The role of genomics in global cancer prevention

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Abstract | Despite improvements in the understanding of cancer causation, much remains unknown regarding the mechanisms by which genomic and non-genomic factors initiate carcinogenesis, drive cell invasion and metastasis, and enable cancer to develop. Technological advances have enabled the analysis of whole genomes, comprising thousands of tumours across populations worldwide, with the aim of identifying mutation signatures associated with particular tumour types. Large collaborative efforts have resulted in the identification and improved understanding of causal factors, and have shed light on new opportunities to prevent cancer. In this new era in cancer genomics, discoveries from studies conducted on an international scale can inform evidence-based strategies in cancer control along the cancer care continuum, from prevention to treatment. In this Review, we present the relevant history and emerging frontiers of cancer genetics and genomics from the perspective of global cancer prevention. We highlight the importance of local context in the adoption of new technologies and emergent evidence, with illustrative examples from worldwide. We emphasize the challenges in implementing important genomic findings in clinical settings with disparate resource availability and present a conceptual framework for the translation of such findings into clinical practice, and evidence-based policies in order to maximize the utility for a population.

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The past decade has seen rapid progress in our understanding of cancer, although many mechanisms by which genomic and non-genomic factors contribute and interact to initiate carcinogenesis, drive invasion and metastasis, and enable the favourable conditions that facilitate cancer progression remain to be elucidated. Large international initiatives have been created to interrogate whole genomes, including those of many thousands of tumours from patients worldwide, in order to identify specific mutation patterns associated with particular causes of cancer (commonly referred to as 'mutational signatures'). Prime examples of such efforts include the Mutographs study funded through the Cancer Research UK (CRUK) Grand Challenges initiative with a focus on five cancer types, and the Sherlock initiative led by the US National Cancer Institute (NCI) with a focus on lung cancer among never smokers. Such global collaborative efforts have driven the science forward to identify and better understand causal factors, and to shed light on new opportunities to prevent cancer. As a result of these efforts, our understanding of the risk of developing cancer that is attributable to moderately and highly penetrant mutations in cancer susceptibility genes across different populations has also improved[1]. In addition, genome-wide association studies (GWAS) have led to the identification of single nucleotide polymorphisms that individually confer a small cancer risk but in combination are associated with clinically relevant effects on cancer risk[2–4]. These discoveries can provide actionable information by enabling estimation of an individual's risk of developing specific cancers with improved accuracy and, with important caveats, by offering opportunities to tailor (or 'personalize') guidance on how to reduce the cancer risk.

As the science of cancer genomics evolves and, with it, the potential to inform prevention practices, such as risk-reduction mastectomy for *BRCA1* or *BRCA2* (*BRCA1/2*) carriers (primary prevention) and enhanced breast screening with MRI (secondary prevention), the effect that this information can have in reducing preventable cancer deaths globally is important to consider. Nevertheless, with limited exceptions outside of the research setting, the clinical applications of these discoveries are available only in high-income countries (HICs) in which robust health care systems and financing can support the implementation of 'precision prevention'. Even in HICs, gross inequities exist in access to and use of clinical cancer genetics services, including tailored risk assessment and risk reduction strategies. Moreover, genomic medicine continues to suffer from

Key points

- Technological advances in germline and tumour genomics are helping to drive progress in elucidating cancer causation at the individual and population level and offer new insights and potential opportunities to prevent certain cancers.
- The understanding of cancer risks attributable to moderately and highly penetrant mutations in cancer susceptibility genes across different populations has also improved, and genome-wide association studies have led to the identification of single nucleotide polymorphisms that individually confer a small cancer risk and in combination are associated with clinically relevant effects on cancer risk.
- In practice, taking cancer genomics data to the clinic remains challenging even within some high-income country settings owing to factors including inequitable access and use of limited genetics resources, particularly among minority ethnic and cultural populations; the disproportionate contribution of genomic data from largely European populations also limits the degree to which such information is generalizable to other populations.
- Optimal strategies to identify individuals at (high) genetic risk for cancer are currently being debated, with evidence increasingly supporting the adoption of population-based genetic testing for individuals with certain cancers.
- The evidence-to-policy gap in cancer genomics is both deep and wide; the efficiency by which knowledge generation, integration, and dissemination can ultimately lead to better population health can be improved through high-quality implementation research.
- While genomics can contribute to the pursuit of global health equity through the open exchange of information, expertise and technology between countries of all income levels, this goal will only be possible if it is integrated with the broader, societal understanding of the utility of cancer genomics; an equity lens must be applied throughout the translational research continuum, ensuring adequate representation in research studies of all major world populations, and ethnic and cultural groups.

a lack of diversity in terms of the populations studied as well as the scientists who lead the research. These disparities further limit opportunities for all to benefit from such discoveries[5–8].

In this Review, we provide an overview of the relevant history and emerging frontiers of genetics and genomics as pertains to global cancer prevention. First, we describe how genetic epidemiology studies are improving understanding of causal factors of cancer risk across populations. Second, we present an overview of progress in research on germline cancer susceptibility, followed by a discussion of the utility of mainstreaming cancer genomics in different public health contexts. Finally, we present a novel population health equity framework for the clinical translation of findings from cancer genomics and prevention studies in order to guide decision making for researchers, health planners and policymakers.

Genetic epidemiology of cancer

Cancers are diseases predicated on the existence of genetic and epigenetic alterations that disrupt key regulatory mechanisms of homeostatic functions such as cell growth and division, among others. Genomic alterations are necessary but insufficient for cancer to occur; a complex interplay of genetic and non-genetic factors (including environmental and/or lifestyle factors) determine the occurrence and nature of initiating events that destabilize the genome of a cell, and whether a given clone harbouring a disrupted genome will display the uncontrolled, dysregulated behaviour that defines cancer.

The identification of causes of cancer and the subsequent elimination (or reduction) of exposures to known cancer-causing agents are the foundations of cancer control. Cancer epidemiological research has been successful in identifying many major carcinogens related to lifestyle and/or the environment and thus ~40% of the cancer burden in any HIC can be explained by known risk factors[9,10]. Tobacco smoking accounts for ~50% of the known cancer risk; body weight, alcohol consumption, diet, exposure to occupational carcinogens and ultraviolet (UV) radiation, and physical inactivity explain most of the remaining environmental risk[9,11]. Simply implementing scientific knowledge about the causes of cancer at a societal level would have a substantial effect on cancer control. The progress in addressing the important role of tobacco as a cause of cancer in HICs, however, has hidden the lack of progress elsewhere. Indeed, only ~25% of the cancer incidence among non-smokers is attributable to known risk factors[9]. Nevertheless, cancer epidemiology supports that all common cancers are largely preventable, at least in principle. In fact, a cancer type can be common in a particular population and rare in another, and most common cancers have undergone large changes in incidence over time[12]. The only explanation for this variability is that the majority of cancers are caused predominantly by modifiable exposures, some known and some yet to be discovered. In 2015, the publication of a modelling study that revealed a correlation between the number of divisions of self-renewing cells and lifetime cancer risk (across 31 tissues of origin) renewed debate over the role of 'bad luck' in causing cancer mutations[13]. The re-emergence of this debate has muddied the waters on the preventability of cancer but we should not lose sight of the fundamental observation that the majority of cancers are, in principle, preventable[14].

Epidemiology studies that have directly measured exposure to suspected risk factors have been instrumental in uncovering most of what we know about the causes of cancer; however, their success in identifying new causes has been limited in the past few years. This lack of progress can be explained by the fact that important risk factors for cancer can be inter-related and difficult to separate (for example, nutritional exposures) and/or hard to measure accurately (for example, physical activity or exposure to air pollutants)[15,16]. Similarly, many environmental exposures are difficult to study in an epidemiological setting because they occur at low levels in some populations. Cancer genomics can enable the elucidation of environmental and/or lifestyle-related risk factors using a number of strategies. Herein, we discuss two specific approaches that have emerged in the past few years.

Mendelian randomization

Family studies have led to the identification of clinically actionable moderate-risk and high-risk variants of cancer predisposition genes[17–19]. However, a substantial proportion of the familial aggregation of cancer remains unlinked to such variants as typically less than one third of the heritability can be attributed to known cancer predisposition variants for each cancer type (a problem referred to as 'missing heritability')[10,20]. In parallel, very large GWAS involving many tens of thousands of well-matched individuals with or without cancer have

Table 1 | **Genome-wide association studies of common cancers**

Tissue of origin	Individuals involved (*n*)	Genetic loci identified (*n*)	Ref.
Breast	147,183 with cancer 130,749 without cancer	214	22
Prostate	79,194 with cancer 61,112 without cancer	148	23
Lung	29,266 with cancer 56,450 without cancer	18	24
Colorectum	58,131 with cancer 67,347 without cancer	95	25
Ovary	29,396 with cancer 68,502 without cancer	12	26
Pancreas	11,777 with cancer 17,248 without cancer	23	27
Kidney	10,784 with cancer 20,406 without cancer	13	28

revealed additional gene variants that increase cancer risk. The largest of such studies illustrate the success of these analyses in identifying common genetic variants with a modest effect on cancer risk, usually modifying risk by ~10–20%[21–28] (TABLE 1).

