original contributions

Implementing Systematic Genetic Counseling and Multigene Germline Testing for Individuals With Pancreatic Cancer

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QUESTIONS ASKED: What are the real-world effectiveness, benefits, and potential barriers to implementing systematic genetic counseling and multigene germline genetic testing (GC/MGT) for all patients with pancreatic cancer (pancreatic ductal adenocarcinoma [PDAC])?

SUMMARY ANSWER: By implementing an automated workflow that offered genetic counseling (GC) referrals directly to patients with PDAC, rates of multigene germline testing (MGT) more than doubled (16.5%-38.0%, $P < .001$), compared with a workflow that relied on oncology providers to initiate GC referral. Although overall GC/MGT rates remained suboptimal even with an automated workflow, we found that the identification of germline pathogenic variants (PVs) frequently led to targeted therapy use for PDAC probands and cascade germline testing for their at-risk relatives.

WHAT WE DID: An iterative process for systematizing GC/MGT was developed in which gastrointestinal oncology providers at the Dana-Farber Cancer Institute (DFCI) were recommended to refer all patients with PDAC for GC (clinician-directed referral). Interim analysis found that < 20% of all patients with new PDAC were completing GC/MGT and that patients who returned to DFCI for > 1 oncologic visit (versus a one-time second opinion) were significantly more likely to complete MGT (odds ratio, 2.8; 95% CI, 1.7 to 4.7). As such, workflows were subsequently changed such that patients with PDAC were automatically offered GC when scheduling their initial oncology consultation (automated referral). Clinical or germline data were collected on a consecutive cohort of patients with PDAC undergoing GC/MGT during a 25-month enrollment period (19-month clinician-directed referrals; 6-month automated referrals), including data on targeted therapy use and cascade genetic testing among those found to harbor germline PVs.

WHAT WE FOUND: Compared with baseline clinician-directed referrals, implementation of automated referrals led to a significant increase in patients with PDAC undergoing GC/MGT (16.5% v 38.0%, $P < .001$), including those undergoing GC/MGT ≤ 7 days of initial oncology evaluation (14.7% v 60.3%, $P < .001$), with preserved PV detection rates (10.0% v 11.2%, $P = .84$). 16 of 28 (57.1%) carriers had relatives who pursued cascade germline testing, and 13 of 26 (50.0%) carriers with incurable disease received targeted therapy based on MGT results.

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATIONS: Our findings suggest that workflows that rely on oncology providers to initiate GC referral for individuals with PDAC are likely to suffer from suboptimal referral rates and may miss the window of opportunity of testing patients who are still well enough to pursue GC and targeted therapies. Even with an automated referral process, however, GC/MGT uptake was suboptimal, and additional data are needed to identify additional barriers to the real-world implementation of universal evaluation. Potential confounders include the fact that clinical practice guidelines from ASCO and the NCCN endorsing the use of universal germline testing were released during the enrollment period, and some patients with PDAC had already pursued germline testing elsewhere prior to coming to our institution. Unfortunately, our study did not routinely collect data on reasons why patients with PDAC did not pursue GC/MGT and likewise did not collect data on why providers may have chosen not to refer certain patients. The study's single institution design may limit generalizability to other practice settings, particularly those with more limited GC resources. These data provide important insights into the effectiveness, downstream benefits, and barriers to systematically offering GC/MGT to patients with PDAC in real-world practice. For those patients with PDAC found to harbor germline PVs, there were tangible changes to management for the probands themselves and their at-risk family members, demonstrating the real-world feasibility and downstream benefits of systematic risk assessment.

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abstract

PURPOSE National guidelines recommend genetic counseling and multigene germline testing (GC/MGT) for all patients with pancreatic ductal adenocarcinoma (PDAC). This study's aim was to assess real-world effectiveness of implementing systematic GC/MGT for all patients with PDAC at a high-volume academic institution.

METHODS An iterative process for systematizing GC/MGT was developed in which gastrointestinal oncology providers at the Dana-Farber Cancer Institute were recommended to refer all patients with PDAC for GC/MGT (clinician-directed referral). Workflows were subsequently changed such that patients with PDAC were automatically offered GC/MGT when scheduling their initial oncology consultation (automated referral). Clinical and germline data were collected on a consecutive cohort of patients with PDAC undergoing GC/MGT during a 25-month enrollment period (19-month clinician-directed referrals; 6-month automated referrals).

RESULTS One thousand two hundred fourteen patients with PDAC were seen for initial oncologic evaluation, 266 (21.9%) of whom underwent GC/MGT. Compared with baseline clinician-directed referrals, implementation of automated referrals led to a significant increase in patients with PDAC undergoing GC/MGT (16.5% v 38.0%, $P < .001$), including those undergoing multigene germline testing (MGT) ≤ 7 days of initial oncology evaluation (14.7% v 60.3%, $P < .001$), with preserved pathogenic variant detection rates (10.0% v 11.2%, $P = 0.84$). 16 of 28 (57.1%) pathogenic variant carriers had relatives who pursued cascade germline testing, and 13 of 26 (50.0%) carriers with incurable disease received targeted therapy based on MGT results.

CONCLUSION Implementation of systematic GC/MGT in patients with PDAC is feasible and leads to management changes for patients with PDAC and their families. GC/MGT workflows that bypass the need for clinician referral result in superior uptake and time to testing. Further investigation is needed to identify other barriers and facilitators of universal GC/MGT.

