PANCREATIC CANCER ACTION NETWORK®

May 24, 2017

David C. Grossman, M.D., M.P.H.
Chairperson
U.S. Preventive Services Task Force
540 Gaither Road
Rockville, MD 20850

Dear Dr. Grossman and Members of the U.S. Preventative Services Task Force:

On behalf of the Pancreatic Cancer Action Network and the more than 50,000 Americans diagnosed with pancreatic cancer each year, we write today in response to the *Draft Research Plan for Pancreatic Cancer: Screening*.

The Pancreatic Cancer Action Network is a scientific evidence based organization. Our responses to the attached questions are to assist the USPSTF in their analysis of the research on pancreatic cancer risk based on the most up-to-date research currently available.

Pancreatic cancer is the toughest of the major cancers with a five-year survival rate in the single digits. The lifetime risk of developing pancreatic cancer is 1.6 percent (for both sexes).[1] It is the third leading cause of cancer-related death in cancers that affect both men and women in the United States and is projected to become the second leading cause of cancer-related death by 2020 [2], underscoring the importance of early detection and effective treatment in reversing the statistics for this disease. However, there is a critical evidence gap in research related to prevention of pancreatic cancer, and there is currently no screening test for pancreatic cancer for the general population.

There is a growing body of evidence that screening for pancreatic cancer would be extremely beneficial to certain high-risk populations, in particular individuals with a strong family history, hereditary pancreatitis, or known inherited cancer syndromes (details provided below). People who are diagnosed with early pancreatic cancer can be candidates for surgery, the only treatment with curative intent for this disease. Therefore, identifying the right populations to screen and the right techniques to use is a high-priority area that deserves further examination. **We strongly urge the USPSTF to consider the information available in the context of the exceptional deadliness of this disease and generate guidance on the usefulness of screening these high-risk populations.**

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While there is currently a need for more research on methods for the early detection of pancreatic cancer in both high-risk and the general population, we are anticipating rapid development in this area, particularly with respect to screening in specific high-risk groups such as new onset diabetics. In response to the Recalcitrant Cancer Research Act of 2012, the National Cancer Institute (NCI) has several new funding mechanisms that focus on early detection of pancreatic cancer. We at the Pancreatic Cancer Action Network are launching an Early Detection Initiative, which includes Targeted Research Grants focused on the identification of biomarkers or imaging techniques to diagnose pancreatic cancer in people with new-onset diabetes and includes a collaborative effort with the Mayo Clinic (NCT02001337) and the NCI. **We will follow up to seek your input on the trial design for this screening study. We anticipate significant advances in this area over the next few years and would ask the USPSTF to consider frequent reviews in this area given the severity and prevalence of this disease.**

We greatly appreciate USPSTF developing the Draft Research Plan for Pancreatic Cancer Screening and applaud your thoroughness with respect to considering a broad range of questions that will need to be asked as the research evidence continues to evolve in this area. We appreciate the request for comments and provide the following comments and information to assist the USPSTF in their research in this field. Please let us know if there's anything else we can help with at this time.

Best wishes,

Lynn M. Matrisian, PhD, MBA
Chief Science Officer

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COMMENTS ON USPSTF PROPOSED KEY QUESTIONS:

Draft: Proposed Key Questions to Be Systematically Reviewed

1. ***Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality?***

There is no screening protocol for pancreatic adenocarcinoma for the general population, making this general question unanswerable with current literature. There are no published randomized clinical trials on an asymptomatic population with a mortality endpoint and no plans to perform one to our knowledge. It poses an ethical dilemma and a recruitment challenge to consider withholding intervention for individuals at risk for a disease with a 5-year survival rate in the single digits. However, multiple studies have shown that screening high-risk individuals is beneficial. [3-5] **We strongly urge the USPSTF to consider the information available in the context of the exceptional deadliness of this disease and generate guidance on the usefulness of screening these high-risk populations.**

Further details are provided below in answer to the highly relevant question regarding screening in subpopulations providing elements that should be considered in generating screening guidelines.

a. Does screening effectiveness vary by clinically relevant subpopulations (e.g., older adults, persons with family history of pancreatic cancer, or persons with diabetes)?