Nevertheless, the findings from these studies do not explain most of the familial risk of common cancers. For example, all known cancer predisposition variants account for only ~4–23% of all breast, prostate, lung and colorectal cancers (10–22% of these cancers are familial, depending on the cancer site), thus indicating that other, possibly rare, genetic susceptibility variants remain to be discovered, including in non-coding and/or regulatory regions of canonical genes[29,30]. The primary aim of these genetic studies has been to improve understanding of disease biology and perhaps inform treatment strategies, but they have also provided data that have been used to elucidate non-genetic causes of cancer in what has been termed a 'Mendelian randomization' approach[31]. A detailed description of this approach is beyond the scope of this Review; herein, we provide a brief overview with examples. The random assortment of alleles at conception has been likened to a randomized controlled trial in which people are randomly allocated to different genotypes rather than interventions. Indeed, Mendelian randomization enables unbiased comparisons on the basis of genetic variation. When a gene variant or even a set of gene variants (G) seems to be associated with a particular exposure (X), G can be used as a proxy of X to study whether it is one of the causes of a particular cancer (Y). Non-genetic confounders (C), that is, confounding factors that are related to both X and Y, do not affect G and therefore Mendelian randomization estimates, while an observational study might reveal an association between X and Y, which could be affected by C (FIG. 1a). For example, researchers might observe an association between obesity and a particular cancer, but this link might be explained by confounding owing to other potential common factors, such as a lack of exercise or a poor diet. Observational studies can attempt to control for these confounding factors, although such control might be only partial or non-existent if the confounder has not been measured or identified. The difficulty in separating out these effects is one of the major challenges in epidemiology and one of the main reasons why epidemiology studies sometimes lead to erroneous conclusions. In addition, observational studies are susceptible to different biases, including reverse causation bias (when early-stage disease has an effect on various exposures) and measurement bias (resulting from differing exposure measurement errors between individuals with and without cancer)[15]. A classic example would be the association between foods rich in β-carotene and lung cancer, which was observed in multiple observational studies but was not replicated in large randomized studies of β-carotene supplements[32].

Studying the association between a gene that is known to influence a modifiable exposure and cancer risk might generate more informative results than those from studies of direct associations between exposures and cancer as the gene is unlikely to suffer from the same confounding as the actual exposure, and various biases, especially reverse causation and measurement biases, can be minimized or even completely ruled out. For example, the main gene that influences obesity is *FTO*[33]. Variants in this gene are unlikely to be associated with other factors, such as social status, physical activity or alcohol consumption, which are all described to affect the risk of obesity. Furthermore, whereas early-stage cancer might affect the patient's weight, it cannot alter genes that influence weight, thereby ruling out the possibility of reverse causation bias. Thus, results from studies of the association between certain *FTO* variants and cancer would provide more convincing proof of causality than epidemiological studies with other designs. Indeed, >900 independent single nucleotide polymorphisms have been shown to have some effect on obesity[34]. These variants have be used to generate a weighted genetic predictor of obesity, and this genetic proxy for obesity, commonly referred as a genetic instrument, has been evaluated in relation to a variety of common cancers using cancer GWAS results and two-sample Mendelian randomization methods, revealing a strong causal link between obesity and cancer usually greater than the effect previously seen in epidemiological studies[35,36] (with ORs 1.05–1.50)[37]. These results suggest that researchers might have underestimated the effect of BMI on the risk of many common cancers.

Mendelian randomization studies can be informative in a number of settings. Among the situations that particularly benefit from Mendelian randomization analyses are those in which the exposure is difficult to measure. For example, a history of diabetes and insulin resistance is a suspected risk factor for numerous cancers, including pancreatic, renal and colorectal cancers[38]. However, evaluating this causality in large population cohorts is difficult, especially in the absence of the collection of fasting blood samples. Conversely, the genetics of insulin resistance has been clearly identified through large studies involving individuals with diabetes[39], resulting in gene scores associated with increased insulin resistance. The application of gene scores as a genetic instrument

b

Cancer type (Y)	SNPs (G)	MR studies for fasting insulin (X) Individuals with cancer (*n*)	Individuals without cancer (*n*)	Ref.	MR estimate OR (95% CI)
Renal cell carcinoma	17	10,784	20,406	[40]	1.82 (1.30–2.55)
Pancreatic cancer	17	7,110	7,264	[41]	1.66 (1.05–2.63)

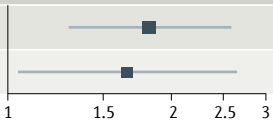

Fig. 1 | **Mendelian randomization approaches in cancer genomic studies. a** | Directed acyclic graph showing the causal relationships (arrows) in a setting when Mendelian randomization (MR) methods can be used to estimate the potential causal effect of a particular exposure 'X' (dashed arrows) on the risk of a particular cancer 'Y'. The presence of non-genetic confounders of the exposure–cancer relationship 'C' that might bias the estimates of this relationship in observational studies does not typically affect MR estimates because the gene variant or a combination of gene variants 'G' associated with X is unlikely to be affected by C. **b** | Studies investigating genetic predisposition to insulin resistance in relation to the risk of cancer highlighted the importance of fasting insulin as a potential risk factor for both renal and pancreatic cancer. SNPs, single nucleotide polymorphisms.

for insulin resistance to genetic data from large series of individuals with or without cancer have highlighted insulin resistance as a potentially important risk factor for both renal and pancreatic cancer[40,41] (FIG. 1b). These studies illustrate two key roles of Mendelian randomization: to help elucidate whether or not an association is truly causal and to identify novel cancer risk factors.

Mendelian randomization studies are not without problems, including the potential for genes to have multiple effects (that is, pleiotropy), many of which remain unknown[42]. Nevertheless, we have already discussed that Mendelian randomization overcomes important sources of bias that arise from direct assessment of the actual exposure and, in general, biases associated with Mendelian randomization studies are likely to be different from those of studies with other designs. This observation raises the idea of triangulation, an approach that involves using different study designs to evaluate a hypothesis and drawing conclusions from the totality of the evidence[43]. For example, a study published in 2017 in which ~77,000 adults in the USA provided information on vitamin use revealed a surprising association between the use of vitamin B_{12} supplements and an increased risk of lung cancer[44]. A subsequent study reported an increased risk of lung cancer associated with genes that influence circulating vitamin B_{12} levels both in a large genetic dataset and in 20 prospective case–control studies in which such circulating levels of this vitamin had been measured[45], supporting a role for vitamin B as a causal factor.

In summary, Mendelian randomization studies provide an alternative method for identifying possible causes of cancer that could be preventable. This design enables some of the known biases of observational studies to be avoided, and is likely to become more widely used in the near future owing to the increasing availability of genomic data from large population cohorts.

Mutation signatures

In parallel with the increasing availability of data on germline DNA variation and specific cancer risks, large international efforts have greatly expanded the availability of somatic genome sequencing data for multiple cancers types, including the Cancer Genome Consortium and the International Cancer Genome Consortium[46]. These initiatives also provide important opportunities for understanding cancer causality. Researchers have long suspected that mutation signatures are associated with particular causes of cancer. Initial studies of patient-derived tissues were focused on mutations in *TP53* and revealed that UV-induced squamous cell carcinomas of the skin commonly harbour cytosine to thymine mutations, either of a single base (C>T) or two bases (CC>TT)[47]. Similarly, non-small cell lung carcinomas frequently harbour C>A mutations[48]. These patterns were confirmed in experimental in vitro models of UV radiation-induced or tobacco-induced carcinogenesis, respectively, thus providing important evidence about causality of specific carcinogens[49,50].

Whole-genome or whole-exome sequencing of tumours has massively expanded the amount of publicly available information on cancer mutations. The latest analyses of whole-genome or whole-exome sequencing data, published this year, involved ~24,000 patients with cancer (encompassing 91 cancer types and harbouring >84 million somatic mutations)[51]. These analyses resulted in a catalogue of mutation signatures across virtually all cancers, including signatures based on single-base or

double-base substitutions (49 and 11 signatures, respectively), four signatures of clustered-base substitutions and 17 signatures based on small insertions or deletions. Some of these signatures are known to be caused by specific environmental exposures other than tobacco or UV radiation, including aflatoxin, aristolochic acid or specific chemotherapeutic agents, whereas others have been linked to endogenous processes, such as different defects in DNA repair or APOBEC-mediated cytosine deamination. Some mutation signatures can also have therapeutic consequences; indeed, targeted agents for the treatment of cancers that have mutation signatures associated with defective homologous recombination repair linked to *BRCA1/2* aberrations are being adopted in routine clinical practice[52]. Overall, however, many of the proposed signatures are not currently associated with known carcinogens or endogenous processes. A comprehensive analysis of mutation signatures across cancer types has the potential to greatly expand our knowledge of cancer causality. One example is an analysis of samples from ~1,700 children with cancer, with results published in 2018, in which a UV radiation exposure signature was detected in eight of 689 patients with B cell acute lymphoblastic leukaemia[53]. The validity of this finding is supported by epidemiological evidence from a study using a geostatistical model to evaluate exposure to UV radiation and from a case–control study[54,55]. In another striking finding, a mutation signature known to be caused by exposure to aristolochic acid has been reported to be present in 12 out of 14 patients with renal cancer from the Balkans[56] as well as in patients with liver cancer throughout Asia[57]; identifying the source of this exposure is clearly a public health priority.

Several large international programmes have been initiated with the aim of performing whole-genome sequencing in thousands of individuals with cancer for whom information on exposure history is available, as well as experimental work to further characterize exposures that are linked to mutation signatures. These efforts will likely provide numerous clues to the causes of cancer, similar to those described, in the near future. Relevant initiatives include the Mutographs (CRUK) and Sherlock (NCI) initiatives. These large mutation sequencing efforts are at early stages, and the extent to which the identification of mutation signatures can help to reveal unknown causes of cancer remains unknown. However, characterization of tumour genomes across populations at a high or low risk of developing specific cancers has enormous potential to help identify the underlying characteristics that drive such differences in cancer risk. Such studies might also enable causes of cancer to be ascertained at the individual level with a high degree of accuracy, and even provide insights into the period in tumour progression during which specific exposures were involved[58].

