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Towards population-based genetic screenings for breast and ovarian cancer: A comprehensive review from economic evaluations to patient perspectives

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ABSTRACT

Genetic testing for hereditary breast and ovarian cancer following genetic counseling is based on guidelines that take into account particular features of the personal and family history, and clinical criteria conferring a probability of having a BRCA mutation greater than 10% as a threshold for accessing the test. However, besides reducing mortality and social impact, the extension of screening programs also for healthy family members would allow a huge saving of the rising costs associated with these pathologies, supporting the choice of the "Test" strategy versus a "No Test" one. Analyses of different health care systems show that by applying the "Test" strategy on patients and their families, a decrease in breast and ovarian cancer cases is achieved, as well as a substantial decrease in costs of economic resources, including the costs of the clinical management of early detected tumors.

In this review, we analyzed the most recent papers published on this topic and we summarized the findings on the economic evaluations related to breast and ovarian cancer population screenings. These results proved and validated that the population-wide testing approach is a more accurate screening and preventive intervention than traditional guidelines based on personal/family history and clinical criteria to reduce breast and ovarian cancer risk.

Contents

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Abbreviations

BRCA	Breast Related Cancer Antigens
FH	Family History
US:	United States
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
MCG	Mainstreaming Cancer Genetics
QALYs	Quality Adjusted Life Years
UK:	United Kingdom
OUH-U:	Oslo University Hospital-Ullevål
LYG	Life Years Gained
AIOM	Italian Association of Molecular Oncology

1. Background

The discovery of the association of the *BRCA1* and *BRCA2* gene mutation with breast and ovarian cancer dates back to about twenty years ago. Over the time, this finding has led to a reorganization of the levels of surveillance, diagnosis and treatment for patients affected by hereditary transmission of pathogenic variants of these genes. Therefore, individuals who meet specific characteristics determined according to well-established guidelines and family history criteria, can access a BRCA genetic testing. However, these selection criteria are not always effective as they fail to identify individuals who are at risk of developing a tumor but do not meet the selection criteria. The introduction of recent technological innovations, such as the Next Generation Sequencing (NGS) methods to detect and diagnose these mutations and the lowering of these selection thresholds, favoring population screening rather than selected populations, allows to prefigure a new scenario that identify in population screening for BRCA, a reality not too distant and certainly possible. The most recent literature in this field endorses the possibility that this operational choice is not only effective in terms of benefits but also in terms of costs.

In this review, we report a detailed literature analysis of articles that performed accurate cost/benefit and cost/effectiveness studies by comparing a "Test" administration strategy versus a "No Test" one. We also analyzed studies that reported the effectiveness of an approach based on population screenings to identify the highest possible number of breast and ovarian cancer patients affected by mutations in the BRCA genes. An accurate identification of these subjects would allow them to participate in appropriate surveillance and treatment programs, also given the advantage in saving costs for the different health systems.

2. Introduction

Breast cancer is the most frequent female malignancy and represents a quarter of all newly diagnosed cancer cases, while ovarian cancer remains one of the deadliest cancers among women [1,2]. Most of these tumors are sporadic, while 5–7% are hereditary. Germline mutations of the tumor suppressor genes *BRCA1* and *BRCA2* account for a large proportion of hereditary breast and ovarian cancers [3,4]. BRCA1 and BRCA2 are involved in DNA repair mechanisms and cell growth control and are, thus, crucial for the physiology of normal cells. Deleterious mutations in the *BRCA1* and *BRCA2* genes confer an increased risk of developing primarily breast and/or ovarian cancer [1,2].

More than 5000 variants of BRCA1 and BRCA2 have been described in each gene [5]. A spectrum of germline mutations, classified as more frequent in single populations, were reported by the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA) and are summarized in Tables 1 and 2 [6]. A substantial variation in mutation type and frequency is observed considering different geographical regions and race/ethnicity. Therefore, a prompt knowledge of population-specific mutational patterns in the *BRCA1* and *BRCA2* genes and their impact on different populations, could lead to more focused clinical strategies for genetic testing [7,8].

