Diagnosis, differentiation and prevention in pancreatic diseases

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CHAPTER 10 - DISCUSSION

The ancient Greek myth of Pandora's box, as an allegory for pancreatic diseases, served as a classical inspiration for the cover of this dissertation. When Pandora's box is yet unopened, few people may know the feeling of true suffering. In a similar manner, it remains unknown to many even the presence and function of the pancreas in the absence of pancreatic diseases. In the myth, upon the box's opening by Pandora, trouble and chaos are released upon the world. This is congruent with the despair of those and their loved ones confronted with a pancreatic cancer diagnosis, [1] one of the most lethal cancers with a short median survival duration and few who are eligible for curative treatment options. [2] In the case of pancreatitis, the all-consuming pain is often described as beyond the realm thought possible. [3] The severe cases can result in months of hospitalization, [4] brushes with death, [5] and significant long-term morbidity. [6, 7] Herein lies the urgency and necessity for improving diagnosis, differentiation and prevention in pancreatic diseases.

ARTIFICIAL INTELLIGENCE & IMAGING

THE RATIONALE OF A SECOND READER IN PANCREATIC CANCER IMAGING

In Chapter 2, we demonstrated that suspicion of a pancreatic mass was present in 50% of CT scans and 50–70% of MRI scans from pre-diagnostic pancreatic cancer patients, compared to only 0–3% in pre-diagnostic controls. Several imaging findings, including pancreatic duct dilation, duct interruption, focal atrophy, and features of acute pancreatitis, were significantly associated with the development of pancreatic cancer. The high prevalence of pre-diagnostic tumor mass suspicion and other secondary findings has been extensively reported in other cohorts. [8-12]

An important aspect to consider is the role of 'radiological errors' that contributed to missed cancer diagnoses upon unblinded reassessment. Beyond technical limitations, a substantial proportion of errors were attributed to human factors, including underreading (57.2% in CT, 45.5% in MRI), faulty reasoning (17.9% in CT, 4.5% in MRI), and satisfaction of search errors (10.7% in CT, 31.9% in MRI). In breast cancer screening, it is has been established that double reading mammographs by two radiologists can lead to a 5-15% sensitivity increase. [13] Introducing a second reader in pancreatic cancer screening, for instance, through the routine involvement of multiple radiologists in multidisciplinary team (MDT) meetings, could be beneficial. However, given the scarce time of these experts, this approach might not be feasible or desirable.

Notably, multiple studies in breast cancer screening have shown that AI algorithms can replace a second human reader while achieving equivalent diagnostic accuracy: a potential cost-effective strategy in an era where specialized radiologists are already strapped for time. [14-16] Our findings, in conjunction with existing literature, underscore the potential for AI-assisted pancreatic cancer screening. This direction is supported by three key considerations: (1) identifiable imaging features precede pancreatic cancer diagnosis, suggesting that earlier recognition could improve detection; (2) second readers can help reduce missed cases; and (3) AI could automate the second reading process. While the detection of radiomics supported pre-diagnostic pancreatic cancer detection has successfully been explored for CT, [17, 18] this field remains unexplored for MRI. This feasibility of AI-assisted pancreatic cancer detection on pre-diagnostic MRI scans will be explored in our future research, made possible by the Hanarth Grant for AI-driven oncological research in rare tumors, of which chapter 4 is the first step.

The long and winding road to clinical implementation of medical AI Chapter 3 provided an opportunity to assess the state of artificial intelligence (AI) in pancreatic disease research at the outset of this thesis. Within the pancreatic diseases section of this review, multiple potential applications for benign and malignant diseases were identified; however, none had achieved regulatory approval or commercial implementation. Four years after writing this summary of literature, little progress has been made in the regulatory approval and widespread implementation of AI algorithms for pancreatic diseases.

Several factors contribute to this stagnation. First, data scarcity remains a major challenge in AI pancreatic disease research. Advancing AI in this field requires large-scale, multi-center collaborations, where federated learning could play a crucial role by allowing algorithm training while ensuring data privacy by remaining within the firewalls of the originating healthcare institutions. [19] Harnessing the power of existing collaborations within pancreatic disease research, such as nationally through the Dutch Pancreatitis Study Group (DPSG) and Dutch Pancreatic Cancer Group (DPCG), [20, 21] or internationally for pancreatic cancer surveillance initiatives including Cancer of the Pancreas Screening (CAPS), PAncreatic CYst Follow-up, an International Collaboration (PACYFIC) and Pancreatic Cancer Early Detection (PRECEDE), [22-24] is the only way to achieve the necessary data quantities for robust algorithm development. Additionally, initiatives aimed at curating large, abdominal radiology specific training datasets, such as the Gastro-Net 5M is for endoscopic images[25], would be beneficial for optimal pre-training conditions. However, in the case of annotated data, attention must also be given to data quality, as prior studies have highlighted significant variability and deficiencies in data annotation of pancreatic imaging datasets. [26]

