Population genetic testing for cancer susceptibility: founder mutations to genomes

William D. Foulkes, Bartha Maria Knoppers and Clare Turnbull

Abstract | The current standard model for identifying carriers of high-risk mutations in cancer-susceptibility genes (CSGs) generally involves a process that is not amenable to population-based testing: access to genetic tests is typically regulated by health-care providers on the basis of a labour-intensive assessment of an individual's personal and family history of cancer, with face-to-face genetic counselling performed before mutation testing. Several studies have shown that application of these selection criteria results in a substantial proportion of mutation carriers being missed. Population-based genetic testing has been proposed as an alternative approach to determining cancer susceptibility, and aims for a more-comprehensive detection of mutation carriers. Herein, we review the existing data on population-based genetic testing, and consider some of the barriers, pitfalls, and challenges related to the possible expansion of this approach. We consider mechanisms by which population-based genetic testing for cancer susceptibility could be delivered, and suggest how such genetic testing might be integrated into existing and emerging health-care structures. The existing models of genetic testing (including issues relating to informed consent) will very likely require considerable alteration if the potential benefits of population-based genetic testing are to be fully realized.

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Introduction

Genetic testing for inherited susceptibility to cancer is well established in outpatient and inpatient health-care facilities around the world. Genetic testing for mutations in cancer-susceptibility genes (CSGs) is typically offered to individuals affected with cancer who are from families in which the pattern of cancer incidence is suggestive of a familial genetic predisposition. The model of delivery varies between health-care systems, but typically involves referral through strata of health-care specialists, repeated evaluation of eligibility for testing, confirmation of family history of cancer, and extensive pre-test counselling. Notably, the criteria for genetic testing vary substantially from country to country, and require expertise to interpret and apply the findings (Table 1). The time-consuming and cost-intensive pre-test evaluations reflect long-standing attitudes centred on rationing access to a highly expensive medical investigation, and a conservatism in the use of genetic testing, which is derived from models of adult-onset genetic disease, such as Huntington disease.[1] These attitudes towards genetic testing are now changing, however. Firstly, the introduction of new DNA-sequencing technologies has made genetic testing much cheaper, more rapid, more high throughput and, therefore, potentially more-widely accessible.[2,3] Secondly, cancer screening programmes, as well as surgical and pharmacological prophylaxis for individuals at high genetic risk of cancer, are increasing in availability and have proven effectiveness.[4–7] Thirdly, among the public, the awareness and appetite of individuals for access to their own genetic data, in order to inform their own health-related decision-making, is growing.[8] Finally, direct-to-consumer genetic testing for CSGs is increasingly available.[9,10] In light of these developments, an alternative strategy is being proposed to challenge the standard, restrictive model: population-based genetic testing for cancer susceptibility. In this Review, we describe the studies of population-based genetic testing for cancer susceptibility that have been performed to date, which have focused on *BRCA1/2*-related breast cancer in founder populations (that is, of *BRCA1/2* mutations that were carried by ancestral founders of, and thus are more prevalent in, certain ethnic or geographical populations), particularly the Ashkenazi Jewish population (Ashkenazim). In addition, we consider strategies for expanding the use of population-based genetic testing for cancer susceptibility and how such approaches might be integrated into health-care systems. We also highlight the numerous and substantial barriers and challenges that would need to be overcome before this approach could be applied more broadly in the wider population.

Department of Human Genetics (**W.D.F.**, **B.M.K.**), Department of Medicine and Oncology (**W.D.F.**), Centre of Genomics and Policy, Genome Quebec Innovation Centre (**B.M.K.**), McGill University, 1205 Docteur-Penfield, Montreal, QC H3A 1B1, Canada. Genomics England 100,000 Genomes Project, William Harvey Research Institute, Barts and The London, Queen Mary University, Charterhouse Square, London EC1M 6BQ, UK (**C.T.**). Institute of Cancer Research, 123 Old Brompton Road, London SW7 3RP, UK (**C.T.**).

Correspondence: W.D.F. william.foulkes@mcgill.ca

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Models for population-based testing

In health-care systems that are publically funded, such as those that exist in the UK and Canada, population-based screening for an adult-onset disorder (for example, breast cancer) does not rely on health professionals to offer the screen and thus regulate access to the test; instead an institutional (usually governmental) agency

Key points

- Traditional methods of identifying high-risk mutations in cancer-susceptibility genes (CSGs), with eligibility focused on family history, are laborious and can exclude more than half of all mutation carriers in a population
- Population-based CSG testing offers an alternative approach whereby genetic testing is offered directly to all persons in a specified age range and/or population group, regardless of personal or family history of cancer
- Population-based testing has proven cost-effective and acceptable to participants in studies of *BRCA1/2* founder (ancestral) mutations in specified populations or ethnic subgroups wherein a narrow range of mutations account for most CSG mutations in the population
- Extending population-based genetic testing to other populations would pose considerable financial challenges in terms of the costs of the genetic-testing infrastructure, irrespective of the decreasing costs of DNA sequencing
- Developing infrastructures for population-based testing of *BRCA1/2* offers the opportunity for broader CSG testing at limited additional cost; a panel-based approach focusing on a restricted number of highly penetrant mutations might currently be the most-acceptable strategy
- CSG testing might shift from bespoke tests towards whole-genome or whole-exome analysis as part of comprehensive population-wide programmes; incorporating such testing into health-care systems, with equitable access for the entire population, will be challenging

contacts eligible members of the population directly, to inform them of the specific screening test available and how they can gain direct access to it. In the perinatal setting in most developed countries, bloodspots are routinely collected from all newborns and are tested for a defined set of metabolic disorders as part of a population public-health programme.[11]

In a population-based programme, distinguishing between screening and diagnostic testing is important. As noted by Wald and Cuckle,[12] the difference is one of purpose. A screening test, such as mammography for breast cancer and the faecal occult blood test for colorectal cancer, typically has limited specificity and, therefore, a low positive predictive value (PPV), but high sensitivity and a high negative predictive value (NPV) in order to capture cases of the disease—that is, to prevent 'false negatives'. Thus, the result of the screening test is used to filter the population, by identifying individuals who are more likely to have disease, although a second modality of testing is thereafter required to diagnose the disease (a diagnostic test). At this second stage, many screens are demonstrated to have been 'false positives'. By contrast, a diagnostic test, such as a biopsy, must have high sensitivity, specificity, PPV, and NPV in order to enable robust diagnosis of (or to otherwise rule out) the disease of interest; typically this type of test is more costly and/or more invasive than the screening test. Conventional paradigms of cancer screening aim to detect a cancer that is already present. In population-based genetic testing for CSG mutations, however, what is actually being offered is population-based diagnostic testing, but for inherited cancer susceptibility rather than prevalent tumours. This paradigm also differs from previous population-based initiatives related to genetic disorders: firstly, most of the emphasis of established screening programmes has been on the detection of childhood-onset conditions;[13] secondly, screening in the newborn setting has typically adhered to the conventional two-stage model discussed, whereby a diagnostic genetic test is only performed following an aberrant result of a lower specificity non-genetic screening test—for example, testing for *PAH* mutations that underlie phenylketonuria in newborns with abnormal metabolite levels in a dried blood spot.[14,15]

Studies of population-based testing

Population-based genetic testing for cancer susceptibility in defined population subgroups, independent of personal or family history of cancer, has only been applied for the *BRCA1/2* genes, mutations in which are associated with a high risk of breast and ovarian cancer.[16] In this context, six studies have been conducted, all in founder populations; five were restricted to Ashkenazi Jewish populations and one was carried out in Poland. Some important aspects of five of these six studies are summarized in Table 2.

