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Identifying pancreatic cancer patients for targeted treatment: the challenges and limitations of the current selection process and vision for the future

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Recent preclinical data have demonstrated that pancreatic adenocarcinoma (PDA) cells with defects in the Fanconi anemia/BRCA2 pathway are hypersensitive to interstrand crosslinking agents. The challenge is to efficiently identify patients who will benefit from these therapies. Patients were chosen for this study by evaluating personal history, ethnic background and family history of pancreatic malignancy. Molecular assays were performed on tissue samples. Patient A developed PDA in the context of a known BRCA2 frameshift mutation (2157delG), suspected because of her personal and multigenerational family history of breast cancer. She was treated with surgical resection, and targeted chemotherapy. Patient A continues to be disease free 32 months after her diagnosis and treatment. Patient B developed PDA in the context of a strong family history of PDA and Ashkenazi Jewish heritage. Genetic analysis on critical DNA repair genes revealed no alterations. This patient did not receive a tailored treatment regimen. This study highlights the challenge of treating PDA patients and selecting those eligible for targeted therapy. The current targeted treatment options for PDA are reviewed. A new multidisciplinary approach for stratifying PDA patients for promising targeted adjuvant therapy and familial risk counseling is proposed.

Keywords: BRCA2, PARP inhibitors, interstrand crosslinking agents, pancreatic ductal adenocarcinoma, familial pancreatic cancer, Fanconi anemia

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1. Introduction

Pancreatic adenocarcinoma (PDA) is often a fatal disease. Although patients are often aware that their family history is significant for pancreatic and other deadly cancers, the ideal management of individuals at increased risk of developing PDA remains an area of debate. Ideally, high-risk families should benefit from effective risk assessment, improved early detection methods as well as rational, targeted therapeutic options (**Table 1**). Unfortunately, most high-risk patients are not adequately identified or stratified for rational therapeutic strategies.

For both familial and sporadic forms of PDA, the only potential for cure is surgical resection, though it is estimated that no more than 20% of patients present

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with resectable disease [1]. As the data from Bilimoria *et al.* have revealed, less than 30% of patients with stage I tumors undergo resection in the US [2]. Even with successful, margin-negative surgical resection, only 15 – 40% of patients survive 5 years [1,3]. The addition of adjuvant chemotherapy, which typically consists of gemcitabine and/or 5-fluorouracil-based chemoradiation, adds minimal clinical benefit [4-6]. Other chemotherapeutic agents and immunologics are now being tested with and without gemcitabine, yet at present show limited improvement in outcome or clinical benefit.

Recently, the pancreatic cancer genome was sequenced, capping off two decades of intense work and providing us with an in-depth molecular understanding of pancreatic tumorigenesis for both sporadic and familial forms of this disease [4,5]. Hence, the next logical step is to translate the understanding of the altered and disrupted biochemical pathways in pancreatic cancer cells and the surrounding stromal cells for the benefit of patients with PDA and their families.

Familial aggregation and genetic susceptibility are thought to play a role in up to 10% of patients with PDA [6]. Although new candidate genes and chromosomal loci for familial PDA susceptibility have been discovered (most recently PALB2) [5], the genetic basis for most familial PDA remains unknown. Risk assessment in such families therefore relies on empiric data from registry-based studies. Software for Mendelian pancreatic (PancPro) cancer risk prediction is also available [7]. The identification of individuals at increased risk of developing pancreatic cancer is a first step towards the early detection and personalized treatment of this disease.

2. Identifying and targeting a defective pathway involved in pancreatic cancer

Several syndromes have been linked to PDA (**Table 1**). Stratifying subgroups of patients that fit into a 'syndrome' or inherited disorder is the first step to identifying a disrupted pathway that is unique to pancreatic cancer cells. For example, Fanconi anemia (FA) is a rare cancer syndrome caused by biallelic mutations in 1 of the 13 gene complementation groups in the FANC/BRCA pathway [8]. This pathway is responsible for the production of several proteins required for repair of DNA damage, specifically DNA interstrand cross-linking (ICL), double-stranded DNA breaks and stalled DNA replication forks [9].