Overall, it is well established that a prompt identification of BRCA1/2 mutation carriers through genetic screening can bring substantial benefits not only for prevention and risk reducing interventions (e.g., prophylactic mastectomy and/or ovariectomy), which significantly reduce morbidity and mortality, but also for the management of the disease, including personalized follow-up approaches and targeted therapies, mainly regarding the use of platinum agents or Poly ADP-ribose polymerase (PARP) inhibitors, which represent a novel class of anti-cancer therapies for patients with BRCA-associated tumors (breast/ovarian cancer but also, recently approved by FDA, for prostate cancer) [9,10]. Importantly, the identification of mutation carriers allows to refer their healthy family members for genetic counseling that may ultimately lead to the detection of additional healthy individuals at higher risk of developing a tumor [11–15].

However, current international guidelines and recommendations for BRCA genetic screening and testing are insufficient for the detection of all mutation carriers and require further optimization and harmonization across countries [11]. Testing is often restricted to women who fulfill high-risk criteria, including subjects who have already developed a tumor, family history (FH) and risk assessment models. This approach has two main limitations: first, it requires that a family member already suffers from cancer, and second, due to lack of information, families at risk may not be readily recognized. Thus, the identification of a woman as a BRCA1 or BRCA2 mutation carrier, only after she develops cancer, is a failure of cancer prevention. Therefore, in order to improve hereditary breast and ovarian cancer screening programs, the extension of BRCA genetic testing to healthy women in the general population would surely contribute to reducing the mortality and the social impact of this peculiar genetic disease. In addition, population screenings would also reduce the overall costs associated with the management of these hereditary syndromes, largely compensating for additional costs derived from the significant increase in genetic testing.

Risk management: from clinical criteria/family history-based testing to mainstream strategy (population screening).

The purpose of mass screening approaches is to identify a significant proportion of at-risk individuals in a cost-effective manner. Indication criteria for genetic testing, after genetic counseling, is based on guidelines that include features of personal and family history, clinical criteria conferring a probability of having a BRCA mutation greater than 10% (set as a threshold for accessing the test), and the information that is commonly used for the identification of tumors associated with hereditary predisposition (namely, number of affected relatives, type of neoplasm, multiple primitive tumors, age at diagnosis, gender, histological-, immunohistochemical and molecular characteristics of the tumors). However, these criteria have significant limitations, and several reports showed that, depending on the complexity and a limited availability of adequate clinical information, this approach could miss the identification of more than 50% of subjects carrying BRCA mutations [12,14,16–21]. A recent study conducted in the USA estimated that, between the years 2000 and 2010, only 20% of eligible individuals were indeed

Table 1
Ten most frequently observed mutations by self-identified race/ethnicity (%) (by family).