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INTRODUCTION

Recent studies of unselected cohorts of patients with pancreatic ductal adenocarcinoma (PDAC) have demonstrated that 4%-10% harbor germline pathogenic variants (PVs) in high- or moderate-penetrance cancer susceptibility genes.[1-7] Therefore, in mid-2018, National Comprehensive Cancer Network (NCCN) guidelines recommended testing all patients with PDAC with a multigene germline panel including breast cancer genes (*ATM*, *BRCA1/2*, and *PALB2*), Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, and *EPCAM*), and others.[8] Furthermore, recent developments in targeted therapies have shown promise for patients with PDAC with specific germline PVs.[9-14]

Since all the cancer susceptibility genes implicated in PDAC risk confer risk of other cancer types and have autosomal dominant inheritance patterns, there are considerable preventive implications for the healthy at-risk relatives of patients with PDAC found to harbor such germline PVs.[15-17] Unfortunately, cascade testing (genetic testing for at-risk relatives of the proband with a known PV) has been notoriously difficult to routinely perform in cancer genetics,[18] with various well-described barriers including inadequate access to genetics providers, poor communication regarding the implications of a hereditary susceptibility to probands and family members, financial concerns, and belief that cancer is inevitable.[19]

Despite the justifiable enthusiasm for systematically offering multigene germline testing (MGT) to all

patients with PDAC, the question of how to effectively deliver high-quality genetic counseling and MGT (GC/MGT) on a large-scale basis has been vexing in other malignancies. Universal testing is likely to be a particular challenge in PDAC, where patients may have a short time frame for receiving GC/MGT given the disease's inherently poor prognosis. This study's aim was to study the real-world effectiveness and barriers of implementing systematic GC/MGT for all patients with PDAC at a single high-volume institution.

METHODS

In late 2016, the Dana-Farber Cancer Institute (DFCI) Center for Cancer Genetics and Prevention implemented a new iterative workflow to facilitate GC/MGT for all individuals seen at DFCI for oncologic evaluation of a PDAC diagnosis based on growing data at our institution revealing frequent germline PVs.[20] All oncology providers (medical oncologists, surgical oncologists, and radiation oncologists) in the DFCI Gastrointestinal Cancer Center were recommended to refer all patients with PDAC for GC/MGT beginning December 2016, regardless of clinical factors, such as age at diagnosis or personal or family history of cancer (clinician-directed referral; Figs 1A and 1B). The principal investigator (M.B.Y.) solicited feedback and educated providers about the rationale for universal GC/MGT at faculty meetings.

After a lead-in period to refine workflows, all patients with PDAC (without prior MGT) who were referred for GC/MGT were offered enrollment in the current study beginning February 24, 2017. Three genetic counselors were affiliated with the study to ensure maximal flexibility in scheduling for patients with PDAC, and schedulers prioritized patients with PDAC for particularly prompt in-person genetic counseling (GC) appointments. In some cases, if enrolled patients were too ill to return for in-patient visits, GC was conducted via telephone with MGT kits sent to patients for saliva collection. As an iterative study, GC/MGT referral rates were continually assessed throughout the study period. Interim analysis[21] found that < 20% of all patients with new PDAC were completing GC/MGT and that patients who returned to DFCI for > 1 oncologic visit (v a one-time second opinion) were significantly more likely to complete GC/MGT (odds ratio, 2.8; 95% CI, 1.7 to 4.7).

As such, in October 2018, workflows were changed such that patients with PDAC were automatically offered GC consultation at the time that they arranged their initial oncologic evaluation (automated referral), rather than requiring clinician referral. In the automated referral process (Fig 1C), gastrointestinal oncology new patient coordinators informed patients with PDAC that referral for GC/MGT was considered standard for all individuals with PDAC (see the script, Data Supplement, online only) at the time they were arranging initial oncologic consultation. For patients who agreed to GC referral, they were connected to the cancer

genetics new patient coordinators via warm telephone transfer when possible. When this was not successful (eg, because of schedulers being away from their desk, patient preference, etc), the gastrointestinal oncology coordinators e-mailed the cancer genetics coordinators with the name and contact information of the patient(s) with PDAC who had agreed to GC. For patients with PDAC who declined GC or could not be contacted to arrange GC, a note was added to their new patient oncology visit in the electronic medical record to inform the oncology provider.

All patients with PDAC seen for GC were offered clinical MGT and enrollment in the study. Patients with nonadenocarcinoma histologies of malignant pancreatic neoplasia (eg, neuroendocrine carcinoma, acinar cell carcinoma, etc) were not eligible for study enrollment although individuals with poorly differentiated pancreatic carcinoma not otherwise specified were eligible. This study included all patients with PDAC without prior MGT who consented to enrollment from February 24, 2017, to March 31, 2019.

MGT was ordered as a clinical test through CLIA-certified laboratories, following informed consent. MGT results were provided directly to the participant (or a designee, if preferred by the study participant) by a genetic counselor or a genetics physician by telephone or in-person. All participants were offered in-person post-test consultation with a genetics physician, regardless of results. Germline variants classified as pathogenic or likely pathogenic by the clinical laboratory performing MGT were collectively defined as PVs for the purposes of this study, excluding specific low-penetrance germline variants (APC p.I1307K, CHEK2 p.I157T, CHEK2 p.S428F, or FH p.K477dup) and individuals found to have heterozygous germline variants in genes only associated with autosomal recessive forms of cancer susceptibility (eg, MSH3, MUTYH, NTHL1, and RECQL4). Individuals with germline variants of uncertain significance (VUS) who lacked PVs were included with noncarriers.