Germline markers of risk in the clinic

Multigene panel testing

The discovery of *BRCA1/2* in the mid-1990s launched the era of clinical cancer genetics, beyond the purview of the research setting[59,60]. Genetic counselling and testing for high-risk, and subsequently moderate-risk, cancer susceptibility genes to guide risk-reduction approaches and clinical management is now commonplace in many HICs. However, access to cancer genetics services is uneven and reflects profound inequities in cancer prevention and control and, more broadly, health disparities[6,61–65]. For example, McCarthy et al.[61] reported a population-based study in two US states, which showed that, among 3,016 women diagnosed with breast cancer in 2007–2009, Black women were 40% less likely to undergo *BRCA1/2* testing than white women. Moreover, the disparity persisted, albeit attenuated, after adjusting for clinical and sociodemographic factors as well as attitudes towards genetic testing (OR 0.66). A 2020 report on disparities in risk assessment and referrals for Black and white patients with breast cancer showed that referral rates for patients who met criteria from the US National Comprehensive Cancer Network (NCCN) criteria varied by ethnicity and employment status, with only 75.7% of Black non-Hispanic patients versus 92.7% white non-Hispanic patients referred. Before the 2010s, in settings where clinical cancer genetics services were available, risk assessment frequently included multiple rounds of single-gene testing with long turnaround times, and were therefore costly[66,67]. In the USA, and increasingly in other HICs, multigene panel testing (MGPT) has now become the standard procedure in clinical cancer genetic assessments, in part owing to its cost effectiveness, speed and efficiency[68–74]. Since the incorporation of MGPT into clinical practice in 2012, technological advances, including improvements in the bioinformatics pipelines for variant calling and interpretation, have been rapid and costs have decreased substantially[67,75]. In addition, syndrome-specific testing (for example, *STK11* for Peutz–Jeghers syndrome) was more common in the past and, as such, the selection of genes to be tested for a given patient would tend to include only one or two highly penetrant genes. As a consequence, a negative genetic test might have missed a moderate or low penetrance variant, thereby underestimating the proportion of cancers attributable to genetic predisposition[76–78]. Substantial phenotypic overlap exists among carriers of different mutated genes; MGPT has enabled researchers to address this together with genetic heterogeneity of hereditary cancer syndromes. For example, breast cancer is common among women with a germline *BRCA1/2* mutation, as well as in those with mutations in *PALB2*, *TP53*, *ATM* or *CHEK2*, among others. Furthermore, the fact that *BRCA1/2* mutations account for only ~50% of the identifiable germline cancer predisposition variants has become clear[73,79]. Among women with breast cancer, germline pathogenic variants in genes other than *BRCA1/2* are most commonly observed in *CHEK2*, *ATM* and *PALB2*, corresponding to approximately 11.7%, 9.7% and 9.3% of all variants, respectively[73].

Implementation challenges in the USA

Although MGPT increases carrier detection rates by ~4–6%[67], its rapid implementation has raised concerns regarding its readiness for widespread use. The increasing number of variants of uncertain significance being identified[80,81], discrepancies with variant interpretation and reclassification across laboratories[80–83],

the questionable clinical utility of many genes with unproven causality included on large panels[80,81], and problems with health insurance coverage and reimbursement remain areas of concern for clinicians ordering MGPT[80–84]. Questions also remain regarding the optimal strategies for managing incidental findings[80,85], informed consent[80], and the availability of appropriate pre-test and post-test counselling[80,86]. Despite these concerns and gaps in knowledge, with the increasing use of MGPT clinicians must be prepared to interpret and advise patients regarding results that are sometimes incidental and might be inconsistent with (and therefore cannot explain) a phenotype (that is, a personal and/or family history of cancer). Such scenarios can have important implications for individuals and their families. Initial penetrance estimates and related clinical management recommendations were made using data from affected patients with clear family histories of cancer[87]. In patients recruited from specialized cancer risk assessment ('high-risk') clinics with a relevant personal and/or family history of cancer, cancer risks are close to those original estimates[88]. For example, the results of some large retrospective studies have shown that the risk of breast cancer is similar for *BRCA1/2* carriers with and without a family history of cancer[89,90]; however, a large prospective study of *BRCA1/2* mutation carriers revealed that cancer risk was dependent on the individual's family history of cancer and the mutation location[91]. The true penetrance in carriers of pathogenic variants in genes other than *BRCA1/2* remains largely unknown, particularly for variants not clearly associated with the mutation-related phenotype and/or those identified through population-based approaches. This uncertainty makes counselling to guide an informed risk-management discussion challenging, especially when prophylactic surgery is an option. A salient example is *CDH1*, a gene associated with hereditary diffuse gastric cancer. Carriers of any *CDH1* variant proven to be pathogenic are usually recommended to undergo prophylactic gastrectomy, a procedure associated with considerable morbidity[92]. The lifetime cancer risks associated with this variant had been previously estimated as ~70% in men and ~83% in women[93], but a study published in 2019 reported these risks to be ~42% in men and ~33% in women, raising the question of whether all carriers should be offered risk-reducing surgery[78].

The debate on population-based testing

The utility of population-based genetic testing for cancer susceptibility has been hotly debated for several years[94], mostly in HICs, and might have reached a tipping point. In support of this view, growing evidence suggests that testing remains vastly underutilized worldwide, especially in the USA[95–99], and patterns of use reveal differences in uptake among ethnic groups, potentially widening existing cancer disparities[61,100]. Of note, population testing for genetic predisposition has long existed for some childhood-onset conditions, for which early detection and proper intervention can be lifesaving, in newborn babies[94,101]. The NCCN already recommends genetic testing for all individuals with ovarian, pancreatic or advanced-stage prostate cancer, regardless of age at diagnosis, ethnicity or family history[102]. For women who harbour cancer-predisposing mutations in either *BRCA1* or *BRCA2*, the lifetime risk of breast cancer is ~70%, and the risk of ovarian cancer is 44% and 17% for *BRCA1* and *BRCA2* mutation carriers, respectively[91]. The effect of early detection and prevention in terms of mortality from breast, ovarian or fallopian tube cancer is evident[103–105]. However, Childers and colleagues[98] estimated that among ~1.5 million persons eligible for genetic testing in the USA, only 14.7% and 23.3% had such testing in 2005–2010 and 2015, respectively, leaving ~1 million individuals untested. In addition, Beitsch et al.[96] reported in 2019 that ~50% of patients with breast cancer and a clinically actionable pathogenic or likely pathogenic (P/LP) germline variant did not meet the NCCN criteria for referral to genetic testing. Their study and another one involving women with breast or gynaecological cancer[96,106] found a similar presence of P/LP variants among individuals who met NCCN testing criteria (9.4% and 10.5% in each study, respectively) and in those who did not meet such criteria (7.9% and 9.0%, respectively). A re-analysis of the data from Beitsch et al., considering only variants in genes with a proven association with an increased breast cancer risk, reported a prevalence of P/LP variants in patients meeting and not meeting NCCN genetic testing criteria of 6.5% and 3.8%, respectively[107], suggesting that current guidelines 'reasonably' enable the identification of high-risk patients. Yet, in response to the publication by Beitsch and colleagues, the American Society of Breast Surgeons published a statement in 2019 recommending that MGPT is offered to all individuals with a personal history of breast cancer, and stated that those who had been previously tested might benefit from updated testing[108].

A simple question lies at the centre of this debate: what are the purposes of cancer genetic testing? One is to equip individuals who already have cancer with potentially actionable information — that is, to treat an existing cancer and/or prevent a future cancer. A second aim is to inform unaffected relatives who can then choose to undergo counselling and testing, a process referred to as 'cascade testing', in order to prevent the occurrence of or mortality from a preventable cancer. Cascade testing is predicated on the assumption that unaffected individuals, on learning about their risks, will (mostly) take advantage of tailored risk-stratified prevention strategies, such as enhanced screening protocols, surgical prophylaxis and chemoprevention[109]. However, the traditional approach to identifying families with P/LP variants for the purpose of finding and notifying unaffected individuals at high risk has not been as successful as anticipated[110,111], owing to a variety of factors including costs and insurance coverage (for example, for testing of unaffected relatives)[110], perceptions about the duty to inform relatives, concerns about guilt in passing on risk to offspring, related communication barriers[111–113] and restrictions on direct communication between providers and at-risk relatives[110,112]. Cascade testing rates are estimated to be as low as 20–30%[110,114] for eligible first-degree relatives. Also, some experts have suggested that the identification of high-risk individuals only after a cancer diagnosis constitutes

"a failure of cancer prevention"[95]. At the same time, as patient-initiated testing and direct-to-consumer testing is gaining popularity, particularly in North America, concerns are being raised regarding informed consent, the potential for misinterpretation of results and subsequent inappropriate clinical management[115–117]. Such concerns led to the publication of position statements from the American Society of Human Genetics[118] and the National Society of Genetic Counselors[119], advising that results from direct-to-consumer testing are reviewed by a genetics professional, and that test results are validated in a clinical, Clinical Laboratory Improvements Amendments-certified laboratory. The USA Preventive Services Task Force (USPSTF) 2019 recommendation statement relating to *BRCA1/2*-mutated cancers[120] highlights the (heretofore) missed opportunity to extend counselling and testing in the USA, at least with regard to *BRCA1/2* mutations. They present a grade B recommendation (associated with moderate to substantial benefit) that primary care practitioners use a familial risk assessment tool[3,121–128] to estimate the likelihood of carrying a *BRCA1/2* P/LP variant for all women with a personal or family history of breast, ovarian, tubal or primary peritoneal cancer or for those with an ancestry associated with P/LP variants in *BRCA1/2* (such as an Ashkenazi Jewish ancestry)[129]. The USPSTF also present a strong (grade D) recommendation discouraging the use of routine risk assessment, genetic counselling and testing for women without a personal and/or family history or ethnicity that suggests a *BRCA1/2* P/LP variant[120].

