ORIGINAL ARTICLE

Detection of germline variants using expanded multigene panels in patients with localized pancreatic cancer

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Abstract

Background: Current guidelines recommend genetic testing for all patients with pancreatic cancer (PC).

Methods: Patients with localized PC who received neoadjuvant therapy between 2009 and 2018 were identified. Genetic consultation (including personal and family history of cancer), genetic testing, and variant data were abstracted.

Results: Of 510 patients identified, 163 (32%) underwent genetic counseling and genetic testing was performed in 127 (25%). Patients who underwent genetic testing were younger (median age: 63 vs. 67, p = 0.01). Multi-gene testing was performed in 114 (90%) of 127 patients, targeted gene testing was performed in 8 (6%), and not specified in 5 (4%). Of 127 patients who underwent genetic testing, 20 (16%) had pathogenic (P)/likely pathogenic (LP) variants, observed in ATM (n = 7/105,7%), CHEK2 (n = 3/98, 3%), BRCA1 (n = 2/117, 2%), BRCA2 (n = 2/122, 2%), PALB2 (n = 1/115, 1%), MUTYH (n = 1/98, 1%), CDKN2A (n = 1/94, 1%), STK11 (n = 1/97, 1%), NBN (n = 1/98, 1%), and MSH6 (n = 1/97, 1%). Of 20 patients with either a P/LP variant, nine (45%) had a prior cancer, three (15%) had a first-degree relative with PC, and six (30%) had an any-degree relative with PC.

Conclusion: Pathogenic/likely pathogenic variants were identified in 16% of patients who underwent genetic testing, 60% of which occurred in the homologous recombination pathway.

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Introduction

In the majority of patients with pancreatic cancer, acquired genetic mutations are believed to be responsible for carcinogenesis.[1] However, 5–10% of all patients with pancreatic cancer have an inherited pathogenic variant which may promote the development of the disease.[2] The most commonly inherited cancer susceptibility genes include BRCA2, BRCA1, PALB2, ATM, and CDKN2A.[2] The identification of germline pathogenic variants associated with pancreatic cancer may have important clinical consequences, by providing valuable information to guide treatment decisions in affected patients and facilitating early detection in related at-risk individuals.

The current recommendation from the American College of Medical Genetics and Genomics (ACMG) is to perform germline genetic testing in patients with pancreatic cancer who have a strong family history of pancreatic cancer, breast cancer, ovarian cancer, aggressive prostate cancer, and melanoma.[3] Testing is also recommended for patients of Ashkenazi Jewish ancestry or with a family history of Peutz-Jeghers or Lynch syndromes.[3] Using this selected approach, prior studies have identified germline variants in 8–20% of patients with pancreatic cancer.[4–8] The wide range

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of detection of germline variants may be attributed to differences in the number of genes interrogated, the ancestry of the tested cohort, and the method of variant classification. In addition, variant detection has been reported to be significantly higher among patients with metastatic disease than patients with earlier stage disease.[9,10] The majority of previous studies have been performed in patients with primarily metastatic disease and therefore, the prevalence of clinically actionable germline variants in patients with localized, non-metastatic pancreatic cancer has not been well described. In addition, genetic testing has evolved from single-gene testing to next generation sequencing (NGS), which frequently involves expansive panels of over 70 genes. The objective of this study was to describe the prevalence of clinically actionable germline variants (pathogenic or likely pathogenic) among patients with localized operable pancreatic cancer using evolving multigene panels.

Methods

A prospectively maintained pancreatic cancer database at the Medical College of Wisconsin was reviewed to identify all patients with resectable and borderline resectable pancreatic cancer from 2009-2018. From January 2009 to June 2018, genetic counseling and testing was offered selectively to patients with a personal cancer history (excluding non-melanoma skin cancers) or a family history (breast, ovarian, prostate, melanoma, or pancreatic cancers) suggestive of a hereditary cancer syndrome. Genetic counselors constructed a three-generation pedigree and genetic testing was individualized based on the personal/family history of cancer, insurance coverage for testing, and the genes clinically available for testing. After July 2018, genetic testing was offered to all patients with a new diagnosis of pancreatic cancer. All testing was performed using commercially available laboratories after informed consent was obtained. Variant classification and reporting were conducted per the ACMG guidelines. A variant was considered clinically actionable if it was classified as likely pathogenic or pathogenic. Variants of uncertain significance were reported to the patient but not considered clinically actionable.[11]

