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Impact of geographical location on timing of diagnosis and overall prognosis in pancreatic ductal adenocarcinoma

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IMPACT OF GEOGRAPHICAL LOCATION ON TIMING OF DIAGNOSIS AND OVERALL PROGNOSIS IN PANCREATIC DUCTAL ADENOCARCINOMA

by

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IMPACT OF GEOGRAPHICAL LOCATION ON TIMING OF DIAGNOSIS AND OVERALL PROGNOSIS IN PANCREATIC DUCTAL ADENOCARCINOMA

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma maintains a formidable mortality rate with rising incidence despite extensive research efforts. As of 2021 pancreatic cancer is the third leading cause of cancer-related deaths in the United States despite its incidence representing only 3% of all cancer diagnoses. Given the high mortality rate, research efforts push to improve prognosis by expanding knowledge and tools in the realms of diagnostics, genetics, development of screening modalities, and targeted treatments. Modifications in treatment algorithms have led to only modest improvements in outcome. Current research efforts focus on primary and secondary prevention aimed at modifications of known environmental and hereditary risk factors. Available studies highlight the relationship between relative geography and cancers; however, there is a paucity of research available on the Social Determinants of Health on access to pancreatic cancer care and outcomes.

Proposed Project: Data will be extracted from the Surveillance, Epidemiology, and End Results (SEER) database and combined with US Census data along with medical record information as relevant over a seven-year period from January 1, 2010, through December 31, 2017. Social Vulnerability Index scores will be derived from the available data as a surrogate for Social Determinant of Health and be assigned to each case of pancreatic cancer from 2010-2017. These scores will be grouped by zip code. Analysis

will then be performed to identify the mean stage at time of diagnosis for each zip code. Further analysis will be performed to calculate survival curves for each zip code and cox proportional-hazards will be performed on results to determine statistical significance of SVI with respect to geography.

Conclusions: The proposed study will investigate the impact of geography as a Social Determinant of Health (SDoH) within the United States on the stage at time of diagnosis for pancreatic ductal adenocarcinoma. As a secondary measure, overall survival following diagnosis of pancreatic ductal adenocarcinoma will be examined.

Significance: This study will identify the impact of social determinants of health on geography and correlate the impact on outcomes in pancreatic ductal adenocarcinoma in the United States of America. This study may also identify geographic regions in which the incidence of PDAC is higher than expected which would present a population to investigate for additional screening studies and development of risk prediction models.

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LIST OF ABBREVIATIONS

AJCC.....American Joint Committee on Cancer

BU ..... Boston University

CA19-9.....Carbohydrate Antigen 19-9

CEA.....Carcinoembryonic Antigen

CT ..... Computed Tomography

DFS ..... Disease-Free Survival

ERCP.....Endoscopic Retrograde Cholangiopancreatography

FPC ..... Familial Pancreatic Cancer

FOLFIRINOX..... 5-Fluorouracil, Leucovorin, Irinotecan, and Oxaliplatin

IPMN.....Intraductal Papillary Mucinous Neoplasms

MRI.....Magnetic Resonance Imaging

NCCN ..... National Comprehensive Cancer Network

NED .....No Evidence of Disease

OS .....Overall Survival

PanIN ..... Pancreatic Intraepithelial Neoplasia

PDAC.....Pancreatic Ductal Adenocarcinoma

PNET.....Pancreatic Neuroendocrine Tumors

PET .....Positron Emission Tomography

SDoH.....Social Determinants of Health

SEER.....Surveillance, Epidemiology and End Results

SES..... Socioeconomic Status

SVI ..... Social Vulnerability Index

WHO ..... World Health Organization

INTRODUCTION

Background

Pancreatic cancer is currently the third-leading cause of cancer-related deaths with increasing incidence among Americans.[1] It remains an intractable cancer with an abysmal 5-year survival rate of approximately 10% regardless of stage at diagnosis.[1,2] Overall, cancer management has had many advances in recent decades which have failed to translate to proportionate improvements in pancreatic ductal adenocarcinoma (PDAC) outcomes. High mortality rates persist and are primarily attributed to presentation with late-stage disease and limited therapeutic response. Despite extensive research into pathophysiology and treatment, limited research has been undertaken to understand the geographic relationship of Social Determinants of health in presentation and outcomes in pancreatic cancer.

Pancreatic cancer represents a cacophony of disease processes of which PDAC accounts for approximately 90% of cases. PDAC arises from mutations within pancreatic ductal cells. Current research focuses on the specific cascade of mutations that allows the formation and driving of this disease as potential targets for intervention and potentially prevention.[2] Both hereditary and non-hereditary risk factors have been identified for PDAC. Inherited genetic mutations account for 22-33% of all pancreatic cancers.[3] A more thorough understanding of pathophysiology may lead to identification of additional genetic risk factors. Screening recommendations remain ubiquitous for individuals with known genetic mutations. Without the identification of a low-risk intervention and proof of survival benefit following the intervention, screening has little practical relevance.

Environmental factors associated with PDAC are smoking, diabetes, and obesity. Given that familial genetics account for only a portion of all PDAC diagnoses, current prevention efforts focus primarily on the avoidance of these environmental factors. Population data demonstrates increased incidence of PDAC in North America, Europe and Australia. Prevalence within the United States is highest within non-white Hispanics although relative risk is highest in African Americans. Adjusted for socioeconomic status (SES), there is no statistical significance between overall prognosis and race.[3,4]

Current clinical practice in the United States combines next-generation tumor biopsy sequencing and molecular profiling with anatomic staging information for development of a multidisciplinary treatment plan. Patients with early stage, resectable disease are typically offered resection, including pancreaticoduodenectomy or partial pancreatectomy, in conjunction with chemoradiation. Treatment for late-stage disease focuses on disease palliation utilizing systemic treatment with the goal of optimizing quality of life and improving survival. Currently, surgical resection offers the only potentially curative option in the treatment of PDAC. Through advances in neoadjuvant chemotherapy and locoregional radiation, an increasing number of patients with borderline resectable or unresectable disease have been successfully downstaged to become candidates for potentially curative surgical resection. Targeted treatment options, such as immunotherapy, are being developed as second line treatment options and may be an integral part of management in patients with hereditary PDAC as these genetic changes are well understood.

