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Population Screening for Inherited Predisposition to Breast and Ovarian Cancer

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Abstract

The discovery of genes underlying inherited predisposition to breast and ovarian cancer has revolutionized the ability to identify women at high risk for these diseases before they become affected. Women who are carriers of deleterious variants in these genes can undertake surveillance and prevention measures that have been shown to reduce morbidity and mortality. However, under current strategies, the vast majority of women carriers remain undetected until they become affected. In this review, we show that universal testing, particularly of the *BRCA1* and *BRCA2* genes, fulfills classical disease screening criteria. This is especially true for *BRCA1* and *BRCA2* in Ashkenazi Jews but is translatable to all populations and may include additional genes. Utilizing genetic information for large-scale precision prevention requires a paradigmatic shift in health-care delivery. To address this need, we propose a direct-to-patient model, which is increasingly pertinent for fulfilling the promise of utilizing personal genomic information for disease prevention.

1. INTRODUCTION

Identification of the *BRCA1* and *BRCA2* genes in the mid-1990s ushered in the era of genetic testing for inherited susceptibility to breast and ovarian cancer. In the 25 years since this landmark, *BRCA1* and *BRCA2* have been studied extensively, the risks associated with carrying deleterious (pathogenic or likely pathogenic) variants in these genes have been delineated (81, 112), and effective strategies for early detection and prevention have been shown to reduce morbidity and mortality in carriers (34, 43, 64). An extensive spectrum of variants—more than 5,000 in each gene (87)—have been revealed and assessed for pathogenicity, and biological functions of these genes have been identified that were unknown when they were first discovered (175). This work has led to the development and application of targeted therapy for tumors caused by deleterious variants in these genes (95, 149). In parallel, additional breast and ovarian cancer predisposition genes have been recognized, and the advent of genomic sequencing technologies has revolutionized the testing landscape, enabling simultaneous analysis of multiple genes at greatly reduced cost.

These developments provide the underpinnings of a precision medicine approach to inherited breast and ovarian cancer predisposition. Precision medicine has been defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (127; see also 28). The germline genetic variability underlying cancer predisposition has so far been utilized primarily for cancer therapy, largely in patients with advanced malignancies (168). However, its greatest potential is likely to lie in so-called precision prevention (60, 144, 171); as previously observed, "to identify a woman as a carrier only *after* she develops cancer is a failure of cancer prevention" (79, p. 1091).

Undertaking gene-based prevention at the population level requires a population screening approach. The principles of population screening for disease were originally delineated in 1968 by Wilson & Jungner (183) (see the sidebar titled Principles of Disease Screening) and have served as the foundation of various screening programs, including newborn screening for metabolic and genetic diseases, preconception carrier screening, and screening of adults for hypertension and hypercholesterolemia (78). An underlying assumption of disease screening is that it is intended not to identify all individuals with the disease but rather to cast a wide net

PRINCIPLES OF DISEASE SCREENING

The following principles of disease screening were laid out by Wilson & Jungner (183) in 1968:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once-and-for-all project.

that will capture a significant proportion of at-risk individuals in a cost-effective manner. In this sense, it is fundamentally different from using precision medicine tools as an exhaustive measure to determine treatment options for a specific patient.

In this review, we assess current knowledge of genetic testing for breast and ovarian cancer predisposition within the framework of the 10 population screening principles listed in the sidebar. We focus on population screening for *BRCA1/BRCA2* in Ashkenazi Jews (AJs), since most of the current evidence base for such screening is based on testing pathogenic *BRCA1/BRCA2* founder variants (also called founder mutations) in this population. We also assess other populations, as well as a framework for widening the scope of screening to include additional breast and ovarian cancer predisposition genes.

Deleterious variants in *BRCA1/BRCA2* and other genes implicated in breast and ovarian cancer predisposition also increase the risk for various other malignancies in both women and men. For example, deleterious variants in *BRCA2* are also associated with increased risk for pancreatic cancer in both genders and for prostate cancer in men (126). In this review, we focus on *BRCA1/BRCA2* population screening for prevention of breast and ovarian cancer in women. These malignancies account for the majority of *BRCA1/BRCA2*-associated cancers and for most of the current data.

The founder pathogenic variants common in AJs are 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*. Their combined frequency in unaffected AJs is 1:40 (2.5%) (151). Each of these variants is a frameshift, resulting in a null allele. The formal nomenclature for these variants is NM_007294.3(BRCA1):c.68_69delAG (p.Glu23Valfs), NM_007294.3(BRCA1):c.5266dupC (p.Gln1756Profs), and NM_000059.3(BRCA2):c.5946delT (p.Ser1982Argfs). We use the original names for these variants because they are commonly used in the literature and are more widely familiar. As noted above, we use the term deleterious variant to indicate variants classified as either pathogenic or likely pathogenic using American College of Medical Genetics and Genomics (ACMG) criteria. We use the term carriers to indicate heterozygotes for a deleterious variant.

2. GERMLINE PREDISPOSITION TO BREAST OR OVARIAN CANCER, AND PRINCIPLES OF DISEASE SCREENING

2.1. The Importance of Breast and Ovarian Cancer in Women and the Role of Inherited Predisposition (Principle 1)

Breast cancer is the most common cancer in women globally, excluding nonmelanoma skin cancer. Invasive breast cancer incidence is currently approximately 2.1 million women worldwide (3), including an estimated 268,600 women in the United States alone (4). In women, breast cancer is the leading cause of cancer deaths worldwide (3) and the second leading cause of cancer deaths (following lung cancer) in most developed countries (4). Breast cancer accounts for ~15% of cancer deaths, annually numbering 41,760 and 626,700 women in the United States and worldwide, respectively (3, 4). Ovarian cancer is ~10-fold less common but is the most lethal gynecological malignancy: It accounts for 5% of all cancer deaths, and in the United States, the 5-year survival rate for ovarian cancer is 47%, compared with 90% for breast cancer (4). Ovarian cancer incidence is estimated at 295,414 women globally (19), including 22,530 women in the United States (4).

Family history is a major risk factor for both breast and ovarian cancer, largely as a result of inherited predisposition (167). Deleterious variants in *BRCA1* and *BRCA2* remain the most common cause of hereditary breast and ovarian cancer and have the highest cancer risks for carriers of deleterious variants. However, germline deleterious variants in other genes are also known to increase risk for breast or ovarian cancer: Deleterious variants in *ATM*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, *TP53*, and *STK11* increase breast cancer risk (88, 126), and pathogenic variants in *RAD51C*, *RAD51D*, and *BRIP1*, as well as in the genes underlying Lynch syndrome (*MLH1*, *MSH2*, *MSH6*,

and *PMS2*), increase ovarian cancer risk (88, 126). Other associations remain controversial or uncertain, including the role of some breast cancer genes in ovarian cancer predisposition (e.g., *ATM*), the role of some ovarian cancer genes in breast cancer (e.g., *RAD51C* and *BRIP1*), and the role of other candidate genes (e.g., *RINT1* in breast cancer and *RAD50* in ovarian cancer) (88, 126). Evaluating the roles and associated risks of all proposed breast and ovarian cancer genes is not the purpose of this review. We use accepted gene-risk categories, with moderate-risk genes being those associated with an odds ratio of 2–4-fold for breast or ovarian cancer and high- and low-risk genes being associated with higher and lower odds ratios, respectively (35).

2.2. Attributable Risk of Germline Deleterious Variants to Breast and Ovarian Cancer (Principle 1)

The proportion of breast and ovarian cancer attributable to deleterious variants in *BRCA1/BRCA2* and the other predisposition genes varies between populations (9). Multiple studies of the genetic bases of these malignancies have been performed in cancer patients selected for various criteria, including family history, age at diagnosis, and specific tumor pathology (e.g., triple-negative breast cancer). For population screening, it is important to determine the attributable risk of germline deleterious variants in the general population, i.e., in patients ascertained with minimal bias.

For *BRCA1/BRCA2* in breast cancer, among AJs, ~10% of unselected breast cancer patients are carriers of one of the three common pathogenic variants (80), which account for more than 90% of the *BRCA1/BRCA2* deleterious variant spectrum in AJs (46, 155). In a large cohort of unselected AJ breast cancer patients who underwent sequential testing (*BRCA1/BRCA2* founder variant testing followed by full sequencing), 104/1,007 (10.3%) carried a founder pathogenic variant, and 7/1,007 (0.7%) carried a nonfounder *BRCA1/BRCA2* pathogenic variant (178). In ethnically diverse, unselected women with breast cancer, recent studies using full gene sequencing have found that the carrier rate of *BRCA1/BRCA2* pathogenic variants is ~6% (84, 170). This includes a large cohort of more than 18,000 breast cancer patients who underwent clinical testing (84).

The frequency of deleterious variants in non-*BRCA1/BRCA2* breast cancer predisposition genes is lower than that of *BRCA1/BRCA2*. Reports of multigene panel test (MGPT) results often include variants in genes considered unrelated to breast cancer (e.g., variants in colon cancer genes) or whose association with breast cancer is still uncertain (e.g., *BRIP1* and *NBN* variants other than 675del5). Thus, even the lower rates reported for non-*BRCA1/BRCA2* genes likely overestimate the attributable risk of these genes. In a study of unselected AJ breast cancer patients, the rate of non-*BRCA1/BRCA2* deleterious variants in the entire group was 3.0%, largely explained by a 2.2% rate of *CHEK2* S428F, a founder variant in a moderate-risk gene (178). In diverse unselected breast cancer patients, the rate of deleterious variants in non-*BRCA1/BRCA2* breast cancer predisposition genes is similar: 3.9–4.6% (84, 169, 170). As with AJs, deleterious variants in moderate-risk genes (e.g., *ATM* and *CHEK2*) account for the majority of non-*BRCA1/BRCA2* cases. Importantly, the percentage of breast cancers explained by all high-risk syndromic non-*BRCA1/BRCA2* genes (e.g., *TP53* and *PTEN*) is very low (<0.25%), and ~1% are explained by *PALB2*, which is emerging as a high-risk breast cancer gene (31, 83, 185) (**Table 1**).

