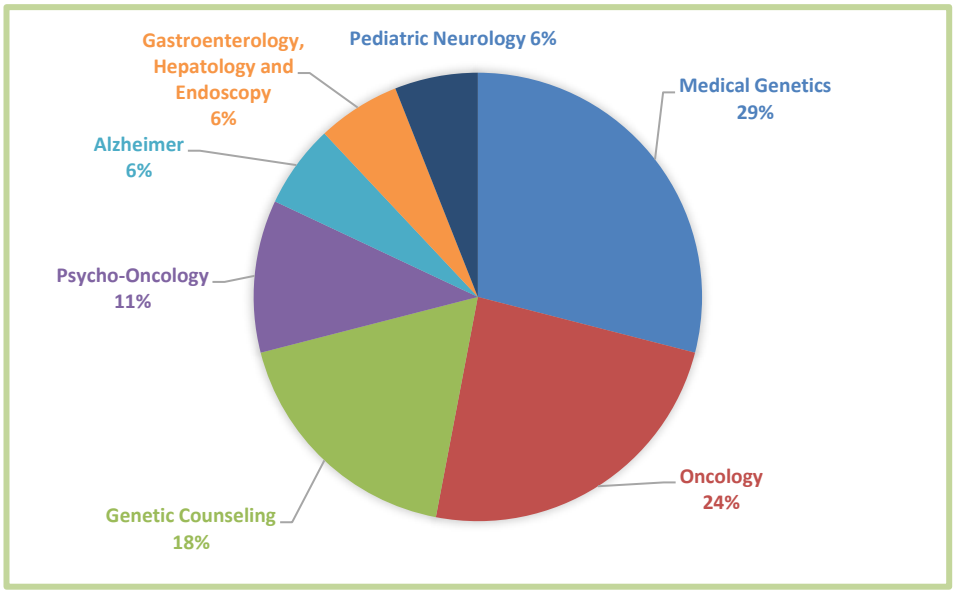


Figure 31 - Subject Area (source: SJR Ranking https://www.scimagojr.com)

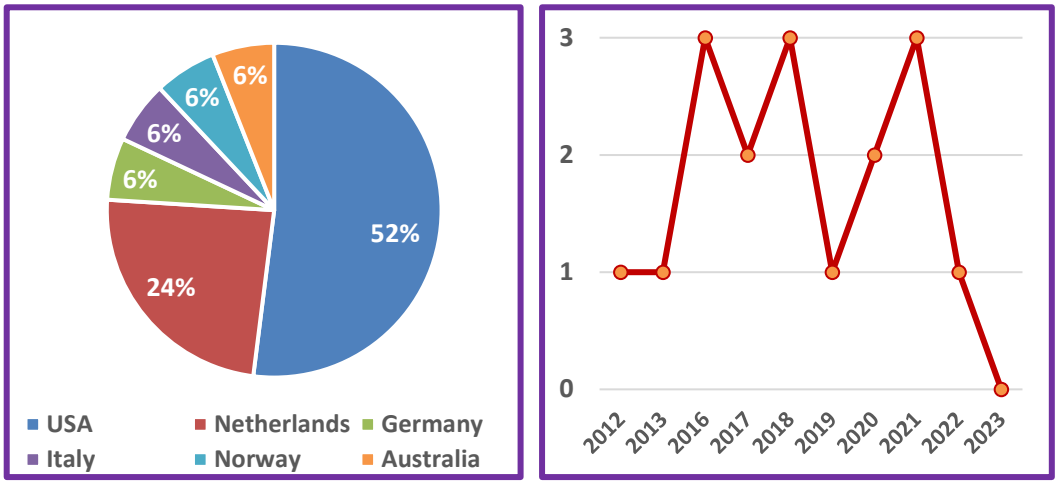


Figure 32 - First Author's Country and publication year from May 2012 to August 2023

First author countries were Americans (53%) and Dutch (23%) showing consolidated research interest even the is not increasing progressively over the time (Figure 32).

General interest was focused on the psychological distress and perceived mutation-risk; then, more relevant emerged research topic was the psychological impact of genetic testing for BRCA1/2 (41%). In Table 3 screened scientific papers have been reported highlighting the details of n.17 research protocol distributed by observational (OB) and randomized control trial (RCT) study designs. Firstly, OB and RCT studies have been conducted mostly in monocentric study.

Table 3 - Details of examined experimental studies

STUDY DESIGN	AUTHORS	SAMPLE SIZE	TARGET SAMPLE (Gender, range age)	GENETIC TEST	PSYCHOLOGICAL MEASURES	STATISTICAL ANALYSIS	OUTCOMES
	Christie et al. (2012)	114	Women, range age 24-69	BRCA1/2	IES	Descriptive analysis. Wilcoxon rank-sum tests	Results showed significant decreases in overall cancer-related distress and intrusive thoughts from pre- to post- genetic counseling.
	Vos et al. (2013)	248	Women, range age 21-26	BRCA1/2	HADs, CSW, IES, IPQ	Descriptive analysis. Multiple regressive analysis. Wilcoxon rank-sum tests. Fisher exact tests.	Before the genetic testing, 27% of all counselees reported a request for psychological help. After results disclosure, 20% needed to receive psychological help. The "worry" correlated moderately/strongly with the request for psychological help.
OB	Voorwinden et al. (2015)	165	154 females, and 11 males, mean age 47.00 (DS: 13,1)	Lynch Syndrome	PPC, GHQ-12, CSW	Descriptive analysis. Multiple regression analysis	Counselees with an unfavorable outcome didn't have more emotional distress but showed significantly more cancer worries. Prognostic factors for cancer worry after genetic testing were pre-existing cancer worries, being single, a high-risk perception of getting cancer testing, and an unfavorable test result. Emotional distress was best predicted by pre-existing cancer worries and pre-existing emotional distress.
	Bradbury et al. (2016)	49	47 female and 2 male, range age 36-68	Cancer multiplex testing	STAI, IES	Descriptive analysis.	Anxiety, depression, uncertainty, and cancer worry didn't significantly increase with multiplex testing

Lumish et al. (2017)	232	Women, age range 21-88	BRCA1/2	IES, MICRA	Descriptive analysis. Regression analysis	Unaffected individuals with a family history of breast or ovarian cancer who received positive results were most significantly impacted by intrusive thoughts, avoidance, and distress. Also modestly elevated among unaffected patients with a family history of breast or ovarian cancer who received variants of uncertain significance (VUS).
Zhu et al. (2018)	63	41 female and 22 male, age range 28-90	CDKN2A	GSRH, MICRA	Fisher exact tests. Welch's t tests. Mixed-design ANOVAs	Both carriers and non-carriers showed no change over time in self-rated health, quality of life, or anxiety levels. Carriers experienced greater test-specific distress and uncertainty than noncarriers, but levels were low
Broady et al. (2018)	2037	Women, age range 19-85	Mixed	STAI, IES	Descriptive analysis. Fisher's exact tests. Regression analysis	Younger age emerged as a predictor. Family history and personal history were only significant predictors for Alzheimer's disease in the participant.
Stump et al. (2018)	18	10 male and 8 female, range age 10-15	CDKN2A/*p16*	CDI-2, STAI-CH	Descriptive analysis. ANOVA. Fisher's exact tests. Wilcoxon rank-sum tests	Anxiety symptoms remained low post-disclosure, while depressive symptoms and cancer worry decreased.
Hoberg-Vetti et al. (2018)	309	Women, mean age 56.1 (SD: 11.5)	BRCA1/2	IES, ISEL	Descriptive analysis, Wilcoxon rank-sum tests. Regression analysis.	Women having genetic testing shortly after a diagnosis of breast or ovarian cancer had a moderate mean level of cancer-related distress, which decrease with the time. Younger age, shorter time since diagnosis, lower less of social support, and a diagnosis of ovarian cancer predicted higher levels of both intrusion and avoidance.
Efthymiou et al. (2020)	122	61 male and 61 female, mean age 55.8 (SD: 10.5)	Pancreatic cancer	IES, PCQ	Descriptive analysis. Wilcoxon rank-sum tests	The questionnaire results showed that the screening/genetic counseling had no effect in mitigation or worsening psychological symptoms overall but did improve the psychological symptoms for the female subgroup.

