ASCO special article abstract

Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion

Elena M. Stoffel, MD[1]; Shannon E. McKernin[2]; Randall Brand, MD[3]; Marcia Canto, MD[4]; Michael Goggins, MD[4]; Cassadie Moravek[5]; Arun Nagarajan, MD[6]; Gloria M. Petersen, PhD[7]; Diane M. Simeone, MD[8]; Matthew Yurgelun, MD[9]; and Alok A. Khorana, MD[6]

PURPOSE An ASCO provisional clinical opinion (PCO) offers timely clinical direction to ASCO's membership and other health care providers. This PCO addresses identification and management of patients and family members with possible predisposition to pancreatic adenocarcinoma.

METHODS ASCO convened an Expert Panel and conducted a systematic review of the literature published from January 1998 to June 2018. Results of the databases searched were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles and contributions from Expert Panel members' curated files.

PROVISIONAL CLINICAL OPINION All patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma. Assessment of risk should include a comprehensive review of family history of cancer. Individuals with a family history of pancreatic cancer affecting two first-degree relatives meet criteria for familial pancreatic cancer (FPC). Individuals (cancer affected or unaffected) with a family history of pancreatic cancer meeting criteria for FPC, those with three or more diagnoses of pancreatic cancer in same side of the family, and individuals meeting criteria for other genetic syndromes associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing. Germline genetic testing for cancer susceptibility may be discussed with individuals diagnosed with pancreatic cancer, even if family history is unremarkable. Benefits and limitations of pancreatic cancer screening should be discussed with individuals whose family history meets criteria for FPC and/or genetic susceptibility to pancreatic cancer.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

J Clin Oncol 37:153-164. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 24, 2018 and published at jco.org on November 20, 2018: DOI https://doi.org/10.1200/JCO.18.01489

Clinical Practice Guidelines Committee approval: September 18, 2018.

Editor's note: Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

Reprint Requests: 2318 Mill Rd, Suite 800, Alexandria, VA 22314; guidelines@asco.org

INTRODUCTION

ASCO has established an approach to offer a rapid response to emerging information in clinical oncology. The provisional clinical opinion (PCO) is intended to offer timely clinical direction to ASCO's oncologists and other health care providers, including primary care physicians. This PCO was prioritized to address a research area where there are emerging data but not a robust landscape of clinical trials. The Expert Panel includes a discussion section on limitations of the research to guide future directions. This PCO should be read with the understanding that randomized clinical trial data are not available for these guidance statements, but it is the opinion of the Expert Panel that the statements made represent the state of the data available.

This PCO addresses identification and management of patients and family members with predisposition to pancreatic adenocarcinoma. Estimates suggest up to 10% of all pancreatic adenocarcinoma cases are familial,[1] and pathogenic germline variants in specific genes have been associated with lifetime risks of pancreatic cancer ranging from 4% to 40%.[2-5] For these high-risk individuals, surveillance offers the potential for early identification of pancreatic neoplasms.[1,2] This PCO addresses how susceptibility to adenocarcinomas of the pancreas should be assessed, who should be genetically tested and/or screened for familial predisposition to pancreatic adenocarcinoma, and what pancreas surveillance strategies should be used in individuals with predisposition to pancreatic ductal adenocarcinoma.

METHODS

This systematic review-based product was developed by a multidisciplinary Expert Panel, which included a patient representative and ASCO guidelines staff with health research methodology expertise. Computerized literature searches of PubMed and the Cochrane Collaboration Library were performed. The searches of

THE BOTTOM LINE

Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion

Research Question

How can individuals at increased risk for pancreatic cancer be identified and managed?

Target Population

People diagnosed with pancreatic adenocarcinoma and families or individuals with concern for genetic predisposition to pancreatic cancer.

Target Audience

Primary care physicians, medical oncologists, nurse practitioners, surgeons, gastroenterologists, internists, and other health care providers.

Methods

ASCO convened an Expert Panel and conducted a systematic review of the literature published from January 1998 to June 2018. Results of the database searches were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles and contributions from Expert Panel members' curated files.

Provisional Clinical Opinion

Research Question 1

How should susceptibility for pancreatic cancer be assessed? What is the role of family history of cancer? Which individuals are considered as having predisposition to pancreatic cancer?

PCO 1.1 Clinical evaluations of people (with or without pancreatic cancer) should include assessment for possible genetic predisposition syndromes, beginning with a review of family history of cancer (including tumor types and ages at diagnosis for all first- and second-degree relatives)[43] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

PCO 1.2 Individuals with a family history of pancreatic cancer affecting two first-degree relatives meet criteria for familial pancreatic cancer. Individuals whose family history meets criteria for familial pancreatic cancer, those with three or more diagnoses of pancreatic cancer in same side of the family, and individuals meeting criteria for other genetic syndromes (Table 1) associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Qualifying Statement. It is important to note that for 90% of families meeting criteria for familial pancreatic cancer, genetic testing does not detect a pathogenic mutation; therefore, there may be additional shared epigenetic, genetic, or environmental factors that contribute to pancreatic cancer risk.

PCO 1.3 Genetic risk evaluation should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer syndromes to determine the most appropriate testing strategy and discuss implications of the findings for family members. Germline genetic testing for patients with pancreatic cancer should be offered in the context of shared decision making[44-47] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Research Question 2

Which individuals should undergo genetic testing for predisposition to pancreatic cancer?

PCO 2.1 All patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma (Table 1). Assessment of risk includes obtaining a personal cancer history and family history of cancers in first- and second-degree relatives. However, recent data demonstrate that many individuals who develop pancreatic cancer in the setting of genetic predisposition lack clinical features or family cancer history typically associated with the corresponding hereditary syndrome. Therefore, germline genetic testing may be discussed with patients with personal history of pancreatic cancer, even if family history is unremarkable (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

PCO 2.2 An individual with a cancer diagnosis is often the best candidate in whom to initiate genetic testing and has the highest likelihood of an informative test result; however, if a cancer-affected individual is not available, testing may be performed in a pancreatic cancer–unaffected individual following genetic risk assessment, with the understanding that a negative test result is considered clinically uninformative.

