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Screening for Pancreatic Cancer—Is There Hope?

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Pancreatic cancer can be a devastating disease. Fewer than 9% of patients with ductal adenocarcinoma of the pancreas are living 5 years after diagnosis. It is estimated that in 2019, about 57 000 people will be diagnosed with pancreatic cancer in the United States and that it may soon over-take colon cancer to become the second-most common cause of cancer-related death.¹ Based on recent progress in the treatment of colon cancer, the best

hope for reducing the cancer-specific mortality of pancreatic cancer may be early diagnosis and treatment.

The US Preventive Services Task Force has issued a recommendation statement against screening for pancreatic cancer in asymptomatic adults (grade D recommendation),² supported by a systematic review and evidence report.³ The recommendation statement acknowledges that screening carries risk and that there is currently no evidence that screening for pancreatic cancer is effective in reducing mortality. There are effective screening programs for other common cancers, including breast, colon and cervix. So why are screening and early diagnosis and treatment of pancreatic cancer so difficult?

There are substantial challenges. First, because of the location of the pancreas, many cancers only present with symptoms at an advanced stage. In addition, pancreatic cancer may progress rapidly. A 2015 analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database found that patients with stage IV pancreatic cancer were, on average, only 1.3 years older than those with stage I disease.⁴ Chromothripsis, in which multiple chromosomal rearrangements occur in a single event on 1 or 2 chromosomes, may drive the rapid progression of some pancreatic cancers.⁵ Furthermore, recent 3-dimensional histological studies suggest that early stage pancreatic cancers often invade the veins, which drain directly to the liver and result in early metastatic spread.⁶ These hypotheses are supported by clinical data that show at diagnosis, more than half of patients with pancreatic cancer present with metastatic disease, and only 10% of patients have localized cancer.

Second, with current technology it is often impossible to distinguish between pancreatic precursors that harbor either early cancer or high-grade dysplasia, which pose a risk great enough to warrant surgical resection, and low-grade precursors that can be safely watched. Thus, up to 60% of patients who undergo surgical resection for a precursor lesion are found to have a lesion with a low risk of progression and not to require surgery at the time.⁷ Because pancreaticoduodenectomy is associated with a mortality of about 2%, some patients who undergo surgery will have no benefit, only potential harms.

Third, the prevalence of pancreatic cancer is low in asymptomatic adults. Thus, an effective screening test for pancreatic cancer would have to be highly specific to achieve a reasonable positive predictive value and to minimize the incorrect identification of healthy individuals.

How can these challenges be addressed?⁸ First, there has been progress in characterizing the curable neoplasms that give rise to advanced, incurable pancreatic cancers. All 3 precursor lesions that lead to pancreatic cancer are known and well-characterized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs). Although high-quality data are lacking, the majority of cancers originate from PanINs, which measure less than 5 mm in diameter and can only be seen using a microscope. Together, IPMNs and MCNs account for about 15% to 30% of cancers.

Second, if screening is to be effective, it is desirable to allow a reasonable period of time during which potentially curable lesions could be detected. Although there are concerns that

pancreatic cancer may rapidly metastasize once invasive disease is present, there are opportunities for detection of potentially curable neoplasms. Comparisons of the average age of patients with noninvasive IPMNs with the average age of patients with IPMNs with associated invasive adenocarcinomas suggest a 3- to 5-year window between the detection of an IPMN and progression to invasive cancer.

Third, curable lesions should be detected before they metastasize. Intraductal papillary mucinous neoplasms and MCNs produce cystic mass lesions, which are easily identified on computed tomography imaging. Although, at present, it is not possible to identify PanINs because they are so small, new highly sensitive techniques have been developed; these can identify tiny amounts of cancer DNA in pancreatic juice and blood samples.⁹ Pancreatic juice, which is produced by the exocrine acinar cells, is interesting in the context of cancer screening because its contents originate in many areas of the pancreas. Novel blood tests can detect a combination of pancreatic cancer DNA and pancreatic cancer-related protein markers. For example, in a multicenter study of 221 patients, results of a multimarker blood test helped identify 64% of patients with early pancreatic cancer; this was achieved while maintaining a high specificity.¹⁰ Twenty percent of patients in this study did not have symptoms that are typically associated with pancreatic cancer. Results of the multimarker blood test helped identify 60% of these patients, 70% of whom were alive, with no evidence of cancer recurrence with a median follow-up of 12 months. This test, which detects the presence of circulating tumor DNA or cancer-associated proteins, has been evaluated in a larger cohort of 1005 patients.¹¹ This and similar tests are currently being prospectively studied.

Fourth, as we have discussed, it is important to distinguish precursor lesions with a reasonable chance of progressing to advanced cancer from those with little or no risk of progression. Recently, there has been progress. Many of the somatic mutations associated with high-grade dysplasia or early invasive cancer, such as *TP53* and *SMAD4*, are known and can be detected in cyst fluid from IPMNs and MCNs. In a recent study of approximately 600 patients with pancreatic cysts, a tumor marker panel was used to distinguish between IPMNs with high-grade dysplasia or early invasive cancer and those with no or low malignant potential with 79% sensitivity and 96% specificity.¹²

Fifth, as noted in the United States Preventive Services Task Force report,² the prevalence of the disease has to be reasonably high in the population to be screened. Although the prevalence of pancreatic cancer is relatively low, groups with significantly increased risk can be identified and their risk quantified.¹³ High-risk populations include individuals with IPMNs or MCNs; a strong family history of pancreatic cancer (at least 2 family members); a germline pathogenic variant in *BRCA1*, *BRCA2*, *p16/CDKN2A*, *PALB2*, *STK11*, *ATM*, *PRSS1*, and the DNA mismatch repair genes;^{14,15} and older individuals with new onset diabetes mellitus.¹³ Surveillance is currently recommended for individuals who are found to have an IPMN or MCN,^{16,17} and the International Cancer of the Pancreas Screening Consortium has developed guidelines for screening high-risk individuals.¹⁸ Studies should evaluate whether the integration of risk factors into recommendations helps to identify subgroups whose underlying disease prevalence is high enough that members of these groups would benefit from screening.