The first study was conducted at a Jewish community centre near Baylor College of Medicine, Houston, TX, USA, and was published in 1997 (Table 2).[17] The intervention was focused on education and did not formally assess any outcomes, but the test results for the Ashkenazi-Jewish-founder *BRCA1* mutation c.68_69delAG (usually referred to as '185delAG') were returned to all participants who wished to receive them. Findings of this small study suggested that there would be considerable interest among the Ashkenazi Jewish community in *BRCA1* genetic testing among those at higher-than-average genetic risk of breast and/or ovarian cancer.

A second study was published in 1997,[18] but is not discussed in detail herein (and is omitted from Table 2) because the main goals of the study were to estimate mutation prevalence and to investigate the penetrance of the three *BRCA1/2* founder mutations that are common in the Ashkenazi Jewish population: *BRCA1* c.68_69delAG (185delAG) and c.5266dupC (5382insC); and *BRCA2* c.5946delT (6174delT). Of note, however, the study cohort included a large number of Ashkenazi Jewish volunteers ($n = 5,318$), who were themselves unlikely to benefit from participation because no-one who underwent testing received their test results.

In 2006, a study was published in which Steven Narod, together with colleagues based in Szczecin, Poland,[19] took the still controversial step of offering direct-to-consumer testing for a high-risk CSG, in this case *BRCA1*, to women with a personal or family history of breast and/or ovarian cancer. In an innovative approach, the Szczecin team used the media, specifically a very popular Polish women's journal 'Twoj Styl' (Your Style),[20] to offer testing for three *BRCA1* mutations that are known to be founder mutations in the Polish population (Table 2). From a population-testing perspective, the key findings were as follows: testing was completed in over 5,000 women (~4% of women tested were *BRCA1*-mutation carriers) in just a few months and at a very low cost per mutation identified (calculated at US$630—at least 50 times less than the costs for similar commercial testing in the USA at that time); no obvious psychological harm was noted; and the majority of the 198 women found to be *BRCA1*-mutation carriers (about half of whom were unaffected by cancer)

Table 1 | Selected guidelines on eligibility for *BRCA1/2* testing for individuals with a personal or family history of breast/ovarian cancer*

Characteristic	Country/province (guideline name)					
	USA (NCCN[88])	UK (NICE[89])‡	Ontario, Canada (MOHLTC[90])	Germany (GC-HBOC/AGO[91])	Australia (EviQ[92])	Netherlands (IKNL/KiMS[93])
Risk threshold for testing in unaffected persons (%)	Not stated	≥10%	>10%	≥20% (calculated risk after applying Cyrillic2.1)	≥20%	~10%
Risk threshold for testing in affected persons (%)	Not stated	≥10%	Not stated	≥10% based on empirical observations or >3 females diagnosed after the age of 51 years	≥10%	~10%
Youngest age at breast-cancer diagnosis at which testing should be offered§	<46 years	Not stated‖	<35 years	<36 years	<40 years if TNBC; based on risk assessment for all other subtypes	<35 years
Oldest age at diagnosis of ovarian cancer at which testing should be offered§	No upper limit for epithelial ovarian cancer¶	Not stated‖	No upper limit for invasive serous ovarian cancer; other subtypes not mentioned¶	No upper limit for epithelial ovarian cancer	70 years if grade 2–3; based on risk assessment in other patients	No upper limit for epithelial ovarian cancer
Male breast cancer alone sufficient criteria to offer testing	Yes	Not stated‖	Yes	Not stated, however, offered within GC-HBOC without reimbursement	Not stated	Yes
Offer testing to members of specific population groups, in the absence of family history	Yes, for Ashkenazi Jewish women with breast cancer diagnosed at any age	Not stated‖	Yes, for Ashkenazi Jewish women with a breast-cancer diagnosis at an age of <50 years or ovarian cancer at any age	Yes, especially affected females from Eastern Europe; screen for the most-common founder mutations	Yes	No
Minimum breast/ovarian cancer family-history criteria for testing an affected person	Two or more breast cancers, with one diagnosed at an age of ≤50 years#	Not stated‖	Three or more breast or ovarian cancers at any age**	Two cases of breast cancer, with one diagnosed before 51 years of age	Not stated‖	Variable, depending on probability of around 10% that counselee is a mutation carrier
Minimum breast/ovarian cancer family-history criteria for testing an unaffected person	FDR of the woman described in the cell above	Not stated‖	Not stated, risk for tested person should be >10%	Calculated risk after applying Cyrillic2.1 >20%	Not stated‖	Variable, depending on probability >10% that counselee is a carrier
Relevance of other cancers	Pancreas and/or prostate cancer can substitute for breast and/or ovarian cancer in some criteria	Not stated‖	Not stated	Pancreatic cancer can substitute for breast and/or ovarian cancer	Not stated	Not stated

*A summary of a number of guidelines is also available at the National Cancer Institute PDQ website.[25] ‡The NICE guidelines focus on familial breast cancer. §In the absence of any other relevant risk factors. ‖Decision is based on risk assessment of person being considered for testing. ¶Ovarian cancer also includes fallopian tube cancer and primary peritoneal cancer. #First-degree, second-degree or third-degree relatives, on the same side of the family. **On the same side of the family. Abbreviations: AGO, Arbeitsgemeinschaft Gynakologische Onkologie (Breast Committee of the German Gynecological Oncology Group); FDR, first-degree relative; GC-HBOC, German Consortium for Hereditary Breast and Ovarian Cancer; IKNL, Integraal Kankercentrum Nederland; KiMS, Kennisinstituut van Medisch Specialisten; MOHLTC, Ministry of Health and Long-Term Care; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; TNBC, triple-negative breast cancer.

took some form of preventive or early diagnostic action following the identification of the mutation. Whether the potential risks of population-based genetic testing (Table 3) were discussed with the study participants is not clear. Given that at least six founder mutations in *BRCA1* are now recognized in the Polish population, in addition to nonfounder mutations in these genes and other probably clinically important mutations in *CHEK2* and *NBN*, the three *BRCA1* mutations tested only accounted for approximately one-half or less of all the clinically-important breast cancer CSGs mutations in Poland.[21,22] Nevertheless, by focusing on three important mutations, it was possible to rapidly investigate the feasibility and acceptability of direct-to-consumer, but physician-led, genetic testing of cancer susceptibility.

On the basis of the outcome of this study, Narod then applied a similar approach in Toronto, Ontario,[23] where a substantial Ashkenazi Jewish population resides. In the 2 weeks following a one-off national newspaper advertisement published in May 2008, over 2,000 phone calls were received by the research team and 2,082 women were offered testing for the three Ashkenazi-Jewish-founder mutations in *BRCA1* and *BRCA2* (Table 2). More than 90% of the women had never been diagnosed with cancer. Only 22 *BRCA*-mutation carriers were identified (1.1%), but a key finding was that under half ($n = 10$) met Ministry of Health of Ontario recommendations for ordering *BRCA* testing,[24] which are stricter than most guidelines (Table 1).[25] On the basis of these recommendations, therefore, the other 11 individuals would have

Table 2 | Studies of population-based genetic *BRCA1/2* mutation testing for breast/ovarian cancer susceptibility