The international Cancer of the Pancreas Screening (CAPS) consortium developed the following recommendation statements on who should be screened, how they should be screened/followed up, when surgery is appropriate and the goals of screening. [6]

Who: High risk individuals based on family history, known genetic cancer associated syndromes or inherited diseases associated with pancreatic cancer. Details provided below.

How: High risk individual should be screened using endoscopic ultrasound (EUS) and/or MRI. Patients with non-suspicious lesions should be followed up every 6-12 months. Patients with indeterminate solid lesions or main pancreatic duct strictures should be followed up at 3 months. [6]

What should be detected during surveillance: Three precursor lesions of pancreatic cancer have been defined. [7]

1. Pancreatic Intraepithelial Neoplasia (PanIN). Most invasive pancreatic adenocarcinoma develop from PanINs occurring in about 80% of pancreas cancers. Finding and identifying PanINs with high grade dysplasia and at high risk of malignancy should be the goal of screening high risk individuals. [5,7,8]
2. Mucinous Cystic Neoplasms (MCN) originate from ovarian-type stroma and almost exclusively present in younger females. [7] About 30% of MCNs are associated with invasive carcinoma (reviewed in Overbeek et. al)[5].
3. Intraductal Papillary Mucinous Neoplasms (IPMN) involve the main pancreatic duct or one of the branches. Certain features of IPMNs are at higher risk including main duct involvement compared to branched duct involvement. [5-7,9]

When should surgery be performed: Surgery should be performed at high volume centers when there is a concerning lesion, including cysts that are 2 cm or larger, mural nodule or solid component, or dilated main pancreatic duct. [6,9]

Where should screening and surgery take place: The CAPS consortium recommends screening in a multidisciplinary setting and surgery performed at a high-volume center with expertise in pancreatic surgery. [6,9]

Goal: The goal of screening high risk individuals is to find advanced precursor lesions or early stage pancreatic cancer. [5,6,9]

The following subgroups have a high risk of developing pancreatic cancer and are included in the CAPS recommendations.

Family history. There is a significant risk increase of pancreatic cancer among first-degree relatives of familial pancreatic cancer with one or more affected family members. [10 11]

The lifetime risk of developing pancreatic cancer increases with the number of first-degree relatives affected:

- One first-degree relative affected – 6 percent (4.5-fold increase)
- Two first-degree relatives affected – 8-12 percent (6.4-fold increase)
- Three or more first-degree relatives affected – 40 percent (32-fold increase)

Hereditary pancreatitis. Hereditary pancreatitis (HP), mostly caused by *PRSS1* mutation, increases the lifetime risk of pancreatic cancer to 25-40 percent.[12] Smoking increases the risk of pancreatic cancer by two-fold in patients with HP.[13] In addition, smokers with HP develop pancreatic cancer 20 years earlier than nonsmokers with HP.[13]

Inherited Cancer syndromes

Peutz-Jeghers syndrome. Individuals with mutations in *STK11/LKB1* have an estimated 36 percent lifetime risk of developing pancreatic cancer.[14,15]

Carriers of a known *BRCA1, BRCA2* pathogenic alteration.

- Ferrone *et al.* report that pancreatic cancer risk increases by about 3.3-fold to 4.9 percent (about one in 20) for women who harbor a *BRCA2* mutation.[16]
- The Breast Cancer Linkage Consortium study reported a 3.5-fold increased incidence of pancreatic cancer in families with *BRCA2* mutations compared with the general population[17], increasing the lifetime risk to 5.3 percent.
- *BRCA1* mutation carriers have a 2.26-fold increased risk of developing pancreatic cancer, a 3.39 percent lifetime risk.[18,19]

Familial Atypical Multiple Mole Melanoma (FAMMM). Individuals with a mutation in *P16/CDKN2A* have an increased risk of pancreatic cancer.[20-23]

