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Targeting pancreatic cancer screening by identification of pathogenic variants of *BRCA2/ BRCA1* in healthy individuals who have no known family history of pancreatic cancer: The arguments for and against.

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ABSTRACT

The majority of patients with pancreatic ductal adenocarcinoma (PDAC) are no longer suitable for treatment with curable intent at the time of diagnosis resulting in a 5-year survival of less than 10 %. Imaging of asymptomatic individuals could identify early cancers, but only with a risk of falsely identifying a benign lesion as malignant. Screening of an unselected population would result in far more such false positives than true early cancers. Selection before screening is therefore essential, but there are very few populations at high enough risk to make screening more beneficial than counterproductive. These populations include carriers of specific mutations in *BRCA2,* and arguably *BRCA1,* who have a family history of PDAC. These pathogenic mutations all have a predictable effect in making loss of Homologous Recombination Repair (HRR) likely in a carrier's lifetime. In this review the impact of such loss of HRR function on the likelihood of PDAC development will be discussed. Furthermore, it will be discussed whether the identification of a germline pathogenic mutation is sufficient to justify carrier surveillance for the development of the malignancy, or whether the current practice of screening only those carriers with a close relative diagnosed with PDAC is justifiable, as only a proportion of carriers are at high risk. The review will go beyond this to discuss whether there is an essential need to better define and stratify those at high risk, so that only high-risk carriers are put on surveillance.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer, with a 5-year survival rate of less than 10 % [1]. The impact of pancreatic cancer on public health is substantial, with projections indicating that it will be the second most common cause of cancer related death by 2030, surpassing breast, prostate, and colorectal cancers that have a much higher incidence [2]. Although, if detected early, surgical resection with adjuvant therapy is potentially curative, in 80 % of cases the cancer is too advanced at the time of detection for curative treatment to even be attempted [3]. Earlier testing and diagnosis would save many lives but the early symptoms are vague and are easily missed by both the patients and their clinicians [4]

Within the TRANSPAN COST action (https://transpan.eu/) which allows regular contact and discussion between basic scientists and clinicians, all of whom are committed to reduce pancreatic cancer mortality and improve quality of life, there is a broad consensus on many things like the justification for screening but still in others like the definition of an autosomal dominant predisposition for PDAC there is a healthy disagreement.

The main body of this review is divided into sections, to make it clear where the views of authors coincide (and so a case is being made to the reader from a position of unanimity) and where the authors disagree, and the conflicting views are being presented for the reader to consider.

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In these sections the authors may disagree on the significance but do not disagree on the veracity of the literature discussed. The first section deals with the justification for screening and details the evidence supporting our shared view that surveillance or screening for PDAC can be justified in some individuals, and when justified it is effective and potentially lifesaving. A distinction is made between surveillance and screening. Screening is applied to a population of individuals, some of whom are at high-risk and some at low risk of the disease. Concerning PDAC it can be justified if the benefit on a population basis of detecting cancer early in the high-risk individuals outweighs any harm that might result from an intervention (ranging from inconvenient testing to unnecessary surgery) in low-risk individuals, who would have been unlikely ever to develop PDAC. In contrast, surveillance is applied to populations where all individuals are at high-risk, some perhaps more than others, but all more than unselected individuals. Thus it is surveillance rather than screening if, for example, individuals with symptomatic hereditary pancreatitis are regularly imaged for PDAC (as all individuals definitely have the risk factor of pancreatitis), but it would be screening rather than surveillance if healthy relatives of PDAC patients were to be imaged for PDAC, since no one claims that all such relatives are at high risk, even if many people would assume that some of them are.

The second section about autosomal dominance or multigenic predisposition for PDAC addresses the question of whether imaging for early PDAC detection in germline *BRCA* carriers is surveillance (as they are all at high-risk) or screening (as some are at high-risk and some are at low-risk). Within this section a disagreement is presented as to whether a single pathogenic germline mutation in *BRCA2* or to a lesser extent in *BRCA1,* necessarily gives a much greater risk of developing PDAC, and whether this can be defined as autosomal dominant predisposition.

The third section discusses whether *BRCA* mutations cause predisposition to PDAC and returns to consensus and lays out evidence that *BRCA* mutations do indeed cause predisposition and should certainly be taken into consideration when deciding who would most benefit from monitoring (whether that is surveillance or screening). A consensus was also achieved concerning the benefit of *BRCA* testing for PDAC patients and the benefits of identifying *BRCA* mutations in cancer patients other than PDAC cases, both for the individual tested and their family as described towards the end of the review. However, not all authors agree that the benefits of identifying a *BRCA* mutation in healthy individuals with no family history of cancer, outweigh the negative impact on the individual and their relatives.

The final section about risks and benefits of germline *BRCA* testing highlights how the author's different views on how *BRCA* mutations predispose to pancreatic cancer result in fundamental differences in opinion about who would benefit from screening for mutations. This section addresses the question of risk and benefit of identification of pathogenic *BRCA* mutations in individuals with no known family history of cancer, from those different positions. Arguments will be put that this allows better healthcare management for these individuals and their families. This argument is based on the deterministic nature of the mutation, such that the decision to include these individuals in a surveillance program can be based on the presence or absence of the mutation. At the other extreme, arguments will be presented that PDAC predisposition is polygenic and although mutations in *BRCA* undoubtedly can contribute to predisposition, the penetrance of the mutation will depend on many other factors, so that there is a continuous or semi-continuous level of risk. Between these two arguments lies a third alternative, that the mutations are autosomal dominant, but only in certain contexts, so that individuals are either at high risk of PDAC or not (*i.e.*, that risk can pragmatically be described as binary).