Study characteristics	Study [location]				
	Richards *et al.* (1997)[17] [Houston, TX, USA]	Gronwald *et al.* (2006)[19] [Poland]	Metcalfe *et al.* (2010)[23] [Toronto, ON, Canada]	Gabai-Kapara *et al.* (2014)[29] [Israel]	Manchanda *et al.* (2015)[35] [North London, UK]
Recruitment strategy	Announcements at Baylor College of Medicine, local Jewish community centre, synagogues, on local news media and radio, and in newspapers and newsletters	Response to advertisement in supplement on breast cancer from an issue of a magazine popular among women (Twoj Styl; October 2001)	Response to a one-time advertisement in a national newspaper (May 2008)	Opportunistic health settings in Israel	Recruited via North London Ashkenazi Jewish community
Design and analysis	Education sessions with baseline questionnaires	Comparison of unaffected carriers and noncarriers	Comparison with provincial testing guidelines; pedigree inspection	Analysis of *BRCA1/2* mutations in female relatives of the screened men to derive age-dependent, birth-cohort-specific risks	RCT of acceptability of population testing; psychological effects and QoL in persons who underwent population screening versus family-history-based testing
Eligibility criteria	Age ≥21 years; Ashkenazi Jewish ancestry	Age >18 years; female sex; diagnosis and/or family history of breast and/or ovarian cancer	Age 25–80 years; female sex; Ontario residents self-identified as Ashkenazi or Sephardic Jewish	Age >30 years; male sex; 4 Ashkenazi Jewish grandparents; no past history of cancer	Age >18 years, 4 Ashkenazi Jewish grandparents, no past history *BRCA* testing (in person or FDR)
Number of individuals genotyped	289 (88% female)	5,024 (100% female)	2,080 (100% female)	8,195 (100% male)	1,034 (66% female)
Mutations tested	2 Ashkenazi-Jewish-founder *BRCA1/2* mutations (*BRCA1* 185delAG [c.68_69delAG]; *BRCA2* 6174delT [c.5946delT])	3 Polish-founder *BRCA1* mutations (mutations not stated in study report)	3 Ashkenazi-Jewish-founder *BRCA1/2* mutations*	3 Ashkenazi-Jewish-founder *BRCA1/2* mutations*	3 Ashkenazi-Jewish-founder *BRCA1/2* mutations*
Mutations identified (%)	13 (4.5%; 2.4% for *BRCA1* and 2.1% for *BRCA2*)	198 (3.9%)	22 (1.1%; 0.5% for *BRCA1* and 0.6% for *BRCA2*)	178 (2.2%; 1.2% for *BRCA1* and 1.0% for *BRCA2*)	22 (2.2%; 1.2% for *BRCA1* and 1.0% for *BRCA2*)
Pre-test counselling	Provided as part of the obligatory educational session; results of *BRCA2* testing were not disclosed	Not provided	Not provided	Not provided	Provided
Psychological outcomes	Not studied	Not formally assessed but seemingly mostly positive	No evidence for harm	Not assessed	No difference between population-screening and family-history groups
Cost per test	NR	Estimated at US$25	NR; but estimated to be less than CAD$50	NR	UK£50

**BRCA1* 185delAG (c.68_69delAG) and 5382insC (c.5266dupC), and *BRCA2* 6174delT (c.5946delT). Abbreviations: FDR, first-degree relative; NR, not reported; QoL, quality of life; RCT, randomized controlled trial.

been unlikely to find out about their mutation status, and their increased cancer risk, outside of the study. At the time of testing, cancer-related distress did not seem to be increased.[26] At 2-year follow up, among the 19 women with *BRCA*-mutations who completed both annual follow-up questionnaires (mean age 46 years), 2 of the 18 women without breast cancer had opted for a bilateral preventive mastectomy and 17 had undergone a preventive oophorectomy.[27] The question of whether the clinical management of these women should be the same as that of those with a stronger family history of cancer was not considered in the study. In a comparison with the traditional clinical approach, the Toronto group found that, by extending their study to 6,179 Ashkenazi Jewish women, they were able to compare the numbers of carriers identified by traditional clinic-based ascertainment with that achieved by their direct-to-consumer model: three times as many unaffected carriers were identified by the latter approach, at no added counselling cost.[28] These findings led the authors to propose that genetic testing for *BRCA* mutations should be offered to all Ashkenazi Jewish women.

Conducting studies in Israel offers several advantages in assessing the role of genetic testing in the Ashkenazi Jewish population, such as the small size of the country and the potential to enroll larger cohorts. These factors were exploited in a health-care-facility-based study by Gabai-Kapara and co-workers,[29] in which 8,195 Israeli Ashkenazi Jewish men were genotyped (Table 2); participation was offered by 'trained recruiters', although the content of discussions before enrolment has not been published. The investigators focused on men in an attempt to avoid the biases inherent in recruiting women to study a disease that nearly always affects only women. Investigators found that 175 of the tested men carried an Ashkenazi-Jewish-founder *BRCA1/2* mutation, resulting in a mutation frequency of 1.14% for *BRCA1* and 1.03% for *BRCA2*, and

Table 3 | Selected risks and benefits of population-based genetic testing for inherited cancer susceptibility

Variable	Factors against testing	Factors in favour of testing
Number of carriers identified and associated risks	Many mutation carriers will be identified, but most will have a lower cancer risk than previously observed in family-based studies	Many more mutation carriers will be identified who face an unequivocally increased risk of breast and ovarian cancer (or other malignancies)
Financial cost of testing	Costs of testing the entire population will be exorbitant	To date, cost-effectiveness studies have suggested an overall benefit of testing, especially in Ashkenazi Jewish populations
Interpretation of mutation result	Even if limited to *BRCA1/2*, variants of unknown significance pose a challenge, especially in underserved communities False-positives will occur (that is, alleles associated with limited or no increased risk will be said to be deleterious)	A very large number of tested people will be provided with a lifelong and unequivocal *BRCA1/2* mutation status (and potentially the status of other genes)
Effect of knowledge of mutation status on behaviour	Unclear whether the number of women that change their behaviour will be sufficient to make a substantial difference to the cancer incidence	Women who are carrying pathogenic mutations will be able to make preventive choices that will reduce cancer incidence
Effect of behaviour on risk	Women could change their behaviour, but the benefits of these changes on cancer incidence might have been overestimated	Risk-reducing surgeries and/or methodologies for early detection will be available to many more women, and cancer risk will diminish for those opting for preventive surgery
Psychological aspects of genetic testing	Psychological distress has not been assessed in persons who have discovered that they carry probable pathogenic mutations years before the likely onset of cancer	Substantial psychological relief after preventive action has been observed
Effect on relationship between the patient and health-care professionals	Health-care professionals might absolve medical responsibility—the concept of 'you're free to make your own mistakes'	Empowering the public to make their own choices—reduced professional barriers to access

2.17% for any Ashkenazi-Jewish-founder *BRCA1/2* mutation. The men seemed to be a reasonable representation of the Israeli male Ashkenazi Jewish population. None of the men received counselling before testing and no results were disclosed until the genetic counsellor had received the findings and the test was repeated, at which point *BRCA*-mutation carriers were asked to refer all of their female relatives for testing. Estimates of mutation penetrance were then established using the results observed in the women tested. The main finding was that the penetrance was found to be just as high for *BRCA1* mutations ascertained by this method as had been observed by this group in a previous study when individuals affected by cancer were used as the probands.[29,30] For *BRCA1*-mutation carriers, the estimated risks of development of breast cancer and ovarian cancer by age 80 were 60% and 53%, respectively; for women with *BRCA2* mutations, the risks were 40% and 62%, respectively.[29] Penetrance estimates in this study,[29] particularly for ovarian cancer, were surprisingly high, especially when considering that previous studies have suggested that familial factors (probably alleles of modifying genes that influence cancer risk[31]) have a strong effect on the risk of cancer development. For example, Metcalfe *et al.*[32] estimated the risk of ovarian cancer development by age the 70 of years in 1,750 *BRCA1*-mutation carriers with a first-degree relative (FDR) affected by ovarian cancer to be about 50%. In the study by Gabai-Kapara and colleagues,[29] however, the same risk estimate was 47% for all 211 female *BRCA1/2*-mutation carriers, not all of whom could have had a FDR with ovarian cancer. Thus, the critical question of cancer risk in the setting of population genetic *BRCA* testing remains incompletely resolved. Nevertheless, cancer-risk models that take into account polygenic susceptibility, such as BOADICEA,[33] exist and can be used to estimate risk with incorporation of the genetic test results.