The attributable risk of known cancer predisposition genes is higher for ovarian cancer than for breast cancer. This is particularly striking among AJs, where the three *BRCA1/BRCA2* founder variants account for ~40% of all epithelial ovarian cancers (66, 125). In ethnically diverse populations, the prevalence of *BRCA1/BRCA2* deleterious variants in large series of unselected ovarian cancer patients was 13–18% (2, 133, 177, 187). The contribution of non-*BRCA1/BRCA2* genes to ovarian cancer is also larger than their contribution to breast cancer. These genes include some recently validated ovarian cancer genes (e.g., *RAD51C*, *RAD51D*, and *BRIP1*) as well as the genes

Table 1 Non-*BRCA1/BRCA2* genes with high penetrance for breast or ovarian cancer

Gene symbol	Syndrome	Nontumor feature(s)	Tumor type(s)	Cancer risk		Carrier rate of deleterious variants in cancer patients	Carrier rate of deleterious variants in controls[a]
				By age 70 years, ascertainment	OR versus controls (95% CI), ascertainment		
Breast cancer							
TP53	Li–Fraumeni syndrome (158)	—	Breast (particularly premenopausal), soft tissue sarcoma, osteosarcoma, adrenocortical, brain	54%, Li–Fraumeni syndrome families (98)	—	—	—
				—	11 (0.61–201), case–control study (169)	0.25% (5/2,000) (169)	0% (0/1,997) (169)
				—	5.37 (2.78–10.4), MGPT case–control study (83)	0.095% (25/26,384) (83)	0.025% (16/64,649) (83)
				—	2.58 (1.39–4.9), MGPT versus database (31)	0.13% (48/38,305) (31)	0.049% (13/26,789) (31)
PTEN	Cowden syndrome/*PTEN* hamartoma syndrome (37)	Macrocephaly, skin lesions (trichilemmomas, papillomatous papules)	Breast, thyroid (nonmedullary), endometrial	77–85%, *PTEN* hamartoma syndrome families (21, 165)	—	—	—
				—	NS, case–control study (169)	0% (0/2,000) (169)	0% (0/1,997) (169)
				—	5.83 (2.43–14.0), MGPT case–control study (83)	0.057% (15/26,384) (83)	0.014% (9/64,649) (83)
				—	12.7 (2.0–258.9), MGPT versus database (31)	0.052% (20/38,179) (31)	0.0041% (1/24,166) (31)

(*Continued*)

Table 1 (*Continued*)

Gene symbol	Syndrome	Nontumor feature(s)	Tumor type(s)	Cancer risk		Carrier rate of deleterious variants in cancer patients	Carrier rate of deleterious variants in controls[a]
				By age 70 years, ascertainment	OR versus controls (95% CI), ascertainment		
Breast cancer							
CDH1	Hereditary diffuse gastric cancer syndrome (76)	—	Lobular breast, diffuse gastric	42.9–52%, *CDH1* families (77, 184)	—	—	—
				—	NS, case–control study (169)	0.05% (1/2,000) (169)	0% (0/1,997) (169)
				—	NS, MGPT case–control study (83)	0.049% (13/26,384) (83)	0.043% (28/64,649) (83)
				—	5.34 (1.6–10.9), MGPT versus database (31)	0.062% (23/37,277) (31)	0.012% (3/25,961) (31)
STK11	Peutz–Jeghers syndrome (115)	Mucocutaneous pigmentation	Colorectal, gastric, pancreatic, breast, ovarian (nonepithelial); gastrointestinal polyps (hamartomas)	32–54%, *STK11* families (115)	—	—	—
				—	NS, case–control study (169)	0% (0/2,000) (169)	0% (0/1,997) (169)
				—	NS, MGPT case–control study (83)	0.0076% (2/26,384) (83)	0.0031% (2/64,649) (83)
				—	NR, MGPT versus database (31)	NR (31)	NR (31)
PALB2	—	—	Breast (including male), ovarian (moderate risk), pancreatic (185)	44% (37–52%) [53% (44–63%) by age 80], *PALB2* families (185)	7.18 (5.82–8.85) (185)	—	—
				—	6.56 (2.29–18.8), case–control study (169)	1.3% (26/2,000) (169)	0.20% (4/1,997) (169)

(*Continued*)

Table 1 (*Continued*)

Gene symbol	Syndrome	Nontumor feature(s)	Tumor type(s)	Cancer risk		Carrier rate of deleterious variants in cancer patients	Carrier rate of deleterious variants in controls[a]
				By age 70 years, ascertainment	OR versus controls (95% CI), ascertainment		
Breast cancer							
				—	3.39 (2.79–4.12), MGPT case–control study (83)	0.97% (257/26,384) (83)	0.33% (212/64,649) (83)
				—	7.46 (5.12–11.9) MGPT versus database (31)	0.80% (241/30,025) (31)	0.11% (29/26,869) (31)
Ovarian cancer							
RAD51C	—	—	Ovarian (88)	—	4.98 (3.09–8.04), MGPT case–control study (83)	0.64% (32/5,020) (83)	0.11% (72/64,649) (83)
					5.12 (3.72–6.88), MGPT case–control study (92)	0.70% (44/6,294) (92)[b]	0.12% (31/26,647) (31), 0.14% (92)
RAD51D	—	—	Ovarian (88)	—	4.78 (2.13–10.7), MGPT case–control study (83)	0.18% (9/5,020) (83)	0.062% (40/64,649) (83)
					6.34 (3.16–11.34), MGPT case–control study (92)	0.19% (11/5,743) (92)[b]	0.023% (6/26,555) (31), 0.03% (92)

Abbreviations: CI, confidence interval; ExAC, Exome Aggregation Consortium; MGPT, multigene panel test; NR, not reported; NS, not significant; OR, odds ratio; —, none (for syndrome or nontumor features) or no data (for cancer risk and carrier rates).

[a]Controls in the case–control study were unaffected women in a mammography screening project, controls in the MGPT case–control study were unaffected women who had MGPT testing, and database controls were allele frequencies in ExAC.

[b]Frequencies are for variants also present or detectable in ExAC, for comparison with controls. The prevalence of all deleterious variants (including large genomic rearrangements and variants not present in the ExAC data set) are slightly higher: 0.79% for *RAD51C* and 0.31% for *RAD51D* (92).

underlying Lynch syndrome. Although largely a colon cancer predisposition syndrome, Lynch syndrome is also associated with increased risk for ovarian cancer. The reported rates of non-*BRCA1/BRCA2* deleterious variants in ovarian cancer are 5.7–6.8% (84, 132, 133), with an ~1% rate of variants in high-risk ovarian cancer genes (*RAD51C* and *RAD51D*) and an ~1.5% rate for all Lynch syndrome genes combined (83, 92) (**Table 1**).

To summarize, *BRCA1* and *BRCA2* account for ~10% and up to 6% of breast cancer in AJs and diverse populations, respectively, and ~40% and ~15% of ovarian cancer in AJs and diverse populations, respectively. Overall, high-risk non-*BRCA1/BRCA2* genes account for less than 1.5% of breast cancer cases and up to 2.5% of ovarian cancer cases.

2.3. Carrier Status for Breast and Ovarian Cancer Predisposition: A Defined Latent/Presymptomatic Stage (Principles 4 and 8)

Deleterious variants in *BRCA1/BRCA2*, as well as in other cancer predisposition genes, clearly increase cancer risk in individual carriers (see Section 2.4). Thus, as long as a carrier of a deleterious variant is unaffected with a specific cancer, carrier status represents a presymptomatic stage for that particular malignancy. In the case of *BRCA1/BRCA2*, a carrier unaffected with any cancer is presymptomatic for any *BRCA1/BRCA2*-associated cancer, whereas a carrier who is affected with breast cancer can still be regarded as presymptomatic for other associated malignancies (e.g., ovarian or pancreatic cancer). The definition of the presymptomatic stage is thus clear cut. The key question is essentially who should be tested to determine whether they are presymptomatic, i.e., carriers.

Currently, the majority of individuals who undergo germline cancer predisposition testing have a personal history of cancer (31, 83). Multiple guidelines issued by various professional bodies focus largely on criteria for selecting affected individuals for testing based on the type of cancer, age at diagnosis, family history, tumor pathology, and in some cases AJ ethnicity (126, 128, 134). In affected women, such testing is performed to inform treatment, but obviously, prevention can be achieved only by identifying carriers before they become affected. Current testing guidelines for unaffected individuals are shown in **Table 2**, which compiles 10 different guidelines from the United States, Europe, and Australia, all published in recent years (2015–2020). Essentially all guidelines recommend genetic testing for unaffected women only if there is a known *BRCA1/BRCA2* deleterious variant in their family (i.e., cascade testing) or if they have a significant family history of *BRCA1/BRCA2*-associated cancers. Comparing the same guidelines over time shows that the threshold for recommending testing has been lowered somewhat. However, except for the most recent version of the National Comprehensive Cancer Center (NCCN) guidelines (version 1.2020) (126), the threshold for genetic testing is a family history that corresponds to an ~10% probability of identifying a germline deleterious variant in *BRCA1/BRCA2* (134) (**Table 2**). With respect to unaffected AJs, some guidelines (12, 86, 126, 128, 134) regard AJ ancestry as one of the risk factors moving the needle toward testing, but this is almost always considered in the context of family history. Among the six risk assessment tools recommended by the US Preventive Services Task Force (USPSTF), only three include AJ ancestry as a risk factor, and the USPSTF explicitly recommends against testing unaffected women without a family history of *BRCA1/BRCA2*-associated cancers (134). The most substantial change in testing recommendations for unaffected women is in the most recent NCCN guidelines, which state that genetic testing can be considered in unaffected women either if they are of AJ ancestry or if accepted risk assessment tools indicate a 2.5–5% probability of identifying a *BRCA1/BRCA2* deleterious variant (126). The 2.5% threshold is consistent with the proportion of AJs who harbor a pathogenic variant.

Family-history-based criteria remain central in updated recommendations, even though they have been repeatedly shown to miss approximately half of *BRCA1/BRCA2* carriers. Among AJs in Israel, a population-based study of *BRCA1/BRCA2* families identified through unaffected males found that 51% had little or no relevant family history (49). In AJ screening trials in the United

Table 2 Eligibility for *BRCA1/BRCA2* testing of individuals without a personal history of breast or ovarian cancer: selected guidelines[a]

Guidelines	Location	Year	Reference(s)	Cancer history in relatives		
				Degree of relationship	*N*	Cancer type[b]
NCCN	United States	2020	126	1 or 2	≥1	■ Breast, age ≤45 ■ Breast, age 46–50, if family history is limited OR if a relative had two primary breast cancers ■ Breast, age ≤60, triple negative ■ Breast, any age if AJ ■ Ovarian ■ Prostate: intraductal or metastatic ■ Prostate: high-grade if AJ ■ Male breast
				1 or 2	≥2	■ Breast, age 46–50, plus a close blood relative[c] with any of the following: breast, ovarian, pancreatic, high-grade prostate, or intraductal prostate cancer ■ Breast plus a close blood relative[c] with any of the following: breast cancer at age ≤50 or ovarian, pancreatic, intraductal prostate, or metastatic cancer ■ High-grade prostate plus a close blood relative[c] with any of the following: breast cancer at age ≤50 or ovarian, pancreatic, intraductal prostate, or metastatic prostate cancer
				1 plus 2 or 3	≥3	■ Breast[c] ■ High-grade prostate plus two close blood relatives[c] with breast or prostate cancer
				Other	—	■ >5% probability of detecting a *BRCA1/BRCA2* deleterious variant ■ May be considered for AJ[d] ■ May be considered for a 2.5–5% probability of detecting a *BRCA1/BRCA2* deleterious variant[d]

(*Continued*)

Table 2 (*Continued*)