Second, regulatory constraints, particularly with the arrival of the European Union's AI-Act, [27] will curb swift clinical implementation of AI innovations, as all medical applications of AI are considered 'high risk' and subject to stringent regulation starting May 2025. [28] These restrictions, including sustained quality management systems and human oversight, are not unwarranted. There is substantial evidence that algorithms developed in controlled test settings often perform suboptimally on real-world data, due to the concept of 'domain shift' when training conditions have a different data distribution due to a different proportion of affected individuals or different acquisition manners. [29] In the context of cancer screening, ethical and legal concerns are at utmost importance to be addressed. These include the potential for AI algorithms to propagate and amplify societal biases, [30] as well as questions regarding liability in cases where inaccurate predictions lead to patient harm. [31]

Despite these challenges, the review also highlighted promising trials of currently regulatory approved AI applications in colorectal polyp detection and differentiation. [32,33] However, even after regulatory approval in this domain, several barriers to widespread clinical adoption remain, including uncertain long-term survival benefits, [34] the absence of standardized reimbursement policies, [35] and operator fatigue caused by excessive false-positive alerts in AI-driven systems. [36] Addressing these issues is essential before widespread implementation can be expected. Nonetheless, the use case of AI in colorectal cancer screening illustrates the trajectory that pancreatic disease algorithms have the potential to ultimately follow.

LIMITATIONS AND FUTURE DIRECTIONS OF AI IN PANCREAS IMAGING

In Chapter 4, we took an initial step in AI-assisted pancreatic disease classification by developing an algorithm that achieves competitive performance with current literature in pancreas MRI segmentation while minimizing annotation workload and maintaining high segmentation quality. We cannot state this with absolute certainty, as to date, there is a lack of a benchmarking dataset for MRI pancreas segmentation, [37] in contradiction to the uncontested NIH benchmarking dataset for pancreas CT segmentation. [38] Recent publication of the multi-center dataset[39] used to develop the algorithm of Zhang et al. [40] might provide a stimulus to pancreatic cancer AI research, as the release of high-quality annotated datasets in previous years through image-based AI competitions has also spurred. [41]

Our study also demonstrated the effectiveness of continuous learning in generating high-quality annotations. This approach allows for efficient dataset expansion with minimal expert correction, crucial given the limited availability of specialized radiologists for such. [42] However, continuous learning has inherent limita-

tions. Maintaining a robust knowledge base requires substantial computational resources, adding to the knowledge base can result in 'catastrophic forgetting' and there are regulatory constraints on post-market modifications to medical AI algorithms due to safety concerns. [43] Even so, the concept of continuous learning fits the tradition of medicine as craftsmanship taught by experts to next generations of health care professionals. [44] Doctors are accustomed to learning how to practice medicine in an apprentice role. From a radiologist's perspective, continuous learning can be likened to training a resident through iterative observations and corrections. As the algorithm evolves, an expert can assess its ability to perform the assigned task based on performance trends, perceived learning capabilities, and encountered challenges. In turn, the trained algorithm could eventually play a role in resident training. [45]

Subsequent research from our group will focus on validating the segmentation algorithm on our 2000 MRI internal dataset from 500 participants of the LUMC CDKN2A pancreatic cancer surveillance cohort. [46] This will be followed by multi-center validation in collaborating centers, and analyses of segmentation performance on longitudinal scans in the same patient. We expect to encounter certain difficulties relating to varying MRI protocols when using historical scans and when collaborating with different centers. This can be considered the main limitation of chapter 4, as the MRI protocol used in this dataset was specifically tailored for the pancreatic cancer screening program at LUMC, in most recent years optimized for detailed pancreas parenchyma evaluation by a smaller field of view and oblique axial plane on a 3T system. [47] We aim to explore the transfer of a T2 based segmentation algorithm to other MRI sequences, so data from all sequences can be incorporated in a pancreatic cancer detection algorithm. Other work from our group has shown that changes in body composition are associated with pancreatic cancer development. [48] Incorporating these changes with the envisioned algorithm detecting pathological changes in the pancreas would serve our objective of creating a multi-model pancreatic cancer risk assessment tool.

