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The Changing Landscape of Chronic Pancreatitis Research Trajectories Over Two Decades: A Global Meta-Analysis Using MeSH Terms

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ABSTRACT

Objectives: Significant progress has been made in research on chronic pancreatitis (CP). It is essential to analyze recent trends in this field to guide future clinical investigations.

Methods: Publications related to CP research from 2000 to 2023 were retrieved from PubMed. An analysis was conducted on Medical Subject Headings (MeSH) terms, publication dates, and affiliations. For MeSH terms with a frequency greater than 30 times, co-occurrence analysis was performed to demonstrate the overall trend of CP research. For those that occurred more than 200 times, heat maps, 3D surface maps, and Ribbon Charts were created to illustrate the trend of changes every 2 years.

Results: A total of 14,260 publications with 6775 MeSH terms from 2000 to 2023 were retrieved, and six clusters were obtained from the co-occurrence analysis. From 2000 to 2023, 35 MeSH terms with decreasing trends and 7 MeSH terms with increasing trends (MH-I) were selected to create a heat map. 7 MH-I were "signal transduction," "inflammation," "quality of life," "diabetes mellitus, type 2," "exocrine pancreatic insufficiency," "islets of Langerhans transplantation," and "transplantation, autologous."

Conclusion: The 21st century has witnessed CP research being propelled by both basic science and clinical research. Pathogenesis research focuses on signal transduction, while clinical research mainly focuses on the CP patients' quality of life, including pain, endocrine and exocrine function of the pancreas, among which pancreatic islet autograft transplantation is currently a hot topic. Emerging research topics such as stem cells and gut microbiota offer novel approaches for CP therapy.

1 | Introduction

Chronic pancreatitis (CP) is a chronic progressive disease characterized by pancreatic fibrosis and inflammation. Its basic pathological features include chronic inflammatory damage to the pancreatic parenchyma, interstitial fibrosis, pancreatic duct dilatation, and pancreatic duct stones [1]. Patients with CP commonly present with recurrent epigastric pain, accompanied by pancreatic exocrine and endocrine insufficiency [2]. Significantly, severe and persistent abdominal pain not only profoundly impacts CP patients' quality of life but also exerts adverse effects on mental health, manifesting as anxiety, depression, or other mood disturbances [3, 4]. Due to the unclear pathogenesis of CP, the field of CP research has long faced challenges from the vast literature, its interdisciplinary nature, and evolving research focus.

Ling-Ying Jiang, Chao Wu, and Kıvanç Görgülü contributed equally to this work.

Key Summary

- Summarize the established knowledge on this subject
  - Chronic pancreatitis (CP) is a progressive inflammatory disease with increasing global incidence and significant impact on patient morbidity and quality of life.
  - Despite extensive research efforts over the past 2 decades, the field lacks a comprehensive analysis of the evolution of research and emerging priorities.
  - Our bibliometric study addresses this gap by analyzing 2 decades of CP research to identify trends, hotspots, and future directions.
- What are the significant and/or new findings of this study?
  - This study represents the most extensive bibliometric analysis of CP research to date, systematically examining 14,260 publications and 6775 Medical Subject Headings (MeSH) terms from 2000 to 2023.
  - Our analysis shows a fundamental shift in CP research from a focus on clinical treatments to studies of disease pathogenesis, with signal transduction and inflammatory pathways emerging as key areas of contemporary research. It highlights specific molecular targets for the development of future therapies in chronic pain.
  - The study presents evidence-based priorities for future research, emphasizing the importance of quality-of-life assessment, management of pancreatic exocrine insufficiency, and islet autotransplantation as the most active and clinically relevant areas.
  - Recent advances for relieving pain concern neuromodulators, celiac plexus blocks, and antioxidant therapy. Emerging research topics such as stem cells and gut microbiota offer novel approaches for CP therapy.

The Medical Subject Headings (MeSH) thesaurus is a controlled vocabulary produced by the National Library of Medicine for indexing, cataloging, and searching in the PubMed database. It is updated annually, and catalogers assign 6-7 MeSH terms to publications [5]. The frequency of MeSH terms within a specific period accurately and timely reflects the research focus, establishing MeSH as an objective bibliometric analysis tool that outperforms basic keyword retrieval. Besides, bibliometric analysis has been widely applied to research on trends across multiple fields, such as acute pancreatitis and autoimmune pancreatitis [6, 7].

However, there is currently a lack of bibliometric analysis in the field of CP. Although numerous CP reviews have been published, most focus on research progress and fail to highlight the overall trends in CP research [1, 2]. Therefore, this study aims to address this gap and explore the direction of future research by conducting a comprehensive bibliometric analysis of CP research using the MeSH terms.

2 | Materials and Methods

2.1 | Data Collection

With the terms "chronic pancreatitis," articles on CP published from January 2000 to December 2023 were retrieved from the PubMed database. The volume of research from major countries was obtained by counting the items of "Affiliation"of corresponding authors. Data on "MeSH terms" and "Date of Publication" were extracted and calculated to illustrate the development and changes of MeSH terminology over time. The methods are listed in the flow chart (Figure 1).

2.2 | Data Processing

After data collection, the annual MeSH vocabulary of CP was collected. The proportion of each MeSH term was defined by its frequency divided by the total number of publications within a specific period. The proportions and frequencies of MeSH terms from 2000 to 2023 were summarized every 2 years. This study primarily focused on MeSH terms with a frequency of 30 or more occurrences. This analysis focused exclusively on formal MeSH terms and excluded their entry terms or synonymous forms mentioned in the text. Notably, common and nonspecific MeSH terms, such as "humans," "pancreas," and "chronic pancreatitis," which lack distinct meanings, are also included in the datasets. Therefore, two independent research panels were established to screen, exclude, and review these standard MeSH terms. In the event of divergence, discussions and negotiations were conducted through joint conferences until a consensus was reached. The specific members of the panels are listed in the supplementary document (supplementary document).

2.3 | Ratio Conversion

The R value was defined as the ratio between the proportion of different time periods for which a MeSH term was referenced and the proportion of its first occurrence during the respective time periods. A higher proportion of publications related to a specific MeSH term corresponds to a larger R value in that year, indicating greater research attention from the scientific community.