Polygenic risk scores

Several commercial genetic testing laboratories in the USA have added polygenic risk scores (PRSs) to their genetic test reports, mainly to better predict lifetime risks and guide risk management for breast cancer, but also for prostate cancer, with additional PRS data likely to be included for other cancer types in the future[3,122]. In the case of breast cancer, a PRS might provide lifetime risk estimates in certain patients similar to those associated with a single moderately or highly penetrant germline mutation in a susceptibility gene (in the absence of such a variant) or they might substantially modify risks predicted by a germline variant (in the presence of such a variant)[2,69,130,131]. Risk models that incorporate family history as well as age, anthropomorphic, reproductive history and other breast cancer risk factors have been widely available for more than two decades. The results of a validation study of the 10-year performance of four such models[130] revealed strengths and limitations of each, and the authors suggested that hybrid models incorporating predictive scores of the best performing family history model plus PRSs might further improve accuracy[88].

At present, PRSs are subject to the same biases that affect virtually all clinical genomic information, including that of the limited ethnic diversity of the data used in their development[132–134]. Indeed, while the research outlined in this Review is relevant to global efforts in cancer prevention, an important caveat is the limited diversity in the populations that have been included in most cancer genomics studies[132]. Most large analyses of either germline or somatic determinants of cancer have predominantly included populations from western Europe or North America and, to a lesser extent, East Asia. Other populations, including those from southern Asia, South America and Africa, are severely under-represented in these studies. Notwithstanding the efforts to improve diversity in genomics research have been undertaken in the past few years (for example, the H3Africa initiative)[133–135], the disproportionate inclusion of populations with a European origin poses important limitations to the generalizability of findings from one population to another and therefore hampers cross-population use of PRSs.

Genomics and prevention: policy considerations

Calls for population testing assume that the uptake and use of cancer prevention services would be high enough to lead to population-level improvements of cancer outcomes, including incidence and cancer-specific mortality, at least for the primary targets of breast, ovarian, tubal, peritoneal and colorectal cancers. Of note, programmes of population screening for genetic predisposition should adopt the WHO criteria[136,137]. Three key aspects should be considered: 1) whether the disease risk for mutation carriers is known; 2) the magnitude of the health burden posed; and 3) whether effective interventions are available. Considering how cancer risk prediction and risk-reduction interventions might be perceived in different populations and countries is also worthwhile. The roles of implementation research are to understand factors that can influence the acceptability of preventive health care interventions, and to adapt and tailor strategies with community-engaged participatory research in order to successfully implement evidence-informed guidelines. Herein, we highlight two founder mutations, *BRCA1/2* (REFS[105,138–157]) and *TP53* (REFS[105,158–160]), with high prevalence in Israel, the USA and the UK, and in Brazil, respectively (TABLE 2).

Lessons from two founder populations

BRCA1/2 in Ashkenazi Jewish individuals. Approximately one in 40 Ashkenazi Jewish individuals carry one of three *BRCA1/2* founder mutations, which comprise >70% of pathogenic mutations in these genes in this population[142,147]. Founder *BRCA1/2* mutations are present in 30–41% of Ashkenazi Jewish women with epithelial ovarian cancer[143–146] and ~10% of those with invasive breast cancer[146,147]. In Israel, several studies were undertaken before implementing screening for founder mutations at the population level[72,156]. Important information gained through these studies includes evidence that penetrance is equivalent in carriers identified in high-risk families and in those identified through population screening programmes, demonstration of the willingness of the community to participate in such programmes, availability of adequate health care services to counsel and follow carriers as well as their relatives, and favourable cost effectiveness[72,157]. The general consensus is that risk-reducing bilateral mastectomy[105,158] and risk-reducing bilateral salpingo-oophorectomy reduce the incidence of breast and ovarian cancer and, to some degree, breast and ovarian cancer-specific mortality,

Table 2 | **Two examples of founder mutation testing in different scenarios**

Aspect	*BRCA1/2* mutations in Ashkenazi Jewish individuals	*TP53* mutation in several Brazilian states
Population	Ashkenazi Jewish individuals in Israel, UK and USA	General population of southern and southeastern Brazil
Founder variants	*BRCA1* c.68_69delAG[1] (p.Glu23fs) *BRCA1* c.5266dupC (p.Gln1756Profs) *BRCA2* c.5946delT (p.Ser1982fs)[140]	*TP53* c.1010G>A (p.Arg337His)[160]
Carriers among total population (frequency)	2.5%[139–141]	0.3%[160,161]
Prevalence in cancer-affected individuals	Epithelial ovarian carcinoma: 31–40%[144–146] Invasive breast cancer: 10%[146,147]	Li–Fraumeni and Li–Fraumeni-like syndromes: 8.6% of women with breast cancer unselected for family history and age at diagnosis, 12% of women diagnosed at ≤45 years of age[161]
Equivalent penetrance in high-risk individuals versus the general population	Yes[147,149–151]	Unknown
Community interest in population screening	Yes[151]	Not assessed
Availability of counselling and follow-up services	Yes[152]	No
Effective cascade testing protocol implemented	Yes[153]	No
Favourable cost effectiveness	Yes[154]	Not assessed
Associated disease risk in mutation carriers is known	Yes[146,149,150]	Partially[162,185]
Disease poses substantial health burden	Yes[145,148,149]	Yes[160]
Latent or early symptomatic stage is recognizable (for example, a suspicious breast mass that is palpable or visible on mammogram)	Yes[a]	Yes[b]
Natural history of disease is understood	Yes[a]	Yes[b]
Appropriate test or examination exists (for example, screening mammograms and/or breast MRI for 'enhanced screening' of women with *BRCA1/2* or *TP53* mutations, beginning at an early age)	Yes[a]	Yes[b]
Successful interventions are available (for example, risk-reducing mastectomy or salpingo-oophorectomy for prevention of breast or ovarian cancer, respectively)	Yes[105,155,156]	Yes[160]

[a]For some *BRCA1/2*-related cancers, such as breast cancer. [b]For some *TP53*-related cancers, such as breast cancer.

with a stronger effect (of either surgery) in carriers of mutations in *BRCA1* than in *BRCA2*; however, the evidence for overall survival is arguably weak, and appears limited primarily to risk-reducing bilateral salpingo-oophorectomy for *BRCA1* mutation carriers[159]. With these caveats, testing of the Ashkenazi Jewish population for the three *BRCA1/2* founder mutations can be considered to satisfy the WHO criteria for population screening for genetic predisposition.

***TP53* in southern and southeastern Brazil.** In southern and southeastern Brazil, an upper middle-income country, the percentage of individuals in the general population who carry a specific founder pathogenic variant *TP53* c.1010G>A (p.Arg337His) is estimated as 0.3%[160]. This variant was initially detected among children with adrenocortical carcinoma and has subsequently been associated with Li–Fraumeni and Li–Fraumeni-like syndromes. Moreover, among women with breast cancer unselected for family history and age at diagnosis, the founder mutation prevalence reaches 8.6%, and increases to 12% in women diagnosed at or under 45 years of age[161]. *TP53* is therefore an important contributor to the cancer burden in this region, yet the access to genetic testing in the public health care system, on which 70% of the Brazilian population depends, is limited. Currently, only one Brazilian state (Paraná) provides coverage for mutation testing at birth within the state newborn baby-screening programme[162]. Broader genetic testing is not covered by public health insurance elsewhere in Brazil, although genetic counselling services are available in a few centres, mainly in capital cities of the southern and southeastern regions. Furthermore, where available, genetic counselling and cancer risk management

remain challenging as the spectrum of associated cancers and age-related penetrance of the founder variant are not fully understood[162]. Finally, the majority of the population in southern and southeastern Brazil remains uninformed of this important regional cancer risk factor, and cost-effectiveness studies on its incorporation in routine health care are not yet available. Thus, the founder *TP53* pathogenic variant in Brazil should be regarded as a public health concern, but public health policies supported by appropriate resource allocation to identify and promote cancer risk reduction in paediatric and adult carriers of this founder mutation have not yet been developed or implemented.

Cost effectiveness

Cost-effectiveness data are also emerging in support of a population-based testing approach over one based on family history and/or clinical criteria. Manchanda et al.[72] evaluated the cost effectiveness of population-based multigene testing (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*) of unselected women in the general population, and found an incremental cost-effectiveness ratio of £21,599.96 per quality-adjusted life year (QALY) or US$54,769.78 per QALY (9.34 or 7.57 days of life expectancy gained). Sun et al.[74] reported that *BRCA1/2* and *PALB2* testing for all unselected women with breast cancer from the USA and UK was extremely cost effective for the respective health care systems, with an estimated £10,464 per QALY (payer perspective) or £7,216 per QALY (societal perspective) for the UK, and US$65,661 per QALY (payer perspective) or US$61,618 per QALY (societal perspective) for the USA, compared with testing on the basis of family history or other clinical criteria.

