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ABOUT COVER

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WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, *etc*. The current columns of *WJGO* include editorial, frontier, field of vision, review, original articles, case report.

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ORIGINAL ARTICLE

Retrospective Study

Identification of patients with pancreatic adenocarcinoma due to inheritable mutation: Challenges of daily clinical practice

Alexander JP Fulton, Angela Lamarca, Christina Nuttall, Lynne McCallum, Rille Pihlak, Derek O'Reilly, Fiona Lalloo, Mairéad G McNamara, Richard A Hubner, Tara Clancy, Juan W Valle

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Abstract

BACKGROUND

Identification of germ-line mutations in pancreatic ductal adenocarcinoma (PDAC) could impact on patient/family.

AIM

To assess the referral pathways for genetic consultations in PDAC.

METHODS

Electronic records of PDAC patients were reviewed retrospectively. Patients eligible for genetic consultation referral were identified following the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) criteria.

RESULTS

Four-hundred patients were eligible. Of 113 patients (28.3%) meeting EUROPAC criteria, 8.8% were referred for genetic opinion. Germ-line mutations were identified in 0.75% of the whole population.

CONCLUSION

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Earlier referrals and increased awareness may be able to overcome the low rate of successful genetic appointments.

Key words: Genetic counselling; Pancreatic adenocarcinoma; Genetic consultation; BRCA; Germline

Core tip: Electronic records of consecutive patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) were reviewed retrospectively. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) criteria were employed to identify patients eligible for genetic consultation referral. Out of 400 eligible patients, 113 (28.3% of the whole population) met referral criteria, only 10 (8.8%) were referred for genetic opinion. There was a low referral rate even for patients fulfilling EUROPAC criteria and a significant number of patients did not attend the consultation due to deteriorating performance status. Earlier referral, and increased awareness may optimise genetic services referral for patients with PDAC.

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INTRODUCTION

The most common form of pancreatic malignancy is pancreatic ductal adenocarcinoma (PDAC), with a 1 in 100 lifetime risk within the general population (up to age 75)[1]. The diagnosis of PDAC is associated with poor survival; 1-year and 5-year survival rates are 20% and 3%, respectively[2], despite surgical intervention and the implementation of chemotherapeutic guidelines outlined by the international experts groups such as the European Society for Medical Oncology (ESMO)[3]. Currently, curative resection and adjuvant chemotherapy with gemcitabine and capecitabine[4,5] or modified-FOLFIRINOX (combined therapy of oxaliplatin, irinotecan, and 5-fluorouracil (5-FU)[6]) is considered standard of care treatment for resectable disease stages; however risk of relapse remains high (66%-92% develop recurrent disease within 2 years)[3]. In the palliative setting, gemcitabine-based treatments or FOLFIRINOX are considered standard options of treatment[3].

Although most cases of PDAC are sporadic (related to non-heritable modifiable risk factors such as smoking, alcohol and pancreatitis[3,7]), a small percentage of cases will arise in the context of a hereditary aberration[8-11], such as germ-line Breast cancer gene (*BRCA1/2*) mutation (reported to be present in around 1% to 4.6% of patients with pancreatic cancer[3,12,13]; higher in other series[14]). The prevalence of *BRCA1/2* mutations in the general population is approximately 1 in 400, two thirds of which are *BRCA2*[15]. Therefore, *BRCA2* mutation is the commonest inherited predisposition for the development of PDAC[16]. A number of other germ-line mutations such as PALB2, CDKN2A, ATM, p53 and mismatch repair genes (MLH1, MSH2, MSH6) are known to also predispose an individual to develop PDAC[17,18]. Germline mutations in these genes are relatively rare[19]; however, when present, they commonly have high penetrance. For example, a germline mutation in CDKN2A confers a 38-fold increased risk of developing PDAC compared to the general population[20,21].

Detection of patients harbouring a germ-line mutation predisposing them to PDAC is initiated by establishing the patients' prior personal history and family history of malignancy, which triggers a referral to genetic services[22]. Approximately 10%-20% of patients diagnosed with PDAC report a prior personal history of cancer or family history of cancer[11,13], requiring a genetic consultation. Previous studies have shown that there is a significant association between presence of germ-line mutation and personal/family history of breast (10.7% of patient with personal/family history of breast cancer were found to have a germ-line mutation *vs* 2.1% of patient without personal/family history of breast cancer who were identified to have a germ-line

aberration; *P*-value < 0.001) and colorectal (11.1% *vs* 2.8%; *P*-value 0.002) cancer[11]. A different study identified an even higher percentage of patients with germ-line mutations (15.1%)[23]. Therefore, when this "selected" population is analysed, around 10%-15% of patients (*i.e.*, 1%-3% of the whole PDAC population)[11,12] are expected to harbour a germ-line mutation which explains the increased predisposition to PDAC. Unfortunately, identification of this patient population remains challenging for clinicians in daily clinical practice and having reliable criteria should help capturing all patients who require referral for genetic opinion.