An established consensus exists that changing clinical practice requires convincing supportive data from some form of randomized trial. Manchanda *et al.*[34,35] conducted the first randomized controlled trial of 'population screening' versus 'family-history-based' *BRCA1/2* genetic testing in Ashkenazi Jewish men and women, who were recruited from the Ashkenazi Jewish community in North London, UK (Table 2). Importantly, this study differed from the previous studies of population-based *BRCA* screening in that all of the 1,042 study participants underwent genetic counselling before genetic testing and were then randomly assigned 1:1 to the population-screening and family-history arms of the trial. In the population-screening arm, all individuals were tested for the Ashkenazi-Jewish-founder *BRCA* mutations, whereas in the family-history arm, only those who fulfiled the UK National Health Service (NHS) criteria for *BRCA1/2* testing (Table 1) were offered the genetic test. Findings of this study confirmed that population-based testing enables more *BRCA1/2*-mutation carriers to be identified than using family history as eligibility criteria for testing (13 out of 530 individuals [2.45%] in the population-screening arm versus nine out of 504 individuals [1.79%] in the family-history arm), and that *BRCA1/2*-mutation carriers ascertained via a population-based approach are not obviously psychologically adversely affected by the process,[34,35] compared with those who have a family history of *BRCA1/2*-associated cancers.[26,27] The perhaps more-critical questions of whether the population-based group would have had equivalent levels of distress if they had not received face-to-face pre-test genetic counselling (as in the other studies), or whether those who tested positive in a population-based study had markedly worse psychological outcomes than those who tested negative, were not addressed in this randomized study. Interestingly, after 3-years of follow-up, of the 468 persons

in the family-history arm who did not meet the criteria for *BRCA* testing (and who were, therefore, not offered testing) 210 have since opted for genetic testing, five of whom were identified as *BRCA1/2*-mutation carriers,[34,35] thus affirming likely acceptability of the population-testing approach if it were generalized. In support of this view, Sharon Plon stated in a recent commentary: "perhaps ... it is time to embrace the potential benefits of population screening...".[36]

Cost-effectiveness of *BRCA* screening

On the basis of cost-effectiveness studies performed to date, the health-economic implications of performing *BRCA1/2* genetic testing of the female Ashkenazi Jewish population aged between 35 and 55 years seem strongly favourable. In one cost–utility analysis, Rubinstein *et al.*[37] modelled the effects of founder *BRCA1/2* mutation screening in the US Ashkenazi Jewish population on ovarian cancer incidence and life expectancy, and assessed the associated costs of genetic testing. Under the assumption of a genetic test for founder mutations that costs US$460, the cost of the programme was estimated at US$8,300 per quality-adjusted life year (QALY) gained.[37] Given that the genetic test would probably cost much less than US$460 now, the expenditure per QALY gained would likely be significantly lower and lie well within the £20,000–£30,000 per QALY that has been deemed affordable by some health-care systems for cancer treatments.[38] Even if one questions a number of the assumptions of the model used, this analysis suggests that if at least 50% of Ashkenazi Jewish women with *BRCA* mutations are prepared to undergo surgical preventive interventions, population-based *BRCA1/2* testing in this group would probably be highly cost-effective—especially compared with other interventions to reduce breast-cancer mortality in the general population of *BRCA1/BRCA2*-mutation carriers, such as the use of MRI-based screening.[39] From another perspective, among almost 1 million Ashkenazi Jewish women aged 35–55 years in the USA, nearly 3,000 ovarian cancers could potentially be prevented by such an approach—if all of the ovarian cancers that would have occurred in mutation carriers were prevented by the prophylactic surgery.

Expanding the use of *BRCA* testing

Challenges to screening the wider population

The studies of *BRCA1/2* testing in the Polish and Ashkenazi Jewish populations described provide useful insights into the effectiveness and acceptability of population-based approaches to *BRCA1/2* testing. Perhaps the key observations are that this form of genetic testing is likely to be cost-effective, is generally acceptable, and is not associated with short-term negative psychological sequelae.

The experience from the Ashkenazi Jewish populations provides data rebutting a number of the concerns around validity, communication, risks, and acceptance of population-based delivery of *BRCA1/2* testing. Analytical validity—that is, the accuracy of the genetic tests—does not seem to be a large problem, at least in testing for the presence of founder mutations in this population, as analytical sensitivity was 99.0% and analytical specificity was 99.9%.[40] The misinterpretation of the results is likely to a bigger issue with use of *BRCA* testing, which can even be a problem when considering the founder mutations. In one analysis of screening for Ashkenazi-Jewish-founder *BRCA1/2* mutations in a clinical setting, 99 of 1,325 clinical interpretations were thought to be discrepant.[41] The major perceived issue in this analysis was that some of the women who tested negative for a founder mutation in *BRCA1/2* were told their risk of breast cancer was at population level, which in some cases would be inaccurate.[41] Very much the same issue would apply in the context of general-population-based genetic testing.

Mutation frequency and mutation spectrum are the major distinctions between a *BRCA1/2*-testing programme in the Ashkenazi Jewish population and in the general population. In the Ashkenazim, >95% of the pathogenic *BRCA1/2* mutations are accounted for by the three founder mutations,[42] and the carrier frequency of these mutations in the Ashkenazi Jewish population is known to be around 1:40 or 1:50 (Table 2).[43,44] In the broader, non-Ashkenazi-Jewish population, founder mutations typically account for <10% of germline *BRCA* mutations, and full analysis of the two *BRCA* genes is required to capture the full mutational spectrum. Furthermore, the overall prevalence of *BRCA* mutations is estimated to be 10-fold lower (approximately 1:400).[45,46]

Health-economic analyses of broader testing

The cost of genetic testing per *BRCA* mutation identified will be much higher in the non-Ashkenazi-Jewish population than in the Ashkenazim: 40-times greater (assuming US$200 per test for the Ashkenazi-Jewish-founder mutations and US$1,000 for a full screen of the two *BRCA* genes).[41] Some studies suggest that overall testing at the population level would, nevertheless, be cost-effective.[47] Cost-effectiveness studies, however, involve complex modelling, and estimates of key parameters used in the model can vary. Indeed, Levine and Steinberg[48] have highlighted scepticism surrounding population-based *BRCA* screening, and demonstrated that a large number of women would need to undergo population-based genetic testing to prevent one case of breast cancer; the authors assumed an 80% penetrance of *BRCA* mutations for the development of breast cancer by the age of 80 years and 100% uptake of a 100% effective cancer-preventive action, and calculated that 375 to 625 women would need to be tested to prevent one case of *BRCA1/2*-related breast cancer.[48] Palomaki[41] has estimated that the cost (assuming US$1,000 per test) per cancer detected early or prevented would be US$760,000. Even as genetic testing becomes cheaper,[9] the costs of *BRCA* screening will remain many times higher in the general population than in the Ashkenazi Jewish population. If we assume, however, that the test actually becomes sufficiently cheap (US$200, for example), we could realistically begin to consider estimating roughly how much testing an entire population of women would

cost. On the basis of US census data, 10,292,000 women between the ages of 30–34 years were living in the USA in 2012;[49] the preceding 5-year age cohort (comprising 25–29-year-old women) was 10,891,000 strong, and the subsequent 35–39-year age cohort contained around 9,719,000 women.[49] Indeed, each subsequent 5-year birth cohort of women up to age 65 harboured roughly the same number of individuals: ~10 million. Thus, an assumption that approximately 2 million women in the USA—specifically, those of rationally selected target age for screening of around 30 years—would be candidates for genetic testing for *BRCA* mutations each year seems valid, because this section of the demographic pyramid seems very square (L. Brody, personal communication). Assuming the test cost of US$200, US$400 million per year would need to be spent on a one-time genetic test for each 1-year birth cohort. This expenditure would be about 20-fold less than the current annual costs of mammography in the USA.[50] To ensure that all the over-30-year-old women are screened in the first round of testing would cost US$14 billion. These figures, however, refer only to the cost of performing the test, and do not cover any of the associated costs related to genetic testing, such as counselling and those related the additional services for which the mutation carriers will be eligible (L. Brody, personal communication).