	Mutation rank	Caucasian	African American	Asian	Hispanic/Latino	Jewish	Other
BRCA1	1	c.5266dup (17%)	c.815_824dup (16%)	c.390C > A (4%)	c.68_69del (12%)	c.68_69del (72%)	c.5266dup (12%)
	2	c.181T > G (6%)	c.5324T > G (7%)	c.5496_5506delinsA (3%)	c.3331_3334del (10%)	c.5266dup (24%)	c.68_69del (17%)
	3	c.68_69del (6%)	c.5177_5180del (5%)	c.470_471del (3%)	c.5123C > A (9%)	c.3756_3759del (0.3%)	c.181T > G (5%)
	4	c.4035del (2%)	c.4357+1G > A (5%)	c.5503C > T (2%)	c.548-?_4185+?del (7%)	c.1757 del (0.3%)	c.5333−36_5406 + 400del (3%)
	5	c.4065_4068del (2%)	c.190T > G (3%)	c.922_924delinsT (2%)	c.211A > G (5%)	c.2934T > G (0.2%)	c.3481_3491del (2%)
	6	c.3756_3759del (2%)	c.68_69del (3%)	c.68_69del(2%)	c.815_824del (3%)	c.5503C > T (0.1%)	c.1687C > T (2%)
	7	c.1687C > T (2%)	c.5467+1G > A (3%)	c.3770_3771del (2%)	c.2433 del (3%)	c.4185+1G > T (0.1%)	c.4065_4068del (2%)
	8	c.4327C > T (2%)	c.182G > A (3%)	c.2635G > T (2%)	c.1960A > T (3%)	c.4689C > G (0.1%)	c.5277+1G > A (2%)
	9	c.2475del (2%)	c.5251C > T (2%)	c.2726dup (2%)	c.3029_3030del (3%)	c.3770_3771del (0.1%)	c.2685_2686del (68%)
	10	c.4186-?_4357+?dup (1%)	c.4484G > T (2%)	c.3627 dup (2%)	c.4327C > T (2%)	c.4936 del(0.1%)	c.4327C > T (1%)
Families		11,258	174	550	408	1852	4583
Unique Mutations		1206	77	240	104	56	765
BRCA2	1	c.5946del (5%)	c.2808_2811del (6%)	c.7480C > T (8%)	c.3264dup (17%)	c.5946del (94%)	c.5946del (5%)
	2	c.6275_6276del(3%)	c.4552 del (6%)	c.3109C > T (6%)	c.2808_2811del (9%)	c.3847_3848del (0.4%)	c.6275_6276del (4%)
	3	c.2808_2811del(3%)	c.9382C > T (5%)	c.3744_3747del (4%)	c.145G > T (5%)	c.1754 del (0.4%)	c.2808_2811del (3%)
	4	c.771_775del(2%)	c.1310_1313del (4%)	c.1399A > T (3%)	c.9026_9030del (3%)	c.9382C > T (0.3%)	c.1813dup (3%)
	5	c.3847_3848del(2%)	c.5616_5620del (4%)	c.5576_5579del (3%)	c.658_659del (3%)	c.5621_5624del (0.2%)	c.5645C > A (2%)
	6	c.5682C > G (2%)	c.6405_6409del (3%)	c.2808_2811del (2%)	c.5542 del (3%)	c.2808_2811del (0.2%)	c.1310_1313del (2%)
	7	c.1813dup (2%)	c.658_659del (3%)	c.7878G > A (2%)	c.3922G > T (3%)	c.4829_4830del (0.2%)	c.3847_3848del (2%)
	8	c.8537_8538del (1%)	c.2957_2958insG (2%)	c.262_263del (2%)	c.1813dup (2%)	c.5238 del (0.2%)	c.5682C > G (1%)
	9	c.658_659del (1%)	c.7024C > T (2%)	c.7133C > G (1%)	c.9699_9702del (2%)	c.9207T > A (0.1%)	c.9672 dup (1%)
	10	c.7934del (1%)	c.6531_6534del (2%)	c.5164_5165del (1%)	c.6275_6276del (2%)	c.3264dup (0.1%)	c.658_659del (1%)
Families		7156	125	538	207	990	2551
Unique Mutations		1242	77	248	91	44	753

Mutational distribution among major ethnic groups. The numbers refer to individuals for whom self-identified ethnicity was recorded [6].

tested, meaning that over one million eligible individuals were not tested [14,25]. It is also estimated that in the USA, with this approach, only 30% of breast cancer patients and 10% of unaffected individuals carrying BRCA mutations were identified [22–25]. These results are in line with other data observed in different countries worldwide, including Italy [26,27].

Therefore, the enormous advantage and the opportunity to prevent tumors in healthy mutation carriers calls into question the adequacy and efficiency of the current clinical approach and opens up a new perspective by offering the test to the general population, regardless of family history or cancer diagnosis. This strategy maximizes primary prevention by allowing the identification of a large number of unaffected carriers. Screening for pathogenic/likely pathogenic variants in hereditary breast and ovarian cancer susceptibility genes in unselected individuals can also be used to assess risk and guide decision-making and surveillance (MRI/mammogram) and prophylaxis (surgery and chemoprevention) for the prevention and early detection of breast and ovarian cancer [28]. Consistent with this observation is the recent knowledge that common single nucleotide polymorphisms (SNPs) of breast and ovarian cancer susceptibility, identified through genome-wide association studies (GWAS) in the general population, have been shown to modify cancer risk for BRCA1/2 carriers. The SNPs alone have a minimal effect on cancer risk, but their combined effect, known as *Polygenic Risk Score (PRS)*, seems to provide a suggestive risk discrimination that can be used to stratify individuals into different risk categories [29–31].

These findings, associated with the reduced costs of genetic testing, and the advent of the NGS technology accompanied by advancements in bioinformatics analysis, will foster the implementation of cost-effective, large-scale genetic screening programs in the health care system.

