Artificial Intelligence in Pancreatic Ductal Adenocarcinoma Imaging: A Commentary on Potential Future Applications

Pancreatic cancer is one of the deadliest cancers worldwide, with a 5-year survival rate of less than 5%.[1] Pancreatic ductal adenocarcinoma (PDAC), the most common and aggressive type of pancreatic cancer, has become a medical emergency in the past decades. PDAC cannot be effectively prevented or screened for and is associated with 98% life expectancy loss and a 30% increase in disability-adjusted life-years.[2,3] Still, research funding for PDAC remains significantly lower than for other cancer types, leading it to be flagged as a neglected cancer by both the European Commission and the United States Congress.[2]

Cross-sectional imaging, namely computed tomography (CT), magnetic resonance (MR), ^{18}fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography (^{18}FDG PET-CT), and endoscopic ultrasound (EUS), play a crucial role in PDAC management. Nevertheless, current international guidelines for image-based stratification, treatment response prediction, and evaluation are heterogeneous and ineffective.[4] Histopathology analysis is considered the criterion standard for PDAC diagnosis and characterization. Still, it remains challenging even for experienced pathologists owing to marked morphologic tumor heterogeneity and the limited amount of tumor tissue in biopsy.[5–7] Moreover, histopathology evaluation of treatment response is imprecise, of limited clinical relevance, and affected by inter-observer variation.[8]

Artificial intelligence (AI) has gained considerable interest in oncology because it has the potential to leverage high amounts of data to produce individualized recommendations based on each patient's clinical picture.[9] As the volume of multi-modal data acquired in routine clinical practice increases, AI can support clinicians and ultimately guide decision making at each step of the patient pathway by focusing on well validated applications at meaningful clinical touch-points.[9] Commercial clinical AI is already a reality for diseases like breast and lung cancer, with multiple FDA-approved products on the market for screening, diagnosis, and tumor characterization.[10] Currently, there are 2 main approaches for image-based AI: radiomics and convolutional neural networks (CNNs). Radiomics predicts an outcome by feeding manually defined texture and shape features extracted from a region of interest to machine-learning models. CNNs, on the other hand, automatically compute the relevant features directly from the imaging during training, in a neural network comprising a sequence of convolutional and pooling operations. Since the introduction of AlexNet in 2012, CNNs have evolved enormously and are now dominating image analysis, but the transition from handcrafted radiomic features to deep learning in the medical domain has been gradual.[11,12]

The number of publications on AI for clinical decision making in oncology has increased exponentially in the past few years.[11] However, AI research in PDAC is still at a preliminary stage compared with other cancer diseases, with limited private and public data sets and a lack of independent external model validation.[13] As a result, no AI applications have been implemented in clinical practice for PDAC.

The first step toward clinically relevant AI is to define the research questions to be addressed by AI algorithms. This should be done based on specific patient pathways, by identifying the critical touch-points that are lacking in clinical practice and where AI could have the greatest impact. For this commentary, an international, multi-disciplinary, multi-institutional expert panel including AI experts, pancreatic radiologists, pathologists, and surgeons came together to define the PDAC patient clinical pathway and derive its main touch-points for AI development.[14] The expert board divided the patient pathway into 5 steps: detection, diagnosis, staging, treatment, and monitoring, as depicted in Figure 1. In each step, the most relevant patient and clinician decision-oriented touch-points for image-based AI research were identified. These touch-points regard clinical decisions that are suboptimal with currently implemented workflows and guidelines and are detailed in the subsequent sections.[9]

PDAC Patient Pathway

Detection

Timely detection is crucial to improve PDAC patients' outcomes, because the 5-year survival increases from only 3% in metastatic patients to 42% when the tumor is still confined to the primary site.[15] According to the Japan Pancreatic Cancer Registry, patients in the earliest disease stage show a survival rate as high as 80.4% but account for only 0.8% of cases.[16] Screening groups at risk for PDAC is still cost-prohibitive owing to the relatively low incidence and the absence of validated noninvasive tumor biomarkers. The most used modality for PDAC detection is multiphase contrast-enhanced CT (CECT). However, early PDAC detection on CECT remains challenging, because lesions are small (<2 cm), present poorly defined margins, and are more often iso-attenuating.[4,17] Radiologists' sensitivity at detecting lesions with size smaller than 2 cm on CECT has been reported to be as low as 58%.[4,17] Contrast-enhanced MRI is highly effective at detecting tumors that are poorly visible on CECT, but it is not yet routinely implemented in the clinic.[18]