The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) published research guidelines for the identification of patients with a potential germ-line mutation who should be referred for genetic consultation (Table 1)[24]. The EUROPAC guidelines have thus far not been implemented in the genetic service diagnostic setting; however they have been agreed at an international level in the research setting. A number of alternative referral guidelines exist even though they have not been extensively evaluated in clinical trial settings. Inter-guideline variation is significant and produces heterogeneity in referral practice. The National Comprehensive Cancer Network (NCCN) guidelines recommend BRCA testing for selected PDAC patients[25]. These include PDAC patients with a first, second or third degree relative with ovarian carcinoma; breast cancer diagnosed under 50 years old; two relatives with breast, pancreatic or prostate cancer at any age or any patient with PDAC and Ashkenazi Jewish ancestry. Additionally, guidelines have also been published by the American College of Gastroenterology (ACG)[26]. Recently, the National Institute for Health and Care Excellence (NICE) guidelines (United Kingdom) have also been updated and provide guidance on this issue[27].

An alternative approach would be to test for germ-line mutations in "non-selected" populations (*i.e.*, when patients are analysed regardless of personal or family history of cancer). When such strategy is pursued, rate of patients identified to have a germ-line aberration may increase up to 3.9%-4.6% out of the whole PDAC population[13,28,29]. Despite this, current clinical practice still relies on analysis of "selected" patients, since this is considered a more cost/effective approach. Genetic testing is only advocated in "non-selected" patients if a mutation rate of 10% or greater exists[30]. Thus, "non-selected" approach in PDAC remains investigational only. In addition, higher mutation rates have also been detected in "selected" and "non-selected" groups in the research setting when broader gene panels testing have been implemented[31-33], however the clinical utility of such mutations is still unclear.

This study aimed to explore the rate of appropriate referrals for a genetic consultation in patients diagnosed with PDAC and the outcome of such referrals in current daily oncology clinical practice. We aimed to identify challenges and potential solutions.

MATERIAL AND METHODS

The study set out to review 400 consecutive patients diagnosed with PDAC. Eligible patients were those diagnosed with PDAC who were seen at The Christie NHS Foundation Trust (Manchester, United Kingdom) between September 2012 and December 2015. Patients with pancreatic malignancies other than PDAC (*e.g.*, neuroendocrine tumours) or with other malignancies arising from the hepato-pancreato-biliary tract were excluded. This study was approved by The Christie NHS Foundation Trust Audit Committee (CE15/1575).

Selection of patients and data collection

Patients were identified through electronic records. Electronic case notes were reviewed retrospectively for data including demographics, diagnosis and treatment. Comorbidities were collected following the Adult Co-morbidity Evaluation (ACE-27) criteria[34]. The focus was on reviewing patient's previous personal malignancy history and family history in order to assess the presence of risk factors[3,7] for PDAC (including personal and family history of cancer) and the percentage of patients meeting criteria for referral for genetic counselling (applying the EUROPAC criteria[35], Table 1). In addition, outcome from such referrals and details regarding other known risk factors, such as smoking or diabetes were collected. Excess alcohol intake was defined as patients having a notation of "excess alcohol intake" in their electronic notes, or having consumed greater than the recommended amount of units in the 2010-2015 United Kingdom guidelines[36]. It was aimed to establish the proportion of patients fulfilling the EUROPAC criteria that were referred to the regional clinical genetics service, and subsequent testing if deemed appropriate. Information on whether the patient had been referred to the genetic service and the

Table 1 European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer criteria[24]

EUROPAC criteria	
Criterion 1	≥ 2 first-degree relatives with pancreatic cancer
Criterion 2	≥ 3 relatives with pancreatic cancer
Criterion 3	Possible associated cancer syndrome (defined as sub-criteria below) in addition to the case of pancreatic cancer being studied
Criterion 3.a: BRCA1/2	Personal/family history (≥ 1 first/second-degree relatives) of breast/ovarian cancer
Criterion 3.b: Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome	Personal/family history of melanoma in ≥ 1 first/second degree relative AND a high total body naevi count (often > 50)
Criterion 3.c: Lynch syndrome	Personal/family history (≥ 1 first/second-degree relatives) of a Lynch syndrome-associated cancer (such as colorectal, endometrial, small bowel, renal)
Criterion 3.d: Peutz-Jeghers syndrome	Oral/mucous membrane pigmentation +/- a personal/family history (≥ 1 first/second-degree relatives) of gastrointestinal cancers in first/second degree relatives

EUROPAC: European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer.

outcome of such referrals was retrieved.

Study objectives

The primary objectives of this study were to assess the appropriateness of referral to genetic services in patients diagnosed with PDAC, and to assess the current referral practice for identification of potential areas of improvement. The primary end-point was the percentage of patients meeting the EUROPAC criteria referred for genetic counselling. Secondary objectives included the frequency of genetic aberration identified and the characteristics of such populations, together with the frequency of any other modifiable risk factors.