The complementation group *FANCD1/BRCA2* is well studied because of the association of the *BRCA2* gene with hereditary breast and ovarian cancer [10]. Genetic alterations in the FANC/BRCA pathway are associated with a 5% lifetime risk of developing pancreatic cancer [11]. There is a growing body of literature documenting *BRCA2* mutations in families with PDA and a limited or even absent history of breast and ovarian cancer [12], suggesting that patients with familial pancreas cancer due to germ-line *BRCA2* mutations may not concurrently meet established criteria for hereditary breast and ovarian cancer syndrome. Yet, case series from multiple institutions have consistently documented pancreatic cancers among patients harboring germ-line *BRCA2* mutations. In fact, mutations in *BRCA2* account for approximately 7% of sporadic PDA cases and 12 – 17% of familial PDA cases [13-17]. These may be conservative estimates because the FANC genes (complement G, C, and N and not others) are not included in these percentages [17,18]. Moreover, pancreatic cancers have been shown to harbor a higher percentage of *FANC/BRCA* mutations than other solid tumors [17]. Of note, *BRCA1* and *BRCA2* mutations are responsible for only 5 – 15% of ovarian cancers [19-22] and only 1% of breast cancers [23].

3. Translating a pathway for targeted therapy

Identifying pancreatic cancers that are defective in the FANC/BRCA pathway has critical therapeutic implications. Previous *in vitro* and *in vivo* work has established that pancreatic cancer cells that have an endogenous disruption of the FANCC and FANCG genes (i.e., both artificial and natural models for FA-deficient pancreatic cancers) are more sensitive to ICL-forming agents, most notably platinum-based drugs [17,24,25]. Also, a new class of drug (PARP inhibitors) selectively inhibits poly(ADP-ribose) polymerase-1 (PARP), an enzyme required for the repair of DNA single-strand breaks [26-28]. These PARP inhibitors may prove to be an effective targeted treatment against pancreatic cancers that harbor mutations in the FANC/BRCA pathway [28-30].

Unfortunately, treatment with these targeted agents in other tumor systems is often complicated by disease relapse, and ultimately the development of drug resistance, as observed with Bcr-Abl inhibitors in chronic myeloid leukemia patients [31]. A recent study generated a naturally occurring BRCA2-deficient pancreatic cancer cell line resistant to both cisplatin and PARP inhibitors. Surprisingly, resistant clones were able to restore the wild-type *BRCA2* reading frame [32,33], most probably accounting for the fact that BRCA2 is the main target of PARP inhibitors and platinum-based drugs. These data strongly suggest that these agents are selectively targeting the genetic defect in *BRCA2*.

Taken together, there is strong rationale to suspect that incorporating platinum agents and PARP inhibitors into treatment strategies will have success against a selected group of pancreatic cancers deficient in the FANC/BRCA pathway. Theoretically, this approach would prove to be less systemically toxic than traditional chemotherapy, and at the same time specifically target the 'Achilles' heel' of the tumor cells. Although the need for FANC/BRCA tumor profiling continues to emerge, it should be noted that germ-line sequencing of *BRCA2* is often complicated by a large financial burden (because the commercially available testing is monopolized at present by Myriad Genetics, Salt Lake City, UT) and the fact that *BRCA2* is classically considered

Table 1. Genetic syndromes with inherited predisposition to pancreatic cancer and potential targeted therapy.

Syndrome/ disease	Gene(s)	Genetic testing considerations	Risk of pancreatic adenocarcinoma	Available targeted therapy/clinical correlates
Hereditary breast/ ovarian cancer syndrome (HBOCS)	*BRCA1* *BRCA2*	NCCN test criteria require personal or family history of breast and ovarian cancer	BRCA1: 2.26-fold [56] BRCA2: 3 – 9-fold [45]	Crosslinking chemotherapeutics (mitomycin C, cisplatin, chorambucil, melphalan) PARP inhibitors
Peutz-Jeghers syndrome (PJS)	*STK11* (*LKB1*)	Diagnosis of index case generally based on clinical findings/ working definition [57]	132-fold; lifetime risk ~ 36% [58]	Reports of a PJS-associated cancer with loss of the wild-type STK11/LKB1 allele together with a germ-line mutation in the other allele. Some sporadic PDAs show somatic mutations of LKB1 [59]
Hereditary pancreatitis	*PRSS1*, *SPINK1*, *CFTR*, *CTRC*	Testing guidelines based on symptoms, with or without family history of pancreatitis [60]	50 – 67-fold; lifetime risk 44% [61,62]	Tumor susceptibility presumably due to mitogenic stimulation and clonal outgrowth of PDA cells as part of the normal healing responses that occur subsequent to repeated rounds of tissue destruction [62]
FAMM melanoma syndrome	*CDKN2A/p16*	Germ-line p16 mutations documented patients/families with multiple melanomas	13 – 39-fold [45]	Somatic p16 alterations identified in 80% of PDAs [63]
HNPCC-Lynch syndrome	*MLH1*, *MSH2*, *MSH6* and *PMS2*	Bethesda Guidelines (tumor MSI/ IHC) and Amsterdam Clinical Criteria II (mismatch repair germ-line studies)	< 5-fold [45]	MSI-H pancreatic cancer may have a better prognosis after resection, possibly owing to intensive immunoreaction to the tumor [64]
Familial adenomatous polyposis (FAP)	*APC*	APC considered in individuals with 20 or more colon adenomas	Relative risk 4.46 [65] Lifetime risk ~ 2% [66]	Some theorize that pancreaticobiliary secretions affect the development of adenomas and cancer in this area [67]
Cystic fibrosis (CF)	*CFTR*	Genotyping identifies patients with class IV and V mutations, which are likely to represent those with a functioning pancreas susceptible to inflammation [68]	Relative risk 5.3 [69]	Modifier genes or environmental factors may be important in stratifying risk, that is, mucin genes involved in both CF and PDA [70]

