



## Evidence Map of Pancreatic Surgery—A living systematic review with meta-analyses by the International Study Group of Pancreatic Surgery (ISGPS)

Pascal Probst, MD<sup>a,b,\*</sup>, Felix J. Hüttner, MD<sup>a,b</sup>, Ömer Meydan, MD<sup>b</sup>, Mohammed Abu Hilal, MD<sup>c</sup>, Mustapha Adham, MD<sup>d</sup>, Savio G. Barreto, MD<sup>e,f</sup>, Marc G. Besselink, MD<sup>g</sup>, Olivier R. Busch, MD<sup>h</sup>, Maximilian Bockhorn, MD<sup>i</sup>, Marco Del Chiaro, MD<sup>j</sup>, Kevin Conlon, MD<sup>k</sup>, Carlos Fernandez-del Castillo, MD<sup>l</sup>, Helmut Friess, MD<sup>m</sup>, Giuseppe Kito Fusai, MD<sup>n</sup>, Luca Gianotti, MD<sup>o</sup>, Thilo Hackert, MD<sup>a</sup>, Christopher Halloran, MD<sup>p</sup>, Jakob Izbicki, MD<sup>q</sup>, Eva Kalkum, MSc<sup>b</sup>, Dezső Kelemen, MD<sup>r</sup>, Hannes G. Kenngott, MD<sup>a</sup>, Rüdiger Kretschmer, MD<sup>b</sup>, Vincent Landré, MD<sup>b</sup>, Keith D. Lillemoe, MD<sup>l</sup>, Yi Miao, MD<sup>s</sup>, Giovanni Marchegiani, MD<sup>t</sup>, André Mihaljevic, MD<sup>a,b</sup>, Dejan Radenkovic, MD<sup>u</sup>, Roberto Salvia, MD<sup>t</sup>, Marta Sandini, MD<sup>a</sup>, Alejandro Serrablo, MD<sup>v</sup>, Shailesh Shrikhande, MD<sup>w</sup>, Parul J. Shukla, MD<sup>x</sup>, Ajith K. Siriwardena, MD<sup>y</sup>, Oliver Strobel, MD<sup>a</sup>, Faik G. Uzunoglu, MD<sup>q</sup>, Charles Vollmer, MD<sup>z</sup>, Jürgen Weitz, MD<sup>aa</sup>, Christopher L. Wolfgang, MD<sup>bb</sup>, Alessandro Zerbi, MD<sup>cc,dd</sup>, Claudio Bassi, MD<sup>t</sup>, Christos Dervenis, MD<sup>ee</sup>, John Neoptolemos, MD<sup>a</sup>, Markus W. Büchler, MD<sup>a</sup>, Markus K. Diener, MD<sup>a,b</sup>

<sup>a</sup> Department of General, Visceral, and Transplantation Surgery, University of Heidelberg, Germany

<sup>b</sup> The Study Center of the German Surgical Society (SDGC), University of Heidelberg, Germany

<sup>c</sup> HPB Department, Southampton General Hospital, Southampton, United Kingdom

<sup>d</sup> Department of Surgery, Lyon Civil Hospital, France

<sup>e</sup> Division of Surgery and Perioperative Medicine, Flinders Medical Centre, Bedford Park, Adelaide, Australia

<sup>f</sup> College of Medicine and Public Health, Flinders University, South Australia, Australia

<sup>g</sup> Department of Surgery, Cancer Center Amsterdam, University of Amsterdam, The Netherlands

<sup>h</sup> Department of Surgery, Amsterdam UMC, University of Amsterdam, The Netherlands

<sup>i</sup> Department of General and Visceral Surgery, University Medical Center Oldenburg, Germany

<sup>j</sup> Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO

<sup>k</sup> Hepato-Pancreatico-Biliary Unit, Department of General Surgery, Trinity College Dublin, Tallaght Hospital, Ireland

<sup>l</sup> Department of Surgery, Massachusetts General Hospital and the Harvard Medical School, Boston, MA

<sup>m</sup> Department of Hepato-Pancreato-Biliary Surgery, Klinikum rechts der Isar, Technische Universität München, Germany

<sup>n</sup> Institute for Liver and Digestive Health, University College London, United Kingdom

<sup>o</sup> Pancreatic Surgery Unit, School of Medicine and Surgery, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

<sup>p</sup> Department of Molecular and Clinical Cancer Medicine, University of Liverpool, United Kingdom