Guidelines	Location	Year	Reference(s)	Cancer history in relatives		
				Degree of relationship	*N*	Cancer type[b]
NICE[e]	United Kingdom	2019	128	1	1	■ Bilateral breast, average age <50
				1 or 2	≥2	■ Breast, average age <50, of which at least one is a first-degree relative ■ Breast and ovarian, age <50, of which at least one is a first-degree relative ■ Two ovarian cases ■ Bilateral breast and breast, age <60 ■ Male breast plus breast, age <50
				1 or 2	≥3	■ Breast, average age <60, of which at least one is a first-degree relative ■ Ovarian and two breast cases, average age <60 ■ Male breast plus two breast cases, average age <60
				≥1	≥4	■ Breast,[c] of which at least one is a first-degree relative
				Other	—	■ ≥10% chance of a deleterious variant in the family ■ >8% risk of developing breast cancer in the next 10 years ■ ≥30% lifetime risk of developing breast cancer
USPSTF	United States	2019	134	Other	—	Assessment of family history based on one of six tools,[f] where a positive result generally corresponds to a 10% chance of identifying a *BRCA1/BRCA2* deleterious variant
ACOG	United States	2019	30	—	—	Hereditary cancer risk assessment for referral to a specialist; genetic testing may be performed using an MGPT
AGO	Germany	2019	6	—	≥1	■ Breast and ovarian ■ Bilateral breast, first case at age <50 ■ Breast, age <35
					≥2	■ Breast, age <50 ■ Breast plus ovarian ■ Ovarian ■ Male breast plus breast or ovarian
					≥3	Breast

(*Continued*)

Table 2 (*Continued*)

Guidelines	Location	Year	Reference(s)	Cancer history in relatives		
				Degree of relationship	*N*	Cancer type[b]
eviQ	Australia	2019	38	1 or 2	≥2	Breast or ovarian plus one or more of the following:[c] additional relative(s) with breast or ovarian cancer, breast cancer at age <50, more than one primary breast cancer in the same woman, breast and ovarian cancer in the same woman, Jewish ancestry, male breast cancer, and/or pancreatic or high-grade prostate cancer
ESMO	Europe	2016	136	Other		Only if relatives are known *BRCA1/BRCA2* carriers
ACMG	United States	2015	12, 63	1 or 2	≥1	■ Breast, age ≤50 ■ Breast, age ≤60, triple negative ■ Two or more primary breast cases in the same person ■ Breast, AJ ■ Breast plus one or more Peutz–Jeghers polyps in the same person ■ Lobular breast plus diffuse gastric in the same person ■ Male breast ■ Breast plus two additional Cowden syndrome criteria[h] in the same person ■ Breast plus one additional Li–Fraumeni syndrome tumor[i] in the same person or in two relatives, one age ≤45
					≥2	Lobular breast in one relative and diffuse gastric in another, one age <50
					≥3	Breast, ovarian, pancreatic, and/or aggressive prostate in close relatives
SEOM	Spain	2015	94	1	≥2[c]	■ Bilateral breast plus another breast cancer, age ≤50 ■ Breast and ovarian ■ Male breast ■ Two breast cases, age <50
					≥3[c]	Direct relatives with breast or ovarian cancer

(*Continued*)

Table 2 (*Continued*)

Guidelines	Location	Year	Reference(s)	Cancer history in relatives		
				Degree of relationship	*N*	Cancer type[b]
SGO	International	2015	86	1, 2, or 3	1–several	■ Breast, age ≤45 ■ Breast plus close relatives[g] with breast cancer at age ≤50 or ovarian cancer ■ Breast, age ≤50 years, with a limited family history ■ Breast plus two or more close relatives[g] with breast cancer ■ Breast plus two or more close relatives[g] with pancreatic or high-grade prostate cancer ■ Two breast primaries, with the first diagnosed at age ≤50 ■ Breast, triple negative, age ≤60 years ■ Breast, AJ ■ Ovarian ■ Pancreatic plus two or more close relatives[g] with breast, ovarian, pancreatic, or high-grade prostate cancer
				1, 2, or 3	≥1	Male breast

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; AJ, Ashkenazi Jewish (one or more AJ grandparent); ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; SEOM, Sociedad Española de Oncología Médica; SGO, Society of Gynecologic Oncology; USPSTF, US Preventive Services Task Force; —, not indicated.

[a]Individuals with a family history of a known *BRCA1/BRCA2* pathogenic variant are eligible for testing under all guidelines.

[b]If no age is indicated, any age at diagnosis fulfills the criterion. Ovarian cancer indicates epithelial cancer, including fallopian tube and peritoneal cancer; pancreatic cancer indicates exocrine cancer; high-grade prostate cancer is defined as one with a Gleason score of 7 or higher.

[c]On the same side of the family.

[d]As part of a study or with pretest education.

[e]The NICE guidelines recommend genetic testing if there is a combined *BRCA1* and *BRCA2* deleterious variant probability of 10% or more. The table lists criteria for referral to a specialist genetic clinic of an individual with no personal history of breast cancer. NICE also includes two additional midlevel risk categories: requesting advice from a genetics specialist clinic regarding referral, and referral to secondary care. Secondary care includes intensive surveillance by a multidisciplinary team and is meant for women whose risk is higher but not sufficiently high for referral to a genetics specialist clinic. Advice request and secondary care criteria are given in **Supplemental Table 1**.

[f]Based on accepted predictive models; see the USPSTF guidelines for the full list.

[g]Close relative is defined as a first-, second-, or third-degree relative.

[h]See table 4 in Reference 63.

[i]See table 7 in Reference 63.

Supplemental Material >

Kingdom (102, 107) and Canada (122), 60% and 55% of individuals with pathogenic variants, respectively, did not fulfill family-history-based criteria. A lack of cancer history in families segregating *BRCA1/BRCA2* pathogenic variants does not reflect lower risk (49, 80) but is rather explained by limited family structure or knowledge of family history (180), multiple males, and the chance occurrence of fewer older females who inherited the familial variant (49). These findings are consistent with observations from multiple case series of unselected cancer patients, which showed that ~50% (13, 66, 67, 80) and up to 77% (124) of those with pathogenic variants detected following a cancer diagnosis lack a suggestive family history.

Beyond the high prior probability required for testing unaffected women, existing guidelines present further barriers to testing. Family-history criteria are often complex (**Table 2**) or involve using risk assessment tools that are not familiar to most clinicians, particularly primary care physicians, who have a critical role in referral (128, 134). Some guidelines require prior testing of affected family members, which can delay or, in the case of refusal, preclude testing of unaffected individuals. Additionally, although the NCCN has now added the option of pretest education for individuals with a modest pretest probability of 2.5–5%, including AJs, all of the guidelines surveyed recommend in-person genetic counseling (GC) both before and after testing. This is difficult to provide at scale and may not be necessary (see Section 2.7).

We note that current policies for *BRCA1/BRCA2* testing contrast with the widely accepted policy of the ACMG, which recommends return of information on *BRCA1/BRCA2* deleterious variants if these are identified as incidental or secondary findings in the course of unrelated genomic tests (e.g., exome sequencing) (59, 71). In this context, deleterious variants in *BRCA1/BRCA2* and other high-penetrance cancer predisposition genes are reported back to patients irrespective of family history and without in-depth specific pretest information because they are deemed medically important. In a study of more than 50,000 individuals in the Geisinger Health System biobank who underwent exome sequencing (mean age of 59.9), 0.5% of participants harbored a *BRCA1/BRCA2* deleterious variant (110). The investigators found not only that 49.4% of carriers did not meet family-history criteria but also that 82% (including many who met clinical testing criteria) had never been tested. Real-life data thus indicate that current strategies and barriers result in significant underascertainment, identifying only ~20% of carriers (159). Critically, improved identification led to early cancer diagnosis in these high-risk individuals (22). Considerable underascertainment of those harboring pathogenic variants was also found in a UK study: Across the London population of 16 million, 90% of AJ *BRCA* carriers and 97% of general-population *BRCA* carriers remain unidentified despite more than 20 years of genetic testing in a centralized health system with free access to care (100). Current testing rates were inadequate to identify the residual pool of *BRCA1/BRCA2* carriers. These findings highlight the need for change and a new paradigm or approach to maximize precision prevention. Regarding non-*BRCA1/BRCA2* genes, some guidelines include criteria for testing specific rare cancer syndromes (e.g., Li–Fraumeni syndrome). However, the underlying assumption is that *BRCA1/BRCA2* sequencing will be performed as part of an MGPT, so the criteria detailed in **Table 2** are often used as the threshold for MGPT.

2.4. The Natural History of Carrier Status for Cancer Predisposition: Breast and Ovarian Cancer Risks in Carriers (Principle 7)

The natural history of cancer predisposition is essentially the risk, by age, that a carrier will develop cancer, assuming no special surveillance or prevention measures are performed. Risk—i.e., penetrance—can vary not only among different genes but also among specific variants in the same gene (81, 148). Beyond such allelic effects, *BRCA1/BRCA2* cancer risks are affected by genetic modifiers (82, 112) and nongenetic factors, such as reproductive history (47) and calendar year at diagnosis (49, 80). The penetrance of cancer predisposition genes has generally been evaluated through ascertainment based on affected individuals or those with a significant family history. Such strategies may overestimate penetrance in the population because they would miss any individuals or families who harbor deleterious variants but have less severe cancer histories. This could be particularly true for moderate- or low-penetrance genes, where risk may be more susceptible to other genetic or nongenetic effects.

2.4.1. Penetrance of the *BRCA1/BRCA2* Ashkenazi Jewish founder variants. Population-based penetrance of the *BRCA1/BRCA2* AJ founder variants was addressed by Gabai-Kapara et al.

(49). In this study, female AJ carriers were identified through healthy AJ males, who were representative of the general AJ population in terms of both carrier frequency and expected family history. The risk for breast cancer in *BRCA1* founder variant carriers was 52% [standard error (SE) 8%] by age 70 and 60% (SE 10%) by age 80, and for *BRCA2* 6174delT carriers it was 32% (SE 9%) by age 70 and 40% (SE 11%) by age 80. The risk for ovarian cancer in *BRCA1* founder variant carriers was 47% (SE 10%) by age 70 and 53% (SE 11%) by age 80, and the risk for *BRCA2* 6174delT carriers was 13% (SE 7%) by age 70 and 62% (SE 18%) by age 80.

These risks are comparable to those found in a recent large prospective cohort study of carriers from multiple ethnic origins that included a separate analysis of the AJ founder variants (81). This study had mixed ascertainment of affected and unaffected carriers through cancer genetic clinics. The breast cancer risk for carriers of the *BRCA1* founder variants by age 70 was 84% [95% confidence interval (CI) 68–94%] for 185delAG carriers and 60% (95% CI 45–75%) for 5382insC carriers [carriers of this variant are not necessarily AJs, since 5382insC is a common *BRCA1* pathogenic variant in central and eastern Europe and is not unique to AJs (55, 172)]. Breast cancer risk for *BRCA2* 6174delT carriers was 41% (95% CI 20–70%) by age 70. Ovarian cancer risks for *BRCA1* carriers by age 70 were 35% (95% CI 20–36%) for 185delAG carriers and 34% (95% CI 13–73%) for 5382insC carriers. Ovarian cancer risk in *BRCA2* 6174delT carriers could not be assessed because of a lack of events.