Differences in measures of population health have been observed in the community amongst socially vulnerable groups. In 1967, in the United Kingdom, the Whitehall Study demonstrated that a higher socioeconomic status correlated to better health overall and that lower socioeconomic status correlated with poorer outcomes.[5] This theory of health inequities was first brought to the United States in 1985 by Margaret Heckler. She convened a task force evaluating health disparities in minorities compared to their White counterparts. This research prompted Michael Marmot and Richard Wilkinson to develop the concept of "Social Determinants of Health" (SDoH) in 1999. Their paper demonstrated that one's social and cultural environment affects disease burden and that a one's social position determines their health, not the inverse. In 2010, the World Health Organization (WHO) defined Social Determinants of Health as "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life."[5] Research continues to recognize that individuals within the United States experience markedly different health care burdens and outcomes despite living in geographically similar locations. A person's zip code can be a stronger predictor of health than certain clinical or genetic factors. To understand this phenomenon, the Centers for Disease Control (CDC) proposed the Social Vulnerability Index (SVI) which acts as a holistic measure of a person's social circumstances. While poorer health outcomes have been linked to SDoH and high SVI, the impact of this has not been explored in pancreatic ductal adenocarcinoma.

Statement of the Problem

Pancreatic ductal adenocarcinoma cases in the United States continue to increase with an estimated 62,210 new cases and 49,830 pancreatic cancer deaths in 2022. PDAC accounts for only 3.2% of all cancer diagnoses but 7.9% of all cancer deaths.[6] The overall lifetime risk of the development of PDAC in the general American population is 1.5%.[7] Without a routine screening method many early symptoms are overlooked as inconsequential or related to a more benign cause. As a result, nearly 90% of PDAC remain undiagnosed until the disease has become metastatic. With the only potentially curative treatment for PDAC being surgical resection for local disease, the vast majority of those affected are resigned to a short survival window following diagnosis. Median overall survival of PDAC remains 10-12 months with treatment for all stages.[8] New PDAC cases are rising an average of 0.5% per year over the past 10 years, further highlighting the importance of improving outcomes and survival. The development of PDAC screening tools, such as cross-sectional imaging, in the general population have been disappointing. Tailoring treatment based upon tumor sequencing has provided only modest improvement in overall survival.[8] The development of PDAC screening tools, such as cross-sectional imaging, in the general population have been disappointing.

A comprehensive approach to improving outcome and survival in PDAC must transcend beyond improving the understanding of biology of the disease and but also account for the impact of health equity and social barriers on adequate healthcare. This proposed study looks to fill that gap in literature by correlating the SVI and geography on

a granular level to more adequately understand disparities in access to care and their impact on outcomes and survival in patients with PDAC in the United States.

Hypothesis

Disparities in healthcare are independently documented amongst socioeconomic strata, race, and geography. Significant heterogeneity in access to care exists amongst geographic areas particularly amongst residents of urban environments. This study aims to correlate the social vulnerability index, as a marker for SDoH, with zip code among patients with PDAC in the United States and assess the disease burden at the time of diagnosis, as measured by clinical staging and survival, measured in months, after diagnosis. By correlating the Social Vulnerability Index with zip code, this venture aims to more completely identify patient populations at high risk for poorer outcomes due to differences in healthcare access. In proving geographic outcomes disparities, attention can subsequently be made at improving PDAC outcomes through population health interventions.

Objectives and specific aims

Current medical treatment options for PDAC offer extremely limited survival benefit. Thus, the impetus of diagnosing patients with early stage resectable or borderline resectable disease, is high in order to extend survival and improve prognosis through increasing the likelihood for surgical resection. With a lack of viable screening modalities for PDAC, the impact of geographic location on timing of diagnosis and its effects on overall prognosis measured in months after diagnosis will be explored. This information will be correlated with SVI to define disparities in patient outcomes for

PDAC in the United States. Identification of at-risk populations will allow for opportunities for development of initiatives aimed at addressing disparities, identify high risk areas that may be helpful in testing screening tools. Geocoding by overlaying SVI with PDAC patient outcomes at the zip code level, the specific aims of this study are to:

1. Primarily describe the stage at the time of diagnosis and survival, in months, by zip code across the United States and relate patient proximity to NCI Cancer Centers to determine the impact of social determinants of health on access to timely cancer diagnosis for patients with PDAC.
2. Secondarily identify centers of excellence whose catchment demonstrate homogeneity of outcomes despite inclusion of zip codes with lower SVI such that their successes can be examined and replicated in areas with the greatest disparities.

REVIEW OF THE LITERATURE

Overview

Cancer in the United States

Through multifaceted oncologic advancements including cancer prevention efforts, standardized screening protocols, improved diagnostics, and targeted treatments the US saw a 31% decline in cancer related deaths between 1991 and 2018. These measures have improved overall survival and disease-free survival for a large subset of cancers. However, some subpopulations and cancer types have not seen these successes. Despite these successes, cancer remains the second leading cause of death in the United States.[4 9]

Solid organ malignancies such as lung, breast and colon have each had landmark oncologic advancements translating to improvement in outcomes. The identification of smoking as the direct cause of 82% of all lung cancers and the subsequent smoking cessation campaign by the United States is perhaps the single greatest oncologic success in recent history. Complete cessation of smoking would translate to the abatement of over 110,000 deaths from lung cancer alone in 2021. In addition to cessation efforts, risk factor identification allowed for the development of a targeted screening protocol. The use of low-dose screening computed tomography (CT) scans in current and past smokers leads to the early diagnosis of pulmonary malignancy. As a result of being able to identify patients with early, curatively resectable disease, mortality has decreased by 20-39%. [4] By identifying a high-risk population in which to implement a screening protocol,

cost burden to the U.S. health system is dramatically reduced and millions of Americans are spared unnecessary radiation exposure. Rapid declines in colorectal cancer in the early 2000's can similarly be attributed to the widespread implementation of screening programs. Screening colonoscopy functions as both a screening tool and a minimally invasive intervention for general and high-risk populations. Despite continual declines in overall colon cancer incidence there has been increasing rates in young people (those <65) prompting a recent change in colonoscopy recommendations. This trend has been mirrored in breast cancer and development of screening mammography protocols in the general population. Similarly, screening recommendations have been adapted in high-risk populations to include magnetic resonance imaging (MRI) or ultrasonography in addition to mammography for amelioration of missed diagnoses. These trends demonstrate the remarkable impact that the identification of high-risk populations and development of a reliable screening tool can have on outcomes.