2.4 | U Value Conversion

To ensure homogenization of R values, zero was set as the baseline. The means (M) and standard deviations (SDs) of the R values for different MeSH terms were calculated. Subsequently, the U value of each MeSH term was obtained using the following equation:

$$U = \frac{P - M}{SD} \quad (1)$$

P refers to the ratio between the proportion of different time periods for which a MeSH term, M refers to mean, and SD refers to standard deviation.

2.5 | Data Visualization

All data were aggregated and tabulated for analysis. Based on the number of publications, all countries were marked using a color gradient, where darker hues indicated higher publication

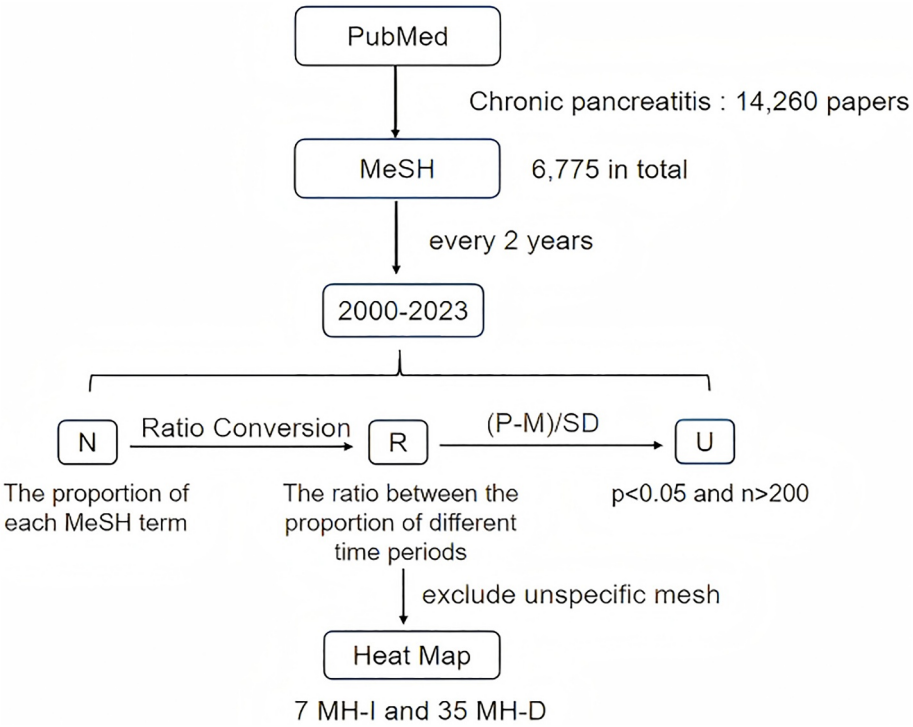

FIGURE 1 | Flow chart. The proportions and frequencies of MeSH terms from 2000 to 2023 were summarized every 2 years. MH-I, MeSH terms with increasing trends. MH-D, MeSH terms with decreasing trends.

output for a given country. Co-occurrence maps were created to investigate the holistic trend of MeSH terms using VOSviewer software (version 1.6.20; Leiden University, Leiden, the Netherlands). MeSH terms were clustered into distinct color-coded groups based on the strength of associations among co-occurring MeSH terms. Based on the results of network visualization, all MeSH terms were colored along a blue-to-yellow spectrum in overlay visualization according to their publication frequencies and dates of occurrence.

By using the U value, heat maps were constructed to illustrate the changes in MeSH terms every two years from 2000 to 2023. MeSH terms with statistically significant changes were filtered out using a threshold of $p < 0.05$, followed by visualization and further analysis as described below.

2.6 | Analysis of Trends

During this period, MeSH terms with increasing trends (MH-I) and decreasing trends (MH-D) were defined by setting an occurrence threshold of "200" every 2 years. Subsequently, the terms were tabulated to create a heat map. 3D Surface Maps and Ribbon Charts were also made using Origin 2022 (OriginLab, Massachusetts, USA).

2.7 | Data Analysis

SPSS software (version 26.0; IBM Corp, Armonk, NY) was used for analysis. Regression analysis was performed to determine the statistical significance of changes in MeSH terms within a given time, and $p < 0.05$ was considered significant.

3 | Results

3.1 | Global Status in CP Research

A total of 14,260 publications on CP from 2000 to 2023 were retrieved from the PubMed database in March 2025. The United States topped the list with 4460 articles published, followed by China (1242 articles), Germany (1161 articles), and the UK (1156 articles) (Figure 2).

3.2 | Co-Occurrence Analysis of MeSH Terms

In total, 6775 MeSH terms were counted after data collection from 2000 to 2023, among which 437 MeSH terms occurred more than 30 times. Through careful screening by two independent research panels, 34 standard MeSH terms with no specific meanings were excluded (Table 1).

In the network visualization, 403 MeSH terms were clustered into six distinct groups (Figure 3A), where the size of the dot was proportional to the frequency of each MeSH term (i.e., larger dots indicated higher term frequency). These clusters were named "treatment and management," "basic research experiment," "pancreatic function," "prognosis and expectation," "genetic factors," and "differential diagnosis," containing 130, 105, 58, 42, 41, and 27 MeSH terms. They were painted in red, green, blue, yellow, purple, and orange, respectively. The top 5 MeSH terms in each cluster are shown in Table 2. In the overlay visualization, the higher the density of blue color, the earlier the occurrence of the MeSH term; the higher the density of yellow color, the later the occurrence of the MeSH term (Figure 3B). The yellow dots were mainly in the clusters of

