The Oncologist, 2023, **28**, 584–595
https://doi.org/10.1093/oncolo/oyad080
Advance access publication 12 April 2023
Review Article

Management of Patients With Pancreatic Cancer Using the "Right Track" Model

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Abstract

Pancreatic cancer is one of the few cancer types in the US with incidence and death rates continuing to rise. As the disease threatens to become the second leading cause of cancer-related deaths in the country, it is imperative to review the best practices currently available to extend and improve patient lives. To provide a roadmap for healthcare professionals detecting, diagnosing, and caring for patients with pancreatic cancer as a supplement to national guidelines focused on recommended treatment regimens, the Pancreatic Cancer Action Network (PanCAN)'s Scientific and Medical Affairs staff and expert Scientific and Medical Advisory Board have created a series of position statements. The statements are based upon scientific evidence and clinical observations published in the literature and research conducted through PanCAN's internal programs and initiatives. This review summarizes the rationale and sources for these position statements related to diagnosis, treatment, and care for pancreatic cancer and provides information about resources to make these recommendations accessible to patients and their medical teams. Pancreatic cancer is a complex and extremely challenging disease. Beyond treatment recommendations outlined in national guidelines, steps can be taken to help patients feel better and live longer. Under the framework of the "Right Track" model—right team, right tests, right treatments, data sharing—PanCAN's position statements can provide supplementary guidance to healthcare professionals for the short- and long-term management of patients with the disease.

Key words: pancreatic cancer; guidelines; PanCAN; position statement; Right Track model.

Implications for Practice

The 10th most commonly diagnosed cancer in the US, pancreatic cancer is infrequently encountered by many healthcare professionals. The position statements presented in this review from the Pancreatic Cancer Action Network are intended to bring awareness and extend national treatment guidelines with a focus on getting patients on the "Right Track," which emphasizes assembling a multidisciplinary team, considering all treatment options—including testing for precision medicine approaches and clinical trials—and providing patients with optimal nutritional and supportive care. Finally, patients and their medical teams are encouraged to share data to strengthen future guidelines and disseminate best practices.

Introduction

With a dismal 12% 5-year survival rate, pancreatic cancer remains a clinical challenge. Pancreatic cancer is the 10th most commonly diagnosed cancer, with 64 050 cases expected in the US in 2023.[1] However, with 50 550 deaths projected, it stands as the country's third leading cause of cancer-related deaths. Even more alarmingly, projections show that pancreatic cancer deaths will surpass those caused by colorectal cancer before 2030, moving pancreatic cancer to the second leading cause of cancer deaths, behind only lung cancer.[2] As opposed to most other cancer types, incidence and death rates for pancreatic cancer continue to rise.

There is some good news, however. The 5-year survival rate from pancreatic cancer has increased from 6% to 12% over

Received: 26 January 2022; Accepted: 17 February 2023.

the past decade, with the rate for patients with early-stage disease nearly doubling from 23% to 44% over that time period as the driver of the overall change.[1,3] Recent changes to the National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) guidelines for the treatment of pancreatic cancer have revealed new standards of care for early- and late-stage disease, with more effective and some personalized options becoming available to patients.[4,5]

In addition to treatments with curative intent, additional steps and interventions are critical to improve quality of life and survival for patients with pancreatic cancer. These include the importance of being cared for by a multidisciplinary team with significant expertise in pancreatic cancer and incorporating supportive care measures into patients' treatment plans as early and robustly as possible. To supplement clinical guidelines for pancreatic adenocarcinoma provided by ASCO and NCCN, the Pancreatic Cancer Action Network (PanCAN) and its advisers have generated a group of position statements for healthcare professionals as well as patients and caregivers. The statements focus on diagnosing, treating, and managing pancreatic cancer, in alignment with the "Right Track" model developed by the Harvard Business School Kraft Precision Medicine Accelerator program.[6] Under the Right Track, patients are advised to compile the right team, undergo the right tests, consider the right treatments, and share their data at every opportunity (Fig. 1).

Position Statements

The following position statements, presented as a bullet point at the beginning of each section, are intended to serve as a roadmap for healthcare providers who are involved with the diagnosis, treatment, and management of patients with pancreatic cancer. Similar statements have been developed that are directed toward patients and caregivers to ensure self-advocacy and an awareness of evidence supporting best practices. A list of the position statements directed toward healthcare professionals and toward patients and caregivers is provided in Table 1, along with resources available through advocacy organizations and the federal government to assist patients in following the "Right Track." Additional information provided in Supplementary Table S1 provides information about resources specifically available to patients with pancreatic neuroendocrine tumors (PanNETs).

Right Team

Choosing a Healthcare Team

- Consulting with a pancreatic cancer specialist, a physician who sees a high volume of patients with pancreatic cancer, improves outcomes.