Clinical data collected included sex, age, PDAC stage or resectability status, treatment history, personal or family cancer history, race, ethnicity, timing of GC, date of death, and status of relatives' cascade testing (when applicable). The cutoff date for data analysis including treatment history and cascade testing was March 1, 2020. The primary end point was uptake of GC/MGT. Secondary end points included time to GC/MGT, germline PV detection, and uptake of targeted therapies (eg, PARP inhibitors), among those with PVs. Bivariate associations of PV status with clinical characteristics were analyzed using Fisher's exact test and Mann-Whitney U test for categorical and continuous variables, respectively. The primary and secondary end points were compared between the two eras of testing (clinician-directed and automated) using Fisher's exact test (for dichotomous outcomes) and Mann-Whitney U test (for continuous outcomes). All P-values were two-sided and considered statistically significant at < .05. Statistical analyses were performed using SPSS software (IBM Corp.
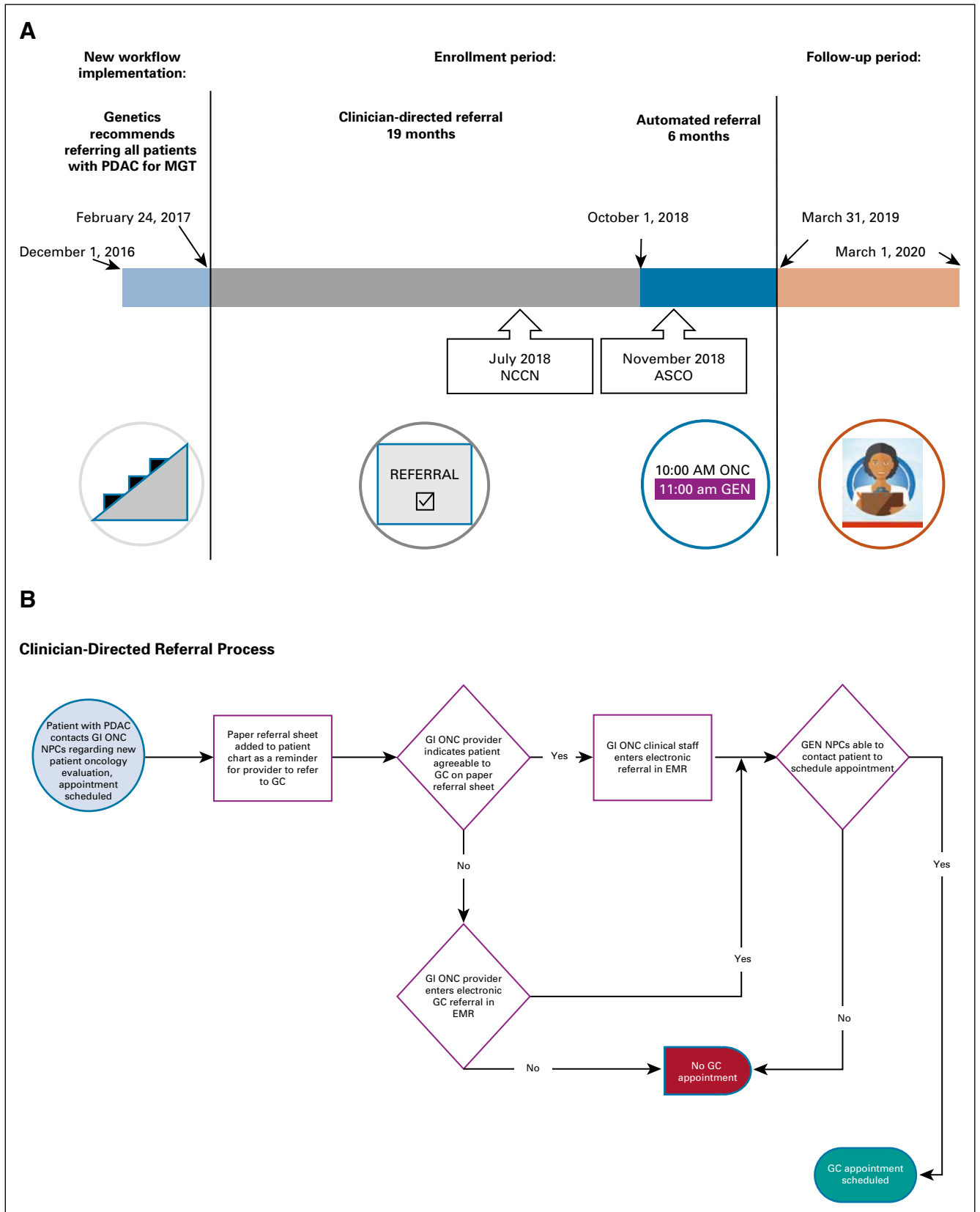
FIG 1. (A) Study enrollment and follow-up timeline. July 2018 NCCN and November 2018 ASCO refer to published recommendations[22,23] for genetic testing of patients with PDAC. (B) Schematic of the clinician-directed referral process. (C) Schematic of the automated referral process. See the script (Data Supplement). (D) Subject enrollment during the two referral periods. DFCI, Dana-Farber Cancer Institute; EMR, electronic medical record; GEN, cancer genetics department; GC, genetic counseling; MGT, multigene germline testing; ONC, oncology department; NPC, new patient coordinator; PDAC, pancreatic ductal adenocarcinoma.
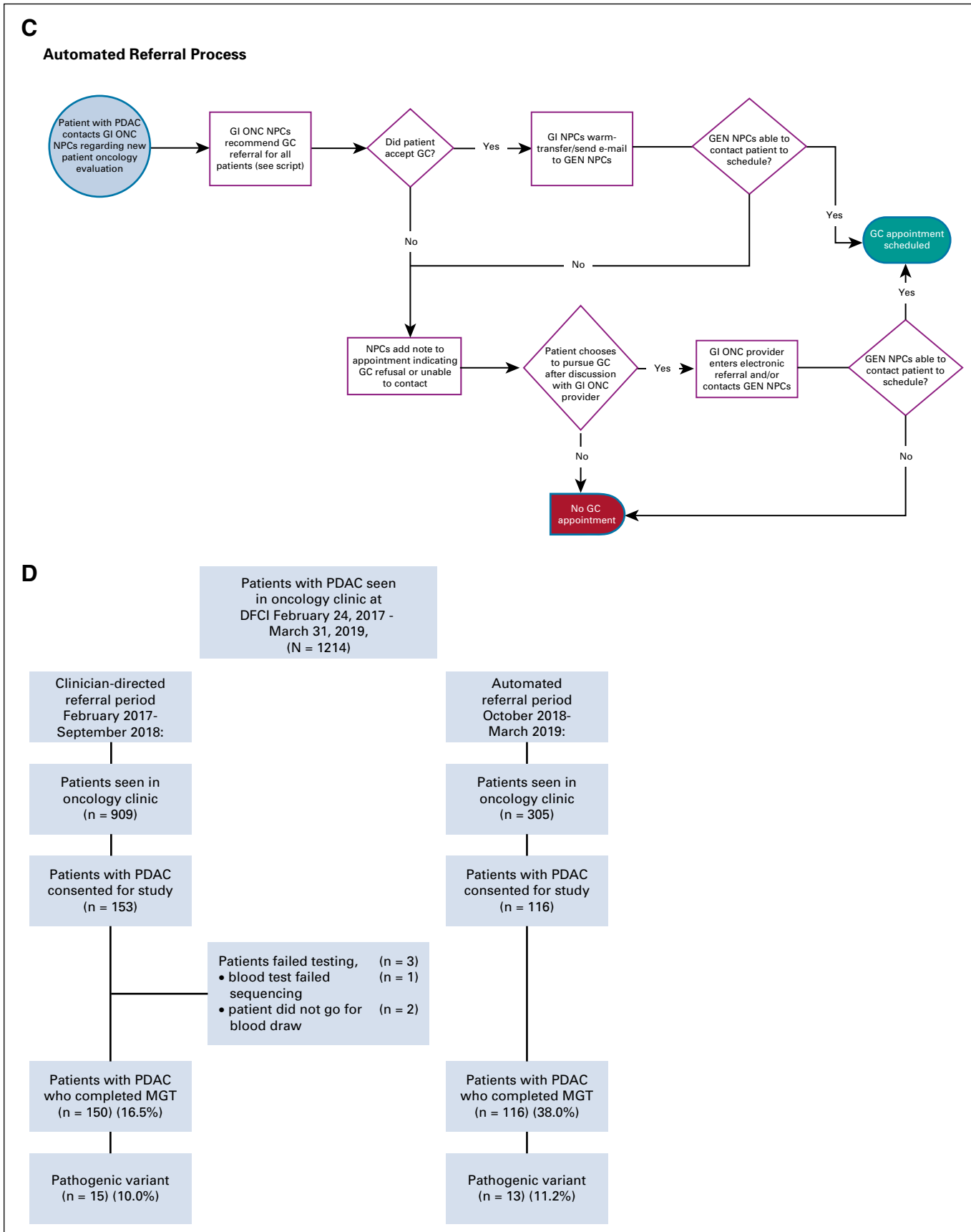
C