<sup>q</sup> University Medical Center Hamburg-Eppendorf, Germany

<sup>r</sup> Department of Surgery, Clinical Center, Medical School, University of Pécs, Hungary

<sup>s</sup> Pancreas Center, The First Affiliated Hospital of Nanjing Medical University, China

<sup>t</sup> Department of Surgery, The Pancreas Institute, University and Hospital Trust of Verona, Verona, Italy

<sup>u</sup> Department of Surgery, Clinical Center of Serbia and School of Medicine, University of Belgrade, Serbia

<sup>v</sup> Hepatobiliopancreatic Surgery Unit, General and Digestive Surgery Service, Hospital Miguel Servet, Zaragoza, Spain

<sup>w</sup> Pancreato-Biliary Unit, Tata Memorial Hospital, Mumbai, India

<sup>x</sup> Weill Cornell Medical College & New York Presbyterian Hospital, NY

<sup>y</sup> Department of Surgery, Regional Hepato-Pancreato-Biliary Unit, Manchester Royal Infirmary, United Kingdom

<sup>z</sup> Department of Surgery, Penn Medicine, University of Pennsylvania, Philadelphia, PA

<sup>aa</sup> Department of General, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany

<sup>bb</sup> Department of Surgery, Johns Hopkins Hospital, Baltimore, MD

Pascal Probst and Felix J. Hüttner contributed equally to this work.

\* Reprint requests: Pascal Probst, MD, Study Center of the German Society of Surgery, University of Heidelberg, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany.

E-mail address: [info@evidencemap.surgery](mailto:info@evidencemap.surgery) (P. Probst);

Twitter: [@evidencemap](https://twitter.com/evidencemap)

<https://doi.org/10.1016/j.surg.2021.04.023>

0039-6060/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<sup>cc</sup> Pancreatic Surgery, Humanitas Clinical and Research Center-IRCCS, Rozzano (MI), Italy

<sup>dd</sup> Humanitas University, Pieve Emanuele (MI), Italy

<sup>ee</sup> Department of Surgery, Metropolitan Hospital, Athens, Greece

## ARTICLE INFO

### Article history:

Accepted 19 April 2021

Available online 27 June 2021

## ABSTRACT

**Background:** Pancreatic surgery is associated with considerable morbidity and, consequently, offers a large and complex field for research. To prioritize relevant future scientific projects, it is of utmost importance to identify existing evidence and uncover research gaps. Thus, the aim of this project was to create a systematic and living Evidence Map of Pancreatic Surgery.

**Methods:** PubMed, the Cochrane Central Register of Controlled Trials, and Web of Science were systematically searched for all randomized controlled trials and systematic reviews on pancreatic surgery. Outcomes from every existing randomized controlled trial were extracted, and trial quality was assessed. Systematic reviews were used to identify an absence of randomized controlled trials. Randomized controlled trials and systematic reviews on identical subjects were grouped according to research topics. A web-based evidence map modeled after a mind map was created to visualize existing evidence. Meta-analyses of specific outcomes of pancreatic surgery were performed for all research topics with more than 3 randomized controlled trials. For partial pancreateoduodenectomy and distal pancreatectomy, pooled benchmarks for outcomes were calculated with a 99% confidence interval. The evidence map undergoes regular updates.

**Results:** Out of 30,860 articles reviewed, 328 randomized controlled trials on 35,600 patients and 332 systematic reviews were included and grouped into 76 research topics. Most randomized controlled trials were from Europe (46%) and most systematic reviews were from Asia (51%). A living meta-analysis of 21 out of 76 research topics (28%) was performed and included in the web-based evidence map. Evidence gaps were identified in 11 out of 76 research topics (14%). The benchmark for mortality was 2% (99% confidence interval: 1%–2%) for partial pancreateoduodenectomy and <1% (99% confidence interval: 0%–1%) for distal pancreatectomy. The benchmark for overall complications was 53% (99% confidence interval: 46%–61%) for partial pancreateoduodenectomy and 59% (99% confidence interval: 44%–80%) for distal pancreatectomy.

**Conclusion:** The International Study Group of Pancreatic Surgery Evidence Map of Pancreatic Surgery, which is freely accessible via [www.evidencemap.surgery](http://www.evidencemap.surgery) and as a mobile phone app, provides a regularly updated overview of the available literature displayed in an intuitive fashion. Clinical decision making and evidence-based patient information are supported by the primary data provided, as well as by living meta-analyses. Researchers can use the systematic literature search and processed data for their own projects, and funding bodies can base their research priorities on evidence gaps that the map uncovers.

© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Introduction

Surgery remains the only chance for cure or long-term improvement in quality of life for patients with pancreatic tumors and chronic pancreatitis.<sup>1,2</sup> Consequently, affected patients not only suffer from a severe disease but are also at risk of complications associated with pancreatic surgery. Morbidity is reported to affect up to 73% of pancreatic surgery patients.<sup>3</sup> Therefore, one of the major research interests in this area is to use high quality trials to identify which surgical procedures pose the lowest complication rate. Furthermore, oncological outcomes in pancreatic cancer may be improved by the choice of surgical approach and radicality.

The quantity and quality of randomized controlled trials (RCTs) for pancreatic surgery is increasing.<sup>4</sup> However, evidence gaps still exist and need to be addressed. Economic resources are limited, and some knowledge gaps have a greater impact than others. Research activities should, therefore, be designed and prioritized based on their clinical and political relevance, in order to avoid conducting redundant or low-quality studies. High-quality evidence at a glance is therefore needed for surgeons, researchers, and funding bodies alike.

The aim of this project was to create a systematic and living review of pancreatic surgery literature with a view to creating an intuitive and perpetually up-to-date Evidence Map of Pancreatic Surgery.

## Methods

This systematic review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,<sup>5</sup> where applicable. The project was prospectively registered (PROSPERO 2019 CRD42019133444), and the protocol was published open access.<sup>6</sup> As described in the protocol, a paper-based publication of the current version of the International Study Group of Pancreatic Surgery (ISGPS) Evidence Map of Pancreatic Surgery will be published every 2 years. These paper-based publications will then become subsequent versions of the web-based evidence map. However, the map content itself is also likely to be developed beyond that of the current version described by this manuscript.

Each aspect of the study process, including screening, data extraction, analysis, creation of the map, and social media presentations was completed by the staff of the Study Center of the German Surgical society (Systematic Review Working Group). The project itself is funded by the Heidelberg Foundation for Surgery (Heidelberger Stiftung Chirurgie, [www.stiftung-chirurgie.de](http://www.stiftung-chirurgie.de)) in Heidelberg, Germany.

### Systematic literature search

A systematic search of all major electronic bibliographic databases relevant for surgery was performed<sup>7</sup>: MEDLINE (via PubMed),

Web of Science, and the Cochrane Central Register of Controlled Trials. No restrictions were applied regarding language or publication date. The search strategy for all databases aimed to cover the whole field of pancreatic surgery and was published in detail in the protocol.<sup>6</sup> The last search for version 1 was performed on April 11, 2021.

### Study selection

Patients with any kind of disease requiring pancreatic surgery were considered eligible. Interventions that aimed to affect surgical outcome, including medical devices (eg, stapler versus scalpel resection in distal pancreatectomy), perioperative management (eg, prehabilitation of patients or intraoperative fluid management), surgical strategy (eg, open versus laparoscopic access to the abdominal cavity), drug use (eg, somatostatin analogs to influence complications), and nutrition (eg, immunonutrition to avoid complications) were included. Interventions like endoscopic retrograde cholangiopancreatography, radiologically guided punctures, or similar were only included when they were compared to a surgical intervention. Moreover, studies on neo/adjuvant treatment or pancreatic transplantation were excluded since they would constitute a separate thematic evidence map.

RCTs and systematic review (SRs) with or without meta-analysis were deemed eligible for inclusion. SRs were only eligible if they met minimum quality requirements, ie, the SR must include at least 2 established literature databases and provide a critical appraisal with validated tools, such as the Cochrane Collaboration tool for assessing risk of bias<sup>8</sup> for RCTs or the ROBINS-I for nonrandomized studies.<sup>9</sup>

Following the recommendations of the Cochrane Collaboration,<sup>10</sup> 2 reviewers independently screened the titles, abstracts, and full texts of the identified articles. A third reviewer resolved any disagreement between the 2 reviewers.