The following cancer-unaffected individuals should be offered genetic risk evaluation:

- Members of families with an identified pathogenic cancer susceptibility gene variant

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Pancreatic cancer–unaffected individuals from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer
- Pancreatic cancer–unaffected individuals from families that meet criteria for familial pancreatic cancer, as outlined in PCO 1.2

(Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

PCO 2.3 Genetic testing in a patient with pancreatic cancer may confirm the diagnosis of a hereditary cancer syndrome and inform management of at-risk family members. Given the possibility that certain germline variants could potentially be used to guide therapeutic decision making and the limited prognosis of many patients with pancreatic cancer, the Expert Panel recommends that consideration of germline testing for inherited cancer susceptibility should be performed early in the disease course for patients with pancreatic cancer (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

PCO 2.4 Several genes have been linked to risk for pancreatic cancer (Table 1). Unless a genetic diagnosis has previously been confirmed in a family member, germline genetic testing should be performed using a multigene panel that includes the genes listed in Table 1. A finding of a pathogenic or likely pathogenic germline variant can confer increased risks of cancers beyond the pancreas for the probands and their families; finding a germline variant of uncertain significance is not considered to be causative of increased cancer susceptibility[47,51] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Research Question 3

What surveillance strategies should be used for individuals with predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers?

PCO 3.1 Pancreatic cancer surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer[2,5,34,37,52] and/or individuals with a family history of pancreatic cancer who carry a pathogenic germline variant in genes associated with predisposition to pancreatic cancer (Table 1). The potential risks, benefits, uncertainties, and limitations of surveillance for pancreatic cancer should be discussed in detail with individuals who are being considered for pancreatic cancer surveillance prior to beginning such surveillance. When possible, pancreatic surveillance should be performed at centers with the appropriate expertise to manage individuals at increased risk for pancreatic cancer. Surveillance may be performed with various modalities, including pancreas protocol magnetic resonance imaging/magnetic resonance cholangiopancreatography and/or endoscopic ultrasound. There are currently no approved biomarkers for screening and surveillance. CA 19-9 is not recommended as a screening test in the general population due to low specificity and sensitivity; its potential utility in pancreatic screening of high-risk individuals has not been established (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

Qualifying Statement. Although large studies confirming mortality benefit of pancreatic screening are lacking, emerging data suggest screening in individuals at high risk is associated with downstaging of incident cancers.[53]

PCO 3.2 There is not yet consensus on pathologic targets for surveillance, but the Expert Panel agrees the ultimate goal should be detection and treatment of high-grade dysplasia to prevent invasive cancer (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

PCO 3.3 The potential risks of surveillance, including the risk of overtreatment and unnecessary resections, should be discussed with the patient. Given the challenges, patients should optimally be managed by an expert multidisciplinary team with experience in pancreatic cancer surveillance. Additional clinical studies are needed to determine the optimal approach for pancreatic surveillance (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

PCO 3.4 There is currently a lack of consensus regarding which lesions discovered by pancreatic imaging require resection. Findings that generally warrant resection include lesions that are solid and/or that are associated with obstructive jaundice and/or dilation of the main pancreatic duct greater than 10 mm. The presence of worrisome features (cyst size greater than 3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct greater than 5 mm, abrupt change in duct caliber, or rapid growth) and the presence of three or more pancreatic cysts in the pancreas of high-risk individuals are associated with an increased risk of neoplastic progression.[53]

Additional Resources More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of PCOs, slide sets, and clinical tools and resources, is available at www.asco.org/gastroinestinal-cancer-guidelines. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

the English-language literature published from January 1998 to January 2018 combined hereditary pancreatic neoplasm terms and screening and intervention-related terms and MeSH headings. Results of the database searches were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles and contributions from Expert Panel members' curated files through June 2018. The Expert Panel met via teleconference and e-mail to formulate the research questions and the recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. The draft manuscript and supplements were circulated to the panel for review and approval. The final manuscript was reviewed and approved by the ASCO Clinical Practice Guidelines Committee.

The members of the PCO Expert Panel are listed in Appendix Table A1 (online only). ASCO PCOs are updated by the Expert Panel on the basis of periodic review and analysis of new, potentially practice-changing information on the topic. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information therein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

PCO and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 40 papers met eligibility criteria and form the evidentiary basis for the PCO recommendations.[2,3,5-42] The papers informed the panel members but, ultimately, did not establish a strong evidence base to craft the recommendations. The results of the literature search identified the gaps in knowledge on the topic, which led to the section highlighting the limitations of the research and future directions. Additional information can be found in the Data Supplement.

ASCO'S PROVISIONAL CLINICAL OPINION

Research Question 1

How should susceptibility for pancreatic cancer be assessed? What is the role of family history of cancer? Which individuals are considered as having predisposition to pancreatic cancer?