In addition to screening programs prompting early intervention, many solid tumor malignancies have seen introductions of new targeted therapies and immunotherapy options for systemic disease. These new treatment modalities have less toxicity while improving quality of life metrics and superior outcomes when compared to traditional chemotherapy. Despite similar initiatives, patients with PDAC have not had similar successes in treatment options. PDAC continues to have one of the poorest survival rates. [10]

Introduction to Pancreatic Cancer

Poor survival in PDAC is attributed to aggressive disease pathophysiology and late diagnosis. Primary pancreatic cancer develops from either the endocrine or the exocrine cells of the pancreas. Pancreatic neuroendocrine tumors (PNET) are derived from the endocrine cells and account for approximately 10% of all pancreatic cancers. With an incidence of < 1 per 100,000, the 5-year survival for PNETs of the pancreas is 22.7%.[11] Comparatively, pancreatic cancer of the exocrine cells arise from the ducts of the pancreas and are known as pancreatic ductal adenocarcinoma (PDAC). These account for approximately 90% of pancreatic cancers. When compared stage for stage with other cancers, PDAC is known to have the poorest prognosis with a median survival of 10-12 months with treatment and 5-6 months without treatment.[8]

Complete pathogenesis of PDAC remains unknown. Extensive research into core genetic alterations of the disease and next generation sequencing has revealed a heterogeneity of mutations leading to the disease and a high overall mutation burden. Current evidence suggests that PDAC can arise from one of two histologically different ductal epithelial precursor lesions: pancreatic intraepithelial neoplasias (PanINs) and intraductal papillary mucinous neoplasms (IPMNs). [2] These precursor lesions have a propensity to develop into cancer as shown in Figure 1. PDAC has been characterized by four common genetic alterations: the oncogenic KRAS mutation, which is found in approximately 92% of PDAC cases, as well inactivation of the tumor suppressor genes CDKN2A, TP53, and SMAD4. Induction of KRAS followed by the loss of TP53 results in the differentiation of epithelial cells into the development of PanINs and extinction of

KRAS leads to regression of disease. [2] Other pathways that have been found to be involved are the TGF-β, WNT, NOTCH, and the Hedgehog signaling pathway. Understanding of these pathways and their propensity to mutate can dictate prevention and intervention strategies. [2]

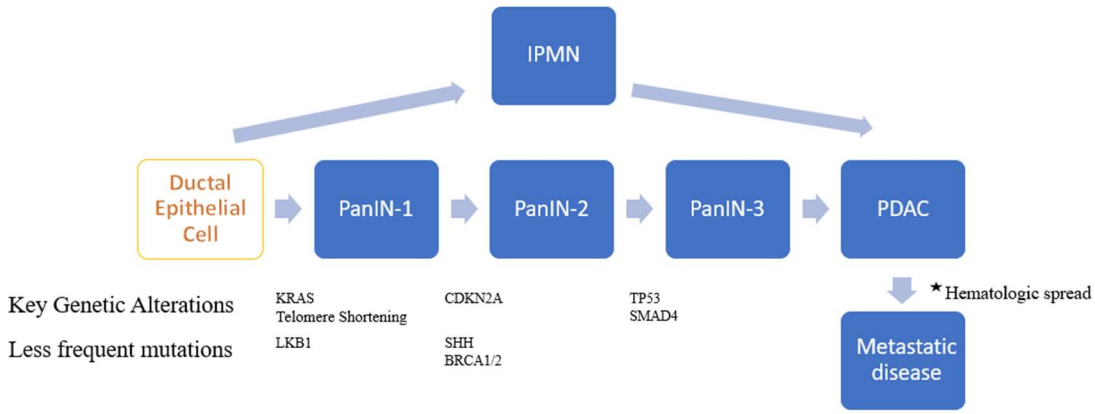

Figure 1: Model of Disease Progression in Pancreatic Cancer (Adapted from Grant 2016)
Pancreatic ductal adenocarcinoma arises from ductal epithelial cells and can arise from either a PanIN or IPMN precursor lesion. Pathogenesis occurs with the use of a series of molecular changes. The common genetic mutations linked to these lesions are indicated as well as when they commonly develop.[2]

PDAC is known to have a poorer stage-to-stage prognosis when compared to other malignancies. The largest barrier to improved outcomes is believed to be the late stage at time of diagnosis. Overall survival in PDAC is stage- dependent. A review of 502 patients with PDAC was published in 2013 by Annals of Surgery. This review, out of Utah, showed a median overall survival (OS) of 38 months in those diagnosed at Stage I. This was followed by a drastic drop with median OS of Stage IIA and IIB of 11 and 14 months, respectively. Stage III median OS was 9 months and those who were not diagnosed until Stage IV had a median OS of 5 months. This research was also consistent

in showing that only 20% of patients present while their disease is considered surgically resectable. In the study, only 30 patients were diagnosed at Stage I whereas 193 of the 502 patients were not diagnosed until they were considered Stage IV.[12]

Commonly, late-stage diagnoses in pancreatic cancer are attributed to the vague, nonspecific symptoms of the disease. Proximity of the portal vasculature allows for early hematologic spread of disease and rapid progression to metastatic disease. Presenting symptoms can range from vague abdominal discomfort or epigastric pain, nausea, anorexia, unintentional weight loss, diarrhea, vomiting and malaise.[13] The pain is often low intensity and the constellation of symptoms is often alternatively explained by a more benign etiology. Complete workup for malignancy by clinicians is frequently pursued only following persistence by the patient in seeking medical care or the presentation of jaundice. Alternatively, a patient may present following the identification of an incidental mass seen on imaging performed for another indication such as trauma.[14]

Diagnosis and Treatment

Following suspected pancreatic cancer, diagnosis is most commonly made with cross-sectional imaging followed by tissue biopsy. Imaging of choice per National Comprehensive Cancer Network (NCCN) guidelines is a pancreatic protocol dual-phase CT.[14] This study has a high sensitivity and specificity, is more cost effective than MRI, and can also be used for staging purposes.[15] Clinical staging can be completed using combination positron emission tomography (PET) and CT. An endoscopic retrograde cholangiopancreatography (ERCP) may be indicated for patients presenting with jaundice in order to alleviate biliary obstruction; this study can be done in conjunction with

endoscopic ultrasound (EUS) for delineation of the mass size, anatomy, proximity to vessels; to evaluate for lymphadenopathy; and to obtain a tissue diagnosis.[14] Staging of pancreatic cancer uses the American Joint Committee of Cancer (AJCC) TNM Staging system based on imaging. Tissue biopsy is typically obtained prior to administration of treatment. An EUS-guided biopsy is preferred due to the decreased risk of seeding when compared to CT-guided biopsy. All biopsy proven malignancies undergo genetic testing and molecular profiling to guide treatment decisions. Genetic counseling is offered to family members in cases of identified inheritable mutations. The work-up is finalized with biochemical testing to include transaminases, bilirubin, and baseline tumor markers [Cancer Antigen 19-9 (CA19-9) and Carcinoembryonic Antigen (CEA)]. In 2016, a study performed by the American Cancer Society demonstrated geographic differences in practice patterns with respect to types of routine cytology performed.[16] Disease burden is characterized along the AJCC convention.[17] Disease is then also classified into the AJCC Stages I-IV. Resectability is determined based upon involvement with the adjacent vasculature and structures, patient baseline performance status, and evidence of metastasis. Following completion of staging, a multidisciplinary approach is used to determine treatment plan. For patients with metastatic or locally advanced disease with poor performance status as based on the Eastern Cooperative Oncology Group (ECOG) scale,[18] systemic treatment is offered for palliation. Treatment options for locally advanced disease with good performance status include clinical trials, systemic therapy, and neoadjuvant chemoradiation in an attempt to downstage to the point of resectability. For borderline-resectable patients, neoadjuvant therapy has become the standard of care