The three models are shown graphically in Fig. 1. In the figure, all models are demonstrated with an average risk, on an arbitrary scale of 5. The populations are divided into groups with each group having a different proportion of PDAC cases. Clearly risk is difficult to define and impossible to know for an individual, as it is quantified based on populations. For example, individual **A** may have a greater chance of having PDAC today than individual **B** (perhaps because A is a long-term smoker), but individual **B** could have more chance of developing PDAC in the next 10 years (perhaps because individual **A** gives up smoking and **B** starts). What we can do however, is to make assumptions about a population of individuals (***P***) that differs from another population (***Q***) in a defined way that means population ***P*** has more risk than population ***Q***. Having defined population ***P*** we can quantify risk, if ***P*** are carries of *BRCA2* mutations they might have a lifetime risk of 14 % (as has been suggested [5]), while population ***Q*** (non-carriers) have a lifetime risk of 1 %. No one can truly say that any individual has a lifetime risk of 14 % (that is only true of the population), but we can say that individuals in population ***P*** have an average risk and that the average risk results in a lifetime risk for the population of 14 %. In the deterministic model, all carriers have the same baseline risk which results from their germline mutation, so while two equivalent carriers of the same *BRCA* mutation will have the same chance of having PDAC (*e.g.* they are in subgroup **f** in the figure) and both will have a risk of 5, two other carriers may have a very different chance of having PDAC than our original pair (*e.g.* in subgroup **k**), but if they are equivalent to each other they will also share the same chance of PDAC and also have a risk of 5. Two equivalent individuals differing only in that one has a BRCA mutation and the other does not, will differ in the chance of having PDAC. In the deterministic model the carrier will have a risk of 5 and a greater

Model	Subgroup of individuals with risk											Suggestion
	a	b	c	d	e	f	g	h	i	j	k	
Autosomal dominant Deterministic	5	5	5	5	5	5	5	5	5	5	5	Surveillance For all or none
Multigenic Variable penetrance	0	1	2	3	4	5	6	7	8	9	10	Screening For all or some
Autosomal dominant Binary context	0	0	0	0	0	0	11	11	11	11	11	Surveillance For some

Fig. 1. Three possible models for how mutations confer risk: This describes a population of BRCA mutation carriers through three different risk models, all with the same overall lifetime PDAC risk (e.g., 14 %). The population is divided into subpopulations (a–f with no PDAC cases to k with the highest PDAC proportion). Autosomal Dominant (Deterministic) means the mutation always increases risk, assigned a value of 5 (e.g., all subpopulations have a 14 % risk). If this level is deemed high enough, all carriers should receive surveillance; otherwise, none should. Multigenic (Variable Penetrance) means the mutation contributes to risk, but other factors determine its extent. While the average risk is 5, individuals vary widely. Because not all have high risk, surveillance isn't universally justified, though screening may be. Autosomal Dominant (Binary Context) means the mutation either confers risk or not, depending on context. If high-risk individuals (e.g., risk of 11) can be identified, only they should receive surveillance.

chance of having PDAC than their near identical twin who has a risk defined as 0. As all individuals are at high-risk, surveillance might be justified. For example, if subgroup **f** is a group of 40-year-olds with a risk of 5 who are predicted to have a 10 % chance of having PDAC, it would be reasonable to put all 40-year-olds with a risk of 5 under surveillance. If surveillance is justified for one it is justified for all. In the next model (variable penetrance) the average risk is still 5 (e.g. for the population as a whole the lifetime risk is 14 %) but some individuals have 0 risk, and some individuals have a risk of 10 (undefined, but much greater than 14 % lifetime risk). Even though some individuals are at low-risk, screening might be justified. Even if it is not justified for all individuals, it might be justified for some if the screened population can be enriched for the higher risk group. In the binary context model, individuals in one context are at high-risk but in all other contexts they are at no elevated risk. If the context can be defined, then surveillance may be justified but only for the high-risk context. Arguments for all three models will be given in the review.

If the only purpose of sequencing *BRCA* genes is for surveillance, then depending on which model is favoured, genotyping of healthy individuals to identify *BRCA* mutations can be seen as beneficial (carriers would benefit from surveillance for PDAC) or counterproductive and potentially harmful (PDAC is very unlikely to be identified but carriers will suffer stress, inconvenience and potential unnecessary treatment). In the deterministic model it is possible to argue that all sequenced individuals will benefit, in the variable penetrance model that some benefit and some are harmed, and in the binary context model it can only be argued (purely from the perspective of surveillance) that carriers with the high-risk context will benefit, all others can only be harmed (thus, genotyping should only occur where there is a strong family history of PDAC).

An argument will be made that the right of an individual to know their own genotype and its potential risks outweighs a clinician mandated approach to genotyping based purely on the clinician's perception of its utility in clinical management, this argument will be disputed.

Although the important questions are left unanswered at the end of this review, the authors assert that additional research on personalised quantification of PDAC risk in germline mutation carriers will provide these answers in the future. In the meantime, the authors support sequencing of the *BRCA* genes in PDAC cases to help manage their individual cancer care, and that where a strong family history supports autosomal dominant predisposition for PDAC, sequencing of the *BRCA* genes is justified to help explain the family history and to offer surveillance to carriers if a pathogenic mutation is discovered. Additionally, although the authors differ on the practical application of the genetic background of each individual in considering surveillance/screening, we all agree that characterisation of the genetic background is vital for research purposes and is the only way to resolve current doubts on management of high-risk populations.