Statistical analysis

Although a formal sample size calculation was not performed for this study, and based on the fact that an infrequent event was been explored (this study was targeting "selected" population, thus 10%-20% of patients would be expected to meet referral criteria; but only around 1% out of the whole population would be expected to be identified a germ-line mutation), a target sample of 400 patients was pre-specified in order to secure enough patient representation. Statistical analysis was carried out using GraphPad Prism and Stata v.12 packages. Frequency tables for each of the variables were created. Continuous variables were analysed by calculating median and range/95% confidence intervals (95%CI). The characteristics of the population of patients meeting the EUROPAC criteria were compared to the cohort of patients who did not meet such criteria: univariate analysis (χ^2 or *t*-test as appropriate according to the type of variable) and multivariable analysis (logistic regression) were performed; variables with P-value < 0.05 in the univariate analysis were included in the multivariable analysis.

RESULTS

In order to identify 400 eligible patients for our analysis, a total of 408 patients were screened; the commonest reason for exclusion was the presence of histological entity other than adenocarcinoma (Figure 1).

Patient demographics

Of the 400 patients in the study, 206 (51.5%) patients were male and 194 (48.5%) were female, with a median age of 67.7 years (range 29.9-94.2). Out of the 400 patients, 338 (84.5%) were referred for consideration of systemic chemotherapy with palliative intent: 230 (57.5% of the 400) went on to receive palliative chemotherapy, of which 94 (40.9%) received gemcitabine single agent (Table 2).

Non-hereditary risk factors for PDAC

A total of 233 patients (74.9%) had a history of alcohol consumption, with 33 of these (14.2%) having a documented history of "excess" alcohol consumption. One-hundred and eighty-seven patients (55.8%) had a personal history of smoking, and 71 patients

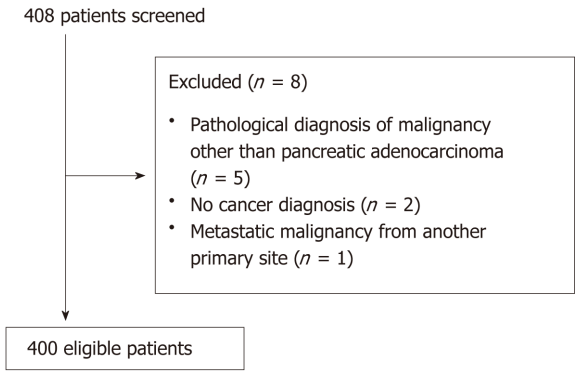

Figure 1 Pancreatic Ductal Adenocarcinoma patient selection flow diagram: A total of 408 patients were screened; 400 patients were eligible. Six patients were excluded due to having diagnoses of other malignancies other than Pancreatic Ductal Adenocarcinoma; the remaining 2 patients excluded did not have a confirmed malignancy and were therefore excluded. *n*: Number of patients.

(21.2%) were active smokers. Additionally, 103 patients had a previous diagnosis of type 2 diabetes mellitus (25.9%). Other risk factors are summarised in Table 3.

Hereditary risk factors; EUROPAC criteria and referrals according to such criteria

Out of the whole population of patients included, 202 patients (50.5%) had a family history of any cancer and 113 (28.3% of patients from the whole population; 33.8% of patients from those 334 who had information regarding family history available) had a prior history of cancer or family history of cancer meeting the EUROPAC referral criteria (Table 4). Of the 113 patients meeting the EUROPAC criteria (as defined in Table 1), 60 patients met criteria 3.a for *BRCA 1/2* testing (53.10%) followed by criteria 3.c (29 patients; 25.7%), criteria 3.d (12 patients; 10.6%), criteria 1 (10 patients; 8.8%) and criteria 3.b (2 patients; 1.8%). Family history of cancer was not recorded in the patient's case notes for 66 of the 400 patients (16.5%).

Only 10 of the 113 patients (8.8%) meeting the referral criteria were referred to the regional genetic service. Moreover, only 4 of these 10 patients referred (40%) were ultimately seen by the genetics team, with one patient identified as having a *BRCA2* mutation identified through this pathway (Figure 2).

A total of 103 patients met the EUROPAC criteria but were not referred. Most of these patients (97 out of 103) attended for palliative chemotherapy and 59 started chemotherapy. Performance status for this subpopulation of patients was poor: ECOG PS2 (22.3%) and PS3 (13.6%). Fifty-three of the 103 patients had a history of smoking, whilst 71 (68.9%) had a history of alcohol consumption.