followed by surgical resection with additional adjuvant therapy after recovery. Patients with resectable disease typically proceed to surgical resection with or without neoadjuvant treatment. Additional treatment may follow surgical recovery depending on tumor characteristics on final pathology of the surgical specimen.[14]

The mainstay in systemic treatment of non-surgical candidates remains standard chemotherapy. In 2018, the standard of care agents were updated to combination fluorouracil, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) in patients with good performance status or gemcitabine + nab-paclitaxel versus the previous standard of care of gemcitabine monotherapy. This decision came after a systemic review of locally advanced disease demonstrated >25% of study participants with tumor regression of 30% or greater. Half of these participants were then able to undergo surgical resection. Median OS was 24.2 months following diagnosis compared to the 22.8 month OS seen with gemcitabine monotherapy.[14,19] In patients with resectable disease with high-risk features or those with borderline resectable disease, these agents have been used neoadjuvantly with the goal of improving OS and achieving no evidence of disease (NED). In resectable patients, this is done to downsize the tumor for optimization of resection margins and to decrease the risk of recurrence. Borderline-resectable patients may have sufficient tumor regression such that they can become surgical candidates.

Standard chemotherapy regimens have been known to have significant toxicity and can severely impact quality of life while a patient is undergoing treatment. The FOLFIRINOX regimen is used only in patients with good performance status because it was found to have grade 3 or 4 adverse events[20] in 75% of patients in its phase III trial.

With this associated toxicity oncology research has moved away from these agents when possible and has moved to immunotherapy and targeted treatments. As of 2020, other agents have shown limited benefit for PDAC. When used they are done in conjunction with standard chemotherapy regimens, as maintenance therapy, or as palliative treatment with the hope of prolonging overall survival alone.[14,19] Germline BRCA positive PDAC has benefitted from the introduction of poly ADP ribose polymerase (PARP) inhibitors as a form of maintenance therapy to limit the toxicity of continuing chemotherapy alone in patients with metastatic disease. The phase 3 POLO trial randomizing patients to Olaparib (a PARP inhibitor) versus placebo showed a median progression-free-survival of 7.4 months compared to 3.8 months in the placebo group. Unfortunately, this study demonstrated no significant improvement in OS and was associated with an increased risk of grade 3 or higher adverse effects.[17] It is currently only approved in germline BRCA positive metastatic disease with no disease progression following 4-6 months of platinum-based treatments. Immune-checkpoint-inhibitor antibodies such as the PD-L1 inhibitor pembrolizumab has been shown to be effective in tumors with mismatch repair deficiencies. A phase II study looked at the use of pembrolizumab in 12 different advanced cancers including PDAC and, given the findings, the FDA granted accelerated approval for the use of pembrolizumab in late-stage patients with high microsatellite instability or mismatch repair deficiencies who have progressed through other options for treatment. The response rates of pembrolizumab in these patients varied from 34.3-62.0%, meaning no response was seen by this treatment in a large subset of the participants.[17] Finally, in the rare event that a neurotrophin receptor kinase (NTRK) gene

fusion has occurred, preliminary studies have showed response to Larotrectinib, an NTRK inhibitor,[17] and the FDA has approved its use in mutation positive patients. Subsequent and maintenance treatment options for patients without actionable mutations, or who have progressed through these lines, are limited to clinical trial enrollment or combinations of alternative standard chemotherapy agents. Popular regimens utilize fluoropyrimidine-based therapy (5-FU), gemcitabine-based therapy, or capecitabine-based therapy. When performance status is no longer adequate to continue or response is dwindling supportive care alone is recommended.[14,21]

Despite only modest gains with these treatment changes prognosis has improved. In the early 2000's five-year survival rate for PDAC was calculated as 2-9%.[10] Based on data from 2012-2018 this has improved to 11.5%.[6] These hard-fought gains have enlightened of areas for continued research and gaps to rectify.

Existing research

Screening

Curative intent to treat for pancreatic cancer can be accomplished only through surgical resection. This knowledge spurred research into a reliable screening tool for the early detection of pancreatic cancer. Existing screening programs for breast, lung and colon cancers has been shown to identify earlier disease and improve outcomes; yet a reliable, validated screening tool for pancreatic cancer remains elusive. Despite many ventures to develop screening tools, as of 2019 the United States Preventative Task force actively recommends against screening for pancreatic cancer in asymptomatic patients due to the inability to prove benefit and the risk to cause harm.[22] Without a validated

screening tool, 80-85% of pancreatic cancers remain undiagnosed until they are considered locally advanced or have metastasized removing surgical resection as a treatment option.[23] A reliable screening test or tool must meet various criteria for it to be clinically successful. According to the AMA Journal of Ethics, the two major objectives of a good screening program are: firstly, early detection of disease when treatment is effective than diagnosis after development of systematic disease (i.e. identification at a surgically resectable stage); and secondly, identification of risk factors that increase the likelihood of developing the disease and use of this knowledge to prevent or lessen the disease by risk factors modification.[24] The test or screening tool must also meet certain criteria such as: a high sensitivity to detect disease; be safe to administer; cost effectiveness; lead to demonstrated improved health outcomes; and the screening tool must be widely accessible.[24] While the importance of identifying a screening tool for pancreatic cancer has been well established, the discovery of a screening tool that fits these criteria has proven much more difficult.

Biomarkers such as serum carbohydrate antigen (CA19-9) and abdominal imaging have been used for decades for routine monitoring of disease response and progression in PDAC. The utility of CA19-9 has not been proven because of its low sensitivity. PDAC has a high disease burden but low prevalence in the general population. In a disease such as PDAC where the general population prevalence is limited but the disease burden in diagnosed individuals is high, a screening test must be highly specific in order to avoid the costs and worry associated with confirmatory testing. Therefore, despite many hopeful attempts utilizing the combination of CA19-9 and

imaging modalities as screening tools for pancreatic cancer, a definitive test has yet to be validated.