PCO 1.1 Clinical evaluations of people (with or without pancreatic cancer) should include assessment for possible genetic predisposition syndromes, beginning with a review of family history of cancer (including tumor types and ages at diagnosis for all first- and second-degree relatives)[43] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

PCO 1.2 Individuals with a family history of pancreatic cancer affecting two first-degree relatives meet criteria for familial pancreatic cancer. Individuals whose family history

TABLE 1. Genes Associated With Increased Risk for Pancreatic Cancer

Gene	Syndrome	Pancreatic Cancer Risk (%)	Other Associated Cancers*
APC	Familial adenomatous polyposis	1-5	Colorectal, upper GI, thyroid, brain
ATM	Ataxia telangiectasia (biallelic)†	1-5	Breast, prostate, gastric
BRCA2	Hereditary breast ovarian cancer syndrome	5-10	Breast, ovary, prostate, melanoma
BRCA1	Hereditary breast ovarian cancer syndrome	2	Breast, ovary, prostate, melanoma
CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	10-30	Melanoma
MLH1, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Lynch syndrome	5-10	Colorectal, uterine, upper GI, ovary, urinary tract, brain, sebaceous neoplasms
PALB2		5-10	Breast, prostate
STK11	Peutz Jeghers syndrome	10-30	Breast, colorectal, upper GI, lung, reproductive tract
TP53	Li Fraumeni syndrome	Not defined	Breast, brain, sarcoma, adrenocortical carcinoma

*Most commonly associated cancers.

†Biallelic *ATM* mutation carriers have ataxia telangiectasia, but a single *ATM* mutation is associated with increased risk for pancreatic cancer.

meets criteria for familial pancreatic cancer, those with three or more diagnoses of pancreatic cancer in same side of the family, and individuals meeting criteria for other genetic syndromes (Table 1) associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Qualifying statement. It is important to note that for 90% of families meeting criteria for familial pancreatic cancer, genetic testing does not detect a pathogenic mutation; therefore, there may be additional shared epigenetic, genetic, or environmental factors that contribute to pancreatic cancer risk.

PCO 1.3 Genetic risk evaluation should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer syndromes to determine the most appropriate testing strategy and discuss implications of the findings for family members. Germline genetic testing for patients with pancreatic cancer should be offered in the context of shared decision making[44-47] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Research Question 2

Which individuals should undergo genetic testing for predisposition to pancreatic cancer?

PCO 2.1 All patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma (Table 1). Assessment of risk includes obtaining a personal cancer history and family history of cancers in first- and second-degree relatives. However, recent data demonstrate that many individuals who develop pancreatic cancer in the setting of genetic predisposition lack clinical features or family cancer history typically associated with the corresponding hereditary syndrome. Therefore, germline genetic testing may be discussed with patients with personal history of pancreatic cancer, even if family history is unremarkable (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Rationale. Recent studies have identified pathogenic germline variants in cancer predisposition genes in 4% to 20% of patients with pancreatic cancer.[2,8,12,21,30,42,44-46,48-50] The prevalence of germline mutations is especially high among individuals of Ashkenazi Jewish ancestry, as a result of the high prevalence of *BRCA1* and *BRCA2* founder mutations in this population. Approximately half of patients with pancreatic cancer found to carry pathogenic genetic variants have no family history of pancreatic cancer and/or do not meet clinical criteria for the hereditary syndrome corresponding to their genetic diagnosis; therefore, patients should not be precluded from an opportunity to benefit from genetic testing just because their personal or family cancer history does not provide positive evidence of an inherited cancer syndrome. Given the potential that this information could be of benefit to the patient directly or to their family, the option of genetic testing should be discussed in the context of shared decision making. Germline genetic testing may not be indicated for patients with incurable pancreatic cancer who lack any living family members or for whom the results will not otherwise change management.

PCO 2.2 An individual with a cancer diagnosis is often the best candidate in whom to initiate genetic testing and has the highest likelihood of an informative test result; however, if a cancer-affected individual is not available, testing may be performed in a pancreatic cancer–unaffected individual following genetic risk assessment, with the understanding that a negative test result is considered clinically uninformative.

The following cancer-unaffected individuals should be offered genetic risk evaluation:

- Members of families with an identified pathogenic cancer susceptibility gene variant
- Pancreatic cancer–unaffected individuals from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer
- Pancreatic cancer–unaffected individuals from families that meet criteria for familial pancreatic cancer, as outlined in PCO 1.2

(Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

PCO 2.3 Genetic testing in a patient with pancreatic cancer may confirm the diagnosis of a hereditary cancer syndrome and inform management of at-risk family members. Given the possibility that certain germline variants could potentially be used to guide therapeutic decision making and the limited prognosis of many patients with pancreatic cancer, the Expert Panel recommends that consideration of germline testing for inherited cancer susceptibility should be performed early in the disease course for patients with pancreatic cancer (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

PCO 2.4 Several genes have been linked to risk for pancreatic cancer (Table 1). Unless a genetic diagnosis has previously been confirmed in a family member, germline genetic testing should be performed using a multigene panel that includes the genes listed in Table 1. A finding of a pathogenic or likely pathogenic germline variant can confer increased risks of cancers beyond the pancreas for the probands and their families; finding a germline variant of uncertain significance is not considered to be causative of increased cancer susceptibility[47,51] (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

Research Question 3

What surveillance strategies should be used for individuals with predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers?

PCO 3.1 Pancreatic cancer surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer[2,5,34,37,52] and/or individuals with a family history of pancreatic cancer who carry a pathogenic germline variant in genes associated with predisposition to pancreatic cancer (Table 1). The potential risks, benefits, uncertainties, and limitations of surveillance for pancreatic cancer should be discussed in detail with individuals who are being considered for pancreatic cancer surveillance prior to beginning such surveillance. When possible, pancreatic surveillance should be performed at centers with the appropriate expertise to manage individuals at increased risk for pancreatic cancer. Surveillance may be performed with various modalities, including pancreas protocol magnetic resonance imaging/magnetic resonance cholangiopancreatography and/or endoscopic ultrasound. There are currently no approved biomarkers for screening and surveillance. CA 19-9 is not recommended as a screening test in the general population because of low specificity and sensitivity; its potential utility in pancreatic screening of high-risk individuals has not been established (Type of recommendation: informal consensus; relative balance of benefits and harms; Strength of recommendation: moderate).