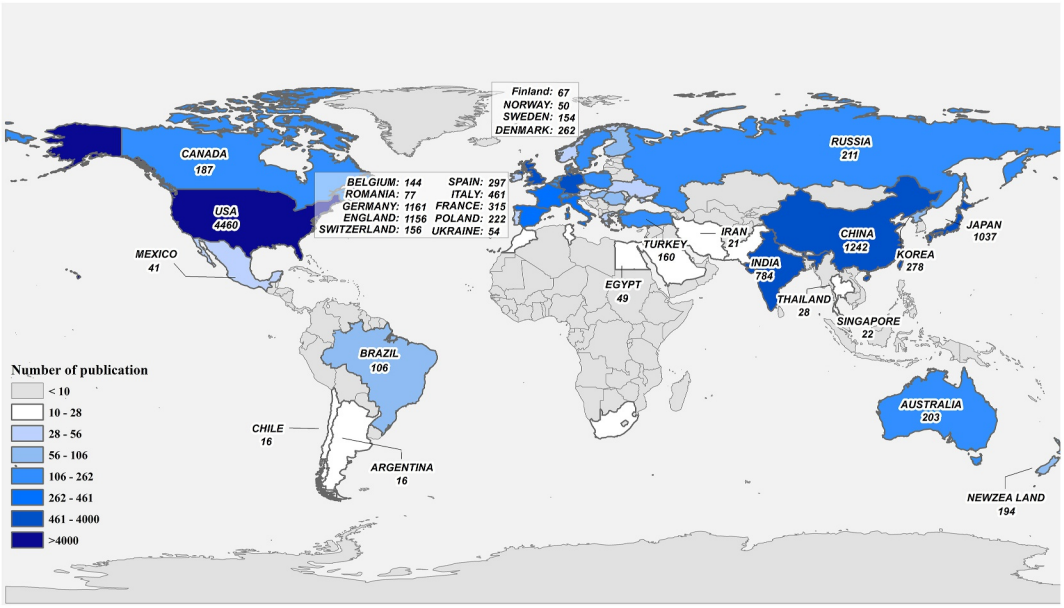

FIGURE 2 | Global contribution of CP research from 2000 to 2023.

TABLE 1 | MeSH terms excluded before analysis.

34 MeSH terms excluded before analysis			
Humans	Pancreatic disease	Japan	Cats
Male	Prospective studies	United States	Models, biological
Female	Case-control studies	Rats	Dog diseases
Pancreatitis, chronic	Cross-sectional studies	Mice	Rats, inbred lew
Pancreatitis	Rats, sprague-dawley	India	cat diseases
Chronic disease	Disease models, animal	China	Mice, inbred balb c
Pancreas	Cohort studies	Mice, knockout	Genes, rats
Animals	Rats, wistar	Mice, transgenic	
Follow-up studies	Mice, inbred c57bl	Dogs	

"basic research experiment", "pancreatic function", and "prognosis and expectation". In the basic research experiment cluster, dots representing "signal transduction," "inflammation," "intestinal mucosa," and "biomarkers" exhibited a higher density of yellow. In the pancreatic function cluster, the density of yellow in the dots for "islets of Langerhans transplantation," "transplantation, autologous," "regeneration," and "cell differentiation" was higher. In the prognosis and expectation cluster, the dots associated with "risk factors," "prognosis," and "time factors" displayed an elevated density of yellow. However, the blue dots were smaller and more scattered across all clusters.

3.3 | Trends of MeSH Terms (Every Two Years)

For MeSH terms with a frequency greater than 200 times, there were 7 MH-I and 35 MH-D ($p < 0.05$) after data processing (Figure 4). Among the 7 MH-I, 3 MeSH terms ("quality of life," "diabetes mellitus, type 2," and "exocrine pancreatic insufficiency") accounted for the highest proportion during 2022–2023, 3 MeSH terms ("islets of Langerhans transplantation," "transplantation, autologous," and "inflammation") reached their peaks during 2018–2020, and the MeSH term "signal transduction" presented its highest proportion during 2014–2015. Among the 35 MH-D terms, "middle-aged," "adult," and "aged" were the top three MeSH terms that decreased the most from 2000 to 2023.

Based on the co-occurrence network visualization (Figure 3A), these 7 MH-I and 35 MH-D terms were identified and assigned to their respective clusters. Then, 7 MH-I were selected to create a 3D Surface Map together (Figure 5). All the MeSH terms presented a rising trend in fluctuation. There were 4 MH-I ("quality of life," "inflammation," "diabetes mellitus, type 2," and "exocrine pancreatic insufficiency") increasing sharply during 2022–2023, and 3 MH-I ("signal transduction," "transplantation, autologous," and "islets of Langerhans transplantation") decreasing sharply since 2022. MH-I "signal transduction" had been increasing since its first appearance but decreased since 2014; the other 6 MH-I showed slight decreasing trends at first, then increased slowly after 2002 or 2004. Besides, 35 MH-D terms were created as 3D Ribbon Charts based on the six clusters (Figure 6).