Cost effectiveness and related economic analyses, along with comparative effectiveness research, provide crucial information for policymakers to consider. However, such data cannot exist in a vacuum. Of equal importance is our ability to translate technological advances and associated scientific findings into action, considering competing health care priorities and the health care system as a whole. The latter must be adequately resourced, organized and otherwise capable of supporting the management of (anticipated) large numbers of unaffected individuals at high risk[163].

Costs have a key role in health policy making, although cost effectiveness is not the same concept as affordability. In addition, understanding the health care system in which cancer genetics services might be introduced is paramount[164]. Supporting the adoption of clinical genetics services for cancer prevention is difficult in settings where universal access to affordable, high-quality health care services (including diagnostic imaging and pathology, surgical capacity, robust referral mechanisms and trained personnel) are lacking. Zheng and colleagues[165] reported a high frequency (11–12%) of P/LP variants among an unselected population of women with breast cancer in Nigeria, making a case for population-based testing in that country. In an accompanying article[164], we suggested that careful consideration was required in aspects including the acceptability of services, and the availability, uptake and affordability of risk-reduction strategies. In addition, ethical, legal and regulatory oversight considerations are needed to protect the confidentiality of personal genetic and health-related information, and thus prevent genetic discrimination in some individuals.

In Brazil, ~20% of women meeting clinical criteria for risk of hereditary breast and ovarian cancer carry a P/LP variant in *BRCA1/2* (REFS[166,167]), yet cancer genetics services are largely unavailable and genetic testing is not covered by the public health care system (Sistema Único de Saúde (SUS)), which covers 70% of the population[168]. Two studies have examined the cost effectiveness of genetic testing for hereditary breast and ovarian cancer patients with SUS coverage, and propose that inclusion of this technology in this health care system is justified. In 2020, Simoes Correa-Galendi et al.[169] reported that the incremental cost-effectiveness ratio for testing at-risk patients for *BRCA1/2* mutations, calculated from the SUS perspective, is close to the cost-effectiveness threshold proposed by the WHO for lower middle-income countries (LMICs). Before this publication, Ramos et al.[170] showed that genetic testing for *BRCA1/2* in high-risk patients with SUS coverage was cost effective when genetic testing was expanded and prophylactic measures were adopted for family members (cascade testing). The incremental cost-effectiveness ratio was estimated at R$908.58 per cancer avoided.

Elsewhere, the Asian BRCA consortium was formed in 2011 to bring together regional experts to consider how to approach capacity building for the management of hereditary breast and ovarian cancers, and to collaborate in related research efforts[171]. In their first report, Nakamura and colleagues[171] described the status of cancer genetics services in 14 Asian countries, nine of which were LMICs at the time of writing. This report addresses the status of training programmes for genetic counsellors, the availability and accreditation methods for research and clinical laboratories, and the adoption of relevant national or international guidelines. The report concluded that disparities in access to cancer genetics services in Asia result from a combination of issues relating to human resources, funding and sociocultural status. Moreover, they described limitations in access to affordable cancer risk-reduction interventions. This discussion calls into question the ethics of introducing cancer genetics services in any setting without opportunities to mitigate the (high) cancer risk for carriers of P/LP gene variants. Moreover, the authors note the lack of regulatory oversight and protection of individuals from genetic discrimination as core issues to address. These opportunities and challenges for the field of clinical genetics have been highlighted more broadly elsewhere[172].

Bridging the evidence–policy gap

In 2018, the estimated global numbers of new cancer diagnoses and cancer-related deaths were 18.1 million and 9.6 million, respectively[173], 70% of which occurred in LMICs. Around 30–50% of these cancers are potentially preventable[174]. For 2030, the prediction is that 24 million people will be diagnosed with cancer, equating to a 32% increase compared with 2018 (REF.[173]). The majority of

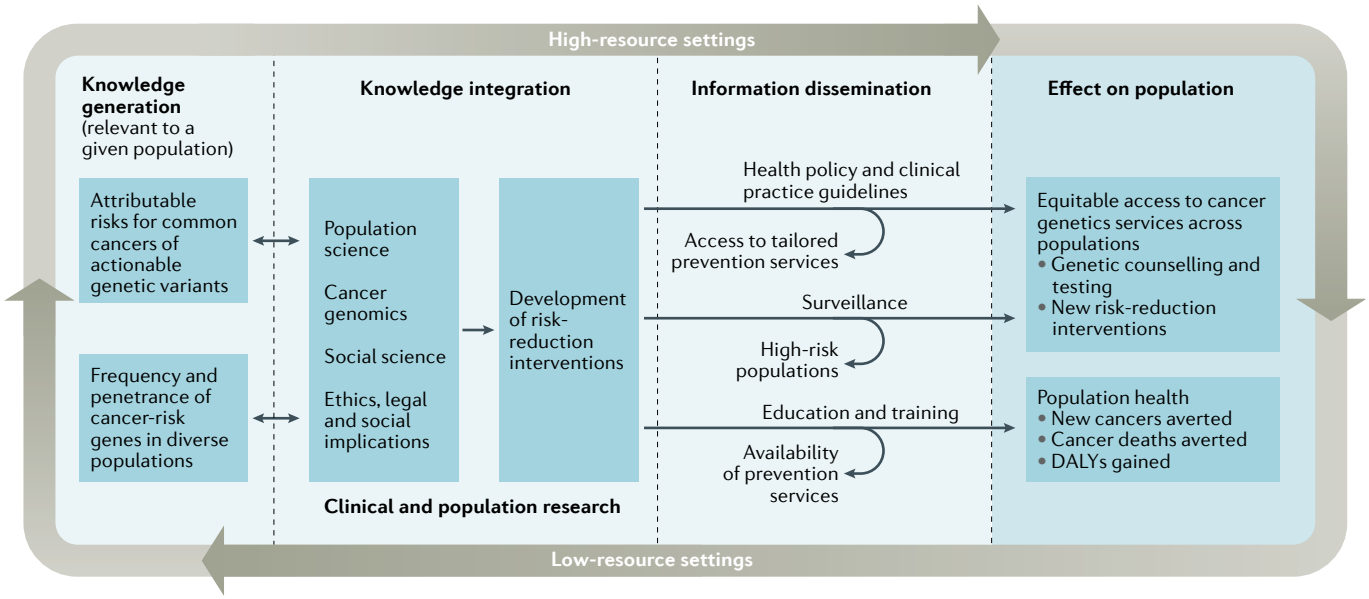

Fig. 2 | **A population health equity framework for the translation of genomics research findings into cancer prevention.** The first three panels depict core elements of cancer genomics translational research, including knowledge generation, knowledge integration and information dissemination relevant to practices and policies in cancer prevention. These panels are not meant to be exhaustive but rather illustrative of each point along the continuum of translational research. For example, genetic discoveries relevant to a given population should include (at least) the attributable risks, the frequency and the penetrance of pathogenic or likely pathogenic variants in cancer susceptibility genes. This knowledge must then be integrated with the broader, societal understanding of the utility of cancer genomics. Furthermore, the processes of knowledge integration and information dissemination should include feedback loops (depicted as 'U-turn' arrows) as health policy and clinical practice guidelines must be continuously updated to reflect not only new scientific discoveries, but also the real-world situation, which is dynamic. Last, we illustrate the potential outcomes of these interventions at the population level, in terms of equitable access to health services and effects on population health. The outermost layer highlights the importance of bidirectional multilateral knowledge exchange between countries of varying resource levels, which can be considered in terms of World Bank income categories, health care system robustness, status of universal health coverage and/or research capacities. DALYS, disability-adjusted life years.

these new patients (and subsequent deaths) will occur in LMICs, which are facing rising rates of many other chronic, non-communicable diseases, including diabetes and cardiovascular disease. In most countries, health care systems have not yet been adequately developed and supported to address this emergent crisis. In 2019, a review of national cancer control plans was undertaken by representatives of the Union for International Cancer Control, the WHO, the NCI and others[175]. Only 27 of 157 countries for which data are available (most of them HICs) mentioned 'genetics' in their national cancer plans (Y. Romero, personal communication). In 2015, ASCO released a policy statement update with the aim of exploring new and emerging technologies in cancer genetics and ensuring their optimal deployment in oncology practice. Recommendations included quality assurance in genetic testing, education of oncology professionals and access to clinical cancer genetic services[80]. These services are growing worldwide, notably in some HICs and upper middle-income countries in Latin America and Asia[171,176–178]; however, severe shortages of qualified genetics health care providers, such as genetic counsellors, occur even in HICs. New models of care that take advantage of telemedicine and other semi-automated strategies for (at least) pre-test genetic counselling, as well as extending genetic services into certain clinical settings, such as breast surgery and gynaecological oncology clinics, can help to address human resources shortages[129], at least in well-resourced settings. Nevertheless, studying the feasibility, acceptability, cost effectiveness and other implementation outcomes will be important to tailor such strategies and optimize utility in different settings and populations.

Conclusions

On average, new scientific discoveries are estimated to take as long as 17 years to be translated into clinical practice[179]. This time frame is sometimes referred to as the evidence to policy or 'know–do' gap[180] in public health, and has been called the 'road less travelled' in cancer genetics[181]. Implementation research will be especially important to ensure that discoveries in cancer genomics can be translated into reductions in mortality from (at least some) preventable cancers. We propose a conceptual framework for a population health equity-informed approach to the translation of genomics research to cancer prevention, drawing from the work of Trinh-Shevrin and colleagues[182] and Burke et al.[183] (FIG. 2). The knowledge generated from translational genetics studies must be integrated with the broader, societal understanding of the utility of cancer genomics, including its ethical, legal and socioeconomic implications. Once integrated, such information can be used to tailor efforts in the development of education and training programmes, the implementation of clinical services, and the policies that govern these.