Treatment

All patients received neoadjuvant therapy which consisted of either chemotherapy alone, chemoradiation alone, or chemotherapy followed by chemoradiation. Chemotherapy consisted of a minimum of two months of induction chemotherapy. Chemoradiation was given at a dose of 50.4 Gy delivered over 28 fractions with concurrent gemcitabine or capecitabine. Staging was performed with computed tomography (CT) imaging and laboratory studies. Pancreatectomies were performed in a standard fashion as previously described.[12,13] Pathologic staging of the surgical specimen was based on the 8th edition of the American Joint Committee on Cancer classification. Additional adjuvant therapy was given at the discretion of the treating physician. Posttreatment surveillance occurred at three to four-month intervals for the first two years and at six-month intervals thereafter. Disease surveillance consisted of physical examination, laboratory studies, and CT imaging.

Statistical analysis

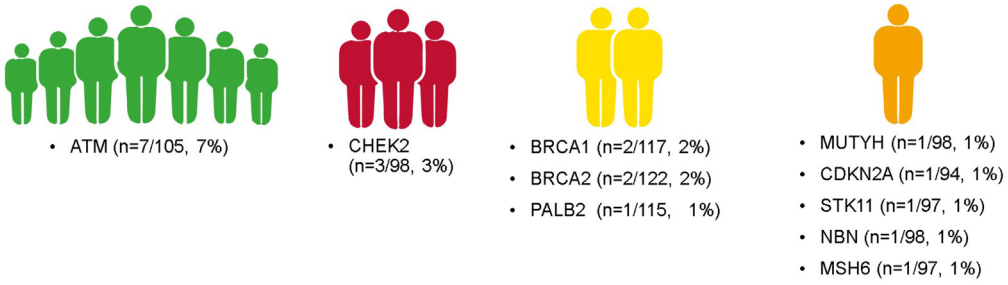
Categorical variables were compared using Fischer's Exact or Chi-squared test. Continuous variables were compared using Wilcoxon rank sum. Survival was calculated from date of diagnosis to date of death or last follow-up. Median overall survival was estimated using the Kaplan Meier method. Univariable and multivariable Cox proportional hazards modeling was performed. Covariates with $p < 0.20$ were included in multivariable models. Statistical significance was defined as a p-value <0.05. Statistical analyses were performed using Stata 14.2 (StataCorp, College Station, Texas). This study was approved by the Institutional Review Board at the Medical College of Wisconsin.

Results

Of 510 patients identified with localized pancreatic cancer, 163 (32%) had a personal history or family history of cancer concerning for a hereditary cancer syndrome and were referred to a genetic counselor. The median age of patients who were and were not referred for genetic counseling was 63 (n = 127, IQR: 13) and 67 years (n = 338; IQR:13), respectively (p = 0.003). Of the 163 patients referred for genetic counseling, 65 (40%) were male and 98 (60%) were female. There was no difference in clinical stage among patients who underwent genetic counseling as compared to patients who did not.

Genetic testing

Of the 163 patients who saw a genetic counselor, 40 (25%) had a personal history of a prior non-pancreatic cancer. A history of pancreatic cancer involving a first-degree relative was present in 31 (19%) and 46 (28%) had any-degree degree relative with pancreatic cancer (Fig. 1). Nine (6%) patients were of Ashkenazi Jewish descent. Of the 163 patients, 127 (78%) underwent subsequent genetic testing and 36 (22%) did not. Genetic testing was not performed for the following reasons: lack of a family history to warrant testing (n = 12/36, 33%); patient declined testing (n = 6/36, 17%) and; the lack of insurance coverage or a prohibitive copay (n = 10/36, 28%). In eight (22%) patients, the reason genetic testing was not performed was unknown. The clinicodemographic details of the 127 patients who received genetic testing are summarized in Table 1. Clinically actionable genetic variants were identified in 20 (16%) patients. Of these 20 patients, nine (45%) had a personal history of a non-pancreatic cancer, three (15%) had a first-degree relative with a history of pancreatic cancer and six (30%) had any-degree relative with a history of pancreatic cancer (Fig. 1).