### Data extraction

Two reviewers using predefined items carried out all stages of data extraction and quality assessment independently. Any disagreement was resolved by discussion and consensus or by consulting a third reviewer. The outcomes of interest were mortality, postoperative pancreatic fistula (graded as biochemical leak, B, or C, if the ISGPS definition<sup>11</sup> was used), delayed gastric emptying (graded as A, B, or C, if the ISGPS definition<sup>12</sup> was used), post-pancreatectomy hemorrhage (graded as A, B, or C, if the ISGPS definition<sup>13</sup> was used), bile leak (graded as A, B, or C, if the International Study Group of Liver Surgery definition<sup>14</sup> was used), chyle leak (graded as A, B, or C, if the ISGPS definition<sup>15</sup> was used), intra-abdominal fluid collection/abscess, overall morbidity (if available, according to the Clavien-Dindo classification<sup>16</sup>), comprehensive complication index,<sup>17</sup> survival (described as 1-, 2-, 3-, 4-, and 5-year survival rates, as well as overall survival), length of hospital stay, and operation time. The full list of extracted items for RCTs and SRs is included in the protocol.<sup>6</sup>

Furthermore, the methodological quality of included RCTs was assessed with the Cochrane Collaboration tool for assessing risk of bias 2.0.<sup>18</sup> Five standard domains of bias were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. These domains were rated as “high risk of bias,” “low risk of bias,” or “some concerns.” Finally, an overall risk of bias judgment was made. The overall risk of bias was considered high risk of bias if at least 1 domain had a high risk of bias or if there were some concerns in 3 or more domains. The overall risk of bias was some concerns if there were some concerns in at least 1 domain. The overall risk of bias was low risk of bias if all domains were rated as

low risk of bias. The blinding of patients, surgeons, data collectors, outcome assessors, and data analysts was assessed as “blinded,” “not blinded,” or “not reported.”<sup>19</sup> Furthermore, information on funding was recorded as “industry,” “independent,” or “not reported.”<sup>20</sup>

### Data synthesis

The ISGPS Evidence Map of Pancreatic Surgery is freely accessible via the internet. All included RCTs and SRs are clustered according to the type of operation, disease, and intervention. Consequently, studies on the same research topics are grouped together, eg, pylorus preservation versus pylorus resection (intervention: surgical strategy) in partial pancreateoduodenectomy (operation) for tumors or chronic pancreatitis (disease). Existing SRs are displayed within the evidence map and are used to identify missing RCTs within a research topic (evidence gap). No quantitative data from SRs are extracted, and no critical appraisal of SRs—despite the quality criteria for inclusion mentioned above—is performed. Ongoing RCTs and unpublished terminated RCTs according to the World Health Organization trial registry are also displayed within the evidence map; these will be replaced as results become available.

### Creation of the evidence map

Instructions and a summary, as well as a section containing definitions and international guidelines, appear in the center of the evidence map. The map itself is configured as a mind map in a manner that is intuitive and hierarchically leads its reader from the center (pancreatic surgery as a whole) via main topics (eg, partial pancreateoduodenectomy) and subtopics (eg, entero-enteric anastomosis) to individual research topics (eg, pylorus preservation versus pylorus resection). Red boxes indicate evidence gaps, and in green boxes, existing studies are shown. Within a research topic, existing RCTs and SRs are plotted with the name of the first author and year of publication. For every study, the conclusion of the article, the citation, and a direct link to the article on the journal homepage are provided. Processed data from RCTs are available for future meta-analyses.

### Quantitative analyses and the Grading of Recommendations Assessment, Development, and Evaluation

R (version 3.6.4) is used for statistical analysis.<sup>21</sup> All RCTs that investigate exclusively 1 type of operation are pooled to create a summary of the ISGPS Evidence Map of Pancreatic Surgery. A pooled complication rate with a 99% confidence interval computed by a meta-analysis of proportions is provided for benchmarking purposes. Further, bubble plots mapping all RCTs by type of operation to type of intervention, type of disease to type of intervention, and type of disease to type of operation are created. Within the bubble plots, the sample size of the trials is expressed by bubble size. If an RCT contains more than 1 operation or disease, the largest group within it is taken to represent the whole sample. The geographical region where a trial took place is indicated by a color code.

Processed data from every RCT are provided to allow for meta-analysis. Continuous values are converted to mean and standard deviation if reported otherwise.<sup>22</sup> The standard deviation is reported as (0) if only the mean was available and as (–2) if only the median was available. Within the processed data, the Clavien-Dindo classification is not displayed if morbidity was only reported as “major complications” or incomplete. If no “a” or “b” subclass was reported for grade 3 or 4 complications, these complications are summarized in the processed data as 3a or 4a, respectively.