MSI: Microsatellite instability (H: High frequency); NCCN: National Comprehensive Cancer Network; PARP: Poly (ADP-ribose) polymerase; PDA: Pancreatic ductal adenocarcinoma.

a breast-ovarian cancer gene. Further, intensive studies sorting through the entire FANC/BRCA pathway in BRCA2 wild-type tumors that appear to have the BRCA phenotype are cumbersome at present, but may become more robust as sequencing technologies become more facile and economical.

The two case studies presented here provide examples of real-life attempts to utilize a multidisciplinary approach for stratifying pancreatic cancer patients for targeted therapy using genetic and family history data. The purpose of this paper is to evaluate a current strategy for stratifying patients for personalized therapy and to propose a broad step-wise approach to identify successfully and treat a subset of pancreatic cancer patients. As early detection assays and targeted therapies rapidly emerge from experimental settings, now is the time to coordinate multidisciplinary teams that consist of

Table 2. Specific genetic mutations of FANC/BRCA previously found in patients and screened for in our patient samples.

Gene	Found in PDA	Sensitive to MMC and platinums	Sequenced (WT/Mut)	Ref.
FANC C	Yes	Yes	Mut/LOH	[18]
FANC G	Yes	Yes	Homozygous deletion	[18]
BRCA2	Yes	Yes	7% Sporadic, 17% FPC	[14,16]

MMC: Mitomycin C; Mut: Mutation; PDA: Pancreatic ductal adenocarcinoma; WT: Wild type.

molecular geneticists, molecular biologists, clinicians and genetic counselors, all with the common goal of providing optimal patient care.

4. Example of two case studies

Two patients were chosen for illustrative purposes based on family history and ethnic background. The purpose of the presentation of these patients is to provide *real-life* examples of the current treatment limitations and to highlight the potential benefits of targeted treatment approaches for pancreatic cancer. In full disclosure, the authors admit to the technical and sample limitations they had with these two patients; and, thus, the speculative data that are presented herein. At the time of surgery, the patients' tumor samples were collected and placed in growth media for cell culture, as is the routine for all resected pancreatic tumors at Thomas Jefferson, based on an IRB-approved informed consent for the banking process. Cell lines were temporarily maintained. Genomic DNA, mRNA and protein were extracted from the cells. DNA was also isolated from laser capture microdissected (LCM) material of patient A's tongue and endometrial cancers. Polymerase chain reaction (PCR) amplification of the specified gene and direct genetic sequencing were performed as described previously [34] to investigate potential mutations or deficiencies in the FANC/BRCA pathway known to be associated with pancreatic cancer (**Table 2**).

4.1 Patient A

At the time of presentation, patient A was a 71-year-old female who was referred to the institution with the incidental finding of a 1.5 cm pancreatic body mass discovered at an outside hospital on CT imaging for cancer follow-up. She had a past medical history significant for breast cancer, endometrial cancer (following tamoxifen treatment), tongue cancer, diabetes mellitus and hypertension. She had previously undergone bilateral mastectomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, and a partial glossectomy with a right neck dissection. The patient's family history (**Figure 1**) was significant for four generations of breast cancer, with at least three relatives also harboring the familial *BRCA2* mutation (2157delgG). At the time of presentation the patient had an elevated CA 19-9 level of 191 (normal < 37 U/ml).

4.2 Patient B

Patient B presented to the authors' institution at 50 years of age with a 6 cm pancreatic body mass that was found during a work-up at an outside hospital for vague pelvic pain. The CT scan performed at this time also revealed hepatic metastases limited to segments II and III of the liver. The patient had elevated serum levels of CEA, CA 19-9 and CA 125 (69.6, 962 and 69, respectively). Before presentation at the institution, the patient underwent endoscopic ultrasound and fine needle aspiration of her pancreatic mass, which confirmed poorly differentiated pancreatic adenocarcinoma. She then received chemotherapy at an outside institution with both gemcitabine and erlotinib. Her personal medical history was otherwise non-contributory, although her ethnicity was Askenazi Jewish.