2.1. The NGS testing strategy

The NGS technology has revolutionized the clinical approach to genetic testing, including the field of molecular oncology. The high potential of the NGS technology, which allows a fast and simultaneous processing of a large number of samples and offers the advantage of defining a more complete and informative disease description for each sample, has determined its routine use in current diagnostic practice. Consequently, studies have been implemented to define the economic profile of the NGS technology and to understand if it produces a benefit that overcomes the

Table 2
Ten most frequently observed mutations by continent of ascertainment (%) (by family).

	Mutation rank	Caucasian	African American	Asian	Hispanic/Latino	Jewish	Other
BRCA1	1	c.68_69del (26%)	c.2641G > T (26%)	c.68_69del (47%)	c.3331_3334del (20%)	c.5266dup (17%)	c.68_69del (10%)
	2	c.5266dup (13%)	c.5266dup (10%)	c.5266dup (14%)	c.5266dup (16%)	c.181T > G (7%)	c.5266dup (8%)
	3	c.181T > G (3%)	c.1374 del (6%)	c.390C > A (2%)	c.68_69del (9%)	c.68_69del (4%)	c.4065_4068del (4%)
	4	c.4327C > T (2%)	c.68_69del (6%)	c.5496_5506delinsA (2%)	c.5123C > A (8%)	c.4035del (2%)	c.3756_3759del (4%)
	5	c.4065_4068del (1%)	c.3228_3229del (6%)	c.5503C > T (1%)	c.211A > G (5%)	c.1687C > T (2%)	c.5503C > T (3%)
	6	c.3756_3759del (1%)	c.303T > G (6%)	c.2934T > G (1%)	c.181T > G (3%)	c.4065_4068del (2%)	c.4186-?_4357+?dup (3%)
	7	c.213-11T > G (1%)	c.4838_4839insC (3%)	c.3770_3771del (1%)	c.548-?_4183 + 8?del (3%)	c.3481_3491del (1%)	c.4327C > T (2%)
	8	c.1687C > T (1%)	c.3268C > T (3%)	c.2726dup (1%)	c.1687C > T (2%)	c.2475del (1%)	c.5278-?_5592+?del (2%)
	9	c.4186-?_4357+?dup (1%)	c.1504_1508del (3%)	c.470_471del (1%)	c.135-?_441+?del (2%)	c.3756_3759del (1%)	c.70_80del (2%)
	10	c.1175_1214del (1%)	c.191G > A (3%)	c.922_924delinsT (1%)	c.5030_5033del (2%)	c.3770_3704del (1%)	c.1961 del (2%)
Families		4669	69	1100	271	11,748	581
Unique Mutations		654	30	187	75	1282	173
BRCA2	1	c.5946del (23%)	c.7934del (47%)	c.5946del (34%)	c.2808_2811del (11%)	c.6275_6276del (2%)	c.5946del (5%)
	2	c.2808_2811del (3%)	c.5946del (4%)	c.7480C > T (4%)	c.5946del (9%)	c.5946del (2%)	c.6275_6276del (2%)
	3	c.8537_8538del (2%)	c.1310_1313del (2%)	c.3109C > T (3%)	c.2T > G (2%)	c.2808_2811del (2%)	c.7977-1G > C (1%)
	4	c.1813dup (2%)	c.6944_6947del (1%)	c.3744_3747del (2%)	c.156_157insAlu (2%)	c.771_775del (1%)	c.5682C > G (1%)
	5	c.6275_6276del (2%)	c.8817_8820del (1%)	c.1399A > T (2%)	c.6037A > T (2%)	c.3847_3848del (1%)	c.3847_3848del (1%)
	6	c.3847_3848del (3%)	c.5213_5216del (1%)	c.5576_5579del (2%)	c.6405_6409del (3%)	c.1813dup (1%)	c.2808_2811del (1%)
	7	c.658_659del (2%)	c.6535_6536insA (1%)	c.2808_2811del (1%)	c.5645C > G (1%)	c.5682C > G (1%)	c.755_758del (1%)
	8	c.9382C > T (1%)	c.774_775del (1%)	c.262_263del (1%)	c.658_659del (1%)	c.1310_1313del (1%)	c.4478_4481del (1%)
	9	c.3264dup (1%)	c.6393 del (1%)	c.8537_8538del (1%)	c.7180A > T (1%)	c.5645C > A (1%)	c.8297 del (1%)
	10	c.55073 dup (1%)	c.5042_5043del (1%)	c.7878G > A (1%)	c.5851_5854del (1%)	c.9026_9030del (1%)	c.250C > T (1%)
Families		3375	170	976	222	10,175	1047
Unique Mutations		660	27	187	58	1315	179

