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Identification of high-risk germline variants for the development of pancreatic cancer: Common characteristics and potential guidance to screening guidelines

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ABSTRACT

Pancreatic cancer (PC) is a product of a variety of environmental and genetic factors. Recent work has highlighted the influence of hereditary syndromes on pancreatic cancer incidence. The purpose of this review is to identify the high-risk syndromes, common variants, and risks associated with PC. The study also elucidates common characteristics of patients with these mutations, which is used to recommend potential changes to current screening protocols for greater screening efficacy. We analyzed 8 syndromes and their respective variants: Hereditary Breast and Ovarian Cancer (*BRCA1/2*), Familial Atypical Multiple Mole Melanoma Syndrome (*CDKN2A*), Peutz-Jeghers Syndrome (*STK11*), Lynch Syndrome (*PMS2*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*), Ataxia Telangiectasia (*ATM*), Li-Fraumeni Syndrome (*TP53*), Fanconi Anemia (*PALB2*), and Hereditary Pancreatitis (*PRSS1*, *SPINK1*, *CFTR*). Of 587 studies evaluated, 79 studies fit into our inclusion criteria. Information from each study was analyzed to draw conclusions on these variants as well as their association with pancreatic cancer. Information from this review is intended to improve precision medicine and improve criteria for screening.

1. Introduction

Pancreatic cancer (PC) is a highly aggressive malignancy with a typical 5-year survival rate of 10% [1,2]. For 2020, the estimated number of new cases of PC and deaths in the United States are 57,600 and 47,060, demonstrating the poor prognoses of PC patients [2,3]. Geographic regions that have high human development indices (HDI), such as North America or Europe, have the highest PC incidence in the world [3]. PC accounted for 8% of all cancer deaths last year, despite its relative rarity [2]. The main form of PC is Pancreatic Ductal Adenocarcinoma (PDAC), which accounts for 93% of all PC cases [1,2]. PC has a lifetime risk of 1.5% [1,2]. Major risk factors include smoking, type II diabetes mellitus, dietary factors, alcohol abuse, age, and pancreatitis [4,5]. Typically, the relative risk for these factors is fairly low (2- or 3-fold).

PC risk may be hereditary in approximately 4–10% of cases [4,6,9]. Familial pancreatic cancer (FPC) is diagnosed when two or more members within a set of first-degree relatives develop PC without the evidence for an identifiable syndrome. The risk increases proportionally with the number of first-degree relatives.

In comparison, hereditary PC occurs when an individual inherits a cancer-inducing syndrome. Some of these syndromes include Hereditary Breast and Ovarian Cancer (HBOC), Familial Atypical Multiple Mole Melanoma (FAMMM), and Lynch Syndrome (LS) [4,6,7]. Examples of genes implicated in hereditary PC include: Breast Cancer Genes 1/2 (*BRCA1/2*), Cyclin Dependent Kinase Inhibitor 2A (*CDKN2A*), ATM Serine/Threonine Kinase (*ATM*), Serine/Threonine Kinase 11 (*STK11*), Tumor Protein 53 (*TP53*), Serine Protease 1 (*PRSS1*), MutS Homolog 2 (*MSH2*), MutL Homolog 1 (*MLH1*), MutS homolog 6 (MSH6), Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*), and Truncated Partner And Localizer Of *BRCA2* (*PALB2*) [4,6,7].

A major challenge in PC treatment is its difficulty to diagnose early-on. When surgical resection is possible, the 5-year survival rate is 37%, but only 10% of cases are detected early enough due to lack of specific symptoms [1,2]. 53% of cases are diagnosed in the

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metastatic setting, having a 5-year survival rate of 3% [1,2]. Consequently, there is growing emphasis into earlier detection of PC.

Although the number of hereditary cases of PC is small relative to no family history of PC (sporadic cases), the identification of high-risk individuals through multigene testing may allow for enhanced screening and earlier detection. The number of variants and varying penetrance make it challenging to identify high-risk ones. Understanding how variants work in tandem may elucidate the process for PC development. Higher-risk genes have been determined in some cases, such as *BRCA1/2* [4–7]. Genetic screening for these genes may improve outcomes for high-risk individuals by enabling high-risk screening protocols and earlier detection.

The aim of this study is to summarize current literature regarding the association of genes, their germline variants, and PC development. Moreover, the study also seeks to incorporate screening criteria and syndrome phenotypes to determine high-risk individuals and genes that require screening.

2. Methods

2.1. Gene identification

An initial query was completed using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) to identify relevant genes, with criteria similar to that of Zhan et al. [7] The relevant genes were identified through the selection of reviews that analyzed germline variants and PC incidence. We utilized this query for gene identification for “reviews” and “systematic reviews” from 01/01/2010 to 12/31/2020: (“pancreatic cancer"[All Fields] OR “pancreatic ductal adenocarcinoma"[All Fields] OR “PDAC"[All Fields]) AND (“germline"[All Fields] OR “germline variants"[All Fields] OR “variant"[All Fields]) AND (“gene"[All Fields] OR “genes"[All Fields])

The initial query yielded 63 results, and the reviews were analyzed to determine relevant genes and syndromes. Some reviews were not analyzed for germline variants due to their irrelevance to the focus of this study. These results were compiled into a list for the second query.