The cost-effectiveness of population-based *BRCA1/2* testing has been considered recently; the conclusions were that such testing can be cost-effective if the genetic test costs $250 or less.[51] However, caveats were recognized: not surprisingly, the authors consider the logistics of "testing more than 100 million women" to be challenging, and they speculate whether money hypothetically assigned to testing would be better spent on earlier or more frequent breast imaging.[51] It will be impossible to determine the likely benefit of such an assignation without undertaking complex cost–benefit analyses comparing various population breast-screening regimens with a one-off population genetic test.

BRCA1/2 testing for all: the debate continues

Consideration of population-based genetic testing for cancer susceptibility, using *BRCA1/2* as the paradigm, has been debated for more than a decade in the public-health arena. When this topic was reviewed by Burke *et al.* in 2001,[52] referencing *BRCA1/2*-testing against the classic criteria for screening programmes proposed by Wilson and Jungner,[53] and again in 2007 by Khoury and colleagues,[54] the conclusion on both occasions was that the knowledge base was insufficient to recommend population-level *BRCA* screening. Khoury and co-workers[54] also outlined the four phases of translational research that should ideally be completed before a population-based genetic test is introduced, and concluded that for population-based *BRCA1/2* testing in asymptomatic women, too many of the research questions remained unanswered. In 2014, the United States Preventive Services Task Force explicitly recommended against population-based *BRCA1/2* testing, giving a D grade (discourage use of this service, 'moderately certain' of conclusion) for women "whose family history is not associated with increased risk",[55] while by comparison offering a B recommendation (service should be offered or provided) for *BRCA1/2* testing for women "who have family members with breast, ovarian, tubal or peritoneal cancer".[55]

In 2014, Dr Mary Claire King and colleagues[56] made a much-publicized call to offer *BRCA1/2* genetic testing to all women in the USA at the age of 30 years, which ignited a debate over the feasibility and suitability of a truly population-based approach to screening for breast CSGs.[57–59] At least one public body has disputed the proposal, particularly in terms of concerns centred around the potential social and ethical sequelae: the official position of the National Society of Genetic Counselors (NSGC) has been one of scepticism, with the society's President-Elect, Joy Larsen Haidle, stating that "genetic counselors have serious concerns about the long-term implications for patients and their families".[60] Other genetic-health professionals have also voiced doubt as to the wisdom of this approach, citing the problems of variants of uncertain significance (VUS), the need for genetic counselling, and the complex cultural considerations.[61]

Population testing for *BRCA1/2* mutations is technically feasible, but the economic data and professional perspectives on the introduction of population-level genetic testing for such mutations are currently very mixed. *BRCA1* and *BRCA2* are, however, only two of over 100 genes for which mutations have been described to confer a statistically significant increase in the risk of cancer, for one or more of >40 tumour types in total.[62] In the era of high-throughput DNA sequencing, if substantial sums of money are to be spent on developing infrastructure to offer genetic testing for *BRCA1/2* mutations to unaffected individuals, why not exploit the powerful new technologies to examine the status of other CSGs in parallel? This subject is discussed in the next section, which is focused on future perspectives of screening for cancer susceptibility.

Population genetic testing beyond *BRCA1/2*

Population-based testing for other CSGs

BRCA1 and *BRCA2* have been in the public spotlight over the past several years, but as introduced previously, over 100 genes with mutations that confer a cancer predisposition have been described. Many of these genes are currently tested for in the clinic based on familial patterns of cancer, in accordance with a paradigm similar to that of *BRCA1/2* testing.[62] Indeed, evaluating the eligibility of any of these other individual genes for population-level testing requires consideration of the gene–cancer relationship against similar key parameters used to evaluate the value of *BRCA* testing: the population carrier frequency of pathogenic mutations in the gene; the penetrance of cancers associated with the pathogenic mutations; the morbidity and mortality associated with these cancers; and the effectiveness of screening and/or prophylactic interventions to prevent the cancer or improve the prognosis. For virtually all of the known CSGs, current figures for these parameters

Box 1 | CSGs for which the ACMG recommends reporting of incidental variants[48]

- Hereditary breast and ovarian cancer: *BRCA1*; *BRCA2*
- Li–Fraumeni syndrome: *TP53*
- Peutz–Jeghers syndrome: *STK11*
- Lynch syndrome: *MLH1*; *MSH2*; *MSH6*; *PMS2*
- Familial adenomatous polyposis: *APC*
- MUTYH-associated polyposis: *MUTYH*
- von Hippel–Lindau syndrome: *VHL*
- Multiple endocrine neoplasia type 1: *MEN1*
- Multiple endocrine neoplasia type 2; familial medullary thyroid cancer (FMTC): *RET*
- PTEN hamartoma tumour syndrome: *PTEN*
- Retinoblastoma: *RB1*
- Hereditary paraganglioma-pheochromocytoma syndrome: *SDHD*; *SDHAF2*; *SDHC*; *SDHB*
- Tuberous sclerosis complex: *TSC1*; *TSC2*
- WT1-related Wilms tumour: *WT1*
- Neurofibromatosis type 2: *NF2*

Abbreviations: ACMG, American College of Medical Genetics; CSG, cancer-susceptibility gene.

comprise wide-ranging and probably inaccurate estimates, often inferred indirectly or derived from data from patient series that are subject to biases.[63] The spectrum of pathogenic mutations in the gene and technical issues associated with detection of mutation classes are additional relevant attributes that influence the value of a population-based genetic-testing programme.

Similar to *BRCA1/2* in the Ashkenazi Jewish population, certain CSGs are characterized by a high proportion of recurrent and/or founder mutations. For example, with regard to the colorectal-polyposis-associated gene *MUTYH*, ~90% of the recognized pathogenic mutations in north-western European populations comprise two mutations: p.G396D and p.Y179C.[64] Unlike the high population frequency of founder *BRCA1/2* mutations in the Ashkenazim, however, the frequency of these *MUTYH* mutations in the respective population is extremely low—the estimated prevalence of biallelic mutations in *MUTYH* in white individuals is 0.01%.[64] For most CSGs, as for *BRCA1/2* in the non-Ashkenazi-Jewish population, the spectrum of pathogenic mutations comprises a vast multiplicity of individually highly rare (private) mutations, unified and identified by a characteristic mechanism (for example, truncation of the protein). Accordingly, for many CSGs, no identifiable ethnic subpopulation is strongly enriched for particular pathogenic mutations, and any population-level testing programme would usefully identify the majority of pathogenic mutations only via full sequence analysis of the entire gene.