Relevant family history (**Figure 2**) includes her father who died from pancreatic cancer at age 70 and a paternal uncle who also died of pancreatic cancer after undergoing a Whipple procedure. Germ-line BRCA1/2 studies were not informative in this patient as she did not carry any of the three BRCA1/2 Ashkenazi Jewish founder mutations (i.e., 187delAG and 5385insC in BRCA1 and 6174delT in BRCA2). Interestingly, there was a distant family history of recurrent pancreatitis, with one relative determined to have a new *PRSS1* variant, C185Y within exon 4 of the gene. At the current time this family member has not developed PDA.

5. Results and clinical course (Table 3)

5.1 Patient A

Tissue samples from the patient's previously resected tongue and endometrial tumors were obtained, microdissected (LCM) and sequenced for the specific germ-line mutation detected by Myriad (Salt Lake City, UT). These samples were then compared with the sequences of her blood leukocytes, normal tissue and her resected PDA (**Figure 3**). The *BRCA2* mutation (2157delG) was documented in all samples. This sequence is responsible for an early stop codon at amino acid position 659 of the BRCA2 protein, and has been reported in many other families [35,36]. However, there was no evidence of loss of heterozygosity (LOH) at the site of the mutation (sequence analysis showed heterozygosity at the site of the mutation) in any of the microdissected lesions, suggesting that most probably another mechanism is responsible for the silencing of the wild-type *BRCA2* allele in the PDA tumor cells; however, other possibilities do exist.

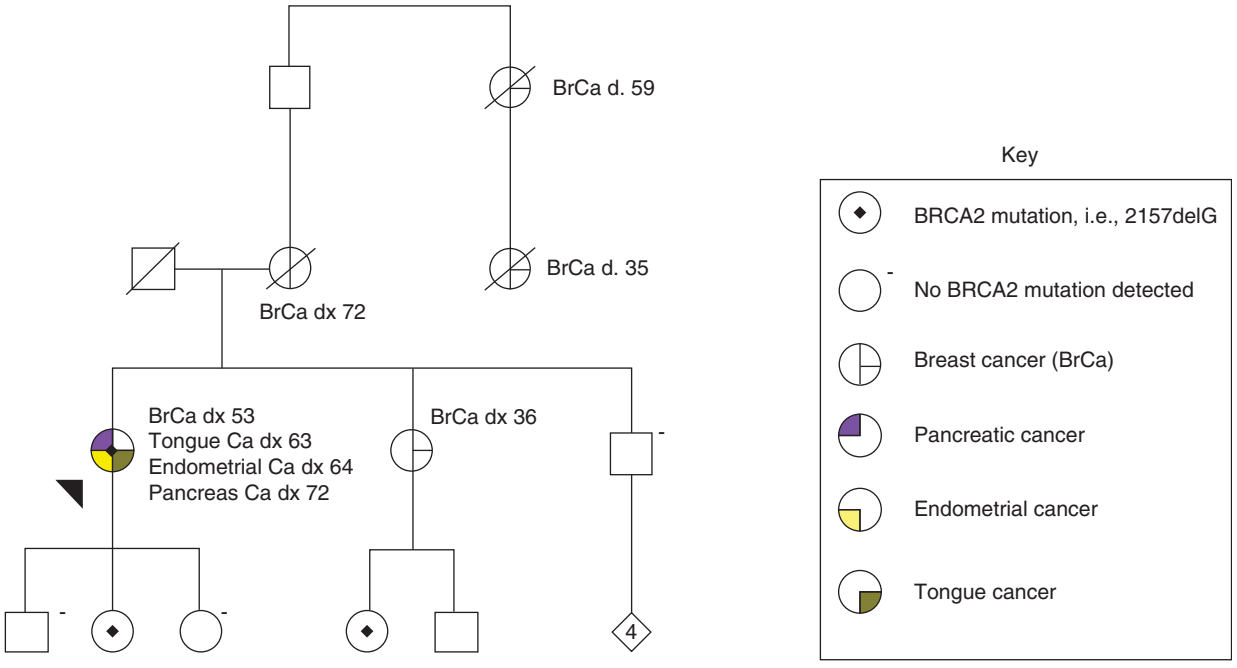

Figure 1. Family tree of patient A.