Automated Referral Process

D

FIG 1. (Continued).

released 2019. IBM SPSS Statistics for Macintosh, Version 26.0, Armonk, NY: IBM Corp.). This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

RESULTS

Over the 25-month enrollment period, 1,214 individuals were seen at DFCI for new outpatient oncologic consultation (medical, radiation, and/or surgical oncology) for a PDAC diagnosis. During the same span, 310 patients with PDAC were seen for GC, of whom 269 (86.8%) consented for the study with 266 (98.9%) undergoing MGT (2 patients did not have blood drawn, and 1 patient's sample failed testing; Table 1; Fig 1D).

TABLE 1. Clinical Characteristics in Patients During Clinician-Directed Versus Automated Referral Periods

Characteristic	All (N = 266)	Clinician-Directed (n = 150)	Automated (n = 116)	P[a]
Sex				
Male	138 (51.9%)	81 (54.0%)	57 (49.1%)	.459
Female	128 (48.1%)	69 (46.0%)	59 (50.9%)	
Ethnicity				
Nonhispanic white	246 (92.8%)	137 (91.9%)	109 (94.0%)	.50
Nonhispanic black	3 (1.1%)	3 (2.0%)	0	
Hispanic or Latino	9 (3.4%)	5 (3.4%)	4 (3.4%)	
Other or unknown	7 (2.6%)	4 (2.7%)	3 (2.6%)	
Ashkenazi Jewish				
No	196 (73.7%)	108 (72.0%)	88 (75.9%)	.337
Yes	32 (12%)	21 (14.0%)	11 (9.5%)	
Unknown	38 (14.3%)	21 (14.0%)	17 (14.7%)	
Age at diagnosis, y (median Q1-Q3)	67 (60-73)	68 (60-72)	67 (61-73)	.529[b]
Stage at diagnosis				
Resectable	93 (35%)	48 (32.0%)	45 (38.8%)	.346
Locally advanced	38 (14.3%)	20 (13.3%)	18 (15.5%)	
Metastatic	135 (50.8%)	82 (54.7%)	53 (45.7%)	
Family history of PDAC in FDR or SDR				
Yes	47 (17.7%)	27 (18.0%)	20 (17.2%)	1.0
No	219 (82.3%)	123 (82.0%)	96 (82.8%)	
Personal history of non-PDAC cancer[c]				
Yes	89 (33.5%)	54 (36.0%)	35 (30.2%)	.360
No	177 (66.5%)	96 (64.0%)	81 (69.8%)	

Abbreviations: FDR, first-degree relative; PDAC, pancreatic ductal adenocarcinoma; Q, quartile; SDR, second-degree relative.

[a]Calculated using Fisher's exact test unless otherwise specified.

[b]Mann-Whitney U test.