2. The justification for screening

The authors of this review agree that early detection of PDAC will save lives and that in order to achieve this it will be necessary to screen individuals without symptomatic disease. The goal of surveillance is to detect PDAC during a potentially curable stage (T1N0M0) [6] Evidence from the John's Hopkins group for improved survival in individuals under surveillance is compelling [7], with a higher proportion of stage I PDAC (31 % vs 10 %), better 5-year overall survival (50 % vs 9 %) and lower PDAC–specific mortality (43 % vs 86 %), compared to age matched individuals diagnosed conventionally following symptoms. Moreover, the bulk of evidence suggests that an incidental finding of PDAC gives greatly improved survival [8]. However, the possibility that some cancers transition from undetectable to untreatable, making surveillance of no value, cannot entirely be ruled out without further consideration. In support of this would be the concept that many incidences of fatal cancer of unknown primary could be PDAC with no detectable primary [9]. Takikawa *et al.* in a study of 207 asymptomatic patients diagnosed with PDAC reported that although incidentally found PDAC cases do have a better prognosis, 40 % of the PDACs found incidentally are already at stage III or stage IV [10], suggesting that asymptomatic cancers can be at an advanced stage. Similarly, the Dutch Familial Pancreatic Cancer Surveillance Study Group originally reported that although they had a high yield for PDAC in individuals with *CDKN2A* germline mutations, the cancers they found were generally advanced and the benefits of surveillance were small [11]. For the purposes of this review, we could claim that this lack of success was a peculiarity of PDAC resulting from germline *CDKN2A* and not relevant to cancers in *BRCA* mutation carriers. However, even if tumorigenesis in *BRCA* mutation carriers does not give a larger window for detection of cancers, there is reason to believe that the window of opportunity seen with *CDKN2A* carriers is adequate to detect treatable cancers. In a later study, the same Dutch group reported that PDAC resection rates in individuals with germline *CDKN2A* mutations improve when detected during surveillance (38.7 % stage I PDAC via surveillance versus 5.5 % of non-surveillance) with corresponding median overall survival of 26.8 vs. 5.2 months [12]. Therefore, early cancers can be detected, and where only advanced cancers were found, those patients probably could have benefitted from surveillance (using the same methodology) if they had been imaged earlier.

Endoscopic ultrasound (EUS) is the most commonly used modality in surveillance as it has high sensitivity to detect small PDAC [6]. Magnetic Resonance Imaging (MRI) has a reported lower sensitivity to detect small PDAC [13], however, the Pancreatic Cancer Early Detection (PRECEDE) consortium (a transnational group of pancreas experts with an interest in pancreatic cancer screening) include both MRI and EUS, as recommended screening modalities due to their complementary nature to detect small PDAC and characterise small cystic lesions [14,15]. Cystic lesions such as Intraductal Pancreatic Mucinous Neoplasias (IPMN) are associated with PDAC, and could be considered as a positive finding in surveillance or screening. However, survival analysis of individuals where IPMNs were not removed suggests that most incidentally observed IPMNs will not progress to PDAC [16] and results from screening in high-risk and lower-risk individuals suggests that the risk of progression is not related to the level of familial predisposition [17].

In conclusion, surveillance of an individual who will probably develop PDAC is justified by the likelihood that a treatable and curable cancer will be detected if the surveillance window is adequately small, but such surveillance will also lead to detection of apparent cancers in individuals who do not yet have the disease, and will thus cause treatment related morbidity many years, even decades before it is necessary. Abnormalities mistaken for PDAC could be considered as false positives, alternatively, some at least could be considered as early signs of tumorigenesis. Surgical resection of all, or part of, the pancreas will eliminate or reduce the chance of death from PDAC but PDAC surveillance can only be justified if the number of people with a low probability of ever developing PDAC who receive unnecessary treatment (false positives) is much less than those saved from unnecessary death from PDAC (true positives).

The National Comprehensive Cancer Network reviewed its guidelines on pancreatic cancer screening in 2023, noting that although in general screening had been restricted to individuals with a family history of pancreatic cancer (first-degree or second-degree relative), "some groups" have recommended pancreas surveillance for carriers of pathogenic (or likely pathogenic) germline mutations in *ATM*, *BRCA1, BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PALB2*, *STK11*, and *TP53*. The latest guidelines make clear that "the panel does not currently recommend pancreatic cancer screening for carriers of pathogenic or likely pathogenic variants in genes other than *ATM, BRCA2, STK11,* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer."[18]. Implicit in this, is an acceptance that not all carriers of pathogenic mutations are at high enough risk to justify screening, and

furthermore that even with the mutations most likely to confer high risk, some carriers (those without a "close family history") are not at a high enough risk.

3. Autosomal dominance or multigenic predisposition for PDAC

If loss of function of a given gene X makes it more likely that a pancreatic cell will develop into PDAC, then two otherwise identical individuals who differ only because one has a single allele of gene X with a loss of function, will differ in cancer risk with the carrier of the mutant allele being at higher risk. As inheriting the mutant allele is assumed to confer greater risk, the phenotype of predisposition is inherited with the mutation, in other words it behaves like an autosomal dominant disease. However, it is impossible to show life-time risk in a new-born individual and it is impossible to know for certain if a carrier of a *BRCA* mutation developed cancer as a direct consequence of the *BRCA* mutation. Many experts would much prefer to say that *BRCA* mutations increase the penetrance of an existing predisposition. In Fig. 2, where gene X is either *BRCA1* or *BRCA2,* loss of function of either gene will cause a defect in homologous recombination repair (HRR) that could result in increased risk. However, that does not mean it is causal as it is possible that the BRCA mutation makes a predisposed individual more likely to develop cancer, but will not make a person who is not predisposed to develop this form of cancer more likely to develop PDAC. Furthermore, there is a disagreement as to whether loss of HRR always increases risk or whether in some contexts it would not.