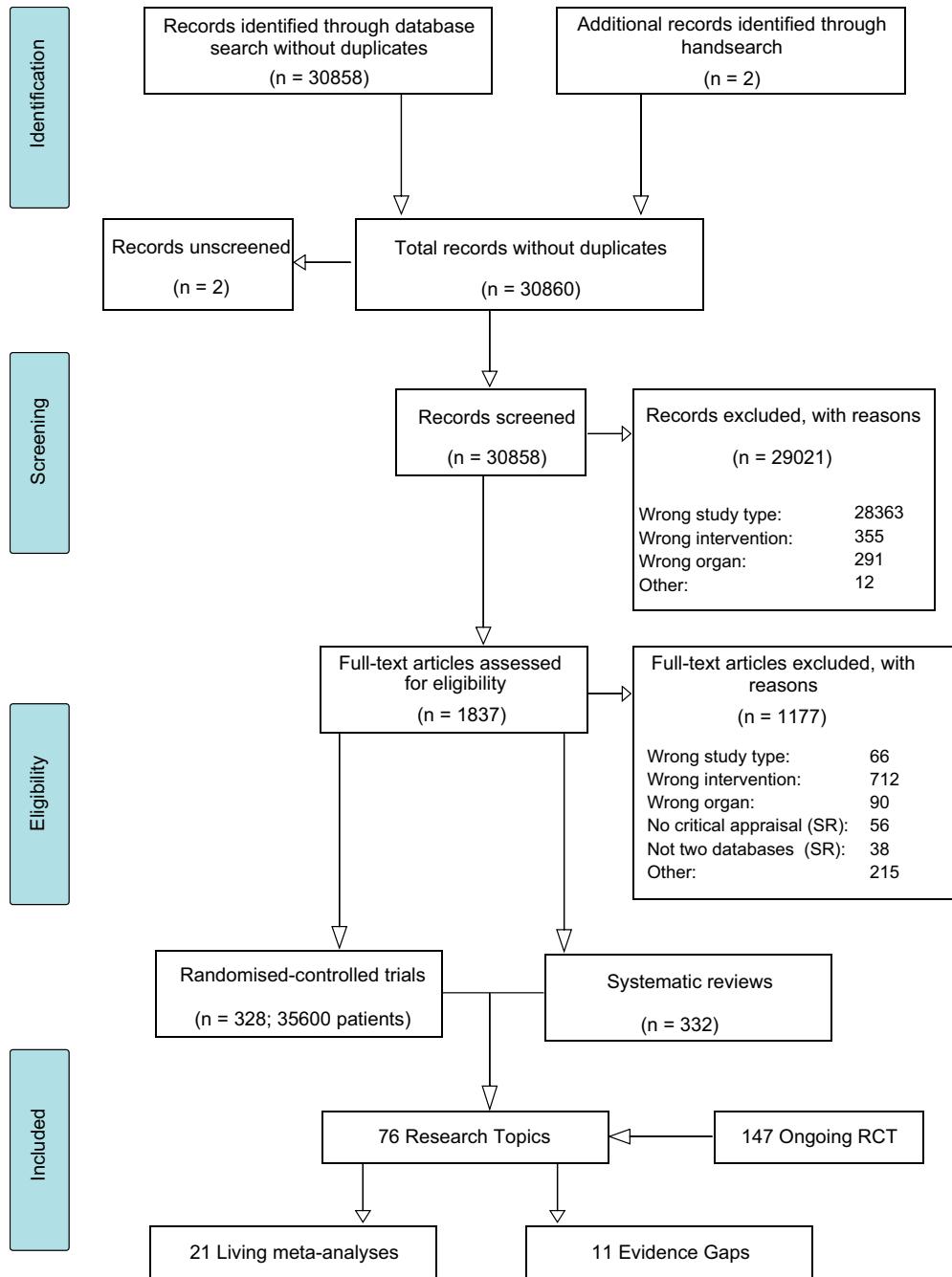


Fig 1. PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Living meta-analyses are performed for research topics if more than 3 RCTs are included and at least 3 data sets for an outcome are available. Dichotomous data are pooled in a Mantel-Haenszel model to estimate odds ratios and associated 95% confidence intervals. For continuous data, mean differences and associated 95% confidence intervals are calculated using an inverse-variance model. A random effects model is used due to general clinical heterogeneity. For dichotomous and continuous data, a prediction interval and an exact *P* value are calculated. Statistical heterogeneity is evaluated via the *I*<sup>2</sup> statistic. An *I*<sup>2</sup> <25% is considered low statistical heterogeneity, and an *I*<sup>2</sup> >75% is considered high statistical heterogeneity.