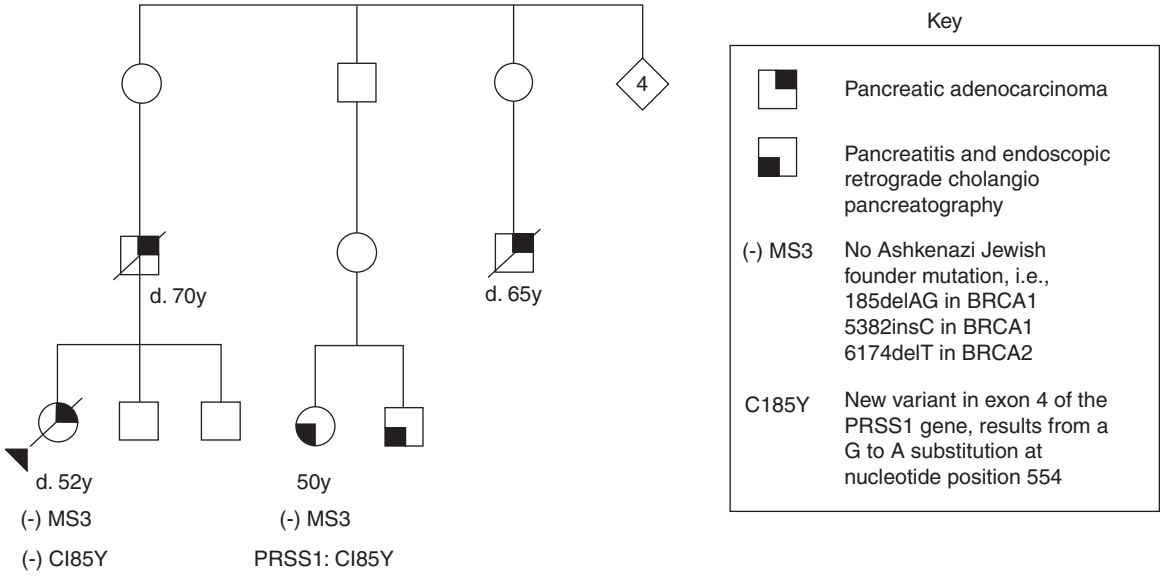

Figure 2. Family tree of patient B.

Three weeks after presentation, patient A underwent a distal pancreatectomy and splenectomy. Her final pathology revealed a pancreatic ductal adenocarcinoma, 1.5 cm in size, which was resected margin negative (T3N0M0), stage IIa. She was treated with tailored adjuvant therapy that included gemcitabine and cisplatin, in addition to capecitabine-based chemoradiation. She is now disease free 32 months from surgery. At risk family members were encouraged to participate in pancreatic surveillance protocols and counseled to avoid exposure to known risk factors, such as smoking, environmental tobacco exposure, occupational asbestos and residential radon [37].

5.2 Patient B

Genetic analysis was performed on multiple candidate genes that are known to have a higher prevalence in the Ashkenazi Jewish population, including *BLOOM*, *FANCC*, *FANCA* and *BRCA2*. No genetic mutations were discovered (data not

Table 3. Patient data – medical history, family history, presentation, treatment and molecular studies performed on tumor samples.

	Medical history	Family history	Presentation	Treatment	Molecular studies	Patient status
Patient A	Breast, endometrial and tongue cancers BRCA2 mutant	Four generations breast cancer Three BRCA2 mutants	1.5 cm isolated pancreatic body mass	Distal pancreatectomy/ splenectomy (T3N0M0) Gemcitabine/cisplatin, capecitabine, radiation	All tumors microdissected and sequenced – found to harbor same BRCA2 mutation (2157delG- early stop codon) No LOH	Disease free 32 months from surgery
Patient B	Ashkenazi Jew BRCA1/2 wild type	Father and cousin died from pancreatic cancer Cousin – PRSS1 mutation	6 cm pancreatic body mass Liver metastases	Unresectable disease NA	Cell line generated Genetic analysis on several critical DNA repair genes (*BLOOM*, *FANCC*, *BRCA2* and *FANCA*) – no obvious alterations FANCA gene – markedly reduced protein/mRNA expression	Deceased