Last, in this framework we illustrate the potential outcomes of these interventions at the population level, which can be seen in terms of equitable access to health services and effects on population health. An aspect to highlight is the importance of knowledge exchange between countries of varying resource levels.

Advances in cancer genomics research are enabling a more nuanced understanding of causal factors and informing opportunities to reduce the risk of certain cancers in some individuals. These discoveries have the potential to improve cancer prevention at the population level, with caveats that we have discussed in this Review. The WHO cautions that while genomics "can contribute to improving global health equity", this purpose can only be achieved if the genomic health divide is "kept in check and ultimately bridged through equitable economic investment, clinical research, and provision and use of genomic services and technologies globally" (REF.[184]). The WHO also acknowledges that this process can be accelerated through the exchange of information, expertise and technologies between HICs and LMICs. Indeed, an equity lens must be applied throughout the translational research continuum, by ensuring adequate representation in research studies of all major world populations, and ethnic and cultural groups. Diversity and inclusion of all who might benefit from such discoveries, as well as the researchers who contribute to the scientific and policy discourse, must also be assured.

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1. Huang, K. L. et al. Pathogenic germline variants in 10,389 adult cancers. *Cell* **173**, 355–370.e14 (2018).
2. Khera, A. V. et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* **50**, 1219–1224 (2018).
3. Zhang, Y. D. et al. Assessment of polygenic architecture and risk prediction based on common variants across fourteen cancers. *Nat. Commun.* **11**, 3353 (2020).
4. Zsofia, K. et al. Genome-wide association studies of cancer. *J. Clin. Oncol.* **27**, 4255–4267 (2010).
5. McClellan, K. A., Avard, D., Simard, J. & Knoppers, B. M. Personalized medicine and access to health care: potential for inequitable access? *Eur. J. Hum. Genet.* **21**, 143–147 (2013).
6. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Roundtable on Genomics and Precision Health. *Understanding Disparities in Access to Genomic Medicine: Proceedings of a Workshop* (National Academies Press, 2018).
7. Sirugo, G., Williams, S. M. & Tishkoff, S. A. The missing diversity in human genetic studies. *Cell* **177**, 26–31 (2019).
8. Yeh, V. M. et al. Can precision medicine actually help people like me? African American and Hispanic perspectives on the benefits and barriers of precision medicine. *Ethn. Dis.* **30**, 149–158 (2020).
9. Brown, K. F. et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br. J. Cancer* **118**, 1130–1141 (2018).
10. Maniolo, T. A. et al. Finding the missing heritability of complex diseases. *Nature* **461**, 747–753 (2009).
11. Islami, F. et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J. Clin.* **68**, 31–54 (2018).
12. Brennan, P. & Wild, C. P. Genomics of cancer and a new era for cancer prevention. *PLoS Genet.* **11**, e1005522 (2015).
13. Tomasetti, C. & Vogelstein, B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* **347**, 78–81 (2015).
14. Gotay, C., Dummer, T. & Spinelli, J. Cancer risk: prevention is crucial. *Science* **347**, 728 (2015).
15. Taubes, G. Epidemiology faces its limits. *Science* **269**, 164–169 (1995).
16. Higginson, J. Changing concepts in cancer prevention: limitations and implications for future research in environmental carcinogenesis. *Cancer Res.* **48**, 1381–1389 (1988).
17. Hall, J. M. et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* **250**, 1684–1689 (1990).
18. Peltomaki, P. et al. Genetic mapping of a locus predisposing to human colorectal cancer. *Science* **260**, 810–812 (1993).
19. Rahman, N. Realizing the promise of cancer predisposition genes. *Nature* **505**, 302–308 (2014).
20. Sampson, J. N. et al. Analysis of heritability and shared heritability based on genome-wide association studies for thirteen cancer types. *J. Natl Cancer Inst.* **107**, djv279 (2015).
21. Weitzel, J. N. et al. Genetics, genomics, and cancer risk assessment: state of the art and future directions in the era of personalized medicine. *CA Cancer J. Clin.* **61**, 327–359 (2011).
22. Shu, X. et al. Identification of novel breast cancer susceptibility loci in meta-analyses conducted among Asian and European descendants. *Nat. Commun.* **11**, 1217 (2020).
23. Schumacher, F. R. et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat. Genet.* **50**, 928–936 (2018).
24. McKay, J. D. et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat. Genet.* **49**, 1126–1132 (2017).
25. Huyghe, J. R. et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat. Genet.* **51**, 76–87 (2019).
26. Phelan, C. M. et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat. Genet.* **49**, 680–691 (2017).
27. Klein, A. P. et al. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. *Nat. Commun.* **9**, 556 (2018).
28. Scelo, G. et al. Genome-wide association study identifies multiple risk loci for renal cell carcinoma. *Nat. Commun.* **8**, 15724 (2017).
29. Kachuri, L. et al. Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction. Preprint at *bioRxiv* https://doi.org/10.1101/2020.01.28.922088 (2020).
30. Frank, C. et al. Population landscape of familial cancer. *Sci. Rep.* **5**, 12891 (2015).
31. Davey Smith, G. & Ebrahim, S. Mendelian randomization: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int. J. Epidemiol.* **32**, 1–22 (2003).
32. Brennan, P. & Wild, C. Genomics of cancer and a new era for cancer prevention. *PLoS Genet.* **11**, e1005522 (2015).
33. Loos, R. J. F. & Yeo, G. S. H. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat. Rev. Endocrinol.* **10**, 51–61 (2014).
34. Yengo, L. et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. *Hum. Mol. Genet.* **27**, 3641–3649 (2018).
35. World Cancer Research Fund & American Institute for Cancer Research. Body fatness and weight gain and the risk of cancer (WCRF, 2018).
36. Yu, D. et al. Overall and central obesity and risk of lung cancer: a pooled analysis. *J. Natl Cancer Inst.* **110**, 831–842 (2018).
37. Mariosa, D. et al. Commentary: what can Mendelian randomization tell us about causes of cancer? *Int. J. Epidemiol.* **48**, 816–821 (2019).
38. Tsilidis, K. K. et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* **350**, g7607 (2015).
39. Scott, R. A. et al. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. *Diabetes* **63**, 4378–4387 (2014).
40. Johansson, M. et al. The influence of obesity-related factors in the etiology of renal cell carcinoma — a Mendelian randomization study. *PLoS Med.* **16**, e1002724 (2019).
41. Carreras-Torres, R. et al. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a Mendelian randomization study. *J. Natl Cancer Inst.* **109**, djx012 (2017).
42. Stearns, F. W. One hundred years of pleiotropy: a retrospective. *Genetics* **186**, 767–773 (2010).
43. Munafò, M. & Davey Smith, G. Repeating experiments is not enough. *Nature* **553**, 400–401 (2018).
44. Brasky, T. M., White, E. & Chen, C. L. Long-term, supplemental, one-carbon metabolism-related vitamin B use in relation to lung cancer risk in the vitamins and lifestyle (VITAL) cohort. *J. Clin. Oncol.* **35**, 3440–3448 (2017).
45. Fanidi, A. et al. Is high vitamin B12 status a cause of lung cancer? *Int. J. Cancer* **145**, 1499–1503 (2019).
46. The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Network. Pan-cancer analysis of whole genomes. *Nature* **578**, 82–93 (2020).
47. Brash, D. E. et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc. Natl Acad. Sci. USA* **88**, 10124–10128 (1991).
48. Hollstein, M., Sidransky, D., Vogelstein, B. & Harris, C. C. p53 mutations in human cancers. *Science* **253**, 49–53 (1991).
49. McGregor, W. G. et al. Cell cycle-dependent strand bias for UV-induced mutations in the transcribed strand of excision repair-proficient human fibroblasts but not in repair-deficient cells. *Mol. Cell Biol.* **11**, 1927–1934 (1991).
50. Denissenko, M. F., Pao, A., Tang, M. & Pfeifer, G. P. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. *Science* **274**, 430–432 (1996).
51. Alexandrov, L. B. et al. The repertoire of mutational signatures in human cancer. *Nature* **578**, 94–101 (2020).
52. Ma, J. et al. The therapeutic significance of mutational signatures from DNA repair deficiency in cancer. *Nat. Commun.* **9**, 3292 (2018).
53. Ma, X. et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* **555**, 371–376 (2018).
54. Coste, A. et al. Residential exposure to solar ultraviolet radiation and incidence of childhood hematological malignancies in France. *Cancer Causes Control* **26**, 1339–1349 (2015).
55. Coste, A. et al. Residential exposure to ultraviolet light and risk of precursor B-cell acute lymphoblastic leukemia: assessing the role of individual risk factors, the ESCALE and ESTELLE studies. *Cancer Causes Control* **10**, 1075–1083 (2017).
56. Scelo, G. et al. Variation in genomic landscape of clear cell renal cell carcinoma across Europe. *Nat. Commun.* **5**, 5135 (2014).
57. Ng, A. W. T. et al. Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. *Sci. Transl. Med.* **9**, eaan6446 (2017).
58. Gerstung, M. et al. The evolutionary history of 2,658 cancers. *Nature* **578**, 122–128 (2020).
59. Miki, Y. et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* **266**, 66–71 (1994).
60. Wooster, R. et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* **265**, 2088–2090 (1994).