Taking into account the totality of the evidence in favour of population-based testing of other CSGs, it would be very difficult to argue that the 'case' for screening any other CSG would outrank that of *BRCA1/2*. Easton *et al.*[63] have argued that the lower bound of the 90% confidence interval for breast-cancer risk of an unaffected woman should be ≥4.0 for the gene to conclusively fall into the high-risk group. Currently, other than *BRCA1*, *BRCA2,* and *TP53*, no CSG associated with breast cancer clearly meets this required standard.[63] Thus, the legitimacy (based on Wilson and Jungner's framework[53]) and health-economic argument for population-based testing of other CSGs individually is likely to be less compelling than the case for screening *BRCA1* and *BRCA2*.

Testing for 'pan-cancer' susceptibility

If the case for population screening for *BRCA1/2* mutations is overall deemed equivocal and for other less frequently mutated CSGs is weaker, the next question would be whether the testing of a set of CSGs in combination would tip the balance in favour of population-based screening for cancer susceptibility. Next-generation sequencing (NGS) technologies support clear economies in large-scale concurrent testing of multiple genes; therefore, a multi-gene approach is clearly commensurate with the direction of travel for the technology. Given that such a gene-panel-based test would be undertaken on only a single sample of blood, a cancer-susceptibility test is operationally entirely feasible. The relevant consideration is, therefore, not to evaluate the public health and health-economic argument for CSGs individually, but rather to collapse the parameters of utility into a single set of metrics for the CSGs as a group. Population testing for 'pan-cancer' susceptibility, however, throws up many more complex questions than are raised by the paradigm of testing for one (or two) well-characterized genes.

The first question would be which genes to include in a pan-cancer susceptibility test. The absolute frequency of mutation carriers in the population for a given CSG becomes less critical when considering a gene panel, although the other aforementioned criteria for legitimacy remain important: namely, knowledge of the penetrance of the mutations for development of different cancer types; that the associated cancers confer substantial morbidity and/or mortality; that interventions are available to prevent or mitigate against the cancer in question; and that a single technology can reliably detect most of the mutations within the spectrum for that gene.

The American College of Medical Genetics (ACMG) has attempted to consider such parameters to assemble a CSG panel for which pathogenic mutations would be 'clinically actionable'—23 CSGs were identified (Box 1).[65] This undertaking was explicitly in the context of providing recommendations for reporting of secondary findings from whole-genome sequencing (WGS) or whole-exome sequencing (WES) studies;[65] however, one could argue that if the mutations are reportable because they are 'actionable', then the 23 CSGs the ACMG identified in this context probably comprise a reasonable consensus list of genes for which the evidence base for an increased cancer risk and the utility of intervention is strong (albeit far from complete).

The next immediate questions, following 'which' genes should be screened, would relate to the 'who' and 'when' of genetic testing. For a population-based programme of *BRCA1/2* testing, there would be clear logic to targeting the programme at women in their late twenties, on account of the sex and age-related penetrance of breast cancer, and also the recommended timings for screening and preventive surgery. With use of a pan-CSG strategy,

however, any rational basis for targeting of testing to a particular age-range, sex, or ethnic group is undermined: the genes are likely to be associated with a range of cancers with variable epidemiological characteristics and that require diverse management strategies. For example, some CSGs, such as *TP53,* confer an increased risk of cancer in childhood, which would necessitate monitoring from an earlier age to ensure actionability.[66] Thus, an additional key question is: how should the potential benefits of pan-cancer screening be harnessed without risking undue harm?

Cancer-panel versus exome/genome approaches

We turn to the question of 'how' population-based screening for cancer susceptibility might be best performed. Simple 'single-gene' testing for *BRCA1* and *BRCA2* mutations remains one option. Testing a panel of CSGs for mutations is the next alternative, and several panels exist that comprise 20–100 genes associated with cancer predisposition and thus capture most of the currently recognized and more clinically useful, higher penetrance, CSGs.[67] Such panels provide a cheap (relative to serial single-gene analyses or whole exome/genome sequencing) way to achieve high-depth coverage of a set of genes and, therefore, provide a technically 'accurate' (high sensitivity and specificity) approach to detection of small mutations. Most large copy-number aberrations can also be detected using this approach to genetic analysis through judicious probe design and powerful bioinformatic approaches, or through adjunctive use of a technology enabling dosage analysis. Cancer-gene panels have increasingly been adopted in the oncology setting for testing of germline susceptibility in patients with cancer.[68]

One could argue, however, that developing the complex infrastructure for a population-level genetic test and then simply testing for a couple or even a panel of CSGs, is a false economy. Numerous other rare but important and treatable genetic conditions exist, such as familial hypercholesterolaemia, for which ascertainment of the condition at a pre-symptomatic stage would be of public-health value.[69] Furthermore, many countries test for several genetic conditions, such as phenylketonuria, as part of the newborn screening programmes, albeit at present typically by use of an assay of metabolites as the first step of screening.[11] As costs associated with genome sequencing fall and the storage of vast genetic data becomes feasible, an alternative model to address all these windows of potential benefit of genetic testing is that of 'one-off' WES/WGS, undertaken as part of the newborn screening programme. The key criticism of this approach is that information relevant only later in life would be revealed.[70,71] For this approach to work, therefore, the population would have to accept long-term storage of their data and would have to accept that it might be, or become, appropriate to release parcels of genomic information at different times of their life—and only for gene-sets for which the risk interpretations have become stable and the clinical applicability is clear.[72] Thus, it is possible that population-level genetic testing for cancer susceptibility will emerge indirectly as a function of a large-scale movement to WES/WGS as a standard single test, thus facilitating the staggered answering of numerous different genetic questions in a multitude of contexts, some of which will be routine and preventive, whereas others will be individualized and responsive. Some of the advantages and disadvantages of various models for delivery of genetic tests for cancer susceptibility are outlined in Table 4.

Recommendations for consideration of WGS as a genetic screening tool were published in 2013,[70] and form an excellent framework for further discussions on this rapidly evolving topic. More recently, the need to remain focused on targeted approaches—for example, in the context of newborn screening[71]—has been emphasized, but various aspects of the approach of screening the whole genome or exome at birth are now being piloted in four different US studies, funded by the NIH.[73] Some of these studies will offer rapid WGS, whereas others will focus on exome sequencing. The overall emphasis of the four studies is on how some form of broad genomic analysis will influence the care of the newborn, but the question of how this information might be used in the long-term will also be considered. Without data from such studies, at present, opinions remain very mixed on the utility of WGS as an approach to improve human health: at one end of the spectrum, some feel WGS at birth is an inevitable development;[74] at the other end, the risks of 'going genomic' as a route to improve public health have been set out by Welch and Burke in an op-ed (opinion) piece in the *Los Angeles Times,* in which they state "Make no mistake about it: these data will scare people—particularly since they are likely to be framed as a 50% increase in your risk of Disease X. But it's just as likely they won't make a difference in your health."[75]

The preferred model for testing of CSGs could potentially be strongly influenced by the context of the health-care delivery system. In health-care systems delivered by a central provider and that are subject to extensive longitudinal evaluation (such as the previously mentioned systems in the UK and Canada), comprehensive population-based genetic testing could emerge as a 'one-off' WGS/WES test (Box 2). Genetic testing for cancer susceptibility would, therefore, be embedded in a more-comprehensive programme of population-based genetic/genomic testing, with standardization of timing of delivery of a 'cancer-susceptibility report'.

Conversely, in health-care systems that are more individual (rather than population-centric), more consumer-driven, more fragmented, and less focused on metrics related to economic delivery of pan-population public-health improvement, such as the US system, it seems probable that individual health-care providers will offer genetic tests serially, on demand, to those individuals covered by an appropriate health-care plan.