BIOMARKERS

Harnessing complementary biomarker profiles in pancreatic cancer detection Chapter 5 demonstrates that combining a methylated DNA panel in pancreatic juice with serum CA 19.9 results in a highly accurate test for detecting pancreatic cancer vs a diverse set of controls. Whilst there have been many promising candidate biomarkers for pancreatic cancer detection, CA 19.9 is the only one recommended by guidelines and awarded with widespread adaption, [49-51] although it's utility and performance in early pancreatic cancer surveillance cohorts is conflicting and understudied. [52-54] Candidate biomarkers can have an inflated performance in pilot studies if the control group only contains persons with a normal pancreas, as mark-

ers such as KRAS are elevated in both chronic pancreatitis and low-grade pre-cursor lesions such as PanIn and IPMN. [55] The interesting aspect of combining biomarkers, as demonstrated in this study, is leveraging distinct performance qualities. The 3-MDM panel had a higher false positive rate for IPMN (17% for 3-MDM vs 9% for CA19.9), and CA 19.9 for chronic pancreatitis patients (35% CA19.9 vs 9% 3-MDM). Other candidate biomarkers have been combined in a similar manner with CA 19.9, [56-58] and this is considered a hopeful development in pancreatic cancer detection. The 3-MDM panel still needs to undergo several steps before it can reach the clinical practice. This is a complex marker panel for which in the current study a Random Forest model was used to determine optimal methylated DNA cut-off values, and a continuous scale of CA19.9 instead of the established cut-off value of 37 U/ml. There is to date an unmet need for commercial assay development with set cut-off values. What is an acceptable cost for such a test is dependent on national healthcare system values, intended use population and expected merit.

General considerations in pancreatic cancer screening and surveillance
Although this thesis pertains mainly to the technical aspects of pancreatic cancer screening including imaging and biomarkers, it is important to place these innovations into the clinical setting of pancreatic cancer screening and surveillance. Current international guidelines recommend pancreatic cancer surveillance for individuals with a lifetime risk exceeding 5%.[22] This threshold is a consensus based minimum risk level at which the benefits of active surveillance, through imaging and/or blood-based biomarkers, are thought to outweigh potential harms. However, the rationale behind choosing the 5% cutoff remains insufficiently articulated. Although the 5% lifetime risk threshold is currently upheld in guidelines, the definition of which patient populations fall within this category is constantly evolving over time with improvements in risk quantification and results from established surveillance cohorts. It remains to be determined whether the 5% threshold represents an economically suitable strategy or if a higher threshold, such as 10%, would be more appropriate. Adopting a higher threshold would limit screening to a narrower group, predominantly individuals with CDKN2A mutations or Peutz-Jeghers syndrome, [59] potentially improving both clinical efficacy, ethical acceptability and economic feasibility, at the expense of the potential of more surveillance detected cases. Returning to Dr. Suresh Chari's sieve model discussed in the introduction, which outlines the need for risk enrichment in the general population due to the low incidence of pancreatic cancer, important ethical questions arise. Is it justifiable to subject the general population to the psychological burden and potential harms of screening for a highly lethal disease? One critical issue is that even slight deviations from 100% specificity in a low-prevalence setting can result in an unacceptably high number of false positives. This can lead to unnecessary diagnostic procedures, anxiety, and healthcare costs. For any screening or surveillance program to be con-

Table 1

Criteria Wilson & Junger (1968) [60]
The condition sought should be an important health problem.
There should be an accepted treatment for patients with recognized disease.
Facilities for diagnosis and treatment should be available.
There should be a recognizable latent or early symptomatic stage.
There should be a suitable test or examination.
The test should be acceptable to the population.
The natural history of the condition, including development from latent to declared disease, should be adequately understood.
There should be an agreed policy on whom to treat as patients.
The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
Case-finding should be a continuous process and not a "once and for all" project.

sidered ethical and implementable, it should meet the well-established Wilson and Junger criteria (**Table 1**). [60]

Although the research field strives to identify defining risk factors that could bring 100% of pancreatic cancer cases into defined enriched populations eligible for screening, this is currently a pipe dream until we can ensure that screen detected cases are early stage and curatively treatable. This is congruent with the position taken by the US Preventive Task Force recommendation statement in 2019. [61] As this thesis aims to demonstrate, the first step in doing so is by improving the sensitivity of early-stage disease detection of our diagnostic while maintaining high specificity, and doing this at an acceptable burden to the at-risk population (see **Figure 1**).

