Rethinking Pancreatic Cancer Modelling: A Systematic Literature Review of Graph Neural Networks

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***Abstract*—Pancreatic cancer remains a difficult disease to analyze due to its subtle appearance on scans and the wide variation seen across patients. Recent progress in Artificial Intelligence has improved image-based diagnosis, but many existing methods still struggle to capture complex patterns within the data. Graph Neural Networks have emerged as a promising approach because they can represent relationships between different patches of an image or between different types of patient information. A systematic literature review was carried out to identify studies that use GNNs for pancreatic cancer diagnosis and classification, and to understand how these methods compare to traditional deep-learning models. The findings show growing research interest in areas such as early detection, tumor localization, subtype classification and fusing various modalities of data. The purpose of this review is to map the development of GNN-based research in pancreatic cancer and highlight where these methods may support more reliable and flexible diagnostic tools in the future.**

Keywords—pancreatic cancer, graph neural networks, multimodal fusion, medical technology, deep learning, systematic literature review

I. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most difficult malignancies to detect and characterize, due in large part to its late presentation, limited treatment windows and persistently low survival outcomes. Early-stage disease is challenging to recognizes on imaging, particularly on non-contrast CT (NCCT) where lesions may appear subtle and poorly demarcated. Variability in pancreatic shape and surrounding anatomy further complicates segmentation and interpretation, and these difficulties are intensified by substantial molecular heterogeneity. Foundational genomic work has shown that PDAC comprises multiple transcriptomic subtypes with distinct biological profiles [1], contributing to variation in imaging appearance and progression patterns. Such complexity highlights the need for computational methods that can capture relationships operating across both spatial and biological scales.

Convolutional Neural Networks (CNN) have supported advances in pancreas segmentation and prognostic analysis [5][6], yet they remain limited by their fixed-grid structure and reduced ability to model long-range or irregular anatomical relationships. These constraints are particularly relevant in PDAC, where accurate assessment often depends on interpreting diffuse spatial cues.

Graph Neural Networks (GNN) provide a flexible alternative by representing imaging regions or multimodal variables as interconnected nodes, enabling models to encode structural dependencies. Recent studies demonstrate improvements in early detection and spatial reasoning through causal graph design and geometry-aware representations [7][12], while broader analyses in oncology further support the suitability of graph-based approaches for modeling complex tumor behavior [4].

This paper is divided into five sections. Section I introduces the motivation for applying GNN to PDAC. Section II outlines the methodological stages of a SLR. Section III reports the findings and characteristics of the included studies. Section IV discusses their implications, including relevance to the PANOPTIC system and remaining research gaps. Section V concludes with a concise synthesis of the review outcomes and outlines future directions for developing clinically robust, multimodal GNN-based models for PDAC.

II. Research Methodology

This review followed a systematic literature review framework aligned with PRISMA guidance, incorporating conventions from biomedical evidence synthesis alongside considerations relevant to ML and GNN. Study selection followed PRISMA reporting standards, with explicit documentation of record identification, screening, eligibility assessment and inclusion, as summarized in Fig. 1.

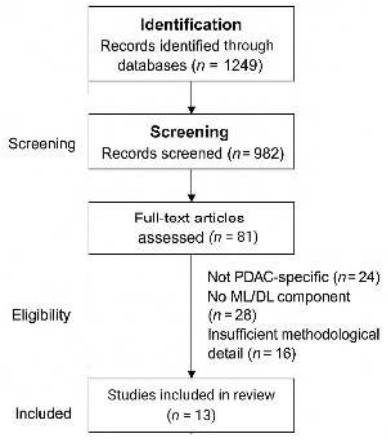

Fig. 1.PRISMA Flow Diagram

A. Research Questions

The research questions highlighted on Table I were formulated to guide the review.

TABLE I. RESEARCH QUESTIONS

Research Questions	Description
RQ1	How have GNN architectures been designed and adapted to model the anatomical, radiological and biological characteristics of PDAC?
RQ2	What imaging modalities, datasets and multimodal features have been used in GNN-based PDAC research, and how do this influence diagnostic, segmentation or prognostic performance?
RQ3	What conceptual and empirical advantages do GNN models offer over traditional CNN-based approaches in PDAC?