Evidence has shown that patients who are treated by multidisciplinary teams with significant experience diagnosing, managing, and treating pancreatic cancer have better outcomes and longer survival than those treated by healthcare professionals who see few patients with pancreatic cancer (defined as fewer than 15-16 annually).[7,8] While more data have focused on high-volume surgeons, a study in the Netherlands showed that patients with metastatic pancreatic cancer who received palliative chemotherapy showed a 1-year survival rate of 21.3% if treated in a high-volume treatment center, defined as more than 22 cases annually, compared to

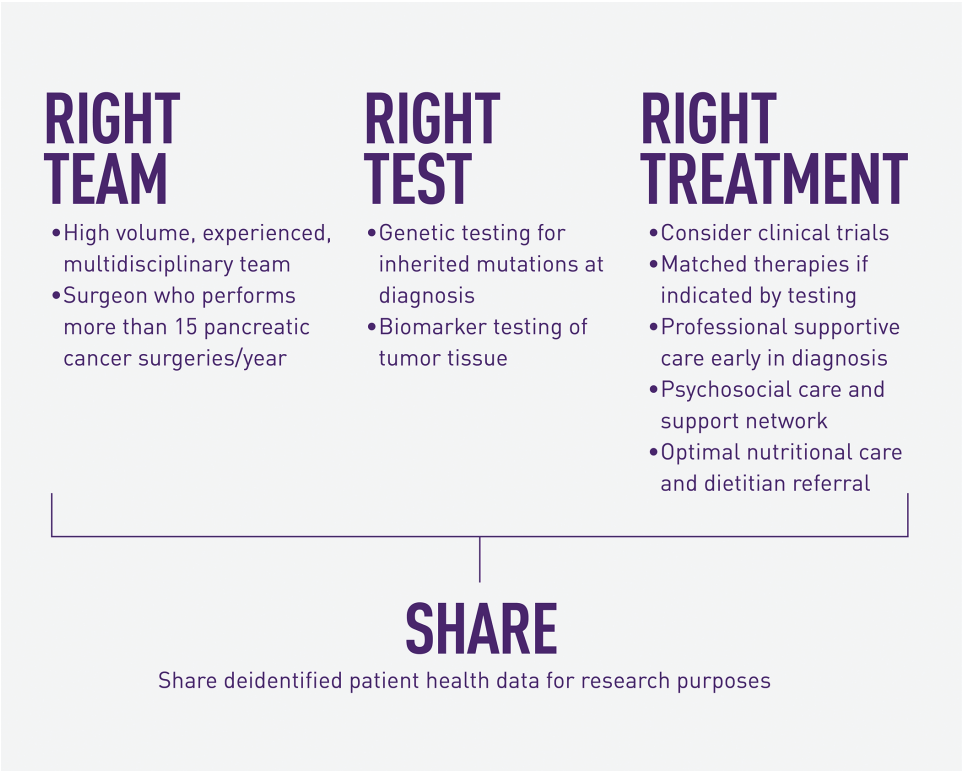

Figure 1. The "Right Track" model helps guide healthcare professionals and patients to compile the right team, undergo the right tests, consider the right treatments, and share their data at every opportunity.

Table 1. Position statements developed by PanCAN, along with resources available through advocacy organizations and the federal government to assist patients in following the "Right Track".