61. McCarthy, A. M. et al. Care segregation, physician recommendation, and racial disparities in BRCA1/2 testing among women with breast cancer. *J. Clin. Oncol.* **34**, 2610–2618 (2016).
62. Cragun, D. et al. Racial disparities in BRCA testing and cancer risk management across a population-based sample of young breast cancer survivors. *Cancer* **123**, 2497–2505 (2017).
63. Reid, S. et al. Disparities in BRCA counseling across providers in a diverse population of young breast cancer survivors. *Genet. Med.* **22**, 1088–1093 (2020).
64. Peterson, J. M. et al. Racial disparities in breast cancer hereditary risk assessment referrals. *J. Genet. Couns.* **29**, 587–593 (2020).
65. Cruz-Correa, M. et al. Clinical cancer genetics disparities among Latinos. *J. Genet. Couns.* **26**, 379–386 (2017).
66. Walsh, T. et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc. Natl Acad. Sci. USA* **107**, 12629–12633 (2010).
67. Graffeo, R. et al. Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. *Breast Cancer Res. Treat.* **160**, 393–410 (2016).
68. Gallego, C. J. et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis. *J. Clin. Oncol.* **33**, 2084–2091 (2015).
69. Li, H. et al. Breast cancer risk prediction using a polygenic risk score in the familial setting: a prospective study from the breast cancer family registry and kConFab. *Genet. Med.* **19**, 30–35 (2017).
70. Kurian, A. W. et al. Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer. *JAMA Oncol.* **4**, 1066–1072 (2018).
71. Asphaug, L. & Melberg, H. O. The cost-effectiveness of multigene panel testing for hereditary breast and ovarian cancer in Norway. *MDM Policy Pract.* **4**, 2381468318821103 (2019).
72. Manchanda, R. et al. Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. *J. Natl Cancer Inst.* **110**, 714–725 (2018).
73. Buys, S. S. et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer* **12310**, 1721–1730 (2017).
74. Sun, L. et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. *JAMA Oncol.* **5**, 1718–1730 (2019).
75. Kamps, R. et al. Next-generation sequencing in oncology: genetic diagnosis, risk prediction and cancer classification. *Int. J. Mol. Sci.* **18**, E308 (2017).
76. Kapoor, N. S. et al. Multigene panel testing detects equal rates of pathogenic BRCA1/2 mutations and has a higher diagnostic yield compared to limited BRCA1/2 analysis alone in patients at risk for hereditary breast cancer. *Ann. Surg. Oncol.* **22**, 3282–3288 (2015).
77. Crawford, B. et al. Multi-gene panel testing for hereditary cancer predisposition in unsolved high-risk breast and ovarian cancer patients. *Breast Cancer Res. Treat.* **163**, 383–390 (2017).
78. Roberts, M. E. et al. CDH1 penetrance estimates in clinically ascertained families vs families ascertained for multiple gastric cancers. *JAMA Oncol.* **5**, 1325–1331 (2019).
79. Hauke, J. et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German consortium for hereditary breast and ovarian cancer. *Cancer Med.* **7**, 1349–1358 (2018).
80. Robson, M. E. et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J. Clin. Oncol.* **33**, 3660–3667 (2015).
81. Eccles, D. M. et al. BRCA1 and BRCA2 genetic testing — pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann. Oncol.* **26**, 2057–2065 (2015).
82. Hall, M. J. & Forman, A. D. Gene panel testing for inherited cancer risk. *J. Natl Compr. Cancer Netw.* **12**, 1339–1346 (2014).
83. Mersch, J. et al. Prevalence of variant reclassification following hereditary cancer genetic testing. *JAMA* **320**, 1266–1274 (2018).
84. Clain, E. et al. Availability and payer coverage of BRCA1/2 tests and gene panels. *Nat. Biotechnol.* **33**, 900–902 (2015).
85. Cheng, D. T. et al. Comprehensive detection of germline variants by MSK-IMPACT, a clinical diagnostic platform for solid tumor molecular oncology and concurrent cancer predisposition testing. *BMC Med. Genomics* **10**, 33 (2017).
86. Henn, J. et al. Diagnostic yield and clinical utility of a comprehensive gene panel for hereditary tumor syndromes. *Hered. Cancer Clin. Pract.* **17**, 5 (2019).
87. Chen, S. et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. *J. Clin. Oncol.* **24**, 863–871 (2006).
88. Evans, D. G. et al. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a clinical cancer genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* **8**, 155 (2008).
89. Gabai-Kapara, E. et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc. Natl Acad. Sci. USA* **111** (39), 14205–14210 (2014).
90. Metcalfe, K. A. et al. The risk of breast cancer in BRCA1 and BRCA2 mutation carriers without a first-degree relative with breast cancer. *Clin. Genet.* **93**, 1063–1068 (2018).
91. Kuchenbaecker, K. B. et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* **317**, 2402–2416 (2017).
92. van der Post, R. S. et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J. Med. Genet.* **52**, 361–374 (2015).
93. Pharoah, P. D., Guilford, P. & Caldas, C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* **121**, 1348–1353 (2001).
94. Foulkes, W., Knoppers, B. & Turnbull, C. Population genetic testing for cancer susceptibility: founder mutations to genomes. *Nat. Rev. Clin. Oncol.* **13**, 41–54 (2016).
95. King, M., Levy-Lahad, E. & Lahad, A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker award. *JAMA* **312**, 1091–1092 (2014).
96. Beitsch, P. D. et al. Underdiagnosis of hereditary breast cancer: are genetic testing guidelines a tool or an obstacle? *J. Clin. Oncol.* **37**, 453–460 (2019).
97. LaDuca, H. et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet. Med.* **13**, 1–9 (2019).
98. Childers, C. P., Childers, K. K., Maggard-Gibbons, M. & Macinko, J. National estimates of genetic testing in women with a history of breast or ovarian cancer. *J. Clin. Oncol.* **35**, 3800 (2017).
99. Nielsen, S. M. et al. Genetic testing and clinical management practices for variants in non-BRCA1/2 breast (and breast/ovarian) cancer susceptibility genes: an international survey by the evidence-based network for the interpretation of germline mutant alleles (ENIGMA) clinical working group. *JCO Precis. Oncol.* https://doi.org/10.1200/PO.18.00091 (2018).
100. Kurian, A. W. et al. Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. *J. Clin. Oncol.* **37**, 1305–1315 (2019).
101. Khoury, M. J., McCabe, L. L. & McCabe, E. R. Population screening in the age of genomic medicine. *N. Engl. J. Med.* **348**, 50–58 (2003).
102. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. *NCCN* https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf (2019).
103. Heemskerk-Gerritsen, B. A. M. et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res. Treat.* **177**, 723–733 (2019).
104. Finch, A. P. et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *J. Clin. Oncol.* **32**, 1547–1553 (2014).
105. Domchek, S. M. et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* **304**, 967–975 (2010).
106. Yang, S. et al. Underdiagnosis of hereditary breast and ovarian cancer in Medicare patients: genetic testing criteria miss the mark. *Ann. Surg. Oncol.* **25**, 2925–2931 (2018).
107. Taylor, A. & Tischkowitz, M. Caveat emptor: the perils of panel testing in hereditary breast cancer. *J. Clin. Oncol.* **37**, 2176–2177 (2019).
108. Manahan, E. R. et al. Consensus guidelines on genetic testing for hereditary breast cancer from the American Society of Breast Surgeons. *Ann. Surg. Oncol.* **26**, 3025–3031 (2019).
109. Hughes, S. K. A pathway for identifying women at increased risk for breast cancer and providing personalized management and risk reduction. *Oncol. Issues* **32**, 38–47 (2017).
110. Caswell-Jin., J. L. et al. Cascade genetic testing of relatives for hereditary cancer risk: results of an online initiative. *J. Natl Cancer Inst.* **111**, 95–98 (2019).
111. MacDonald, D. J. et al. Selection of family members for communication of cancer risk and barriers to this communication before and after genetic cancer risk assessment. *Genet. Med.* **9**, 275–282; erratum **9**, 483 (2007).
112. Forrest, K. et al. To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clin. Genet.* **64**, 317–326 (2003).
113. Ricker, C. N. et al. Patient communication of cancer genetic test results in a diverse population. *Transl. Behav. Med.* **8**, 85–94 (2018).
114. Landsbergen, K., Verhaak, C., Floor Kraaimaat, F. & Hoogerbrugge, N. Genetic uptake in BRCA-mutation families is related to emotional and behavioral communication characteristics of index patients. *Familial Cancer* **4**, 115–119 (2005).
115. Joseph, L. et al. The spectrum of clinical utilities in molecular pathology testing procedures for inherited conditions and cancer: a report of the association for molecular pathology. *J. Mol. Diagn.* **18**, 605–619 (2016).
116. Tandy-Connor, S. et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet. Med.* **20**, 1515–1521 (2018).
117. Farmer, M. B. et al. Adverse events in genetic testing: the fourth case series. *Cancer J.* **25**, 231–236 (2019).
118. Hudson, K., Javittm, G., Burke, W. & Byers, P. ASHG statement on direct-to-consumer genetic testing in the United States. *Am. J. Hum. Genetics.* **81**, 635–637 (2007).
119. Wade, C. H. & Wilfond, B. S. Ethical and clinical practice considerations for genetic counselors related to direct-to-consumer marketing of genetic tests. *Am. J. Med. Genet. C Semin. Med. Genet.* **142C**, 284–292 (2006).
120. US Preventive Services Task Force. et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US preventive services task force recommendation statement. *JAMA* **322**, 652–665 (2019); erratum **322**, 1830 (2019).
121. Biswas, S. et al. A two-stage approach to genetic risk assessment in primary care. *Breast Cancer Res. Treat.* **155**, 375–383 (2016).
122. Jia, G. et al. Evaluating the utility of polygenic risk scores in identifying high-risk individuals for eight common cancers. *JNCI Cancer Spectr.* **4**, pkaa021 (2020).
123. Fischer, C. et al. Evaluating the performance of the breast cancer genetic risk models BOADICEA, IBIS, BRCAPRO and Claus for predicting BRCA1/2 mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium. *J. Med. Genet.* **50**, 360–367 (2013).
124. Ashton-Prolla, P. et al. Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. *BMC Cancer* **9**, 283 (2009).
125. Bellcross, C. A. et al. Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. *Genet. Med.* **11**, 783–789 (2009).
126. Hoskins, K. F., Zwaagstra, A. & Ranz, M. Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. *Cancer* **107**, 1769–1776 (2006).
127. Oros, K. K. et al. Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. *Clin. Genet.* **70**, 320–329 (2006).
128. Gilpin, C. A., Carson, N. & Hunter, A. G. A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. *Clin. Genet.* **58**, 299–308 (2000).
129. Domchek, S. & Robson, M. Broadening criteria for BRCA1/2 evaluation: placing the recommendation in context. *JAMA* **322**, 619–621 (2019).
130. Terry, M. B. et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol.* **20**, 504–517 (2019).
131. Mavaddat, N. et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am. J. Hum. Genet.* **104**, 21–34 (2019).