Qualifying Statement. Although large studies confirming mortality benefit of pancreatic screening are lacking, emerging data suggest screening in individuals with high risk is associated with downstaging of incident cancers.[53]

PCO 3.2 There is not yet consensus on pathologic targets for surveillance, but the Expert Panel agrees the ultimate goal should be detection and treatment of high-grade dysplasia to prevent invasive cancer (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

Rationale. Although survival of patients with screen-detected cancers is improved relative to those who present with symptomatic cancers, many patients with screen-detected pancreatic cancers will die as a result of their disease.[40,53] In individuals who carry genetic alterations and families with a high prevalence of pancreatic cancer, the prevalence of pancreatic abnormalities (mostly small pancreatic cystic neoplasms of low-malignant potential) is higher than in the general population.[35,54] Early experience of pancreatic screening programs indicates that pancreatic cancers detected by screening are downstaged.[40,53]

PCO 3.3 The potential risks of surveillance, including the risk of overtreatment and unnecessary resections, should be discussed with the patient. Given the challenges, patients should optimally be managed by an expert multidisciplinary team with experience in pancreatic cancer surveillance. Additional clinical studies are needed to determine the optimal approach for pancreatic surveillance (Type: informal consensus; relative balance of benefits and harms; Strength of statement: moderate).

PCO 3.4 There is currently a lack of consensus regarding which lesions discovered by pancreatic imaging require resection. Findings that generally warrant resection include lesions that are solid and/or that are associated with obstructive jaundice and/or dilation of the main pancreatic duct greater than 10 mm. The presence of worrisome features (cyst size greater than 3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct greater than 5 mm, abrupt change in duct caliber, or rapid growth) and the presence of three or more pancreatic cysts in the pancreas of high-risk individuals are associated with an increased risk of neoplastic progression.[53]

PATIENT-CLINICIAN COMMUNICATION

Cancer-unaffected individuals with a relative diagnosed with pancreatic cancer face the uncertainty of knowing if they too are at risk for the disease. Communication between patients and clinicians is key to understanding the cancer-unaffected individual's concerns when making decisions about pursuing genetic testing. Cancer-unaffected individuals should fully understand that this risk depends on the extent of their family history and their own medical history and can learn more about their risk by consulting with a clinician with cancer genetics expertise. They should also be aware that such an evaluation may help them better understand their overall cancer risk, but strategies to prevent pancreatic cancer, such as early detection, have not been proven to prevent pancreatic cancer. For cancer-unaffected individuals to make informed decisions, clinicians should describe the potential impact (both medical and emotional aspects) of genetic testing on both the individual and the family.

Cancer-unaffected individuals should also understand that many of the germline mutations associated with an increased risk of pancreatic cancer are also associated with increased risk of other cancers that exceed the lifetime risk for pancreatic cancer. Providers should share that there are effective strategies for prevention and screening of many of these other cancers, such as breast and colorectal cancer, associated with highly penetrant hereditary cancer syndromes (eg, Lynch syndrome, hereditary breast and ovarian cancer) identified in some families affected with pancreatic cancer, so genetic testing is reasonable for cancer-unaffected individuals meeting specific criteria.

It is advisable to provide resources to help patients communicate better with their health care team. Patients should be offered decision-making tools and urged to write down questions in between and in advance of appointments. Patients can be referred to resources that will extend the support and information clinicians are able to provide. For pancreatic cancer, two such resources are the ASCO patient-facing website (www.cancer.net) and the Pancreatic Cancer Action Network (www.pancan.org).

LIMITATIONS OF THE RESEARCH AND FUTURE DIRECTIONS

Utility of Multigene Panels for Clinical Genetic Testing

The prevalence of pathogenic germline variants in genes associated with cancer predisposition is higher among individuals diagnosed with pancreatic cancer, and the diversity of genes implicated provides justification for the use of multigene panel tests (Table 1). The most common germline findings are pathogenic variants in *BRCA1* and *BRCA2*, which have been associated with an estimated 3% and 5% lifetime risk for pancreatic cancer, respectively. *CDKN2A* germline mutations are also identified; in addition to risk of cutaneous melanoma, *CDKN2A* germline variants have been associated with increased risk of pancreatic cancer, with relative risks between 52 and 80.8.[55,56] By comparison, germline variants in *STK11* associated with Peutz Jeghers syndrome, while much rarer, are associated with a much more substantial increase in pancreatic cancer risk (relative risk, 132) as well as increased risk for other cancers.[4] While the rationale for germline sequencing of genes associated with high-penetrance cancer syndromes is well established, the clinical utility of sequencing of moderate-penetrance genes has been challenged. Germline pathogenic variants in moderate-penetrance genes (eg, *ATM*, *CHEK2*) are found in one in every 100 individuals in the general population, but the magnitude of cancer risk increase associated with these pathogenic variants remains to be determined.[50] Additional genetic or environmental factors may modify cancer risk in individuals who carry pathogenic germline variants. A pathogenic or likely pathogenic variant is considered to have potential implications for patients with cancer and their families based on currently available surveillance, prevention, or treatment implications for any associated cancer (Table 1) in either the patient or his or her close family members. For example, many pancreatic cancer susceptibility genes are also included as high- and moderate-penetrance cancer genes in National Comprehensive Cancer Network screening and surveillance guidelines for breast and colorectal cancer.[57,58] Patients who undergo genetic testing using a multigene panel should be counseled regarding the increased likelihood of finding a variant of uncertain significance.

Biomarkers

Despite considerable effort evaluating proteins, circulating tumor DNA, microRNA, exosomes, immunologic markers, and so on, there are currently no proven biomarkers using noninvasively obtained biospecimens (eg, blood, urine, stool) for early detection of pancreatic cancer in asymptomatic individuals.[59-62] A number of factors contribute to this challenging problem. Pancreatic cancer has a low overall annual incidence rate (12.5 per 100,000) and a 1.6% average lifetime risk in the United States[63]; for this reason, even the most diagnostically accurate blood tests may be only suitable for those at increased risk of developing the disease. For this reason, recent efforts have focused on developing blood tests that can detect a panel of cancers so as to increase the pretest probability of a positive test and more comprehensive early cancer detection.[64] In addition, because of the expense and effort of follow-up imaging or invasive diagnostic testing, and the potential for psychological harm due to false-positive tests, only tests with high diagnostic specificity (approximately 99%) are suitable as early detection tests.