Factors associated with patients fulfilling the EUROPAC referral criteria

Characteristics of those patients who did and did not meet the EUROPAC criteria were compared (Tables 5 and 6) using univariate analysis. The following characteristics were statistically significant predictors of fulfilling the EUROPAC criteria in the univariate analysis and were therefore included in the multivariable logistic regression: patient gender (*P*-value 0.0041), comorbidity scale (*P*-value 0.040); malignancy stage (*P*-value 0.015), treatment intent (*P*-value 0.022); alcohol intake (*P*-value 0.025) and family history of any malignancy (*P*-value < 0.0001). The presence of previous alcohol consumption (Odds Ratio (OR) 2.4 (95%CI 1.1-5.1); *P*-value 0.022) and presence of any prior malignancy or family history of malignancy (OR 25.3 (95%CI 8.8-72.6); *P*-value < 0.001) were independent factors for identification of patients likely to meet EUROPAC criteria in the multivariable analysis (Table 7).

Population referred to genetic services and outcome of such referrals

In total, 14 of the 400 patients (3.5%) were referred to the Regional Genetics Service (10 of whom met EUROPAC criteria for referral; 4 were referred despite EUROPAC criteria not being met but suspected to be at high-risk) (Figure 2). Of the 14 patients referred, 5 patients (35.7%) were seen, 3 of whom underwent screening for mutations in BRCA1/2. The remaining 9 patients who were referred to the genetics service were not seen by the genetics team (64.3%) due to the following reasons: patients did not attend the appointment (6 patients), referral criteria not met (2 patients) and patient already known to have a pathogenic mutation in *BRCA2* and genetic consultation and follow-up was already in place (1 patient). One of the patients was referred despite not meeting EUROPAC criteria due to young age at diagnosis (29 years old); although the patient did not attend the scheduled genetic counselling appointment, she was

Table 2 Patient population baseline demographics

Parameter		Frequency	Relative percentage (%)
Patient demographic			
Gender	Male	206	51.5
	Female	194	48.5
Age	Median	67.7 yr	
	Range	29.9-94.2	
Comorbidity grade (according to Adult Comorbidity Evaluation-27)[34]	None	149	37.3[2]
	Mild	164	41[2]
	Moderate	60	15[2]
	Severe	27	6.8[2]
Pathological confirmation of malignancy	Yes	355	88.8[2]
	No[1]	45	11.3[2]
Stage	Localised (I-II)	4	1.0
	Locally advanced (III)	202	50.5
	Metastatic (IV)	194	48.5
Eastern Cooperative Oncology Group Performance Status at time of PDAC diagnosis	0	43	10.8[2]
	1	198	49.5[2]
	2	98	24.5[2]
	3	58	14.5[2]
	4	3	0.8[2]
Treatment characteristics			
Treatment intent at time of referral[3]	Curative	62	15.5
	Palliative	338	84.5
Curative management			
Patient received curative surgery?	Yes	65	16.3
Patient received adjuvant chemotherapy after curative surgery	Yes	42	65.6
	No	22	34.4
	Unknown	1	n/a
Type of adjuvant chemotherapy	5-fluorouracil	1	2.4[2]
	Capecitabine	18	42.9[2]
	Gemcitabine	23	54.8[2]
Palliative management			
Patient received palliative chemotherapy	Yes	230	57.5
	No	170	42.5
Type of palliative chemotherapy	FOLFIRINOX	37	16.1
	Gemcitabine/Capecitabine	60	26.1
	Gemcitabine/Cisplatin	5	2.2
	Gemcitabine NabPaclitaxel	27	11.7
	Gemcitabine monotherapy	94	40.9
	Other[4]	7	3.0

[1]Refers to patients diagnosed based on clinical and radiological data only following agreement in multidisciplinary team discussion.
[2]Indicates rounding error.
[3]Curative treatment intent refers to patients treated with curative surgery (number of patients with curative surgery and number of patients treated with curative intent do not match due to some patients being referred to our centre for consideration of palliative treatment at time of tumour relapse following curative surgery) (3 patients).
[4]Other include: 5FU/oxaliplatin: 3 patients; Gemcitabine + TH-302/placebo: 2 patients; Gemcitabine plus vandetanib/placebo: 1 patient; Capecitabine single agent: 1 patient.
n/a: Not applicable; PDAC: Pancreatic ductal adenocarcinoma; FOLFIRINOX: Folinic acid, 5-fluorouracil (5FU), irinotecan, oxaliplatin; yr: Years.

later identified to have a *BRCA2* mutation (as part of the screening process for an ongoing clinical trial).