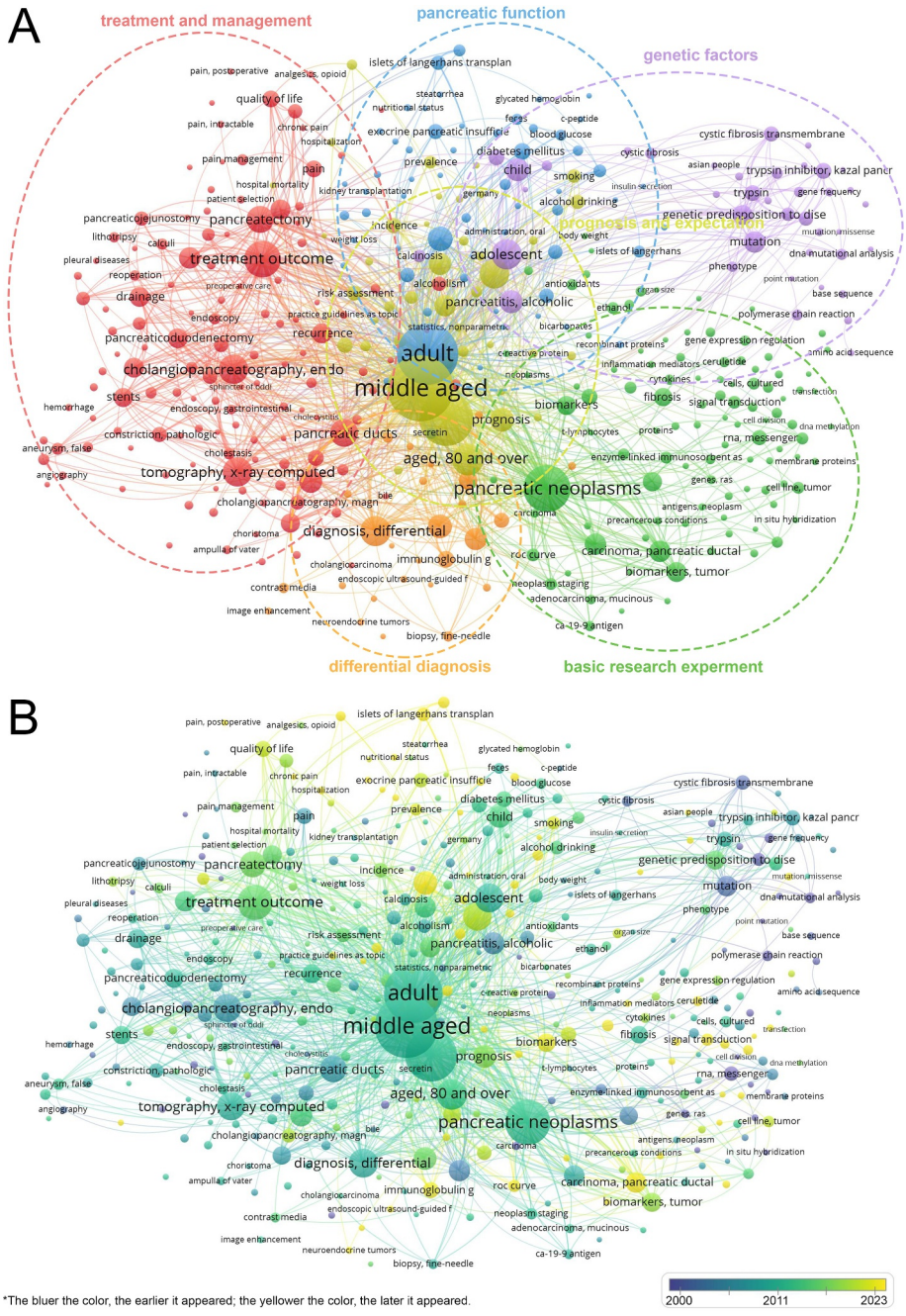

FIGURE 3 | Co-occurrence map of MeSH terms from 2000 to 2023. (A) Network visualization (B) Overlay visualization.

4 | Discussion

Bibliometric analysis of co-occurrence networks provided a global and dynamic understanding of 21st-century CP research. North America, Europe, and East Asia were the major contributors to CP research, a trend also reflected in other scientific research fields [8, 9]. According to Figure 3A, clinical studies continue to drive this engine (CP research). Improving quality of life remains the core objective, with research primarily focusing on pain management and preserving pancreatic endocrine and exocrine function. However, this engine has gradually shifted from clinical to basic gear. Research into the pathogenesis has progressed from genetics to signaling pathways. These discoveries collectively outline a field undergoing transformation.

4.1 | Overall Trend: Shift Gears From Clinical to Basic

According to Figure 6A and 6F, MeSH terms such as "pancreaticoduodenectomy" in the "treatment and management" cluster have been declining since 2000. This indicated a shift in CP research experience from clinical to basic. Clinicians face immense clinical workload pressures, compounded by the protracted duration and intensive follow-up requirements of many clinical studies, which collectively contribute to the scarcity of research outcomes. In contrast, the expanding pool of laboratory researchers facilitates the development of targeted and sustainable directions for basic research. Furthermore, CP remains an etiologically undefined disease, with few breakthroughs

TABLE 2 | Top 5 MeSH terms related to CP research in 5 clusters.

Cluster	MeSH keyword	Occurrence
The treatment	Treatment outcome	1275
	ERCP	830
	Tomography, X-ray computed	819
	Pancreatic ducts	723
	Endosonography	503
Basic research experiment	Pancreatic neoplasms	2103
	Adenocarcinoma	456
	Biomarkers, tumor	382
	Immunohistochemistry	349
	Fibrosis	316
Pancreatic function	Adult	3576
	Young adult	570
	Diabetes mellitus	282
	Exocrine pancreatic insufficiency	232
	Pancreatic function tests	202
Genetic factors	Pancreatitis, alcoholic	522
	Mutation	460
	Genetic predisposition to disease	369
	Trypsin inhibitor, Kazal pancreatic	245
	Trypsin	241
Prognosis and expectation	Middle aged	4137
	Aged	2757
	Aged, 80 and over	948
	Adolescent	889
	Risk factors	811
Differential diagnosis	Diagnosis, differential	877
	Sensitivity and specificity	490
	Predictive value of tests	319
	Reproducibility of results	222
	Survival rate	152

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

emerging in clinical research in recent years. Consequently, clinical research has exhibited a general downward trend, whereas basic research, especially in pathogenesis, has emerged as a research hotspot in the 21st century.

MeSH terms such as "mutation," "trypsinogen," and "RNA, messenger" exhibited downward trends from 2000 to 2023 (Figure 6B and 6E). However, the MeSH terms "inflammation" and "signal transduction" have garnered increasing attention and reached their peaks during 2015–2020 (Figure 5). Over the first decade, trypsinogen activation and genetic mutations emerged as the two primary research focuses. Abnormally activated and uncontrolled inflammatory responses, along with intricate intracellular signaling pathways, are considered essential to the development of irreversible pancreatic fibrosis [10, 11]. Compared to the challenging task of altering genetic predispositions, signaling pathways, and inflammatory mediators offer greater therapeutic targeting potential. The activation of pancreatic stellate cells (PSCs) is a key factor in pancreatic fibrosis [12]. Acinar cells, macrophages, and other cells communicate with PSCs to participate in the development of pancreatic fibrosis. Currently, several pathways, including the MAPK, Smad3, TGF-β, and PI3K-AKT pathways, have been identified as being related to the pro-inflammatory and pro-fibrogenic functions of PSCs [3, 13]. Intervention in these pathways by certain drugs or small molecular substances can affect the activation of PSCs, thereby ameliorating pancreatic fibrosis. It was reported that Dachaihu Decoction alleviated CP via regulating the MAPK signaling pathway [14]; Urolithin A (a gut-derived microbial metabolite) mitigated the severity of chronic alcoholic pancreatitis by inhibiting the PI3K-AKT signaling pathway [15].