Usually but not always, somatic loss of the wild type allele of the *BRCA* gene has been observed in breast and ovarian cancer cases developing in carriers of germline mutations [19]. In PDAC there are fewer reports of carriers losing wild type *BRCA* alleles, which may be at least partly due to fewer publications in total on *BRCA* mutations in PDAC. However, some authors do go as far as to suggest that loss of the wild type allele is only seen in a minority of PDAC cases [20], and in support they cite mouse model data indicating that loss of the wild type allele in PDAC, can only contribute to cancer development if it follows the loss of p53. This would be explained if in some individuals PDAC might occur with or without HRR loss and the inheritance of a mutant *BRCA* allele is just associated with cancer progression but not initiation. Thus, the inheritance of a mutant *BRCA* allele may be associated with cancer development but is not the *a priori* cause.

If an individual's chance of developing PDAC following development of an HRR defect is greater than the probability of developing a cancer without developing an HRR defect, then there is autosomal dominant like predisposition (from Fig. 2, $M_{c1}/(M_{c1}+M_{o1}+M_{o2}) > M_{c2}/(M_{c2}+M_{o3})$). That will clearly not be the case if the likelihood that a cell will develop a defect in HRR and die or develop HRR defect and still not progress to cancer is greater than the likelihood that a cell will not develop HRR and remain benign ($M_{o1}+M_{o2} > M_{o3}$). This can be alternatively expressed as: it is unlikely that any individual carrying a *BRCA* mutation will not develop a defect in HRR in their lifetime, but when they do, it is unlikely that cells with that defect will develop into a cancer because they will usually die, and even if they don't, progression to cancer will not occur during that individual's lifetime. This is in consistent with the need for a *TP53* mutation in the *BRCA2* mutant mouse model and the lack of *BRCA2* loss of heterozygosity in at least some PDAC occurring in carriers of germline mutations [20]).

If there is autosomal dominant predisposition, then cancer surveillance can be justified as all carriers are at high risk. The justification will then depend on lifetime risk, if the proportion of people falsely testing positive in their lifetime is greater than the proportion that would