Early detection, arguably the most pressing issue in PDAC management, can be facilitated by the timely identification of secondary imaging signs predictive of PDAC, such as main

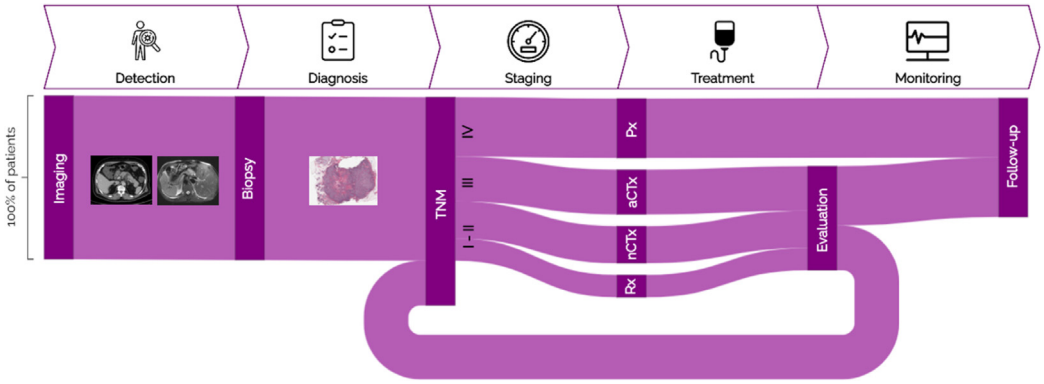

Figure 1. PDAC patient pathway. The steps of the general cancer patient pathway are shown in the top part of the figure. Below, the vertical boxes show the actions/guidelines for PDAC used in each step. The width of the streams represents the proportion of patients that go through each branch of the PDAC patient pathway. aCTx, adjuvant/induction therapy; nCTx, neoadjuvant chemo(radio)therapy; Px, palliative care; Rx, resection.

pancreatic duct cutoff or dilation, parenchymal atrophy, and irregular pancreatic contour.[4,19] These signs are often visible on CECT scans 18 to 12 months before clinical diagnosis, but the reported radiologists' sensitivity for their timely detection is only 44%, limiting the chances of early action.[19]

Recent articles have shown great potential for AI-driven PDAC diagnosis in CT.[13] Chen et al[20] developed an algorithm to distinguish between pancreatic cancer and normal pancreas on portal venous CT, which was trained with a large data set of 2011 cases (546 pancreatic cancer). In a test set of 1473 CT studies (669 malignant) from institutions throughout Taiwan, AI achieved an area under the receiver operating characteristic curve (AUC) of 0.95 (95% confidence interval [CI] 0.94–0.96), with 74.7% (68 of 91, 95% CI 64.5–83.3) sensitivity for malignancies smaller than 2 cm. In the internal test set, AI achieved an AUC of 0.96 (95% CI 0.94–0.99), without a significant difference in sensitivity compared with the original radiologists' report. However, the data sets used for training and testing the algorithms are not consecutive but artificially curated, with control cases being derived from liver and renal donors. In practice, patients with suspicion of PDAC often show one or several pancreatic alterations, and to be clinically relevant AI should be able to distinguish PDAC from other less aggressive pancreatic neoplasms. Training AI models with such artificially curated cohorts could cause performance overestimation.