MeSH terms with a higher density of yellow were mainly clustered around "basic research experiment" and "pancreatic function," indicating that these terms represent emerging research fields. MeSH terms "feces" and "intestinal mucosa," associated with "inflammation," "signal transduction," and "exocrine pancreatic insufficiency," are gaining increasing attention. It means gut microbiota has emerged as a compelling frontier in current CP research. A previous study demonstrated that fecal microbiota transplantation (FMT) in CP mice exacerbates pancreatic fibrosis by increasing CD4+ T cell and macrophage infiltration [16]. Short-chain fatty acids (SCFAs) modulated pancreatic fibrosis by inhibiting macrophage infiltration and M2 phenotype switching. Therefore, modulation of diet-derived SCFAs or G^+ SCFAs-producing bacteria may be considered a novel intervention approach for CP management [17].

4.2 | Clinical Study: Concentrate on Improving Quality of Life Instead of Technical Success

As the most crucial part of CP research, clinical studies are reflected in the clusters of "treatment and management", "pancreatic function", and "prognosis and expectation" (Figure 3A). According to Figure 5, the MeSH term "quality of life" showed the most significant increase among all MeSH terms and reached its peak during 2022–2023. Timely and accurate assessment of CP patients' quality of life is of great significance for correctly evaluating the rationality and effectiveness of clinical medical measures.

Pain is a key factor affecting the quality of life of CP patients, and medication is the primary treatment for pain relief. Recent advances in pain management concern neuromodulators, celiac plexus blocks, and antioxidant therapy. Multiple studies have indicated that antioxidants might play a potential role in mitigating pancreatic fibrosis in CP. However, these studies reached different conclusions regarding pain relief and improvement in the quality of life [18–20]. A Danish research team investigated the effects of neuromodulation on abdominal pain in CP

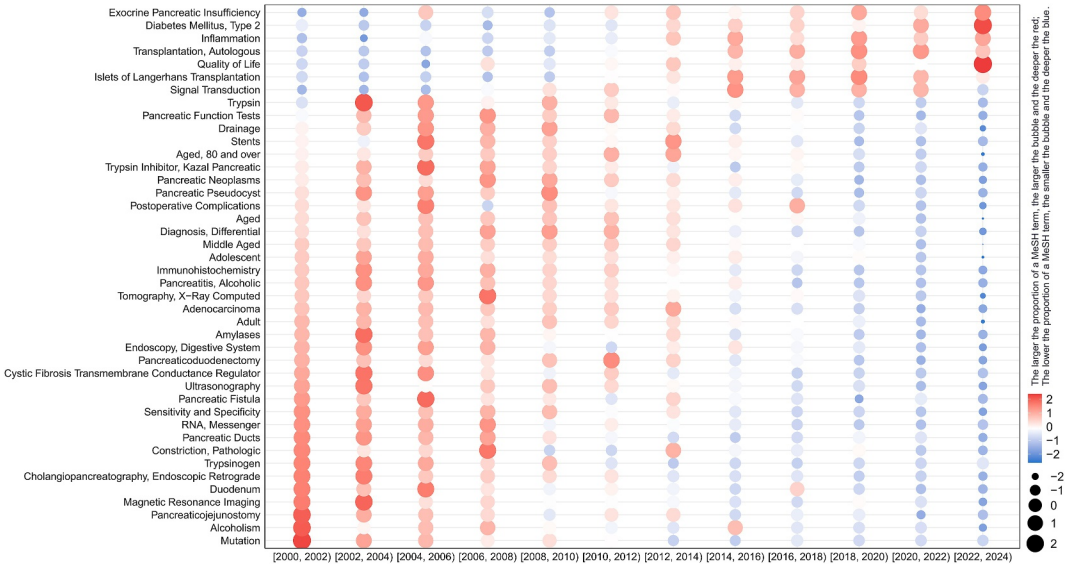

FIGURE 4 | Heat map of main MeSH terms with significant trends from 2000 to 2023 ($p < 0.05$ and $n > 200$).

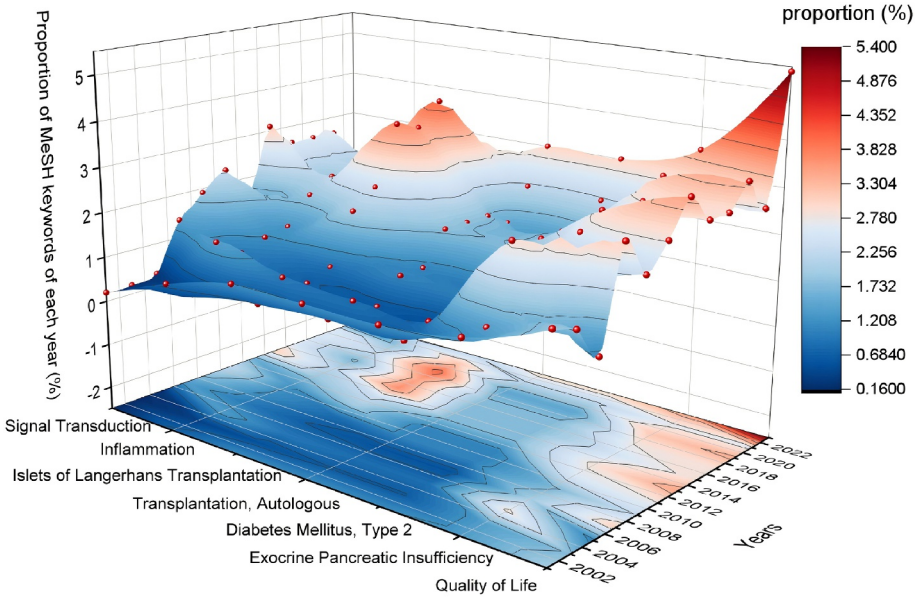

FIGURE 5 | Relative proportions of MeSH terms with increasing trends from 2000 to 2023 ($p < 0.05$, $n > 200$).

patients using low-voltage (1000 Hz) electrical stimulation of the spinal cord, but the results showed that neuromodulation was ineffective in alleviating pain in CP patients [21]. Mesenchymal stem cells (MSCs) have shown potential for treating chronic pain, potentially exerting analgesic effects by modulating pain transmission pathways and inflammatory responses [22]. Preventing acute-on-chronic flares in chronic pancreatitis is also a critical factor affecting the quality of life. Recent studies have explored whether statins can serve as a preventive treatment, but results indicate that they do not reduce recurrence rates [23]. It remains a research hotspot for measures to alleviate pain and acute-on-chronic flares in chronic pancreatitis, which require more studies offering fresh perspectives.