[c]Excluding nonmelanoma skin cancer.

28 of 266 (10.5%) participants had ≥ 1 PV found on MGT (9 ATM [1 with concomitant PALB2], 4 BRCA1, 7 BRCA2, 2 CDKN2A, 1 CHEK2, 1 NBN, 3 PMS2, and 1 STK11; Table 2). Of note, the individual with the germline STK11 PV was known to harbor this variant from prior single-gene germline testing because of clinical features of Peutz-Jeghers syndrome, but had not had prior MGT. There was no significant difference between PV carriers and non-carriers with regard to sex, age at PDAC diagnosis, race, stage, personal cancer history, or family history of PDAC (Appendix Table A1, online only). An additional 13 of 266 (4.9%) participants were found to harbor low-penetrance germline variants or heterozygous germline variants in genes only associated with autosomal recessive forms of cancer susceptibility and were thus considered noncarriers for the purposes of this analysis. 96 of 266 (36.1%) participants had ≥ 1 germline VUS.

During the clinician-directed referral period, 150 of 909 (16.5%) patients with PDAC seen for oncologic evaluation were enrolled in the study and underwent GC/MGT versus 116 of 305 (38.0%) patients with PDAC in the automated referral period (P < .001). There was no significant difference in the fraction of participants found to harbor PVs in the clinician-directed versus automated referral periods (15/150 [10.0%] v 13/116 [11.2%], P = .84). Time from initial oncologic appointment at DFCI to GC/MGT was significantly shorter in the automated referral period, with 70 of 116 (60.3%) undergoing GC/MGT ≤ 7 days from initial oncology appointment (v 22/150 [14.7%], P < .001 in the clinician-referral period; Table 3).

Sixty-six patients (24.8%) were seen for their GC appointment immediately prior to (9 patients seen in GC 1-7 days prior to oncology) or on the same day as their oncologic appointment (with 60 of 66 [90.9%] such appointments occurring during the automated referral period). 133 of 266 (50%) participants had died as of data analysis, 9 of whom died 1-30 days from receiving MGT results and 6 of whom died prior to the return of MGT results.

Of the 28 participants with germline PVs, 26 were eligible for targeted therapy at the time of analysis based on having incurable disease and 13 (50%) of whom received targeted palliative systemic therapy based on their PV. 16 of 28 (57.1%) participants with germline PVs had ≥ 1 at-risk relative(s) who had undergone cascade testing at the time of analysis.

DISCUSSION

In this single-institution study of individuals undergoing routine PDAC oncologic care, we studied the implementation of systematic GC/MGT first through a workflow in which clinicians initiated a genetics referral and later through an automated process in which patients were directly offered genetics referral. The uptake of GC/MGT referrals in this study improved significantly with a change in workflow to an

TABLE 2. Germline Variants, Targeted Therapy, and Cascade Testing in Pathogenic Variant Carriers

Gene	Genetic Change (Nucleotide Position)	Age at Diagnosis/ Sex	Stage at Diagnosis	Targeted Therapy	Known Cascade Testing
ATM and PALB2	ATM c.7638_7646del; PALB2 Exons 12-13 deletion	65/female	Resectable	Yes, olaparib	Yes
ATM	c.1339C>T	69/female	Metastatic	Yes, niraparib[a]	No
ATM	c.3802delG	59/male	Metastatic	Yes, niraparib[a]	Yes
ATM	c.1899-1G>T (splice acceptor)	67/male	Resectable	No	Yes
ATM	c.7638_7646del	87/female	Locally advanced	No	Yes
ATM	c.7408T>G	60/male	Locally advanced	No	No
ATM	c.5762+1G>T (splice donor)	63/female	Resectable	No	Yes
ATM	c.185+1del (splice donor)	47/female	Metastatic	No	No
ATM	c.4642_4645del	72/female	Locally advanced	No	No
BRCA1	c.815_824dupAGCCATGTGG	62/female	Metastatic	Yes, olaparib[a]	No
BRCA1	c.4327C>T	58/male	Metastatic	Yes, olaparib[a]	No
BRCA1	c.68_69delAG	63/male	Resectable	No	No
BRCA1	c.4689C>G	60/male	Resectable	No	Yes
BRCA2	5'UTR_EX1del	49/female	Metastatic	Yes, niraparib[a]	Yes
BRCA2	c.7007+2T>G (splice donor)	53/male	Locally advanced	Yes, olaparib	No
BRCA2	c.7988A>T	57/male	Metastatic	No	Yes
BRCA2	c.5350_5351del	72/female	Metastatic	No	Yes
BRCA2	c.6275_6276del	78/male	Locally advanced	Yes, niraparib[a]	Yes
BRCA2	c.7977-1G>C (splice acceptor)	75/male	Resectable	Yes, olaparib	Yes
BRCA2	c.6275_6276delTT	62/male	Metastatic	Yes, olaparib	Yes
CDKN2A	c.335_337dupGTC	69/female	Resectable	Yes, bcl2/MEKi[a]	Yes
CDKN2A	c.159G>C	75/female	Metastatic	No	Yes
CHEK2	c.234_262del	82/male	Locally advanced	No	No
NBN	c.1142delC	56/female	Metastatic	No	No
PMS2	Del exon 14	68/male	Resectable	No	No
PMS2	c.1A>T (initiator codon)	52/male	Locally advanced	Yes, nivolumab[b]	Yes
PMS2, CHEK2 (mosaic)	PMS2 c.137G>T; CHEK2 c.989del	69/male	Metastatic	No	No
STK11	c.157dupG	53/male	Locally advanced	Yes, everolimus	Yes

Abbreviation: MEK = mitogen-activated protein kinase enzyme.

[a]Treatment administered on a clinical trial.