In total, 3 patients in the whole patient population (0.75%) were found to harbour a germ-line mutation (all were *BRCA2* mutations). One patient had a history of smoking and two had a history of alcohol consumption. No other modifiable risk factors were met for these patients. All three patients found to have a *BRCA2* mutation had a

Table 3 Non-inheritable risk factors for pancreas cancer in patients included in study

Non-heritable risk factors		Frequency	Relative percentage (%)
Smoking			
Smoker (active or ex-smoker)	Yes	187	55.8
	No	148	44.2
	Unknown	65	n/a
Active smoker	Yes	71	21.2
	No	264	78.8
	Unknown	65	n/a
Alcohol			
Alcohol consumption	Yes	233	74.9
	No	78	25.1
	Unknown	89	n/a
"Excess" consumption	Yes	33	14.2
	No	200	85.8
Pancreatitis			
Previous pancreatitis	Yes	11	2.8
	No	386	97.2
	Unknown	3	n/a
Diagnosed > 2 yr before PDAC	Yes	6	54.6
	No	5	45.5
IPMN			
Past medical history of IPMN	Yes	3	0.8
	No	394	99.2
	Unknown	3	n/a
Diabetes			
Type 2 diabetes mellitus	Yes	103	25.9
	No	295	74.1
	Unknown	2	n/a
Diagnosed > 2 yr before PDAC	Yes	39	57.4
	No	29	42.7
	Unknown	35	n/a
Type 1 diabetes mellitus	Yes	5	1.3
	No	393	98.7
	Unknown	2	n/a

n/a: Not applicable; PDAC: Pancreatic Ductal Adenocarcinoma; IPMN: Intraductal Papillary Mucinous Neoplasm.

family history of any malignancy, although only two met EUROPAC criteria. The patient who didn't meet the EUROPAC criteria had a maternal grandmother with metastatic liver cancer from an unknown primary and was referred on an age at diagnosis basis (patient age 29 years at diagnosis). Both patients meeting the EUROPAC criteria fulfilled criterion 3.a (as defined in Table 1) [one patient's mother and maternal grandmother had breast cancer, the second patient was noted to have a strong family history of breast and ovarian cancer on the maternal side].

DISCUSSION

This study identified multiple challenges for adequate genetic referral and genetic counselling for patients diagnosed with PDAC. Our results highlighted the necessity to improve referral practice to the Regional Genetic Services in patients with PDAC when the EUROPAC criteria are implemented. The low rate of patients actually referred to genetic services when meeting referral criteria, along with the high percentage of referred patients who were too unwell to attend by the time of the genetics appointment, are areas for improvement. Adjustments in the referral criteria

Table 4 Entire patient population family history of malignancy and whether European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer referral criteria were met

Risk Factor		Frequency	Relative percentage (%)
Any personal[1]/family history of cancer	Yes	202	50.5
	No	132	33.0
	Unknown	66	16.5
Any personal[1] or family history of cancer meeting EUROPAC[24] criteria	Yes	113	28.3
	No	221	55.2
	Unknown	66	16.5
Criteria met	Criterion 1 (≥ 2 first-degree relatives with pancreatic cancer)	10	8.8
	Criterion 3.a (Personal/family history (≥ 1 first/second-degree relatives) of **breast/ovarian cancer)**	60	53.1
	Criterion 3.b [Personal/family history of melanoma in ≥ 1 first/second degree relative AND a high total body naevi count (often > 50)]	2	1.8
	Criterion 3.c [Personal/family history (≥ 1 first/second-degree relatives) of a Lynch syndrome-associated cancer (such as colorectal, endometrial, small bowel, renal)]	29	25.7
	Criterion 3.d (Oral/mucous membrane pigmentation +/- a personal/family history (≥ 1 first/second-degree relatives) of gastrointestinal cancers in first/second degree relatives)	12	10.6

[1]In addition to the diagnosis of PDAC. EUROPAC: The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer.

(*i.e.*, inclusion of patients diagnosed with PDAC below the age of 40 years old) and increased awareness within clinicians are potential solutions to this problem.

Assessment of prior personal and family history of malignancy are the cornerstones for identification of adequate referrals for genetic consultation in patients diagnosed with PDAC (so called "selected" population). Based on previous research, around 10-20% of all patients diagnosed with PDAC would meet criteria for referral for genetic testing on the basis of multiple cases of PDAC within a family[12] or due to presence of other personal/family history of cancer[11,13]. Interestingly, our study identified that almost 30% of the whole population met any of the EUROPAC criteria for referral for genetic assessment. This percentage is slightly higher to previously reported and may require adequate resources[11,13]. In the study by Holter and colleagues, out of the 306 patients explored 52 patients (16.9%) had previous personal history of cancer, and 59 (19.3%) and 37 (12.1%) patients had family history of breast/ovarian or pancreatic cancer, respectively[13]. Similar rates were seen in the study by Grant *et al*, in which 12.4%, 13.9% and 19.7% of all 290 patients analysed had family history of colorectal, pancreas and breast cancer, respectively[11]. In our study, most of the patients who met the EUROPAC criteria (as defined in Table 1) did so due to the presence of a first degree relative with breast or ovarian cancer (Criterion 3.a) or due to family history of colorectal cancer (Criterion 3.c), which is likely to be related to the high incidence of these malignancies[16,37]. In contrast, only 8.8% of patients were suitable for referral based on suspected familial PDAC (EUROPAC criterion 1 and 2). EUROPAC criteria may therefore need some refinement: (1) further details may be required for identification of patients/family members with family history of colorectal likely to have Lynch syndrome, and (2) similarly, a potential upper age threshold of breast cancer diagnosis may be of interest to prevent referral of sporadic mutation cases.