Despite little breakthrough in therapeutic methods, clinicians have conducted numerous studies on various factors that affect quality of life. According to Figure 5, the MeSH terms "diabetes mellitus, type 2," "islets of Langerhans transplantation," "transplantation, autologous," and "pancreatic exocrine insufficiency (PEI)" showed an overall increasing trend within the recent 24 years. CP is the most common cause of pancreatic diabetes, accounting for about 80% of type 3c diabetes (T3cDM) [24]. However, there is currently no test to discriminate T3cDM from the much more prevalent type 2 diabetes (T2DM), which has become a current research challenge. The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer conducted a DETECT study to evaluate a mixed meal test as a diagnostic method for distinguishing patients with new-onset diabetes secondary to PDAC and/or CP (T3cDM) from those with T2DM [25]. A Scandinavian single-center observational study demonstrated that total pancreatectomy with islet autotransplantation (TPIAT) can significantly alleviate pain and

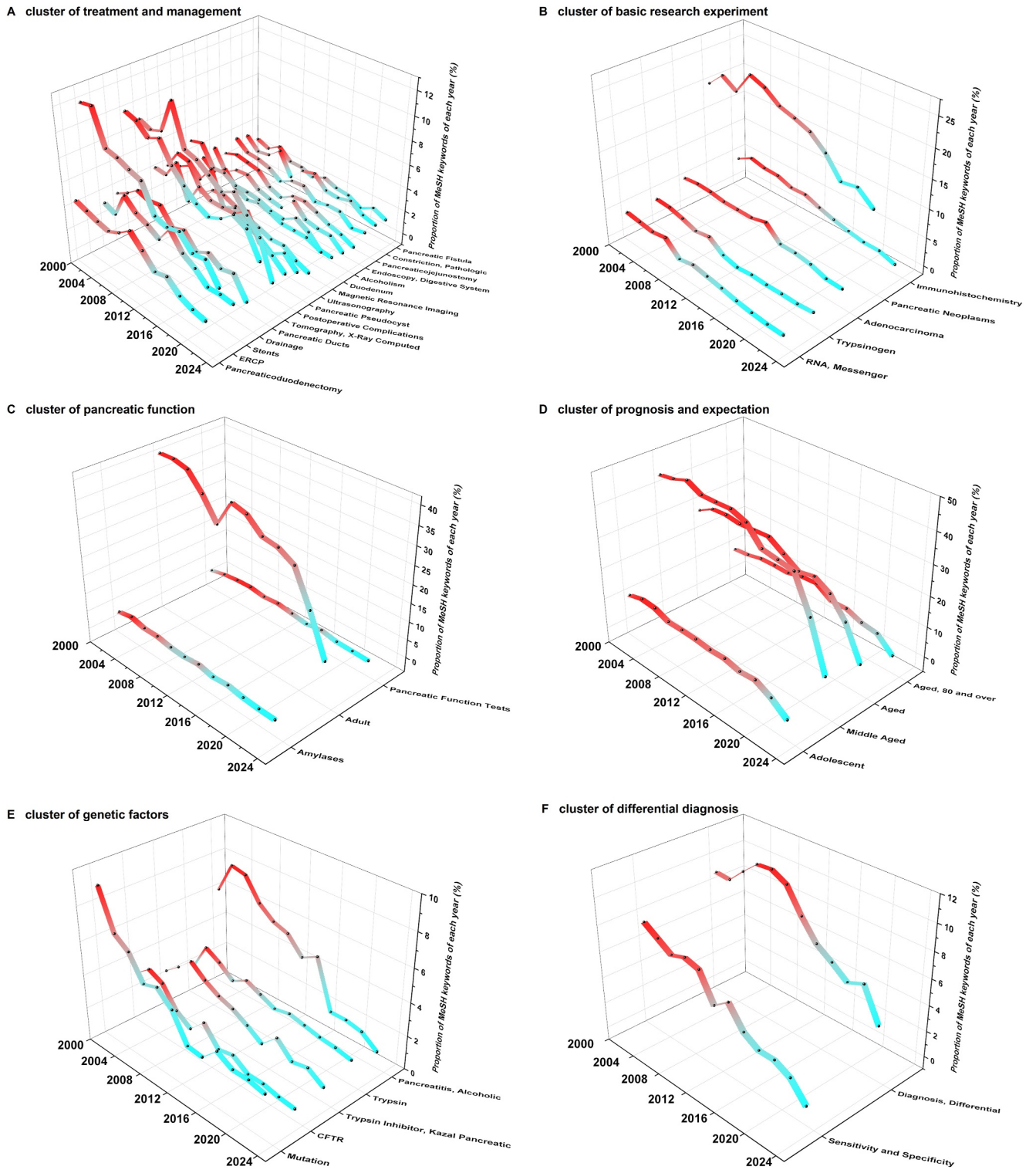

FIGURE 6 | Clusters and their relative proportions of MeSH terms with decreasing trends from 2000 to 2023.

improve the quality of life [26]. Autologous pancreatic islet transplantation is an emerging treatment option for pancreatic endocrine insufficiency. Further studies are still needed to improve its survival rate.

According to Figure 3B, MeSH terms "regeneration" and "cell differentiation" appear in yellow, indicating an emerging occurrence. Closely associated with the MeSH terms "islets of Langerhans transplantation" and "transplantation, autologous," stem cell therapy can be applied to not only islet transplantation but also the treatment of complications (e.g., diabetes and PEI), although relevant research remains scarce. VX-880 is an allogeneic, fully differentiated islet cell replacement therapy currently undergoing Phase 1/2 clinical trials [27]. For T3cDM, future stem cell therapies may explore avenues such as repairing damaged islet tissue and suppressing pancreatic inflammatory

responses. Previous studies have demonstrated the in vitro induction of human stem cells into pancreatic exocrine cells, characterized by the production of detectable amylase, trypsin, and elastase activity. Nevertheless, reports of restoring pancreatic exocrine function through cell replacement remain scarce [28, 29]. Ito et al. have preliminarily demonstrated the feasibility of pancreatic exocrine tissue transplantation through animal studies; however, the selection of the implantation site remains the most significant challenge [30].