Regarding early detection, Mukherjee et al[21] studied whether a radiomics-based AI algorithm could detect PDAC at the prediagnostic stage (3–36 months before clinical diagnosis). The study included 155 patients and an age-matched cohort of 265 subjects with normal pancreas for model development and an independent internal set of 176 patients and 80 publicly available control cases for testing.[21] The model achieved a high AUC of 0.98 (95% CI 0.94–0.98), significantly outperforming 2 radiologists who independently reviewed images in the test set (mean AUC 0.66, 95% CI 0.46–0.86).[21]

Despite these promising early results, the identification of small lesions and secondary anatomic signs is still widely disregarded in AI-based detection research, and most studies do not disaggregate performance based on tumor size and stage.[13] In addition, there is a lack of research on lesion localization and a general absence of well curated data sets, with positive and negative cases being retrieved from completely different populations, which does not reflect the clinical landscape and can introduce bias.[13] For AI to improve PDAC detection, it is crucial to acquire and make publicly available well curated, multi-modal data sets that contain a significant proportion of small (<2 cm or even <1 cm) tumors, which should be treated as a subgroup of interest when reporting model performance.

Diagnosis

PDAC symptoms are mostly nonspecific in early disease stages, and because lesional appearances are heterogeneous on CECT, patients are often initially misdiagnosed with other, more common abdominal diseases with similar symptomatology (eg, gallbladder diseases, acute or chronic pancreatitis, duodenum cancer).[18,19] Initially misdiagnosed patients are reported to present higher rates of abdominal pain, weight loss, and acute pancreatitis than correctly diagnosed patients and are at a higher risk of advanced disease.[18] Histopathology assessment is the current criterion standard for PDAC diagnosis confirmation and is usually based on EUS fine-needle cytology or biopsy. Nevertheless, the morphologic distinction of PDAC from other lesions on small biopsies or cytology samples can be challenging, especially given the minimal amount of lesional material that is often contained in these samples.[19]

CT with or without contrast is the main modality for PDAC detection. Park et al[22] developed a deep-learning model to differentiate images with pancreatic neoplasms (PDAC, neuroendocrine neoplasm, solid pseudopapillary neoplasm, intraductal pancreatic mucinous neoplasm, serous cystic neoplasm, and mucinous cystic neoplasm) from images without pancreatic abnormalities. The authors trained the model in a data set of 852 patients (503 pancreatic neoplasms) and tested it in 2 neoplasm-enriched consecutive data sets (one internal and one external) of patient

undergoing contrast CT scans. Furthermore, 2 board-certified radiologists independently interpreted the CT images of the test sets. In the internal test set AI achieved an AUC of 0.91 (95% CI 0.89–0.94), showing no statistically significant difference from the radiologists' performance. However, radiologists performed significantly better than AI in the external test set (AI: AUC 0.87, 95% CI 0.84–0.89; radiologist 1: AUC 0.95, 95% CI 0.93–0.97; radiologist 2: AUC 0.96, 95% CI 0.94–0.97).

Current research separates detection, defined as the distinction between PDAC patients and healthy control subjects, from differential diagnosis, defined as the distinction between PDAC and other types of pancreatic lesions.[13] The previously described studies indicate that AI trained with large data sets can approach expert-level performance.[22,23] However, both studies focus on binary classification as opposed to differential diagnosis, and the evidence for radiologists' performance is limited because no multi-institutional reader studies have been conducted. It is crucial to move toward well curated data sets including a panoply of relevant pancreatic alterations that should be distinguishable from PDAC. In the future, research should strive toward a single use case for radiology-based AI in PDAC diagnosis that includes both the detection of a lesion and its correct classification among a variety of pancreatic diseases. The current priority is the curation of large data sets with representative percentages of each lesion type and the integration of different imaging modalities that offer complementary information regarding lesion characterization. Research in AI for histopathologic PDAC diagnosis is scarce.[13] Although histopathology is considered the criterion standard for confirming PDAC diagnosis, it is a time-consuming process that suffers from non-uniform implementation in clinical practice and inter-observer variability.[13] Developing powerful AI models for histopathologic PDAC diagnosis is fundamental to advancing AI research at all steps of the patient pathway. Such models would optimize clinical workflows and empower the generation of reliable ground truth that could be used to develop AI with other (noninvasive) modalities in a timely and cost-effective manner.