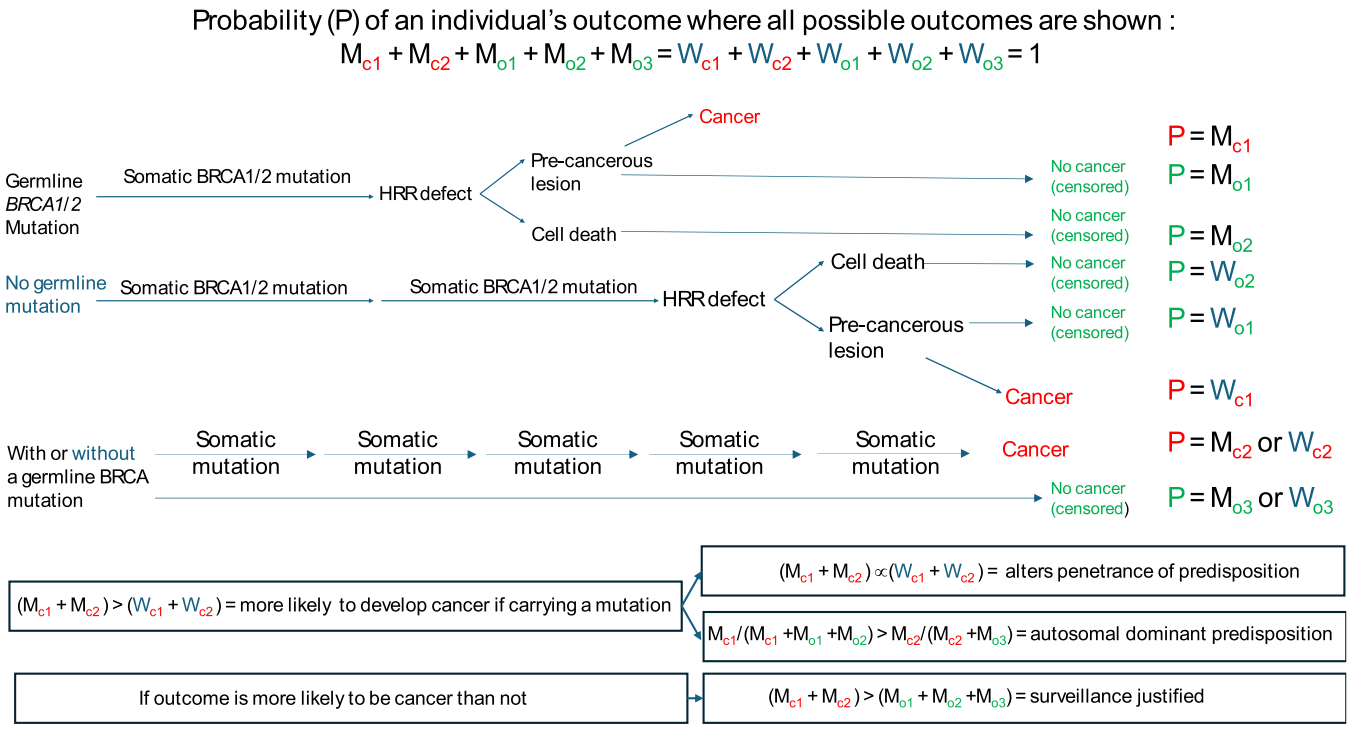

Fig. 2. A germline mutation in a *BRCA* gene could predispose to cancer. This figure proposes two populations: one with *BRCA* mutations (M) and one without (W). Each can be divided into five possible outcomes. Individuals either develop cancer (uncensored) or remain cancer-free (censored). Cancer cases can arise from non-cancerous lesions with or without a homologous recombination repair (HRR) defect. Those without cancer may have no HRR-deficient lesions or lesions that have not yet progressed. Somatic *BRCA* mutations can impair HRR, leading to mutation accumulation. While some mutations kill cells, others create precancerous lesions, which may or may not develop into cancer. Cancer can emerge without an HRR defect via multiple somatic mutations influenced by germline variants. If cancer risk with *BRCA* mutations is merely proportional to risk without them, other factors define predisposition, and the mutation only increases penetrance. But if the proportion of HRR-deficient carriers who develop cancer is significantly more than the proportion of individuals without HRR-defect who develop cancer then this suggests an autosomal dominant predisposition. If the probability of cancer in *BRCA* carriers exceeds that of remaining cancer-free, surveillance is justified as early cancer detection benefits patients, and most false positives will still occur in individuals who would have developed PDAC without intervention.

develop PDAC more people will be harmed than can possibly be helped. Thus, the number of people receiving curative or preventative treatment will be much higher than the small number receiving unnecessary treatment.

4. Do BRCA mutations cause predisposition?

Historically, germline mutations in the *BRCA2* cancer susceptibility gene have been associated with an increased risk of PDAC with the jury still out on the role of *BRCA1* germline mutations and PDAC risk. A recent study using data from over 5000 families with *BRCA1* and *BRCA2* germline pathogenic variants reported increased lifetime risk of PDAC, with a cumulative risk to age 80 years of 2.5 % for *BRCA1* and *BRCA2* carriers [21]. This compares to greater than 50 % lifetime risk for breast cancer for *BRCA2* and greater than 40 % lifetime risk for *BRCA1* [22].

In one United States study, families with an apparent autosomal dominant predisposition (defined as 2 first-degree relatives with PDAC, 3 first-, second-, or third-degree relatives with PDAC or 1 first-degree and 1 s-degree relative with PDAC if one PDAC occurred at age <55) had a BRCA mutation prevalence of 18.9 %, with a 7.7 % prevalence in moderate-risk individuals (defined as 2 first-, second-, or third-degree relatives with PDAC, patients with one first-degree relative with PDAC at an age younger than 55, and not otherwise meeting criteria for high-risk) [23]. This compares to just 2.5 % in unselected PDAC cases [24] suggesting a causal relationship with predisposition accounts for at least some of the association between *BRCA* mutations and PDAC.

The best evidence of the association between *BRCA* germline mutations and autosomal dominant predisposition for breast and ovarian cancer comes from the rare ethnic group of Ashkenazi Jews (AJ). In this population, the association of *BRCA* mutations with breast cancer is also linked to an early age of breast cancer diagnosis. Where there is an early age of onset (<50) in a family there is a lifetime risk for breast cancer in carriers of approaching 100 %, and there is generally loss of heterozygosity in breast cancer tissue, suggesting that loss of HRR function is related to development of cancer in the majority of cases. In contrast, there are individuals carrying *BRCA* mutations, where breast cancer does not develop early, and where loss of heterozygosity in breast cancer tissue is not seen, suggesting that there is no causal link and at most the mutation is increasing an underlying predisposition for breast cancer (penetrance). Of 211 breast cancer patients from the AJ population who had a known relative with pancreatic cancer, early breast cancer diagnosis was significantly related to prevalence of germline *BRCA1/2* mutations (21.1 % for those 50 years of age or under compared to 6.9 % for those over 50 years old, $p = 0.003$), strongly suggesting that in these PDAC relatives, the *BRCA* mutation was indeed autosomal dominant for predisposition for breast cancer [25]. The Myriad II model for breast cancer risk suggests that the prevalence of *BRCA* mutations in the 211 patients should be 11.8 %, while the observed percentage was 14.2 %, suggesting that *BRCA1/2* mutations increase risk for both breast and pancreatic cancer even though the difference was not statistically significant, $p = 0.15$). Mutation prevalences were 15.4 %, 15.3 %, and 8.6 % in first-, second- and third-degree relatives respectively ($p = 0.58$). The percentage of 3rd degree relatives of a *BRCA* carrier who carry *BRCA* mutations is considerably less, therefore, there is only weak evidence overall that PDAC cases are more likely to be related to breast cancer cases in carrier populations. However, in the carriers least likely to have autosomal dominant predisposition (i.e. the older breast cancer cases), the percentages are 13.2 %, 4.4 % and 0 (compared to 18.5 %, 22.7 % and 18.8 % in the breast cancer cases of 50 years or less) [25]. Thus, there is stronger evidence linking *BRCA* mutations to PDAC in cases where the association with breast cancer is less compelling. Of note, 26 of the probands (12 %) had more than one PDAC case in the family (compared to 33 % who had more than 2 additional breast cancer cases). Thus, in the majority of these families, *BRCA* mutations are primarily associated with breast cancer, with pancreatic cancer occurring in only a minority of cases.