Mega et al. (2020)	31	26 females and 5 males, mean age 66.0 (SD: 12.8)	Alzheimer's disease (AD) and frontotemporal dementia (FTD)	BDI, HDRS, STAI, 12-item short form Health Survey, Brief-COPE, WHOQOL, RSA, HLC, BFQ	Descriptive analysis	Affected individuals with moderate-severe cognitive impairment had major depressive disorder, psychiatric hospitalization, or suicide attempt.
Culver et al. (2020)	1264	1009 females and 255 males (age range 17-92)	Cancer panel testing	MICRA	Descriptive analysis, Regression analysis	Participants carrying a high- or moderate-risk had significantly higher uncertainty, distress, and total MICRA scores and significantly fewer positive experiences than participants with negative result.
Vlaskamp et al. (2021)	63	55 were a parent (age range 29-66) and 8 were a patient (age range 21-42)	Epilepsy	GCOS-18, STAI	Descriptive analysis. Fisher's exact tests. ANOVA.	Empowerment was increased after pre-test counseling compared to baseline, and a further increase was seen after post-test counseling compared to after pre-test counseling. the mean anxiety score during the genetic counseling trajectory, but the effect size was small, and the differences were not statistically significant.
Talati et al. (2021)	115	Women, mean age 31(IQR: 27.34)	Prenatal trio exome sequencing (trio-ES)	HADs, MICRA, PAGIS	Descriptive analysis. Wilcoxon rank-sum tests. Kruskal-Wallis test. Spearman's correlation. Linear regression.	Women who received positive results had greater post-sequencing distress compared with women who receive negative results, including generalized distress and test-related distress. They also had worse psychological adaptation to results.
Isselhard et al. (2022)	125	Woman, range age 19-72	BRCA 1/2	HADs, FPI-R	Descriptive analysis. Regression analysis. ANOVA.	Participants were found to have higher anxiety levels than general female population regardless of mastectomy decision. Breast cancer worry was higher among woman opted for risk-reducing mastectomy and did not decrease over time. Woman who did not opt for surgery experienced decreasing levels of breast cancer worry. Woman with a pathogenic variant BRCA1, younger woman and woman with higher breast cancer worry were more likely to opt for surgery.

RCT	Wevers et al. (2016)	265	Women, range age 19-79	BRCA1/2	IES, HADS, CSW, EORTC QLQ-C30	Descriptive analysis	Significant change over time in almost all psychological measures, except cognitive function, insomnia, and diarrhea
	Steffen et al. (2017)	781	Women, mean age 56.6 (SD:7.7)	BRCA1/2	IES, PPC, BSI, 12-item SF-12v2 Health Survey, ISEL	Multiple regression analysis	Women without cost barriers had higher testing uptake. Psychological distress and perceived comparative mutation risk moderated the effect of counseling and testing. Uptake between in-person counseling versus telephone counseling didn't differ at low levels of distress and risk but differed at high distress and high perceived comparative risk.

Abbreviation of study design*: OB: Observational study; RCT: randomized clinical trial.*
Abbreviation of psychological measures*: General Health Questionnaire (GHQ-12); Quality of Life (EORTC-Q30); Cancer Worry Scale (CSW); Impact of Event Scale (IES); Hospital Anxiety and Depression Scale (HADs); Illness Perception Questionnaire (IPQ); Quality of life (Short Form-12 SF-12); State-Trait Anxiety (STAI); The Perceived Personal Control (PPC); Brief Symptom Inventory (BSI); Multidimensional Impact of Cancer Risk Assessment (MICRA); General Self-Rated Health (GSRH); Children's Depression Inventory-2 (CDI); State Trait Anxiety Inventory-Children (STAI-CH); Interpersonal Support Evaluation List (ISEL); Personal Consequences Questionnaire (PCQ); Beck Depression Inventory (BDI); Hamilton Depression Rating Scale (HDRS); Coping Orientation to Problems Experienced Inventory (Brief-COPE); Resilience Scale for Adults (RSA); Multidimensional Health Locus of Control scale (HLC); Big Five Questionnaire (BFQ); Genetic Counseling Outcome Scale (GCOS-18); Psychological Adaptation to Genetic Information Scale (PAGIS); Freiburg Personality Inventory (FPI-R); World Health Organization Quality of Life-short version (WHOQOL)*

Considering the RCT studies, our review included n. 2 RCT (12%): both researches were focused on psychosocial dimensions in patients exposed to high risk for HBOC mutation. Finding highlighted no stress and worry dimensions comparing patient groups featured by high/low risk for HBOC mutation. More, in test-retest study (range time of 12 months), the perceived stress dimension was moderated by the genetic counseling. Considering the observational studies, the 71% of them[208–217,139,218] investigated the emotional variables in patients affected by various cancer diagnosis (BRCA1/2, CDKN2A, pancreatic cancer, Lynch syndrome), and asking for genetic counselling. Research protocols had based on pre-, post- and follow-up genetic counselling sessions and outcome of psychological evaluations showed no sever psychopathological symptoms. High stress, psychological distress and worries are relevant in patients with high risk for genetic mutation. In fact, avoidance, psychological distress, and intrusive thoughts emerged related to the cancer diagnosis. More, predictive behaviors for mental discomfort appeared: family history for disease, youthful age, short time from the cancer diagnosis, low social support, high risk self-perception for life. The emotional traits of BRCA1/2 mutation patients having family/personal history of cancer have been investigated in n.5 observational studies[139,210–213,215–217]: no study evidenced significant signs of anxiety, depression and stress in pre- and post- genetic counselling. However, Christie's et al.[210] showed a reduced intrusive thought cancer-related in result disclosure. Then, Culver et al.[211] evaluated the psychosocial outcome in patients asking for genetic counselling for more common cancer diagnosis: high stress, distress and worries cancer-related in patients categorized high risk for cancer than moderate-low risk. Mental impact in pancreatic cancer dealt with in Efthymiou's study evidencing emotional differences during genetic counselling[212]. Screening protocols did not detect psychological benefits in brief time, whereas female patients showed a positive mental outcome having genetic counselling. CDKN2A genetic test for melanoma risk cancer and emotional impact have been investigated in n. 2 observational studies (12%)[216,218]. Both studies detected no distress, depressive signs and worries in test-retest genetic counselling. Last, prognostic factors for psychological discomfort after Lynch syndrome have been investigated in Voorwinden's study[217]: it evidenced no mental disorder differences between patients with positive/negative genetic counselling outcome; however, patients with mutation outcome showed higher level of worries for cancer. Voorwinden's et al.[217] highlighted that the pre-existing emotional distress is predictive factor, whereas the pre-existing worries could be considered the prognostic factor.

Other studies focused on the mental disorders undergoing genetic counselling in pre-, post- and follow-up sessions. Broady et al.[209] investigated the emotional dimensions in complex genetic disease as well cardiovascular disease, HBOC cancer, lump cancer, colon cancer, melanoma, Alzheimer disease, multiple sclerosis, lupus, Crohn disease, thyroid disease, glaucoma, type 2 diabetes. Findings highlighted the family/personal history for disease might considered a predictive factor for genetic diagnosis. Mega et al.[219] evidenced as emotional stability and motivation determined the desire to learn the outcome for genetic counselling in Alzheimer disease and front-temporal dementia. Vlaskamp et al.[220], evaluated psychological dimensions as the empowerment and anxiety-related genetic diagnosis of epilepsy. The study evidenced the enhanced empowerment in patients after genetic counselling. Last, Talati et al.[221] elaborated the maternal psychological impact of Prenatal trio exome sequencing (trio-ES) to detect the fetal pathogenic variants. Authors showed anxiety in pre genetic testing session and the influence of emotions in decision making process. However, the screened reviews showed the interest in genetic counselling over time dealing with the mental health interplay to analyses the magnitude of impact on mental health in chronic disease condition.

Considering the mental health assessment, as reported in Table 2, the examined studies applied psychological testing based on screening self-report tools. The testing applied could be categorized into three groups of evaluating instruments: a) emotional dimensions, b) quality of life indexes and c) genetic impact measures. Taking into account the emotional dimensions, the applied tests were: General Health Questionnaire (GHQ-12)[222], Hospital Anxiety and Depression Scale (HADs)[223], Illness Perception Questionnaire (IPQ)[224], State-Trait Anxiety (STAI)[225], The Perceived Personal Control (PPC)[226], Brief Symptom Inventory (BSI)[227], Children's Depression Inventory-2 (CDI)[228], State Trait Anxiety Inventory-Children (STAI-CH)[229], Interpersonal Support Evaluation List (ISEL)[230], Personal Consequences Questionnaire (PCQ)[231], Beck Depression Inventory (BDI)[232], Hamilton Depression Rating Scale (HDRS)[233], 12-item short from Health Survey[234], Coping Orientation to Problems Experienced Inventory (Brief-COPE)[235], World Health Organization Quality of Life-short version (WHOQOL)[236], Resilience Scale for Adults (RSA)[237], Big Five Questionnaire (BFQ)[238], Freiburg Personality Inventory (FPI-R)[239]; the common feature of above psychological testing is being brief self-report useful for mental screening. Regarding the measurement for quality of life indexes the applied testing were composed of: Quality of Life (EORTC-Q30)[240], Cancer Worry Scale (CSW)[241], Impact of Event Scale (IES)[242], Quality of life (Short Form-12 SF-

12)[243], Multidimensional Impact of Cancer Risk Assessment (MICRA)[244], General Self-Rated Health (GSRH)[245], Life Orientation Test – Revised (LOT-R) scale[246]; common features of them were the general evaluation of quality of life indexes. Last, genetic impact measures applied in the reviewed studies have been: Genetic Counseling Outcome Scale (GCOS-18)[247], Psychological Adaptation to Genetic Information Scale (PAGIS)[248]; the analysis of psychological measurement of genetic disease risk highlighted the reduced applying of tailored testing for mental health and the impact of genetic consultation disclosure on quality of life. According to the above testing, comparing the three categories of measurements seemed to intensively deal with mostly independent psychological factors than specific psychological variables related to genetic disease risk for mental health. Scientific and related clinical efforts should be toward to point out tailored psychological testing to process the individual factors impacting the genetic disease.