B. Literature Search Strategy

To identify relevant literature, a comprehensive search strategy was developed to capture studies across oncology, medical imaging and ML domains, particularly GNNs. The search used combined Boolean strings to capture variations in terminology across PubMed, IEEE Xplore, ACM Digital Library, ScienceDirect, ResearchGate and arXiv, covering publications from 2016 through 2025. Searches were limited to English-language publications between 2016 and 2025 and included peer-reviewed articles and reputable preprints. Full search strings for each database are provided in Table II.

TABLE II. SEARCH STRATEGY

Database	Full Search String
PubMed	("pancreatic cancer"[Title/Abstract] OR "PDAC"[Title/Abstract]) AND "CT"[Title/Abstract] AND ("GNN"[Title/Abstract] OR "deep learning"[Title/Abstract])
IEEE Xplore	"pancreatic cancer" AND CT AND ("graph neural network" OR "GNN" OR "deep learning")
ACM Digital Library	All: ("pancreatic cancer" OR "PDAC") AND "deep learning"
ScienceDirect	TITLE-ABS-KEY("pancreatic cancer") AND TITLE-ABS-KEY("CT") AND ("deep learning" OR "graph neural network")
ResearchGate	"pancreatic cancer" AND ("deep learning" OR "GNN")
arXiv	("PDAC" AND "CT") AND ("GNN" OR "graph neural network" OR "deep learning")

C. Screening Process

The review process began with a title and abstract assessment, during which studies unrelated to pancreatic cancer were excluded, along with those focused solely on traditional ML or CNN architectures unless they offered relevant context for understanding the limitations motivating graph-based approaches.

Full-text screening then assessed methodological relevance, ensuring that included studies employed ML or GNN architectures directly for PDAC imaging or contributed conceptual insights applicable to PDAC graph modeling.

During the screening stage, studies were evaluated using a set of predefined inclusion and exclusion criteria to ensure relevance and methodological clarity. The criteria applied in this review are summarized in Table III.

TABLE III. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	Exclusion Criteria
Studies related to pancreatic cancer or PDAC	Studies not related to pancreatic cancer
Studies using CT imaging	Non-imaging studies or unrelated imaging modalities
Research involving deep learning or GNN methods	Papers without computational modeling
Peer-reviewed articles or reputable preprints	Editorials, opinions or non-scientific sources
Sufficient methodological detail and reported outcomes	Missing methods, missing results or unclear reporting

D. Quality Criteria for Study Selection

To ensure that only robust and relevant studies were retained, each publication was evaluated against three core quality criteria. The first requirement was that the methodological procedures be described with sufficient clarity, including details of the dataset and analytical approach, so that the findings could be understood and, where possible, replicated.

Secondly, studies needed to be directly related to pancreatic cancer or contribute essential background knowledge for understanding graph-based modeling. This included research on segmentation, radiomics and imaging biomarkers, multimodal prognostic modeling, molecular subtyping, multimodal fusion and bioinformatics foundations, along with broader oncology-focused GNN work [4].

Finally, each study had to report meaningful results or provide a clear conceptual contribution. Most studies presented measurable outcomes such as performance metrics, while surveys and theoretical papers were included if they offered clear insights relevant to the review. Studies that did not meet these criteria were excluded, ensuring that the final set of papers reflected a suitable level of clarity, relevance and contribution to the research questions.

E. Quality Assessment

To appraise the methodological strength of each study, a simplified QUADAS-2 framework was used. This tool examines areas where bias may arise, including the transparency of data selection and the adequacy of methodological descriptions that underpin confidence in reported results.

This was combined with basic checks commonly used in ML research, including whether the model design was explained in enough detail to be reproduced, how the study handled imbalanced data and whether baseline methods or external validation were provided [10].