[b]Tumor testing revealed intact mismatch repair protein on immunohistochemistry as well as microsatellite stability and low tumor mutational burden on tumor sequencing.

automated referral system, and time to GC was significantly shorter after automation with 25% of patients seen on the same day as their oncology appointment or shortly before the oncology appointment. Importantly, however, germline PV rates did not drop with the automated referral approach, indicating that overall PV detection was reliant primarily on the number of individuals referred for GC/MGT, rather than clinician discretion. Patients with PDAC, their families, and their clinicians commonly acted upon MGT findings through both cascade testing in at-risk relatives and also the uptake of PARP inhibitors and other germline-directed targeted PDAC therapies. These findings demonstrate both the feasibility and downstream benefits of systematic GC/ MGT in individuals with PDAC.

The concept of screening all individuals with a particular cancer for inherited susceptibility has precedent in other cancer types, most notably ovarian cancer where guidelines from the NCCN and others have recommended germline BRCA1/2 testing for all patients since 2007, with updated guidelines now broadening this to MGT.[22,23] Despite such recommendations, data have shown that < 30% of patients with ovarian cancer undergo germline evaluation in real-world practice.[24] Now that clinical practice guidelines from the NCCN[22] and ASCO[23] endorse GC/MGT for all patients with PDAC, the lessons and failures from over a decade's worth of experience in ovarian cancer should provide valuable insight into devising strategies for successful real-world implementation in PDAC.

TABLE 3. GC and MGT Rates With Clinician-Directed Referrals Versus Automated Referrals

Parameter	All (N = 266)	Clinician-Directed Referral (n = 150)	Automated Referral (n = 116)	P[a]
PV detection	28/266 (10.5%)	15/150 (10.0%)	13/116 (11.2%)	.84
Time from Onc app to GC (median)	30 days (IQR 1-91)	42 days (IQR 20-126)	0 days (IQR 0-56)	< .001[b]
Time from MGT to results (median)	13 days (IQR 10-19)	13 days (IQR 11-19)	12 days (IQR 9-18)	.021[b]
GC ≤ 7 days from first Onc app	92 (34.6%)	22 (14.7%)	70 (60.3%)	< .001
GC ≤ 30 days from first Onc app	135 (50.8%)	58 (38.7%)	77 (66.4%)	< .001

Abbreviations: App, appointment; GC, Genetic counseling; IQR, interquartile range; MGT, multigene germline testing; Onc, Oncology; PV, pathogenic varia.
[a]Calculated using Fisher's exact test unless otherwise specified.
[b]Mann-Whitney U test.

Our data demonstrate that simply directing providers to refer all patients with PDAC results in poor uptake of GC/MGT, mirroring such historical lessons from ovarian cancer.[24] Although processes were designed so as to facilitate prompt and flexible GC scheduling once referral was initiated, our data suggest that a key barrier to GC/MGT uptake with a clinician-directed workflow may be the time from initial oncology evaluation to GC. PDAC may be a particularly challenging disease in which to implement universal GC/MGT because of the complex therapeutic, symptomatic, endoscopic, and psychosocial needs inherent to the disease,[15] and the long time to GC in the clinician-directed referral arm of this study may reflect the prioritization of these other critical aspects of care over hereditary risk assessment. The lethality of PDAC further amplifies the importance of prompt GC/MGT, as illustrated by the observation that 15 of 266 (5.6%) enrollees in our study died ≤ 30 days of receiving MGT results, thereby precluding these individuals from having the opportunity to therapeutically benefit from the results.

By implementing an automated referral process for GC consultation, we achieved a significant increase in GC/MGT uptake and a reduction in time to GC consultation. Even with these improvements, however, the overall GC/MGT uptake was < 40%, highlighting the need to identify additional barriers and facilitators to universal germline evaluation. Several factors may have contributed to this low uptake, including the possibility that participants underwent GC/MGT at another institution, lack of patient understanding about the importance of GC/MGT, the potential of patients with PDAC to have been too symptomatic and/or overwhelmed to have undergone GC, and an inability of schedulers to make contact with each patient with PDAC to offer GC/MGT referral. None of these factors were directly measured in this study, and these remain important areas to investigate in future implementation analyses.

In the numerous recent studies,[1-7] one consistent and critical finding has been that a large fraction of patients with PDAC with PVs lack obvious clinical features of inherited cancer risk (eg, young age and classic family history patterns) and would thus presumably go undiagnosed by phenotype-directed genetic testing practices. In our study,

we likewise observed no significant differences in clinical characteristics between PV carriers and noncarriers nor a difference in PV detection rate among PDAC participants referred in the clinician-directed versus the automated referral period. Thus, performing germline testing on patients with PDAC in a more systematic and automated manner did not lead to a lower risk cohort of individuals undergoing evaluation, but rather, the 10%-12% PV detection rate was preserved with larger numbers of patients with PDAC undergoing MGT. Increasing the denominator of patients with PDAC undergoing MGT led directly to an increase in PV detection.

One key potential benefit of universal GC/MGT in patients with PDAC is the facilitation of cascade testing, in which at-risk relatives undergo their own testing for the familial PV identified in the PDAC proband. Given that the established PDAC susceptibility genes are all linked to risks of non-PDAC cancers for which there are evidence-based methods of prevention (eg, salpingo-oophorectomy and mastectomy in *BRCA1/2*), the familial benefits of universal MGT are potentially quite significant.[15] Although no studies to date have examined the cost-effectiveness of universal MGT in PDAC, numerous analyses[25-27] have consistently demonstrated that the cost-effectiveness of systematic screening for various inherited cancer syndromes is heavily reliant on the uptake of cascade testing among at-risk relatives. While the body of literature on cascade testing remains limited, data suggest that historical rates of cascade testing in Lynch syndrome and *BRCA1/2* have been low (< 30%), indicating that this is a major barrier to achieving the full preventive impact from universal hereditary cancer risk assessment.[28-32] Encouragingly, with relatively short follow-up, > 50% of participants with a PV in our study had at least one at-risk relative pursue cascade testing, demonstrating the potential for universal GC/MGT to facilitate downstream cancer prevention.