Geographic distribution of *BRCA1* and *BRCA2* gene mutations [6].

incremental costs, compared to the targeted-gene approach. The net result depends on whether or not these tests were reimbursed. This element should be considered together with several others, such as emerging costs per patient, outgoing costs per patient and overall impact on expenditure to estimate the variation in unit costs in relation to the organizational context (production volumes) and technology used, to guarantee its optimal use in different health care systems [32]. These studies will eventually identify excess and waste in the use of NGS technologies, which would affect their effective validity. The strong variability emerging from current evidence of the cost-effectiveness of NGS, in contrast to the targeted-gene approach, for reimbursement and/or recommendation decisions, is essentially attributable to the type of target patients and to the characteristics of the therapies once the mutations have been identified. Moreover, often no distinction is made about who will cover the costs of the therapies after the NGS test (in comparison with the targeted-gene test or "No Test" approach) [33–36]. Generally, the cost of a test performed by the NGS technology represents a very low percentage of the total cost of all clinical and diagnostic iter per patient. The use of the NGS technology in clinical practice is, indeed, robust and reliable even in the face of potential technical issues regarding the identification of a myriad of variants of unknown significance (VUS) that need to be periodically re-evaluated according to the upcoming evidence. Moreover, the risk to miss large deletions and complex rearrangements during the analysis should be taken into consideration [21,37]. It is predicted that this kind of issues would be overcome in a close future with novel artificial intelligence supported NGS sequencing platforms providing very dynamic and specific sequencing data with more information, higher quality and lower costs [36]. At the moment, however, the capacity in generating sequencing data is consistently higher than the possibility of the medical community (oncologists, geneticists, biologists) to interpret the generated data and to understanding the biological and clinical significance that guide the decision-making process. Current trends in big-data analysis techniques and the advancement of artificial intelligence algorithms, could lead to the development of decision-supporting tools or to the creation of Consortia between hospitals in order to help healthcare professionals in the identification and management of patients with specific genetic characteristics [38–42].

2.2. General population-based screening for the identification of a significant proportion of at-risk individuals as a cost-effective cancer prevention strategy

Several recent papers attempted to demonstrate how the population or "mainstream" screening approach of administering the BRCA genetic test can be advantageous in terms of cost-effectiveness and cost-benefit compared to the familiar history-based/guidelines strategy [12–14]. The Mainstreaming Cancer Genetics (MCG) Project study, carried out in the UK during the years 2013–2017, revealed the benefit of a population screening, which reduced the number of deaths from cancer over 50 years compared to the strategy based on family history. This approach also entails an advantage in terms of spending, with a ratio found in the predictive model of $ 1330 for discounted Quality Adjusted Life Years (QALYs)[1] and with a probability of cost-effectiveness greater than 99%, and a willingness-to-pay threshold of $ 26,184 per QALY [22]. Another recent study highlighted that, following the current patient selection criteria according to family history or clinical criteria, only 20–30% of the patients would pass the standard access threshold to the tests, while 97% would remain not identified, thus losing the possibility of implementing the correct preventive measures to manage the disease [43]. Furthermore, when we consider the possibility of applying tests containing multigenic panels to the same set of patients, the chance of finding important information that aids disease prevention and treatment purposes are further expanded. This study was carried out on data from 54,000 to 240,000 women with breast cancer in the UK and in the USA, respectively, at a cost of £ 10,464/QALY in the UK and $ 65,661/QALY in the USA. From the probabilistic sensitivity analysis, multigenic tests were found to be convenient from 98% to 99% in the UK and from 64% to 68% in the USA. The data show that, in one year, 2101 and 9733 new cases were identified and 633 and 2406 deaths were prevented in the UK and in the USA, respectively.