Explainability was also considered, informed by prior work showing that users often struggle to interpret model outputs [2]. Although some GNN studies used relatively small datasets they were included due to the early stage of research in this area, and their limitations were considered when reviewing the evidence [7][12].

TABLE IV. DATA EXTRACTION FIELDS USED IN THE REVIEW

Category	Extracted Fields
Study Metadata	Author, year, publication type
Dataset	Sample size, modality, centre type
Model	Architecture type, graph formulation

Baselines	CNN or ML comparators
Evaluation	Metrics reported, validation type
Outcomes	Detection, segmentation, prognosis
Limitations	Dataset bias, validation gaps

III. Findings

The final study set comprised 13 publications from 2016 to 2025, reflecting the interdisciplinary development of PDAC research across computational oncology, medical imaging, bioinformatics and explanatory machine learning.

A. Characteristics of the Included Studies

TABLE V. CLASSIFICATION OF INCLUDED STUDIES

Study	Task	Data (n)	Modality	Model Type	Key Metric(s)	Main Finding
[1]	Subtyping	456	Genomic	Statistical	Survival	Identified molecular subtypes
[5]	Prognosis	201	CT + Clinical	CNN-based ML	C-index	Prognostic baseline
[6]	Prognosis	303	CT + Clinical	CNN-based ML	AUC, C-index	Multimodal baseline
[11]	Segmentation	1223	CECT	CNN	Dice	Strong segmentation baseline
[10]	Prognosis	1006	CT + Clinical	CNN-based DL	AUC	End-to-end CNN benchmark
[7]	Detection	1006	NCCT	Causal GNN	Sensitivity, AUC	Higher sensitivity than CNN
[12]	Segmentation	268	CECT	Geometric GNN	Dice	Dice improvement over CNN
[9]	Prognosis	98	DWI MRI	ML	AUC	Imaging biomarker baseline
[13]	Detection	200+	CT	ML	Accuracy, Sens.	Feature-selection baseline
[3]	Survey	–	Multimodal	Conceptual	–	Multimodal fusion review
[4]	Survey	–	Multimodal	Conceptual	–	GNN theory in oncology
[8]	Survey	–	Omics	Conceptual	–	DL in bioinformatics
[2]	Explainability	–	ML	Conceptual	–	Human-in-the-loop insights

B. Quality of Evidence

Study quality differed across methodological clarity, dataset robustness and technical transparency. Multicenter datasets provided greater generalizability through broader imaging and demographic variation [7][11], while single-center studies remained more limited in scope [5][9]. Annotation quality was strongest in segmentation datasets [11][12], though early NCCT cases were more prone to misidentification due to subtle visual patterns [7].

Prognostic studies often included incomplete clinical or molecular variables, reducing consistency and limiting suitability for graph-based integration. Technical reporting also varied: GNN-focused studies described graph construction and message passing in sufficient detail for reproducibility [7][12], while multimodal studies provided rich feature sets but lacked graph formulations [10]. Work on interpretability underscored ongoing challenges in diagnostic AI, though not specific to GNNs [2]. Surveys and conceptual papers contributed foundational insights but offered no empirical validation [4][8].

Overall, evidence strength was highest in segmentation and GNN-based early detection, moderate in multimodal prediction and largely conceptual for molecular and survey studies. These patterns align with the risk-of-bias assessment in Table V, which indicates persistent issues in dataset diversity, annotation consistency and validation practices that limit overall reliability.