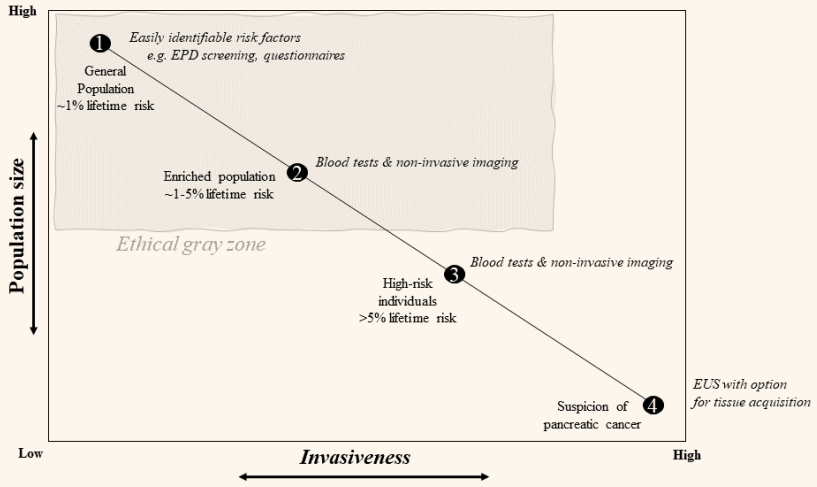

Figure 1. *Desirability of invasiveness in regards to population size in pancreatic cancer screening. The 'gray zone' defines the populations pancreatic cancer screening that encounters ethical limitations.*

PRAGMATIC POST-ERCP DISCHARGE MANAGEMENT AND THE VALUE OF NEGATIVE FINDINGS

Chapter 6, another topic within the realm of pancreatic diseases, similarly aimed to validate and combine two methods for disease detection in an effort to increase diagnostic performance. Whilst the sensitivity of both methods combined led to an increased sensitivity for post-ERCP adverse event detection, the performance can hardly justify clinical implementation. As another study on the UT-2 dipstick demonstrated that the increased performance was mainly driven by the presence of abdominal pain, [62] it would be interesting to study whether clinician judgement in the post-endoscopy suite can accurately predict post-ERCP adverse event occurrence. This could potentially be combined with early warning signs (EWS) and procedural difficulty rating at the end of post-procedural observation in an attempt to for pragmatic standardization of post-ERCP discharge management.

Despite not recommending the UT-2 dipstick or risk-factor tool for clinical implementation, there is value in negative finding research. This study is the third recent study demonstrating sub-par performance of the UT-2 dipstick for post-ERCP pancreatitis detection, providing sufficient substrate to not recommend further research be conducted for the indication of safe-discharge management after ERCP. [62, 63] Unfortunately, one of these studies has to date only been published in abstract form. [63] There is sufficient substantiation on the difficulty of publishing clinical studies with negative findings. [64] Publication bias can lead to future skewed systematic reviews and meta-analysis, and we must strive to counteract the disinterest in negative findings, as this could lead to further research or unjust clinical implementation into ineffective interventions.

RISK PREDICTION AND PREVENTION IN POST-ERCP PANCREATITIS

Chapter 7 explored how advanced endoscopists of the Netherlands who perform ERCPs consider post-ERCP pancreatitis risk factors and their self-reported use of prophylactic measures. The following findings warrant further attention.

To or to not? Universal and combined post-ERCP pancreatitis prophylaxis Although the proportion of endoscopists who report using PD stents to prevent post-ERCP pancreatitis significantly rose over time, 22% reported never using PD stents. This is concerning, as PD stents have proven to be the most effective measure in preventing post-ERCP pancreatitis. [65] Because rectal NSAIDs have likewise proven to protect against post-ERCP pancreatitis, it is logical to prefer this risk reduction intervention, as PD stents that luxate can cause an additive pancreatitis risk endoscopists might not want to risk. Results from the added arm of the FLUYT trial, [66] in which the additional value of PD-stents to NSAID use after inadvertent PD cannulation is studied, will provide more insight into the additional benefits of combining preventative measures. And although the strategy of universal NSAID

application is widely adapted in the Netherlands, there remains a discrepancy with the United States where the cost prohibitive aspect of rectal diclofenac/indomethacin administration limits it's use to the high-risk patient category, [67] but where PD-stent placement is more widely adapted. [68]