Lynch Syndrome. Individuals with mutations in *MLH1, MSH2, MSH6 and PMS2* have a lifetime risk of approximately 3.7 percent up to the age of 70 (8.6-fold increase).[24]

Incidental cyst findings:
Pancreatic cysts are identified in about 20% of MRIs and 3% of CT scans. [25] Two different consensus guidelines on the management of incidental cysts findings currently exist, the 2012 International Association of Pancreatology and the 2015 American Gastroenterological Association guidelines. [26,27] While there are some differences between the management of incidental findings of pancreatic cysts[28], it is agreed that surgical resection is indicated for malignant or higher risk cysts. In addition, cyst size, presence of solid components, and pancreatic duct involvement should be evaluated to identify the higher risk patients that would benefit from further surveillance. [26-28]

Other high-risk populations:
New-onset Diabetes

- Type 2 diabetes has also been associated with an increased risk of pancreatic cancer, overall odds ratio (OR) = 1.8 (95% CI = 1.5–2.1) compared with non-diabetics.
- Risk is highest in new-onset diabetics (duration less than two years before diagnosis) OR = 2.9 (95% CI = 2.1–3.9) and decreases with duration of diabetes OR = 1.4 (95% CI = 1.0–2.0) for diagnosis more than 15 years before pancreatic cancer diagnosis.[29,30]
- Approximately 1 percent of new-onset diabetics develop pancreatic cancer within three years of their diabetes diagnosis.[31]

Smoking

- Analysis of 12 case-control studies shows that current smokers have a 2.2-fold increased risk of pancreatic cancer compared to never smokers.[32,33]
- Smoking cessation reduces this risk; smokers who had quit for one to 10 years are reported to have risk estimates of 1.64, and those who had quit for 15-20 years have a risk estimate of 1.12.[32]
- 25 percent of pancreatic cancer cases are attributed to cigarette smoking.[33,34]
- About 22 percent of deaths due to pancreatic cancer are smoking-attributable mortalities.[35]

Obesity

- Various studies shown to link increased body mass index (BMI) to pancreatic cancer.[33]
    - The risk is estimated at 1.55-fold greater for individuals with a BMI > 35 compared with individuals with a BMI of 18.9 to 24.9.[34]
    - 15.1 percent of patients (identified through the Nurses' Health Study [NHS] and Health Professionals Follow-Up Study [HPFS]) with pancreatic cancer had a BMI > 30.[36] Other studies indicate 6.5 to 7.0 percent of pancreatic cancer patients had a BMI >35, 19 percent of patients had a BMI > 30.[37,38]
- High BMI risk is independent of the risk of pancreatic cancer due to diabetes.[33,34]

What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?

We agree that the USPSTF should systematically review the diagnostic accuracy of screening tests for pancreatic cancer. It is anticipated that there will be new screening tests and regular advances in the types and accuracy of screening tests for pancreatic cancer over the next several years. Currently,

endoscopic ultrasound-guided fine-needle aspiration (EUS/FNA) is most accurate with 99 percent sensitivity and 100 percent specificity, but is only used for diagnostic purposes in cases of strong suspicion of pancreatic cancer.[39] MRI is also utilized and CT/PET is used for staging.

Draft: Proposed Contextual Questions
Contextual questions will not be systematically reviewed and are not shown in the Analytic Framework.

We agree these questions provide contextual background and provide the following information for your consideration in your research plan.

1. ***What tools are available for assessing risk of pancreatic adenocarcinoma in primary care?***

- PancPRO – a risk assessment model for pancreatic cancer[40]
- Genetic testing
- Family history questionnaire
- Smoking history
- Screening of new-onset diabetes using standard protocols such as fasting glucose and Hemoglobin A1c. Further assessment of elevated CA19-9 and weight loss can be done after positive diabetes results.[41-43]

2. ***What is the natural history and prognosis of early- versus late-stage pancreatic adenocarcinoma?***

Patients who are diagnosed with localized/early-stage pancreatic cancer and are eligible for surgery have much better outcomes than those diagnosed with advanced-stage disease. The five- year survival of patients with localized disease is 27 percent, regional disease 11 percent and metastatic disease 2 percent.[44]