Sixth, evidence should be developed to establish whether early detection of pancreatic cancer results in improved survival. For example, though there was no control group, a 2018 multicenter study in Japan found that 80% of patients with stage I pancreatic cancer were alive 10 years after diagnosis.¹⁹ Outcomes are similar for patients with small, low-stage cancers detected by screening.^{20,21}

As we celebrate the 50th anniversary of the moon landing, we marvel at the enormous advances needed to bring President John F. Kennedy's vision to reality. Although the challenges of effective screening for pancreatic cancer are also daunting, they offer another opportunity for medicine to overcome adversity and to make another vision a reality.

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REFERENCES

1. 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 Res.* 2014;74(11):2913–2921. doi:10.1158/0008-5472.CAN-14-0155 [PubMed: 24840647]
2. Henrickson NB, Aiello Bowles EJ, Blasi PR, et al. Screening for pancreatic cancer: US Preventive Services Task Force recommendation statement [published online August 6, 2019]. *JAMA.* doi:10.1001/jama.2019.10232
3. US Preventive Services Task Force. Screening for pancreatic cancer: updated evidence report and systematic review for the US Preventive Services Task Force [published online August 6, 2019]. *JAMA.* doi:10.1001/jama.2019.6190
4. Yu J, Blackford AL, Dal Molin M, Wolfgang CL, Goggins M. Time to progression of pancreatic ductal adenocarcinoma from low-to-high tumour stages. *Gut.* 2015;64(11):1783–1789. doi:10.1136/gutjnl-2014-308653 [PubMed: 25636698]
5. Notta F, Chan-Seng-Yue M, Lemire M, et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. *Nature.* 2016;538(7625):378–382. doi:10.1038/nature19823 [PubMed: 27732578]
6. Noë M, Rezaee N, Asrani K, et al. Immunolabeling of cleared human pancreata provides insights into three-dimensional pancreatic anatomy and pathology. *Am J Pathol.* 2018;188(7): 1530–1535. doi:10.1016/j.ajpath.2018.04.002 [PubMed: 29684363]
7. Dal Molin M, Springer S, Masica D, et al. A multi-modality test to guide the management of patients with pancreatic cysts. *Gastrointest Endosc.* 2019;89(6)(suppl):AB143–AB144. doi:10.1016/j.gie.2019.04.193

8. Lennon AM, Wolfgang CL, Canto MI, et al. The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia? *Cancer Res.* 2014;74(13):3381–3389. doi:10.1158/0008-5472.CAN-14-0734 [PubMed: 24924775]
9. Suenaga M, Yu J, Shindo K, et al. Pancreatic juice mutation concentrations can help predict the grade of dysplasia in patients undergoing pancreatic surveillance. *Clin Cancer Res.* 2018;24(12):2963–2974. doi:10.1158/1078-0432.CCR-17-2463 [PubMed: 29301828]
10. Cohen JD, Javed AA, Thoburn C, et al. Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. *Proc Natl Acad Sci USA.* 2017;114(38):10202–10207. doi:10.1073/pnas.1704961114 [PubMed: 28874546]
11. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science.* 2018;359(6378): 926–930. doi:10.1126/science.aar3247 [PubMed: 29348365]
12. Singhi AD, McGrath K, Brand RE, et al. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut.* 2018;67(12):2131–2141. doi:10.1136/gutjnl-2016-313586 [PubMed: 28970292]
13. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology.* 2019;156(7):2024–2040. doi:10.1053/j.gastro.2019.01.259 [PubMed: 30721664]
14. Roberts NJ, Norris AL, Petersen GM, et al. Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. *Cancer Discov.* 2016;6(2):166–175. doi:10.1158/2159-8290.CD-15-0402 [PubMed: 26658419]
15. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA.* 2018;319(23):2401–2409. doi:10.1001/jama.2018.6228 [PubMed: 29922827]
16. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol.* 2018;113(4): 464–479. doi:10.1038/ajg.2018.14 [PubMed: 29485131]
17. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut.* 2018;67(5): 789–804. doi:10.1136/gutjnl-2018-316027 [PubMed: 29574408]
18. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* 2012. doi:10.1136/gutjnl-2012-303108
19. Kanno A, Masamune A, Hanada K, et al.; Japan Study Group on the Early Detection of Pancreatic Cancer (JEDPAC). Multicenter study of early pancreatic cancer in Japan. *Pancreatology.* 2018;18(1):61–67. doi:10.1016/j.pan.2017.11.007 [PubMed: 29170051]
20. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. *Gastroenterology.* 2018;155(3):740–751.e2. doi:10.1053/j.gastro.2018.05.035 [PubMed: 29803839]
21. Vasen H, Ibrahim I, Ponce CG, et al. Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. *J Clin Oncol.* 2016;34(17):2010–2019. doi:10.1200/JCO.2015.64.0730 [PubMed: 27114589]