Thus, among AJs, it is clear that the breast and ovarian cancer risks are high even in female carriers ascertained at the population level and are similar to those found through cancer genetics clinics. By age 80, the combined population-based risk for either breast or ovarian cancer risk was 83% (SE 7%) for *BRCA1* founder variant carriers and 76% (SE 13%) for *BRCA2* 6174delT carriers (49).

2.4.2. Penetrance of *BRCA1/BRCA2* deleterious variants in other populations. Over the years, multiple studies have addressed the penetrance of deleterious variants in *BRCA1/BRCA2*. Penetrance estimates were based originally on high-risk families, then on case series of cancer patients, and later on cancer genetics clinics serving an ever larger and less selected population (for a meta-analysis of earlier studies, see 25). Two large recent prospective cohort studies from cancer genetics services found that, by age 70, breast cancer risk was 60–66% in *BRCA1* carriers and 55–61% in *BRCA2* carriers, and ovarian cancer risk was 41–58% in *BRCA1* carriers and 15–16.5% in *BRCA2* carriers (81, 112). Cancer risks continued to rise from age 70 to age 80.

The most notable difference between the risks found in ethnically diverse carriers and those found in AJ carriers is the higher ovarian cancer risk for *BRCA2* in AJs. This finding is explained by the fact that the data on *BRCA2* AJ founder variant testing reflects the risks associated with the 6174delT variant, which is located in the *BRCA2* ovarian cancer cluster region (51, 81, 148).

From a population screening perspective, experience from the AJ studies suggests that in non-AJs, cancer risks for *BRCA1/BRCA2* carriers at the general-population level will be of similar magnitude to those observed in large, clinic-based studies. This reflects the high penetrance of *BRCA1/BRCA2* deleterious variants.

2.4.3. Cancer risks in non-*BRCA1/BRCA2* breast/ovarian cancer predisposition genes. Data on cancer risks associated with deleterious variants in non-*BRCA1/BRCA2* genes are much more limited, particularly data on population-based risks. Many of the non-*BRCA1/BRCA2* genes were identified in parallel with the development and increased use of MGPTs. Consequently, penetrance estimates are often based on a case-versus-database-control approach, where the cases are clinically tested affected individuals and variant frequencies among cases are compared with variant frequencies in public databases [e.g., the Exome Aggregation Consortium

(ExAC) database (72), now available through the Genome Aggregation Database (gnomAD; **https://gnomad.broadinstitute.org**)] (31, 92). Even so, most of the non-*BRCA1/BRCA2* genes are moderate-risk genes (e.g., *ATM* and *CHEK2*) (35). For some genes commonly included in gene panels (e.g., *MRE11A*), it remains unclear whether an association with breast or ovarian cancer exists (88, 126). We limit our review of cancer risk to established high-risk genes since we propose that, at this point, only high-risk genes should be considered for population screening. The rationale for excluding moderate-risk genes is the greater uncertainty regarding risk for carriers of moderate-risk genes, lower predictive value for cancer because of the lack of high penetrance, and the weaker evidence for their appropriate management. Since clinical utility is the cornerstone of selecting genes for testing, these uncertainties currently limit the clinical utility of identifying variants in moderate-risk genes. However, estimates of clinical utility may change, and evaluation of specific genes should be an ongoing process.

Risks for carriers of high-risk non-*BRCA1/BRCA2* genes are shown in **Table 1**. For breast cancer, these genes are *TP53*, *PTEN*, *CDH1*, *STK11*, *PALB2* (which is emerging as a high-risk gene), and *NF1* (not shown in **Table 1** because it is not included in most breast cancer MGPTs). Deleterious variants in all of these genes except for *PALB2* are associated with specific cancer syndrome phenotypes, some including noncancer features (**Table 1**). Prior to the genomic era, carriers were identified based on prior clinical suspicion of the relevant syndrome; indeed, as mentioned above, *NF1* is still not included in most breast cancer MGPTs, partly because carriers of truly deleterious variants are expected to be identified based on clinical manifestation of neurofibromatosis. The high-risk non-*BRCA1/BRCA2* genes for ovarian cancer, excluding some of the Lynch syndrome genes, are *RAD51C* and *RAD51D*. Risk estimates are shown in **Table 1**. The original risk estimates in syndromic cancer genes were based on family studies in clinically identified carriers. Currently, most carriers are identified via MGPTs, with estimates based largely on a case–control design, particularly in genes with very low carrier rates (e.g., *RAD51D*).

2.5. Accepted Treatment Surveillance and Prevention Measures in *BRCA1/BRCA2* Carriers (Principles 2 and 3)

The ultimate purpose of disease screening is to enable disease prevention or early detection (183). Identifying individuals who are presymptomatic or harbor latent disease is therefore justified only if there are effective ways to prevent the disease or to detect it early and achieve improved outcomes. In *BRCA1* and *BRCA2* carriers, risk-reduction surgeries significantly reduce the risk of breast and ovarian cancer and reduce both disease-specific and overall mortality. Surveillance measures exist for early detection of breast cancer, but there is more limited evidence of their effects on disease prognosis.

2.5.1. Breast cancer surveillance. For *BRCA1/BRCA2* carriers, most international guidelines recommend annual magnetic resonance imaging (MRI) and/or mammograms for breast cancer surveillance after age 25–30 (44, 126, 128). Alternate breast imaging (MRI and mammograms) is performed every 6 months (126). In general, MRI has higher sensitivity but lower specificity than mammograms, which results in higher false-positive rates and a greater need for recall, breast biopsies, and additional imaging (131). However it is more useful in younger women with denser breast tissue, which is particularly relevant to carriers. A recent systematic review by the USPSTF reported sensitivities of 63–69% for MRI, 25–62% for mammograms, and 66–70% for both modalities combined; specificity was reported as 91% or higher for either modality alone or combined (131). However, there is currently no evidence for an effect of intensive surveillance on mortality (131).

2.5.2. Breast cancer prevention. Breast cancer prevention falls into two major categories: surgical prevention and chemoprevention.

2.5.2.1. Surgical prevention. Risk-reducing bilateral mastectomy (RRBM) reduces the risk of breast cancer by 90–95% (145). A recent cohort study found that in *BRCA1* carriers it reduces both breast cancer–specific mortality [hazard ratio (HR) 0.06, 95% CI 0.01–0.46] and overall mortality (HR 0.40, 95% CI 0.20–0.90). There was no effect on mortality in *BRCA2* carriers, who had lower breast cancer mortality than *BRCA1* carriers (64). The overall complication rates of mastectomy are not insignificant, with rates of ~32–50% reported, although most are minor complications (33, 131). RRBM rates vary substantially across countries, with reported rates ranging from ~5% to ~50% (118, 119). Some studies indicate that RRBM has a negative impact on body image and sexual pleasure, but some found no detrimental impact on sexual activity, habit, discomfort (18), anxiety, depression, or quality of life (18, 69, 129) and reported high cosmetic satisfaction rates (69, 179). A recent systematic review found that although body image and psychological symptoms may worsen in some women after surgery, most measures returned to baseline at a later date (131). RRBM is cost-effective for preventing breast cancer in *BRCA1/BRCA2* carriers (57).

2.5.2.1. Chemopreventions. Several chemoprevention trials have evaluated tamoxifen, raloxifene, and the aromatase inhibitors anastrozole and exemestane for prevention of breast cancer in high-risk women. These studies included *BRCA1/BRCA2* carriers, but none were specific to carriers. A USPSTF review showed that tamoxifen [relative risk (RR) 0.69, 95% CI 0.59–0.84], raloxifene (RR 0.44, 95% CI 0.24–0.80), and aromatase inhibitors (RR 0.45, 95% CI 0.26–0.70) are associated with a lower risk of invasive breast cancer after 3–5 years of use compared with placebo (130). Tamoxifen (RR 1.93, 95% CI 1.33–2.68) and raloxifene (RR 1.56, 95% CI 1.11–2.60) are associated with increased risk of thromboembolism, and tamoxifen is associated with an increased risk of endometrial cancer (RR 2.25, 95% CI 1.17–4.41), while aromatase inhibitors have a negative impact on bone and musculoskeletal health (32, 130). In a direct comparison study, tamoxifen was superior to raloxifene in preventing invasive breast cancer, though raloxifene had a better toxicity profile (176). Reduction in cancer risk is found predominantly for estrogen-receptor-positive but not estrogen-receptor-negative breast cancer or ductal carcinoma in situ. However, there is no explicit evidence for the efficacy of chemoprevention specifically in *BRCA1/BRCA2* carriers (126), and no mortality impact has been demonstrated. Nevertheless, guidelines for *BRCA1/BRCA2* carriers either recommend chemoprevention (128, 134) or indicate that it should be considered (126).

2.5.3. Ovarian cancer surveillance. Current modalities for ovarian cancer surveillance in *BRCA1/BRCA2* include cancer antigen 125 (CA-125) biomarker testing and pelvic ultrasound. These methods have been evaluated in a few international single-arm studies utilizing CA-125 biomarker testing and imaging by transvaginal ultrasound. These nonrandomized studies were not designed to evaluate an impact on mortality/survival, and currently there is no evidence that surveillance improves these outcomes. Phase 1 of the UK Familial Ovarian Cancer Screening Study (UKFOCSS) utilized annual transvaginal ultrasound with CA-125 testing and reported a sensitivity of 81.3–87.5%, a positive predictive value (PPV) of 25.5%, and a negative predictive value (NPV) of 99.9% (153). Only 31% of the cancers were early stage. Annual surveillance using absolute CA-125 and transvaginal ultrasound is thus not effective and not advocated.

Subsequent trials utilized mathematical algorithms based on longitudinal biomarkers that have been shown to double the number of ovarian cancers detected compared with an absolute cutoff/threshold rule (117). A strategy of more frequent surveillance (testing every 3–4 months) using the longitudinal CA-125-based Risk of Ovarian Cancer Algorithm (ROCA) was evaluated in

high-risk women over age 35 in the UKFOCSS phase 2 study (4,348 women, 13,728 woman-screen-years) (154) and the US Cancer Genetics Network (CGN) and Gynecological Oncology Group (GOG) trials (3,692 women, 13,080 woman-screen-years) (162). The UKFOCSS phase 2 study demonstrated a statistically significant stage shift with ROCA-based screening, finding that 7/19 (36.8%) of ovarian cancers were stage IIIb or IV if diagnosed within 1 year of the last screening, whereas 17/18 (94.4%) of ovarian cancers were stage IIIb or IV if diagnosed after 1 year following the last screen ($p = 0.001$) (154). Within 1 year of screening, this study showed high sensitivity (94.7%) and NPV (100%), with a PPV of 10.8%. The CGN and GOG trials also found that frequent ROCA-based CA-125 testing (every 3 months) was more sensitive than cutoff-based testing and reported downstaging at cancer diagnosis but low (4.6%) PPV (162).