Personal and Family History of Patients with Genetic Variant

	Total (n=163)	No Genetic Testing (n=36)	No Genetic Variant (n=107)	Genetic Variant (n=20)	p-value
Ashkenazi Jewish Descent, n (%)	9 (6)	1 (4)	8 (8)	0	0.58
Personal History of Other Cancer, n (%)	40 (25)	6 (17)	25 (24)	9 (45)	0.07
First-Degree Relative with History of PC, n(%)	31 (19)	9 (25)	19 (18)	3 (15)	0.60
Any-Degree Relative with History of PC, n (%)	46 (28)	13 (36)	27 (25)	6 (30)	0.46

Figure 1 Identified clinically actionable variants (n = 20)

Expansion of genetic testing

Between 2009 and 2013, genetic testing was performed using targeted single variant analysis, full gene sequencing analysis, and/or large rearrangement analysis for BRCA1, BRCA2, and PALB2. Following 2013, a variety of multigene panel testing was performed with an increasing number of genes. Currently, all gene panels utilize the following genes (at a minimum); APC, ATM, BMPR1A, BRCA1, BRCA2, CDKN2A, CDK4, EPCAM, FANCC, MLH1, MSH2, MSH6, PALB2, PALLD, PMS2, SMAD4, STK11, and TP53. Additionally, during this time, the referral practice evolved from selected referrals to genetic counseling to unselected referrals starting July 2018 (Fig. 2). Between 2009 and 2012, no genetic variants were identified and this increased to 40% of patients who underwent genetic testing by 2016 with the expansion to a 34-gene panel. We observed that larger gene panels ranging from 60-70 genes yielded similar proportions of identified variants. However, when access to genetic testing was expanded to include all patients regardless of pedigree or personal history of cancer, the prevalence of clinically actionable variants dropped. Following the transition to universal germline testing for patients with pancreatic cancer, 28 patients were tested of whom four (14%) had a germline variant identified.

Clinically actionable variants

Fig. 1 summarizes the different clinically actionable genetic variants identified among the 127 patients who underwent testing. The most common variant involved the ATM gene (n = 7/105, 7%), followed by genes associated with hereditary breast and ovarian cancer syndrome (n = 2/117, 2%, BRCA1; n = 2/122, 2%, BRCA2; n = 1/115, 1%, PALB2). CHEK2 mutations occurred in 3/98 (3%) patients and 5 patients had a variety of variants identified. There were no differences in age, gender, or race between patients who were found to have clinically actionable variants as compared to those who underwent genetic testing with no variant identified (Table 1). Among the seven patients with an identified variant in ATM, four (57%) had a personal history of cancer – one patient with melanoma, one patient with uterine cancer and melanoma, one patient with breast cancer, and one patient with bladder cancer. Of the five patients with variants in hereditary breast and ovarian cancer genes, two had a personal history of breast cancer. Of three patients with a CHEK2 variant, one (33%) had a personal history of melanoma. There was one patient with a MSH6 variant who had a personal history of colorectal cancer however the pedigree did not meet Amsterdam criteria. The one patient with a MUTYH variant had a history of breast cancer. The three patients with variants in STK11, CKDN2A, and NBN did not have a personal history of other cancers. Of 127 patients who underwent genetic testing, 50 (39%) had resectable disease and 77 (61%) had borderline resectable disease. Of the 50 patients with resectable disease, 13 (26%) had a clinically actionable variant compared to 7 (9%) of 77 patients with borderline resectable disease ($p = 0.01$).

Treatment and overall survival

Treatment details of the patients who underwent genetic testing is summarized in Table 1. Of the five patients with a hereditary breast and ovarian cancer syndrome variant, three (60%) patients received neoadjuvant treatment that included oxaliplatin. One patient did not receive a platinum agent as part of neoadjuvant therapy as germline testing result returned after neoadjuvant therapy had been completed. The remaining patient did not receive a platinum agent during neoadjuvant therapy for unspecified reasons. No differences among surgical resection rates were identified by variant status, however there were increased rates of N0 disease among patients with no genetic

Table 1 Clinicopathologic characteristics of patients who underwent genetic testing