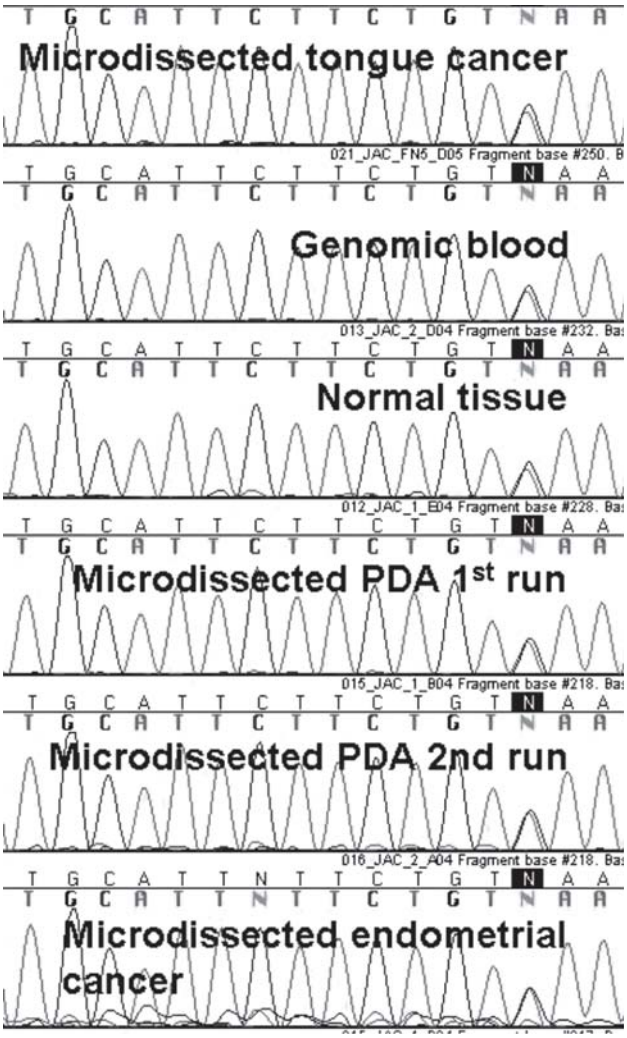

Figure 3. BRCA2 gene sequence – patient A. Laser captive microscopy tumor samples from each tumor indicated were used as material for genomic DNA extraction and template for PCR and then direct sequencing of the *BRCA2* gene. The data indicate that the 2157 delG mutation was present in all samples. Note that loss of heterozygosity was not observed at these sites with direct sequencing, thus inactivation of the other allele is most probably due to an alternative mechanism. 1st and 2nd run refer to two separate LCM samples run as templates for PCR amplification and then sequenced.

shown). Although patient B did not have a history of pancreatitis, she was also tested for the C185Y variant found in her cousin and determined to be wild type for this variant, suggesting it may not segregate with the PDA in this family. However, this cousin is now being monitored for the development of PDA.

After counseling and consent, the patient was taken to the operating room in the hope of performing a resection of her primary tumor via distal pancreatectomy, as well as hepatic cytoreduction via a left lateral segmentectomy. Unfortunately she was found to have significant tumor burden with metastatic disease and omental implants. Surgical palliation was limited to an intraoperative celiac nerve block using 50% alcohol. The patient died within 12 months of her initial diagnosis.

For the purposes of familial risk counseling, she was determined to have a 92.2% likelihood of harboring a pancreas cancer susceptibility mutation using the PancPro model [7]. Each of her siblings was therefore quoted an 11.5% lifetime risk of developing PDA, with registry-based clinical and research surveillance protocols encouraged.

6. A proposed model for screening to stratify familial pancreatic cancer patients for targeted therapies

Based on the authors' experience and the fact that so far no reliable clinical test has been developed to stratify familial pancreatic cancer patients for targeted therapy, the following step-wise approach is proposed (**Figure** 4). First, any patients, based on family history, who qualify as having the familial form of pancreatic cancer should go through a systematic screening process. Such a strategy should include the following screening items: i) genomic DNA of patients with a history of *BRCA2* mutations in their families will be sent for sequencing to Myriad Genetics (Salt Lake City, UT); ii) patients with at least two or more relatives who have been diagnosed with pancreatic, ovarian, or breast cancers will be screened by a molecular assay that the authors and others are developing (see section 7); and iii) any suspicious genes discovered in the assay will allow us to move to the next step of direct sequencing of the specific gene(s) (e.g., *PALB2*, *BRCA2*, *FANC* and *FANCG*). Recently, a newly described gene, *FANCN/PALB2*, was directly linked to familial pancreatic cancer and the protein is a binding partner of *BRCA2* [5]. *PALB2* should be included in the screening process, because in theory tumors mutated in *PALB2* will be sensitive to a targeted therapeutic strategy. Templates used to screen include patients' primary tumors surgically excised and processed, as described in section 5. Alternatively, both xenografted primary tumors that have been surgically excised and constitutional DNA from patient blood samples can be utilized to confirm genetic abnormalities, although these methods may not be as informative for expression-based studies. Ultimately, this strategy demands diverse expertise that comes from a team effort (**Figure** 4) with the shared goal of identifying candidate patients for rationale therapy. In a parallel yet separate project, Thomas Jefferson University and the Jefferson Pancreas, Biliary and Related Cancer Center have recently established the Jefferson Pancreas Tumor Registry. This registry will serve as a resource for identified patients and their families.