In 1979, Hilary Koprowski *et al.* first described CA19-9. Carbohydrate Antigen 19-9 was first explored due to its association with colorectal malignancies, but two years later it was discovered that it was more commonly associated with PDAC. Researchers thought that this may serve as an efficacious and cost-effective diagnostic tool for pancreatic cancer. Meta-analyses of CA19-9 have since shown many limitations.[25,26] By far the largest limitation in CA19-9 as a screening tool for PDAC is its low sensitivity to PDAC. Elevation in CA19-9 is seen in in a variety of conditions such as inflammatory bowel diseases, gallstones, pancreatitis, and other solid organ malignancies. In a retrospective clinical study out of Texas, an elevated CA19-9 level of 100 U/mL was found to be 68% sensitive and 98% specific.[25] The biomarker is a sialylated Lewis blood group antigen and is absent in 6% of the white population and 22% of the black population of the United States. Because of this, these individuals will never generate a detectable level. The potential for a high rate of false negatives tests introduces racial disparity in utilizing CA19-9 as a screening and diagnostic biomarker.[25,26] Carcinoembryonic antigen (CEA) is an additional biomarker that was identified to be commonly elevated in patients with PDAC. While CEA has showed improved diagnostic accuracy over CA19-9, when used in isolation, it has been unable to significantly identify between PDAC and chronic pancreatitis.[12] Utilizing both CA19-9 and carcinoembryonic antigen (CEA) increased specificity to 84%. The combination of CA19-9 with CA 125, another common tumor biomarker, also had improved sensitivity

over CA19-9 alone.[27] In 2017, Ge *et al.* set out to compare the diagnostic accuracy of five common tumor biomarkers for pancreatic cancer using a meta-analysis. The study aimed to evaluate and compare accuracy of 5 common tumor biomarkers (CA242, CEA, CA125, microRNAs, and the KRAS gene mutation) in combination with CA 19-9 for the diagnosis of pancreatic cancer. The analysis reviewed articles from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials with respect to the above tumor markers in diagnosis of PDAC until 2017. The study was the first to explore combining various biochemical tests of varying success into a testing panel that was both easy to use and was cost effective. Unfortunately, as a meta-analysis, the information gleaned from the study was limited by available research. Results of this meta-analysis have yet to be published.[28] A similar combination screening approach was suggested out of Germany and later published in the International Journal of Cancer. The research introduced combination miRNA serum-exosome biomarkers and a panel of proteins for PDAC diagnosis. Tumor exosomes are extracellular vesicles that function as signaling molecules from a malignant cell to a surrounding cell but are not created by non-malignant cells. They can be detected in body fluids introducing an alternative possibility for a non-invasive measurement tool. The study collected serum from patients with PDAC, chronic pancreatitis, benign pancreatic tumors, and from healthy blood donors. Unlike with CA 19-9, these markers were found to differ in malignancy versus inflammation making them more specific for PDAC. The study additionally discovered that the combination of S-Exo CIC and miRNA markers have a sensitivity of close to 1.0 when combined and may be useful as a future screening tool. The study size included less than 250 total

participants and will need to undergo larger cohort trials prior to validation as a reliable screening or diagnostic tool.[29] Using a serum biomarker or panel of biomarkers as a screening tool is promising given their noninvasive collection and potential low cost. Unfortunately, the results of this protocol have yet to be published.[26]

While imaging is widely accepted for its efficiency and efficacy in diagnostic scenarios of PDAC, it continues to be advised against as a screening modality by the USPTF.[13] The recommendation is based on conclusions obtained via systematic review of the benefits and harms of current imaging-based screenings.[13] Following a review of 824 articles, researchers were unable to confidently conclude that the proposed screenings were able to improve cancer morbidity or mortality. Furthermore, while the screening did, in fact, identify PDAC, it also identified a number of other lesions including precursor lesions such as PanINs, IPMNs, benign pancreatic lesions. Harm from screenings have also been seen with one quarter of patients undergoing EUS reporting mild pain following the procedure and 6% experiencing adverse events related to the administration of anesthesia. MRI and CT scans are limited in their ability to find small primary tumors, are not widely available to the public, and are costly. Given the low annual incidence of PDAC, the number needed to treat would be prohibitively high. Along with abdominal imaging alone, FDG-positron emission tomography (PET) scans have been studied to see if they may be of use in early pancreatic cancer diagnosis. These scans visualize lesions as areas of increased glucose metabolism consistent with tumor growth. Combined PET-CT has been shown to be the most sensitive diagnostic tool, but again, has poor sensitivity in early stage PDAC due to the resolution (lesions must be

larger than 1 cm), poor specificity for malignancy and a high cost. These modalities expose patients to large doses of radiation without significant benefit.[30] Using EUS/ERCP as a follow up study to MRI or CT imaging with concerning findings led to the development of acute pancreatitis in 10% of patients, among other complications. The retrospective study concluded that imaging-based screening in populations with familial risk may have improved staging at time of diagnosis; however, the widespread use in the general population remains unproven. Another group examined the role of yearly MRI and endoscopic ultrasonography in high-risk patients, as defined as the presence of a familial predisposition for the development of PDAC. This timing and imaging modality fell short in proving itself to be an effective screening tool given the rapid progression of the disease seen in familial PDAC.[22,31] Data is lacking regarding the incidence of individuals undergoing resection for radiographic lesions of unclear malignant potential and being found to have no evidence of malignancy on final pathology. Efforts continue to focus on the creation of a reliable, validated screening tool in PDAC research.

Risk Factors

Current screening for pancreatic adenocarcinoma is non-standardized and performed only in select subsets of high-risk individuals. High-risk individuals are stratified by the presence of hereditary or non-hereditary risk factors. These risk factors are summarized in Table 1. In 2012, a multidisciplinary international consortium was held for consensus of screening recommendations in high-risk individuals. Candidates for screening included: first-degree relatives of patients with familial pancreatic cancer with at least two first-degree relatives affected; patients with Peutz-Jeghers syndrome; and

p16, BRCA2, and HNPCC mutation carriers with at least one affected first degree relative. Screening should consist of initial EUS and or MRI/magnetic resonance cholangiopancreatography. Consensus on intervals for imaging, age to initiate screening, and age to discontinue screening remained unsettled.[32] Frequency of screenings should be tailored to the temporal relationship between identification of precancerous lesions to extra-pancreatic spread. Yu J*, et al.* attempted to address this issue with the use of regression models on average age at time of diagnosis correlated with stage at diagnosis. After adjusting for cofactors, they found a 13-14 month difference in age between those diagnosed with T1 staged cancers and T3/T4 staged cancers. While this study is a first step in an approach to determine necessary time increments between screenings it failed to differentiate between familial and non-familial PDACs which are known to have different rates of progression. Further confirmation of this data, and discreet identification of familial versus non-familial PDAC, may guide annual screening protocols in high-risk populations.