	Statements for healthcare professionals	Statements for patients and caregivers	Services available
Right team			
Choosing a healthcare team	Consulting with a pancreatic cancer specialist, a physician who sees a high volume of pancreatic cancer patients, improves outcomes.	Pancreatic cancer is a complex disease best evaluated by a team of specialists. An ideal team would include expertise in radiology, gastroenterology, medical oncology, radiation oncology, surgery, pathology, supportive care, and nutrition. It is recommended that patients consult with a multidisciplinary team whenever possible.	PanCAN maintains information about specialists, including surgical, medical and radiation oncologists, gastroenterologists, dietitians and more. The National Pancreas Foundation provides a list of National Pancreas Foundation Centers of Excellence who focus on providing multidisciplinary care to patients. National Cancer Institute maintains information on designated cancer centers. The National Pancreatic Cancer Foundation provides listings of hospitals and providers through their Pancreatic Cancer Advocacy helpline.
High-volume surgeon	Although 20% of pancreatic cancer patients may be eligible for surgery, data show that up to half of those patients are told they are ineligible. It is important for patients to be evaluated by a surgeon who performs a high volume of pancreatic surgeries (more than 15 per year).	For eligible patients, surgery is the best option for long-term survival of pancreatic cancer. Data show high volume surgeons at high volume hospitals have higher success rates and fewer complications. It is strongly recommended that you have a high-volume pancreatic surgeon (more than 15 surgeries per year) perform the surgery.	PanCAN maintains information on high volume surgeons.
Right tests			
Precision medicine	Patients treated with matched therapies selected through biomarker or genetic testing can live longer. Healthcare professionals are encouraged to follow guideline recommendations that all patients undergo genetic testing for inherited mutations at diagnosis and for patients to undergo biomarker testing of their tumor tissue unless clinically contraindicated.	Every pancreatic cancer patient is different. Patients who receive treatment based on their biology can live longer. It is strongly recommended that all pancreatic cancer patients get genetic testing for inherited mutations as soon as possible after diagnosis and biomarker testing of their tumor tissue to help determine the best treatment options. Patients should discuss both tests with their care team. Genetic testing for inherited mutations can also inform family members of risk regardless of family history.	The tests can be available through the treating institution and can be covered by insurance plans. PanCAN provides free tumor testing through the Know Your Tumor precision medicine service. Cancer Commons provides access to virtual tumor boards with experts in pancreatic cancer.
Right treatment			
Clinical trials	Pancreatic cancer patients who participate in clinical research have better outcomes. Clinical trials can advance research and improve treatment options.	Every treatment available today was approved through a clinical trial. It is strongly recommended that patients consider clinical trials at diagnosis and during every treatment decision.	PanCAN offers up-to-date clinical trial information that can be personalized through the on-line Clinical Trial Finder or by calling a Patient Services Case Manager. Cancer Commons provides access to virtual tumor boards with experts in pancreatic cancer and can also provide information on clinical trials. The Clinicaltrials.gov website offers a database of past and ongoing clinical trials. The Lustgarten Foundation provides information on clinical trials through their online clinical trials matching service.

Table 1. Continued

	Statements for healthcare professionals	Statements for patients and caregivers	Services available
Nutritional care	Optimal nutritional care, including supplemental pancreatic enzymes, improves patient outcomes and is critical for quality of life.	Good nutritional care improves outcomes and is critical for your quality of life. It is recommended that patients have access to pancreatic enzymes and see a registered dietitian.	PanCAN provides a booklet or fact sheets about diet and nutrition and can help find registered dietitians with oncology experience. The National Pancreas Foundation publishes a cookbook for patients with pancreatic diseases including pancreatic cancer. The Academy of Nutrition and Dietetics provides listings od registered dietitians and includes information on their specific specialties, including oncology.
Patient support	Support for the patient improves quality of life and overall well-being. A support system of caregivers, family, friends, healthcare professionals and a patient advocate is important to address and manage the needs of the patient.	Seeing healthcare professionals who focus on symptom management and supportive care improves outcomes and is critical for your quality of life. It is strongly recommended that symptom management and supportive care should be provided early in your diagnosis as well as during and after treatment.	PanCAN offers support and one-to-one, personalized education for patients and their families through Patient Services Case Management help line. PanCAN offers peer-to-peer connections to someone in the Survivor & Caregiver Network. Let's Win Pancreatic Cancer provides access to survivor stories. CancerCare offers a support group for pancreatic cancer caregivers facilitated by an oncology social worker. The National Pancreatic Cancer Foundation has an advocacy help line and can provide counseling, grief and emotional support. Inspire has an online pancreatic cancer support resource which allows patients and caregivers to connect with each other.
Share data			
Sharing health data	Deidentified patient health data provides researchers with crucial details that can lead to improved treatments and better patient outcomes.	Patient health data and disease experiences provide researchers with crucial details for discoveries that can lead to improved treatments and better patient outcomes. The release of information that could identify a specific patient is not essential for this purpose. It is recommended that patients share their health data for research and educational purposes and provide consent for its use with trusted parties.	PanCAN offers an on-line Patient Registry with multiple survey questionnaires. The National Pancreas Foundation offers a Patient Registry for all pancreas diseases including pancreatic cancer.

11.6% if treated in a lower-volume treatment center (hazard ratio 0.76).[9] In another example, a retrospective analysis of patients with locally advanced pancreatic cancer in the National Cancer Database identified a benefit of patients being treated at high-volume or academic centers, showing a median overall survival of 14.3 vs. 11.2 months (univariate and multivariable hazard ratio of 0.75 (0.69-0.82) and 0.84 (0.76-0.92)) when comparing high- and low-volume treatment centers.[10]

Patients are encouraged to seek a second opinion to explore all available options and feel confident with their care team and their recommendations.

- Although 20% of patients with pancreatic cancer may be eligible for surgery, data show that up to half of those patients are told they are ineligible. It is important for patients to be evaluated by a surgeon who performs a high volume of pancreatic surgeries (more than 15 per year).