2.2. Literature selection

Query 2 includes certain syndromes that have been associated with germline mutations of some of these genes. The PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was used. The criteria included all studies until the date of 3/31/2021: (“pancreatic cancer"[All Fields] OR “Pancreatic ductal adenocarcinoma"[All Fields] OR “PDAC"[All Fields] OR (“pancreas"[All Fields] AND “cancer"[All Fields])) AND (“germline"[All Fields] OR “variant"[All Fields] OR “variants"[All Fields] OR “germline variants"[All Fields]) AND ((“BRCA"[All Fields] OR “*BRCA1*"[All Fields] OR “*BRCA2*"[All Fields] OR “HBOC"[All Fields] OR “Hereditary Breast and Ovarian Cancer"[All Fields]) OR (“*ATR*"[All Fields] OR “*ATM*"[All Fields] OR “Ataxia Telangiectasia"[All Fields]) OR (“*CDKN2A*"[All Fields] OR “FAMMM"[All Fields] OR “Familial Atypical Multiple Mole Melanoma"[All Fields]) OR (“*PRSS1*"[All Fields] OR “*SPINK1*"[All Fields] OR “*SPINK2*"[All Fields] OR (“pancreatitis"[All Fields] AND (“hereditary"[All Fields] OR “chronic"[All Fields])))) OR (“*TP53*"[All Fields] OR “P53"[All Fields] OR “CHEK1"[All Fields] “CHEK2"[All Fields] OR “Li-Fraumeni Syndrome"[All Fields]) OR (“*STK11*"[All Fields] OR “Peutz-Jeghers"[All Fields] OR “PJS"[All Fields]) OR (“*MLH1*"[All Fields] OR “*MSH2*"[All Fields] OR “*MSH6*"[All Fields] OR “*PMS2*"[All Fields] OR “*EPCAM*"[All Fields] OR "“Lynch Syndrome"[All Fields]) OR (“*APC*"[All Fields] OR “*FAP*"[All Fields] OR “Familial Adenomatous Polyposis"[All Fields]) OR (“*PALB2*"[All Fields] OR “*FANCA*"[All Fields] OR “*FANCC*"[All Fields] OR “*FANCG*"[All Fields] OR “Fanconi Anemia"[All Fields]) OR (“*CFTR*"[All Fields]))

2.3. Study selection

Studies were screened by keywords in the title or abstract, and studies that were not pertinent were excluded. All studies examining only PNETs and non-adenocarcinomas were excluded. Studies were included if they assessed the amount of PC patients with a specific variant of a gene or syndrome listed above and the risk with the relative variants. Studies were also included if they provided the type of mutation or the protein modification. Additionally, studies used in systematic reviews or meta-analyses were included if the studies followed similar criteria and were accessible. Information from the studies would be compared to the screening guidelines established by National Comprehensive Cancer Network (NCCN) and the International Association of Cancer of the Pancreas Screening (CAPS) consortium [8,9]. Variants within the studies, phenotypes, and common cancers were compiled into a table (Table 1).

3. Results

3.1. Literature selection

Of 587 studies, 79 were included in the final study. 509 were excluded as duplicates, not fitting study criteria, only examining PNETs and non-adenocarcinomas, or being irrelevant. 5 additional studies were pulled from systematic reviews and used to supplement current research. Certain studies were added, but not included in the final count, that provided information on the genes and their protein functions.

3.2. Variant and phenotype table

Table 1 compiles information on the pathogenic/likely pathogenic variants and their common phenotypes for patients with PC.

Table 1
Table summarizing the Pathogenic/Likely Pathogenic variants as established by Clinvar and the common cancer/phenotypes reported in the literature with these germline mutants.

Gene	Pathogenic/Likely Pathogenic Variant	Associated Cancers	Other notable Phenotypes	References
ATM	c.103C > T	Breast	Family history of cancers	[15,18,23,46,64,68,70–73,81]
	c.170G > A	Prostate		
	c.5549delT	Colon		
	c.3038dupA	Melanoma		
	c.3G > A	Glioma		
	c.1564_1565del	Lung		
	c.6100C > T	Sarcoma		
	c.6228delT	Prostate		
	c.8185C > T	Breast		

Table 1 (*continued*)