DEFINING 'RISKY BUSINESS' IN POST-ERCP ADVERSE EVENTS

Continuing on another topic in which there is not full consensus: what exactly defines a high-risk patient? How can this be stratified in future trials? Trials are often conducted in expert centers, some of which have managed to decrease their PEP rates to 5% or lower, providing few events that yield statistical power, and requiring large numbers of patients to be enrolled. There is also discussion whether all patients should be enrolled in post-ERCP adverse event prevention trials, or only those at intermediate to high-risk, a tricky situation as frequently this only becomes clear with the occurrence of procedural risk factors such as inadvertent PD cannulation, challenging enrolment efforts. Alternative proxy outcome measures for adverse events could facilitate rapid trial enrollment and conduction, such as necessity to prolong post-ERCP hospital admission due to any procedure related cause. That being said, it can be defended that the only meaningful post-ERCP pancreatitis episodes are the 5-10% that result in a severe cases, as this is the group that bear the brunt of the morbidity and mortality. [69] In summary, post-ERCP pancreatitis research would benefit from a consensus definition established by community and tertiary providers of 'the high-risk patient' that warrants extra post-ERCP adverse event prevention efforts, and acceptable (proxy) outcome measures for post-ERCP adverse event trials.

ABSTINENCE AS A RISK AVOIDANCE STRATEGY

The best way to prevent a post-ERCP pancreatitis though, is to not expose those who don't need a therapeutic ERCP to the risk of the procedure. There are several ways to do so. The most common indication for an ERCP is choledocholithiasis. [70] In **chapter 8**, we explored how additional imaging to ERCP is applied in the clinical practice. Based on aggregated complication risks, for every 10 ERCPs prevented, 1 case of post-ERCP pancreatitis can be prevented. [69] For 28% of patients who underwent additional imaging in our study, ERCPs were avoided. According to these assumptions, for every MRCP/EUS performed, the number needed to image to prevent one ERCP would be 3.57, and number needed to image to prevent one case of pancreatitis would be 35.7. It is yet to be demonstrated whether performing additional imaging prior to every ERCP for choledocholithiasis would be a logistically feasible and cost effective approach.

Besides choledocholithiasis, pancreaticobiliary malignancies with obstructive jaundice are the second most frequent therapeutic indication for ERCP. [70] Recent literature has suggested that patients with malignant biliary drainage indications who are drained transpapillary by ERCP with self-expandable metal stents have an

exceptionally high chance of developing pancreatitis.[71, 72] This is especially fraught as this could theoretically delay oncological treatment past the short potential curative window of pancreatic cancer. Innovations in EUS guided common bile duct (EUS-CBD) drainage could provide a pancreas-avoiding alternative,[73, 74] although the procedure is still undergoing technical refinement and long-term clinical success has yet to be proven beyond doubt.

CONCLUSION

Pandora's myth does not end with only the release of despair into the world. Once all evil has been spread, one thing remains in the box: Hope. Therefore, 'Living with Hope' is a very aptly named patient organization for pancreatic cancer advocacy in the Netherlands.[75] It has been established that research spending on pancreatic cancer lags behind other cancers with a higher incidence rate,[76] despite its violent mortality rates. As a final plea, we should continue to foster the curiosity of opening Pandora's box by mitigating the devastating impact of pancreatic diseases through sustained research and focusing on the hope that remains.

REFERENCES

1. Engebretson A, Matrisian L, Thompson C. Pancreatic cancer: Patient and caregiver perceptions on diagnosis, psychological impact, and importance of support. Pancreatology 2015;15:701-707.
2. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin 2025;75:10-45.
3. Boije K, Drocic A, Engström M, et al. Patients' Perceptions of Experiences of Recovering From Acute Pancreatitis: An Interview Study. Gastroenterology Nursing 2019;42.
4. Schepers NJ, Bakker OJ, Besselink MG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2019;68:1044-1051.
5. Wolbrink DRJ, van de Poll MCG, Termorshuizen F, et al. Trends in Early and Late Mortality in Patients With Severe Acute Pancreatitis Admitted to ICUs: A Nationwide Cohort Study. Critical Care Medicine 2022;50.
6. Hollemans RA, Hallensleben NDL, Mager DJ, et al. Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. Pancreatology 2018;18:253-262.
7. Hart PA, Bradley D, Conwell DL, et al. Diabetes following acute pancreatitis. The Lancet Gastroenterology & Hepatology 2021;6:668-675.
8. Singh DP, Sheedy S, Goenka AH, et al. Computerized tomography scan in pre-diagnostic pancreatic ductal adenocarcinoma: Stages of progression and potential benefits of early intervention: A retrospective study. Pancreatology 2020;20:1495-1501.