Staging

After histopathology diagnosis, the most used method for PDAC staging is the TNM classification by the American Joint Committee on Cancer (AJCC). The local tumor extent (T stage), the dissemination to the regional lymph nodes (N stage), and the metastatic spread to distant sites (M stage) are used to stratify patients, determine their prognosis, and indicate treatment and monitoring strategy.[24] Nevertheless, the TNM classification's predictiveness for overall survival (OS) is not reliable.[25] A 2018 multi-center study aiming to validate the 8th-edition AJCC TNM in a cohort of 1525 patients receiving pancreatoduodenectomy reported a concordance index of 0.57 (95% CI 0.55–0.60) for OS prediction.[26]

AI for PDAC staging lacks a solid reference standard.[13] TNM staging and histopathologic grade do not correlate sufficiently with OS and suffer from inter-reader variability.[13] A recent systematic literature review identified 13 publications on AI for PDAC staging, of which only 1 considered OS as the ground truth.[13] A study by Chaddad et al[27] divided patients into short- and long-term survivors with a set threshold, achieving 0.72 AUC on an internal testing set, but no external evaluation was performed. In the absence of an international consensus that relates surrogate end points, AI research using clinically obtained low- and high-grade differentiation and predictive TNM is not clinically relevant. Future AI research should focus on discovering new data-driven staging biomarkers that relate histopathology and imaging to OS.

Treatment

The most common treatment options for PDAC are resection and chemo(radio)therapy, in particular with the use of FOLFIRINOX and gemcitabine-abraxane.[2] Surgical resection (Rx) is the only option for potential long-term survival, but as shown in Figure 1 it is suitable for only a minority (10%–15%) of patients (stages I and II). Most patients are diagnosed in later disease stages (III and IV), where Rx is no longer possible owing to metastasis or extensive vessel involvement.[28] Imaging assessment of tumor-vascular contact primarily determines eligibility for Rx, but there are no widely accepted evidence-based guidelines for appropriate tumor resectability criteria.[4,29] As a result, the 5-year survival rate of resected PDAC patients is only 30% to 58%, with 69% to 75% of patients relapsing within 2 years.[1,30]

As illustrated in Figure 1, most patients receive chemo(radio)therapy at some point during treatment.[31] Neoadjuvant chemo(radio)therapy (nCTx) intends to optimize surgical outcome in patients with resectable disease, and adjuvant chemo(radio)therapy (aCTx) is used to down-stage non-resectable patients. After aCTx, patients may become resectable and undergo Rx or be referred to palliative care (Px), which is intended to suppress disease-related pain and lengthen the patient's life. Although most patients experience chemotherapy-induced toxicity, often with limited efficacy due to biological resistance, a priori prediction of chemotherapy response is still not possible in current clinical work-up.[32,33]

Treatment response prediction with the use of AI is a challenging task. Healy et al[34] performed a retrospective, international, multi-center study for prognostication in resectable cases with the use of radiomics of preoperative CT scans combined with clinical factors. The training cohort included 352 patients from 5 Canadian hospitals, and the model was tested on an external set of 215 from 34 hospitals in Ireland. The clinical-radiomic model discrimination (c-index 0.545, 95% CI 0.543–0.546) was higher than TNM (c-index 0.525, 95% CI 0.524–0.526), with $P < .001$. Despite superiority to TNM, the low model discrimination results in limited clinical utility for potential treatment decisions. Another study, by Yao et al,[35] used deep learning for preoperative survival prediction and achieved a c-index of 0.667 with an in-house development cohort of 296 cases, but no external validation was

performed. These studies indicate that pre-operative imaging might not contain sufficient information to predict prognosis and should be combined with other data modalities such as clinical variables, histopathology, genomics, and other imaging modalities.

AI research for treatment response prediction disproportionally focuses on post-surgery patient outcome.[13] Given that 80% to 85% of patients are diagnosed with non-resectable disease, AI research on prediction of response to resection will have a minor impact on improving overall PDAC patients' outcomes.[36] Instead, research efforts should focus on later disease stages, predicting response to (neo-) adjuvant and palliative CTx. Future AI research should consider multiple treatment options for a given patient, providing the most favorable suggestion based on survival as the outcome measure.