Overall, around 1% of patients from the whole series had a germ-line mutation identified, in keeping with expected results for population of patients tested based on clinical criteria such as EUROPAC[12] (so called "selected" population). It is worth mentioning that our study identified a patient with *BRCA2* germ-line mutation who was diagnosed at a young age and who was tested due to this reason (as per local criteria), even in the absence of meeting EUROPAC criteria for referral. Based on this, it could be considered for EUROPAC criteria to expand to include patients diagnosed

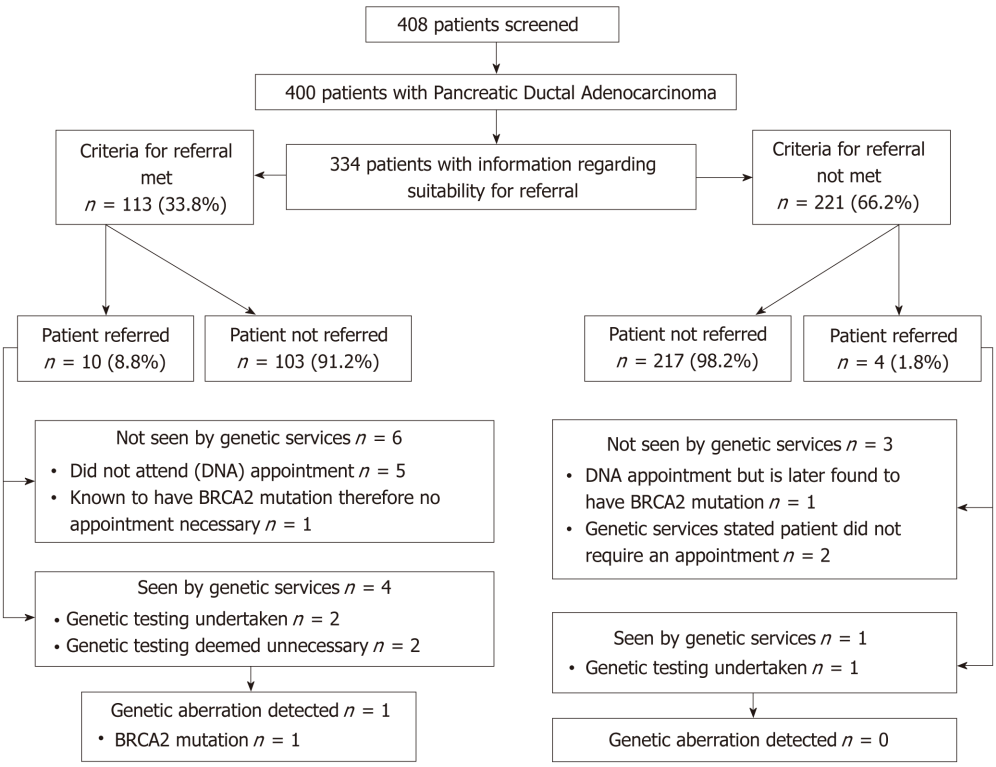

Figure 2 Flow diagram of patients' suitability for referral using European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer criteria, along with referral outcome. DNA: Did not attend.

with PDAC at a young age, although the exact age cut-off cannot be determined from our study.

Although the rate of patients expected to harbour germ-line aberrations is low, the clinical implications of carrying such a mutation, for both patients and families, are significant. Firstly, identification of such germ-line aberrations would allow for these patients and their families to undergo appropriate genetic counselling, which could include screening for other relevant malignancies (*i.e.*, breast cancer). Families at risk of developing PDAC could also benefit from an effective screening programme, even though such screening has yet to be defined for PDAC[38]. Detection of pancreatic cancer via screening would identify a greater proportion of patients with earlier stage tumours, which has been shown to have a better overall survival[38]. Secondly, for patients harbouring a germ-line *BRCA* mutation, approaches using Poly (ADP-ribose) polymerase (PARP) inhibitors[39] or DNA-damage agents such as platinum compounds are considered to be more efficacious[40]. PARP inhibitors are already in use for the treatment of ovarian tumours harbouring a BRCA mutation, demonstrating prolonged progression-free survival in these patients[41,42]. In PDAC, a phase II clinical trial using olaparib, a PARP inhibitor, in PDAC patient with either germ-line BRCA1 or BRCA2 mutated PDAC achieved a response rate of 21.7%[43] even after progression on an average of two prior lines of treatment[43]. Additionally, a phase II clinical trial assessing the utility of the PARP inhibitor veliparib in previously treated BRCA or PALB2- mutated PDAC showed single-agent activity of veliparib in the PDAC cohort[44]. These encouraging results have promoted the evaluation of PARP inhibitors earlier in the treatment pathway of patients with advanced PDAC (*e.g.*, the POLO clinical trial exploring the benefit of maintenance olaparib compared to placebo following induction platinum-based chemotherapy; www.clinicaltrials.gov: NCT02184195). Whilst results regarding the role of PARP inhibitors in patient carriers of germ-line *BRCA* mutations diagnosed with PDAC are awaited, the hypothesis that platinum-based chemotherapy achieves better outcomes (response rate or progression-free survival) in this population of patients[45] remains strong; although clinical data are mostly limited to retrospective series[46,47].