Gene	Pathogenic/Likely Pathogenic Variant	Associated Cancers	Other notable Phenotypes	References
	c.9022C > T			
	c.9139C > T			
	c.1369C > T			
	c.7630-2A > C			
	c.741dupT			
	c.3802del			
	c.5932G > T			
	c.1931C > A			
	c.3801delG			
	c.8874_8877			
	c.4776+2T > A			
	c.7456C > T			
	c.742C > T			
	c.1065+1G > T			
	c.8395_8404delTTTCAGTGCC			
BRCA1	c.68_69delAG	Colon	Family history of cancers	[12–16,18–20,23–28,46,61,64,68,70,71]
	c.5266dupC	Rectum		
	c.181T > G	Liver	HBOC	
	c.70_80del	Uterus	Development of PC before 50	
	c.187delAG	Cervix		
	c.4507	Bladder	Higher occurrence of other cancers in women	
	c.5385insC	Kidney		
	c.6699C > A	Breast		
	c.213-12A > G	Ovarian		
	c.4986+3G > C	Melanoma		
	c.178C > T	Lung		
	c.300T > G	Head/Neck		
	c.843_846del	Skin		
	c.895_896del	Testicular		
	c.929del	Gallbladder		
	c.962G > A	Sarcoma		
	c.1175_1214del			
	c.1360_1361del			
	c.1953_1956del			
	c.1961del			
	c.2071del			
	c.2274A > T			
	c.2338C > T			
	c.2405_2406del			
	c.2681insGC			
	c.2719_2722del			
	c.2702_2703del			
	c.2934T > G			
	c.2973_2979del			
	c.2999del			
	c.32454_3255del			
	c.3649_3650insA			
	c.3700_374del			
	c.3756_3759del			
	c.3759dup			
	c.4117G > T			
	c.4327C > T			
	c.4986+6T > C			
	c.5106del			
BRCA2	c.5946delT	Colon	Family history of cancers	[12,14–28,46,61,64,68,70,71,73,81]
	c.5636G > T	Rectum		
	c.2808_2811del	Liver	HBOC	
	c.3545_3546del	Uterus		
	c.5909C > A	Cervix	Development of PC before 50	
	c.2928delC	Bladder		
	c.7682A > C	Kidney	Higher occurrence of other cancers in women	
	c.6085G > T	Breast		
	c.6373dup	Ovarian		
	c.3967A > T	Melanoma		
	c.1189C > T	Lung		
	c.4965G > C	Head/Neck		
	c.6951_6952del	Testicular		
	c.6444dup	Gallbladder		
	c.3847_3848del	Brain		
	c.4478_4481del	Sarcoma		
	c.87551G > A	Prostate		
	c.1813del			
	c.1929del			
	c.5682C > G			

(*continued on next page*)

Table 1 (*continued*)

Gene	Pathogenic/Likely Pathogenic Variant	Associated Cancers	Other notable Phenotypes	References
	c.6037A > T			
	c.3744_3747del			
	c.5350_5351			
CDKN2A[a]	c.71G > C	Melanoma	FAMMM	[15,18,20,23,29–39,46,62,68,70,81]
	c.301G > T	Ovarian		
	c.97_98insc	Lung	PC onset before 50	
	c.457G > T	Breast		
	c.169G > A	Bladder	Melanocytic Nevi	
	c.377T > A	Colorectal		
	c.47T > G	Gynecologic		
	c.149A > G			
	c.240_253del			
	c.47G > A			
	c.97dup			
	c.161G > A			
	c.193G > C			
	c.60_61ins			
	c.193+1G > A			
	c.194-3653G > T			
	c.194-3635dup			
	c.194−3585C > A			
	c.194−3573T > G/C			
	c.184-3553G > A			
	c.194-3549G > C			
	c.194-3541G > T			
	c.159G > C/A			
	c.167G > T			
	c.172C > T			
	c.176T > G			
	c.194T > C			
	c.202_203del			
	c.212A > G			
	c.213C > A			
	c.219C > T			
	c.225_243del			
	c.283del			
	c.286del			
	c.44G > A			
CFTR	c.2991G > C[c]		Chronic Pancreatitis	[95,96]
	c.1624G > T[c]		Cystic Fibrosis	
	c.3935A > G		Acute Pancreatitis	
MLH1	c.1210_1211	Colon	Family history of cancers	[18,23,56,57,62–64,68,70,73]
	c.1852A > G	Breast		
	c.677+3A > G	Uterine	Lynch syndrome	
	c.1153C > T	Breast		
		Bowel		
		Brain		
		Ovary		
MSH2	c.1226_1227del	Renal Pelvis	Family history of cancers	[23,46,56–58,61,63,64,66,68,70,71,81]
	c.1046C > T	Ureter		
	c.1204C > T	Carcinoma	Lynch syndrome	
	c.942+3A > T	Colon		
	c.1906G > C	Brain		
	c.1786_1788del	Ovary		
		Kidney		
		Colorectal		
MSH6	c.3312dupT	Colorectal	Family history of cancers	[15,18,23,56,57,64,68,81]
	c.3202C > T	Uterine		
	c.1707delC	Brain	Lynch syndrome	
	c.2194C > T	Ovary		
	c.125_126insT			
PMS2	c.2174+1G > A	Colorectal	Family History of Cancers	[46,62,68]
	c.52A > G	Uterine		
		Brain	Lynch syndrome	
		Ovary		
PALB2	c.707dupT	Prostate	Family history of cancers	[15,18,20,23,68,71,73,80,83–85]
	c.2386C > A	Breast		
	c.3256C > T	Uterine	Fanconi Anemia	
	c.2509G > T			
	c.3456dupA			
	c.3113G > A			
	c.393_394insC			
	c.1653T > A			
	c.3362del			
	c.1240C > T			

Table 1 (*continued*)

Gene	Pathogenic/Likely Pathogenic Variant	Associated Cancers	Other notable Phenotypes	References
	c.3116del c.C3256T c.3549C > G/A c.3456dupA c.2366C > A c.839delT c.1240C > T c.508_509delAG c.3116delA c.2509G > T			
PRSS1	c.365G > A[c] c.86A > T[c]	N/A	Hereditary Pancreatitis	[89]
STK11[b]	c.541A > G c.543C > G/A c.200T > C c.910C > T c.367C > T c.109C > T c.418del	Ovarian Colorectal Stomach Bowel Breast Cervix Uterine Testicular Lung	PJS Polyps Mucocutaneous pigmentation Cancer Onset before 50	[40–54,61,68]
SPINK1	c.101A > G[c]	N/A	Acute pancreatitis Chronic Pancreatitis Pancreatic Pain Ductal Abnormalities Cholestasis Calcification	[90,91,93]
TP53	c.542G > A/C c.916C > T c.742C > T c.818G > T c.844C > T c.847C > T c.524C > A	Prostate Lymphoma Breast Melanoma Rectal Esophageal Liver Sarcoma	Family history of cancers Li-Fraumeni Syndrome Onset of PC before 50	[18,23,61,64,68,71,74,76]

[a] For CDKN2A variants, consider viewing Chan et al. [2021] due to their high levels of CDKN2A variant reporting [35].
[b] More severe phenotypes for STK11 variants occurred with truncating phenotypes.
[c] Genes are heavily associated with Pancreatitis and have been found in PC patients.