In conclusion, there can be no doubt that *BRCA* mutations are associated with cancers including PDAC, but it is difficult to show whether a specific individual is predisposed to cancer. Note that even if a carrier develops cancer, this does not mean they were predisposed by the mutation, as the literature shows that there are cancers that develop in *BRCA* mutation carriers where the activity of the protein has not been lost in the tumour. In terms of populations, it cannot be ruled out that *BRCA* mutations simply increase an existing level of predisposition for cancer rather than causing the predisposition, thus the correct definition would be high penetrance and not predisposition. A causal link is supported by families where early onset breast cancer (<50 y.o.) is associated with loss of BRCA function. However, if autosomal dominance can be assumed on that basis in these families it must be rejected on the same grounds in other families where no such associations are seen. Evidence for autosomal dominance in PDAC is less strong (at least partly because of smaller number of cases available), and if it is assumed to exist in at least some families, then it is notable that families with assumed autosomal dominant predisposition for breast cancer are the least likely to have autosomal dominant predisposition for PDAC and *vice versa*.

5. Identification of BRCA mutations in PDAC cases benefits the patient regardless of family history

New treatments and preventive strategies targeting *BRCA* mutations are continually being developed, and knowing your BRCA status allows access to clinical trials and novel therapies tailored to BRCA-related cancer risks. For example, BRCA defective tumours respond better to platinum-based chemotherapies and poly (ADP-ribose) polymerase inhibitors, which may improve overall survival [26]. In PDAC, the phase III POLO trial showed that patients with metastatic disease who carry germline *BRCA* mutations showed improved progression-free survival with maintenance olaparib, identifying them as a distinct group well-suited for personalized treatment [27].

6. Identification of *BRCA* mutations in individuals without a family history of PDAC

A recent study of *BRCA* germline mutation prevalence in 65,108 unselected cancer patients, and 38,153 controls reported 315 variants previously assigned as pathogenic. The Odds Ratio (OR) for development of PDAC in *BRCA2* mutation carriers was 10.7 (95 % CI 5.1–22.6) an even higher OR 12.6 (95 % CI 3.7–42.8) was seen for *BRCA1* carriers, this corresponds to a cumulative lifetime risk of 14 and 16 % respectively [5]. Although detection of a germline *BRCA1* mutation in a PDAC case is associated with a greatly increased probability of having a family history of ovarian cancer (OR 75.9, 95 % CI 5.9–649.8), it was not associated with the probability of a family history of PDAC OR < 0.05 (95 % CI 0.0–8.2) [5]. To put this in context, detecting a *BRCA1* mutation in a biliary tract cancer was associated with family history of PDAC albeit not a significant association (OR 3.0 95 % CI 0.1–23.2). The discovery of a pathogenic germline *BRCA2* mutation in a PDAC case did give an elevated probability of a history of PDAC albeit not significant (OR 1.8, 95 % CI 0.3–6.3) but this was much lower than the increased probability if a *BRCA2* mutation was found in a prostate cancer case (OR 4.3, 95 % CI 2.3–7.5). This study confirms the association of BRCA mutations and PDAC, further suggesting that a family history of PDAC (and hence prospective risk for family members) can be predicted by testing for *BRCA* mutations in cancers other than PDAC.

A recent prevalence meta-analysis of germline *BRCA* testing of 16,621 PDAC patients which was mainly performed in populations of European descent (88.7 %) from high-income countries (91.2 %) [28], showed wide ethnic disparities in genetic testing in PDAC, even though there was a higher age-adjusted incidence rate among certain minority ethnic groups [29,30]. In order to determine the significance of pathogenic variants in *BRCA* and other cancer risk genes on PDAC risk,

germline testing must be rolled out to include more ethnicities and low-income countries.

In conclusion, identification of *BRCA* mutations in individuals with cancers other than PDAC can indicate high risk of PDAC and restriction of *BRCA* testing according to current practice is biased against certain groups implying that individuals at risk will be missed. Furthermore, even if identification of a mutation does not necessarily mean that a carrier is at greater risk of PDAC, they may be at greater risk of developing breast and/or ovarian cancer and prostate cancer[31]. Thus, it can be argued that testing for *BRCA* mutations in healthy individuals, even in the absence of family history is of benefit to the carriers promoting proactive risk management, uncovering hidden risk and allowing early cancer detection.

7. Risks and benefits of a germline *BRCA* test 6

The arguments above highlight the potential benefits of *BRCA* testing in providing a comprehensive understanding of cancer risk and enabling informed, proactive health management. None of the authors of this review doubt these potential benefits and all of the authors are aware that there are well-established risks. *BRCA* germline testing may have a negative psychological impact, raising anxiety and reducing quality of life. There is also the risk of potential misuse of this genetic information and ethical dilemmas generated within families about whether or not to share test results and a false sense of security when receiving a negative result [32,33].