TABLE VI. RISK OF BIAS SUMMARY FOR INCLUDED STUDIES

Bias Domain	Assessment Criteria	Risk Level Across Included Studies	Notes
Selection Bias	Diversity of dataset sources, inclusion clarity, recruitment consistency	Moderate to High	Studies relied on single-center datasets with limited demographic and acquisition variability [5][9].
Annotation Bias	Quality of labels, consistency, expert agreement	Moderate	Segmentation datasets had strong annotations [11][12], but early detection tasks suffered from subtle lesion appearance and inconsistent protocols [7].
Model Reporting Bias	Transparency of architecture, training details, reproducibility	Low to Moderate	GNN papers were generally detailed [7][12], while multimodal studies provided results but lacked graph-related reporting [10].
Performance and Validation Bias	Use of external validation, robustness testing, overfitting control	High	Very few studies performed multicenter validation or robustness testing, limiting reliability [10][11].
Publication Bias	Tendency to publish positive/novel findings	High	Only a small number of PDAC GNN studies exist, increasing the likelihood that inconclusive results remain unpublished.
Confounding Bias	Handling of missing variables, dataset imbalance and feature selection	Moderate	Prognostic datasets contained incomplete variables and imbalanced classes [5][6][9][10].

C. Findings Related to Research Questions

a) RQ1. GNN architecture and structural modeling

Across the included work, GNNs demonstrated clear benefits when structural priors were integrated into graph

design. Directed message passing improved detection in low-contrast conditions by enforcing structured information flow across neighboring regions [7]. Geometry-aware representations further improved spatial reasoning by modeling continuity and boundary transitions more effectively than grid-based operations [12]. Broader theoretical analyses emphasize that complex systems and molecular patterns in PDAC operate through relational dependencies [1][4], reinforcing the suitability of graph formulations.

b) RQ2: Modalities, datasets and multimodal features used in GNN-based PDAC research

The reviewed GNN models were applied across NCCT and contrast-enhanced CT (CECT), demonstrating adaptability to diverse imaging conditions. NCCT required models to rely on relational cues rather than intensity differences [7], while CECT supported sharper anatomical delineation for segmentation tasks [12]. Evidence from segmentation and prognostic studies indicates substantial variability in anatomy and clinical variables [9][10][11], suggesting the value of multimodal integration. Conceptual and bioinformatics studies show that clinical, radiomic and molecular attributes form interconnected patterns and could be incorporated as heterogeneous graph features [8][13].

c) RQ3: Comparative advantages of GNNs over CNNs in PDAC analysis

GNNs consistently outperformed CNNs in tasks requiring structural reasoning. CNNs operate on rigid grids and struggle with irregular shapes, long-range dependencies and sparse clinical features [11]. GNNs address these constraints through edge-based message passing, resulting in improved sensitivity in early detection [7] and stronger geometric consistency in segmentation [12]. Interpretability research suggests that graph-based reasoning may align more closely with human decision processes than CNN feature maps [2]. These findings highlight the conceptual and practical advantages of GNNs across PDAC modeling.

IV. Analysis and Discussion

A. Synthesis of Findings in Relation to the Research Questions

Across the reviewed studies, there is a clear movement toward relational modeling approaches that better represent the structural variability of pancreatic cancer. For RQ1, GNN demonstrated advantages by capturing dependencies between regions rather than relying on isolated local features. Directed and geometry-aware graph designs improved both early detection and spatial delineation, reflecting the relational nature of PDAC patterns identified in imaging and molecular studies [4][12].

For RQ2, findings show that graph-based methods adapt effectively across imaging modalities. NCCT required reliance on structural cues, where GNNs outperformed convolutional models [7], while CECT supported clearer anatomical graph construction [12]. Multimodal research further indicates that meaningful predictive information spans imaging, clinical variables and molecular features, all of which form interconnected structures suitable for graph representation [3][8][10][13].

For RQ3, evidence shows that GNNs address key limitations of CNNs by modeling long-range relationships, irregular anatomy and heterogeneous features more effectively [5][6][11]. This contributed to improved boundary modeling and early detection performance, while offering potential interpretability advantages through explicit relational pathways [12]. Overall, the synthesis suggests that GNNs provide conceptual and functional benefits for tasks requiring structured or multimodal reasoning in PDAC.

B. Theoretical, Computational and Biological Frameworks Underpinning GNN Approaches

The suitability of GNNs for PDAC modeling is grounded in several complementary theoretical and domain-specific frameworks. At the biological level, molecular profiling studies demonstrate that PDAC exhibits subtype-specific patterns organized through interconnected gene and pathway relationships [1]. These patterns reflect network-like behavior rather than isolated feature variation, supporting the use of relational models.