If more than 2 interventions are compared within a research topic, a state-of-the art Bayesian network meta-analysis is

performed. Either linear or logistic random effects models are applied. Pooled effect estimates obtained in the network meta-analysis (adjusted mean differences or log odds ratios) are provided with 95% credibility intervals. Furthermore, a treatment ranking based on the probability of being the most efficient arm is carried out.

If more than 10 trials are available, funnel plots are created and tested for asymmetry to evaluate the risk of publication bias using the Harbord test.<sup>23</sup> Funnel plots are only displayed in case of statistically significant asymmetry.

Furthermore, for each outcome in the meta-analyses, the certainty of the evidence is rated using the Grading of Recommendations Assessment, Development and Evaluation system.<sup>24,25</sup> This system includes limitations in the design from the risk of bias

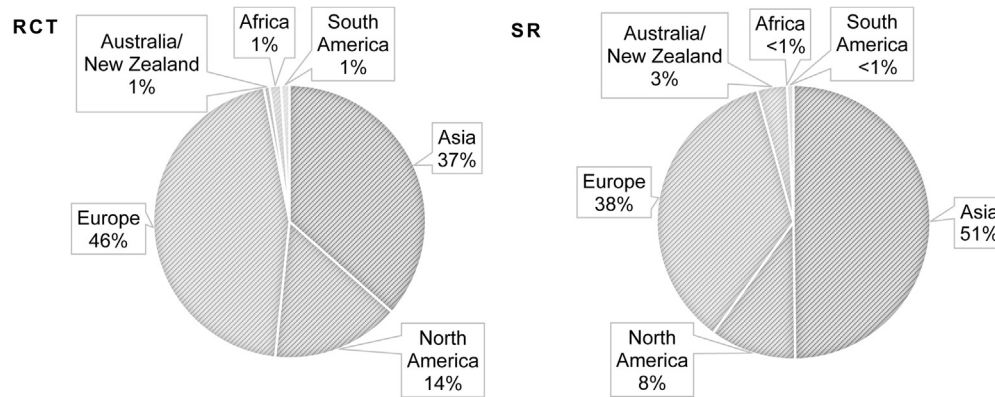


Fig 2. Origin of included studies.

assessment as mentioned above, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and publication bias. Thus, the certainty of evidence is rated as “very low,” “low,” “moderate,” or “high” for each outcome.

#### Living systematic review and meta-analyses

The map will be updated at least every 3 months, according to the above-mentioned steps. Moreover, relevant new articles found by hand search or discovered via social media will be scrutinized and added immediately. All new RCTs and SRs will be added to the map under their respective research topics. The date of last update will be reported in the center of the map. Meta-analyses will be renewed when new RCTs become available, thus resulting in living meta-analyses. For every meta-analysis, the date of calculation will be provided. These updated meta-analyses will be peer-reviewed by members of the ISGPS unaffiliated with the University of Heidelberg.

## Results

The ISGPS Evidence Map of Pancreatic Surgery is freely accessible via [www.evidencemap.surgery](http://www.evidencemap.surgery). This paper-based publication represents version 1. Altogether, 30,860 articles were found via systematic literature search, and 29,021 articles were excluded after title and abstract screening. Of these 1,837 articles, 328 RCTs (including 35,600 patients) and 332 SRs were eventually included. These articles were grouped into 76 research topics. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of this process.

#### Origin and topics of included studies

The highest number of RCTs has, so far, been conducted in Europe (46%), followed by Asia (37%) and North America (14%). Other geographical regions—Africa, Australia and New Zealand, and South America—contributed around 1% each (Fig 2, RCT). Regarding SRs, the most studies were conducted in Asia (51%), followed by Europe (38%), North America (8%), and Australia/ New Zealand (3%). South America and Africa contributed less than 1% (Fig 2, SR).

Bubble plots are shown in the summary of the evidence map online. The 3 bubble plots show that RCTs for operations other than pancreatoduodenectomy are scarce and that even fewer RCTs exist for relatively rare diseases such as neuroendocrine neoplasms or intraductal papillary mucinous neoplasms.

#### Critical appraisal (bias)

The summary of the quality assessment is shown in Table I. The overall risk of bias judgment was deemed high in 54% of RCTs. In 36% of RCTs, there were some concerns, and the remaining 10% of RCTs had a low risk of bias. About 23% of patients were blinded; however, most of the RCTs did not report blinding of study contributors. Funding remained unclear in half of the RCTs. Apparently, 9% of RCTs were sponsored by industry, and 43% were nonindustry funded.