Variable	Total (n = 127)	No Genetic Variant (n = 107)	Genetic Variant (n = 20)	p-value
Male sex, n (%)	50 (39)	44 (41)	6 (30)	0.35
Age at diagnosis, median (IQR)	63 (13)	63 (13)	62 (11.5)	0.43
Race, n (%)				0.54
Caucasian	117 (92)	99 (92)	18 (90)	
African American	6 (4)	5 (5)	1 (5)	
Hispanic	2 (2)	2 (2)	0	
Other	2 (2)	1 (1)	1 (5)	
Resectability, n (%)				0.01
Resectable	50 (39)	37 (35)	13 (65)	
Borderline Resectable	77 (61)	70 (65)	7 (35)	
CA19-9 at diagnosis, median (IQR)	136 (352)	93 (246)	317 (580)	0.18
Neoadjuvant Therapy, n (%)				0.02
Chemoradiation	41 (33)	30 (28)	11 (55)	
Chemotherapy	12 (9)	9 (8)	3 (15)	
Chemotherapy and Chemoradiation	74 (58)	68 (64)	6 (30)	
Completed Neoadjuvant Therapy and Resection, n (%)	101 (80)	87 (81)	14 (70)	0.24
T Stage, n (%)				0.69
T0	5 (5)	5 (6)	0	
T1	34 (35)	28 (34)	6 (43)	
T2	47 (49)	41 (50)	6 (43)	
T3	10 (11)	8 (10)	2 (14)	
N Stage, n (%)				0.01
N0	55 (57)	52 (63)	3 (21)	
N1	33 (35)	25 (31)	8 (58)	
N2	8 (8)	5 (6)	3 (21)	
Lymphovascular Invasion, n (%)	23 (23)	19 (22)	4 (31)	0.51
Perineural Invasion, n (%)	66 (66)	53 (62)	13 (93)	0.02
Received Adjuvant Therapy, n (%)	61 (62)	51 (61)	10 (71)	0.44

variant identified compared to those with a genetic variant identified (52 (63%) of 87 vs. 3 (21%) of 14, respectively; p = 0.01, Table 1). Of the entire cohort of 510 patients, six (1%) patients were lost to follow-up during the neoadjuvant treatment period, none of whom were referred to genetic counseling. Of the remaining 504 patients, the median overall survival was 24 months; 22 months for the 379 patients who did not undergo genetic testing, 22 months for the 20 patients with a clinically actionable variant, and 39 months for the 107 patients who underwent genetic testing but had no clinically actionable variant identified (p = 0.001; Fig. 3). Of the 504 patients, 350 (69%) completed all neoadjuvant therapy and surgery and had a median overall survival of 40 months; 38 months for the 249 patients who did not undergo genetic testing, 26 months for the 14 patients with an identified genetic variant, and 46 months for the 87 patients who underwent genetic testing with no clinically actionable variant identified (p = 0.05). In a multivariable Cox proportional hazards model including all patients who completed neoadjuvant therapy and surgery, N2 disease (HR:2.78, 95% CI 1.73–4.47, p < 0.001) was associated with an increased risk of death, while lack of an identified genetic variant (among those who received genetic testing) was associated with a decreased risk of death (HR:0.63, 95% CI 0.41–0.97, p = 0.04; Table 2). However, in an adjusted hazards model which included only patients who received genetic testing, there was no difference in risk of death among patients who did or did not have an identified genetic variant.

Discussion

The importance of identifying inherited, single-gene, highly penetrant pathogenic variants in patients with pancreatic