Treatment Monitoring

Following curative resection, histopathology analysis of the resected specimen is performed to confirm the diagnosis of PDAC and to map the extent of disease. This includes the assessment of lymph node metastases, tumor permeation along lymphatics and blood vessels, and the clearance to the resection margins (resection margin status).[37] Nevertheless, the prognostic value of these parameters is still controversial, with several studies reporting no significant relationship to survival.[37–39] The main reason for the low predictive power of histopathology findings is the lack of standardized evaluation, consensus definitions, and reporting approaches.[40,41]

In patients undergoing CTx, imaging is critical for determining therapeutic response and selection of the next treatment approach, because acquiring a biopsy could lead to increase of inflammation.[41] The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (2009) is the current standard for evaluating CTx. This is a purely morphologic set of criteria that quantitatively tracks tumor burden changes based on alterations to the lesions' size. Although RECIST shows some success in monitoring response based on metastases assessment, it is ineffective when considering the primary tumor, because PDAC lesions present poorly defined borders and significant heterogeneity in regression/progression patterns.[41] Furthermore, CTx often results in necrotic, fibrous, or inflammatory changes, which translate into an apparent enlargement of the lesion in CT/MR scans that can be misinterpreted as tumor progression.[41]

Current histopathologic tumor regression grade (TRG) systems for PDAC are based on a semi-quantitative evaluation of the destruction of cancer cells, the amount of residual viable cancer, or the extent of fibrosis induced by treatment. However, current TRG systems are based on imprecise criteria that are difficult to apply, and a standardized and widely accepted grading system for the histologic evaluation of TRG in pancreatic cancer has not yet been established.[8,42,43] These factors make RECIST and histopathology TRG insufficient for predicting local oncologic response in PDAC patients.[40,41]

In a recent literature review, we found 2 publications regarding treatment evaluation and no publications for follow-up.[13] The study by Janssen et al[44] takes a step in the direction of more objective and reproducible TRG systems for patients undergoing nCTx by automatically segmenting relevant structures on whole-slide images of resection specimens.

Nasief et al[45] proposed an AI model based on delta radiomics from daily longitudinal scans to predict response

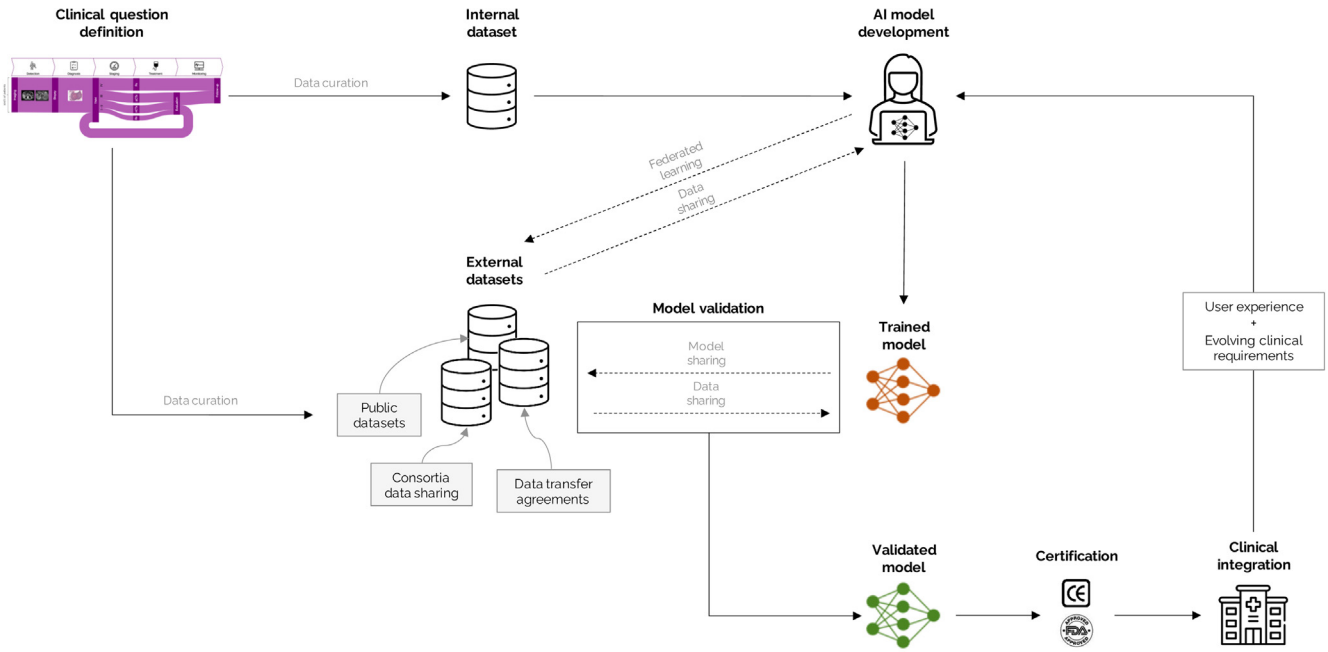

Figure 2. Schematic representation of the steps and technical requirements for the development of clinically relevant artificial-intelligence applications from the definition of the research question to clinical integration.