Table 1. Known Risk Factors for the Development of Pancreatic Cancer.

Risk factors for pancreatic cancer divided by hereditary versus non-hereditary along with the increased relative risk for the development of pancreatic cancer compared to the general population without that risk factor. [10,33]

Non-Hereditary	
Risk Factor	**Relative Risk**
Cigarette smoking	1.7
Obesity	1.6
Alcohol consumption	1.6 risk in those that drink > 6 drinks per day
Diabetes Mellitus	1.5-2
Chronic Pancreatitis	2-3
Hereditary	
Risk Factor	**Relative Risk**
BRCA2	2.2-5.9
PALB2	2.37
BRCA1	1.6-4.7
MMR	0.0-10.7
STK11	76.2-139.0
P16/CDKN2A	14.8-80.0
PRSS1	53-87

Despite established relationships of non-hereditary risk factors in PDAC, screening studies have largely avoided these populations. Rationale for this gap in literature is unclear but may be a result of large variations in risk prediction. Non-hereditary risk factors are further characterized by being either modifiable or non-modifiable. The majority of modifiable risk factors are lifestyle choices known to negatively impact the pancreas, leading to dysfunction and possible progression to malignancy. While new-onset diabetes in patients > 50 years old is commonly a

manifestation of early PDAC, the association between diabetes diagnosis in younger populations and PDAC does not follow a linear path.[34] Similarly, while smoking is associated with increased rates of PDAC, unlike in lung cancer, there has been no direct causation definitively proven between smoking history and PDAC.[35] This lack of direct causality limits research aimed at the establishment of a valid screening tool for patients with non-hereditary PDAC as the majority of these patients will never develop disease.

While a single modifiable risk factor is unlikely to progress to PDAC, the combination of these risk factors along with non-modifiable risk factors increases chances. Incidence of PDAC is commonly broken down by location (country or state), sex, age, and race. A review performed by Midha *et al.* in 2016 identified race as a risk factor for PDAC within the United States and found that compared to non-Hispanic Whites, African Americans have increased incidence while Asian Americans and Pacific Islanders have decreased incidence. African Americans are also more likely to be diagnosed at a later stage and are less likely to undergo surgery for their disease.[35] African Americans have a 50-90% increased incidence of PDAC and yet survival is up to 20% less when compared to other races.[35,36] These differences between race have failed to be explained by differences in genetic susceptibilities. Instead, the incidence and outcomes are thought to be related to SDoH. African Americans broadly experience higher rates of alcohol use, tobacco use, obesity, and incidence of diabetes due to decreased SES as well as poorer access to care. African Americans are more likely to experience health inequities at higher rates than White patients. For example, African Americans are less likely to be seen by a medical oncologist or surgeon than their white

counterparts. [36] Zhu *et al.* demonstrated, through propensity score matching analysis and Cox models, that when SES was adjusted for, or an equal access healthcare system was used in these populations, the differences in overall survival were no longer present.[37]

African Americans experience lower overall socioeconomic status, lower levels of education, lower income, and higher rates of housing instability than their White counterparts. These experiences, known colloquially as Social Determinants of Health, directly translate into poorer healthcare related outcomes. The WHO identifies SDoH as factors above a person's control in society that directly shape the conditions of their daily life. SDoH have been well established to access to adequate care and overall outcomes with respect to PDAC. Those diagnosed with PDAC are more likely to have been regularly exposed to pesticides or had an occupational exposure to carcinogens such as migrant farm workers or non-citizens working in poorer conditions.[3] Similarly, lower socioeconomic status and lower levels of education have been associated with delayed initiation of treatment and inferior or incomplete treatment protocols while those private insurance are more likely to undergo surgical resection than those with state- or federally funded insurance. [37] These findings begin to highlight the implications of SDoH on PDAC but there remains a paucity of information exploring the specific relationship between access to health care and PDAC.

Access to cancer care is specifically known to impact patient outcomes.[37–41] A retrospective review published in 2020, examined risk factors, diagnosis, and treatments and identified geography within the United States as a non-modifiable risk factor for pancreatic cancer. The risk was attributed to differences in morbidity and mortality of

rural versus urban areas as well as differences in socioeconomic environment and lifestyle by region.[42] Evidentiary support of this claim is lacking. The combination of these variables into a Social Vulnerability index and coordination of this with geographical location on PDAC diagnosis and outcomes has yet to be explored.

In 2008, overall geographic access to cancer care in the United States was reviewed collectively by the Dartmouth Medical School, Dartmouth-Hitchcock Medical Center, and Dartmouth College and later published to the American Cancer Society. Access to care was determined by looking at travel time to the nearest cancer center by zip code. Methodology included assigning all NCI-designated Cancer Centers and academic medical centers a geocode based on latitudes and longitudes. A geographic centroid was then developed for each zip code in the United States. With this information closest travel times for a person to receive cancer care was estimated with road distance and travel speeds. Characteristics including race/ethnicity, income, education, and region from the 2000 U.S. Census were then analyzed. This study concluded that there was a larger travel burden for Native Americans and nonurban individuals. It also showed a regional disadvantage in the Southern United States. Strengths of the study included its methodology in determining location as well as the calculation of time accounting for variables that may occur. The use of U.S. Census data also allowed for accuracy in reporting of statistics of the areas studied. Limitations of this study are primarily on the inability to incorporate other social factors or specifics of the healthcare system into conclusions. The only conclusions that can be drawn from this study are the average distance that one must travel for this type of care and where this differs. In order to draw

conclusions about how that distance/time may affect care one also must take into account social factors such as: availability of transportation in terms of reliability and affordability; health insurance acceptance by the nearest center; and constraints related to time away from employment. [39]