Bioinformatics literature also emphasizes that omics data are inherently non-Euclidean, with interactions defined by regulatory and molecular networks that cannot be represented effectively through convolution-based architectures [8]. This positions graph learning as a method capable of capturing dependencies that extend beyond spatial texture.

From a computational perspective, GNNs provide mechanisms for explicitly modeling relationships between regions or features. Directed graph designs allow structured information flow, contrasting with CNNs that lack defined pathways for inter-region inference [7]. Geometry-informed graphs further demonstrate how spatial continuity and deformation can be represented through connectivity patterns rather than fixed grids, supporting more robust anatomical modeling [12].

TABLE VII. FRAMEWORKS OF KEY SOURCES

Framework / Theory	Key Source	Relevance to PDAC GNN Modeling
Molecular subtype graph structures	Bailey et al. [1]	Supports genomically informed node attributes and pathway-level graph architectures
Bioinformatics network representation	Min et al. [8]	Demonstrates suitability of GNNs for non-Euclidean omics data
Multimodal fusion architecture theory	Louahem M'Sabah et al. [3]	Guides integration of clinical, radiomic and molecular features as heterogeneous graph nodes
Causal graph theory	Li et al. [7]	Enables directed message passing mirroring anatomical and inferential radiology
Geometric graph theory	Zhao et al. [12]	Provides a formal basis for 3D anatomical graph construction
Systems oncology graph models	Gogoshin & Rodin [4]	Establishes biological justification for relational tumor modeling

C. Implications for the PANOPTIC Project

PANOPTIC is envisioned as a multimodal graph-based decision support system integrating CT imaging, clinical variables and molecular features to support detection, segmentation and prognostic assessment in PDAC.

The evidence synthesized in this review yields several concrete implications for the ongoing development of PANOPTIC. Learnings from multimodal literature consistently indicates that PDAC-related signals are distributed across heterogeneous data sources rather than isolated within a single modality [3][8]. Representing these heterogeneous inputs as nodes within a shared graph structure provides a principled mechanism for encoding such interactions and reflects the relational nature of PDAC biology and clinical reasoning.

Building on this, GNN offer a practical means of addressing limitations inherent to convolutional architectures, such as fixed grid representations and local receptive fields, which constrain their ability to model long-range dependencies and irregular anatomical structures. In contrast, GNNs enable information propagation across non-local regions through explicit connectivity, allowing spatial, geometric or causal relationships to influence inference. Evidence from causality-informed and geometry-aware graph models demonstrates improved sensitivity and segmentation performance over CNN baselines in such settings [7][12], supporting their integration within PANOPTIC for structurally challenging PDAC tasks.

GNNs enable interpretability at the level of nodes and edges, allowing reasoning to be traced across anatomical regions, clinical variables and their relationships [2]. Within PANOPTIC, graph-specific attention mechanisms can quantify the contribution of pancreatic subregions or adjacent structures to detection and segmentation outputs, while edge-level attribution can reveal which spatial or cross-modal relationships most strongly influenced a prediction. These capabilities support transparent reasoning, facilitate error analysis and align model outputs with clinical expectations, strengthening the role of graph-based systems in PDAC research and decision support.

TABLE VIII. IMPLICATIONS TO PANOPTIC

Evidence Source	Insight	Application to PANOPTIC
Li et al. [7]	Causal message passing improves NCCT detection	Implement causal GNN layers for multimodal integration
Zhao et al. [12]	Geometry-aware graph segmentation outperforms CNNs	Use anatomical graph priors for pancreas ROI modeling
Bailey et al. [1]	PDAC subtypes have distinct biological networks	Encode subtype embeddings as graph node attributes
Kaissis [5], Keyl [6], Schuurmans [10]	Survival depends on multimodal features	Incorporate clinical + imaging + lab nodes
Qu [9]	DWI biomarkers capture progression risk	Add quantitative MRI features to node feature vectors
Bobes-Bascarán [2]	Interpretability critical for clinical adoption	Use attention-based interpretability tools on graph edges/nodes