Another study, carried out in Norway, at Oslo University Hospital and Hammerfest Hospital (Finnmark) performed a cost-effectiveness analysis based on models that, once again, compared the traditional family history approach with the ones performed on all breast cancer patients. Specifically, the two approaches were: 1) the traditional FH approach used as a standard at Oslo University Hospital, Ullevål (OUH–U) in 2013; and 2) the intervention (test on all patients with breast cancer) performed in 2014 and 2015 in the same hospital. In this study, 535 breast cancer patients were tested for BRCA status (using sequencing technologies and gene fragment analysis). The national data on mortality rates and costs referred to the year 2014 and a discount rate of 3% was applied. The incremental cost-effectiveness ratio was calculated in euros (€) per year of life gained (LYG, Life Years Gained).[2] The results showed that the total healthcare costs (healthcare perspective) per LYG was € 40,503 and the corresponding figure for the societal perspective was € 5669. The data was confirmed by univariate sensitivity analysis. The BRCA diagnostic test performed on all patients with breast cancer was superior to the FH approach and more cost-effective at the thresholds used in Norway (€ 60,000 - € 80,000/LYG) [44].

All the mentioned studies highlight the cost-effective characteristic of the "mainstream" screening method compared to the family history-based approach with a gain for health care systems, with a cost-effective percentage between 84% and 93% in simulations in the UK and in the USA, respectively [12,14,45].

Additional studies will have to be developed in order to confirm these results in other countries, including Italy, starting from the data already generated on the advantage of the "Test" versus "No Test" approach in patients with BRCA mutation and family members, where the decrease in costs for treatment of ovarian and breast cancer cases corresponded to € 7,052,221.00 and € 18, 244, 182.13, respectively, and was calculated on the general population of patients with breast and ovarian cancer [46,48].

In Italy, as shown by the 2019 report of the Italian Association of Medical Oncology (AIOM), about 150,000 people carry the mutation in the *BRCA 1* and *2* genes and, considering the 53,500 estimated new cases of breast cancer, 5–7% are linked to hereditary factors, 25% of which are associated with a BRCA mutation (936 cases). Of the 5300 new cases of ovarian cancer, 15% are attributable to alterations in the *BRCA* genes (795 cases). Moreover, 4–5% of all patients with pancreatic cancer have a pathogenic variant of *BRCA1* or *BRCA2* (675 cases out of 13,500). In families with breast or ovarian cancers associated with pancreatic cancers, the presence of a BRCA mutation can be estimated to 25% [11]. Considering that most of these citizens do not know that they are carriers of a BRCA mutation, and due to the fact that genetic tests are not yet widespread enough, the challenge, also in this scenario, is to extend genetic screening to all healthy individuals.

A recent study by Manchanda and colleagues [13] explores for the first time the cost-effectiveness of population-based BRCA testing in women aged 30 years and older across different countries and health care systems such as the UK, the USA and the Netherlands (high-income countries), China and Brazil (upper-middle income countries), and India (low-middle income countries). The results confirm once again how the population-based BRCA screening approach, considering both the societal perspective and the payer perspective, is cost saving and highly cost-effective, respectively, compared with clinical criteria/FH-based testing in the mentioned countries except for India (where the costs of BRCA testing need to be lowered in order to reach cost-effectiveness), with a possibility to prevent tens of thousands more breast and ovarian cancer cases than the current clinical strategy (Table 3).

Finally, *The Screen Project*, a population screening project currently taking place in Canada, aims to analyze the entire Canadian population aged 18 years and older in order to identify as many mutation carriers as possible and to reduce the morbidity and mortality of breast cancer, ovarian cancer, prostate cancer and other types of cancers at a very affordable cost ($ 165) [47]. To achieve this goal, *The Screen Project* was designed to take into account five specific points: 1) measure the feasibility of BRCA genetic tests between Canadian men and women using a guided approach directed to consumers; 2) determine the frequency of BRCA1 and BRCA2 mutations in unselected Canadians; 3) assess the level of satisfaction among the participants following a consumer-led approach to genetic testing; 4) measure the psychological impact related to the definition of a positive or negative genetic test result among the participants; 5) estimate the number of breast and ovarian cancers prevented in Canada through a consumer-driven approach to BRCA genetic testing. Preliminary data show that the frequency of BRCA1 and BRCA2 mutations in the general population

[1] QALY (Quality Adjusted for Life Years) is one of the most used units for measurement of utility cost analysis, which takes into account not only the number of years of life gained, but also the quality of life (less illness and disability, etc.). In practice, the usefulness of an intervention expressed in QALY, results from the years of life of a subject multiplied by a coefficient that summarizes the state of health of the same subject: QALY = n. Years x quality of life coefficient. QALYs can be used to compare the results of different interventions/health treatments with the same purpose: for example, to compare a surgical treatment with a pharmacological therapy of the same disease.