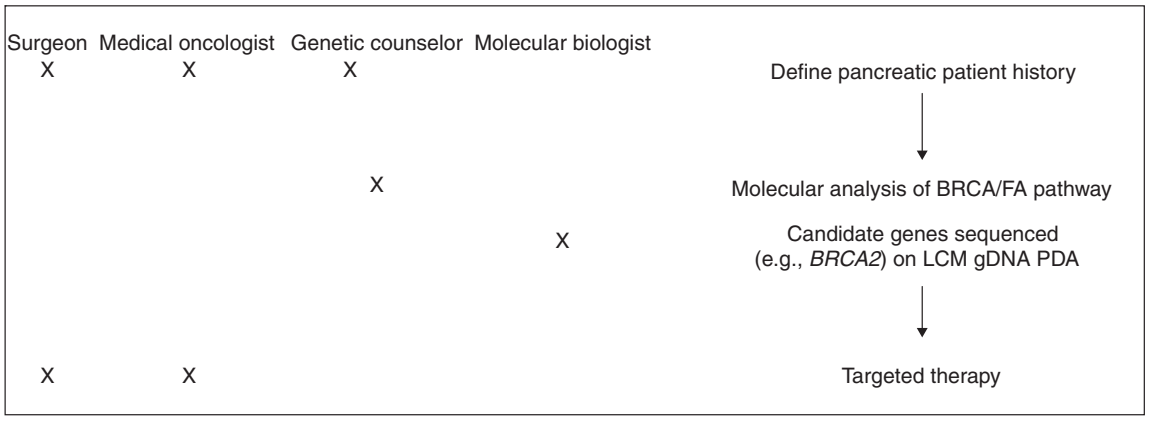

Figure 4. Proposed step-wise approach to identify and treat a subset of pancreatic patients that includes surgeons, medical oncologists, genetic counselors, pathologists, and molecular biologists.

7. Expert opinion

In this perspective, two patients were presented that the authors attempted to stratify for optimal treatment based on their individual family histories and the molecular evaluation of their tumors (**Table 3**). The purpose of these case presentations and subsequent treatment strategies was to demonstrate the limitations and challenges that exist at present in the treatment of this disease. Currently, there exist robust models of genotype-based anticancer therapy: i) imatinib for the treatment of chronic myeloid leukemia with the *bcr-abl* translocation; ii) gefitinib for the treatment of non-small-cell lung cancers found to have *EGFR* mutations [38]; and iii) the use of Herceptin as first-line therapy in Her2-positive breast cancer patients regardless of age or previous adjuvant therapy. Also relevant to this editorial is the recent release of promising data from an early phase trial of a PARP inhibitor in patients (mostly ovarian and breast cancer patients) who carry BRCA mutations [26].

Further, an extensive number of *in vitro* and *in vivo* studies have shown that pancreatic cancer cells with mutations in the FANC/BRCA pathway are more sensitive to targeted agents, specifically ICL agents and more recently PARP inhibitors [9,17,24,25,27-30,39]. Unlike most preclinical pharmacogenomic models, the hypersensitivity of FANC/BRCA-deficient cells to ICL agents (and also PARP inhibitors) [27] remains consistent throughout multiple preclinical models [40]. Rigorous studies to depict the clinical relevance of genetic variants in such targeted genes as *BRCA2* have already been performed [41] and future studies should continue to explore drug–gene variant relationships. Thus, the overwhelming preclinical work from multiple laboratories and studies warrants the need for more efficient ways to identify these patients. Recently, another BRCA2-related gene was shown to be commonly disrupted in familial pancreatic cancer (*PALB2*) [5]. Functionally, this finding is significant because *FANCN/PALB2* is linked to the FANC/BRCA pathway and increases the percentage of familial pancreatic cancers most probably defective in this pathway. Future work will reveal whether mutations in *PALB2* will have the same therapeutic significance as *BRCA2* and related *FANC* genes.

Two aspects of this targeted approach that need to be addressed in the future are genetic heterogeneity within a tumor and resistance to therapy. Theoretically, functional defects in genome maintenance genes would appear to be a gateway for further mutational and clonal events. Thus, therapeutically targeting this pathway appears logical, except when accounting for genetic resistance mechanisms such as restoration of BRCA2 mutations [35]. Specifically, the Achilles' heel of the tumor (i.e., BRACA2) can also be responsible for altering the therapeutic target and thus creating tumor cells resistant to a targeted treatment strategy [32,42]. In response to this concept, recent work has shown that the concept of 'synthetic lethality' could essentially slow down this resistance mechanism in tumor cells [43]. For example, platinum-based therapy followed by a PARP inhibition strategy or vice versa could inhibit such a resistance mechanism.