5.4 Outcome and perspective

Current literature regarding the mental health impact of genetic counselling for Quality of Life and wellness of non-communicable chronic diseases appeared increasing over the time; the strengthens of examined studies was the person-centered approach dealing with the emotional dimensions that should be managed during the consultations. Genetic counselling appeared fundamental to understand the risk related to own disease factors as the management of healthy/unhealthy behaviors related to perceived risk, the family history, personal relationships, lifestyles and then compliance to medical recommendations appeared for relevant indexes to outcome analyze the genetic impact. The complexity of clinics and from daily diagnostic and treatment practices to the everyday experience of those living with the risk of disease might be addressed in counselling setting to favoring improved Quality of Life in genetic risk increasing the mental adaptation to tailored chronic condition. Our finding highlighted the need to enhance the clinical indexes in genetic counselling to improve the patient-centered approach on the efficacy of health management and monitoring. According to that, the empowering of communication of genetic risk information should be the part of a general trend towards to more personalized medicine based on active behavior and awareness behaviors for patient perspective. Future Research Program should be addressed to improve all evidence-based outcome in the integration of biomarkers and psychological dimensions towards to genetic counselling protocol structured on

personalized medicine by tailored patient-centered approach: reviewed literature showed the increasing of interest to this topic over the time. However, the investigations should be addressed on tailored psychological evaluations exploring ever standardized tests, and not only self-report assessment. Future research protocols should be addressed to identify the individual factors as well personality and emotional regulation and then the communication field to enhance and boost healthy behaviors plotting counselling genetic setting by tailored patient-centered approach.

CHAPTER 6. BRCA GENETIC RESULT DISCLOSURE FOR WOMEN WITH BREAST CANCER: INFLUENCE OF +/- PREDISPOSITION GENETIC MUTATION[2]

6.1 Introduction

Pathogenic germline variants in Breast Cancer, named BRCA, are inherited in an autosomal dominant manner and underlie hereditary Breast and Ovarian Cancer (HBOC) syndrome[249]. Due to the relevance of pathogenic in medical management of patients, genetic testing has become integral to the care of cancer patients to tailor the surgical management[250], pharmacological treatment, and survivorship monitoring[251]. As the genetic information disclosed in BRCA1/2 genetic testing is about probabilities and not certainties, complex distress issues may arise. Confirmation of carrier status is described by many women as overwhelming and, indeed, constitutes a life-changing event. Previous studies showed that women might experience short and long-term distress after the disclosure for their predisposition for BRCA1 or BRCA2 mutation[252]. Though distress often decreases over time, women evidenced high levels of distress in the long-term[253–255].

[2]Ranieri, J., Guerra, F., Cilli, E., Brancati, F., Di Giacomo, D. (2023). BRCA genetic result disclosure for women with Breast Cancer: influence of +/- predisposition genetic mutation. Mediterranean Journal of Clinical Psychology 11(2). https://doi.org/10.13129/2282-1619/mjcp-3805

Defense mechanisms of suppression, repression, dissociation, displacement, and omnipotence moderated cancer diagnosis, suggesting that a repressive and apparently self-confident defensive functioning is characteristic of people who developed malignant tumors: higher use of neurotic defenses and lower use of obsessional defenses characterized cancer patients, indicating a specific defensive profile of cancer[256]. Relevant factor could influence over the time the emotional regulation dealing with the cancer experience: dispositional optimism appears to be an important factor in terms of how cancer patients perceive and experience their illness and adjust to the treatment process[257]: self-efficacy in maintaining activity and independence domain might favor the dispositional optimism toward to the indirect effect on physical well-being and depressive symptoms associated with medical condition[258,259]. Specifically, optimistic patients felt more self-efficacious in maintaining their daily activities and independence, favoring the increasing of physical well-being and simultaneously to decreasing depression signs[257]. More, fighting spirit for adjusting to cancer could make to perceive higher social support levels[260]. The perceptions of the efficacy of a physical rehabilitation course after surgery by organizational aspects of the structure and aspects of emotional attention as well as the professional competence could contribute to the perceptions of well-being, efficacy of, and satisfaction with a physiotherapy treatment in cancer rehabilitation[261]. More, studies highlighted that genetic testing could be associated with psychological benefits in negative disclosure and has no substantial adverse psychological consequences for positive disclosure[252,18]. Predictive factors for psychological well-being influence after genetic testing results might be having young children[262,263], having lost a relative due to breast/ovarian cancer, doubting of the validity of the result and having a high level of cancer risk perception, but being BRCA1/2carrier was not[264,265]. Considering the scenario, the topic still needs to be investigated as the literature on the emotional impact of BRCA test results did not provide solid conclusions. Even few, studies highlighted the genetic testing could not be considered stressing event for Breast Cancer women affecting their Quality of Life[266]. Moreover, limitations of several studies about the psychological impact of BRCA genetic counseling are related to experimental design issues as heterogeneous samples based on BRCA1/2 mutation with and without personal history of cancer, using not specific instruments, general well-being scales, non-standardized measures; results should be interpreted with caution, and they cannot be generalized to this clinical population. Albeit the genetic testing/counseling is increasing progressively in oncological clinical practice, psychological impact of BRCA genetic testing has been an under-researched area in oncological population; few studies have examined a wide

range of possible predictive individual factors for psychological adaptation after genetic testing for hereditary cancer[217].

Aim of the study was to examine the implication of clinical psychological in BRCA genetic result post-disclosure dealing with the emotional health of patients undergoing genetic testing depending to the personal resources.

6.2 Materials and Methods

6.2.1 Ethics Statement

The study has been approved by the Institutional Review Board (IRB) of the University of L'Aquila, Italy (Prot. No. 123775/2020). Informed consent was obtained from each participant, and the study adhered to the guidelines outlined in the Declaration of Helsinki[267].

6.2.2 Sample

Participants were composed of n = 32 female patients in range age 30 - 55 years, who have a BC diagnosis and who underwent BRCA mutation testing. Eligible participants were approached to be enrolled in the study at the Medical Oncology Division (Director Prof. E. Ricevuto) of S. Salvatore Hospital ASL1 Abruzzo in L'Aquila (Italy). We contacted 38 eligible patients, of whom 32 provided written informed consent.

The participants were divided into two groups based on BRCA mutation testing result: the BRCA+ group, composed of 16 patients who tested positive for a fault (mutation) on 1 of the BRCA genes (BRCA1 or BRCA2), and the BRCA- group, composed of 16 patients who tested negative for a fault (mutation) on BRCA genes (BRCA1 and BRCA2). Table 4 reported the demographic and clinical characteristics of the participants.

Table 4 - Demographic and clinical data of the sample

Demographic indexes		BRCA+ Group (N. 16)	BRCA- Group (N. 16)	Total (N. 32)
Age (M±SD)		44.3±5.31	46.1±5.52	45.2±5.41
Education (%)				
	No high school	12,5	6,25	9,4
	High school degree	43,75	37,5	40,6
	Undergraduate degree	43,75	56,25	50
Marital status (%)				
	Married/with partner	81,25	81,25	81,25
	Single/divorced	18,75	18,75	18,75
Occupation (%)				
	Unemployed	18,75	25	21,9
	Employed	68,75	50	59,4
	Self-employed	12,5	25	18,7
Number of children (%)				
	0	18,75	18,75	18,75
	1	25	31,25	28,1
	2	50	43,75	46,8
	>2	6,25	6,25	6,25
Clinical indexes				
TNM stage (%)				
	0	6,25	6,25	7,4
	I	56.25	50	63
	II	12,5	18,75	18,5
	III	6,25	12,25	11,1
Histological subtype (%)				
	DCIS	12,5	6,25	9,37
	IDC	56,25	75	65,62
	ILC	0	12,5	6,25
Molecular subtype (%)				
	Luminal A	18,75	50	40,7
	Luminal B	25	25	29,6
	HER2+	0	6,25	25,9
	TN	25	18,75	3,7
Primary surgical treatment (%)				
	Mastectomy	37,5	37,5	37,5
	Lumpectomy	62,5	62,5	62,5
Pharmacological treatment* (%)				
	Hormonal therapy	56,25	68,75	62,5
	Radiotherapy	43,75	56,25	50
	Chemotherapy	56,25	50	53,12

Note. * = drugs are not mutually excluding, TNM = tumor, nodes, metastases, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, DCIS = ductal carcinoma in situ, TN = triple negative

The inclusion and exclusion criteria of the study were reported in Figure 33.