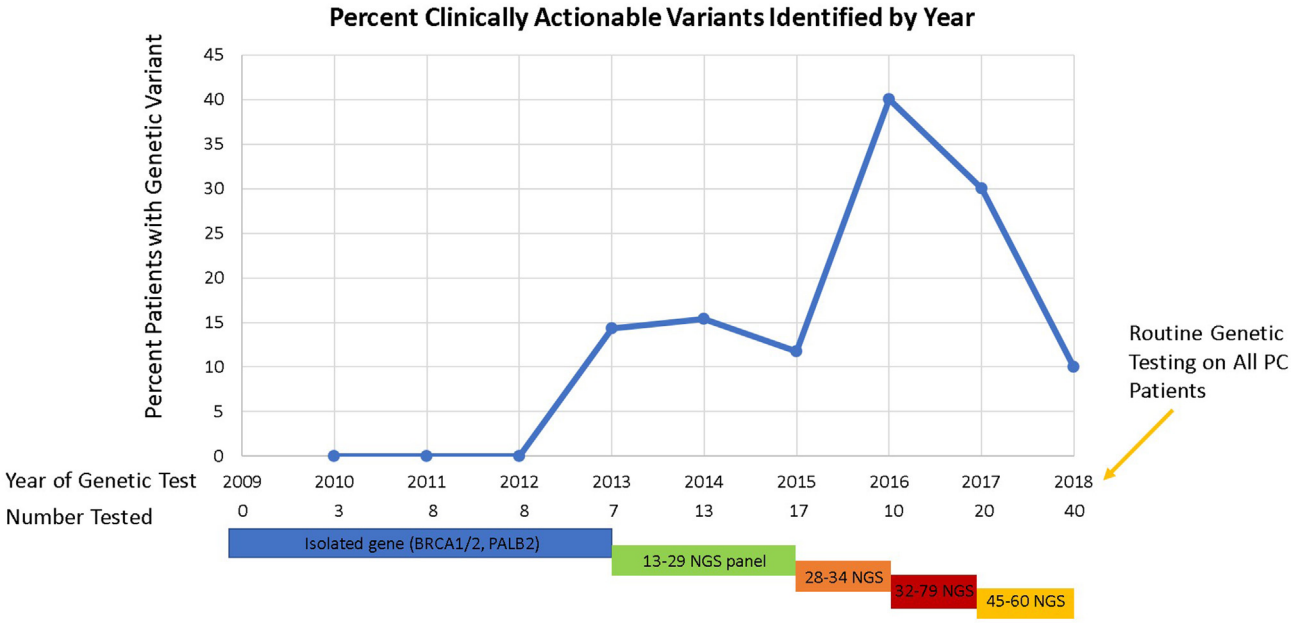


Figure 2 Changes in detection of genetic variants over time. Rates of detection were affected by the introduction of multigene testing panels and the number of patients in whom testing was performed

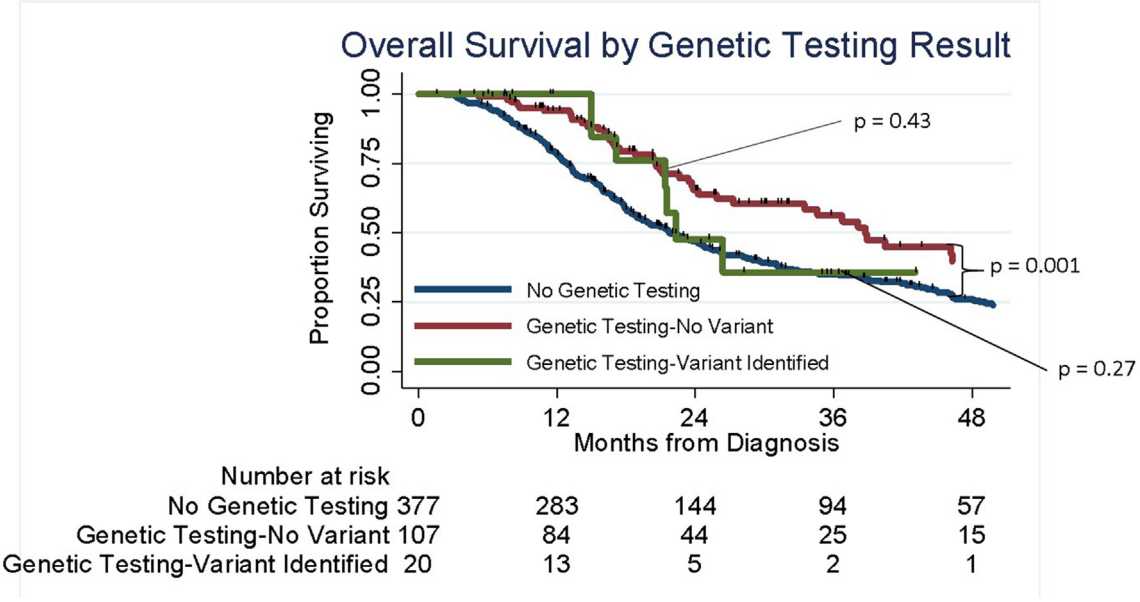


Figure 3 Median overall survival by genetic testing result (n = 504)

cancer has important clinical relevance. Those patients with hereditary breast and ovarian cancer syndromes (BRCA2, BRCA1, PALB2) represent a clinically meaningful subset of patients with pancreatic cancer among whom variant status may significantly alter treatment options.[14] In the current study, we described the prevalence of germline pathogenic variants in one of the largest consecutive series of patients with localized pancreatic cancer who received genetic counseling and underwent genetic testing. We observed that one third of patients with newly diagnosed pancreatic cancer had a personal or family history which was suspicious for a hereditary cancer syndrome. Of these 163 patients, 78% elected to pursue genetic testing. Of the 127 patients that were tested, 20 (16%) patients were found to have clinically actionable germline pathogenic variants, most frequently affecting the DNA damage repair pathways including ATM (35%) and the hereditary breast and