4. Discussion

4.1. BRCA1/2 (HBOC)

Germline variants in the *BRCA1/2* genes have been implicated in Hereditary Breast and Ovarian Cancer syndrome (HBOC) – an autosomal dominant condition [10]. *BRCA1/2* are tumor suppressor genes in the DNA Damage Response (DDR) that repair double stranded DNA breaks (dsDNA) [11]. While better recognized for its association with breast cancer, HBOC has been associated with PC risk [10].

According to the NCCN guidelines, the absolute risk of developing PC with a *BRCA1/2* pathogenic variant is less than 5% and 5–10%, respectively [8]. Multiple studies have demonstrated odds ratios ranging from 2 to 7 in *BRCA1* and 5–10 in *BRCA2* [12–17]. Considering the current NCCN guidelines on *BRCA1/2* screening, there is enough evidence to suggest that *BRCA1/2* should always be included in multigene panels.

There is a growing amount of research into the frequency of *BRCA1/2* variants in apparently sporadic cases. Shindo et al. (2017) discovered 12/854 patients of sporadic PC with a *BRCA2* pathogenic truncating variant ($P < 0.001$), and 3/854 with *BRCA1* ($p = 0.7625$) [18]. In this case, sporadic PC refers to cases of PC that do not have any family history of PC or other cancers associated with HBOC. With the most recent study from 2018 by Blair et al. previous estimates place *BRCA1/2* variant frequency in sporadic cases around 3–5%, where most cases have a BRCA2 variant [17–22]. Therefore, these estimates could justify screening family members of patients with apparently sporadic cases of PC for *BRCA2* variants and PC, not *BRCA1*, with the typical NCCN guidelines. It could also justify screening patients with known *BRCA2* variants for PC without a first-degree blood relative developing PC.

It is important to address screening the subset of patients with previous family or personal history of HBOC-related cancers and FPC, particularly in women. Of 9 patients with a PC diagnosis and a *BRCA1/2* variant, 7/9 (78%) had a family history of HBOC, and all had a personal history of an HBOC-related cancer [23]. 6/9 (66%) of the patients were women as well [23]. In a cohort of 1171 females with previous Ovarian cancer in Ontario, the relative risk of PC for *BRCA1/2* pathogenic variants was 3.1 (95% CI = 0.45–21) and 6.6 (95% CI = 1.9–23) [24]. Another study found that 4 out of 8 females (50%) with *BRCA1/2* variants had either a previous history of Breast Cancer or a family history of PC [25]. The NCCN guidelines do not provide information on screening with these conditions, but they do advise PC screening at 50 years old or 10 years earlier than the youngest PC case in the family [8]. Further work should assess if earlier PC screening would prove fruitful to women with *BRCA1/2* variant and a family history.

Some variants have higher risks or common phenotypes. Ashkenazi Jewish (AJ) families with cases of FPC often exhibit

founder mutations including *BRCA2* c.5946delT, *BRCA1* c.68_69delAG, and *BRCA1* c.5266dupC [7,26–28]. 5.5% of these founder mutations are found within the AJ community, and 24% of the patients with PC and a founder mutation had a previous cancer with breast (9/35) and prostate (8/35) [27]. One study found that 4/5 (80%) patients with PC and the *BRCA2* c.5946delT mutation had a family history of HBOC-related, pancreatic, and lung cancers [18]. All of these patients exhibited PC onset before 65, with the youngest being 42 [18]. These results demonstrate that certain variants have higher risks with PC development, associations with previous cancers, or are common in certain ethnic groups. More information on these variants' phenotypes and PC risk could provide stronger insight into the identification of high-risk individuals and the most effective measures for PC screening.

Another group, the International Cancer of the Pancreas Screening (CAPS) consortium, have similar agreements with BRCA1/2 as the NCCN guidelines. The main difference is that their 2019 consensus argued for potentially screening for PC at 45 years old, rather than 50 years old in *BRCA1/2* mutation carriers [9]. Younger screening in *BRCA2* could help improve patient outcomes, but the relatively small number of patients that develop PC at that age cannot fully justify that decision. More research could illuminate that earlier screening may be necessary based on current trends of PC incidence and *BRCA2* mutations.

4.2. Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

FAMMM syndrome is an autosomal dominant genodermatosis where a patient has multiple melanocytic nevi and a family history of melanoma [29]. The occurrence of FAMMM syndrome is characterized by a disorder in the *CDKN2A* gene, which produces the tumor suppressor proteins that inhibit CDK4 and CDK6 at the G1/S checkpoint: p16(INK4a) and p14(ARF) proteins [29–31]. Therefore, mutations in *CDKN2A* inhibit its ability to prevent cell cycle progression to the S phase, which could result in uncontrolled and rapid cell proliferation. Current NCCN estimates place the absolute risk for PC for FAMMM kindreds to be greater than 15% [8].