Even though a significant number of patients met criteria for referral for genetic consultation, less than 10% of them were actually referred. Patients with any family history of cancer and/or alcohol consumption were the ones with increased risk of meeting EUROPAC criteria, thus the ones that may require in depth consideration. This may help clinicians to focus on a specific population of interest and increase the appropriate referral rate to genetic services.

Table 5 Univariate analysis exploring demographic characteristics as factors predictive of meeting European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer criteria

		Patients who did not meet criteria for referral (*n* = 221)		Patients who did meet criteria for referral (*n* = 113)		Univariate analysis
		Frequency	Relative percentage	Frequency	Relative percentage	*P* value
Demographic characteristics						
Gender	Male	120	54.3	48	42.5	0.0041
	Female	101	45.7	65	57.5	
Age (yr)	Mean (95%CI)	66.3 (64.9-67.7)		67.2 (65.4-68.9)		0.4726
Comorbidity grade (ACE-27)[34]	None	75	33.9	45	39.8	0.040
	Mild	97	43.9	39	34.5	
	Moderate	28	12.7	24	21.2	
	Severe	21	9.5	4	4.4	
Pathological confirmation of malignancy	Yes	194	87.8	102	90.3	0.499
	No	27	12.2	11	9.7	
Stage	Localised	4	1.8	0	0	0.015
	Locally advanced	120	54.3	46	40.7	
	Metastatic	97	43.9	67	59.3	
ECOG performance status	0	21	9.45	14	12.4	0.534
	1	107	48.4	58	51.3	
	2	60	27.2	25	22.1	
	3	32	14.5	14	12.4	
	4	1	0.5	2	1.8	
Treatment characteristics						
Treatment intent	Curative	38	17.2	9	7.9	0.022
	Palliative	183	82.8	104	92.0	
Curative surgery	Yes	38	17.2	13	11.5	0.171
	No	183	82.8	100	88.5	
Adjuvant chemotherapy	Yes	23	10.4	9	7.9	0.465
	No	197	89.6	104	92.0	
Palliative chemotherapy	Yes	125	56.6	65	57.5	0.867
	No	96	43.4	48	42.5	

ACE-27: Adult Co-morbidity Evaluation- 27; ECOG: Eastern Cooperative Oncology Group; 95%CI: 95% confidence interval.

This study identified a significant number of patients who had absent documentation of any family history of cancer from the medical notes which may be reflection of lack of awareness within clinicians. In addition, a significant number of patients were referred but not seen due to poor performance status. Earlier referral in the patient pathway (for example at the first point of contact, *e.g.*, with surgical/gastroenterology teams) may avoid this from happening. In addition, these patients could be offered the opportunity to provide DNA for storage and for future analysis as appropriate (*i.e.*, to provide relatives with genetic information should the patient become too unwell to attend genetic services).

Regarding non-inheritable risk factors, 25% of patients in this cohort who had type 2 diabetes mellitus had their diabetes diagnosed within 2 years of their PDAC diagnosis. This is in keeping with research demonstrating a significantly higher prevalence of PDAC in patients with new onset type-2 diabetes[48]. The most commonly noted modifiable risk factors in this study were, as expected, cigarette smoking[49] and alcohol consumption[50]. The reduction of exposure to these risk factors would hopefully lead to a reduction in PDAC incidence, along with the incidence of many other malignancies.

The inherent limitations of retrospective studies apply to this study. For example, the number of patients with missing information for many of the risk factors explored in this study is likely related to a reporting bias. In order to reduce any selection bias, this was a consecutive series of patients and the demographic characteristics identified in this study are in keeping with national averages[51] and the distribution of

Table 6 Univariate analysis exploring risk-factors predictive of meeting European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer[24] criteria