9. Kang J, Clarke SE, Abdolell M, et al. The implications of missed or misinterpreted cases of pancreatic ductal adenocarcinoma on imaging: a multi-centered population-based study. Eur Radiol 2021;31:212-221.

10. Parker RA, Zhou Y, Puttock EJ, et al. Early features of pancreatic cancer on magnetic resonance imaging (MRI): a case-control study. Abdom Radiol (NY) 2024;49:1489-1501.

11. Toshima F, Watanabe R, Inoue D, et al. CT Abnormalities of the Pancreas Associated With the Subsequent Diagnosis of Clinical Stage I Pancreatic Ductal Adenocarcinoma More Than 1 Year Later: A Case-Control Study. American Journal of Roentgenology 2021;217:1353-1364.

12. Boekestijn B, Feshtali S, Meijer AC, et al. MRI screening in hereditary pancreatic cancer: value of various sequences in the detection of early pancreatic cancer. Annals of Pancreatic Cancer 2020;3.

13. European Commission: Directorate-General for H, Consumers, Perry N, et al. European guidelines for quality assurance in breast cancer screening and diagnosis: Publications Office of the European Union, 2006.

14. McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. Nature 2020;577:89-94.

15. Salim M, Wåhlin E, Dembrower K, et al. External Evaluation of 3 Commercial Artificial Intelligence Algorithms for Independent Assessment of Screening Mammograms. JAMA Oncology 2020;6:1581-1588.

16. Lång K, Josefsson V, Larsson AM, et al. Artificial intelligence-supported screen reading versus standard double reading in the Mammography Screening with Artificial Intelligence trial (MASAI): a clinical safety analysis of a randomised, controlled, non-inferiority, single-blinded, screening accuracy study. Lancet Oncol 2023;24:936-944.

17. Mukherjee S, Patra A, Khasawneh H, et al. Radiomics-Based Machine-Learning Models Can Detect Pancreatic Cancer on Prediagnostic CTs at a Substantial Lead Time Prior to Clinical Diagnosis. Gastroenterology 2022;163:1435-1446 e3.

18. Korfiatis P, Suman G, Patnam NG, et al. Automated Artificial Intelligence Model Trained on a Large Data Set Can Detect Pancreas Cancer on Diagnostic Computed Tomography Scans As Well As Visually Occult Preinvasive Cancer on Prediagnostic Computed Tomography Scans. Gastroenterology 2023;165:1533-1546.e4.

19. Rieke N, Hancox J, Li W, et al. The future of digital health with federated learning. npj Digital Medicine 2020;3:119.

20. van Grinsven J, van Brunschot S, van Santvoort HC, et al. The Value of a 24/7 Online Nationwide Multidisciplinary Expert Panel for Acute Necrotizing Pancreatitis. Gastroenterology 2017;152:685-688.e6.

21. Strijker M, Mackay TM, Bonsing BA, et al. Establishing and Coordinating a Nationwide Multidisciplinary Study Group: Lessons Learned by the Dutch Pancreatic Cancer Group. Annals of Surgery 2020;271.

22. 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 2013;62:339-47.

23. Sprij ML, Meziani J, Bruno MJ, et al. Pancreatic Cyst Follow-up, an International Collaboration PACYFIC study. 2023.

24. Huang C, Simeone DM, Luk L, et al. Standardization of MRI Screening and Reporting in Individuals With Elevated Risk of Pancreatic Ductal Adenocarcinoma: Consensus Statement of the PRECEDE Consortium. American Journal of Roentgenology 2022;219:903-914.

25. Boers TGW, Fockens KN, van der Putten JA, et al. Foundation models in gastrointestinal endoscopic AI: Impact of architecture, pre-training approach and data efficiency. Medical Image Analysis 2024;98:103298.

26. Suman G, Patra A, Korfiatis P, et al. Quality gaps in public pancreas imaging datasets: Implications & challenges for AI applications. Pancreatology 2021;21:1001-1008.

27. Regulation (EU) 2024/1689 of the European Parliament and of the Council of 13 June 2024 laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828 (Artificial Intelligence Act), 2024.