The Whipple procedure (pancreaticoduodenectomy) is an extremely complex operation that requires a highly skilled surgical team.[11,12] For patients with known or suspected locoregional pancreatic cancer, national guidelines recommend referral to a multidisciplinary team of specialists, including both a surgeon and a medical oncologist.[5,13] However, cancer care in the US is often poorly coordinated, which leads to less treatment and higher costs. The potential consequences of poor referral and care coordination are significant as national data suggest that approximately 50% of patients with resectable pancreatic cancer who are healthy enough to undergo surgery do not receive it; furthermore, only 35% receive multimodal treatment.[14-18] A 2007 study described a national failure to operate on early-stage pancreatic cancer, noting that only 28.6% of patients with resectable pancreatic cancer received surgery, and there has been limited improvement in the national surgery rate since then.[14,19] Related to the failure to operate, the multimodal treatment rate (delivery of surgery and chemotherapy) is also low in the US with only 28%-37% of eligible patients receiving multimodal treatment.[16,18,20] A study from California evaluated compliance with NCCN guidelines for pancreatic cancer and found that guideline-concordant treatment ranged from 5% to 57% among 50 large hospitals in California, suggesting that not all high-volume hospitals routinely provide guideline-based care.[20] Additional research is needed to develop best practices for pancreatic cancer care coordination and identify high-performing health systems not only based on surgical volume but also multimodal treatment care coordination.

With increased attention toward pancreatic tumors that are deemed locally advanced or borderline resectable, the expertise and partnership between the surgeon and medical and radiation oncologist, as well as coordination with an expert nursing team, take on even more importance to determine whether the patient is a candidate for upfront surgery and, if so, whether to employ neoadjuvant treatment strategies. Treatment approaches for patients whose tumors are deemed borderline resectable are also critically important to facilitate eventual successful surgery with curative intent. For these reasons, the assessment of surgical resectability, the performance of the surgery itself, and the management of complications or recurrence are most successful when conducted by an experienced and specially trained surgeon who is well integrated into a multidisciplinary team.[21-23]

Right Tests

Genetic (Germline) and Biomarker Testing and Precision Medicine

- Patients treated with matched therapies selected through biomarker or genetic testing can live longer. Healthcare professionals are encouraged to follow guideline recommendations that all patients undergo genetic testing for inherited mutations at diagnosis and for patients to undergo biomarker testing of their tumor tissue unless clinically contraindicated.

Genetic Testing for Inherited Mutations

Routine genetic (germline) testing for all patients with pancreatic cancer is now recommended in both the pancreatic adenocarcinoma and the genetic/familial high-risk assessment sections of the NCCN guidelines.[5,24] These guidelines recommend genetic counseling and germline testing for all individuals diagnosed with exocrine pancreatic cancer, and first-degree relatives of individuals diagnosed with exocrine pancreatic cancer in the event that the individual who had pancreatic cancer cannot be tested. Because the disease is highly aggressive and the option to test the affected relative may not be available in the future, there may be significant benefit to family members in testing patients near the time of diagnosis.

For genetic testing, guidelines indicate the advantage of multigene testing through CLIA/CAP-certified laboratories, and the avoidance of direct-to-consumer or ancestry testing that is not approved for clinical use.[24] An ASCO provisional clinical opinion lists 13 genes associated with increased risk for pancreatic cancer (Table 2).[25] Evidence has shown a similar rate of germline alterations in patients who do and do not have a known family history of pancreatic cancer or other cancer types, contributing to the recommendation for all patients to undergo this testing.[15,26,27] Note that, in a case study of 3030 patients with pancreatic cancer, 5.2% of patients without a known family history of pancreatic cancer were found to have a germline mutation, emphasizing the importance of germline genetic testing of patients even in the absence of a family history of the disease.[15] The value of germline genetic testing for patients extends beyond personalized treatment options and can also provide valuable information for their family members. "Cascade testing" of family members, if applicable, can then inform them of potential risk for pancreatic cancer and other cancers and suggest consideration of participation in surveillance studies or other screening methodologies, which now includes imaging tests or blood-based detection tests.[24,28,29]

Tumor Biomarker and Genetic Testing for Treatment Options

Tumor biomarker testing and genetic testing are key components of the "right tests" section of the Right Track model primarily because of their potential impact on identifying precision treatment options. These tests were not routinely offered to patients prior to an update to the 2020 ASCO guidelines for metastatic pancreatic cancer that includes germline and somatic testing.[4] Nihilism in the field and concerns about the nearly universal presence of oncogenic KRAS mutations and other "undruggable" alterations led

Table 2. Genes associated with increased risk for pancreatic cancer.