Figure 33 - Inclusion and exclusion criteria

6.3 Measures

6.3.1 Sociodemographic Variables

Two types of participant information were also collected. First, demographic data were collected through participants' self-reports. Second, clinical data were obtained from participants' medical records regarding BC stage, treatments, therapies, and BRCA genetic testing result.

6.3.2 Psychological Measurement

The psychological battery was composed of five self-reports that measure emotional (depression, anxiety, psychological distress, post-traumatic stress) and personality traits, detailed as follows (Figure 34).



Figure 34 - Psychological battery

Impact of Event Scale-Revised (IES-R)[268,269]. It is a 22-item self-report questionnaire to measure the subjective response to a specific traumatic event, especially in the response sets of intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like reexperiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations, and ideas), and hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle), as well as a total subjective stress IES-R score. Scores higher than thirty-three are of concern, the higher the score the greater the concern for post-traumatic stress and associated health and well-being consequences. Italian version was applied.

Depression, Anxiety, and Stress Scale (DASS-21)[270]. The DASS-21 is a clinical assessment that measures the three related states of depression, anxiety, and stress. It has twenty-one questions and takes about 3 min to complete. Each subscale measuring the emotional traits is composed of seven items. Italian version was applied.

Difficulties in Emotion Regulation Scale-20 (DERS-20)[271]. The DERS is a test to assess individual differences in the ability to identify, accept and manage emotional experiences; the test is composed of six indexes: a) Non acceptance, b) Goals, c) Impulse, d) Awareness, e) Strategies, f) Clarity. Italian version was applied.

Multidimensional Impact of Cancer Risk Assessment (MICRA)[244]. MICRA is a 25-item instrument designed to assess the specific impact of result disclosure after genetic testing. It assesses both negative and positive responses to testing experience. Each item is measured on a 4-point Likert-scale. It is composed by three subscales: Distress, Uncertainty and Positive Experience. Except for Positive Experience, higher scores indicate more genetic test-related distress. Italian version was applied.

Big Five Inventory-10 (BFI-10)[272]. The BFI-10 evaluates the five personality dimensions on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree), each with two items: openness (OP), conscientiousness (CO), emotional stability (ES), extraversion (EX), and agreeableness (AG). Italian version was applied.

6.4 Procedure

Medical staff in the Medical Oncology Division ASL1 L'Aquila (Director Prof. E. Ricevuto) identified eligible patients, who were then enrolled during a scheduled follow-up by medical protocol. Genetic testing was executed in the Medical Genetics Unit of ASL1 L'Aquila (Director Prof. F. Brancati). Participation in this study was voluntary, and the submission of a signed informed consent form was mandatory. The participants took approximately 30 minutes to complete the psychology battery. Participants completed the measures during their scheduled follow-up. Data were collected anonymously. The psychological evaluation was conducted in a quiet dedicated room. The tests were administered by trained psychologists who were blinded to the objectives of the study. Independent clinical psychologists scored the tests.

6.5 Study Design

In this observational study, the participants were divided into two groups based on BRCA genetic testing result (i.e., BRCA+ and BRCA- groups).

Descriptive statistics were computed to examine their characteristics. One-way analysis of variance (ANOVA) and correlation analysis were conducted using the data collected from participants. All statistical analyses were conducted using Jamovi[273]. All the tests were two-tailed, and the level of statistical significance was defined as $p < 0.05$. Post-hoc tests (with Tuckey correction) were conducted to further examine significant group differences.

6.6 Results

Participants were BC patients having mean age of 45.2 ± 5.41 years; most patients (63%) had a localized cancer (TNM I cancer stage), 65,62% of tumors were invasive lobular carcinoma, 40,7% were Luminal A molecular subtype. 62,5% of the patients undergone a lumpectomy surgical intervention, 37,5% undergone mastectomy prior to genetic counseling and testing. Most patients (62,5%) were in hormonal therapy. The psychological evaluations of the study highlighted interesting emotional patterns. Firstly,

we wanted to detect the emotional dimensions in BC patients distributed in BRCA+/BRCA- subgroups. The non-parametric One-way ANOVA (Kruskal-Wallis test) was performed comparing the IES-R, DASS-21, DERS and MICRA scores by BRCA+ and BRCA- groups. Statistical analyses showed a significant difference in IES-R score ($\chi2 = 4.0$; $\varepsilon2 = 0.12$; $p = 0.04$), evidencing the higher PTSD risk and higher hyperarousal in the BRCA+ than BRCA- group ($\chi2 = 4.7$; $\varepsilon2 = 0.15$; $p = 0.02$); DERS test showed significant differences: impulse index appeared higher in BRCA- than BRCA+ group ($\chi2 = 4.8$; $\varepsilon2 = 0.15$; $p = 0.02$); even MICRA test showed significant differences: higher distress index ($\chi2 = 7.4$; $\varepsilon2 = 0.24$; $p = 0.006$) and lower positive experiences index in BRCA+ than BRCA- group ($\chi2 = 6.9$; $\varepsilon2 = 0.22$; $p = 0.009$). In Table 5 and Figure 35 are represented detailed data.

Table 5 - Raw score and non-parametric one-way ANOVA (Kruskal-Wallis test)

		χ^2	df	p	ε^2
IES-R		4.0003	1	0.045*	0.12904
	Avoidance	3.6472	1	0.056	0.11765
	Intrusion	2.7780	1	0.096	0.08961
	Hyperarousal	4.7948	1	0.029*	0.15467
DASS-21		0.4121	1	0.521	0.01329
	Depression	0.7660	1	0.381	0.02471
	Anxiety	0.0722	1	0.788	0.00233
	Stress	0.3438	1	0.558	0.01109
DERS-20		0.0804	1	0.777	0.00259
	Non acceptance	0.0518	1	0.820	0.00167
	Awareness	0.8684	1	0.351	0.02801
	Goals	0.4455	1	0.504	0.01437
	Clarity	1.0093	1	0.315	0.03256
	Impulse	4.8291	1	0.028*	0.15578
MICRA		8.7644	1	0.003*	0.28272
	Distress	7.4882	1	0.006*	0.24156
	Uncertainty	2.8923	1	0.089	0.09330
	Positive experiences	6.9240	1	0.009*	0.22335