3. ***What is the role of biomarkers or multiple-biomarker panels in screening for pancreatic adenocarcinoma?***

A blood test for the antigen CA19-9 is the only pancreatic cancer biomarker in routine clinical use but has not been validated as a screening test for pancreatic cancer (reviewed by Poruk, references therein[45]). CA19-9 is not expressed in about 10 percent of individuals, and elevated CA19-9 levels may be due to other noncancer-related physiological changes, reducing the sensitivity and specificity of this biomarker. However, changes in CA19-9 are used for treatment management in CA19-9-positive pancreatic cancer patients.

REFERENCES

1. Howlader N NA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer research.* 2014;74(11):2913-2921.
3. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevoy SV, Kalloo AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2006;4(6):766-781; quiz 665.
4. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2004;2(7):606-621.
5. Overbeek KA, Cahen DL, Canto MI, Bruno MJ. Surveillance for neoplasia in the pancreas. *Best Practice & Research Clinical Gastroenterology.* 2016;30(6):971-986.
6. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijt I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M, International Cancer of Pancreas Screening C. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* 2013;62(3):339-347.
7. Hruban RH, Maitra A, Kern SE, Goggins M. Precursors to Pancreatic Cancer. *Gastroenterology Clinics of North America.* 2007;36(4):831-849.
8. Hruban RH, Takaori K, Canto M, Fishman EK, Campbell K, Brune K, Kern SE, Goggins M. Clinical importance of precursor lesions in the pancreas. *Journal of hepato-biliary-pancreatic surgery.* 2007;14(3):255-263.
9. Ngamruengphong S, Canto MI. Screening for Pancreatic Cancer. *The Surgical clinics of North America.* 2016;96(6):1223-1233.
10. Tersmette AC, Petersen GM, Offerhaus GJA, Falatko FC, Brune KA, Goggins M, Rozenblum E, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, Hruban RH. Increased Risk of Incident Pancreatic Cancer Among First-degree Relatives of Patients with Familial Pancreatic Cancer. *Clinical Cancer Research.* 2001;7(3):738-744.
11. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griffin C, Cameron JL, Yeo CJ, Kern S, Hruban RH. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer research.* 2004;64(7):2634-2638.
12. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK, Jr., Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *Journal of the National Cancer Institute.* 1997;89(6):442-446.
13. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *Jama.* 2001;286(2):169-170.
14. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz–Correa M, Offerhaus JA. Very high risk of cancer in familial Peutz Jeghers syndrome. *Gastroenterology.* 2000;119(6):1447-1453.

15. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJP, Keller JJ, Westerman AM, Scott RJ, Lim W, Trimbath JD, Giardiello FM, Gruber SB, Offerhaus GJA, de Rooij FWM, Wilson JHP, Hansmann A, Möslein G, Royer-Pokora B, Vogel T, Phillips RKS, Spigelman AD, Houlston RS. Frequency and Spectrum of Cancers in the Peutz-Jeghers Syndrome. *Clinical Cancer Research.* 2006;12(10):3209-3215.

16. Ferrone CR, Levine DA, Tang LH, Allen PJ, Jarnagin W, Brennan MF, Offit K, Robson ME. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(3):433-438.

17. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *Journal of the National Cancer Institute.* 1999;91(15):1310-1316.

18. Lynch HT, Deters CA, Snyder CL, Lynch JF, Villeneuve P, Silberstein J, Martin H, Narod SA, Brand RE. BRCA1 and pancreatic cancer: pedigree findings and their causal relationships. *Cancer genetics and cytogenetics.* 2005;158(2):119-125.

19. Thompson D, Easton DF, Breast Cancer Linkage C. Cancer Incidence in BRCA1 mutation carriers. *Journal of the National Cancer Institute.* 2002;94(18):1358-1365.

20. Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WHJ, Tucker MA. Increased Risk of Pancreatic Cancer in Melanoma-Prone Kindreds with p16INK4 Mutations. *New England Journal of Medicine.* 1995;333(15):970-975.