Table 2 Cox proportional hazards model

Variable	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age at diagnosis	1.01	1.00–1.02	0.05	1.01	0.99–1.02	0.51
Borderline Resectable (Ref: Resectable)	1.49	1.19–1.88	0.001	1.21	0.88–1.67	0.24
N Stage (Ref: N0)	–	–	–	–	–	–
N1	1.22	0.86–1.72	0.27	1.40	0.98–2.02	0.07
N2	2.39	1.52–3.74	<0.001	2.78	1.73–4.47	<0.001
Received Adjuvant Therapy (Ref: No Adjuvant Therapy)	0.69	0.52–0.91	0.009	0.76	0.55–1.06	0.11
Genetic Testing (Ref: None)	–	–	–	–	–	–
Genetic Testing + Variant	0.66	0.31–1.40	0.28	0.90	0.36–2.23	0.82
Genetic Testing - Variant	0.53	0.38–0.74	<0.001	0.63	0.41–0.97	0.04

ovarian cancer genes (25%). There were no differences in age, personal history of prior cancer, or family history of pancreatic cancer between patients by variant status, suggesting that clinical history is inadequate to determine which patients will have a genetic variant.

Previous reports of germline testing in patients with pancreatic cancer have reported the prevalence of clinically actionable variants to range from 8-20% among patients referred for genetic counseling based on a strong personal or family history of cancer.[4–8] In a prior study of 175 patients with advanced pancreatic cancer, genetic testing for hereditary breast and ovarian cancer syndrome, Lynch syndrome, and Familial Atypical Multiple Mole Melanoma Syndrome, identified a clinically actionable variant in 15% of patients referred for genetic counseling. Of note, a significant proportion (20%) of patients were of Ashkenazi Jewish ancestry and the most common variants identified involved the BRCA2 gene.[4] In the multicenter PACGENE consortium study, which included 515 unrelated kindreds with at least two family members with pancreatic cancer, comprehensive analysis of BRCA1, BRCA2, PALB2, and CDKN2A revealed pathogenic variants in 8% of patients, with BRCA2 mutations being the most common (4%).[8] In our cohort, the most common gene variant involved the ATM gene, but only 6% of our cohort was of Ashkenazi Jewish ancestry. Since both BRCA2 and ATM have the highest gene penetrance among the genes commonly included in multigene testing for pancreatic cancer, it is not surprisingly that both genes have been described to have the highest prevalence in this population.[7] Detection of pathogenic variants within the DNA damage repair pathway are clinically important as these tumors may be exquisitely sensitive to poly-ADP ribose polymerase (PARP) inhibitors and platinum-based chemotherapies.[5,14,15]

Germline variants in cancer susceptibility genes can also be found in patients who lack a pedigree of inherited cancer risk. In a large study of patients with a variety of advanced cancers, 1040 patients underwent unselected testing for 76 cancer susceptibility genes. In total, 18% of patients had cancer susceptibility gene in 18% identified and 10% involved moderate-to-highly penetrant variants.[9] The authors report that only 9.7% of patients would have had the variants detected if clinical guidelines for genetic testing based on personal history of cancer or pedigree were followed. Using an unselected approach among only patients with advanced pancreatic cancer, clinically actionable variants have been reported to range from 3.8-3.9%.[6,16] One of the first described experiences of unselected genetic testing involved 708 patients and 3.8% of patients had an identifiable clinically actionable variant using a 13-gene panel.[16] In a cohort of 854 patients, a 32-gene panel identified a deleterious variant in 31 (3.9%) patients, with the most common variant arising in BRCA2 (n = 12, 1%).[6] In that study, the majority (82%) of patients with a deleterious germline variant had a family history of other cancers but only 15% had a family history suggestive of a familial cancer syndrome.[6] With unselected testing, it is not unexpected that the detection of clinically actionable variants falls rapidly. In our current study, using a selected approach, the detection rate of clinically actionable variants was 16% (20/127), however using an unselected approach, the overall detection rate of clinically actionable variants would be at least 3.9% (n = 20/504). Despite relatively low detection rates, current National Comprehensive Cancer Network guidelines now recommend routine germline testing for all patients with pancreatic cancer regardless of the presence or absence of a hereditary cancer syndrome in the family. This is driven largely by the strong emerging evidence that therapeutic options are expanded for patients with variants to include platinum-based therapeutics, PARP-inhibitors, and even immunotherapy options.[5,14,15]