The above study showed the limited availability of academic and NCI-designated cancer centers to certain geographical locations. A study performed by Zhu *et al.* in 2020 narrowed this research further by specifically focusing on racial and socioeconomic disparities with respect to pancreatic cancer across facility type. The study performed a query of the National Cancer Database from 2004-2015. It then considered the variables of survival status and demographics including facility type (academic, integrated, or community) at which the patient received their care, race, insurance status, education, and income and performed statistical analysis based on these characteristics. Conclusions of this study were: neither higher income nor private insurance correlated with earlier stage at diagnosis; those treated at academic centers tended to have lower stage at diagnosis when compared to community facilities; and African Americans and other non-White races were diagnosed at a later stage and less likely to receive treatment than Whites with these treatments tending to be delayed when compared to their White counterparts.[37] Limitations of this study included the use of the National Cancer Database alone as the database is known to capture only approximately 70% of cancers in the United States. These 70% of cases were also not generalizable to the United States as a whole. The study population excluded patients who were uninsured and who were from rural populations. As 10% of Americans are uninsured and 14% are considered to live in rural

communities, this study failed to represent a large portion of the United States. Along with these exclusions, the baseline population studied was 84.8% White, 11.8% African American, and 3.3% other racial backgrounds which is not representative of the racial cross-section in the United States population. [37,38]

Since the publication of the above study, additional research investigated the association between rectal cancer, cancer center volume, and geography. The retrospective review showed that geographic location did impact treatment adherence and outcomes.[43] Another study from California studied the impact of SDoH with respect to prostate cancer incidence and mortality including how geographic location impacted patient outcomes.[40,43] In terms of PDAC, a review written by the University of Utah School of Medicine identified volume-outcome related mortality following pancreaticoduodenectomy. While overall mortality rates with pancreaticoduodenectomy have decreased overall, there has been a proven volume-outcome relationship seen where improved outcomes are seen when performed by a surgeon highly familiar with the procedure and increased annual cases compared to performance at community hospitals where fewer cases are performed annually.[12,44] Further studies relating PDAC outcomes to geographical location are limited.

By comparing SVI with outcomes in PDAC based on geography, efforts can be made to intervene on regions where disparities exist, be used to predict risk, and guide screening recommendations. This was previously done with colorectal screenings. With the identification of higher incidence rates in African Americans over Whites in the United States, the age at which to start cancer screening was lowered in African

American patients first.[45] The novel research of introducing SVI accepts to create a holistic measure characterizing social circumstances which is then related to health outcomes. High social vulnerability has been associated with poor outcomes in certain investigated diseases such as diabetes. In 2020, an article in *Surgery* characterized the relationship between SVI and outcomes of elective hepatopancreatic surgeries. The authors demonstrated a higher burden of high SVI patients at low-volume centers with decreased quality of care. Additionally, patients the lowest SVI were more likely to experience shorter length of stay, decreased 90 day readmission, decreased 90 day mortality, and absence of postoperative surgical complications.[46] The importance of understanding the implications of SDoH on PDAC outcomes as potentially modifiable risk factors is pivotal in order to make efforts to improving outcomes in the future.

METHODS

Study design

This retrospective cohort analysis will use the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) Research Plus database to obtain data regarding incidence of PDAC from January 1, 2010- December 31, 2017. The information will be combined with residential address at time of diagnosis which will be obtained via death certificates, census data from 2010, and with hospital records used only as needed for acquisition of pertinent historical information. The residential addresses will be sorted based on zip code at time of diagnosis. SVI scores will be calculated using the 14 social factors based on U.S. Census information. SVI data are condensed into the themes of socioeconomic status, household composition, minority status and language, and English Language Proficiency, housing and transportation.[47] Further information gathered from SEER database will include age at diagnosis, stage at time of diagnosis, length of time from diagnosis to death. Type of institution, academic vs community, where care was given will also be obtained. Survival curves and Cox proportional hazard models will be performed on the gathered information to achieve the study aims of identifying disparities in pancreatic ductal adenocarcinoma based on geographic location in relation to SVI within the United States.

Study population and sampling

Source population for this proposed study will come from the SEER 22 research database which accounts for 48% of the U.S. Population.[48] Data will be taken from January 1, 2010- December 31, 2017. Start parameter was chosen based on the

introduction of FOLFIRINOX to clinical practice in 2010. Endpoint was determined based on the availability of 5-year survival statistics. The sample population will include all age groups equal or greater than 18 and all race/ethnicities.[49] Information regarding PDAC deaths including age, ethnicity and residential address at time of diagnosis will be obtained the U.S. census reports and then information regarding diagnosis, stage at time of diagnosis, timing of diagnosis, and treatments received will be obtained from medical records. SVI data will be obtained from the 2010 U.S. Census. Patients with non-PDAC pancreatic cancer will be excluded from the study. Patients with incomplete data sets or whose medical records cannot be accessed will be also excluded from the study. Participants will be deidentified. Each participant, along with their stage at time of diagnosis and their overall survival length will then be aggregated by zip code.

Sample size will be all participants who qualify based on the above criteria. In 2010 there were over 40,000 new pancreatic cancer cases and this has increased yearly with there being approximately 53,700 in 2017.[50,51] Assuming that PDAC is the cause of 90% of all pancreatic cancer cases and the SEER database accounts for approximately 50% of these cases this will remain a large sample size of approximately 200,000-300,000 individuals. Calculations will then be made using an alpha level of 0.05 and a beta level of 0.20.

Intervention

The intervention is designed to better understand the impact of SDoH, with SVI as a surrogate, on the stage of their pancreatic cancer at time of diagnosis as well as their

overall survival. As this is a retrospective observational study conducted previously collected data.

Study variables and measures

Participants will be pooled by zip code and stratified based on staging at time of diagnosis and overall survival. Time points for each zip code will be calculated and measured in months. Measures will include the median stage at diagnosis for each zip code, median overall survival for each zip code, the number of events (deaths) that occurred at time, t (5-year survival rate) and the number of censored subjects, or those who have not reached the event (death) at the time measured (time of data collection).

Recruitment

This study will be using patient's already stored data which is HIPPA compliant along with publicly published information. If further information is required beyond this, researchers will first reach out to the treatment centers and participants will be contacted through these locations.

Data collection

Stored on online HIPPA compliant data storage, the data will be collected from the SEER Plus Database. Other patient demographics will be obtained from medical records as well as public death certificates. Collection will occur once and will include data from 2010-2017. This data will be stored via an internal, password protected, HIPPA compliant database with patient information deidentified prior to statistical analysis.

Data analysis

Populations will be stratified by zip code in which they lived at time of diagnosis. Pancreatic cancer incidence and mortality rates will be calculated per 100,000 individuals and further stratified based on stage at time of diagnosis. Survival analyses will be performed to calculate time to death to determine 1- and 5-year survival rates for each zip code. Following this, the data will be applied to cox proportional-hazards models to determine associations between SVI and outcomes by zip code. Secondary analysis was performed to calculate the relationship between SVI and proximity to an NCI-cancer center with outcomes and OS.

Timeline and resources

The study will be divided into four phases and the timeframe along with personnel needed for each of these phases is listed in Table 2.