#### Map content

The current map consists of 7 main topics: “partial pancreatoduodenectomy,” “distal pancreatectomy,” “pancreatitis,” “trauma,” “palliative measures,” “various perioperative interventions,” and “other surgical aspects.” The main topic, partial pancreatectomy, contains 6 subtopics (“pancreatic anastomosis,” “entero-enteric anastomosis,” “bile duct anastomosis,” “drainage,” “surgical aspects,” and “minimally invasive surgery”) with 27 individual research topics. The main topic, distal pancreatectomy, contains 4 subtopics: “drainage,” “minimally invasive surgery,” “pancreatic remnant,” and “surgical aspects.” A total of 15 research topics are plotted. The main topic, pancreatitis, is divided into the subtopics “chronic pancreatitis” and “acute pancreatitis,” containing a total of 6 research topics. “Trauma” and “palliative measures” comprise 1 research topic each. Various perioperative interventions is another main topic, with 3 subtopics (“pharmaceutical cotreatments,” “nutrition,” and “minimally invasive surgery”) and 17 research topics in total. Finally, the main topic, other surgical aspects, entails research topics that do not fit into any of the other main topics. Living meta-analyses are performed for 21 out of 76 research topics (28%). Table II summarizes the map contents and shows if a living meta-analysis is conducted.

Evidence gaps, ie, missing RCTs, were identified within 11 out of 76 research topics (14%): “total versus partial pancreatoduodenectomy,” “autologous coverage after partial pancreatoduodenectomy,” “robotic versus laparoscopic partial pancreatoduodenectomy,” “radical antegrade modular pancreatosplenectomy versus standard distal pancreatectomy,” “cecal axis resection in distal pancreatectomy,” “robotic versus laparoscopic distal pancreatectomy,” “time point of surgery for chronic pancreatitis,” “multivisceral resection in pancreatic surgery,” “resection versus nonsurgical management of pancreatic neuroendocrine tumors,” “frozen section analysis during pancreatic surgery,” and “volume-outcome relationship in pancreatic surgery.”



**Table 1**  
Summary of the quality assessment of the ISGPS Evidence Map of Pancreatic Surgery (version 1)

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
Low risk of bias	190 (58%)	100 (30%)	284 (87%)	73 (22%)	148 (45%)
Some concerns	129 (39%)	224 (68%)	39 (12%)	249 (76%)	168 (51%)
High risk of bias	9 (3%)	4 (1%)	5 (2%)	6 (2%)	12 (4%)
Overall risk of bias judgment					
33 (10%)	Low risk of bias				
118 (36%)	Some concerns				
177 (54%)	High risk of bias				
	Patients	Physicians	Data collectors	Outcome assessors	Statisticians
Blinded	74 (23%)	40 (12%)	37 (11%)	30 (9%)	5 (2%)
Not blinded	61 (19%)	94 (29%)	63 (19%)	12 (4%)	12 (4%)
Not reported	193 (59%)	194 (59%)	228 (70%)	286 (87%)	311 (95%)
Funding					
30 (9%)	Industry				
142 (43%)	Nonindustry				
156 (48%)	Unclear				

ISGPS, International Study Group of Pancreatic Surgery.

Ongoing and unpublished terminated RCTs are displayed within their respective research topic.

### Benchmarks

Forest plots of benchmarks are displayed in the summary of the evidence map online. In 17,039 patients from 160 RCTs undergoing partial pancreateoduodenectomy, the benchmark for mortality was 2% (99% confidence interval [CI]: 1%–2%; range: 0%–22%;  $I^2 = 77\%$ ). The benchmark for overall complications was 53% (61 RCTs; 7,474 patients; 99% CI: 46%–61%; range: 15%–133%;  $I^2 = 91$ ), and the benchmark for postoperative pancreatic fistula according to the ISGPS definition was 14% (99 RCTs; 12,013 patients; 99% CI: 12%–17%; range: 0%–66%;  $I^2 = 89\%$ ). In 3,011 patients from 24 RCTs undergoing distal pancreatectomy, the benchmark for mortality was <1% (99% CI: 0%–1%; range: 0%–3%;  $I^2 = 29\%$ ). The benchmark for overall complications was 59% (1,058 patients; 99% CI: 44%–80%; range: 32%–100%;  $I^2 = 86\%$ ), and the benchmark for postoperative pancreatic fistula according to the ISGPS definition was 23% (3,016 patients; 99% CI: 17%–30%; range: 5%–60%;  $I^2 = 90\%$ ).

Further benchmarks are available in the summary of the online map.