Familial risk assessment for pancreatic cancer, as it occurs in the context of well-recognized syndromes, has implications beyond therapeutic strategies and into the arenas of pre-symptomatic susceptibility testing and endoscopic surveillance. Although stratifying patients based on family history is a logical and important start, efficient screening methods aimed at identifying early pancreatic neoplasia are needed, so that the disease can be detected when it is most treatable (i.e., resectable) [44,45].

In 2007, Brand *et al.* published a review on the advances in counseling and surveillance for patients deemed to be at high risk for developing pancreatic cancer (> 10-fold increased risk or considered to be high risk based on expert opinion) [45]. There is no commonly accepted set of criteria for exactly which patients should be screened and sent for genetic testing, what screening methods are best or at what age screening should begin in these selected patients [46]. The most

commonly used and studied screening method is endoscopic ultrasound (EUS) with pancreatic juice sampling [44,46-50]. Other methods include the use of endoscopic retrograde cholangiopancreatography, CT scans and MRI/magnetic resonance cholangiopancreatography (MRCP) (please refer to this citation for a more extensive discussion about this topic) [46]. Classically the decision on when to begin screening is based on the recommendations for colon cancer screening: starting at age 50 years, or 10 years earlier than the earliest age of onset of colon cancer in the family [45]. A recent study published by McFaul *et al*. on anticipation in familial pancreatic cancer has caused many to recommend starting screening even earlier, at age 45, or 15 years earlier than the earliest occurrence of pancreatic cancer in the family [51]. A positive smoking background has been shown to decrease significantly the age of onset of pancreatic cancer, and this should be factored into the timing of the first screen as well [52,53].

Both cases presented in this paper stress the importance of early detection in order to utilize targeted therapy. Patient A presented with a localized pancreatic tumor that was completely resectable. Unfortunately, patient B presented late into her disease course. Her tumor prototype represents a possible new candidate gene in the FANC/BRCA pathway in PDA (although the FANCN/PALB2 gene was not sequenced at the time of this study). Owing to her late diagnosis and an unidentifiable gene defect, she was unable to benefit from surgical and targeted therapy. Her case highlights the need for an assay to detect a disruption in the FANC/BRCA pathway. Such a diagnostic test would complement patient medical history and provide scientific rationale for an individualized targeted treatment strategy (**Figure 4**). Promising approaches to develop this clinical assay are now being pursued and have been proposed by others. For example, an *ex vivo* FANCD2 or RAD51 foci formation assay with a reliable BRCA2 immunohistochemisty test could rapidly decipher whether patients' tumors are defective in this pathway. Further, more exquisite strategies such as a preoperative dose of a targeted therapy and then subsequently analyzing for PARP or other related enzyme activity in patients' tumor cells may help to stratify patients for selective therapies. Recent evidence has demonstrated that *PTEN* status may be relevant for this line of targeted therapy as well [54].

Several anecdotal case histories and recent reports of success in early phase PARP inhibitor studies of selected patients in breast and ovarian cancers support this notion to stratify pancreatic patients for this targeted therapy [26]. Chalasani *et al*. recently reported the case of a patient who presented with metastatic pancreatic cancer and a family history significant for multigenerational breast cancer; she was determined to harbor a germ-line *BRCA2* mutation. Although she eventually succumbed to her disease, the patient had a significant response to mitomycin C [55], supporting the need for further research and clinical trials in this area. The two patients presented here also represent real-life examples of how using a targeted approach to the treatment of PDA might be undertaken, and also highlight the need for a consensus strategy for identifying, counseling and screening for high-risk individuals.

As we enter a modern era of medicine, undoubtedly new targeted and rational strategies will emerge (**Table 1**). These case studies highlight several obstacles that will be faced as an attempt is made to transition into personalized therapy for pancreatic cancer. First, as experimental findings unravel new 'druggable' pathways in subsets of PDA patients, reliable clinical tests need to be developed in order to identify these patients. Second, institutions and scientists need to focus on treating subgroups of patients instead of putting resources into finding one cure for one tumor type. Third, truly to break drug resistance, targeting multiple genes and pathways within a patient population will need to be focused on. Finally, surgeons, oncologists, clinical genetics professionals and molecular biologists need to organize now and communicate in order to begin to stratify patients for promising treatment strategies (**Figure 4**). We appear to be on the threshold of a new era in the rational management of pancreatic cancer patients.

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Declaration of interest

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