Although there is a higher yield of positive test results from multigene testing as compared to limited gene-specific testing, the clinical value of this approach remains to be proven. In the current study, we observed that variant detection rates were a function of both the size of the gene panel and the number of patients tested. As the multigene panel expanded, so did the identification of less common genetic variants (i.e., NBN, MUTYH). However, unlike ATM and BRCA2, the penetrance of less common genetic variants

is unclear, and to date, these variants have no specific therapeutic options. Additionally, between 2015 and 2016, the detection of pathogenic variants increased at least 2-fold (15%–40%) as compared to 2013–2015, despite having relatively similar sized panels. Although the 2015–2016 panel was incrementally larger, it was enriched for genes with biologic significance to the pancreatic cancer (CHEK2, CDKN2A, MUTYH, etc …). After 2016, larger panels did not yield an increased rate of detection of pathogenic variants, because, these genes have not been associated with pancreatic cancer. More information is needed regarding genotype–phenotype correlations and the impact of age and gender to better risk stratify these variants as high-, moderate-, or low-penetrant genes. In addition, there is growing evidence that more common variants, such as CHEK2, have disease odds ratios which are marginally significant, and therefore the impact of such variants on personal treatment and cascade testing may be modest. As multigene panels become increasingly available, the most challenging barrier for providers may be the ability to acquire and maintain the expertise necessary to interpret and counsel patients on the test results, given the rapidly changing landscape of genomic medicine. Alternatively, genetic counselors may be best equipped to provide pre- and post-test counseling, which may impact not only the patient but related family members, and therefore should be included in the multidisciplinary care of these patients. Inevitably, if guidelines continue to support unselected germline testing for patients, it will be critical to develop a long-term strategy to address the persistent shortage of genetic counselors.

A recent study compared the incidence of high risk dysplastic lesions or pancreatic cancers based on the presence or absence of an identified germline variant among a cohort of patients undergoing pancreatic cancer screening.[17] In that study, among the 464 patients enrolled in a high-risk pancreatic cancer screening program, when adjusted for age and sex and accounting for death as a competing event, the cumulative incidence of pancreatic cancer over 16 years was higher in the deleterious germline mutation group vs the familial risk group (hazard ratio [HR] = 2.85, 95% confidence interval [CI] = 1.0–8.2, P = 0.05). The likelihood of pancreatic cancer or high-grade dysplasia was also higher in the germline mutation group (HR = 2.81, p = 0.02), with elevated risk also observed when presence of clinically worrisome features on pancreatic imaging was included in the endpoint (HR = 3.13, P < 0.001). Additional studies are needed to further validate this preliminary association of biologic aggressiveness with known germline pathogenic variants in patients with pancreatic cancer.

This study is limited by its retrospective nature which predisposes bias at multiple levels. At an institutional level, non-Caucasian patients were underrepresented in our cohort and the prevalence of detected variants may not accurately reflect a more heterogenous population. At a provider level, prior to July 2018, germline testing was performed at the discretion of the treating physician, with each physician having had different thresholds for referral. At the patient level, not all patients were able to undergo genetic testing either due to financial circumstances or other preferences. Socioeconomic status may be an important confounding factor, as patients with financial stress were not only more likely to decline germline testing but also may have barriers to receiving treatment (transportation, social support, etc…) that impacts survival. For these reasons, our observations should be confirmed in larger multicenter studies.

Conclusion

Clinically actionable germline variants were identified in 16% of patients with localized pancreatic cancer who underwent genetic testing. The presence of a clinically actionable variant was not predicted by younger patient age, personal history of a prior cancer, or a family history of pancreatic cancer. Despite current guidelines, the added value of a universal approach to germline testing for patients with pancreatic cancer may be dependent on the availability of variant-specific therapeutic options and improved understanding of gene penetrance. The necessary infrastructure for such widespread genetic testing and interpretation may not be feasible at most institutions at this time and needs to be developed to accommodate expanding recommendations.

Conflict of interest

None to declare.

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