Overall, surveillance data for longitudinal CA-125 algorithm-based screening performed every 3–4 months in high-risk women who decline risk-reducing surgery appear promising, and newer algorithms are being developed (17). A project evaluating this approach, called Avoiding Late Diagnosis of Ovarian Cancer (ALDO), is currently ongoing in the United Kingdom. However lessons learned from ovarian cancer surveillance studies show that this strategy is effective only if clinicians and patients are willing to undertake surgery (bilateral salpingo-oophorectomy) based solely on a rising biomarker, without any radiological corroboration of an abnormality. Based on the available evidence, for *BRCA1/BRCA2* carriers, current guidelines emphasize prevention rather than surveillance. The latest NCCN guidelines indicate that surveillance should be considered only on an individual basis at the clinician's discretion (126), and in the United Kingdom there is no recommendation for ovarian cancer screening in carriers (128).

2.5.4. Ovarian cancer prevention. Risk-reducing salpingo-oophorectomy (RRSO) is the most effective way of preventing ovarian cancer in *BRCA* carriers. It is usually performed by laparoscopy and involves removing both tubes and ovaries along with peritoneal cytology. The complication rate is 3–5%. A protocol for sectioning and extensively examining the fimbria (SEE-FIM) is used for pathological examination (116), and ~5% of female *BRCA* carriers are detected to have an occult serous tubular in situ carcinoma or microscopic invasive cancer (99, 141), which are not identifiable via CA-125 testing or imaging. Of these lesions, 70% are tubal rather than ovarian (141), and a large proportion would be missed without a serial section protocol. This is important for patient management since women with microscopic invasive cancer require completion of surgical staging as well as chemotherapy. Most of these cases are likely to be early-stage disease with excellent survival if appropriate treatment is given, whereas missing them would result in inappropriate management and poorer outcomes.

RRSO has been reported to reduce ovarian cancer risk by 80–96% in *BRCA1/BRCA2* carriers (41, 73, 74, 147), with meta-analyses showing a 79–81% overall reduction in ovarian cancer risk (111, 146). There is a small (2–4%) residual risk of primary peritoneal cancer (24, 42). While earlier studies reported a reduction in breast cancer risk, more recent literature controlling for biases showed no such reduction (65). Importantly, RRSO reduces mortality, with a 79% reduction in ovarian cancer–specific mortality, 56% reduction in breast cancer–specific mortality, and 60–68% reduction in all-cause mortality (34, 111). RRSO has also been shown to be a cost-effective intervention for ovarian cancer prevention both in *BRCA1/BRCA2* carriers (5) and in individuals at lower risk levels (105).

RRSO is typically offered after age 35–40 for *BRCA1* carriers and after age 40–45 for *BRCA2* carriers. Decision-making may be affected by numerous factors and is a dynamic process, and timing needs to be individualized following informed counseling. A wide range of uptake rates of up to ~70% are reported in the literature (50, 101, 119). RRSO is associated with high satisfaction (rates of up to 97%) along with some regret (rates of ~5%) (96).

RRSO in premenopausal women leads to premature menopause, which has been associated with increased risks of heart disease, stroke, osteoporosis, vasomotor symptoms, mood changes, sleep disturbance, reduced libido, vaginal dryness, sexual dysfunction, and neurocognitive decline, predominantly in women who are unable to use hormone replacement therapy (39, 137, 152, 161). Vasomotor symptoms and sexual dysfunction are not fully alleviated by hormone replacement therapy, with symptom levels remaining above those of women who retain their ovaries (96, 97). As a result, some women delay oophorectomy until after menopause, which may be detrimental, particularly in *BRCA1* carriers. Hormone replacement therapy until age 50 in carriers who have undergone RRSO has not been associated with increased breast cancer risk in carriers and can be offered (8, 54). While early salpingectomy and delayed oophorectomy have been proposed as an attractive alternative, this approach remains well within the research arena (48).

2.5.5. Surveillance and prevention in carriers of deleterious variants in non-*BRCA1/BRCA2* breast/ovarian cancer predisposition genes. Direct evidence on surveillance and prevention measures in carriers of deleterious variants in non-*BRCA1/BRCA2* cancer predisposition genes is limited. In general, the same modalities used in *BRCA1/BRCA2* carriers are also utilized in carriers of other breast and ovarian cancer predisposition genes. However, this approach raises significant questions, particularly with regard to risk-reduction surgeries, which may not be warranted for many of the moderate- or low-penetrance genes. In particular, RRBM has not been shown to improve survival even in *BRCA2* carriers (64). However, exceptions may exist with regard to RRSO in carriers of deleterious variants in moderate-risk ovarian cancer genes (e.g., *BRIP1* and *PALB2*) because there are no clearly effective means for early cancer detection, and RRSO at these risk levels prevents cancers and is cost-effective. Another exception is Lynch syndrome: Although some Lynch syndrome genes are associated with only moderate ovarian cancer risk, Lynch syndrome carriers often undergo hysterectomy for prevention of endometrial cancer, and RRSO is often performed in the same procedure. There is a limited evidence base for recommendations regarding the ages at which surgical prevention or RRSO should be offered for carriers of some of the moderate-risk genes. Clinically, carriers of deleterious variants in non-*BRCA1/BRCA2* cancer predisposition genes are often managed based on family history (126).

2.6. Laboratory Testing Suitable for Population Screening (Principle 5)

MGPTs and genetic testing for specific deleterious variants have a very high analytic validity (>95%) (36, 93, 160). In the population screening context, the main concerns regarding the choice of an appropriate test for variant detection are the test's sensitivity and specificity and its PPV and NPV. The PPV and NPV also depend on the background frequency of deleterious variants. A further consideration is whether to report variants of unknown significance (VUSs) in the screening setting.

2.6.1. *BRCA1/BRCA2* laboratory testing in Ashkenazi Jews. Options for testing *BRCA1/BRCA2* in AJs include testing for the three founder pathogenic variants or full gene sequencing. The advantages of founder variant testing include significantly lower cost and the lack of VUSs. Data from AJ breast cancer patients who were sequentially tested first by founder variant testing (80) and then by using full gene sequencing (178) indicated that the sensitivity of testing the three founder *BRCA1/BRCA2* pathogenic variants for detection of all *BRCA1/BRCA2* variants in AJs is 94% (104/111). This figure is consistent with other data on the frequency of nonfounder *BRCA1/BRCA2* deleterious variants in AJs (46, 155). The sensitivity of full *BRCA1/BRCA2* sequencing would in principle be almost complete, but certain classes of variants, such as

rearrangements, are difficult to detect, and human errors occur. The rates of false identification of individuals as *BRCA1/BRCA2* carriers are extremely low, so the specificity of both founder variant testing and full sequencing of *BRCA1/BRCA2* is likely close to 100%, with false positives related largely to human (e.g., sampling) error. The prevalence of founder pathogenic variants is 1:40 (151), and the prevalence of nonfounder deleterious variants in the AJ population would be expected to be similar to the lower mean range in other populations, i.e., ~1:300 (113). Assuming 94% sensitivity and 99.99% specificity, the PPV of testing for the founder variants is 99.6%, and the NPV is 99.8%. For full gene sequencing, assuming 98% sensitivity and 99.99% specificity, the PPV is 100% and the NPV is 100%. Founder variant testing in AJs thus achieves predictive values that are only negligibly smaller than full *BRCA1/BRCA2* sequencing (<0.5% difference), at a much lower cost, while circumventing the issue of VUSs.

The predictive value for cancer diagnosis in carriers is approximated by the penetrance. A formal calculation, based on the attributable risks of *BRCA1/BRCA2* deleterious variants for breast and ovarian cancer in AJs, shows that for breast and ovarian cancer combined, the PPV for cancer in carriers is 67% for founder testing and 71% for full *BRCA1/BRCA2* sequencing. Even in AJs, as detailed above, the majority of ovarian cancer cases and the large majority of breast cancer cases are not caused by germline *BRCA1/BRCA2* deleterious variants, resulting in an NPV of ~88% for breast and ovarian cancer. However, any individual precision prevention application will account for a small fraction of affected individuals, and the overall utility of the population genetic screening approach can be evaluated by cost-effectiveness analyses.

2.6.2. *BRCA1/BRCA2* laboratory testing in ethnic groups other than Ashkenazi Jews. There are ethnic groups other than AJs with founder deleterious variants in *BRCA1/BRCA2*. However, in the majority of populations, identifying any significant fraction of *BRCA1/BRCA2* deleterious variants requires full sequencing of *BRCA1* and *BRCA2*. The sensitivity and specificity of *BRCA1/BRCA2* full sequencing are the same as in AJs. The PPV and NPV therefore hinge on the penetrance as well as the background frequency of pathogenic variants.

Historically, epidemiological estimates suggested a 1:150 carrier frequency for a major dominant breast cancer predisposition gene (the allele frequency was estimated as 0.0033) (27). This estimate included all dominant breast cancer predisposition alleles, i.e., not only *BRCA1/BRCA2* pathogenic variants. Direct determination of carrier frequency became possible with large-scale genomic sequencing. In the Lifepool study of 1,997 cancer-free Australian women, the combined carrier frequency of *BRCA1* and *BRCA2* (based on full sequencing as part of an MGPT) was 1:153 (169). These women were ascertained through a population-based mammography screening program, and their mean age was 59.9 (169). Many carriers will have become affected by age 60, so this prevalence is likely to be lower than the population prevalence at age 30. In the Geisinger biobank, among 50,276 individuals who underwent whole-exome sequencing, the prevalence of *BRCA1/BRCA2* pathogenic variants was 1:180 (0.56%) (110). Compared with the health system's entire population, biobank participants were older (mean age of 59.9 for biobank participants, versus 50.1 for the entire population) and enriched for relevant cancers, although overall there were few participants with a previous breast or ovarian cancer diagnosis (1.7% in the biobank versus 0.1% in the entire system). Excluding participants with a previous breast or ovarian cancer diagnosis, the carrier rate among women in this biobank was 1:277 (0.36%). Similarly to Australian controls, the older age of this study group suggests that this figure is an underestimate of carrier prevalence at younger ages.

An analysis of publicly available variant data from two large databases [the Exome Variant Server (EVS; **http://evs.gs.washington.edu**) and ExAC (data currently in gnomAD)] that excluded Cancer Genome Atlas samples found a combined *BRCA1/BRCA2* carrier rate of 1:166 in

EVS and 1:161 in ExAC (113). Notably, carrier rates varied widely in different ethnic groups, ranging from 1:123 in Europeans to 1:626 in Africans (113). Attributable risk data in non-AJs are less robust than those in AJs, but even if the attributable risk of *BRCA1/BRCA2* is 2–3% for breast cancer and 10% for ovarian cancer, the PPV for cancer in carriers would be greater than 60%, which is significantly higher than those of many accepted disease screening strategies. For example, the PPV of fecal occult blood testing for significant adenomas or colon cancer is 24–33% (26), and the PPV of dual-energy X-ray absorptiometry osteoporosis screening for any major fracture is 12% (173).