Gene	Pancreatic cancer risk (%)	Syndrome	Most common other associated cancers	Patients with germline alterations in this gene (%)	Number and percentage of patients with alteration with family history of pancreatic cancer
APC	1-5	Familial adenomatous polyposis	Colorectal, upper GI, thyroid, brain		
ATM	1-5	Ataxia telangiectasia (*if biallelic)*	Breast, prostate, gastric	2.28	11/69 (15.9%)
BRCA1	2	Hereditary breast ovarian cancer	Breast, ovary, prostate, melanoma	0.59	2/18 (11.1%)
BRCA2	5-10	Hereditary breast ovarian cancer	Breast, ovary, prostate, melanoma	1.95	7/59 (11.9%)
CDKN2A	10-30	Familial atypical multiple mole melanoma	Melanoma	0.33	5/10 (50%)
MLH1, MSH2, MSH6, PMS2 (+ EPCAM, not observed in Hu et al)	5-10	Lynch syndrome	Colorectal, uterine, upper GI, ovary, urinary track, brain, sebaceous	0.50	2/15 (13.3%)
PALB2	5-10		Breast, prostate	0.40	2/12 (16.7%)
STK11	10-30	Peutz Jeghers syndrome	Breast, colorectal, upper GI, lung, reproductive track		
TP53	Not defined	Li Fraumeni syndrome	Breast, brain, sarcoma, adrenocortical	0.20	2/6 (33.3%)

The selection of genes, risk, syndrome, and other associated cancers is as described by the ASCO-convened Expert Panel to evaluate susceptibility of pancreatic cancer as an ASCO provisional clinical opinion.[25] The percent of patients with germline alterations in the indicated genes, and percent of those patients that had a family history of pancreatic cancer, is from Ref. [15]

researchers and clinicians to believe no meaningful information would be gleaned from these tests. However, a deep whole-exome sequencing effort of 150 pancreatic tumors through The Cancer Genome Atlas (TCGA) revealed that 42% of patients' tumors had at least one alteration that would align with a clinical trial option available at the time.[30] A study of 336 pancreatic tumors from patients treated at Memorial Sloan Kettering Cancer Center reported potentially actionable findings in 26% of cases.[31] A real-world analysis of the first 1000 patients to receive reports through the Pancreatic Cancer Action Network's Know Your Tumor precision medicine service similarly revealed actionable alterations in 26% of patients' tumors.[32] The key finding of the study was that patients with an actionable alteration in their tumor who went on matched therapy had a median overall survival (OS) of 2.58 years, showing a statistically significant OS improvement over patients with actionable alterations who went on unmatched therapy (mOS 1.51 years) or who did not have an actionable alteration (mOS 1.32 years).[32] A majority of those detected alterations were in the homologous recombination pathway including BRCA1/2 mutations, allowing the addition of platinum-based chemotherapy as well as PARP inhibitor therapy. What is clear is that many of the clinically meaningful alterations found are only present in very small subsets of patients, underscoring the importance of multigene next-generation sequencing panels offered from dedicated and experienced companies in order to identify potentially rare alterations with clinical implications.

Treatment options for the patients with pancreatic cancer with actionable alterations detected in their tumor ranged from targeted therapies approved in a tumor-agnostic manner, off-label drugs approved for other cancer types or clinical trials. While the OS advantage for patients treated with matched therapies was statistically and clinically significant, there remain the majority of patients who do not have matched treatment options available, reinforcing the need for additional lab-based and clinical research efforts to identify new drug targets and develop more effective therapies personalized to patients' tumors.

The sections below indicate examples of actionable tumor and germline alterations identified in patients with pancreatic cancer.

DNA Damage Repair Alterations

The largest subset of patients with pancreatic cancer who can benefit from a precision medicine approach are those with DNA damage repair alterations.[33,34] Somatic or germline alterations in BRCA1/2, PALB2, ATM/ATR/ATRX, or other DNA repair genes including CHEK1/2, RAD50, and the FANC genes have been implicated. Data has shown that treatment with a platinum-based chemotherapy regimen is especially effective in this subset of patients—for pancreatic cancer, that can include oxaliplatin as part of the FOLFIRINOX regimen, cisplatin, or other agents.[35] Studies have also demonstrated that the survival benefit of patients whose tumors have DNA damage repair alterations does not extend to chemotherapies without platinum, suggesting the alterations themselves are not prognostic markers that elicit a survival advantage.[36]

Olaparib was approved in late 2019 for the maintenance treatment of patients with metastatic pancreatic cancer who have a germline BRCA mutation and whose tumor had a response to platinum-based chemotherapy.[37] The approval was based on a reported progression-free survival advantage, although later data suggested no evidence of an improvement in overall survival.[38] The addition of olaparib to the oncologist's arsenal for treating pancreatic cancer nonetheless represented a step toward allowing patients a chemotherapy break and providing an oral drug in the maintenance setting as well as demonstrating the importance of germline genetic testing alongside tumor biomarker testing.