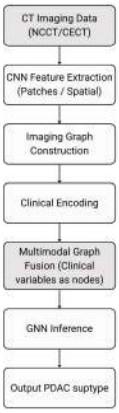

Fig. 2. PANOPTIC Conceptual Architecture Diagram

D. Limitations of the Evidence Base

Although the implications offer a constructive direction for PANOPTIC, they emerge from an evidence base with notable constraints. Many datasets were single-center with narrow demographic and acquisition profiles, reducing generalizability, and few multicenter investigations applied GNNs directly [5][11]. Dataset quality varied considerably, with inconsistent annotation protocols and subtle lesion appearance contributing to unreliable labels, particularly in early detection tasks [7][12]. Prognostic and multimodal datasets often contained incomplete variables, constraining graph construction and reducing reproducibility.

A further limitation is the small number of genuine GNN studies applied to PDAC, creating a narrow empirical foundation and increasing susceptibility to publication bias, as only positive or technically novel results tend to be disseminated. The limited number of PDAC-specific GNN studies increases susceptibility to publication bias, as negative or inconclusive findings are less likely to be reported, which can lead to overgeneralization.

Methodologically, no study proposed a fully multimodal GNN despite strong theoretical support [1][3][8], and external validation, robustness testing and interpretability analyses remained limited [2]. These constraints underscore the need for larger datasets, standardized annotations and more comprehensive evaluation frameworks.

E. Proposed Future Work

Taken together, these limitations motivate three substantive directions for future research. First, there is a clear need to develop heterogeneous GNN architectures that explicitly integrate imaging, clinical, and molecular data within a unified representational framework. Most existing PDAC GNN studies rely on single-modality CT imaging, despite strong evidence that tumour behaviour and prognosis are shaped by interactions between radiological features, clinical variables, and molecular markers [1][3][8]. Heterogeneous graphs, in which nodes and edges represent different entity types and relations, would enable richer relational reasoning beyond anatomical structure and address the limited biological context captured by current CNN and single-modality GNN models.

Secondly, interpretability must be treated as a core design requirement rather than a post-hoc addition. Future models

should incorporate graph-aware explanation mechanisms, such as node- and edge-level attention weights, subgraph importance scoring, or gradient-based saliency methods, to make relational decisions transparent and clinically meaningful [2]. Such mechanisms can support clinician trust by revealing which features, relationships, or patient factors drive predictions.

Thirdly, progress depends on rigorous and standardised benchmarking practices. Future work should adopt multicentre datasets with external validation, report discrimination metrics such as AUC and F1-score alongside calibration measures including Brier score and calibration curves and assess clinical utility using decision curve analysis [5][9][11]. Consistent evaluation protocols are essential for improving reproducibility, comparability, and translational relevance.

V. Conclusion

This review finds consistent evidence that GNN offer measurable advantages over CNN for selected pancreatic cancer tasks, particularly where spatial relationships and anatomical context are critical. Geometry-aware graph models achieved higher segmentation accuracy than strong CNN baselines, with reported Dice score improvements from approximately 0.48 to above 0.60 in anatomically complex pancreatic regions, alongside improved lesion localisation rates [12]. In early detection using NCCT, causality-driven GNNs demonstrated higher sensitivity than CNN-based approaches, indicating improved robustness in low-contrast settings where conventional models often struggle [7]. These gains were attributed to the ability of graph-based models to capture structural and relational information, rather than increased network depth.

Despite these advantages, the current evidence base remains limited. Only a small number of PDAC-specific GNN studies report direct quantitative comparisons with CNNs, and statistical significance testing is inconsistently documented across studies [7], [12]. In addition, most evaluations rely on single-centre datasets and lack external validation, which constrains generalisability. Overall, the findings support the use of GNNs as a promising extension to CNN-based pipelines for PDAC analysis, particularly for segmentation and early detection, while highlighting the need for larger multicentre studies and standardised evaluation to confirm these benefits more broadly.

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