2.6.3. Laboratory testing for non-*BRCA1/BRCA2* genes. If only actionable genes clearly associated with high penetrance are considered candidates for large-scale screening, then the MGPT-related issues are similar in AJs and non-AJs. As discussed above, high-penetrance non-*BRCA1/BRCA2* variants are significantly less common (**Table 1**). For example, the frequency of *RAD51C* variants in unaffected individuals tested by an MGPT was 1:860–1:898 (31/26,647–72/64,649), and their attributable risk to ovarian cancer was 0.64–0.7%. Assuming only deleterious variants are reported, the addition of rare high-penetrance genes is largely a cost–benefit consideration, although it should be recognized that test specificity is a greater issue for variants in genes that are very rare a priori.

2.6.4. Variants of unknown significance in genetic screening tests. The complexities of VUSs have been raised as a major argument against genetic screening. VUS rates increase with the number of genes included in a test; they are also more common in understudied populations and in more recently investigated genes. The major concern is that reporting VUSs could lead to inappropriate anxiety and overtreatment. We believe this can be resolved by a policy decision to not report VUSs in the screening setting. This policy is ethically justifiable because screening is not meant to identify 100% of individuals at risk. Indeed, nonreturn of VUSs is already the policy in preconception carrier screening, in reporting secondary or incidental findings in genomic tests, and in return of results in clinical biobanks. Although this approach limits sensitivity (resulting in a certain proportion of false negatives), it has two critical benefits: (*a*) It increases specificity (minimizing false positives), and (*b*) for *BRCA* screening, it may free policy makers to expand testing and improve the currently dismal rate of carrier ascertainment (100, 142). Forgoing screening because of a fear of VUSs precludes identification of carriers with clearly deleterious variants, and this will be true for any application of precision prevention.

2.7. The Acceptability of Strategies for a Population Screening Process (Principle 6)

GC has long been considered a key component of the cancer risk assessment process (14). Its main elements are education regarding cancer genetics; the likelihood of developing cancer and of carrying a genetic susceptibility variant; the benefits, risks, and limitations of genetic susceptibility testing; and appropriate cancer screening and prevention strategies. The goal is to empower the patient to make informed decisions regarding screening, prevention, and genetic testing by providing the necessary genetic, medical, and psychosocial information. Attention to psychosocial issues is critical for effective GC (15, 89).

As detailed above, existing guidelines (**Table 2**) recommend testing for *BRCA* deleterious variants only with pre- and posttest in-person GC. Pretest GC is provided to collect familial information, evaluate the patient's cancer risk, generate a differential diagnosis, educate the patient (e.g., on inheritance and penetrance), prepare the patient for all possible test results, and

determine the appropriate genetic test. Posttest counseling is provided to explain test results, consider possible risk-reduction interventions based on a risk–benefit analysis and patient preference, discuss familial implications, and present available resources. GC has been shown to be accompanied by high satisfaction and to enhance genetic knowledge. In the context of cancer genetics, it has been shown to reduce worry, anxiety, and depression related to cancer; improve responses to cancer risk-management strategies such as screening, chemoprevention, and preventive surgery; and reduce long-term distress (reviewed in 23, 70, 131).

Despite its success, it should be recognized that this labor-intensive and time-consuming process is unique in clinical medicine. Historically, it developed when genetics was a niche field serving a more limited clientele who were tested for reproductive or predictive purposes, the implications of which were largely nontherapeutic—e.g., decisions regarding prenatal testing or predictive testing for untreatable conditions such as Huntington's disease. Compared with the rapid changes in genetic and genomic laboratory testing, the GC aspects of the testing process have been slow to evolve. However, there is a clear need for change in order to provide both for ever growing demand and for a different patient profile. Importantly, if genomics is to be used for precision prevention, testing will increasingly include individuals with low a priori risk, for the majority of whom the full pretest discussion will most likely prove to be less relevant (90, 91).

We evaluated studies of the cancer genetics pretest process with a view toward an alternative approach that would be feasible at the large scale of population screening. To this end, we reviewed studies of modalities other than traditional in-person GC. We evaluated studies that also included unaffected participants (as opposed to studies limited to participants with breast or ovarian cancer) and were published in the past decade (since 2009), which are more likely to be representative of the current landscape of genomic testing and greater public awareness. The studies identified offered three alternative models: telephone counseling, telegenetic counseling (GC provided remotely by live videoconferencing, with both visual and audio access), and group counseling. Results of these studies are detailed in the **Supplemental Appendix** and **Supplemental Table 2**. Briefly, in unaffected individuals, telephone, telegenetic, and group counseling modalities were largely noninferior to traditional GC for psychosocial outcomes. However, they were associated with lower rates of fulfilling appointments and undergoing genetic testing. Telephone and telegenetic counseling afford convenience, availability, and accessibility, particularly for geographically distant patients, but may not improve waiting times or reduce staff requirements, although they did reduce costs, as did group GC (with or without a decision aid) (**Table 3**, **Supplemental Table 2**). Taken together, all three modalities likely represent an incremental rather than paradigmatic change in GC provision.

Supplemental Material >

2.7.1. Mainstreaming. Two other models for a pretest process that could be relevant to unaffected patients are mainstreaming and direct genetic testing. Mainstreaming engages nongeneticist clinicians to order genetic testing, typically with support from genetics clinicians (114). In this model, patients are referred to GC only after testing and only when a positive or inconclusive result is obtained. It has been studied and implemented largely in the oncology setting, particularly for oncologists' direct referral of ovarian cancer patients for genetic testing. Studies of mainstreaming in ovarian cancer patients found that referral rates and uptake were very high (89–100%) (52, 143, 163) compared with those of traditional GC (15–31%) (40). Patient waiting times were significantly reduced (52, 143), and satisfaction was high (29, 52, 143). In this scheme, all carriers are meant to have posttest GC by a geneticist; actual observed referral rates have ranged from 78% (143) to 100% (52). In principle, mainstreaming could be adapted to unaffected individuals, in which case the family physician, gynecologist, or breast surgeon could offer genetic testing during surveillance or routine appointments. However, mainstreaming is highly

Table 3 ***BRCA1/BRCA2*** **screening studies performed in Ashkenazi Jews**

	Manchanda et al. (2015, 2019) (102, 107)	Manchanda et al. (2016) (104)	Manchanda et al. (2019) (103)	Wiesman et al. (2017) (181)	Metcalfe et al. (2010, 2012) (120, 122)	Lieberman et al. (2017) (90, 91)
Study location	United Kingdom	United Kingdom	United Kingdom	United States	Canada	Israel
Study design	Randomized controlled trial, population screening versus family-history-based testing	GC clinics (clusters) randomized to GC or DVD-GC	Prospective cohort, population screening versus family-history-based testing	Prospective cohort, open-access recruiting	Prospective cohort, open-access recruiting	Prospective cohort, self-referred versus recruiter enrollment
Number of participants	1,034 (GCaPPs)	936 (GCaPPs)	935 (GCaPPs)	189	2,080 women, 162 (7.8%) with personal cancer history	1,771, unaffected
Mean age	54.3 years (SD = 14)	53.9 years (SD = 15)	53.8 years (SD = 15)	50 years (range 25–75)	49.3 years (range 23–79)	52 years (SD = 13, range 25–89)
Pretest process	IP-GC	IP-GC or DVD-GC	IP-GC	■ High-risk participants: IP-GC ■ Low-risk participants: group GC	Written information	Written information
Genetic test	Founder variants in *BRCA1/BRCA2*	Founder variants in *BRCA1/BRCA2*	Founder variants in *BRCA1/BRCA2*	■ High-risk participants: tailored testing (founder variants in *BRCA1/BRCA2*, gene sequencing, or MGPT) ■ Low-risk participants: founder variants in *BRCA1/BRCA2*	Founder variants in *BRCA1/BRCA2*	Founder variants in *BRCA1/BRCA2*
Posttest process	■ Carriers: IP-GC ■ Noncarriers: mail ■ Control group of noncarriers (same number as carriers): IP-GC	■ Carriers: IP-GC ■ Noncarriers: mail ■ Control group of noncarriers (same number as carriers): IP-GC	■ Carriers: IP-GC ■ Noncarriers: mail ■ Control group of noncarriers (same number as carriers): IP-GC	■ All participants: telephone and mail ■ Carriers: IP-GC ■ Carriers and high-risk noncarriers: results given to health-care provider	■ Carriers: phone and IP-GC within 3 days ■ High-risk noncarriers: phone and mail ■ Low-risk noncarriers: mail	■ Carriers: IP-GC ■ High-risk noncarriers: IP-GC ■ Low-risk noncarriers: mail

(*Continued*)

Table 3 (*Continued*)

	Manchanda et al. (2015, 2019) (102, 107)	Manchanda et al. (2016) (104)	Manchanda et al. (2019) (103)	Wiesman et al. (2017) (181)	Metcalfe et al. (2010, 2012) (120, 122)	Lieberman et al. (2017) (90, 91)
Outcomes	Acceptability, psychological health, quality of life, prevalence of founder variants in *BRCA1/BRCA2*	Testing uptake, cancer risk perception, knowledge, satisfaction, relevance, adequacy, emotional impact and understanding, counseling duration, cost-minimization analysis	Interest, intention, uptake, attitude toward *BRCA* testing	Benefits and barriers of implementing AJ *BRCA* founder pathogenic variant population screening in a clinical setting	Satisfaction, cancer-related distress, cancer risk perception, uptake of risk-reduction options	Uptake, posttest counseling compliance, satisfaction, anxiety, distress, knowledge, motivators for or barriers to testing
Satisfaction	NA	DVD-GC was noninferior to IP-GC for increase in satisfaction	NA	Among the low-risk cohort who participated in group GC, 97% felt comfortable learning in a group, 8% would have preferred IP-GC, and no one felt intimidated or pressured by the group	■ Pretest process: 81% were satisfied with written information, and 19% (56% of carriers and 18% of noncarriers) preferred pretest IP-GC ■ Genetic testing: All participants were highly satisfied, with no significant difference between carriers and noncarriers ■ Posttest process: 22% of noncarriers would have preferred posttest IP-GC instead of follow-up by phone or mail	■ >90% of participants were satisfied at enrollment, with satisfaction increasing over the next 6 months ■ Satisfaction was higher in the self-referred cohort than in the recruiter-enrolled cohort (at enrollment, $p < 0.001$; at 6 months, $p = 0.02$) ■ SWHD score was high (>25) for all participants but was higher in the self-referred cohort than in the recruiter-enrolled cohort (at enrollment, $p < 0.001$; at 6 months, $p = 0.01$) ■ After 6 months, both satisfaction with testing and SWHD score were also high among carriers

(*Continued*)

Table 3 (*Continued*)