Biomarkers of Immunotherapy Responsiveness

Pembrolizumab, a PD-1 checkpoint inhibitor, represented the first cancer drug to receive FDA approval in a tumor-agnostic setting, being approved for the treatment of advanced, treatment-refractory pediatric or adult solid tumors with high microsatellite instability or mismatch repair deficiency.[39] The approval was later expanded to include tumors with high tumor mutational burden, and dostarlimab was likewise approved for mismatch repair-deficient recurrent or advanced solid cancers with no alternative options.[40] Separate studies have shown that 1%-3% of pancreatic tumors have high microsatellite instability or mismatch repair deficiency and approximately 1% of pancreatic tumors have high tumor mutational burden, alterations that can lead to the administration of a PD1-based checkpoint inhibitor.[39,41,42]

KRAS

Whereas the vast majority of patients with pancreatic cancer have *KRAS* mutations in their tumor, the most common sites of *KRAS* mutations found in pancreatic tumors are not yet considered druggable. However, the recent approvals of sotorasib and adagrasib, which target KRAS G12C mutations in non-small cell lung cancer that are also found in about 1% of pancreatic tumors, open a door to future therapies that directly target mutant KRAS and its effectors.[43,44] Preliminary results from the phase I/II KRYSTAL-1 clinical trial (NCT03785249) showed a partial response in 5/10 patients with heavily pretreated pancreatic cancer that expresses KRAS G12C upon treatment with adagrasib.[45] Through the phase I/II CodeBreaK100 clinical trial (NCT03600883), 8/38 patients with previously treated metastatic pancreatic cancer that expressed KRAS G12C showed a partial response from sotorasib.[46] These results highlight the difficulty in treating patients with pancreatic cancer with KRAS-targeted therapies and suggest they almost certainly need to be used in combinatorial regimens to unlock their maximum potential. Inhibitors of KRAS G12D, such as MRTX1133, provide promise targeting a mutation much more commonly found in pancreatic tumors. Preclinical studies have shown indications of efficacy of MRTX1133 in pancreatic cancer cell lines and xenograft and autochthonous mouse models[47,48] Investigational drugs that target other mutations within KRAS, as well as pan-specific KRAS inhibitors, are on the horizon through lab-based and clinical research.

KRAS Wild-Type Pancreatic Cancer

Interestingly, patients with KRAS wild-type tumors have a longer survival (mOS 720 days) compared to patients with KRAS mutations (mOS 420 days).[49] Alterations in downstream effectors of the KRAS pathway can occur in patients whose pancreatic tumors lack constitutively active KRAS. For example, BRAF alterations are observed and the combination of dabrafenib and trametinib was recently FDA approved for unresectable or metastatic solid tumors with a BRAF V600E mutation.[50] KRAS wild-type tumors are also more likely to

be microsatellite instable (4.7% vs. 0.7%) and have a high tumor mutational burden (4.5% vs. 1%) than KRAS mutant tumors,[51] though this relationship is not consistently seen.[49]

For patients whose pancreatic tumors express wild type KRAS, fusions in the RAS/MAPK pathway may play an oncogenic role, such as RAF, ALK, and others.[52,53] Rarer but meaningful alterations found through biomarker testing of pancreatic tumors include NTRK gene fusions, which are now treatable with larotrectinib and entrectinib,[39,54] and RET fusions, treatable with selpercalinib[55] through tumor-agnostic approvals. Although rare, these potentially clinically meaningful findings can only be acted upon if the patient's tumor has undergone thorough testing in order to consider all relevant treatment options.

Right Treatments

Considering Clinical Trials

- Patients with pancreatic cancer who participate in clinical research have better outcomes. Clinical trials can advance research and improve treatment options.

Several studies comparing survival rates for patients treated within clinical trials to real world outcomes have shown advantages to treatment within clinical trials in cancer in general as well as pancreatic cancer specifically.[56-58] In a comparison of survival with pancreatic cancer in the SEER database vs. those enrolled in 27 different trials, median survival was higher in 98% of the individual clinical trial arms by an average of 3.7 months ($P = .001$) and the differences were greatest for patients with metastatic pancreatic cancer.[56] Similarly, a study analyzed overall survival of patients enrolled in SWOG national clinical trials vs. those in SEER, looking at trials with an average 2-year survival of 50% or greater (defined as good prognosis trials) and those with less than 50% 2-year survival (poor prognosis). Their results showed that trial participation was associated with better survival for 9 of 10 poor-prognosis studies ($P < .001$), although not associated with improved survival for all 11 good-prognosis studies and the impact of trial participation endured for only one year.[58] Among patients identified through the National Cancer Database with the top 10 tumors with the highest trial enrollment rates, without stratification, median survival for those enrolled in a trial vs. those not enrolled was 60.0 vs. 52.5 months (hazard ratio, 0.876; 95% CI, 0.845-0.907; $P < .0001$).[57]