Table 2. Timeline and Resources. Planned timeline for the completion of proposed study along with the personnel needed for completion of each phase.

Phase	Timeline for Completion	Key personnel needed
Phase I: IRB submission and approval	1 month	1. Primary investigator
Phase II: Data Collection	4 months	1. Primary investigator 2. Student workers
Phase III: Data Analysis	3 months	1. Primary investigator 2. Statistician
Phase IV: Conclusions made and results published	3 months	1. Primary investigator 2. Statistician

Limited resources will be needed for the study aside from manpower and time. It will require computers with software capabilities capable of running statistical analyses as well as BU credentialing for access to the SEER Plus database.

Institutional Review Board

All proposed studies using data of human subjects are to be submitted to the Boston University Medical Campus IRB for approval. The proposed study will be submitted for exempt review due to the retrospective nature of the study with the use of the SEER national database, a set of existing data which has previously been de-identified with no interventions directly planned in conjunction with the study as well as the absence of use of vulnerable populations. This is in accordance with BU standard 45 CFR 46.101(b) which states that that "research involving the collection of existing data… if these sources are publicly available or the information is recorded by the investigator in such a manner that the subjections cannot be identified directly…"

CONCLUSION

Discussion

The United States is celebrated for its diverse population, yet inherent disparities are ubiquitous. Outcomes and survival rates result from nonmedical factors in addition to available treatments. There is no knowledge on the potential impact that distance or specific location may have on stage at time of diagnosis or on overall survival. Aside from geographic limitations to accessing care, little research has explored the impact of SDoH on geography to identify disparate outcomes in patients with PDAC. Access to reliable transportation options and insurance is impacted by more than geography, but

also SDoH. Early diagnosis of PDAC is a vital focus in determining outcomes and is heavily influenced by not only the quality of care, but also the ability to and the manner in which patients access care. This study would help to fill a few of these gaps in current literature. Other studies have performed similar analyses as this proposal such as in prostate cancer and rectal cancer showing that this research shall be generalizable to other cancers in addition.

A strength of this study is the utilization of SEER database, representing the largest cancer registry in the United States. Unfortunately, despite this distinction, the registry currently accounts for only 47.9% of the United States population. This includes San Francisco-Oakland SMSA, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Greater Georgia, Idaho, New York, Massachusetts, Illinois, and Texas. While this populational data includes full states and all demographics within these states, the populations included are primarily urban and may miss important trends in rural areas.[48] Also, in areas where there are fewer diagnosed cases of PDAC, some zip codes may need to be combined for adequate sample size. While biases have attempted to be avoided with respect to this study, the nature of a survival analysis introduces the possibility of censoring as it is impossible to calculate the overall survival in patients who were still living at the time of data collection. A potential obstacle of the study may be obtaining the required demographic information of the participants that are not obtained directly from the database itself but are obtained

through U.S. Census data and medical records. While this has been accomplished in prior similar studies it has not been attempted in a study of this scale.

Summary

Pancreatic ductal adenocarcinoma recently became the third leading cause of cancer-related deaths in the United States. Advancements in treatments lack significant improvements with 5 year OS of 11% for all stages.[52] Patients diagnosed at Stage 1A have a 5-year survival of over 80% while those diagnosed with advanced disease have a 5-year overall mortality approaching 100% thereby emphasizing the necessity of early diagnosis in improvement of outcomes. Research into an adequate screening tool for the general population has yet to show benefit. Despite the inability to screen all patients, there has been some success and improved prognosis by using imaging as a screening tool in high-risk populations. Currently high-risk screening is limited to those with familial genetic syndromes who are followed with imaging +/- biomarkers. As information about the usefulness of screening in these populations becomes better understood, screening may be expanded to include other high-risk individuals. With this hope, it is important to identify all at-risk populations. Current research has identified many additional risk factors such as: age, African American race, diabetes mellitus, a history of pancreatitis, smoking history, obesity, and alcohol assumption. Many of these risk factors have been linked to populations which are most impacted by Social Determinants of Health. Geography has also been identified to impact outcomes in PDAC as it impacts the availability of care. There is scarcity of information regarding the relationship between these factors. The proposed study will explore community-level

vulnerability beyond geography and SDoH. It will fill this gap of literature by identifying the impact on geographical location within the United States, in conjunction with known impacts of SDoH, on the factors of stage at time of diagnosis as well as overall survival from PDAC.

Clinical and public health significance

Identification of the impact of SVI with respect to geography within the United States adds another level of understanding to the complexities of care for populations at high risk for developing PDAC. Assessing the burden of SDoH on outcomes will increase knowledge on high-risk populations and fill in gaps on social influences and access to adequate health care for PDAC. This information will have public health significance by identifying geographic areas whose outcomes are most likely to negatively affected by SDoH and highlighting areas where the greatest impact can be made. These areas would be excellent opportunities to develop pilot projects aimed at impacting outcomes in PDAC through social programs, institution of early screening programs aimed at early diagnosis, and community outreach and education to successfully support patients through rigorous PDAC treatment. On an individual clinician level, understanding the impact of SDoH and geography may help to inform inherent biases as well as tailor diagnostics and therapeutics in order to accommodate the expanded needs of socially vulnerable patients and subsequently improve outcomes.

LIST OF JOURNAL ABBREVIATIONS

AMA J Ethics	AMA Journal of Ethics
Am J Epidemiol	American Journal of Epidemiology
Am J Health Promot	American Journal of Health Promotion
Ann Surg	Annals of Surgery
CA Cancer J Clin	CA: A Cancer Journal for Clinicians
Cancer Causes Control	Cancer Causes & Control: CCC
Cancer Cytopathol	Cancer Cytopathology
Cancer Lett	Cancer Letters
Cancer Med	Cancer Medicine
Curr Mol Med	Current Molecular Medicine
Dig Dis Sci	Digestive Diseases and Sciences
Int J Cancer	International Journal of Cancer
J Am Coll Surg	Journal of the American College of Surgeons
J Clin Oncol	Journal of Clinical Oncology
J Gastrointest Oncol	Journal of Gastrointestinal Oncology
J Natl Compr Cancer Netw	Journal of the National Comprehensive Cancer Network: JNCCN
J Palliat Med	Journal of Palliative Medicine
JAMA Oncol	JAMA Oncology
Nat Rev Gastroenterol Hepatol	Nature Reviews. Gastroenterology & Hepatology
Oncol Rev	Oncology Reviews
Pathol Res Pract	Pathology, Research and Practice
Technol Cancer Res Treat	Technology in Cancer Research & Treatment
World J Gastroenterol	World Journal of Gastroenterology

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