Note. * $p < .05$

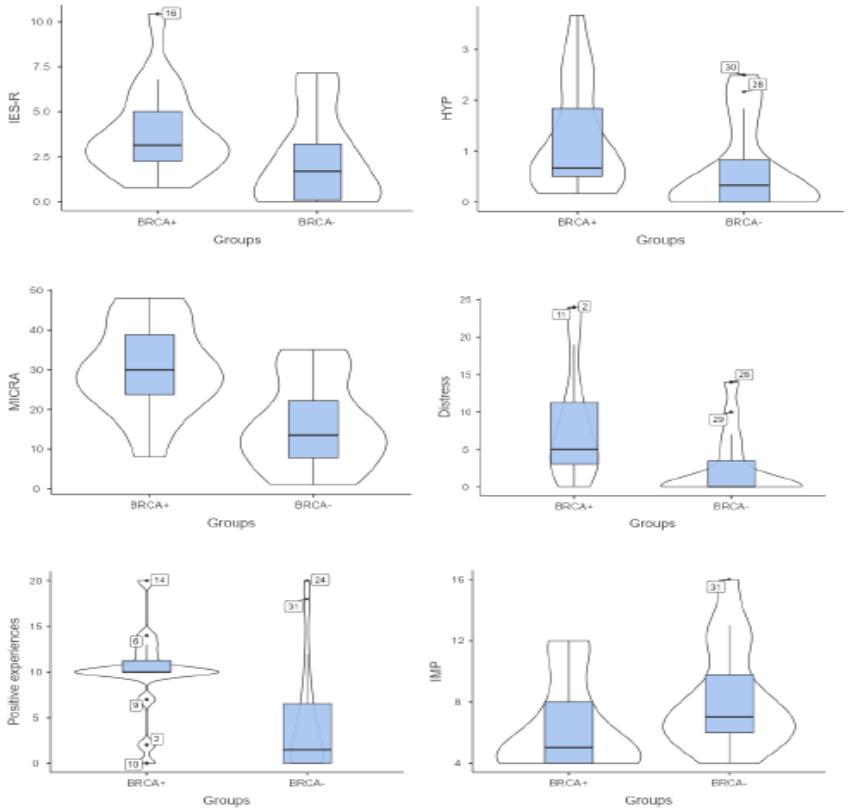


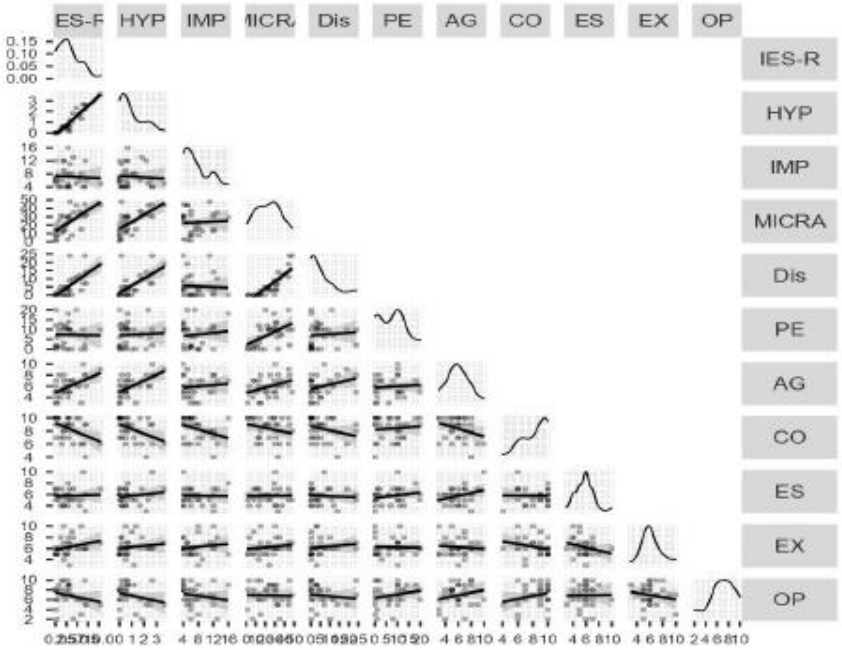
Figure 35 - Violin Plots for IES-R, DERS and MICRA scoring in BRCA groups

Then, we wanted to examine the correlation between emotional dimensions (PTSD risk, hyperarousal, and impulse) and personality traits. Pearson's correlation evidenced the Hyperarousal index (IES-R) and Agreeableness trait (BFI-10) were positively correlated ($p < .001$), MICRA score and Agreeableness trait (BFI-10) were positively correlated ($p = 0.044$), and the Hyperarousal index (IES-R) and Conscientiousness trait (BFI-10) were negatively correlated ($p = 0.016$). Table 6 and Figure 36 reported the Pearson's correlation matrix.

Table 6 - Correlation Matrix (Pearson's r) of emotional dimensions of the sample

		IES-R	*HYP*	*IMP*	MICRA	*Dis*	*PE*	*AG*	*CO*	*ES*	*EX*	*OP*
IES-R *HYP*	Pearson's r	0.938***	—									
	p-value	< .001	—									
DERS-20 *IMP*	Pearson's r	-0.059	-0.075	—								
	p-value	0.750	0.684	—								
MICRA	Pearson's r	0.654***	0.644***	0.058	—							
	p-value	< .001	< .001	0.753	—							
Dis	Pearson's r	0.690***	0.636***	-0.050	0.837***	—						
	p-value	< .001	< .001	0.788	< .001	—						
PE	Pearson's r	-0.019	0.052	0.110	0.505**	0.077	—					
	p-value	0.918	0.778	0.548	0.003	0.675	—					
BFI-10 *AG*	Pearson's r	0.500**	0.582***	0.111	0.359*	0.324	0.083	—				
	p-value	0.004	< .001	0.545	0.044	0.071	0.653	—				
CO	Pearson's r	-0.424*	-0.424*	-0.326	-0.236	-0.250	0.092	-0.304	—			
	p-value	0.016	0.016	0.069	0.193	0.168	0.617	0.091	—			
ES	Pearson's r	0.056	0.182	-0.002	0.023	-0.057	0.218	0.317	-0.028	—		
	p-value	0.759	0.318	0.992	0.900	0.755	0.230	0.078	0.881	—		
EX	Pearson's r	0.249	0.131	0.133	0.135	0.123	-0.031	-0.078	-0.245	-0.237	—	
	p-value	0.170	0.475	0.466	0.461	0.503	0.865	0.672	0.176	0.192	—	
OP	Pearson's r	-0.221	-0.251	-0.175	-0.029	-0.115	0.210	0.211	0.236	0.013	-0.161	—
	p-value	0.225	0.167	0.337	0.873	0.532	0.249	0.247	0.193	0.943	0.378	—

Note. * p < .05, ** p < .01, *** p < .001, AG = Agreeableness, CO = Conscientiousness, ES = Emotional Stability, EX = Extraversion, OP = Openness, HYP = Hyperarousal, IMP = Impulse, IES-R = Impact of Event Scale-Revised, MICRA = Multidimensional Impact of Cancer Risk Assessment, Dis = distress, PE = positive experiences



Note. AG = Agreeableness, CO = Conscientiousness, ES = Emotional Stability, EX = Extraversion, OP = Openness, HYP = Hyperarousal, IMP = Impulse, IES-R = Impact of Event Scale-Revised, MICRA = Multidimensional Impact of Cancer Risk Assessment, Dis = distress, PE = positive experiences

Figure 36 - Correlation matrix plot for IES-R, impulse, MICRA and personality traits

6.7 Discussion

Study aimed to examine the psychological dynamics following the genetic testing for BRCA mutation in women after BC diagnosis dealing with the emotional health related to the personal resources. Scope was to investigate the adaptive strategies to BRCA genetic testing results disclosure comparing positive/negative oncological patients in emotional features and their correlation with personality traits. As expected, positive genetic mutation women presented genetic testing-related distress, especially in the response sets of hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle) and a less positive experience. Mild to strong correlations emerged between PTSD risk and personality traits: highly agreeable women, who prioritize family members' feelings in their health-related decision making and women low in conscientious that have low self-control and consider most health-related decisions quickly, are at

high risk of PTSD and hyperarousal after genetic testing results disclosure[274]. Also, correlation between concerns that are very specific to the high-risk cancer clinical setting and personality traits emerged: highly empathetic women, who naturally identify with the emotional experiences of others (i.e., family members) presented elevated concerns about personal and family vulnerability and these concerns can have an impact on health care decision making. Unexpectedly, negative mutation women showed higher difficulties in emotion regulation, mostly affected the maintaining control behavior when feeling negative emotions. We hypothesize that it could be caused by limited awareness about the origin of their illness, and this could have an impact on emotion regulation abilities and long-term management of clinical pathway. In literature, the emotional regulation seemed to be involved in the healthy/unhealthy adaptive behaviors and related negative outcome for health[201,275,276]; dispositional optimism, as well defensive responses to stressful life events could be related to the outcome of emotional dimensions[256,257]. Clinical aspects and personality traits in disease treatments appeared correlated to the coping strategies for emotional regulation[276,277]. A study highlighted how the coping strategies in facing stressful situations and traumatic experiences connected to cancer diagnosis would be associated with the perceived social support derived from various sources. According to the literature[265,278,279], our finding confirmed the psychological influence of genetic testing on wellbeing of BC patients, and more drawing clinical perspective for positive/negative disclosure regarding the predictors for psychological distress. The BRCA counseling could be a stressing step in oncological clinical practice featuring the psychological health of patients; BRCA+/- results disclosure impact the emotions dimensions of patients and paving the way for tailored psychological setting toward to reinforce adaptive behaviors and coping strategies for better compliance and adherence to pharmacological treatments. Evidence from systematic reviews illustrates that a genetic counseling intervention does not appear to increase distress and therefore could improve the accuracy of individuals' perceptions of their personal risk[280]. Longitudinal study highlighted the positive mutation did not show higher levels of anxiety or depression over time (short/long term follow up); on contrary, the most powerful predictor of mid and long term pathological anxiety level was the level of anxiety at baseline[252]: our finding allows to explain better this outcome figuring out the emotional regulation in BRCA+ as key psychological factor. Negative emotions into hyperarousal dimension, as well anger, irritability, hypervigilance, difficulty concentrating, heightened startle seemed influence massively the adaptive behaviors of BC patients.