A key finding in the incidence of PC and FAMMM syndrome is that the p16(INK4a) protein is somatically inactivated in 95% of PC cases [29,30]. Although it is not an assessment of germline risk, the overall occurrence of *CDKN2A* mutations affecting the p16(INK4a) isoform in PDAC cases solidifies *CDKN2A* as a high-risk gene. In cases with germline pathogenic variants, a majority of the reported variants in patients with PC occurs in the p16 isoform with many occurring directly in the p16 region of the protein, thereby demonstrating the significance of this region to PC development [30–36]. The p14 isoform has also been implicated, but there are significantly less reported variants on the protein in PC incidence, which could be due to the fact that p14 variants have a tendency to be implicated in other cancers [36].

There are a few areas that need greater data collection of FAMMM phenotypes, which may be valuable for developing better patient screening algorithms. One area is the occurrence of *CDKN2A* mutations and FPC *without* evidence of FAMMM syndrome. In a European study, 6/28 (21%) PC families without FAMMM phenotypes had a *CDKN2A* deleterious variant, which could indicate a need to alter current screening methods [37]. More research on this area needs to be done before any conclusions can be made, though. But, the occurrence of melanoma within an FPC family could be a strong indicator for a *CDKN2A* mutation and should follow NCCN screening guidelines.

The p16-leiden Dutch founder mutation (c.225_243del19) has been demonstrated to cause a 17% risk in development of PC by 75, and the c.335_337dup variant has an occurrence greater than 60% in the Swedish population with PC [30,38]. Thus, individuals with these variants should be considered especially high-risk. These variants tend to propagate in Caucasian individuals, especially in the Netherlands, North America, Australia, and other locations in Europe [16,21,30,39].

Current NCCN guidelines for *CDKN2A* recommend screening at the age of 40 years or 10 years younger than the youngest age a relative developed PDAC for individuals of FAMMM kindreds [8]. The guidelines are sufficient in that regard, but the occurrence of PC in *CDKN2A*-mutation-positive families without FAMMM syndrome may indicate that screening should occur earlier for families with melanoma development and a FAMMM variant.

Interestingly, previous CAPS recommendations for *CDKN2A* argued that PC screening should happen for patients with variants in the p16 region in the absence or presence of a relative with PC, but they do not provide consensus on *CDKN2A* mutations in general [9]. In the 2019 consortium, though, the group came to the consensus that all *CDKN2A* germline variants should undergo PC screening [9]. Based on current information, this was the correct decision because of the instances of PC development without mutations in the p16 region. Due to the risk associated with the *CDKN2A* p16 isoform and growing research into the p14 isoform, screening for patients with the mutations in general will provide better outcomes. Though, it is important to recognize that many of the deleterious variants tend to occur in in p16 region or are more highly reported.

4.3. Peutz-Jeghers Syndrome (PJS)

Peutz-Jeghers Syndrome (PJS) is a rare, autosomal dominant condition that is associated with gastrointestinal polyposis, mucocutaneous pigmentation, and cancer predisposition [40,41]. Specifically, PJS is highly associated (94–96%) with pathogenic variants in the *STK11* gene, which produces serine-threonine kinase 11 [41–43]. An interesting finding for those affected by PJS is that 45% of individuals do not have a family history of the syndrome [41]. The function of *STK11* is context dependent, but it demonstrates a role in tumor suppression in the pancreas. *STK11* is an upstream kinase of the AMP-activated protein kinase (AMP) and Mitogen-activated protein kinase (MAPK) pathways, and a defective *STK11* is associated with the development of pancreatic neoplasms [44,45].

Despite the rarity of PJS, the overall risk of pancreatic cancer development is greater than 15%, with a cumulative lifetime risk of 36% [8,41,46]. Identification of individuals with PJS and an *STK11* variant would categorize them as a high-risk group, which may justify earlier screening methods. It is also important to note that individuals with *STK11* have extremely high penetrance of PJS such that PJS almost always occur in the presence of these deleterious mutations [12,41,47–49]. The mean age of PC diagnosis for PJS-afflicted individuals is around 41–52 years, but a fair amount of cases occur after age 60 [41,50,51].

Current NCCN guidelines state that screening of individuals with PJS and a family history of PC should either begin at 30–35 years of age or 10 years younger than the youngest person with PJS and PC in the family [9]. In comparison, the CAPS consortium recommends that screening should occur for all individuals with *STK11* at age 40, regardless of family history [9]. PC patients with PJS also have demonstrated a family or a personal history of breast, colon, and ovarian cancers [52–56]. The risk of other cancers in PJS individuals illustrates that screening of all individuals with PJS, even those without a family or personal history of PC, may be justified around the age of 40.

While these guidelines vary slightly, there is a definitive understanding that pathogenic *STK11* variants confer significant risk towards PC development and earlier onset. Considering the early

onset of PC in PJS patients, both guidelines are justified to identify these earlier cases. Therefore, earlier screening at around 35 years old for all individuals with germline variants may help to improve patient outcomes. Furthermore, screening guidelines could include both recommendations if differences in PC development are found to occur in PJS patients with FPC versus those patients without it.