Table 1. Summary of Methodologic Guidelines for Developing Clinically Relevant Artificial Intelligence (AI) for Pancreatic Ductal Adenocarcinoma (PDAC) Care

Step	Guidelines
Study population	The study population should be clearly defined and representative of the target patient population, sufficiently covering the relevant real-world heterogeneity and diversity. The study population ideally should contain consecutive patients reflecting a variety of pancreatic neoplasms (cystic lesions, benign conditions as pancreatitis, and malignant varieties, such as neuro-endocrine tumors) and PDAC. Demographic factors such as age, sex, race, and ethnicity should be considered and clearly described.
Ground truth	The ground truth for testing sets should be as strong as possible. Histopathology confirmation (from biopsy or resected tissue) is the most reliable ground truth for detection and diagnostic tasks. For cases where histopathology is unavailable, follow-up should be performed to confirm death by pancreatic cancer or that cancer did not develop (negative cases). For treatment response, staging, and prognostication tasks, the only reliable ground truth currently is survival. Intermediate metrics, such as TNM, RECIST, and resection margin, should not be considered.
Sample size	The sample size should be large enough to ensure statistical power and generalizability. The sample size should be determined by appropriate statistical methods and consider the data set's variability and complexity. For external predictive performance evaluation, as a rule of thumb, the sample should contain at least 100 events per outcome.
Evaluation criteria	Clinical success criteria must be determined and described, including an analysis of the potential risks of prediction errors. Uncertainty estimation should be integrated into model development, and performance should be reported with respect to model uncertainty. It is advised to perform a feasibility check at an early stage to assess whether the expected benefit of AI outweighs development and maintenance costs.
Exploratory data analysis (EDA) elements	EDA should be performed to identify data quality issues, missing values, outliers, and other anomalies. EDA should also be used to identify potential confounding variables and assess their impact on the outcomes of interest. Because AI is data driven, the distribution of vendors, modalities, settings, and average longitudinal information acquired in a clinical setting should be considered.
Image quality	Image quality should be enough for AI modeling, with minimal noise, distortion, and artefacts, while representing real-world heterogeneity and diversity. An additional validity check could be performed by randomly sampling a portion of the data and manually checking it for errors. The proportion of errors should be reported. The AI that is developed should be generally applicable to imaging acquired in hospitals around the world and therefore should be robust to variations in image quality.
Image selection criteria	Images should be selected based on relevant clinical features and diagnostic criteria. The selection criteria should be transparent, reproducible, and consistent with established clinical guidelines. Confounding image factors, such as biliary stents, should be considered and reported for both disease and control patient groups.
Data processing	Duplicate data parameters should be identified and removed to ensure that the data set is not biased or over-represented by certain features or samples. The Observational Medical Outcomes Partnership common data model strategy, in which clinical parameters from different centers with various naming and classification systems can be handled and translated to a common format, should be used. Highly correlated features should be identified and combined through techniques such as hierarchic clustering. Missing data imputation is generally recommended over complete case analysis where incomplete data are excluded.
Anonymization regulations	Data should be anonymized to protect patient privacy and comply with relevant regulations, such as HIPAA. Anonymization should be performed with the use of appropriate methods that preserve the integrity and utility of the data.
Long-term sustainability of data sets	Data sets should be regularly updated and maintained to ensure their long-term sustainability and relevance. This includes the incorporation of new data sources and the use of appropriate data management and curation practices.

to nCTx. That study included 90 patients divided into good and poor responders based on a modified Ryan scheme for histopathology-based TRG, and the model achieved an AUC of 0.98 in the independent test set (40 patients).