Further strength of our finding is related to emotional impact for BRCA-: genetic testing is a stressor that could influence the mental health of BC patients by the impulsivity behaviors: tendences to act without thinking, low level of concentration, restlessness, and high risk for aggressive behavior as well psychosocial disorders. Bakos's study showed that informing women that they are not at high cancer risk may not suffice to lower their elevated risk perception or change their self-image[281]. The transition required to redefine one's self-image requires time, emotional support, multiple opportunities for clarification and a profound change in awareness. Mutation-negative women may require additional help in redefining their cancer risk perception.

The genetic testing integrated by psychological counseling into personalized medicine is becoming urgent: our research strongly highlighted the protective influence of conscientiousness traits for negative emotions (hyperarousal index); on contrary women having high level of agreeableness personality traits have tendence to be exposed to the higher psychological distress for genetic result disclosure and related perceived stress: usually, individuals with high agreeableness have the tendence to put others needs before their own and in genetic testing the fear of risk of cancer for own sons for disease risk as well low Quality of Life and well-being. The clinical practice amplified and improved the relevance of genetic testing into oncological medical cure to manage the risk for cancer and to tailor better surgical/pharmacological treatments; at same time, our finding spotted the risk for mental disease and psychosocial deficits in genetic results disclosure making the oncological care affecting the Quality of Life of patients. Adherence and compliance are fundamental for intensive oncological treatments and for that the collaboration and active engagement of the patients are necessary: negative psychological signs during the caring could compromise the efficacy of personalized medicine paradigm[282–284].

6.8 Conclusions

Our study featured the psychological influence of BRCA genetic testing result disclosure: it is a relevant oncological clinical practice for better health management of BC patients by medical approach. Both, negative and positive BRCA result disclosure need to deal with the emotional regulation in genetic testing; coping strategies as well personal resource, personality traits and social/family support influence the Quality of Life for oncological care, However, genetic testing needs to be integrated by psychological counseling to manage better the impact of result disclosure (whatever the outcome is) to manage better the physical and mental health of patients into efficient personalized medicine toward to the improvement of patient compliance and adherence into well-being perspective and Quality of Life maintaining. Our study has some limitations. First, the sample size of the study is small: we need to enlarge the data to consolidate our finding. Second, the lack of longitudinal data to verify the trend of performance as well the ability of patients to manage the own mental health. Our study is ongoing, and we are going to overcome those limits making our primary data consolidated outcome for solid clinical practice.

CHAPTER 7. PERCEIVED RISK CANCER AND GENETIC COUNSELING: BIOPSYCHOLOGICAL PERSPECTIVE TO BOOST LIFESTYLE MEDICINE[3]

7.1 Introduction

The fear of developing cancer, or the fear of cancer recurrence (FCR), is a known health concern in cancer-affected individuals, survivors of cancer, and individuals with an increased hereditary risk of cancer. Several studies have dealt with FCR in patients diagnosed with breast cancer[285–288]: anxiety, depression, post-traumatic stress disorders, and psychosocial problems are the most frequent psychological and behavioral symptoms[201,289,290]. In a recent review, Paperàk et al.[288] proposed a study focused on identifying the most effective psychotherapeutic approaches in managing FCR: authors have identified Cognitive Behavioral Therapy (CBT), Acceptance and Commitment Therapy (ACT), and mindfulness-based interventions as the most frequent and most effective in managing patients' emotional balancing in oncology. However, authors have highlighted the need to incorporate evidence-based psychotherapy into FCR treatment as the challenge for future research. A related issue is the fear of developing cancer. The most common hereditary cancer syndrome is Hereditary Breast and Ovarian Cancer (HBOC), which is an inherited genetic condition[291]. This means that the cancer risk is passed from generation to generation in a family. The condition is responsible for 10–15% of all breast cancers and 24% of epithelial ovarian cancers[292].

Under review at Journal of Genetic Counseling[3]

Genetic testing is slowly becoming a regular part of clinical practice. It provides an opportunity to enhance health promotion and long-term health outcomes by identifying at-risk individuals before cancer develops[293]. A recent exploratory review focused on the patient perspective in perceived genetic-mutation risk (GMr) highlighted the need to enhance the clinical indices in genetic counselling to improve the patient-centered approach dealing with the mental-health interplay and to analyze the magnitude of the impact on mental health in chronic-disease conditions, which could be psychologically integrated[294]. High stress, psychological distress, and worries are relevant in patients at a high risk of genetic mutations. Indeed, avoidance, psychological distress, and intrusive thoughts have emerged as related to cancer diagnosis[208,209,214,216,295]. Studies have revealed that predictive behaviors for mental discomfort include family history of disease, young age, short time since cancer diagnosis, low social support, and high-risk self-perception of life[169,296,297]. The clinical implications of the above studies are that probands' educational level and relatives' age for cascade genetic screening should be considered during genetic counselling. Besides the negative impacts on quality of life, mental health, and psychosocial wellbeing, cancer worry modulates health-related behaviors such as lifestyle choices and screening participation. Worry levels seem to correlate with a subjectively perceived risk of cancer; however, the relationship between cancer worry and screening behavior seems to be complex and is likely non-linear[200,287,298,299]. Genetic counselling, such as on worry about developing breast cancer, the impact of worries on daily life, and risk perception in women attending a counselling session for breast cancer gene 1/gene 2 (BRCA1/2) mutations is relevant in this context. It is an emerging topic on integrated care towards boosting the lifestyle-medicine perspective[300].

This study aimed to investigate the role of cancer worry in the psychological dimensions of patients undergoing genetic testing and to analyze its moderating effect thereon. We hypothesized that fear of developing cancer, or FCR, could moderate the mental health of patients undergoing comprehensive genomic DNA testing.

7.2 Methods

7.2.1 Participants

The participants (n. 55; n. 42 females) had a mean age ± DS: 45.6±13.5 and age range 19-73 years. They were classified into two groups based on genetic-testing indications and were reported in Figure 37.

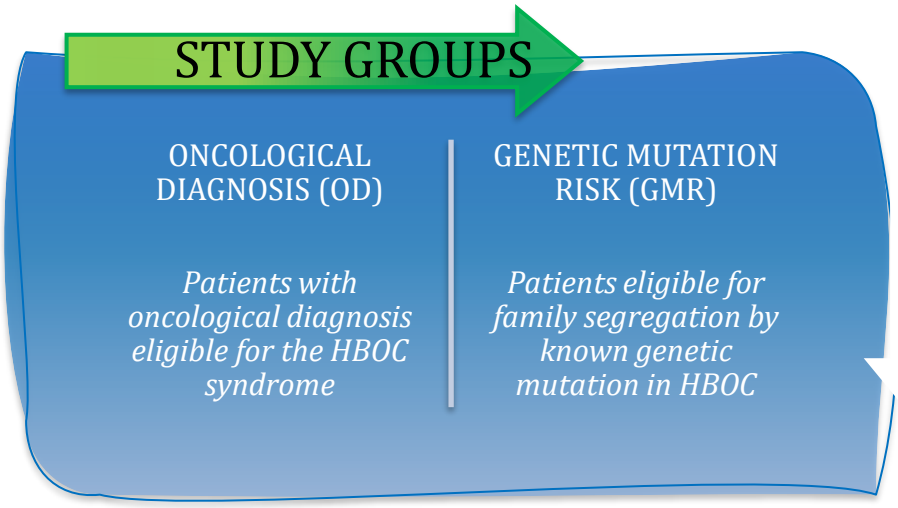


Figure 37 - Study groups

The OD group comprised 24 participants (mean age ± SD: 49.9±10.2), while the GMr group comprised 31 participants (mean age ± SD: 42.3±15.0). Eligible participants were approached to be enrolled in the study at the Medical Genetic Division (Director Prof. F. Brancati) of San Salvatore Hospital ASL 1 Abruzzo (Italy). Inclusion criteria included patients older than 18 years with oncological diagnosis eligible for HBOC genetic testing and/or for family segregation by known genetic mutation in HBOC. Exclusion criteria were (a) psychiatric disorders; (b) alcohol or substance abuse; (c) mood-modifying medications; and (d) neurological disorders.

7.2.2 Instrumentation

The psychological battery comprised three standardized tests reported in Figure 38.