4.4. Lynch Syndrome (LS)

Lynch syndrome (LS), or hereditary non-polyposis colorectal cancer (HPNCC), is an autosomal dominant disorder that is characterized by increased risk for cancers, specifically colorectal and endometrial cancer [57,58]. The syndrome is associated with four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) and the *EPCAM* gene [57,58]. The EPCAM gene can undergo mutations that cause it to form a long mRNA with its adjacent MSH2 gene, eventually resulting in MSH2's promoter hypermethylation and lowered expression [57,58]. Mismatch repair (MMR) genes fix mismatched bases. Deleterious mutations can occur that cause cancerous protein products and increase cancer incidence by ineffective DNA repair.

Individuals with LS follow a common pattern: Patients are born with a heterozygous genotype for these genes [57,58]. Cancer risk increases when the functional allele undergoes a somatic second hit and becomes non-functional, so no functional protein is produced [57,58]. Mutations in MMR genes and the occurrence of LS in individuals is associated with microsatellite instability (MSI), which stands as a common marker for identifying whether a patient has LS [57,58]. In regards to PC, a review found that MSI is a poor diagnostic due to its low prevalence in PC cases (~2%), and it may hold more prognostic value [59]. Therefore, MSI should only be used for identifying patients with LS that may be more at-risk for PC.

The gene responsible for PC development in LS patients follows similar patterns in other cancer incidences. PC incidence seems to have a higher occurrence for *MLH1* and *MSH2* mutations, followed by *MSH6* and *PMS2* [12,16,24,47,60–71]. Kastrinos et al. (2009) discovered that 31/47 PC patients had an *MSH2* mutation, 13/47 with *MLH1*, and 3/47 with *MSH6* [66]. The study also found that 8 of 13 (62%) families with multiple PC cases had an *MSH2* mutation, 4 (30.8%) for *MLH1*, and 1 (7.7%) for *MSH6* [66]. Mutations have often been seen to present with a cancer diagnosis prior to the onset of PC, which is typically a form of colorectal or breast cancer [24,65,66]. Therefore, it is important to recognize that individuals with LS should be getting tested for PC through MSI or IHC testing at the age of 50, even in the absence of family with PC.

Current NCCN guidelines and studies establish that the risk for PC is around 5–10% by age 70 and a relative risk of 8.6 for patients with LS [8,49]. However, our study found insufficient evidence to conclude that *PMS2* and *EPCAM* variants play a role in PC risk in comparison to the other 3 genes associated with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*). The NCCN guidelines for PC-screening have determined that screening should only occur for individuals with *MLH1*, *MSH2*, *MSH6*, and *EPCAM* variants and a family history of PC [8]. Comparatively, the CAPS guidelines recommend screening at 45 years of age with known *MLH1*/*MSH2* variants, but not for *MSH6* and *EPCAM* [9]. Considering the discrepancies in screening, screening patients with PMS2 and EPCAM variants may be low-yield, so screening should only occur in the case of patients with Lynch syndrome for these variants. For those with germline pathogenic or likely pathogenic variants in the other 3 genes, the guidelines recommend screening at the age of 50 or 10 years prior from the first family member with PC [8].

4.5. Ataxia Telangiectasia (A-T)

Ataxia Telangiectasia (A-T), AKA Louis-Barr syndrome, is an autosomal recessive disorder that is estimated to affect 1 every 40–100 thousand births [72]. A-T is a DNA damage response (DDR) syndrome that leads to cerebellar degeneration, telangiectasia, and a predisposition to cancer development [72]. The syndrome occurs due to deleterious mutations in the *ATM* gene, leading to a dysfunctional protein product. *ATM* protein is a serine/threonine kinase that is crucial to NHEJ and HRR for double strand breaks, DNA repair processes, and apoptosis [72].

Absolute risk estimates are between 5 and 10% in patients with *ATM* mutations and a relative risk of 3.2 (95% CI, 0.44–14.2) [8,62]. Two studies that the most patients with PC and a commonly mutated gene had a variant within the *ATM* gene (69/249, OR = 5.72; OR = 10.7) [15,68]. Variants in *ATM* are also considered to be one of the most common germline mutations in PC patients, ranging from 1 to 34% [73].

It is important to recognize that *ATM* mutations are associated with other forms of cancer. Many of these cancers are breast, colorectal, and pancreatic [18,23,69,71]. It is also common to have individuals with earlier diagnoses of breast or other cancers prior to their PC diagnosis [18,23,69,71]. Even after excluding patients without a family history of PC, Hu et al. (2018) calculated an OR of 10.55 ($p < 0.001$), indicating that *ATM* mutations may cause apparently sporadic PC as well [12]. Furthermore, all of these studies analyzed patients that only inherited one mutant allele and did not exhibit A-T. Yurgelun et al., [2019] found that 44% of patients with an ATM mutation and PC had undergone a somatic second hit in the resected tumor, which could indicate that risk may increase with loss-of-heterozygosity [71]. Additionally, the results may demonstrate that PC development could be due monoallelic inactivation as well. Either way, pathogenic ATM germline variants likely increase the risk of PC through loss-of-heterozygosity, monoallelic inactivation, or a combination of both. Therefore, current NCCN screening guidelines for individuals with *ATM* mutations at age 50 or 10 years younger than the first PC case in the family are valid [8]. CAPS guidelines recommend screening at 45 years of age with an *ATM* variant, but the relatively few cases below 50 years of age does not warrant screening at this point [9]. As a result, screening for PC in *ATM*-mutated patients beginning at the age of 50 is the most effective course of action for these afflicted individuals.