[2] LYG (Life Years Gained): Life Years Gained is a modified mortality measure where remaining life expectancy is taken into account. This method ascribes more weight to young target populations, because saving the life of an infant yields more life years than saving life of an old person. Life years are calculated as the remaining life expectancy at the point of each averted death.

Table 3
A summary of major findings of the cited studies for economic evaluations.

Study	Country	Year	Population	Screening approach	Familiar History (FH) approach	Total costs	Results
Manchanda R et al. [13]	UK, USA, Netherlands (high-income countries/HIC), China, Brazil (upper−middle income countries/ UMIC) and India (low −middle income countries/LMIC)	2020	All general population of women ≥30 years compared with clinical-criteria/FH-based testing	**societal perspective**: $18.568 (UK)/$21,951 (USA)/$24,642 (NL)/ $7687 (China)/$6314 (Brazil)/$30,968 (India) **payer perspective**: $2543 (UK)/$7250 (USA)/$2748 (NL)/$820 (China)/$834 (Brazil)/ $634 (India)	**societal perspective**: $18,623 (UK)/$21,982 (USA)/$24,750 (NL)/ $7568 (China)/$6153 (Brazil)/$30,779 (India) **payer perspective**: $2336 (UK)/$7122 (USA)/$2239 (NL)/$665 (China)/$586 (Brazil)/ $369 (India)	**societal perspective**: cost-saving in HIC (UK-ICER = $5639/QALY; USA-ICER = $4018/ QALY; Netherlands-ICER = $11,433/QALY); appears cost-effective in UMIC (China-ICER = $18,066/QALY; Brazil-ICER = $13,579/ QALY); not cost-effective in LMIC (India-ICER = $23,031/QALY). **payer perspective**: highly cost-effective in HIC (UK-ICER = $21,191/ QALY, USA-ICER = $16,552/QALY, Netherlands-ICER = $25,215/QALY); cost-effective in UMIC (China-ICER = $23,485/ QALY, Brazil−ICER = $20,995/ QALY); not cost-effective in LMIC (India-ICER = $32,217/QALY)	Population-based BRCA testing can prevent an additional 2319 to 2666 BCE and 327 to 449 OC cases per million women than the current clinical strategy. Findings suggest that population-based BRCA testing for countries evaluated is extremely cost-effective across HIC/UMIC health systems, is cost-saving for HIC health systems from a societal perspective, and can prevent tens of thousands more BC/OC cases
Manchanda R et al. [16]	UK, USA	2019	Jewish Population	£21,599.96/QALY (UK)/ $54,769.78/QALY (USA)	na	na	Sensitivity analyses demonstrated that population testing remained cost-effective over 84% and 93% of simulations for UK and US health systems, respectively
Zhang L et al. [19]	Australia	2019	Preventive population genomic screening to all adults aged 18−25 years in Australia, assuming a 71% testing uptake, compared with current estimated rates of targeted testing (15% for cancer gene testing and 5% for preconception carrier screening)	AUD$12,973 ($8532 to $19,759]/DALY[a] prevented)	AUD$200 to $1200 per test	AUD$651(448−865) million	Screening would prevent an estimated 73,728 (53,303 to 104,266) DALYs and save AUD$311 million ($168 to $517 million) in treatment costs through prevention, for a net health system cost of AUD$302 million ($0 to $573 million), above current expenditure
Kemp Z et al. [22]	UK, Malaysia	2019	HBOC patients (mainstream	MGC Criteria: $59,746 (testing)/MCG Plus Criteria: $73,792 (testing)	MGC Criteria: $57,691 (no testing)/MCG Plus Criteria: $71,046 (no testing)	**Test**: MCG Criteria: $175, 259.610 ($1330 per QALYs)/MCG Plus Criteria: $193,587.091 ($1225 per QALYs) **NO Test**: $172,525.741 ($1330 per QALYs)/MCG Plus Criteria: $190,223.417 ($1225 per QALYs)	With use of the MCG criteria, the model estimates that 804 cancers and 161 deaths would be prevented per year of testing over the subsequent 50 years. With use of the MCG plus criteria, 1020 cancers and 204 deaths are estimated to be prevented per year over 50 years
Sun L. et al. [43]	USA, UK	2019	All patients with BC (strategy A) compared with the current practice of BRCA testing using clinical- or FH-based criteria (≥10% pathogenic variant risk) (strategy B).	£18,772/LYGs (UK)/ $18,652/LYGs (USA)	£18,755/LYGs (UK)/ $18,639/LYGs (USA)	£11,817/LYGs(UK)/	Strategy A was associated with an additional 419-day increase in life expectancy for UK and 298 days for US BRCA1/ BRCA2/PALB2 pathogenic variant carriers