One challenge to the evaluation of candidate biomarker tests is the lack of prediagnostic biospecimens obtained from asymptomatic individuals with early-stage cancers.[59] Serum CA19-9 has been used as a biomarker of pancreatic cancer progression in patients but has limitations, because

around 10% of individuals are negative for Lewis antigen a or b (a-b-), and do not have detectable CA19-9.[65,66] This reduces its value to use alone as a screening biomarker. Furthermore, CA-19-9 may also be elevated in patients with nonmalignant diseases, including liver cirrhosis, chronic pancreatitis, cholangitis, and other GI cancers.[67]

There is no evidence on the clinical utility or validity of the use of circulating tumor DNA for screening outside of clinical trials.[68] Initial studies in the setting of pancreatic cancer screening indicate that the percentage of patients with stage I cancer who have detectable circulating tumor DNA is low, and its detection is associated with a poorer outcome.[69,70] More recently, multimarker panels have been evaluated to improve biomarker diagnostic performance. In principle, combining multiple markers with high diagnostic specificity could improve diagnostic sensitivity, but high circulating tumor marker levels will often reflect higher tumor burden rather than early detection. Rigorous testing and validation of potential biomarkers, used either alone or in combination, in high-risk individuals, is a need in the field and an area of active investigation.

Another area of active investigation is understanding the relationship of pancreatic cancer diagnosis with a prior diagnosis of recent or new-onset diabetes (NOD) in individuals older than 50 years. There is a six- to eight-fold higher risk of being diagnosed with pancreatic cancer within 3 years of first meeting glycemic criteria for NOD, with a 3-year incidence of being diagnosed with pancreatic cancer of 0.5% to 1%.[71,72] Notably, with the diagnosis of pancreatic cancer in the setting of new-onset diabetes is often accompanied by recent weight loss.[73,74] Additional research is needed in this area, as there are currently no published studies evaluating the utility of an NOD diagnosis in individuals with an inherited/familial predisposition to pancreatic cancer.

Thresholds for Surgical Resection

Solid lesions of the pancreas, in particular those that are concerning to represent a possible adenocarcinoma of the pancreas, and other features that are considered high risk (ie, concerning for pancreatic cancer), such as obstructive jaundice, mural nodules of diameter 5 mm or more, and marked dilatation of the main pancreatic duct (diameter greater than 10 mm), generally require surgical resection. Worrisome features (eg, cyst size greater than 3 cm, thickened/enhancing cyst walls, small mural nodules, dilated main pancreatic duct 5 to 9 mm, abrupt change in duct caliber, and/or rapid cyst growth [greater than 5-mm increase in diameter within 2 years])[53] often represent advanced premalignant lesions, although the neoplastic grade of these lesions cannot be reliably determined by imaging. There is no consensus about which of these lesions in which patients are of sufficient concern to warrant pancreatic resection. Published reports on the indications and yield of pancreatic resection in the high-risk setting are based on limited numbers of patients.[35,75-78] Discussions about indications for surgical resection should be undertaken by experienced clinicians in a multidisciplinary setting. There are also many patients with minor pancreatic imaging abnormalities; the degree and extent of these varies considerably, and they often have uncertain neoplastic significance and are monitored. Pancreatic resection is not currently indicated in high-risk individuals without an identifiable pancreatic lesion.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[79-82] For patients with pancreatic cancer specifically, it has been known for more than a decade that African Americans have a higher incidence and a higher risk of presenting with advanced-stage disease and are less likely to undergo surgical treatment of resectable disease.[83,84] These racial disparities do not appear to have improved in recent years.[85] There are also substantial regional variations in utilization of multimodality therapy in treatment of pancreatic cancer.[86] Awareness of these disparities in access to care should be considered in the context of this provisional clinical opinion, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

COST CONSIDERATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of costs through deductibles and coinsurance.[87,88] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer screening.[89,90]

Discussion of cost should be an important part of shared decision making.[91] Formal cost-effectiveness strategies for germline genetic testing in pancreatic cancer and pancreatic imaging in individuals at increased risk for pancreatic cancer are not available. However, given the substantial costs of diagnosis and treatment of pancreatic cancer as well as the lethality of the disease, early diagnosis is likely cost-beneficial to society. Indeed, the potential benefits of genetic testing can be extrapolated from results of cost-effectiveness studies of *BRCA* genetic testing in ovarian cancer, for instance.[92] Genetic testing costs have diminished considerably but still can present a barrier to access, especially if not covered by third-party payers. A

transparent discussion about potential out-of-pocket costs of genetic testing as well as surveillance imaging should be conducted with patients and families.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment March 30 through April 13, 2018. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation in four questions. A total of five people responded to the survey questions with six written comments received. A total of 100% of the five respondents either agreed or agreed with slight modifications to the first section. A total of 100% of the five respondents either agreed or agreed with slight modifications to the second section. A total of 80% of the five respondents either agreed or agreed with slight modifications to the third section, and 20% disagreed. A total of 80% of the five respondents either agreed or agreed with slight modifications to the fourth section, and 20% disagreed. Expert Panel members reviewed comments from all sources and determined to revise the recommendations with minor language changes. All changes were incorporated prior to ASCO Clinical Practice Guidelines Committee review and approval.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources is available at www.asco.org/gastroinestinal-cancer-guidelines. Patient information is available at www.cancer.net.