4.6. Li-Fraumeni Syndrome (LFS)

Li-Fraumeni Syndrome (LFS) is an autosomal dominant condition that predisposes individuals to cancer through mutations of the tumor suppressor protein, *TP53* [74,75]. *TP53* is a protein vital to the regulation of the cell cycle and works by recognizing DNA damage. If the protein becomes activated, it binds to *TP53*-binding elements in DNA to activate transcription for proteins that promote apoptosis, senescence, and DNA-repair. Individuals impacted by *TP53* germline mutations tend to be heterozygous for the allele, but mutant *TP53* also acts upon the wild-type protein and can mitigate the impact of the tumor suppressor protein [74,75].

The absolute risk imposed by a germline mutation is around 5–10%, and the relative risk is around 7.3 (95% CI, 2–19) [8,76]. Evidence for the association between P53 germline mutations and PC is limited. However, Cicenas et al., [2017] has implicated *TP53* as a crucial protein in the prevention of PC as 70% of all PC cases have a mutated *TP53* protein [77]. P53 germline mutations can significantly increase the risk for PC in individuals.

An important point to recognize is the propensity for PC patients with *TP53* mutations to have a prior personal or family history of

other cancers. Hu et al., [2018] found that, of 6 patients with PC and a *TP53* mutation, two of these patients had breast cancer previously [12]. Along those same lines, Dudley et al., [2018] demonstrated two female patients with *TP53* mutations that had 7 previous diagnoses for other cancers beginning around 30 years old, including breast, sarcomas, and melanoma [23]. While the research on *TP53*-mutated PC is relatively sparse, these cancer incidences follow already identified patterns. Malkin et al., [2011] showed that cancer risk for *TP53* is much greater for female patients, and cancer incidence has a tendency to be early-onset in these cases [74]. Therefore, it is important to incorporate this information into current screening guidelines for known *TP53*-mutant patients.

Current NCCN guidelines state that screening should begin at age 50 or 10 years younger than the earliest occurrence of PC in a family member with the mutant allele [8]. Considering the limited amount of data, this approach is the most justified. Future work may determine the relationship of PC incidence in those patients with a prior history of a specific cancer as well as the difference in PC incidence based on sex.

Finally, it is important to address *TP53* variants that could increase the risk for PC. Interestingly, the majority of pathogenic variants for *TP53* occurs in its DNA-binding domain (DBD) [75]. The DBD region includes amino acids 102–298 in the *TP53* protein product. Some of the currently identified pathogenic variants include c.847C > T (p.R283C), c.542G > C (p.R181P), c.524C > A (p.R175H), and c.742C > T (p.R248W), which are mutational hotspots in PC cases [18,23,55,69,75]. The higher prevalence of DBD variants in the implication of PC cases and cancer in general could improve the effectiveness of identifying high-risk individuals as these cases could be encouraged to get more frequent screening for PC. Therefore, these results demonstrate that it could be effective to vary screening guidelines based on the specific variant, but more research needs to be done on this subject.

4.7. PALB2-associated Fanconi Anemia (FA)

Fanconi Anemia is an autosomal recessive condition that affects the blood and implicates the DNA repair process. While Fanconi Anemia is relatively rare in the United States (about 1 out of 136000 newborns), about 1 in 181 people are carriers of a Fanconi Anemia pathogenic variant [78]. Genes associated with FA include *BRCA2*, *PALB2*, FANCC, FANCG, FANCA, FANCF, and FANCM in the incidence of PC [7,8,79–85]. *PALB2* has the most research and evidence for the increased incidence of PC. Current NCCN guidelines place the absolute risk for FPC at 5–10% [8].

Recent research has illuminated the poorer prognoses and familial histories of cancer for PC patients with a germline *PALB2* variant. Borecka et al., [2016] found that mean age of onset for PC was significant lower for *PALB2* carriers than non-carriers (51 vs. 63 years) [86]. As a result, current screening guidelines for NCCN recommend PC screening beginning around age 50 or 10 years from the earliest onset in the family, while CAPS recommends screening at 45 years of age or 10 year earlier than age of onset for blood relative with PC [8,9]. Additionally, PC occurrence in *PALB2* carriers is highly associated in families with a prior history of PC and breast cancer [80,85,86]. However, there are still occurrences of sporadic PC in patients [16,86]. Therefore, screening should be done for patients with or without a family history of other cancers. Lastly, the upregulation of *PALB2* in PC patients is associated with poorer outpatient survival due to its potential impact on tumor cell migration and EMT signaling pathway-associated genes [85]. *PALB2* upregulation may be a critical prognostic and diagnostic marker for PDAC progression, and screening of these *PALB2*-mutation carriers could prove beneficial for PC identification and earlier treatment.

A variety of *PALB2* variants have been identified in PC cases. Many of these mutations are frameshift or nonsense mutations in Table 1, which is typical of tumor suppressor pathogenic variants [7,18,23,55,64,84,86,87]. Subsequently, more work is needed before any conclusions can be made.