AI research for treatment monitoring is lagging behind.[13] Clinically relevant AI applications should directly predict OS and recurrence from large well curated radiology and pathology data sets. In addition, AI algorithms for treatment monitoring should strive to assist clinicians by indicating the best action at a given time-point, such as timely termination of treatment to prevent unnecessary comorbidities, selecting re-staging time-points, adjusting the treatment regime, or choosing the optimal schedule for long-term patient follow-up.

The Path for Clinically Relevant AI in PDAC

Powered by the advent of deep learning, developments in computing technology, and massive growth in available clinical data, AI holds the potential to bring transformative changes into health care. PDAC is particularly suited to benefit from AI research and the development of commercial applications, because current clinical practices still lead to poor patient outcomes. However, it is essential that research is performed to high quality standards and focuses on clinical validity, utility, and usability.[9]

In Figure 2, we propose the necessary steps to develop clinically relevant AI for PDAC management, leading to commercial applications that can be incorporated into clinical workflows and advance patient care.

The first step is to define the clinical question to be addressed by AI. This should be done based on the PDAC patient pathway by identifying the critical clinical touch-points lacking in clinical practice and where AI could have the most significant impact. For this commentary, such moments and subsequent opportunities for AI research were identified in consensus by a consortium of expert clinicians and AI researchers from multiple international institutions.[14] We propose that for radiology and pathology AI to advance PDAC care, future research should focus on early diagnosis, data-driven tumor characterization, survival-based patient staging, and treatment response prediction and monitoring.

Following the research question definition, it is crucial to identify and curate large multi-institutional data sets for model development and validation. The data sets should be prepared with the specific research question in mind, particularly concerning ground truth selection. The ground truth definition is the most crucial step for model development, because it determines how a model is optimized and its clinical applicability. Therefore, the ground truth should always be defined by actual patient outcomes, such as overall or disease-free survival, as opposed to intermediate clinical variables, such as TNM staging, histopathology-based tumor response scores, margin status, and RECIST. In addition, there is an urgent need for more high-quality public data sets. The only publicly available PDAC imaging data sets are from Medical Segmentation Decathlon (MSD) and The Cancer Genome Atlas (TCGA). The MSD data set contains CT imaging for patients with pancreatic malignancies (neuro-endocrine tumors, pancreatitis, PDAC, cysts). The limitation of the MSD data set is the absence of a pathology-proven diagnosis for each case, because the data set does not provide the distribution of types of lesions. The TCGA data set contains whole-slide images for patients with PDAC, and its major limitation is the incomplete clinical information regarding the type of treatment and OS, which are known for only a small subset. Large well curated multi-institutional private and public PDAC data sets are essential for AI development and testing. These data sets are necessary to compare different AI solutions and translate the developed models into the clinic by validating the AI algorithms externally.

During the AI model development step, internal data sets are used for model training and optimization. External data can also be integrated at this step either by direct data sharing with the developing center or via federated learning, where the training code is shared with the external data center. Federated-learning approaches have the advantage of facilitating data privacy assurance but come with the risk of increased complexity in model development and data standardization.

Once the model has been trained, it is crucial to perform external validation with data sets that have not been used for the model development step. Then it is possible to assess the model's generalizability to new cohorts and get an accurate performance metric. The external validation can be done by data sharing or model sharing. The model-sharing approach has the advantage of ensuring data privacy and not requiring any transfer agreement. The Grand Challenge platform is an example of an online service that allows the developing center to upload AI algorithms, which become accessible to the external center to validate with their data.

After a model is externally validated, it should be submitted for approval by the appropriate certification authority before it can be implemented into clinical workflows. This is a cyclical process, as clinical requirements and user experience will lead to necessary improvements to the AI models, which should continually be updated and re-certified to meet clinical needs.

The methodologic guidelines for developing clinically relevant AI for PDAC care are summarized in Table 1. We based these recommendations on relevant guidance documents for clinical AI-based prediction models, specifying each step to the particular use-case of PDAC.[46]

In conclusion, the future of AI in PDAC lies in addressing relevant clinical questions, establishing multi-institutional collaborations for the curation of large-scale data sets, and integrating multiple data modalities into well designed study protocols.

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