28. Aboy M, Minssen T, Vayena E. Navigating the EU AI Act: implications for regulated digital medical products. npj Digital Medicine 2024;7:237.

29. Kondrateva E, Pominova M, Popova E, et al. Domain shift in computer vision models for MRI data analysis: an overview: SPIE, 2021.

30. Uche-Anya E, Anyane-Yeboa A, Berzin TM, et al. Artificial intelligence in gastroenterology and hepatology: how to advance clinical practice while ensuring health equity. Gut 2022;71:1909-1915.

31. Elamin S, Duffourc M, Berzin TM, et al. Artificial Intelligence and Medical Liability in Gastrointestinal Endoscopy. Clinical Gastroenterology and Hepatology 2024;22:1165-1169.e1.

32. Kudo S-e, Misawa M, Mori Y, et al. Artificial Intelligence-assisted System Improves Endoscopic Identification of Colorectal Neoplasms. Clinical Gastroenterology and Hepatology 2020;18:1874-1881.e2.

33. Repici A, Badalamenti M, Maselli R, et al. Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. Gastroenterology 2020;159:512-520.e7.

34. Halvorsen N, Hassan C, Correale L, et al. Benefits, burden, and harms of computer aided polyp detection with artificial intelligence in colorectal cancer screening: microsimulation modelling study. BMJ Med 2025;4:e001446.

35. Mori Y, Kudo S-e, East JE, et al. Cost savings in colonoscopy with artificial intelligence-aided polyp diagnosis: an add-on analysis of a clinical trial (with video)☒. Gastrointestinal Endoscopy 2020;92:905-911.e1.

36. Chung GE, Lee J, Lim SH, et al. A prospective comparison of two computer aided de-

tection systems with different false positive rates in colonoscopy. npj Digital Medicine 2024;7:366.

37. Dishner KA, McRae-Posani B, Bhowmik A, et al. A Survey of Publicly Available MRI Datasets for Potential Use in Artificial Intelligence Research. J Magn Reson Imaging 2024;59:450-480.

38. Holger R. Roth AF, Evrim B. Turkbey, Le Lu, Jiamin Liu, and Ronald M. Summers. Data From Pancreas-CT. In: Archive TCI, ed, 2016.

39. Bagci U, Zheyuan Zhang, Elif Keles, and Halil Ertugrul Aktas. PanSegData. OSF, 2025.

40. Zhang Z, Keles E, Durak G, et al. Large-scale multi-center CT and MRI segmentation of pancreas with deep learning. Medical Image Analysis 2025;99:103382.

41. Prevedello LM, Halabi SS, Shih G, et al. Challenges Related to Artificial Intelligence Research in Medical Imaging and the Importance of Image Analysis Competitions. Radiology: Artificial Intelligence 2019;1:e180031.

42. Alexander R, Waite S, Bruno MA, et al. Mandating Limits on Workload, Duty, and Speed in Radiology. Radiology 2022;304:274-282.

43. Pianykh OS, Langs G, Dewey M, et al. Continuous Learning AI in Radiology: Implementation Principles and Early Applications. Radiology 2020;297:6-14.

44. O'Mahony S. The Thing Itself: Medicine as Craft. Gastroenterology 2025;168:637-639.

45. Duong MT, Rauschecker AM, Rudie JD, et al. Artificial intelligence for precision education in radiology. British Journal of Radiology 2019;92.

46. Klatte DCF, Boekestijn B, Wasser MNJM, et al. Pancreatic Cancer Surveillance in Carriers of a Germline CDKN2A Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up. Journal of Clinical Oncology 2022:JCO.22.00194.

47. Boekestijn B, Feshtali S, Vasen H, et al. Screening for pancreatic cancer in high-risk individuals using MRI: optimization of scan techniques to detect small lesions. Familial Cancer 2024;23:295-308.

48. Klatte DCF, Weston A, Ma Y, et al. Temporal Trends in Body Composition and Metabolic Markers Prior to Diagnosis of Pancreatic Ductal Adenocarcinoma. Clin Gastroenterol Hepatol 2024;22:1830-1838.e9.

49. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738-753.

50. The European Study Group on Cystic Tumours of the P. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67:789.

51. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut 2020;69:7-17.

52. Levink IJM, Jaarsma SC, Koopmann BDM, et al. The additive value of CA19.9 monitoring in a pancreatic cyst surveillance program. United European Gastroenterol J 2023;11:601-611.