4.3 | Clinical and Translational Implications

Currently, research focus is shifting from treatment to basic pathogenesis, with signal transduction and inflammatory pathways emerging as key areas. Cells, cytokines, and signaling pathways represent the core mechanistic drivers of pathogenesis and will remain a central focus in future investigations. Pain, as a key factor affecting quality of life, is recommended to be managed through medication, endoscopy, or surgery according to *the 2025 CP Guideline* [2]. However, detailed reports on emerging therapeutic approaches such as neuromodulation, antioxidant therapy, and stem cell therapy for pain remain scarce. Future guidelines should focus on developing more systematic and innovative pain management approaches to improve patients' quality of life with CP. Preventing acute-on-chronic flares in CP will also be a key focus of future research.

According to our research, gut microbiota and stem cell therapy, though less studied, hold tremendous potential for development. It remains unclear which signaling pathways participate in the "pancreas-gut axis" and how gut microbiota may serve as molecular therapeutic targets [31]. Stem cell therapy in islet transplantation and the treatment of complications also constitute a research gap that warrants further investigation. These issues will not only provide fresh perspectives on the pathogenesis of CP but also deliver novel diagnostic tools and therapeutic strategies.

Overall, this research possesses the following advantages: Firstly, we charted the research trajectory of CP since 2000. We have identified signal transduction, gut microbiota, quality of life, pain, and stem cell therapy as key areas for future research. Secondly, we introduced U-values and R-values to standardize the measurement of MeSH terms, enabling comparable trends across different periods and terms. Concurrently, we established dual independent expert panels to conduct manual reviews of high-frequency MeSH terms, which significantly enhanced the specificity and clinical relevance of the terminology.

Nevertheless, this study also has some limitations. First, there might be a bias in selection, as other databases not included in the MeSH index could not be included in the study. Second, since the aim of our study was to analyze the changing trends of MeSH terms, the data analysis was based on the proportion ratio rather than frequency. Therefore, the data processing could only show the trend of the MeSH term, while different MeSH terms could not be compared. Further studies may be conducted to compare MeSH terms with relevant data processing.

In a word, the research hotspots in the field of CP since the 21st century were analyzed through bibliometric analysis. Currently, research focus shifts from treatment to basic pathogenesis research. Signal transduction is a key factor in the pathogenesis of CP, particularly in relation to inflammation. This basic research heralds a new era of precise treatment for CP. Clinical research mainly focuses on the quality of life, including pain, endocrine and exocrine functions of the pancreas, among which pancreatic islet autograft transplantation is currently a hot topic. More pain treatment methods are urgently needed. Besides, emerging research topics such as stem cells and gut microbiota offer novel approaches for CP treatment.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov, reference number 32.

References

1. S. S. Vege and S. T. Chari, "Chronic Pancreatitis," *New England Journal of Medicine* 386, no. 9 (2022): 869–878, https://doi.org/10.1056/nejmcp1809396.

2. N. Thierens, R. C. Verdonk, J. M. Lohr, H. C. van Santvoort, S. A. Bouwense, and J. E. van Hooft, "Chronic Pancreatitis," *Lancet* 404, no. 10471 (2025): 2605–2618, https://doi.org/10.1016/s0140-6736(24)02187-1.

3. O. J. Hines and S. J. Pandol, "Management of Chronic Pancreatitis," *BMJ* 384 (2024): e070920, https://doi.org/10.1136/bmj-2023-070920.

4. M. Makar, Z. Vodusek, W. Xia, P. Greenberg, and G. G. Abdelsayed, "Rising Prevalence of Anxiety and Depression in Chronic Pancreatitis: A Nationwide Analysis," *Pancreas* 51, no. 4 (2022): 325–329, https://doi.org/10.1097/mpa.0000000000002019.

5. Medical Subject Headings, Accessed January 14, 2025, https://www.nlm.nih.gov/mesh/meshhome.html.

6. C. Han, Z. Q. Dong, Z. S. Li, and L. H. Hu, "Historical Review of Acute Pancreatitis Research Over the Last 80 Years," *Pancreas* 52, no. 5 (2023): e263–e274, https://doi.org/10.1097/mpa.0000000000002249.

7. X. D. Zhang, Y. Zhang, Y. Z. Zhao, C. H. Zhou, and D. W. Zou, "Autoimmune Pancreatitis: A Bibliometric Analysis From 2002 to 2022," *Frontiers in Immunology* 14 (2023): 1135096, https://doi.org/10.3389/fimmu.2023.1135096.

8. T. Zhang, X. Ma, W. Tian, et al., "Global Research Trends in Irritable Bowel Syndrome: A Bibliometric and Visualized Study," *Frontiers of Medicine* 9 (2022): 922063, https://doi.org/10.3389/fmed.2022.922063.

9. Z. Yang, Z. Xie, J. Wan, et al., "Current Trends and Research Hotspots in Pancreatic Stellate Cells: A Bibliometric Study," *Frontiers Oncology* 12 (2022): 896679, https://doi.org/10.3389/fonc.2022.896679.

10. M. Chang, W. Chen, R. Xia, Y. Peng, P. Niu, and H. Fan, "Pancreatic Stellate Cells and the Targeted Therapeutic Strategies in Chronic Pancreatitis," *Molecules* 28, no. 14 (2023): 5586, https://doi.org/10.3390/molecules28145586.

11. J. Xue, V. Sharma, M. H. Hsieh, et al., "Alternatively Activated Macrophages Promote Pancreatic Fibrosis in Chronic Pancreatitis," *Nature Communications* 6, no. 1 (2015): 7158, https://doi.org/10.1038/ncomms8158.

12. P. A. Hart and D. L. Conwell, "Chronic Pancreatitis: Managing a Difficult Disease," *American Journal of Gastroenterology* 115, no. 1 (2020): 49–55, https://doi.org/10.14309/ajg.0000000000000421.

13. G. Jin, W. Hong, Y. Guo, Y. Bai, and B. Chen, "Molecular Mechanism of Pancreatic Stellate Cells Activation in Chronic Pancreatitis and Pancreatic Cancer," *Journal of Cancer* 11, no. 6 (2020): 1505–1515, https://doi.org/10.7150/jca.38616.