4.8. Hereditary Pancreatitis (HP) genes

Hereditary pancreatitis is an autosomal dominant condition that typically begins around 20 [85]. It usually presents idiopathically, and for non-alcohol cases of pancreatitis, it accounts for approximately 8.7% of these cases [88,89]. Lowenfels et al., [1997] found the SIR of PC for people with HP to be around 53, with a cumulative risk of 40% by the age of 70 that successively increases over the age of 50 [90]. Therefore, HP is a rarer condition, but association of HP with PC development justifies an assessment of its genetic risk factors. The most common genes associated with pancreatitis and PC are *PRSS1*, *SPINK1*, and *CFTR* [88]. There is not enough data available on these genes to be able to draw accurate conclusions on PC development, but inferences can be drawn from the overall occurrence of HP prior to PC.

PRSS1's protein product is the serine-1 protease and cationic trypsinogen, which can be converted into cationic trypsin and is a major driver of acute and chronic pancreatitis. *PRSS1* is a fairly uncommon cause of HP (approximately 1%), so frequency identification in PC is difficult to ascertain [7]. The highest risk variants are c.86A > T (p.N29I) and c.365G > A (p.R122H), where the Arg-122 codon seems to be a mutational hotspot in the *PRSS1* gene [89].

SPINK1 is a trypsin inhibitor that is upregulated during pancreatic inflammation. The inhibitor acts upon trypsin and attempts to prevent autodigestion by the protease in pancreatic cells. A study found that 3.3% percent of the *SPINK1* group developed PC versus 0.99% non-*SPINK1* group ($p = 0.1$) [91]. The most common pathogenic variant is c.101A > G (p.N34S), but Muller et al., [2019] found that the p.N34S mutation was insufficient to cause PC without the influence of other genetic or environmental factors [91–93]. More work is needed to accurately identify the relationship between *SPINK1* and PC incidence through the mechanism of pancreatitis.

Lastly, *CFTR* (Cystic Fibrosis Transmembrane Receptor) is a protein found in epithelial cells of the pancreas that transfers chloride and bicarbonate ions between the apical side of the cell and the cell interior. Protein deficiency is associated with disease pathogenesis, including cystic fibrosis and pancreatitis [94]. Studies on *CFTR* variants and PC incidence demonstrated that most cases of PC with *CFTR* variants developed in patients who exhibited pancreatitis symptoms [95,96]. There is a large amount of common, mild *CFTR* variants, so it is difficult to identify some high-risk ones.

According to CAPS recommendations, screening of individuals with HP for PC should begin at 40 years of age or 20 years after pancreatitis onset, whichever comes first [9]. Considering that PC rarely develops in these mutants without pancreatitis development, this recommendation is reasonable. Therefore, screening at 40 years of age in patients with pancreatitis and variants in these genes would be beneficial to improving patients' outcomes.

4.9. Comparison with previous reviews

It is important to compare the work of this study with the reviews by Zhan et al., [2018] and Gentiluomo et al., [2022] [7,97]. In the review by Zhan et al., [2018], the study focused on primarily consolidating information on the common germline mutations and syndromes that are implicated in the development of PC [7]. The study also provides the pathogenic variants that have been noted in the literature as well, such as *BRCA2* c.5946delT [7]. Gentiluomo et al., [2022] follows a similar route with this study in that the

researchers provide some information on patient characteristics and highlight the more notable variants, but they also cover a wider range of conditions beyond hereditary syndromes by addressing high-risk loci and other genes [97]. In contrast, our study took a more in-depth approach on the phenotypic characteristics of the patients noted in the studies. This analysis provided the ability to compare the data with current PC screening guidelines to see if any updates can be made to improve patient outcomes, which did not occur in the other studies. Moreover, the study noted similar pathogenic variants and provided substantial future directions for researchers to focus on when trying to identify genotype-phenotype correlations. Lastly, the study also wants to make note that a more standardized protocol to reporting variants within genes and patient characteristics could help create more nuanced, personalized screening guidelines.

5. Conclusion

Overall, the influence of germline variants on PC development is extremely complex due to the various mechanisms by which these variants can cause carcinogenesis. Therefore, multi-gene panels are recommended for patients with any of these conditions or for patients with a family history of PC. These panels create a more specific understanding of the genetic risk of the proband to PC development and could guide more effective PC screening methods.

This study's original aim was to analyze literature to help identify genotype-phenotype correlations for variants, but more data is needed to complete this for these syndromes. This problem stemmed from the lack of information on the pathogenic variants found in the patients as many of the studies only stated the patients had mutations in a gene. As a result, this study attempted to highlight those variants that were focused on in the other literature. It would be extremely beneficial to reviewers if a standardized protocol could be used to report germline variants and phenotypes in all future literature when analyzing germline mutations in these PC-associated genes.

The screening conclusions made by this study have substantial overlap with the NCCN guidelines for PC screening of individuals in families with germline variants. Although this study finds that the NCCN guidelines are currently sufficient, the review intends to add certain items to consider when establishing screening guidelines for these variants. This study should help guide future research to help determine if more nuanced screening for certain genes, or potentially variants, is needed to optimize screening protocol for high-risk patients.

This study illuminates some of the high-risk syndromes and conditions that could lead to PC development. Further, it aims to provide information on the characteristics of the patients, such as their age or family history of other associated cancers, so there can be a more specific assessment of PC risk of known high-risk patients. Future work is needed to identify specific risks associated with specific germline mutations in each of the described genes. In addition, future perspectives should also focus on the possibility of specific variants and their potential treatment implications.

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