	Manchanda et al. (2015, 2019) (102, 107)	Manchanda et al. (2016) (104)	Manchanda et al. (2019) (103)	Wiesman et al. (2017) (181)	Metcalfe et al. (2010, 2012) (120, 122)	Lieberman et al. (2017) (90, 91)
Knowledge	NA	DVD-C was noninferior to IP-GC for increase in knowledge	*BRCA*-related knowledge was positively associated with intention to undergo testing ($p = 0.013$)	NA	NA	■ Knowledge score was ~7.0/10 at enrollment and at 6 months and was higher in the self-referred cohort ($p < 0.001$) ■ Knowledge score was significantly higher among carriers (8.7/10) ($p < 0.001$)
Psychological measures	■ Up to 3 months after receiving test results: There was no significant difference between population screening and family-history-based testing for anxiety, health-specific anxiety, depression, distress, overall quality of life, and uncertainty associated with genetic testing ■ At 3 years after receiving test results: There was no significant difference between population screening and family-history-based testing for health-specific anxiety, depression, distress, overall quality of life, and uncertainty associated with genetic testing ■ Population screening participants had a significantly greater reduction in long-term anxiety and overall anxiety and depression	DVD-C was noninferior to TC for risk perception	NA	NA	■ At 1 year after testing: Noncarriers had no change in distress, whereas carriers had a significantly increased IES score (25.3/75 versus 7.1/75 at baseline, $p = 0.0002$) ■ At 2 years after testing: Carriers had a significantly decreased IES score (18.9/75, $p = 0.0002$) compared with their scores after 1 year; IES scores decreased among carriers who had both RRBM and RRSO ($p = 0.02$) or only RRSO ($p = 0.04$) and did not change among carriers who did not have either surgery	■ At enrollment: Participants exhibited low distress (IES score of 5.8/75); distress was higher by 0.8/75 points among self-referred participants; STAI6 anxiety scores were similarly low (10/24 overall) in both groups ■ At 6 months after testing: Distress slightly decreased (not significant), and anxiety was stable; compared with noncarriers, carriers had significantly higher distress (IES score of 19.9/75, $p < 0.001$) and anxiety (STAI6 score of 12.6/24, $p = 0.016$)

(*Continued*)

Table 3 (*Continued*)

	Manchanda et al. (2015, 2019) (102, 107)	Manchanda et al. (2016) (104)	Manchanda et al. (2019) (103)	Wiesman et al. (2017) (181)	Metcalfe et al. (2010, 2012) (120, 122)	Lieberman et al. (2017) (90, 91)
Uptake	88% of participants opted for genetic testing	89% of participants opted for genetic testing; DVD-GC was equivalent to GC for uptake of genetic testing	Before GC, 96% of participants expressed interest in genetic testing, and 60% indicated a clear intention to be tested; after GC, 88% opted for testing	191 (47%) of registrants made appointments; of those, 189 (99%) attended the appointments, and all 189 were tested	NA	67% of recruiter-enrolled participants were tested; uptake is not assessable in the self-referred cohort
Counseling process outcomes	NA	DVD-GC resulted in a 20.5-min reduction in IP-GC time, for a cost savings of £14/participant	NA	Group GC for the low-risk cohort was thought to be an efficient and well-received way of handling a small, homogeneous group	Participants expressed high satisfaction without pretest GC	Among interviewed carriers, 11/14 (79%) had a positive attitude toward stepwise knowledge—i.e., receiving a limited amount of information at the pretest stage and detailed GC in cases of carrier status or significant family history
Health behavior	NA	NA	NA	NA	At 2 years after testing, 19/22 carriers provided information: All 19 had had a mammogram and MRI screening, and 18 (95%) had had ovarian cancer screening; 1 was diagnosed with breast cancer, and 2 of the remaining 18 (11.1%) had undergone RRBM (mean age 36.2); 17 (89.5%) had undergone RRSO (mean age 47.5)	All post-childbearing carriers interviewed had undergone RRSO

Abbreviations: AJ, Ashkenazi Jewish; DVD-GC, DVD presentation followed by in-person genetic counseling; GC, genetic counseling; GCaPPs, Genetic Cancer Prediction Through Population Screening study; IES, Impact of Event Scale; IP-GC, in-person genetic counseling; MGPT, multigene panel test; MRI, magnetic resonance imaging; NA, not assessed; RRBM, risk-reducing bilateral mastectomy; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation; STAI-6, six-item State-Trait Anxiety Inventory; SWHD, Satisfaction with Health Decision scale.

dependent on non-geneticist health-care providers and has not been easily transferable to most non-oncologists. For example, while gynecological and oncological surgeons in the United Kingdom have implemented mainstreaming, breast surgeons have reported feeling a lack of expertise in providing GC and support for patients regarding testing decisions and have raised concerns about the time commitment required (61).

The possibility of offering genetic services during routine provision of primary care has also been evaluated (123). Primary-care providers have reported multiple barriers, chiefly insufficient knowledge and skills to counsel patients about genetic risk and appropriate management. Similar concerns, including concerns about the ethical, social, and legal implications, were raised specifically regarding provision of cancer genetics care (62). Some studies showed an increase in providers' knowledge and confidence after an educational intervention (182) or from using suitable electronic tools (157). However, mainstreaming to non-geneticist clinicians requires retraining to achieve the necessary expertise. Mainstreaming would also shift a large part of the burden from genetic counselors to other clinical providers, and logistical issues, especially staff resources and time allotments, would need to be resolved.

2.7.2. Direct genetic testing. In direct genetic testing, testing is performed without pretest GC. It can be performed within a medical framework offering clinical support or through direct-to-consumer commercial testing, outside the medical setting. In the medical setting, direct genetic testing shifts the balance of care to the posttest stage, so that the main counseling interaction, including risk assessment and recommendations, is already informed by the test results.

2.7.2.1. Direct genetic testing in a clinical setting. Few studies have compared outcomes of direct genetic testing to testing after pretest GC, and only two included unaffected participants. The American *BRCA* Outcomes and Utilization of Testing (ABOUT) study (7) was a retrospective study of individuals who had *BRCA* testing performed through Aetna (a commercial health insurer) in community settings. Investigators compared knowledge, understanding, and satisfaction between patients who did (36.8%) or did not (73.2%) receive pretest GC. Scores for all measures were greater in individuals who received pretest GC. Women who received pretest GC reported significantly greater knowledge about *BRCA* and expressed greater understanding and greater satisfaction. Pal et al. (135) studied the uptake of cancer risk-management strategies among 438 female *BRCA* carriers from the Inherited Cancer Registry (ICARE) database. They showed that uptake rates of risk-reduction surgeries were similar among those whose tests were ordered by genetics professional and those whose tests were ordered by other health-care providers (oncologists, surgeons, and others). However, MRI rates were significantly higher when pretest GC and the *BRCA* test were provided and ordered by a genetics professional (135).

Six studies of universal testing have been performed in unaffected AJs in the past decade (**Table 3**). In two of these, the pretest process included only written information materials (90, 91, 120, 122). In both studies, GC support was available before testing. After testing, all carriers and high-risk noncarriers communicated with a genetic counselor. In both studies, satisfaction with testing was high for both carriers and noncarriers, and a large proportion of participants indicated that they would recommend the same process for others. Even so, 19% of all participants (121) and 55.6% (121) and 21% (90) of carriers indicated that, in retrospect, they would have preferred to have pretest in-person GC. Distress was low among noncarriers and in the short term was significantly higher among carriers. In the long term, the distress level decreased, and there was high compliance with screening recommendations and with RRSO (95% in women over age 35) (120). There are various differences in the designs of the six studies, but it appears that uptake of genetic testing was higher in studies with pretest in-person GC than it was in those with direct

genetic testing (88% versus 47–67%) (**Table 3**). In all studies, the mean age of participants was 50 or older, an age by which many carriers will have become affected; it is therefore important to develop strategies that capture younger women, preferably around age 30, the recommended age for initiating surveillance in carriers.

2.7.2.2. Direct-to-consumer genetic testing. Direct-to-consumer genetic testing has been available since the early 2000s, allowing consumers to access their own genetic information without clinician involvement and with no GC (1). These tests are generally performed using mail-in saliva kits and are relatively inexpensive. This simplified process circumvents the testing barriers described above and provides greater autonomy (150, 174). However, it also lacks the clinical support necessary to follow up on medical information that can be revealed by direct-to-consumer genetic testing. These tests originally focused on single-nucleotide polymorphism (SNP)–based risk assessments for complex diseases such as type 2 diabetes and osteoporosis, but in 2018, the US Food and Drug Administration authorized the company 23andMe to provide a personal genome service genetic health risk report for selected *BRCA1/BRCA2* variants (53). This report provides results on the three *BRCA1/BRCA2* AJ founder variants to all tested individuals regardless of their ancestry.

For direct-to-consumer genetic testing, in general, SNP-based risk assessment results have not been associated with increased test-related or general distress and anxiety (20). There are conflicting reports on whether findings of increased disease risk lead to changes in health behaviors such as diet or exercise (58; reviewed in 164). Most tested individuals do not share their results with medical professionals: Survey studies found that 10.4% and 1% of individuals shared results with a genetic counselor, while 26.5% and 39% shared results with another physician or health-care provider (16, 75, respectively). However, none of these studies included results of carrier status for highly penetrant genes. 23andMe performed a study on their own return of direct-to-consumer testing for *BRCA* AJ variants (45). Among 25 newly identified carriers, 11 were women; 3 of them experienced moderate anxiety, and none had severe anxiety. Regarding risk-reduction surgery, of the 11 women, RRBM was performed by 1 and planned by 3, RRSO was performed by 3 and planned by 4 (after completion of childbearing), and 9 shared information with at least one health-care provider (45).

It is important to recognize that, beyond the specific *BRCA* AJ variants approved for testing, there have been significant concerns regarding the analytical validity of non-medical-grade direct-to-consumer genetic testing (166), which can have false-positive rates as high as 40%. This is obviously a critical issue, and results obtained from such tests must be reconfirmed by diagnostic testing.

Another emerging model in this landscape is the hybrid model of direct testing, where a clinician orders a medical-grade test and communicates the result, but the test itself is sent and often paid for by the patient (140). The hybrid model thus combines the features of medically based mainstreaming while still offering patient convenience and choice. Concerns include issues related to cost and insurance coverage, continuity of care, and selection of the correct test.

To summarize, direct testing can be performed in a full medical setting that omits only pretest GC, in a hybrid fashion, or completely in the hands of the patient–consumer. While these processes are already being utilized, no randomized or comparative studies have evaluated their performance compared with one another or with traditional GC (140).

2.7.3. A direct-to-patient approach. Optimally, the goal would be to strike a balance that provides individual autonomy but does so through informed choices, a process that would maintain a clinical framework to ensure that the appropriate medical-grade tests are performed and that

patients have access to professional interpretation of their results and provision of appropriate care. We suggest the term direct-to-patient as embodying these goals.

For population screening of AJs for the *BRCA1/BRCA2* founder variants, we believe that the streamlined process has been shown by us and by others (**Table 3**) to strike such a balance. In the pretest stage, this process includes written and/or web-based information or education materials and a standardized self-administered family-history questionnaire. Optional access to a counselor through a telephone or telegenetic help line in the pretest stage has potential merit and addresses the need raised by some participants in the AJ population testing studies. After testing, only at-risk individuals (i.e., carriers and those noncarriers who have a significant family history) are recalled for in-person GC. We recognize that different health systems may need adaptable, context-specific pathways that result in different models for implementation while maintaining the principles of population screening.