Estimates of the percent of patients with pancreatic cancer who participate in clinical trials vary but rates are typically estimated to be low, below 5%.[59] For a disease in which the standards of care offer modest survival advantages, participation in clinical trials offers access to new, potentially more effective therapeutic options and combinations. Analyses of the pancreatic cancer clinical trial landscape over the years have shown improvement in alignment of trial design with patient characteristics, such as fewer trials designed for patients in the adjuvant setting and more trials available for treatments offered as post-adjuvant and maintenance therapy.[2,60] The increase in trials testing maintenance therapies, as well as more clinical trials testing treatments offered as second-line and beyond in recent years, suggest advancements in the field and overall improvements in patient outcomes and ability to tolerate multiple treatment regimens. Many patients are now reaching the third-line setting, making clinical trials very important to expand options for treatment.

An increase in experimental therapies being tested in the phase 0 setting could allow more rigorous analyses to determine which agents warrant additional testing and is hopefully a sign of novel agents coming to future larger-scale trials. An increase in phase I/II trials was also observed, which creates efficiency. There are several clinical trial platforms using a master protocol approach that are underway and provide hope for increased efficiency and accelerated development of new therapeutic options for patients with pancreatic cancer.[61] One is PanCAN's Precision Promise response-adaptive clinical trial (NCT04229004), which functions as a phase II/III trial, allowing for simultaneous registration-ready analyses of investigational treatments against 2 standards of care for patients with metastatic pancreatic cancer. Another example is the MORPHEUS-Pancreatic Cancer study of multiple immunotherapy-based combinations (NCT03193190). The UK-based Precision-Panc (NCT04161417) utilizes a master protocol to provide tumor biomarker testing for patients, which then stratifies them to sub-studies within the trial.[62] These platform studies offer the possibility to rapidly introduce and exclude therapies that appear ineffective or toxic by maintaining an ongoing clinical trial structure.

Nutritional Care

- Optimal nutritional care, including supplemental pancreatic enzymes, improves patient outcomes and is critical for quality of life. Consultation with a dietitian is recommended.

Both pancreatic cancer and its treatment—especially surgery—can dramatically impact a patient's digestive tract. It is not uncommon for patients to present with persistent abdominal discomfort, diarrhea, abnormal stools, and/or weight loss. Weight loss associated with pancreatic cancer can be caused by several conditions, including cachexia, sarcopenia, malabsorption, malnutrition, and anorexia. Identifying the cause in each patient will facilitate healthcare teams to recommend the appropriate interventions to allow weight stabilization or gain.[63] Malabsorption caused by pancreatic exocrine insufficiency can often be mitigated by supplemental pancreatic enzyme therapy, although barriers to success include improper prescription or use of the enzymes as well as inaccessibility due to high cost.[64,65] The role of a registered dietitian, preferably someone with experience and expertise treating patients with cancer, is critical to ensuring that the patient has an appropriate caloric and nutritional intake through their diet and in determining whether enzyme replacement or other supplements are necessary, as well as guiding the patient to the appropriate dose and administration of these supplements.[64]

Supportive Care

- Support for the patient improves quality of life and overall well-being. A support system of caregivers, family, friends, healthcare professionals, and a patient advocate is important to address and manage the needs of the patient.

It is common for patients with pancreatic cancer—and their caregivers—to feel overwhelmed and isolated. Evidence has shown that individuals with strong social networks, or

with the perception of strong social networks, have better outcomes.[66,67] Interactions with others through support groups, volunteer networks and more, can help a patient and their loved ones feel supported and less alone.[68] In addition, the prevalence of depression, anxiety, and suicidality among patients with pancreatic cancer warrants close monitoring for these symptoms by their healthcare teams.[69,70]

- Referring your patients to professionals focused on symptom management and supportive care early in their diagnosis improves outcomes and is critical for patients' quality of life.

Pancreatic cancer and its treatments can cause dramatic and debilitating symptoms and side effects, including weight loss and malnutrition, a compromised immune system, fatigue, pain, and depression.[63,69,71,72] There is literature specifically addressing some of these issues for patients with pancreatic cancer, for example pancreatic cancer-associated weight loss (PAWL)[63] and management of pancreatic cancer pain,[72] with discussion of the effectiveness and cautions concerning standard and complementary medications and interventions. An important point is that medications and interventions with palliative intent should be administered throughout the patient's experience with the disease and not reserved for end-of-life care.[73,74] Evidence has shown the importance of treating the whole patient, not just their tumor. Managing symptoms and side effects not only improves the patient's quality of life but it also increases survival by allowing the patient to better tolerate treatment and ensure proper nutrition, a functioning immune system, and more physical activity. Resources for supportive care can be found in Table 1.

Sharing Health Data

- Deidentified patient health data provides researchers with crucial details that can lead to improved treatments and better patient outcomes.