As targeted therapies are now becoming viable treatments for some PDACs,[12,20,33] the other major potential benefit of universal GC/MGT is its ability to identify therapeutic opportunities for the PDAC proband themselves. The most notable example is the recent Food and Drug Administration approval of the PARP inhibitor olaparib as

maintenance therapy in patients with advanced PDAC with germline *BRCA1/BRCA2* PVs,[12] with ongoing speculation[34] that PARP inhibitors might also have benefit for patients with PDAC who harbor germline PVs in other homologous recombination genes (eg, *PALB2* and *ATM*). One recent analysis[33] demonstrated a median 12-month overall survival improvement for patients with PDAC with a somatic or germline abnormality who received therapy matched to their genomic findings versus those who received standard unmatched therapy (hazard ratio, 0.42; 95% CI, 0.26 to 0.68), highlighting the powerful therapeutic potential of such findings. With the high uptake of targeted therapies and cascade genetic testing among PV carriers and their relatives, respectively, our study's findings demonstrate that the theoretical rationale for universal GC/MGT in PDAC indeed translates into tangible real-world changes in management, with such downstream effects likely contributing to improved outcomes for the PDAC probands themselves, opportunities for cancer prevention in at-risk relatives, and a favorable cost-effectiveness profile for such efforts.

Our data also illustrate a number of barriers that threaten to limit the real-world effectiveness of universal GC/MGT. Previous publications discussing universal GC/MGT in PDAC have hypothesized that a major barrier to implementing such systematic testing will be the growing shortage of genetic counselors.[2] Even with abundant genetic counselor availability, however, referral rates in this study were disappointingly low, indicating that other factors are also barriers to real-world implementation of universal MGT. Our findings suggest that workflow relying on oncology providers to initiate the genetics workup is likely to suffer from suboptimal referral rates and may miss the window of opportunity of testing patients who are still well enough to pursue GC and targeted therapies.

A key limitation is this study's single institution design, which limits generalizability to other settings, particularly those with more limited GC resources. Furthermore, the availability of research funding to help defray the costs of clinical MGT may have artificially enhanced participants' willingness to undergo testing. These potential limitations, however, would have biased our results toward higher GC/MGT usage, and our findings of low referral or testing rates and the potential underlying barriers are all likely to be generalizable to real-world settings. Another limitation is the study's inability to assess specific reasons why providers failed to refer patients with PDAC for GC/MGT and reasons why patients may have declined referral. Notably, the NCCN first recommended consideration of universal GC/MGT in all patients with PDAC in mid-2018[3] with ASCO providing a similar recommendation later the same year,[23] both of which resulted in some patients with PDAC having already pursued GC/MGT prior to coming to DFCI. Finally, our cascade testing data may have been incomplete, since such data relied on report by the PDAC proband.

These data provide important insights into the effectiveness, downstream benefits, and barriers to systematically offering GC/MGT to all patients with PDAC in real-world practice. Changing from clinician-directed to automated referral workflows more than doubled the uptake of GC/MGT without any decline in PV detection rates. For those with PVs, there were tangible changes to management for the PDAC probands and their at-risk family members, demonstrating the real-world feasibility of systematic risk assessment. Even with an automated referral process, however, GC/MGT uptake was suboptimal, and additional data are needed to identify additional barriers to the real-world implementation of universal GC/MGT. Based on these data, however, we conclude that optimizing the real-world implementation of universal MGT will require workflows that directly offer GC/MGT to patients with PDAC, rather than relying on clinician referral.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al: Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med 21:213-223, 2019

2. Shindo K, Yu J, Suenaga M, et al: Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol 35:3382-3390, 2017

3. Hu C, Hart SN, Polley EC, et al: Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA 319:2401-2409, 2018

4. Grant RC, Selander I, Connor AA, et al: Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology 148:556-564, 2015

5. Brand R, Borazanci E, Speare V, et al: Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma. Cancer 124:3520-3527, 2018

6. Lowery MA, Wong W, Jordan EJ, et al: Prospective evaluation of germline alterations in patients with exocrine pancreatic neoplasms. J Natl Cancer Inst 110:1067-1074, 2018

7. Johns AL, McKay SH, Humphris JL, et al: Lost in translation: Returning germline genetic results in genome-scale cancer research. Genome Med 9:41, 2017

8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) genetic/familial high-risk assessment: Breast, ovarian, and pancreatic. Version 1.2021. nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

9. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al: Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 33:244-250, 2015

10. de Bono J, Ramanathan RK, Mina L, et al: Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov 7:620-629, 2017

11. Shroff RT, Hendifar A, McWilliams RR, et al: Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious *BRCA* mutation. JCO Precis Oncol 2018:PO.17.00316, 2018

12. Golan T, Hammel P, Reni M, et al: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 381:317-327, 2019

13. Klumpen HJ, Queiroz KC, Spek CA, et al: mTOR inhibitor treatment of pancreatic cancer in a patient with Peutz-Jeghers syndrome. J Clin Oncol 29:e150-e153, 2011

14. Lemery S, Keegan P, Pazdur R: First FDA approval agnostic of cancer site—When a biomarker defines the indication. N Engl J Med 377:1409-1412, 2017

15. Yurgelun MB: Germline testing for individuals with pancreatic cancer: the benefits and challenges to casting a wider net. J Clin Oncol 35:3375-3377, 2017