Table 3 (*continued*)

Study	Country	Year	Population	Screening approach	Familiar History (FH) approach	Total costs	Results
Norum J. et al. [44]	Norway	2018	Patients with FH vs all patients with BC	€ 17.84	€ 13.33	€40,503 for Life Years gained (LYG)	Diagnostic BRCA testing of all patients with BC was superior to the FH approach and cost-effective within the frequently used thresholds (healthcare perspective) in Norway (€60 000–€80 000/ LYG)

[a] DALY: one DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population (World Health Organization definition).

is estimated to be between 1 in 200 and 1 in 400, respectively. Among the first 150 people tested, 5 were identified with a BRCA mutation but only 2 of which meet the enrollment criteria according to guidelines for access to the test financed with public funds. Clearly, this screening model allows the identification of more mutation carriers in the population before they are diagnosed with cancer. Therefore, this data strongly supports the benefit of a population screening that, in terms of prevention and treatment, would reduce both cancer incidence and mortality.

2.3. Patient perspective: implication and ethical considerations

The topics discussed in this review are focused on the economic aspects related to the introduction, in current clinical practice, of population screenings for patients with BRCA mutation and the impact of this intervention on different health care systems worldwide. The ethical aspects are not of secondary importance as the collected data contains sensitive information. In the specific case of hereditary tumors, this approach would translate into managing healthy individuals at great risk of developing a cancer before its diagnosis as they would be classified as “risk-affected patients”.

In addition, the management of the Incidental Findings (IFs) is directly related to the big data generation of NGS technologies. IF is a group of mutations or variations that may have clinical implications and are found accidently during genetic analyses carried out for a different medical purpose. As these findings are often not interpretable and may be of uncertain significance, there is a clear need for sharing guidelines to support the most appropriate management of these findings, in ethical, clinical and research contexts.

3. Conclusions

Recent studies show that an approach based on current guidelines for the administration of genetic tests is not only limiting in order to identify the highest possible number of patients with mutations and not belonging to the so-called high-risk families, but in this perspective, it is also less cost-effective than a screening carried out on the entire population which would intercept mutated but still healthy individuals. It is therefore desirable for the future a “dam fishing effect” scenario in which, the more patients will be identified as mutated, the sooner and better they will be treated with the result of a lower impact on public health costs due to delayed care.

A hypothetical scenario can be outlined, based on available data, in order to perform economic evaluations that prove the validity of the discussed approach, both in terms of cost-effectiveness and improvement of the public health, to aid the decision-making processes of future health policies to ultimately make genetic testing available for the whole population. At the present time, it is believed that this approach must be validated in the so called “Real World”, with a pragmatic analysis approach involving NGS genetic testing of a reduced number of individuals. Notably, a high number of tests would lead to a significant reduction in the total costs, which would not exceed a few hundreds of euros per patient.

Author contributions

FF, MV, MAP and MF contribute to the study concept and design, to manuscript preparation, editing and review. All authors read and approved the final manuscript.

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Declaration of competing interest

FF, MV and MAP are employees of Cogentech Ltd Benefit Corporation, MF is a consultant for Cogentech srl activities. Cogentech Ltd Benefit Corporation is a private limited company owned by the no-profit research institute IFOM (FIRC Institute of Molecular Oncology) whose mission is to provide technological services for the post-genomic era to researchers and clinicians. Cogentech services are dedicated to members of the international scientific community and clinicians who wish to use them for diagnostic purposes. Cogentech specifically, provides and develops genetic tests of susceptibility to various hereditary cancers including those related to the evaluation of BRCA gene mutations in patients with breast and ovarian cancer. In this perspective, the topic of the manuscript is related to general public benefits and a positive impact on cancer patients and society, at large, interests that are part of the mission of Cogentech Ltd Benefit Corporation activity. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials

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