14. X. Li, Z. Yan, X. Cao, et al., "Dachaihu Decoction Alleviates Chronic Pancreatitis by Regulating MAPK Signaling Pathway: Insights From Network Pharmacology and Experimental Validation," *Journal of Ethnopharmacology* 337, no. Pt 1 (2025): 118833, https://doi.org/10.1016/j.jep.2024.118833.

15. S. Mehra, S. Srinivasan, S. Singh, et al., "Urolithin A Attenuates Severity of Chronic Pancreatitis Associated With Continued Alcohol Intake by Inhibiting PI3K/AKT/mTOR Signaling," *American Journal of Physiology - Gastrointestinal and Liver Physiology* 323, no. 4 (2022): 375–386, https://doi.org/10.1152/ajpgi.00159.2022.

16. L. Liu, T. Zhang, Y. Sui, et al., "Gut Microbiota Affects Pancreatic Fibrotic Progression Through Immune Modulation in Chronic Pancreatitis," *Microbial Pathogenesis* 177 (2023): 106035, https://doi.org/10.1016/j.micpath.2023.106035.

17. L. L. Pan, Z. N. Ren, J. Yang, et al., "Gut Microbiota Controls the Development of Chronic Pancreatitis: A Critical Role of Short-Chain Fatty Acids-Producing Gram-positive Bacteria," *Acta Pharmaceutica Sinica B* 13, no. 10 (2023): 4202–4216, https://doi.org/10.1016/j.apsb.2023.08.002.

18. N. Singh, V. Ahuja, V. Sachdev, et al., "Antioxidants for Pancreatic Functions in Chronic Pancreatitis: A Double-Blind Randomized Placebo-Controlled Pilot Study," *Journal of Clinical Gastroenterology* 54, no. 3 (2020): 284–293, https://doi.org/10.1097/mcg.0000000000001178.

19. R. Dhingra, N. Singh, V. Sachdev, A. D. Upadhyay, and A. Saraya, "Effect of Antioxidant Supplementation on Surrogate Markers of Fibrosis in Chronic Pancreatitis: A Randomized, Placebo-Controlled Trial," *Pancreas* 42, no. 4 (2013): 589–595, https://doi.org/10.1097/mpa.0b013e31826dc2d7.

20. G. R. Kirk, J. S. White, L. Mckie, et al., "Combined Antioxidant Therapy Reduces Pain and Improves Quality of Life in Chronic Pancreatitis," *Journal of Gastrointestinal Surgery* 10, no. 4 (2006): 499–503, https://doi.org/10.1016/j.gassur.2005.08.035.

21. H. A. Gulisano, E. Eriksen, C. R. Bjarkam, A. M. Drewes, and S. S. Olesen, "A sham-controlled, Randomized Trial of Spinal Cord Stimulation for the Treatment of Pain in Chronic Pancreatitis," *European Journal of Pain* 28, no. 9 (2024): 1627–1639, https://doi.org/10.1002/ejp.2315.

22. R. P. Chow, K. Nguyen, W. Gou, et al., "A Novel Cellular Therapy to Treat Pancreatic Pain in Experimental Chronic Pancreatitis Using Human Alpha-1 Antitrypsin Overexpressing Mesenchymal Stromal Cells," *Biomedicines* 9, no. 11 (2021): 1695, https://doi.org/10.3390/biomedicines9111695.

23. L. Guilabert, K. CáRDENAS-JaéN, A. Vaillo-Rocamora, et al., "Simvastatin in the Prevention of Recurrent Pancreatitis: A triple-blinded Randomised Clinical Trial (The SIMBA Trial)," *Gut* (2026), https://doi.org/10.1136/gutjnl-2025-337154.

24. M. S. Petrov and M. Basina, "DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and Classifying Diabetes in Diseases of the Exocrine Pancreas," *European Journal of Endocrinology* 184, no. 4 (2021): 151–163, https://doi.org/10.1530/eje-20-0974.

25. P. A. Hart, D. K. Andersen, K. J. Mather, "Evaluation of a Mixed Meal Test for Diagnosis and Characterization of PancrEaTogEniC DiabeTes Secondary to Pancreatic Cancer and Chronic Pancreatitis: Rationale and Methodology for the DETECT Study From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: Erratum." *Pancreas* 48, no. 1 (2019): e9, https://doi.org/10.1097/MPA.0000000000001168.

26. A. Waage, A. Khan, K. J. Labori, et al., "Implementation of a Nationwide Program for Total Pancreatectomy and Islet Autotransplantation in Chronic Pancreatitis: A Scandinavian Single-Center Observational Study," *Scandinavian Journal of Surgery* (2024): 14574969241298985.

27. G. Hwang, H. Jeong, H. K. Yang, et al., "Efficacies of Stem Cell Therapies for Functional Improvement of the β Cell in Patients With Diabetes: A Systematic Review of Controlled Clinical Trials," *International Journal of Stem Cells* 12, no. 2 (2019): 195–205, https://doi.org/10.15283/ijsc18076.

28. L. Huang, A. Holtzinger, I. Jagan, et al., "Ductal Pancreatic Cancer Modeling and Drug Screening Using Human Pluripotent Stem Cell- and Patient-Derived Tumor Organoids," *Nature Medicine* 21, no. 11 (2015): 1364–1371, https://doi.org/10.1038/nm.3973.

29. M. Hohwieler, A. Illing, P. C. Hermann, et al., "Human Pluripotent Stem Cell-Derived Acinar/Ductal Organoids Generate Human Pancreas Upon Orthotopic Transplantation and Allow Disease Modelling," *Gut* 66, no. 3 (2017): 473–486, https://doi.org/10.1136/gutjnl-2016-312423.

30. K. Ito, K. Matsuura, Y. Mihara, et al., "Delivery of Pancreatic Digestive Enzymes Into the Gastrointestinal Tract by Pancreatic Exocrine Tissue Transplant," *Scientific Reports* 9, no. 1 (2019): 5922, https://doi.org/10.1038/s41598-019-42362-z.

31. Y. F. Qiu, J. Ye, J. J. Xie, et al., "Pancreatitis Affects Gut Microbiota via Metabolites and Inflammatory Cytokines: An Exploratory Two-Step Mendelian Randomisation Study," *Molecular Genetics and Genomics* 299, no. 1 (2024): 36, https://doi.org/10.1007/s00438-024-02125-6.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270200-sup-0001-suppl-data.docx.