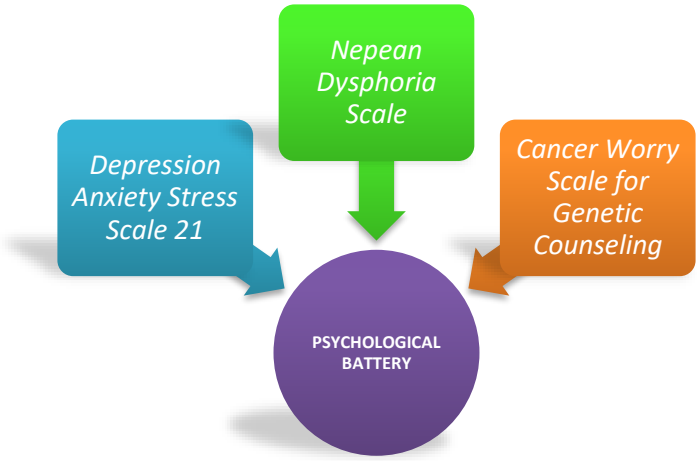


Figure 38 - Psychological battery

Depression anxiety Stress Scale 21 (DASS-21)[270]. The DASS-21 is a self-administered questionnaire that measures the degree of severity of the core symptoms of depression, anxiety, and stress. It comprises 21 questions with responses on a 4-point Likert-type scale.

Nepean Dysphoria Scale (NDS)[301]. The NDS is a self-administered questionnaire that requires respondents to provide ratings of the frequency with which they have experienced dysphoria-relevant symptoms on a scale from 0 ('not at all') to 4 ('every day, most of the time'): irritability, discontent, interpersonal resentment, and surrender.

Cancer Worry Scale for Genetic Counseling (CWS-GC)[302]. The CWS-GC measures anxiety that is specific to breast cancer and cancer-/genetic-risk perception. It comprises 7 items and the scoring is based on cancer worry and cancer-risk perception. Cancer worry is an emotional reaction to the threat of cancer. Cancer-risk perception is a cognitive dimension that refers to one's belief about the likelihood that an adverse event, such as cancer, occurs. The internal consistency measured by Cronbach´s alpha is ≥ 0.70.

7.2.3 Procedures

Medical staff in the Medical Genetic Unit identified enrolled patients, who were then recruited before genetic testing. The participants were outpatients recruited from ambulatory care after the first scheduled genetic counselling. They were divided into two groups based on genetic-testing indications: oncological diagnosis eligible for HBOC genetic testing and patients eligible for family segregation by known genetic mutation in HBOC. Written consent was obtained from all the participants at the time of enrolment. Trained clinical psychologists (blinded to the objectives of the study) attended genetic counselling and conducted the psychological evaluations in a quiet room. The evaluations lasted for 20 minutes. The participants completed the measures during their first genetic counselling. Data were collected anonymously.

7.2.4 Data analyses

We conducted an observational study. Descriptive analyses were performed on demographic and clinical data. The normality test (Shapiro–Wilk test) was then conducted to examine the variables. Thereafter, Pearson's correlation and Generalized Linear Mediation (GLM) analyses were performed to verify the influence of negative emotion as a mediator of psychological dimensions. All statistical analyses were conducted using Jamovi[273]. The level of statistical significance was $p < 0.05$.

7.3 Results

Fifty-five subjects were considered eligible and invited to participate in the study. Descriptive analyses were conducted on demographical data. Table 7 reports the data.

Table 7 - Demographic data of sample

	Sample (N = 55)
Demographics	
Age (years)	X 45.6 SD±13.5
Gender: n (%)	
Male	13 (23.6%)
Female	42 (76.4%)
Marital Status: n (%)	
Single	11 (19.9%)
Married	44 (80.1%)
Educational level: n (%)	
Graduate	31 (56.4%)
No graduate	24 (43.6%)
Occupational status: n (%)	
Unemployed	17 (30.8%)
Employed	28 (51.0%)
Self-employed	10 (18.2%)
Genetic testing condition	
Typology: n (%)	
Oncological Diagnosis eligible for HBOC	24 (43.6%)
Family segregation by known genetic mutation in HBOC	31 (56.4%)

Legend: M= mean value; SD= standard deviation; %=percentage

The sample comprised 55 individuals divided into 24 (43.6%) patients with oncological diagnosis eligible for HBOC and 31 (56.4%) subjects for family segregation by known genetic mutation in HBOC. Almost all were females (76,4%), married (80,1%), and employed (69,2%).
First, we analyzed the detected psychological data. Table 8 reports the mean values and standard deviations of the sample for standardized psychological testing (DASS-21, CWS, NDS).

Table 8 - Raw scores of psychological evaluations and Shapiro-Wilk

			Shapiro-Wilk	
	Mean	**SD**	**W**	**p**
DASS-21				
Depression	10.55	10.35	0.87	< .001
Anxiety	7.75	7.92	0.86	< .001
Stress	14.98	9.98	0.95	0.015
CWS				
Cancer Worry	56.36	22.68	0.84	< .001
Risk Perception	57.76	20.26	0.93	0.003
NDS				
Irritability	8.25	7.55	0.88	< .001
Discontent	6.67	6.16	0.87	< .001
Interpersonal resentment	4.56	4.99	0.84	< .001
Surrender	3.96	4.01	0.85	< .001

Legend: DASS-21 = Depression Anxiety Stress Scale -21; CWS = Cancer Worry Scale; NDS = Nepean Dysphorya Scale

The Shapiro-Wilk test was conducted, and except for the cancer-worry index, all the variables were not normally distributed, as reported in Table 8. We then sought to verify the relationships among the psychological emotions using Pearson's correlation test. Table 9 reports the elaboration-data outcome. Statistical analyses highlighted the extensive positive correlation among almost all the evaluated psychological dimensions. In particular, the cancer-worry index showed positive correlations with the depression, anxiety, and stress variables, as well with negative emotion (discontent). The cancer-risk perception index was correlated with irritability and surrender. Moreover, the psychological dimensions of DASS were significantly related to the negative emotions (NDS indexes).

Finally, the GLM model was estimated to determine the predictive effect of cancer worry on dysphoria (NDS indexes: irritability, discontent, interpersonal resentment, and surrender), depression, anxiety, and stress. Linear regression analyses showed a significant mediation effect of the cancer-risk perception index on the psychological dimensions of depression ($\beta = 0.38$; $z = 2.66$; $p =< 0.008$), anxiety ($\beta = 0.28$; $z = 2.03$; $p =< 0.04$) and stress ($\beta = 0.38$; $z = 3.00$; $p =< 0.003$); regarding dysphoria, cancer-risk perception significantly moderated the irritability ($\beta = 0.31$; $z = 2.22$; $p =< 0.02$) and discontent ($\beta = 0.29$; $z = 2.10$; $p =< 0.03$) dimensions. No significant differences were found between the two groups (OD vs. GMr) (Figure 39).

Table 9 - Pearson correlation test on psychological dimensions

		CWS - CG			DASS-21			NDS			
		Cancer Worry	Risk Perception	Depression	Anxiety	Stress	Irritability	Discontent	Interper Resent	Surrender
Depression	Pearson's r	0.27 *	0.40 **	—						
	p-value	0.044	0.002	—						
Anxiety	Pearson's r	0.29 *	0.34 **	0.78 ***	—					
	p-value	0.033	0.010	<.001	—					
Stress	Pearson's r	0.39 **	0.48 ***	0.80 ***	0.70 ***	—				
	p-value	0.003	<.001	<.001	<.001	—				
Irritability	Pearson's r	0.17	0.33 *	0.63 ***	0.45 ***	0.56 ***	—			
	p-value	0.225	0.015	<.001	<.001	<.001	—			
Discontent	Pearson's r	0.31 *	0.37 **	0.68 ***	0.52 ***	0.58 ***	0.84 ***	—		
	p-value	0.021	0.006	<.001	<.001	<.001	<.001	—		
Interper Resent	Pearson's r	0.09	0.23	0.52 ***	0.33 *	0.45 ***	0.78 ***	0.63 ***	—	
	p-value	0.511	0.096	<.001	0.015	<.001	<.001	<.001	—	
Surrender	Pearson's r	0.22	0.28 *	0.68 ***	0.47 ***	0.59 ***	0.89 ***	0.90 ***	0.70 ***	—
	p-value	0.113	0.037	<.001	<.001	<.001	<.001	<.001	<.001	—

Note. * p < .05, ** p < .01, *** p < .001

Legend: DASS-21 = Depression Anxiety Stress Scale -21; CWS = Cancer Worry Scale; NDS = Nepean Dysphoria Scale