Obstacles to widespread population testing

Understanding the genes

BRCA1/2 are two extremely well-characterized CSGs, but many uncertainties remain regarding the cancer risks associated with mutations in these genes and how

Table 4 | Advantages and disadvantages of various models for delivery of genetic tests for cancer susceptibility*

Models	Advantages	Disadvantages	Comments
Standard model (semi-opportunistic genetic testing based on family history)	Established Harm limited Strong health-professional input	Misses many mutation carriers Restrictive: driven by special interests	Could be modified to improve throughput (for example, simplify eligibility criteria and/or use telephone-based rather than in-person pre-test counselling)
Ethnic-group-specific	Testing is technically straightforward Interpretation is straightforward Relatively cheap Already successfully trialled for *BRCA1/2* testing	Benefits and harms are restricted to a limited population—hence approach is discriminatory	The only form of population-based testing that has been attempted is for founder *BRCA1/2* mutations. There are no other combinations of genes/ethnic groups for which a limited set of founder mutations are sufficiently common to warrant testing. Such targeting is not only efficient, but as a matter of resource allocation, can serve to ensure sustainability of universal health-care systems
Population-based testing for single genes or gene families	Focuses on the most well-studied and clinically-relevant genes	Limited in scope Costly Unlikely to have longevity	*BRCA1/2*, mismatch repair genes, and *MUTYH* are the most obvious candidates for testing, as the associated cancer-susceptibility syndromes are relatively common (for Mendelian diseases) and a clear path exists for early diagnosis and/or prevention; could be expensive and wasteful programme, if subsequent decision-making is to extend beyond single genes
Risk-adjusted, population-based CSG panels	Identification of priority groups would focus on those at highest risk Risk estimates more reliable for limited gene sets	Identification of priority groups is probably so complex as to be impossible	Given the current estimates of lifetime cancer risk, most families will contain cancer-affected persons; therefore, developing a workable family-history-based tool that could meaningfully identify a subset of the population truly enriched for pan-cancer genetic susceptibility seems infeasible
Across-the-board population-based CSG panels	Administratively and technically relatively simple	Very costly to implement Interpretation of data is highly complex, and risk estimates are uncertain Age at which testing should be offered is unclear	This is the most obvious current use of next-generation sequencing to prevent and/or ameliorate cancer, and is already popular with direct-to-consumer companies and private individuals. Could be an expensive and wasteful population-based programme if subsequent decisions extend beyond only CSG data
Across-the-board, population-based WGS/WES	Administratively simple, 'one-shot deal' A virtual sub-panel of CSGs is interrogated	Bioinformatics, information storage, access, ethical and timing issues	These WGS data would offer the opportunity for routine interrogation not just for CSGs, but also for factors relevant to other medical conditions, such as familial hypercholesterolaemia or genetically-determined cardiac conduction defects; in the long term, approach is likely to be more cost-effective than alternatives
Testing of tumour using CSG-panel or WES/WGS testing in patients with cancer	Patient population enriched for CSGs by virtue of having developed cancer Provides information on germline and tumour at the same time Results directly applicable	Limited opportunities for prevention in the person tested Parallel examination of germline also required to confirm findings in tumour tissue	Several companies are offering targeted tumour panels that contain numerous CSGs; inevitably, use of these panels has led to the quasi-incidental identification of inherited mutations in CSGs. Such uncoordinated initiatives might jeopardize a more-rational, population-based approach to genetic testing for CSGs; on the other hand, unaffected relatives might be more receptive to this information than those without relatives affected by cancer

*All models assume a much more limited informed consent process compared with the standard model. Of note, however, even under the 'standard model' the findings of a study published in 2015 have indicated that only 38% of women undergoing *BRCA1/2* testing in the USA actually meet with a genetic professional prior to testing;[94] whether this low percentage is advantageous or disadvantageous is open to debate.[95] Abbreviations: CSG, cancer-susceptibility gene; WES, whole-exome sequencing; WGS, whole-genome sequencing.

they can be best managed; for many other CSGs, our understanding of which cancers they are implicated in and the associated risks is even poorer. The 'established' risks of cancer we currently use are generally derived from studies in individuals and/or families ascertained on the basis of a strong pattern of relevant disease. We do not know the appropriate cancer risks that are applicable to unaffected probands in the general population, but we have to assume the risks will be lower and less-precisely estimated.[63] Prospective studies of mutation carriers that are not biased by identification based on family history are urgently required, but necessarily require large-scale collaboration and long follow-up durations to yield precise risk estimates. In addition, we will require accurate models that incorporate genetic predisposition factors (high, intermediate, and low penetrance of mutations for cancer), together with lifestyle and environmental factors, and that are able to determine how these factors interact.

The evidence-base that screening programmes for the respective cancers associated with a particular CSG offer the opportunity to alter the natural history of the diseases is mixed.[76–78] Moreover, the estimated effectiveness of screening is predicated on accurate estimates of disease risk in the mutation carriers—the actual effectiveness of cancer screening will be diminished if the true cancer risks are lower than the estimates used. If preventive interventions (such as preventive oophorectomy) are favoured over cancer screening and early detection, what level of cancer risk would justify such intervention? Estimating the risk–benefit function of more-widespread application of chemoprophylaxis (with tamoxifen or aspirin, for example)—given the diverse, context-dependent and age-related adverse effects of these drugs—will be a challenging, but necessary, aspect of implementation of widespread CSG testing. Anticipating that broader identification of mutation carriers in the general population is inevitable,

Box 2 | The dilemma of all or nothing genetic susceptibility testing

Population testing for breast-cancer susceptibility in restricted populations, such as Ashkenazi Jewish individuals, has a number of attractive features: it is a common, serious disease with a substantial genetic component. If increased risk could be established early in life, at-risk women might take preventive action. Many other conditions with a substantial genetic component also exist that could also warrant attention—both cancer and noncancer-related conditions, affecting both men and women from all population subgroups. The infrastructure required to successfully implement population-based genetic testing for breast cancer susceptibility could be extended (without necessarily increasing the testing costs) to many other conditions. The question then would be when to offer the test and when to deliver the test results (these two events would not necessarily be closely related in time). As we have discussed in this Review, population-based testing for breast-cancer susceptibility among the Ashkenazim has a strong rationale. If one objects to such testing, one is likely to also reject other forms of genetic testing for cancer susceptibility; however, if one accepts testing in this selected subgroup, in principle, it would seem appropriate to extend genetic testing beyond *BRCA1/2*, and beyond the Ashkenazim, to include everyone, with susceptibility screening perhaps carried out once in a lifetime. A middle ground, for example, of testing all women aged 30 years and above for *BRCA1/2* mutations, might fail to find favour with health economists, ethicists, or the general population. Too radical for some and not radical enough for others: such is the dilemma of all or nothing approaches.

focused prospective research is urgently required to avoid a tidal wave of ad-hoc screening, surgical intervention, and chemoprophylaxis, which could be at best ineffective, and at worst actively harmful.

Managing variants of uncertain significance

The optimal management of families in which a VUS is detected is an issue that has plagued clinical genetics for 20 years.[79] The findings of large-scale sequencing studies demonstrate that variation in genes is common, and that the frequency of these variants falls along a continuum—from very common through to extremely rare (private). That variants at the upper end of this frequency continuum cannot be pathogenic is generally accepted, whereas variants at the lower end of the frequency spectrum have historically been treated as 'guilty until proven innocent'. Occasional rare missense mutations in the *BRCA* genes have indeed been demonstrated via robust genetic epidemiological analyses to be pathogenic, although the vast majority of rare *BRCA1/2* missense mutations are not pathogenic—they are just rare.[80]

In a programme of wider screening of CSGs, test results will probably be managed by a larger set of clinicians, and unless a prudent approach is applied as a universal matter of policy, the burden of rare VUS could thwart the success of such efforts. If we are ever to expand genetic testing to the general population, particularly if we are to test more disease-associated genes, reporting back all rare variants to patients as 'variants of uncertain significance', with the concordant complex counselling is infeasible; a mechanism needs to be in place that enables patient re-contact for occasional situations in which the VUS is definitively re-classified as pathogenic.