		Patients who did not meet criteria for referral (*n* = 194)		Patients who did meet criteria for referral (*n* = 98)		Univariate analysis
		Frequency	Relative percentage	Frequency	Relative percentage	*P* value
Personal past medical history						
Smoker (active or ex-smoker)	Yes	108	55.7	55	56.1	0.941
	No	86	44.3	43	43.9	
Active smoker	Yes	45	23.2	16	16.3	0.173
	No	149	76.8	82	83.7	
Alcohol consumption	Yes	131	70.8	75	83.3	0.025
	No	54	29.2	15	16.7	
"Excess" alcohol consumption	Yes	24	12.9	5	5.6	0.060
	No	161	87.0	85	94.4	
Previous pancreatitis	Yes	7	3.2	1	0.9	0.195
	No	213	96.8	112	99.1	
Pancreatitis diagnosed > 2 yr before PDAC	Yes	5	2.3	0	0	0.3493
	No	2159	97.7	113	100	
Past medical history of IPMN	Yes	0	0	0	0	n/a
	No	220	100	113	100	
Type 2 diabetes mellitus	Yes	61	27.7	27	23.9	0.453
	No	156	72.3	86	76.1	
Type 2 diabetes mellitus diagnosed > 2 yr before PDAC	Yes	22	11.0	11	10.6	0.910
	No	178	89.0	93	89.4	
Type 1 diabetes mellitus	Yes	2	0.9	3	2.7	0.215
	No	218	99.1	110	97.4	
Family past medical history						
Any family history of cancer	Yes	93	42.1	109	96.5	< 0.0001
	No	128	57.9	4	3.5	

Please note that patients for whom data regarding the variable analysed in this table was missing has been omitted for this analysis. IPMN: Intraductal Papillary Mucinous Neoplasm; PDAC: Pancreatic ductal adenocarcinoma.

chemotherapy regimen usage was also reflective of current evidence for the treatment of PDAC. Prospective studies are required to further explore the potential role of extending the current EUROPAC criteria. Comparison of referral cohorts across multiple centres when various referral guidelines are applied and any bearing this has on germ-line mutation identification would provide quantitative comparisons between guidelines. This is one potential avenue of pursuit which was not addressed in this study. The multitude of other referral guidelines could also have been implemented in this study (*e.g.*, NICE, NCCN, ACG and local guidelines)[25-27] in order to develop a comprehensive review of referral guidelines, which in turn would enable comparison of positive and negative aspects of different guidelines, in order to produce or implement the most efficacious one. Testing for other germline mutations which predispose individuals to developing PDAC would also be another area of improvement for this study. Identifying such mutations would have enabled potential genetic counselling for family members. This study was a single centre experience, however it was in a high throughput tertiary hospital. Further analysis of referral to genetic services for potential germline mutations would benefit from the inclusion of multiple centres using numerous referral criteria.

In summary, identification of germ-line mutations, such as *BRCA2*, may have important implications for patients (with respect to choice of treatment, often in the clinical trial setting) and their families. This study identified that an increased awareness among pancreatic cancer clinicians and earlier referral in the patient pathway may ensure that patients fulfilling the EUROPAC criteria are assessed by expert clinical genetics teams. Moreover, the EUROPAC referral criteria may need to be broadened to include extremely young patients regardless of other criteria being met before implementation into the clinical setting.

Table 7 Multivariable logistic regression analysis exploring factors predictive of meeting European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer criteria

Characteristic	Multivariable analysis (logistic regression)	
	OR(95%CI)	*P* value
Gender: Female (Ref) *vs* male	0.7 (0.4-1.2)	0.211
Comorbidity scale: None/mild (Ref) *vs* moderate/severe	1.1 (0.5-2.2)	0.787
Stage: Localised/locally advanced (Ref) *vs* metastatic	1.5 (0.8-2.9)	0.207
Treatment intent: Curative (Ref) *vs* metastatic	2.0 (0.8-5.4)	0.158
History alcohol consumption: No (Ref) *vs* yes	2.4 (1.1-5.1)	0.022
Family history of any malignancy: No (Ref) *vs* yes	25.3 (8.8-72.6)	< 0.001

Ref: Reference variable; OR: Odds Ratio; 95%CI: 95% confidence interval.

ARTICLE HIGHLIGHTS

Research background

Approximately 10% of patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) report a significant family history of cancer, requiring genetic consultation; 10% of those referred are expected to have a germ-line predisposition (*i.e.*, 1% of the whole PDAC population).

Research motivation

Referrals for genetic consultations for patients diagnosed with pancreatic ductal adenocarcinoma are many times overlooked, probably due to a lack of awareness.

Research objectives

To understand current referral pathway for genetic consultation and areas for potential improvement.

Research methods

In this study, electronic records of consecutive patients diagnosed with PDAC were reviewed retrospectively. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) criteria were employed to identify patients eligible for genetic consultation referral.

Research results

Of 400 patients eligible, 113 patients (28.3% of the whole population) met referral criteria, only 10 (8.8%) were referred for genetic opinion. Germ-line mutations (*BRCA2*) were identified in three patients (0.75% of the whole population); one patient was tested due to young age at presentation (not conforming to EUROPAC criteria).

Research conclusions

There was a low referral rate even for patients fulfilling EUROPAC criteria. A significant number of patients did not attend the genetic consultation due to deteriorating performance status.

Research perspectives

Earlier referral, increased awareness of genetic services/testing amongst clinicians, together with the use of appropriate referral criteria may be required to optimise genetic services referral for patients with PDAC.

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