53. Fahrmann JF, Schmidt CM, Mao X, et al. Lead-Time Trajectory of CA19-9 as an Anchor Marker for Pancreatic Cancer Early Detection. Gastroenterology 2021;160:1373-1383.e6.

54. Choe JW, Kim HJ, Kim JS, et al. Usefulness of CA 19–9 for pancreatic cancer screening in patients with new-onset diabetes. Hepatobiliary & Pancreatic Diseases International 2018;17:263-268.

55. Löhr M, Klöppel G, Maisonneuve P, et al. Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. Neoplasia 2005;7:17-23.

56. Chan A, Prassas I, Dimitromanolakis A, et al. Validation of Biomarkers That Complement CA19.9 in Detecting Early Pancreatic Cancer. Clinical Cancer Research 2014;20:5787-5795.

57. Kim J, Bamlet WR, Oberg AL, et al. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. Sci Transl Med 2017;9.

58. Brand RE, Nolen BM, Zeh HJ, et al. Serum biomarker panels for the detection of pancreatic cancer. Clin Cancer Res 2011;17:805-16.

59. Bogdanski AM, Acedo P, Wallace MB, et al. Recommendations, evidence and sustainability of screening for pancreatic cancer in high-risk individuals. Best Practice & Research Clinical Gastroenterology 2025:101974.

60. Wilson J, Jungner G. Principles and practice of screening. WHO: Geneva 1968;69:1085.

61. Force UPST. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA 2019;322:438-444.

62. Rainio M, Lindström O, Udd M, et al. Repeated Negative Urine Trypsinogen-2 Dipstick Test Rules Out Diagnosis of Post-ERCP Pancreatitis. J Clin Gastroenterol 2021;55:361-366.

63. Obaitan I, Rosenheck M, Wehbe H, et al. S117 Diagnostic Accuracy of the Urine trypsinogen-2 Dipstick Test in Early Post-ERCP Pancreatitis Prediction. Official journal of the American College of Gastroenterology | ACG 2023;118:S93-S94.

64. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. Journal of Clinical Epidemiology 2000;53:207-216.

65. Buxbaum JL, Freeman M, Amateau SK, et al. American Society for Gastrointestinal Endoscopy guideline on post-ERCP pancreatitis prevention strategies: methodology and review of evidence. Gastrointestinal Endoscopy 2023;97:163-183.e40.

66. Sperna Weiland CJ, Smeets X, Kievit W, et al. Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory

drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT): a multicentre, open-label, randomised, controlled trial. Lancet Gastroenterol Hepatol 2021;6:350-358.

67. Elmunzer BJ, Hernandez I, Gellad WF. The Skyrocketing Cost of Rectal Indomethacin. JAMA Intern Med 2020;180:631-632.

68. Avila P, Holmes I, Kouanda A, et al. Practice patterns of post-ERCP pancreatitis prophylaxis techniques in the United States: a survey of advanced endoscopists. Gastrointest Endosc 2020;91:568-573.e2.

69. Akshintala VS, Kanthasamy K, Bhullar FA, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: an updated systematic review and meta-analysis of 145 randomized controlled trials. Gastrointest Endosc 2023;98:1-6.e12.

70. Bishay K, Meng ZW, Khan R, et al. Adverse Events Associated With Endoscopic Retrograde Cholangiopancreatography: Systematic Review and Meta-Analysis. Gastroenterology 2025;168:568-586.

71. Onnekink AM, Gorris M, Bekkali NL, et al. Endoscopic sphincterotomy to prevent post-ERCP pancreatitis after self-expandable metal stent placement for distal malignant biliary obstruction (SPHINX): a multicentre, randomised controlled trial. Gut 2025;74:246-254.

72. Tol JAMG, van Hooft JE, Timmer R, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut 2016;65:1981-1987.

73. Fritzsche JA, Fockens P, Besselink MG, et al. Endoscopic ultrasound-guided choledochoduodenostomy using single-step lumen-apposing metal stents for primary drainage of malignant distal biliary obstruction (SCORPION-p): a prospective pilot study. Endoscopy 2023;56:47-52.

74. Fritzsche JA, Fockens P, Besselink MG, et al. Optimizing EUS-guided choledochoduodenostomy with lumen-apposing metal stents for primary drainage of malignant distal biliary obstruction (SCORPION-IIp): a prospective pilot study. Gastrointestinal Endoscopy 2024.

75. Living with Hope.

76. Carter AJR, Nguyen CN. A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding. BMC Public Health 2012;12:526.