Redefining the classic duties of physicians

Without a doubt, the use of genetic testing in the general population for cancer susceptibility will affect the 'classic' duties of physicians, particularly if testing of a CSG panel is undertaken and even more so if that CSG panel is examined as part of a broader programme of WES/WGS in population testing. Limiting ourselves to the four traditional duties of physicians, which are to obtain informed consent; to treat; to follow up; and to maintain professional secrecy, it is self-evident that the use and the storage of DNA for diagnostic testing will greatly affect the two latter duties. The process of obtaining consent will become more complex, but the duties of follow up and confidentiality could well surpass obtaining consent and delivering treatment in terms of the burden placed on physicians, owing to the accumulation of WGS information, interpretation of which will almost certainly need to be repeatedly revisited over time and as the interests of biological relatives become part of the 'treatment'.[72]

In the field of medical genetics, the importance of pretest counselling has long been recognized when obtaining informed consent. Under new approaches to consent, the duty to inform will probably be firstly population-based, and then individualized for those screened and subsequently identified as 'at risk'. In other words, general information, such as what the process is, what data might be obtained, and how these data will be used, will be relayed to obtain initial consent to screening, before further consent is obtained for diagnostic and treatment purposes to follow up on the risk factors identified. Communicating the nature of WES/WGS, the possibility of unknown and variable secondary findings, and the possible implications of any future results will require a major investment in defining the 'contents' of the duty to inform.[81] The study of genetics brings its own well-known challenges, such as the discovery of carrier status, of disease predispositions, or of rare diseases with attendant reproductive, prevention, and treatment choices. Physicians can only be responsible for following the existing professional norms of the time. Hence, establishing scientific standards, as well as primers on what to communicate to the public and to individuals concerning such population-based testing, is paramount if large-scale sequencing is to become part of the standard of care.

The duty to treat encompasses not only decisions on appropriate treatment, but also the decision to offer the genetic screen itself. Fear of future or actual liability for false positives, for ordering tests or interventions, or for not doing so, and for misinterpretation is not unfounded, considering the need to reinterpret or 'refresh' WGS results over time. Thus, in this setting, the duty to treat might well be surpassed by the duty to follow up. Invalidated findings or requests for further tests owing to the revelation of secondary findings, and the possible need to re-contact individuals over time when the meaning of variants identified changes, could well transform the duty to follow up after population-based genetic testing into the most important professional duty of physicians. Traditionally, however, the duty of the physician to follow up only applied to the immediate treatment at hand and was not an open-ended duty to follow without limit over time.[82]

The duty of physicians to maintain confidentiality has always been central with regard to genetic information, for fear of stigmatization and of discrimination in terms of employment or insurance coverage.[83] If the health-care system was to offer such population-based screening/diagnostic tests, the results will be held in the medical record with possible attendant socioeconomic consequences. Moreover, genetic analysis has long raised the issue of a possible ethical duty to warn (or not) identifiable at-risk family members.[84] Such an ethical duty to warn is discretionary in most countries, and will, in all likelihood, be limited to those findings that are clinically significant and medically actionable. As the costs of genetic testing decrease, however, this nascent duty to warn might in fact be halted in its tracks, as both individuals and their relatives could easily have their own genome sequenced and be actively involved as partners. Indeed, such personal genetic-profiling empowerment could potentially shift some of the emerging responsibilities described away from physicians, and on to individuals themselves. This scenario would have its own risks and benefits. The individuals would need to be suitably informed of the implications of their genotypes and their roles in managing any risks identified for such a shift in responsibilities to work.

To delineate these emerging duties of health professionals in targeted population-based genetic testing programmes, Burton *et al.*[85] have highlighted that "…appropriate systems for inviting and recalling people for risk assessment and screening need to be in place. Second, there should be a standard protocol for taking consent, performing genetic sampling and using a standardized risk assessment tool to integrate genetic data from individuals with environmental, lifestyle and hormonal data. Third, the level of cancer risk will dictate the care pathway followed, with different pathways being followed for each risk stratum."

Conclusions

We have reviewed the current standard model for CSG testing and considered population-based testing of CSGs, expanding on the familiar paradigm of testing for founder *BRCA1/2* mutations. The existing practice of focused *BRCA1/2* testing in the Ashkenazi Jewish population arose as a result of the distinctive cost–benefit characteristics in this group: the prevalence of *BRCA* mutations is approximately 10-fold higher than in the general population and most of the mutations present among this ethnic group can be detected through a cheap, technically simple, and clearly interpretable test for three mutations. Expansion of *BRCA1/2* testing into the broader population, in which the mutation frequency is much lower and the much broader mutational spectrum requires the use of more costly and complex full-gene sequencing, necessarily shifts the cost–benefit substantially downwards. Furthermore, given the opportunity costs of establishing a much broader programme of genetic testing in the general population, the justification for testing only *BRCA1/2* as opposed to a broader sweep of CSGs, or indeed a broader set of disease susceptibility genes, is questionable.

Testing of CSGs is becoming more widespread as a result of advances in oncology and the growth of the direct-to-consumer market. Owing to the improved technology for genetic testing, increased opportunity for screening/prophylactic intervention, and increased public appetite for predictive genetic knowledge, interest in testing for CSGs in people unaffected by cancer will inevitably expand. For this reason, we could see a potential interim phase in which some health-care providers offer a CSG panel to their patients as part of a preventive-care incentive, but anticipate that this approach would be prevalent only in more consumer-driven health-care models. Given the recent announcement by President Obama of a Precision Medicine initiative in the USA[86] and large-scale genome sequencing programmes within other routine national health-care systems (such as the UK 100,000 Genomes project),[87] it seems entirely plausible that over the next decade we shall witness ever-expanding routine use of WGS/WES in multiple contexts within routine health-care, public-health, and research programmes, the totality of which will begin to approximate and might be subsumed by a more-comprehensive population-level approach, particularly in more-socialized health-care models.

Central expert guidance will be required as to which genes should be tested, which levels of risk are communicated, and how results relating to rare variants could be returned. Additional research is urgently needed to accurately characterize the risks and effectiveness of the interventions available for CSG-mutation carriers. For all these new programmes to be successfully implemented by health professionals, genetics will need to be centrally placed in the medical teaching curriculum. Developing new competencies in communication, counselling, bioinformatics, and epidemiology will be important. Moreover, equitable access to both testing and counselling must be universally available.

Review criteria

Literature on population testing for cancer susceptibility was retrieved from PubMed using various combinations of the following search terms: "population-based", "mutation", "*BRCA1/BRCA2*", "Narod", "Burke", "panel", "cancer-susceptibility gene", "breast cancer", "Ashkenazi", "epidemiology", "next-generation sequencing", and "diagnostic tests". The search was limited to documents written in English, dating from 1980 to July 2015. Literature on physician duties was retrieved using PubMed, Google Scholar, and the HumGen International database, an online resource for documents specializing in legal and socioethical issues in human genetics. To focus on pertinent documents, the keywords "physician", "genetic testing", "population screening", "whole-genome sequencing", "consent", "confidentiality", and "liability", were used in various combinations. The search was limited to documents in English and French dating from 2005 to 2015.

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Author contributions

W.D.F. devised the outline of the review. W.D.F., B.M.K., and C.T. contributed equally to researching data for the article, discussion of content, writing the manuscript, and review/editing before submission.