With a disease with relatively rare incidence and such poor survival rates, it is imperative to learn as much as possible from diverse patient experiences. The immense benefit of patients participating in clinical research or undergoing genetic and biomarker testing can be measured by the patient's access to information and interventions that can improve their survival as well as knowledge gained for the scientific and clinical communities to learn from and build upon.

The inclusion of patient-reported outcomes (PROs) across cancer clinical trials has been shown to lead to improved outcomes for participants.[75] Through international surveys of patients, caregivers, and healthcare professionals, the Core Set of Patient-reported Outcomes in Pancreatic Cancer (COPRAC) was developed to define the most meaningful PROs to measure in this disease setting.[76] General quality of life, general health, physical ability, ability to work/do usual activities, fear of recurrence, satisfaction with services/care organization, abdominal complaints, and relationship with partner/family as the PROs were identifies as the PROs that all groups deemed the most important.

Incorporating PROs into clinical trials and clinical care can also improve communication between the patient and their care team, lead to earlier intervention for severe side effects and symptoms and provide insight into whether the patient's disease is responding to treatment.

Registries available online and through apps can provide a user-friendly opportunity for patients to share real-time information about their health and wellbeing.[77,78] As data are inputted from patients and their caregivers, trends can become apparent regarding symptoms, side effects and treatment responses.

Discussion

Overall, the statements described above have the potential to have a significant impact on the diagnosis, treatment, and care of patients with pancreatic cancer—today and into the future. As researchers in the lab and clinic work to identify novel biomarkers to enhance early detection, explore new targeted therapies and immunotherapy approaches and work toward more personalized, more effective, and less toxic treatment options for patients, these statements will continue to evolve and grow as well.

The statements outlined above are intended to provide a roadmap for healthcare professionals involved in the diagnosis, treatment, and care of this extremely challenging disease in conjunction with professional organization guidelines for pancreatic adenocarcinoma such as those from NCCN[5] and ASCO.[4] Developed by PanCAN staff and Scientific and Medical Board members, PanCAN uses the patient-facing statements (Table 1) as a guide for the information disseminated to patients, caregivers, and healthcare professionals through patient services and to guide research programs, including the Know Your Tumor precision medicine service, the Patient Registry, the Precision Promise adaptive clinical trial platform, the Early Detection Initiative, and the SPARK data aggregation platform. Information and resources for patients and healthcare professionals consistent with the "Right Track" are also available from other advocacy organizations, as listed in Table 1 for patients with pancreatic adenocarcinoma and Supplementary Table S1 for patients with pancreatic neuroendocrine tumors. These statements and their supporting documentation are being published in the scientific literature to extend their reach and improve the care provided to patients in a variety of clinical settings.

The authors acknowledge disparities in access and quality of care, and barriers that may preclude patients from being able to get on the "Right Track." Efforts are underway to identify and address challenges related to geography, socioeconomic status, race/ethnicity, and other factors that impact patient care and outcomes.

While there have been significant advancements and momentum in the field of pancreatic cancer scientific and clinical research, outcomes for patients remain dismal. In partnership with advisers and other key opinion leaders, PanCAN will remain diligent in its efforts to provide evidence-based information and resources to patients and their families and to support and conduct research to continue to move the field forward. As progress is made, the position statements outlined herein may also change and evolve.

Conflict of Interest

The Pancreatic Cancer Action Network has received donations for research purposes from AbbVie, Amgen, AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Corcept Therapeutics,

Covance, Elevation Oncology, Eli Lilly, FibroGen, Fujifilm Pharmaceuticals USA, Genentech, GlaxoSmithKline, GRAIL, Immunovia, Ipsen Biopharmaceuticals, Johnson & Johnson, Merck Sharpe & Dohme, Mirati Therapeutics, Novartis Pharmaceuticals, Novocure, Pfizer, Rafael Pharmaceuticals, Servier Pharmaceuticals, Takeda Pharmaceuticals North America, Tempus Health, Trisalus Life Sciences, Tyme, and ViewRay. Jordan Berlin reported consulting/advisory relationships with Insmed, Bayer, Ipsen, Clovis, QED, and Mirati, research funding from Novartis (Array), Abbvie, Astellas, Atreca, Bayer, Dragonfly, I-Mab, Lilly, Incyte, Karyopharm, EMD Serono, Boston Biomedical, PsiOxus, Symphogen, Pfizer, BMS, Transcenta Therapeutics, and Dragonfly, and DSMB for Novocure, Pancreatic Cancer Action Network, Karyopharm, and AstraZeneca. The other authors indicated no financial relationships.

Author Contributions

Conception/design: All authors. Data analysis and interpretation: A.R., L.M. Manuscript writing: A.R. Final approval of manuscript: All authors.

Data Availability

No new data were generated or analyzed in support of this research.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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