7.1. Context specific risk

The management of high-risk individuals (HRI), both in terms of genetic testing and surveillance, is currently performed according to European and international guidelines, including those of the International Cancer of the Pancreas Surveillance Consortium (CAPS) consensus recommendations [6], the National Comprehensive Cancer Network (NCCN) [34], the American Gastroenterological Association (AGA) [35], the American Society for Gastrointestinal Endoscopy (ASGE)[36] and the PDAC early detection consortium (PRECEDE) [37]. In essence all guidelines are based on the assumption of an autosomal dominant predisposition either due to an indirect risk linked to a demonstrable autosomal dominant condition (Hereditary Pancreatitis); or to a family history consistent with autosomal dominant predisposition (for example 2 or more PDAC cases in first degree relatives from two or more generations); or the detection of a pathogenic germline mutation previously associated with PDAC predisposition. In the latter case a caveat may be imposed, that even with such a mutation, surveillance is only justified if there is also at least one first degree relative with PDAC. The reason for that is that not all mutations thus far identified in PDAC patients, are within families with evidence of autosomal dominant predisposition. This is demonstrated in Lynch syndrome caused by mutations in mismatch repair (MMR) genes. Such families can be divided into Lynch I where PDAC is not seen, and Lynch II where PDAC is often observed, consistent with an autosomal dominant predisposition for PDAC [38]. Similarly, *CDKN2a* mutations are observed in families with Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome and no PDAC, but also in families with multiple PDAC cases (FAMMM-PC) [39]. Mutations in genes associated with the Fanconi Anaemia complex of homologous recombination repair genes (*BRCA1*, *BRCA2* and *PALB2*) are most frequently associated with autosomal dominant predisposition for breast and ovarian cancer or the autosomal recessive syndrome Fanconi Anaemia, without cases of PDAC; but many families have also been reported consistent with autosomal dominant predisposition for PDAC but without a similar risk of breast or ovarian cancer in most cases [40,41]. Even the inclusion of a PDAC case does not guarantee that the family is high-risk as shown by the two families included on the European Registry of Hereditary Pancreatitis and Familial PDAC (EUROPAC) and shown in Fig. 3: Family A is almost certainly at high risk as shown by the multiple PDAC cases, while family B undoubtedly is at high risk of breast cancer but other than the mutation there is no support for autosomal dominant predisposition for PDAC.

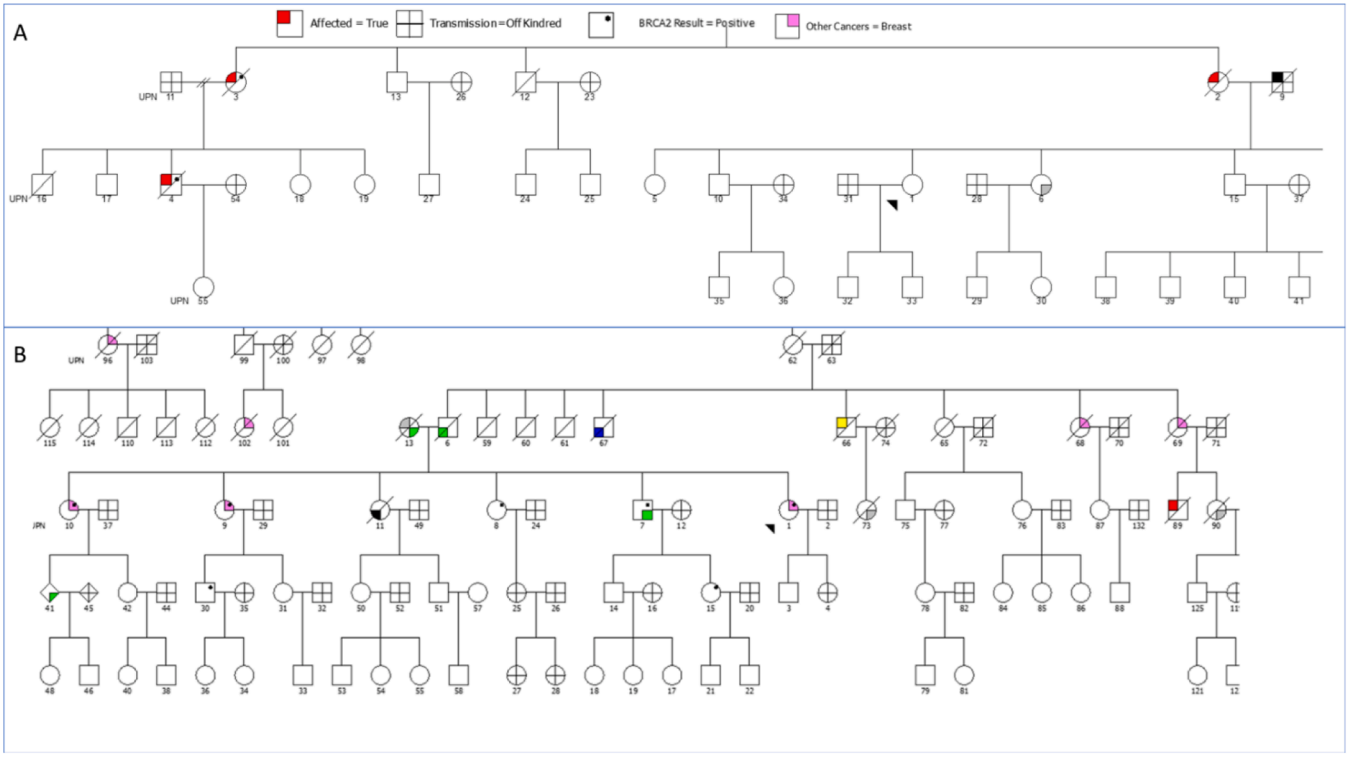

Fig. 3. Two families with the same mutation. Family A is consistent with autosomal dominant predisposition. Family B is not.