132. Wojcik, G. L. et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature* **19**, 1 (2019).
133. Gurdasani, D., Barroso, I., Zeggini, E. & Sandhu, M. S. Genomics of disease risk in globally diverse populations. *Nat. Rev. Genet.* **20**, 520–535 (2019).
134. Martin, A. R. et al. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* **51**, 584–591 (2019).
135. Human Heredity & Health in Africa. *H3Africa* https://h3africa.org/index.php/consortium (2020).
136. Andermann, A., Blancquaert, I., Beauchamp, S. & Déry, V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull. World Health Organ.* **86**, 317–319 (2008).
137. Wilson, J. M. & Jungner, Y. G. Principles and practice of mass screening for disease (WHO, 1968).
138. Levy-Lahad, E. et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. *Am. J. Hum. Genet.* **60**, 1059–1067 (1997).
139. Oddoux, C. et al. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat. Genet.* **14**, 188 (1996).
140. Roa, B. B., Boyd, A. A., Volcik, K. & Richards, C. S. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat. Genet.* **14**, 185 (1996).
141. Struewing, J. P. et al. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat. Genet.* **11**, 198 (1995).
142. Hartge, P. et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am. J. Hum. Genet.* **64**, 963–970 (1999).
143. Frank, T. S. et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J. Clin. Oncol.* **20**, 1480–1490 (2002).
144. Hirsh-Yechezkel, G. et al. Population attributes affecting the prevalence of BRCA mutation carriers in epithelial ovarian cancer cases in Israel. *Gynecol. Oncol.* **89**, 494–498 (2003).
145. Lu, K. H. et al. A population-based study of BRCA1 and BRCA2 mutations in Jewish women with epithelial ovarian cancer. *Obstet. Gynecol.* **93**, 34–37 (1999).
146. King, M. C., Marks, J. H. & Mandell, J. B. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* **302**, 643–646 (2003).
147. Warner, E. et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J. Natl Cancer Inst.* **91**, 1241–1247 (1999).
148. Antoniou, A. et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am. J. Hum. Genet.* **72**, 1117–1130 (2003).
149. Satagopan, J. M. et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin. Cancer Res.* **8**, 3776–3781 (2002).
150. Satagopan, J. M. et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol. Biomarkers Prev.* **10**, 467–473 (2001).
151. Shkedi-Rafid, S. et al. BRCA genetic testing of individuals from families with low prevalence of cancer: experiences of carriers and implications for population screening. *Genet. Med.* **14**, 688–694 (2012).
152. Metcalfe, K. A. et al. Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening. *Breast Cancer Res. Treat.* **133**, 735–740 (2012).
153. Lieberman, S. et al. Familial communication and cascade testing among relatives of BRCA population screening participants. *Genet. Med.* **20**, 1446–1454 (2018).
154. Rubinstein, W. S., Jiang, H., Dellefave, L. & Rademaker, A. W. Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: a call for dialogue. *Genet. Med.* **11**, 629 (2009).
155. Domchek, S. M. et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol.* **7**, 223–229 (2006).
156. Rebbeck, T. R. et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N. Engl. J. Med.* **346**, 1616–1622 (2002).
157. Manchanda, R. et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *Am. J. Obstet. Gynecol.* **217**, 578. e1–578.e12 (2017).
158. De Felice, F. et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. *Ann. Surg. Oncol.* **22**, 2876–2880 (2015).
159. Eleje, G. U. et al. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. *Cochrane Database Syst. Rev.* **8**, CD012464 (2018).
160. Achatz, M. I. & Zambetti, G. P. The inherited p53 mutation in the Brazilian population. *Cold Spring Harb. Perspect. Med.* **6**, a026195 (2016).
161. Giacomazzi, J. et al. Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. *PLoS ONE* **9**, e99893 (2014).
162. Custódio, G. et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. *J. Clin. Oncol.* **31**, 2619–2626 (2013).
163. Robson, M. & Domchek, S. Broad application of multigene panel testing for breast cancer susceptibility — Pandora's box is opening wider. *JAMA Oncol.* **5**, 1687–1688 (2019).
164. Ginsburg, O. & Brennan, P. Genetic testing for breast cancer in the era of multigene panels: can we make an impact on population health? *J. Clin. Oncol.* **36**, 2817–2819 (2018).
165. Zheng, Y. et al. Inherited breast cancer in Nigerian women. *J. Clin. Oncol.* **36**, 2820 (2018).
166. Fernandes, G. C. et al. Prevalence of BRCA1/BRCA2 mutations in a Brazilian population sample at risk for hereditary breast cancer and characterization of its genetic ancestry. *Oncotarget* **7**, 80465–80481 (2016).
167. Alemar, B. et al. Prevalence of Hispanic BRCA1 and BRCA2 mutations among hereditary breast and ovarian cancer patients from Brazil reveals differences among Latin American populations. *Cancer Genet.* **209**, 417–422 (2016).
168. Achatz, M. I. et al. Recommendations for advancing the diagnosis and management of hereditary breast and ovarian cancer in Brazil. *JCO Glob. Oncol.* **6**, 439–452 (2020).
169. Simoes Correa-Galendi, J., Del Pilar Estevez Diz, M., Stock, S. & Müller, D. Economic modelling of screen-and-treat strategies for Brazilian women at risk of hereditary breast and ovarian cancer. *Appl. Health Econ. Health Policy* https://doi.org/10.1007/s40258-020-00599-0 (2020).
170. Ramos, M. C. A. et al. Cost effectiveness of the cancer prevention program for carriers of the BRCA1/2 mutation. *Rev. Saude Publica* **52**, 94 (2018).
171. Nakamura, S. et al. Current status of the management of hereditary breast and ovarian cancer in Asia: first report by the Asian BRCA consortium. *Public Health Genomics* **19**, 53–60 (2016).
172. Manolio, T. A. et al. Opportunities, resources, and techniques for implementing genomics in clinical care. *Lancet* **394**, 511–520 (2019).
173. Bray, F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **68**, 394–424 (2018).
174. Bray, F. & Soerjomataram, I. Population attributable fractions continue to unmask the power of prevention. *Br. J. Cancer* **118**, 1031–1032 (2018).
175. Romero, Y. et al. National cancer control plans: a global analysis. *Lancet Oncol.* **19**, e546–e555 (2018).
176. Della Valle, A. et al. A snapshot of current genetic testing practice in Lynch syndrome: the results of a representative survey of 33 Latin American existing centres/registries. *Eur. J. Cancer* **119**, 112–121 (2019).
177. Ashton-Prolla, P. & Seuanez, H. N. The Brazilian Hereditary Cancer Network: historical aspects and challenges for clinical cancer genetics in the public health care system in Brazil. *Genet. Mol. Biol.* **39**, 163–165 (2016).
178. Kwong, A. et al. Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in Asian countries. *J. Med. Genet.* **53**, 15 (2016).
179. Westfall, J. M., Mole, J. & Fagnan, L. Practice-based research — "Blue Highways" on the NIH roadmap. *JAMA* **297**, 403–406 (2007).
180. Lenfant, C. Shattuck lecture — clinical research to clinical practice — lost in translation? *N. Engl. J. Med.* **349**, 868–874 (2003).
181. Schully, S. D. et al. Translational research in cancer genetics: the road less traveled. *Public Health Genomics* **14**, 1–8 (2011).
182. Trinh-Shevrin, C. et al. Defining an integrative approach for health promotion and disease prevention: a population health equity framework. *J. Health Care Poor Underserved* **26**, 146–163 (2015).
183. Burke, W. et al. The path from genome-based research to population health: development of an international public health genomics network. *Genet. Med.* **8**, 451–458 (2006).
184. World Health Organization. Human genomics in global health. *WHO* https://www.who.int/genomics/en/ (2020).
185. Ferreira, A. M. et al. Clinical spectrum of Li-Fraumeni syndrome/Li-Fraumeni-like syndrome in Brazilian individuals with the TP53 p.R337H mutation. *J. Steroid Biochem. Mol. Biol.* **190**, 250–255 (2019).

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