16. Schwark AL, Stadler ZK: Should we lower our threshold for germline genetic assessment in pancreatic adenocarcinoma? JCO Precis Oncol 2, 2018

17. Syngal S, Furniss CS: Germline genetic testing for pancreatic ductal adenocarcinoma at time of diagnosis. JAMA 319:2383-2385, 2018

18. Lieberman S, Lahad A, Tomer A, et al: Familial communication and cascade testing among relatives of BRCA population screening participants. Genet Med 20:1446-1454, 2018

19. Landsbergen K, Verhaak C, Kraaimaat F, et al: Genetic uptake in BRCA-mutation families is related to emotional and behavioral communication characteristics of index patients. Fam Cancer 4:115-119, 2005

20. Aguirre AJ, Nowak JA, Camarda ND, et al: Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. Cancer Discov 8:1096-1111, 2018

21. Yurgelun MB, Chittenden AB, Ukaegbu CI, et al: Implementing universal genetic counseling (GC) and multigene germline testing (MGT) for pancreatic cancer (PC) patients (pts). J Clin Oncol 36:1512, 2018 (15 suppl)

22. Lowery MA, Kelsen DP, Capanu M, et al: Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. Eur J Cancer 89:19-26, 2018

23. Stoffel EM, McKernin SE, Brand R, et al: Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. J Clin Oncol 37:153-164, 2019

24. Kurian AW, Ward KC, Howlader N, et al: Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. J Clin Oncol 37:1305-1315, 2019

25. Tuffaha HW, Mitchell A, Ward RL, et al: Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers. Genet Med 20:985-994, 2018

26. Eccleston A, Bentley A, Dyer M, et al: A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer. Value Health 20:567-576, 2017

27. Ladabaum U, Wang G, Terdiman J, et al: Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis. Ann Intern Med 155:69-79, 2011

e244 Volume 17, Issue 2

28. Suthers GK, Armstrong J, McCormack J, et al: Letting the family know: Balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. J Med Genet 43:665-670, 2006

29. Fehniger J, Lin F, Beattie MS, et al: Family communication of BRCA1/2 results and family uptake of BRCA1/2 testing in a diverse population of BRCA1/2 carriers. J Genet Couns 22:603-612, 2013

30. Frey MK, Kahn RM, Chapman-Davis E, et al: Prospective feasibility trial of a novel strategy of facilitated cascade genetic testing using telephone counseling. J Clin Oncol 38:1389-1397, 2020

31. Blandy C, Chabal F, Stoppa-Lyonnet D, et al: Testing participation in BRCA1/2-positive families: Initiator role of index cases. Genet Test 7:225-233, 2003

32. Sharaf RN, Myer P, Stave CD, et al: Uptake of genetic testing by relatives of lynch syndrome probands: A systematic review. Clin Gastroenterol Hepatol 11:1093-1100, 2013

33. Pishvaian MJ, Blais EM, Brody JR, et al: Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: A retrospective analysis of the Know Your Tumor registry trial. Lancet Oncol 21:508-518, 2020

34. Patel R, Fein D, Ramirez CB, et al: PARP inhibitors in pancreatic cancer: From phase I to plenary session. Pancreas (Fairfax) 3:e5-e8, 2019

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Implementing Systematic Genetic Counseling and Multigene Germline Testing for Individuals With Pancreatic Cancer

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APPENDIX

TABLE A1. Clinical Characteristics in Patients With a Germline Pathogenic Variant Versus Patients Without a Pathogenic Variant

Characteristic	All (N = 266)	PV Carriers (n = 28)	Noncarriers (n = 238)	P[a]
Sex				
Male	138 (51.9%)	16 (57.1%)	122 (51.3%)	.69
Female	128 (48.1%)	12 (42.9%)	116 (48.7%)	
Ethnicity				
Non-Hispanic white	246 (92.8%)	26 (92.8%)	220 (92.8%)	.93
Non-Hispanic black	3 (1.1%)	0	3 (1.3%)	
Hispanic or Latino	9 (3.4%)	1 (3.6%)	8 (3.4%)	
Others or unknown	7 (2.6%)	1 (3.6%)	6 (2.5%)	
Ashkenazi Jewish				
No	196 (73.7%)	24 (85.8%)	172 (72.3%)	.547
Yes	32 (12%)	2 (7.1%)	30 (12.6%)	
Unknown	38 (14.3%)	2 (7.1%)	36 (15.1%)	
Age at diagnosis, y (median Q1-Q3)	67 (60-73)	63 (57-71)	68 (61-73)	.157[b]
Stage at diagnosis				
Resectable	93 (35%)	8 (28.6%)	85 (35.7%)	.074
Locally advanced	38 (14.3%)	8 (28.6%)	30 (12.6%)	
Metastatic	135 (50.8%)	12 (42.9%)	123 (51.7%)	
Family history of pancreas cancer in FDR or SDR				
Yes	47 (17.7%)	7 (25.0%)	40 (16.8%)	.296
No	219 (82.3%)	21 (75.0%)	198 (83.2%)	
Personal history of non-PDAC cancer[c]				
Yes	89 (33.5%)	11 (39.3%)	78 (32.8%)	.528
No	177 (66.5%)	17 (60.7%)	160 (67.2%)	
Testing period				
Clinician-directed	150 (56.4%)	15 (53.6%)	135 (56.7%)	.841
Automated	116 (43.6%)	13 (46.4%)	103 (43.3%)	

Abbreviations: FDR, first-degree relative; PDAC, pancreatic ductal adenocarcinoma; PV, pathogenic variant; Q, quartile; SDR, second-degree relative.
[a]Calculated using Fisher's exact test unless otherwise specified.
[b]Mann-Whitney U test.
[c]Excluding nonmelanoma skin cancer.