7.2. PDAC predisposition as a multigenic condition

The last 30 years have seen tremendous technological and analytical advances in the study of genetic diseases. We moved from twin and small family studies, analysing very small groups of individuals and few mutations with Sanger sequencing, to analysing populations of millions of individuals, comparing their entire genomes, using genome wide association studies (GWAS) and next generation sequencing (NGS). This revolution led to the accumulations of unprecedented information, that, in some cases, translated into a better understanding of the genetic architectures of complex diseases. GWAS and NGS data challenged many traditional views such as the idea of strictly dividing high penetrance variants (previously referred to as mutations) and low penetrance variants (previously referred to as polymorphisms), in favour of acknowledging that risk alleles are distributed in populations according to a continuous spectrum of frequencies and effect sizes (penetrance) [42]. Additionally, GWAS data analysis showed that the majority of the susceptibility alleles were not in genes, rapidly shifting the attention from coding regions to non-coding and regulatory regions. The ability to interrogate entire genomes also posed what was called the missing heritability (MSH) problem. In the nineties, twin and family-based studies estimated the heritability of several human traits, but following GWAS this estimation was generally much lower than expected and therefore researchers were trying to understand how and where to find the genetic variants that could close the gap. The first guess was that the MSH problem would have been solved by identifying low frequency and rare variants through whole exome and whole genome approaches. However, it has now become apparent that the cumulative contribution of common variants overshadows that of rare variants [42]. The collective effect of common variants is usually calculated with polygenic scores (PGS). There are several methods to compute a PGS, the simpler one is to add the Odds Ratio (OR) or betas of the individual SNPs for everyone in the study, to obtain a single value for each participant, according to this formula:

$$PGS_i = \sum_{j=1}^{n} Xij$$

Where n is the number of SNPs used to build the score and X_{ij} is the number of risk alleles (0, 1 or 2) for the participant i at the SNP j. For more details, please refer to Galeotti *et al*[43].

For PDAC around 30 common (minor alle frequency > 0.05) susceptibility loci were identified, all with a small effect on the probability of developing the disease (ORs ranging from 1.12 to 1.47) [44–46]. However, the effect of the PGS is larger and shows a statistical significance comparable with those of GWAS hits ($p < 10^{-8}$) [43]. It is logical to think that adding SNPs through new GWAS will increase the effect of the PGS and decrease the p value of the association. Nevertheless, what we have learned from other cancers is that the larger the samples' size becomes, the smaller the effect of each new individual variant is. The consequence is that we will reach a point where the nth SNP will have an effect so modest in the general population that it is negligible individually. A new concept has received a lot of attention, namely that instead of using a polygenic paradigm we should use a hologenic one (*i.e.*, looking at the same time at all genetic variants) and we should consider that complex traits are the results of tens of thousands of genetic variants (with a continuous distribution across frequency and effect sizes) that interact with the context in which they co-exist be it the environment or other polymorphisms [47]. Testing only for high penetrance mutations, completely ignoring the specific context, is potentially dangerous. Individuals bearing *BRCA1/2* mutation may never develop PDAC because they have a favourable PGS, and on the other hand individuals with a high load of common risk alleles could have a very high risk of PDAC regardless of their *BRCA1/2* status. An additional layer of complexity is that structural germline variations (defined as insertions, deletions and transversions of more than 50 bps) have largely been ignored in genetic epidemiology of PDAC. Considering that they could go up to megabases in length, it is likely that they could have a large effect size and be responsible for the MSH. With long read sequencing currently becoming cheaper, it would be easier to account for them in large-scale studies and possibly include them in genetic testing alongside single nucleotide variants.

8. Conclusion

We support PDAC surveillance of at least some carriers of *BRCA* mutations. Arguments have been presented that screening of all carriers is counterproductive and therefore harmful, as some (perhaps most) will not be at high-risk. This is an argument not a fact, but it represents an important consideration. The authors of the present review consider themselves to be experts in this field, and largely like-minded, yet agreement on this issue given our present understanding is not possible. However, we must disclose that none of the authors is a clinician, which gives us the freedom to explore and express diverse perspectives without the immediate pressures of clinical decision-making. The fact that even experts in the field cannot agree highlights the complexity of the issue. The solution to such an impasse is to ask for more research to identify or exclude factors that determine the risk of PDAC in mutation carriers. Meanwhile, one question is whether it is ethical to continue to inform healthy individuals of their carrier status, another is whether it is ethical to not allow an individual the right to know their carrier status. Provided that individuals are given adequate information about the implications of *BRCA* germline testing, the right to know is voluntary and is a personal choice. The autonomy to choose should be maintained at all times, but it comes with the risk of unnecessary medical interventions and treating carriers of *BRCA* mutations as patients, even though they are currently healthy. Furthermore, the increased associated cost of genotyping, surveillance and unnecessary treatment of benign conditions may starve areas with limited access to healthcare, widening further health disparities. These arguments reflect the complexity of the decision to undergo *BRCA* germline testing and highlight the importance of personalized, informed discussions between patients and healthcare providers, with the latter made aware of the different valid perspectives.

CRediT authorship contribution statement

Conceptualization: WG; **Funding acquisition:** DC; **Methodology:** WG, JE, DC; **Writing – Original Draft:** WG, JE, AK, DC, FC; **Writing – Review & Editing** WG, JE, AK, DC, FC;

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Declaration of Competing Interest

None

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Data availability

No data was used for the research described in the article.

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