Related ASCO Guidelines

- Locally Advanced Pancreatic Cancer[93] (http://ascopubs.org/doi/10.1200/JCO.2016.67.5561)
- Metastatic Pancreatic Cancer[94] (http://ascopubs.org/doi/10.1200/JCO.2018.78.9636)
- Potentially Curable Pancreatic Cancer[95] (http://ascopubs.org/doi/10.1200/JCO.2017.72.4948)

AFFILIATIONS

[1]University of Michigan, Ann Arbor, MI
[2]American Society of Clinical Oncology, Alexandria, VA
[3]University of Pittsburgh, Pittsburgh, PA
[4]Johns Hopkins University, Baltimore, MD
[5]Pancreatic Cancer Action Network, Los Angeles, CA
[6]Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH
[7]Mayo Clinic, Rochester, MN
[8]New York University Langone Health, New York, NY
[9]Dana-Farber Cancer Institute, Boston, MA

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EQUAL CONTRIBUTION

E.M.S. and A.A.K. were Expert Panel Co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABLITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.01489.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Matthew H.G. Katz, MD, Jeremy Kortmansky, MD, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this PCO. Dr. Khorana acknowledges research support from the Sondra and Stephen Hardis Chair in Oncology Research and the National Heart, Lung and Blood Institute (U01HL143402, R34 HL127156).

REFERENCES

1. Stoffel EM: Screening in GI cancers: The role of genetics. J Clin Oncol 33:1721-1728, 2015
2. Canto MI, Harinck F, Hruban RH, et al: International Cancer of the Pancreas Screening (CAPS) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 62:339-347, 2013
3. Kastrinos F, Mukherjee B, Tayob N, et al: Risk of pancreatic cancer in families with Lynch syndrome. JAMA 302:1790-1795, 2009
4. Giardiello FM, Brensinger JD, Tersmette AC, et al: Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 119:1447-1453, 2000
5. 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
6. Childs EJ, Chaffee KG, Gallinger S, et al: Association of common susceptibility variants of pancreatic cancer in higher-risk patients: A PACGENE study. Cancer Epidemiol Biomarkers Prev 25:1185-1191, 2016
7. Del Chiaro M, Zerbi A, Falconi M, et al: Cancer risk among the relatives of patients with pancreatic ductal adenocarcinoma. Pancreatology 7:459-469, 2007

8. Dudley B, Karloski E, Monzon FA, et al: Germline mutation prevalence in individuals with pancreatic cancer and a history of previous malignancy. Cancer 124: 1691-1700, 2018
9. Flores K, Dinh K, Rouleau E, et al: Identification of genetic risk for pancreatic adenocarcinoma. Cancer Genet 208:559-563, 2015
10. Ghiorzo P, Fornarini G, Sciallero S, et al: CDKN2A is the main susceptibility gene in Italian pancreatic cancer families. J Med Genet 49:164-170, 2012
11. Grant RC, Denroche RE, Borgida A, et al: Exome-wide association study of pancreatic cancer risk. Gastroenterology 154:719-722.e3, 2018
12. 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
13. Hahn SA, Greenhalf B, Ellis I, et al: BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 95:214-221, 2003
14. Hall MJ, Dignam JJ, Olopade OI: Family history of pancreatic cancer in a high-risk cancer clinic: Implications for risk assessment. J Genet Couns 17:365-372, 2008
15. Harinck F, Kluijt I, van der Stoep N, et al: Indication for CDKN2A-mutation analysis in familial pancreatic cancer families without melanomas. J Med Genet 49: 362-365, 2012
16. Lal G, Liu G, Schmocker B, et al: Inherited predisposition to pancreatic adenocarcinoma: Role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res 60:409-416, 2000
17. Mocci E, Milne RL, Méndez-Villamil EY, et al: Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. Cancer Epidemiol Biomarkers Prev 22:803-811, 2013
18. Potjer TP, van der Stoep N, Houwing-Duistermaat JJ, et al: Pancreatic cancer-associated gene polymorphisms in a nation-wide cohort of p16-Leiden germline mutation carriers; a case-control study. BMC Res Notes 8:264, 2015
19. Reiss KA YS, Judy R, Symecko H, et al: Retrospective survival analysis of patients with advanced pancreatic ductal adenocarcinoma and germline *BRCA* or *PALB2* mutations. JCO Precis Oncol 10.1200/PO.17.00152, 2018
20. Roberts NJ, Norris AL, Petersen GM, et al: Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov 6: 166-175, 2016
21. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al: Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 121:4382-4388, 2015
22. Vasen HF, Gruis NA, Frants RR, et al: Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer 87:809-811, 2000
23. Zhen DB, Rabe KG, Gallinger S, et al: BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: A PACGENE study. Genet Med 17:569-577, 2015
24. Catts ZA, Baig MK, Milewski B, et al: Statewide retrospective review of familial pancreatic cancer in Delaware, and frequency of genetic mutations in pancreatic cancer kindreds. Ann Surg Oncol 23:1729-1735, 2016
25. Klein AP, Brune KA, Petersen GM, et al: Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 64:2634-2638, 2004
26. Ohmoto A, Yachida S, Kubo E, et al: Clinicopathologic features and germline sequence variants in young patients (≤40 years old) with pancreatic ductal adenocarcinoma. Pancreas 45:1056-1061, 2016
27. Permuth-Wey J, Egan KM: Family history is a significant risk factor for pancreatic cancer: Results from a systematic review and meta-analysis. Fam Cancer 8: 109-117, 2009
28. Schenk M, Schwartz AG, O'Neal E, et al: Familial risk of pancreatic cancer. J Natl Cancer Inst 93:640-644, 2001
29. Schulte A, Pandeya N, Fawcett J, et al: Association between family cancer history and risk of pancreatic cancer. Cancer Epidemiol 45:145-150, 2016
30. 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
31. Syngal S, Brand RE, Church JM, et al: ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 110:223-262, 2015; quiz 263
32. Tersmette AC, Petersen GM, Offerhaus GJ, et al: Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res 7:738-744, 2001
33. Wang L, Brune KA, Visvanathan K, et al: Elevated cancer mortality in the relatives of patients with pancreatic cancer. Cancer Epidemiol Biomarkers Prev 18: 2829-2834, 2009
34. Bruenderman EH, Martin RC II: High-risk population in sporadic pancreatic adenocarcinoma: Guidelines for screening. J Surg Res 194:212-219, 2015
35. Canto MI, Hruban RH, Fishman EK, et al: Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 142:796-804, 2012; quiz e14-15
36. Konings IC, Harinck F, Poley JW, et al: Prevalence and progression of pancreatic cystic precursor lesions differ between groups at high risk of developing pancreatic cancer. Pancreas 46:28-34, 2017
37. Lu C, Xu CF, Wan XY, et al: Screening for pancreatic cancer in familial high-risk individuals: A systematic review. World J Gastroenterol 21:8678-8686, 2015
38. Mocci E, Guillen-Ponce C, Earl J, et al: PanGen-Fam: Spanish registry of hereditary pancreatic cancer. Eur J Cancer 51:1911-1917, 2015
39. Sud A, Wham D, Catalano M, et al: Promising outcomes of screening for pancreatic cancer by genetic testing and endoscopic ultrasound. Pancreas 43: 458-461, 2014
40. Vasen H, Ibrahim I, Ponce CG, et al: Benefit of surveillance for pancreatic cancer in high-risk individuals: Outcome of long-term prospective follow-up studies from three European expert centers. J Clin Oncol 34:2010-2019, 2016
41. Verna EC, Hwang C, Stevens PD, et al: Pancreatic cancer screening in a prospective cohort of high-risk patients: A comprehensive strategy of imaging and genetics. Clin Cancer Res 16:5028-5037, 2010
42. 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 10.1038/s41436-018-0009-5 [epub ahead of print on July 2, 2018]
43. Lu KH, Wood ME, Daniels M, et al: American Society of Clinical Oncology expert statement: Collection and use of a cancer family history for oncology providers. J Clin Oncol 32:833-840, 2014
44. Lucas AL, Frado LE, Hwang C, et al: BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer 120:1960-1967, 2014
45. 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
46. Holter S, Borgida A, Dodd A, et al: Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol 33: 3124-3129, 2015

47. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015
48. Klein AP: Genetic susceptibility to pancreatic cancer. Mol Carcinog 51:14-24, 2012
49. Lowery MA, Wong W, Jordan EJ, et al: Prospective evaluation of germline alterations in patients with exocrine pancreatic neoplasms. J Natl Cancer Inst 10.1093/jnci/djy024 [epub ahead of print on February 28, 2018]
50. Hu C, Hart SN, Bamlet WR, et al: Prevalence of pathogenic mutations in cancer predisposition genes among pancreatic cancer patients. Cancer Epidemiol Biomarkers Prev 25:207-211, 2016
51. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405-424, 2015
52. Bartsch DK, Slater EP, Carrato A, et al: Refinement of screening for familial pancreatic cancer. Gut 65:1314-1321, 2016
53. Canto MI, Almario JA, Schulick RD, et al: Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology 155:740-751.e2, 2018
54. de Jong K, Nio CY, Hermans JJ, et al: High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol 8:806-811, 2010
55. Goldstein AM, Struewing JP, Fraser MC, et al: Prospective risk of cancer in CDKN2A germline mutation carriers. J Med Genet 41:421-424, 2004
56. Potjer TP, Kranenburg HE, Bergman W, et al: Prospective risk of cancer and the influence of tobacco use in carriers of the p16-Leiden germline variant. Eur J Hum Genet 23:711-714, 2015
57. Daly MB, Pilarski R, Berry M, et al: Genetic/Familial high-risk assessment: Breast and ovarian version 1.2018. NCCN Clinical Practice Guidelines in Oncology 2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
58. Provenzale D, Gupta S, Ahnen DJ, et al: Genetic/familial high-risk assessment: Colorectal version 3.2017. NCCN Clinical Practice Guidelines in Oncology 2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
59. Chari ST, Kelly K, Hollingsworth MA, et al: Early detection of sporadic pancreatic cancer: Summative review. Pancreas 44:693-712, 2015
60. Kenner BJ, Chari ST, Cleeter DF, et al: Early detection of sporadic pancreatic cancer: Strategic map for innovation--a white paper. Pancreas 44:686-692, 2015
61. Kenner BJ, Chari ST, Maitra A, et al: Early detection of pancreatic cancer-a defined future using lessons from other cancers: A white paper. Pancreas 45: 1073-1079, 2016
62. Young MR, Wagner PD, Ghosh S, et al: Validation of biomarkers for early detection of pancreatic cancer: Summary of the Alliance of Pancreatic Cancer Consortia for Biomarkers for Early Detection workshop. Pancreas 47:135-141, 2018
63. Surveillance, Epidemiology, and End Results Program: Cancer stat facts: Pancreatic cancer https://seer.cancer.gov/statfacts/html/pancreas.html
64. Cohen JD, Li L, Wang Y, et al: Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science 359:926-930, 2018
65. Gui JC, Yan WL, Liu XD: CA19-9 and CA242 as tumor markers for the diagnosis of pancreatic cancer: A meta-analysis. Clin Exp Med 14:225-233, 2014
66. Tempero MA, Uchida E, Takasaki H, et al: Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res 47:5501-5503, 1987
67. Duffy MJ, Sturgeon C, Lamerz R, et al: Tumor markers in pancreatic cancer: A European Group on Tumor Markers (EGTM) status report. Ann Oncol 21: 441-447, 2010
68. Merker JD, Oxnard GR, Compton C, et al: Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol 36:1631-1641, 2018
69. Lee B, Cohen J, Lipton LR, et al: Potential role of circulating tumor DNA (ctDNA) in the early diagnosis and post-operative management of localised pancreatic cancer. J Clin Oncol 35, 2017 (suppl; abstr 4101)
70. Cohen JD, Javed AA, Thoburn C, et al: Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. Proc Natl Acad Sci USA 114:10202-10207, 2017 (suppl 15)
71. Chari ST, Leibson CL, Rabe KG, et al: Probability of pancreatic cancer following diabetes: A population-based study. Gastroenterology 129:504-511, 2005
72. Aggarwal G, Rabe KG, Petersen GM, et al: New-onset diabetes in pancreatic cancer: A study in the primary care setting. Pancreatology 12:156-161, 2012
73. Sah RP, Nagpal SJ, Mukhopadhyay D, et al: New insights into pancreatic cancer-induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol 10:423-433, 2013
74. Hart PA, Kamada P, Rabe KG, et al: Weight loss precedes cancer-specific symptoms in pancreatic cancer-associated diabetes mellitus. Pancreas 40:768-772, 2011
75. Brentnall TA, Bronner MP, Byrd DR, et al: Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. Ann Intern Med 131:247-255, 1999
76. Canto MI, Goggins M, Hruban RH, et al: Screening for early pancreatic neoplasia in high-risk individuals: A prospective controlled study. Clin Gastroenterol Hepatol 4:766-781, 2006
77. Canto MI, Goggins M, Yeo CJ, et al: Screening for pancreatic neoplasia in high-risk individuals: An EUS-based approach. Clin Gastroenterol Hepatol 2:606-621, 2004
78. Langer P, Kann PH, Fendrich V, et al: Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. Gut 58: 1410-1418, 2009
79. US Cancer Statistics Working Group: U.S. Cancer Statistics: 1999–2012 Incidence and Mortality Web-based Report. https://gis.cdc.gov/Cancer/USCS/DataViz.html
80. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. http://seer.cancer.gov/csr/1975_2013/
81. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, The Commonwealth Fund, 2008
82. American Cancer Society: Cancer facts and figures for African Americans 2016-2018. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-047403.pdf
83. Chang KJ, Parasher G, Christie C, et al: Risk of pancreatic adenocarcinoma: Disparity between African Americans and other race/ethnic groups. Cancer 103: 349-357, 2005
84. Singal V, Singal AK, Kuo YF: Racial disparities in treatment for pancreatic cancer and impact on survival: A population-based analysis. J Cancer Res Clin Oncol 138:715-722, 2012
85. Khawja SN, Mohammed S, Silberfein EJ, et al: Pancreatic cancer disparities in African Americans. Pancreas 44:522-527, 2015
86. Kasumova GG, Eskander MF, de Geus SWL, et al: Regional variation in the treatment of pancreatic adenocarcinoma: Decreasing disparities with multimodality therapy. Surgery 162:275-284, 2017

87. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34:2925-2934, 2016
88. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 33:2563-2577, 2015
89. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32: 306-311, 2014
90. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011 (suppl 3)
91. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
92. 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
93. Balaban EP, Mangu PB, Khorana AA, et al: Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:2654-2668, 2016
94. Sohal DPS, Kennedy EB, Khorana A, et al: Metastatic pancreatic cancer: ASCO clinical practice guideline update. J Clin Oncol 36:2545-2556, 2018
95. Khorana AA, Mangu PB, Berlin J, et al: Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:2324-2328, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Elena M. Stoffel
Research Funding: Cancer Prevention Pharmaceuticals (Inst)

Randall Brand
Honoraria: InVitae
Research Funding: Ambry Genetics (Inst)
Patents, Royalties, Other Intellectual Property: Y. Liu, R.E. Brand, P. Wang, Shikhar Fnu, Spatial-domain low-coherence quantitative phase microscopy, US Provisional Patent filing, US 61/332881, 2010

Marcia Canto
Research Funding: C2 Therapeutics, Cosmo Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Royalties from UpToDate, online

Michael Goggins
Patents, Royalties, Other Intellectual Property: Royalty related to licensing as a codiscoverer of PALB2 as a pancreatic cancer susceptibility gene to Myriad Genetics

Matthew Yurgelun
Research Funding: Myriad Genetics

Alok A. Khorana
Honoraria: Janssen, Halozyme, Pfizer, Bayer, AngioDynamics, Pharmacyte Biotech
Consulting or Advisory Role: Sanofi, Janssen, Halozyme, Bayer, Pfizer, Pharmacyte Biotech
Research Funding: Amgen (Inst)
Travel, Accommodations, Expenses: Janssen, Pfizer, Bayer

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Hereditary Pancreatic Provisional Clinical Opinion Expert Panel Membership

Name and Designation	Affiliation/Institution	Role/Area of Expertise
Alok A. Khorana, Co-chair	Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH	Medical oncology
Elena M. Stoffel, Co-chair	University of Michigan, Ann Arbor, MI	Gastroenterology
Arun Nagarajan, PGIN representative	Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH	Medical oncology
Randall Brand	University of Pittsburgh, Pittsburgh, PA	Gastroenterology
Cassadie Moravek, patient representative	Pancreatic Cancer Action Network, Los Angeles, CA	
Gloria M. Petersen	Mayo Clinic, Rochester, MN	Epidemiology/genetics
Diane M. Simeone	New York University Langone Health, New York, NY	Surgical oncology
Marcia Canto	Johns Hopkins University, Baltimore, MD	Gastroenterology
Matthew Yurgelun	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Michael Goggins	Johns Hopkins University, Baltimore, MD	Gastroenterology
Shannon E. McKernin	American Society of Clinical Oncology, Alexandria, VA	ASCO Staff

Abbreviation: PGIN, Practice Guidelines Implementation Network.