2.8. The Cost-Effectiveness of *BRCA1/BRCA2* Population Screening (Principle 9)

A health economic evaluation is essential to evaluate the costs and consequences of different health strategies and interventions. This evaluation assists health-policy decision-making in achieving efficient resource allocation across interventions. For interventions to be sustainable, they must be cost-effective and affordable. A few studies have evaluated the cost-effectiveness of population-based *BRCA* testing in the Jewish population. An initial cost–utility analysis compared an absence of testing against population-based *BRCA* testing in AJ women aged 35–55 and showed that population testing was cost-effective (156). However, this study was limited in its interpretation because it compared against a lack of testing instead of against the true standard of care, which is clinical-criteria- or family-history-based testing. Additionally, this study examined only management and outcomes related to ovarian cancer and excluded those related to breast cancer.

Manchanda et al. (106) published a cost-effectiveness analysis comparing population-based *BRCA* founder variant testing with clinical-criteria- or family-history-based testing from the Genetic Cancer Prediction Through Population Screening (GCaPPS) trial and showed that population testing reduced costs for the UK health system, with a discounted incremental cost-effectiveness ratio (ICER) of −2,079 British pounds per quality-adjusted life year (GBP/QALY). Probabilistic sensitivity analysis showed that 94% of the simulations were cost-effective. Population testing was also found to reduce breast and ovarian cancer incidence by 0.62% and 0.34%, respectively, leading to 508 fewer breast cancer cases and 276 fewer ovarian cancer cases in a population of 80,940 UK AJ women undergoing testing. Overall, reduction in treatment costs led to a discounted cost savings of £3.7 million. These findings were based on an ∼2.5% *BRCA* prevalence found in individuals with four AJ grandparents. However, 25% of UK (56) and 44% of US (139) Jewish marriages are with non-Jews; hence, some Jewish individuals may have just one, two, or three AJ grandparents, and the prevalence of *BRCA1/BRCA2* founder variants is proportionally lower in these groups.

An updated cost-effectiveness analysis comparing population-based *BRCA* testing with clinical-criteria- or family-history-based testing in individuals with varying levels of AJ ancestry reconfirmed that population-based *BRCA* testing remained cost-effective in all these scenarios for both the US and UK health systems (108). Population testing remained cost-saving in AJ women with two to four AJ grandparents, with ICERs ranging from −2,960 GBP/QALY to −1,254 GBP/QALY for the United Kingdom and −19,587 USD/QALY to −12,013 USD/QALY for the United States. For individuals with one AJ grandparent, population testing was cost-effective for the UK analysis (ICER of 863 GBP/QALY) and cost-saving for the US analysis

(ICER of −2,542 USD/QALY) (108). Probabilistic sensitivity analysis showed that ≥95% of simulations were cost-effective for population testing at the 30,000-GBP/QALY UK willingness-to-pay threshold and the 100,000-USD/QALY US willingness-to-pay threshold. This result suggests that, compared with the current policy of clinical-criteria- or family-history-based testing, population testing of individuals with one to four AJ grandparents is highly cost-effective.

Compared with AJs, the prevalence of the *BRCA1/BRCA2* AJ founder variants is lower in non-Ashkenazi, Sephardi Jews (0.5–1%, largely *BRCA1* 185delG) (10, 11, 107). One cost–utility analysis used a Markov model to compare the lifetime costs and effects of clinical-criteria- and family-history-based *BRCA1* testing with those of universal population-based *BRCA1* testing in all Sephardi Jewish women. Population testing was cost-effective, with an ICER of 67.04 GBP/QALY for the UK population and 308.42 USD/QALY for the US population (138). All simulations were cost-effective for population testing in a probabilistic sensitivity analysis. Overall, there appear to be good data showing that population-based *BRCA* founder variant testing is cost-effective in the Jewish population and may be cost-saving in most scenarios.

While there are robust data supporting population-based *BRCA* testing in the Jewish population, corresponding data in the non-Jewish general population are much more limited but starting to emerge. In a recent study, Manchanda et al. (109) evaluated testing for a six-gene panel of largely high-penetrance breast and ovarian cancer genes (*BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, and *BRIP1*). The authors compared population screening of this panel with standard clinical-criteria- or family-history-based *BRCA1/BRCA2* testing as well as with clinical-criteria- or family-history-based testing for the panel in general-population British and American women over 30 years. They showed that unselected population testing with this six-gene panel was extremely cost-effective compared with either of the above clinical-criteria- or family-history-based restricted testing strategies. The ICERs for population screening with this six-gene panel were 21,599.96 GBP/QALY and 54,769.78 USD/QALY for the United Kingdom and United States, respectively, values that are well below the willingness-to-pay thresholds for both countries (30,000 GBP/QALY and 100,000 USD/QALY, respectively). Probabilistic sensitivity analysis showed that this population-based panel testing was cost-effective in 83.7% and 92.7% of simulations for the UK and US health systems, respectively (109). By comparison, clinical-criteria- or family-history-based panel testing was cost-effective in only 16.2% and 5.8% of simulations and clinical-criteria- or family-history-based *BRCA1/BRCA2* testing was cost-effective for only 0.1% and 1.5% of simulations for UK and US women, respectively.

A new population testing strategy for *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, and *BRIP1* could potentially prevent thousands more breast and ovarian cancer cases over and above the current policy. In the study by Manchanda et al. (109), using this panel prevented 1.86% and 1.91% of breast cancers and 3.2% and 4.88% of ovarian cancers in UK and US women, respectively, which translates to preventing 2,420 and 2,386 breast cancer cases and 657 and 655 ovarian cancer cases per million, respectively. The overall population impact was estimated to be an additional 64,493 breast cancer cases and 17,505 ovarian cancer cases prevented in UK women and an additional 237,610 breast cancer cases and 65,221 ovarian cancer cases prevented in US women (109). Most of the impact stemmed from *BRCA1/BRCA2* carriers. Zhang and colleagues (85, 186) showed that population testing for *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, cystic fibrosis, spinal muscular atrophy, and fragile X syndrome in all Australian individuals aged 18–25 in Australia was extremely cost-effective, with an ICER of 7,286 AUD/QALY. Compared with the current clinical strategy, this approach could potentially reduce variant-attributable cancers by 28.8%, cancer deaths by 31.2%, and cases of cystic fibrosis, spinal muscular atrophy, and fragile X syndrome by 24.8% (186).

2.9. Health-System Considerations: Available Facilities and the Sustainability of Population Screening (Principles 3 and 10)

As detailed above, population screening encompasses multiple health-system components. In most developed countries, the facilities for outreach, laboratory testing, GC, and medical surveillance and prevention already exist. However, population screening presents challenges of both scale and structure that are present at both ends of the process—identifying women who are at high risk and caring for those found to be at risk.

One significant challenge of scale is sufficient staffing: There will be a need for additional genetic counselors, who are critical in any medical model of population screening. In addition, mainstreaming or direct-to-patient approaches require non-geneticist clinicians (particularly primary care providers) to take on a greater role, which will require retraining and support, including ongoing access to genetics professionals. Structurally, it is important to define which clinician is responsible for follow-up of unaffected women who are at high risk for cancer. Possible alternatives, depending on the health system, may include specialized clinics or the primary care provider; any of these options will necessitate allocation of appropriate resources.

Creating population screening programs will thus require varying degrees of reorganization or restructuring of certain services, especially to achieve the necessary scale while ensuring that they remain continuous and sustainable. These adaptations will be specific to each health system, depending on its general structure and local regulations (e.g., on data security and privacy). Some countries with more centralized health systems may choose to create formal screening programs, while other countries may opt for open-access universal testing within a dispersed medical system. Importantly, creating an appropriate system for large-scale genetic testing for disease prevention has implications far beyond screening for breast and ovarian cancer. Indeed, creating such a system is an urgent imperative for genomic information to become useful in disease prevention.

3. FUTURE DIRECTIONS AND CONCLUSION

The long-standing principles of disease screening (see the sidebar titled Principles of Disease Screening) offer a framework for evaluating genetic population screening for cancer prevention. There are a number of avenues of further research in this area. Implementation research, which may be health-system specific, is necessary to determine optimal means of performing screening. Further developments in risk stratification will need to be examined, such as the inclusion of moderate-risk genes and/or polygenic risk scores. The meaning of VUSs and the appropriate policy for return of VUSs in screening tests should also be examined, particularly as appropriate and robust monitoring and management strategies for VUSs evolve in the future. As further studies are undertaken and data emerge, we expect that a population screening strategy could incorporate testing for a larger range of moderate- to high-penetrance genes, so long as this is based on established clinical utility and clear therapeutic benefit.

There is a consensus that *BRCA1/BRCA2* deleterious variants are clinically actionable and that it is medically worthwhile for carriers to be aware of their genetic status (71). Preventive strategies in carriers, particularly RRSO, have been shown to be lifesaving (111). Yet current schemes identify less than 20% of all carriers (110) and probably less than 10% of unaffected carriers (68). Overall, an estimated 90–97% of at-risk carriers in the population remain unidentified (100). In this review, we have examined population screening of AJs for *BRCA1/BRCA2* deleterious variants as a paradigm for a precision prevention strategy and assessed such screening in the light of established principles of disease screening. We believe this analysis clearly shows that testing for the founder variants fulfills these criteria. In non-AJ populations, emerging data on the frequency of *BRCA1/BRCA2* deleterious variants suggest that full sequencing of these genes may similarly

fulfill screening criteria. Population screening in both AJs and non-AJs, or at the very least open access to testing, may begin to address the major gaps in carrier identification.

Fulfilling the promise of cancer genetics for precision prevention requires transforming the testing process from a limited activity subject to multiple barriers into a public health endeavor. We believe it is incumbent on medical systems to enable a direct-to-patient model. This model would remove barriers to facilitate testing in a responsible manner and offer a framework for appropriate care.

A shift in scale also entails a shift in perspective. Common arguments against universal sequencing-based genetic screening have included the existence of VUSs, the question of testing for low- and moderate-risk or very rare genes, and the fact that individual genes account for only a small percentage of all cancer cases. These arguments may be viewed as examples of perfect being the enemy of very good. If unequivocal medical actionability is the paramount consideration, it is certainly possible to not report VUSs and to not test low- or moderate-penetrance genes in the screening setting. If testing is cost-effective, then it is worthwhile to screen for prevention of even a small percentage of cancer cases. There are also significant challenges that health systems will need to address, particularly mainstreaming and scaling the use of genomic information to optimize prevention. These issues are important topics for further implementation research, but they should not keep us from doing what is already possible.

DISCLOSURE STATEMENT

R.M. has received honoraria from AstraZeneca and MSD for advisory board meetings. S.L. has received honoraria from AstraZeneca for talks at national meetings. E.L.-L. has received honoraria from AstraZeneca for a scientific advisory board meeting and a talk at a national meeting.

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