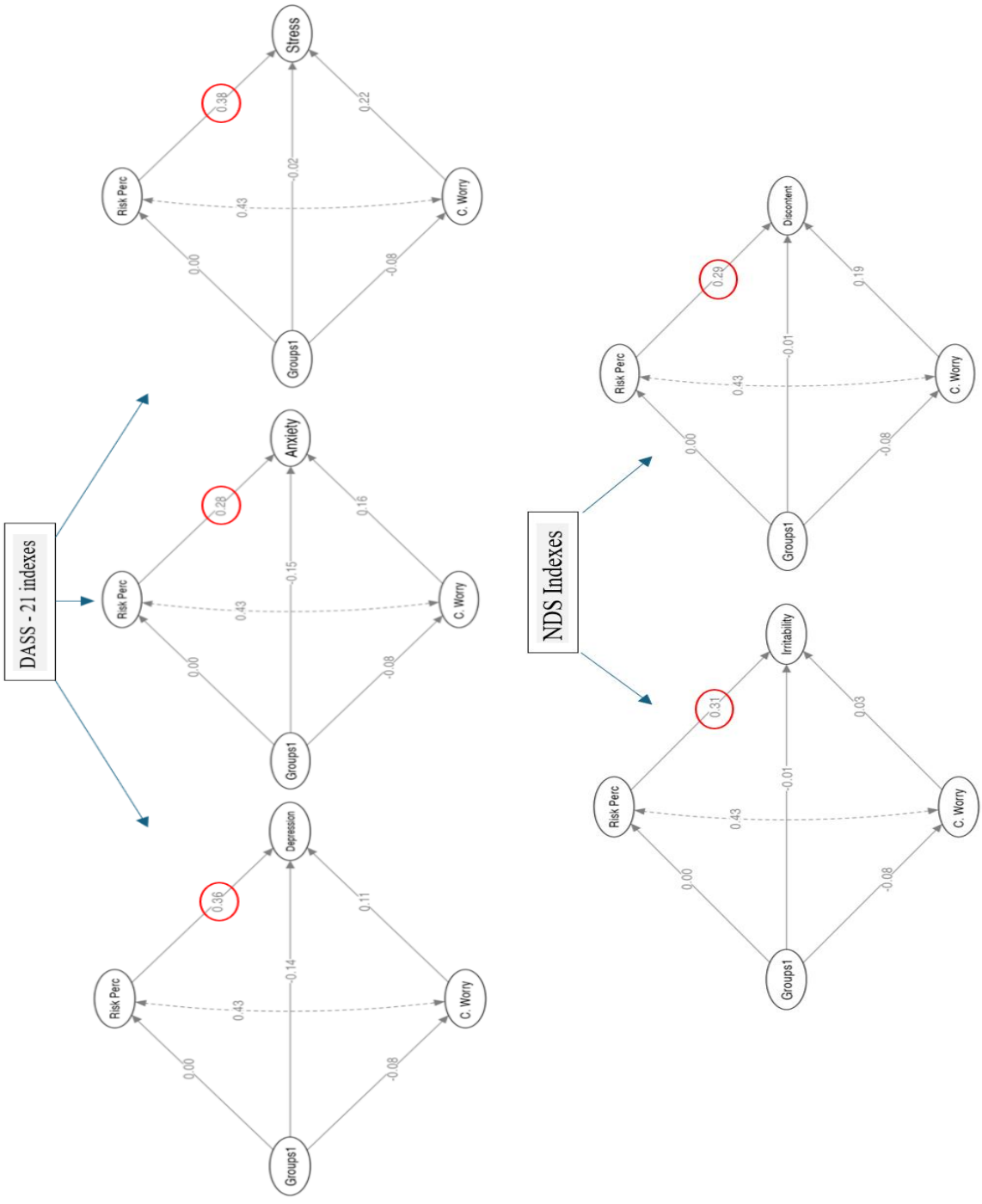


Figure 39 - Statistical Diagram of GLM regarding to the impact of Cancer Worry indexes on psychological dimensions

7.4 Discussion

The study aimed to explore the role of cancer-worry in the psychological dimensions of patients with high-risk of oncological diagnosis. Our interesting finding could significantly and practically contribute to psycho-educational and therapeutic interventions as part of clinical support for patients dealing with FCR or fear of developing cancer. Our study evidenced the relevance of cancer worry in the management of genetic counselling, which should be more relevant during the communication process and family members' engagement in testing and risk-reducing strategies. Indeed, a genetic specialist can allow a patient to discuss not only the risks associated with genetic cancer syndromes but also the psychological or emotional impact these syndromes may have on families. Genetic counselling turns out to be a complex communication process in which patient engagement should be exploited. It is an emerging topic, as highlighted by Samadder et al.[292]: indeed, only 1.7% of 143 clinicians felt confident in their ability to interpret risk based on family history and to provide a patient with screening, treatment, and/or risk-reduction recommendations. Individuals' ability to comprehend and dynamic adaptability are simultaneously required to promote adherence to the patient-life perspective: the integration of genetic information and medical, psychosocial, and familial implications of hereditary disease represent core genetic counselling based on a patient-centered approach. In our opinion, increased patient understanding may lead to improved communication between family members who are at risk and may also increase adherence to screening and/or risk-reduction recommendations. If a patient's personal and/or family history is suggestive of a hereditary predisposition, referral to a genetics clinic and/or genetic counsellor can provide an in-depth assessment of personal and family history in the context of hereditary cancer[292]. Based on the finding, we suggest clear integration of genetic counselling by communication and emotional specialists as well clinical psychologists to better manage the impact of genetic disclosure on patients' and relatives' lives. The influence of cancer worry on dysphoria traits was that patients/relatives who underwent genetic testing felt vulnerable. Moreover, considering our preview study[201], in oncological patients dealing with a BRCA genetic result, the limited knowledge about the origin of their illness could impact their emotion-regulation processes and then the long-term clinical-pathway management. Additionally, unexpectedly negative BRCA-mutation women showed high difficulties in emotion regulation, which mostly affected the maintenance of intentional behavioral control during stressful events. In previous studies, emotional regulation seemed to be involved in healthy/unhealthy adaptive behaviors and the related

negative outcome for health[275,303,304]; dispositional optimism as well defensive responses to stressful life events could be related to the outcome of emotional dimensions[257]. Additionally, clinical characteristics and personality traits in disease treatments appeared correlated to the coping strategies for emotional regulation[277,304]. Genetic counselling could be a stressing step in oncological clinical practice featuring patients' psychological health; BRCA+/- results disclosure impact patients' emotion dimensions, paving the way for a tailored psychological setting toward reinforcing adaptive behaviors and coping strategies for improved accuracy of individuals' perceptions of their personal risk[280]. As well defined by Hammer-Hansen et al.[305]: "*the care for patients with serious conditions is increasingly guided by genomic medicine, and genomic medicine may equally transform care for healthy individual if genomic population screening is implemented*" (pag.1).

The BPS model[101,306] could be the tailored lens to innovate the genetic-counselling process. The model represents a theoretical framework that incorporates three relevant components (biological, psychological and social) into individuals' quality of life: all three interact in daily living, shaping people's protective scenario and risk perspectives; their interplay determines the cause, manifestation, and resolution of an illness or risk thereof. Genomic medicine oriented to the BPS approach in the counselling process could be the driving force for efficient and integrated genomic-risk assessment. The updated setting based on a patient-centered approach, tailoring clinical practice on the integration of physical, mental, and social factors to patients' and relatives' wellbeing, seems to be a fruitful research and practice scenario to enhance healthcare and patient lives.

7.4.1 Study Limitations

Potential limitations of the study include the sample size, which could be expanded in future studies to provide more robust evidence, and the inability to establish causal relationships among the investigated variables in the network statistical analysis to exploit the research outcomes.

7.4.2 Practice implications

Genetic-cancer risk assessment is defined as an interdisciplinary standard of care practice that employs genetic and genomic tools to identify individuals and families with inherited cancer risk[307]. Genetic counselling encompasses both physical and psychological aspects of health. Resta et al.[68] define it as assisting individuals to comprehend and adapt to both genetic information and the medical, psychosocial, and familial implications of hereditary disease. The role of a genetic specialist is to support individuals and relatives through an in-depth disclosure promoting the adaptative process to a genetic scenario[68,308]. To our knowledge, this is the first research protocol to evaluate emotion regulation (psychological testing) during genetic counselling based on the BPS model, which is oriented to the patient-centered approach and reinforces the need to tailoring clinical practice on the integration of physical, mental, and social factors to patients' and relatives' wellbeing.

7.5 Conclusion

The need for an interplay between genetic and psychological specialists was identified in a recent investigation[147] suggesting that increased skills are required in

a the recognition and management of emotional patient reactions

b the recognition of adaptative and maladaptive behaviors to life-altering information.

The key core of genetic counselling lies in applying multidisciplinary counselling and psychotherapy skills to explore emotions and concerns, usually in the context of patient education, and facilitating decision-making and adaptation. It is well documented that interprofessional collaborative care can improve patient safety, quality of care, and provider satisfaction and retention[147].

Human study and informed consent

The study was approved by the Institutional Review Board (IRB) of the University of L'Aquila, Italy (Prot. No. 47/2022). It was conducted according to the guidelines of the Declaration of Helsinki[267].

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