21. Lynch HT, Fusaro RM. Pancreatic cancer and the familial atypical multiple mole melanoma (FAMMM) syndrome. *Pancreas.* 1991;6(2):127-131.

22. Lynch HT, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. *Familial cancer.* 2008;7(1):103-112.

23. Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *International journal of cancer.* 2000;87(6):809-811.

24. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with lynch syndrome. *Jama.* 2009;302(16):1790-1795.

25. Megibow AJ, Baker ME, Gore RM, Taylor A. The Incidental Pancreatic Cyst. *Radiologic Clinics.* 2011;49(2):349-359.

26. Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang J-Y, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology.* 2012;12(3):183-197.

27. Vege SS, Ziring B, Jain R, Moayyedi P, Adams MA, Dorn SD, Dudley-Brown SL, Flamm SL, Gellad ZF, Gruss CB, Kosinski LR, Lim JK, Romero Y, Rubenstein JH, Smalley WE, Sultan S, Weinberg DS, Yang Y-X. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts. *Gastroenterology.* 2015;148(4):819-822.

28. Chiang AL, Lee LS. Clinical approach to incidental pancreatic cysts. *World Journal of Gastroenterology.* 2016;22(3):1236-1245.

29. Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case–control studies. *Cancer Causes & Control.* 2010;22(2):189-197.

30. Klein AP. Genetic Susceptibility to Pancreatic Cancer. *Molecular carcinogenesis.* 2012;51(1):14-24.

31. Chari ST, Leibson CL, Rabe KG, Ransom J, De Andrade M, Petersen GM. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. *Gastroenterology.* 2005;129(2):504-511.

32. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2012;23(7):1880-1888.

33. Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH. Recent progress in pancreatic cancer. *CA: a cancer journal for clinicians.* 2013;63(5):318-348.

34. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. *Digestive diseases.* 2010;28(4-5):645-656.

35. Centers for Disease C, Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. *MMWR. Morbidity and mortality weekly report.* 2008;57(45):1226-1228.

36. Yuan C, Bao Y, Wu C, Kraft P, Ogino S, Ng K, Qian ZR, Rubinson DA, Stampfer MJ, Giovannucci EL, Wolpin BM. Prediagnostic Body Mass Index and Pancreatic Cancer Survival. *Journal of Clinical Oncology.* 2013.

37. McWilliams RR, Matsumoto ME, Burch PA, Kim GP, Halfdanarson TR, de Andrade M, Reid-Lombardo K, Bamlet WR. Obesity adversely affects survival in pancreatic cancer patients. *Cancer.* 2010;116(21):5054-5062.

38. Fleming JB, Gonzalez RJ, Petzel MQ, Lin E, Morris JS, Gomez H, Lee JE, Crane CH, Pisters PW, Evans DB. Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. *Archives of surgery.* 2009;144(3):216-221.

39. Rösch T, Lorenz R, Braig C, Feuerbach S, Rudiger Siewert J, Schusdziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointestinal Endoscopy.* 1991;37(3):347-352.

40. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(11):1417-1422.

41. Damiano J, Bordier L, Le Berre JP, Margery J, Dupuy O, Mayaudon H, Bauduceau B. Should pancreas imaging be recommanded in patients over 50 years when diabetes is discovered because of acute symptoms? *Diabetes & metabolism.* 2004;30(2):203-207.

42. Ogawa Y, Tanaka M, Inoue K, Yamaguchi K, Chijiiwa K, Mizumoto K, Tsutsu N, Nakamura Y. A prospective pancreatographic study of the prevalence of pancreatic carcinoma in patients with diabetes mellitus. *Cancer.* 2002;94(9):2344-2349.

43. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *The Lancet. Oncology.* 2009;10(1):88-95.

44. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: a cancer journal for clinicians.* 2016;66(1):7-30.

45. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, Firpo MA, Mulvihill SJ. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. *Current molecular medicine.* 2013;13(3):340-351.