### Social media concept and mobile app

In addition to the map's website ([www.evidencemap.surgery](http://www.evidencemap.surgery)), a mobile app is available for Android and iPhone (EVIglance app).

Further, a social media presence for the ISGPS Evidence Map of Pancreatic Surgery was established. Twitter presentations on research topics (with and without surveys) are published regularly (@evidencemap). Updates are shared via Facebook (fb.com/evidencemap), where the inaugural presentation of the evidence map was streamed from the World Pancreas Forum in Bern, Switzerland on February 6, 2020. Finally, every video created concerning the ISGPS Evidence Map of Pancreatic Surgery is available on YouTube. Professionals and patients are thus provided with an interactive forum via social media and are also able to contact the study team directly via email ([info@evidencemap.surgery](mailto:info@evidencemap.surgery)).

### Discussion

Ideally, overviews of scientific literature must be up-to-date, comprehensive, critically appraised, and presented in a lucid way. The ISGPS Evidence Map of Pancreatic Surgery aims to provide pancreatic surgeons, other medical professionals, students, and patients alike with such a resource. After a systematic review of literature, all existing evidence from RCTs and SRs on pancreatic surgery are included, assessed, and plotted in the intuitive form of a mind map. The body of evidence that the map provides will be updated at least every 3 months and made freely accessible at [www.evidencemap.surgery](http://www.evidencemap.surgery); thus, health care professionals, patients, and funding bodies can access a living overview of highly relevant data.

This project combines 2 innovative methods of evidence-based medicine: a living systematic review and evidence mapping. The fact that published data derived from SRs are at risk of being outdated or redundant with the ever-increasing body of evidence in literature, a living SR, which results in a higher level of validity,<sup>26–28</sup> helps to overcome this problem. Evidence mapping is an emerging approach, but the term has not yet been universally defined.<sup>29,30</sup> The ISGPS Evidence Map of Pancreatic Surgery envisions a novel interpretation of evidence mapping, plotting the available evidence in the form of a mind map allows processed evidence to be presented by topic and at a glance. Besides fulfilling the needs of evidence-based medicine, this project also addresses the issue of how best to use modern technology to communicate scientific data. Consequently, the map is freely available via the internet, and its scope, contents, and updates are (and will continue to be) distributed via a variety of social media platforms.

The ISGPS Evidence Map of Pancreatic Surgery addresses the needs of all stakeholders in the health care system. First, in times of economic constraints, there is a need to avoid wasteful expenditure in medical research. However, science should remain as unrestricted as possible and should be allowed to follow international trends, like the use of octreotide or robotic surgery. Without a global strategy, important knowledge gaps remain and result in multiple publications on less urgent questions. A harmonization by national and international funding bodies to support important research projects might be the solution. However, it is difficult for interdisciplinary funding bodies to maintain a regular overview of the existing research in a specific field, such as pancreatic surgery.

**Table II**  
Tabular view of the research topics of the ISGPS Evidence Map of Pancreatic Surgery (version 1)

	Living meta-analysis
Partial pancreatoduodenectomy	
Pancreatic anastomosis	
Pancreaticogastrostomy versus pancreaticojejunostomy	✓
Stenting	
Stenting versus no stenting of pancreatic anastomosis	✓
External versus internal stenting of pancreatic anastomosis	✓
Techniques	
Duct-to-mucosa versus invagination	✓
Binding versus conventional pancreatic	
Mattress suture versus duct-to-mucosa	
Other anastomotic techniques	
Additional interventions	
Duct occlusion versus pancreatic anastomosis	
Autologous coverage	
Fibrin sealants	✓
Entero-enteric anastomosis	
Pylorus-preservation versus resection	
Pylorus-preserving versus classical Whipple procedure	✓
Antecolic versus retrocolic gastroenteric anastomosis	✓
Billroth II versus Roux-en-Y for enteric reconstruction	✓
Braun entero-enterostomy	✓
Other anastomotic techniques for gastro-/duodenojejunosomy	
Bile duct anastomosis	
Biliary drainage before partial pancreatoduodenectomy	
Techniques for biliodigestive anastomosis	
Drainage	
Intra-abdominal drainage versus no drainage	
Early versus late removal of intra-abdominal drainage	
Type of drainage	
Surgical aspects	
Extended versus standard lymphadenectomy	✓
Surgical approach to partial pancreatoduodenectomy	
Isolated Roux-en-Y pancreaticojejunostomy	✓
Energy device dissection	
Minimally invasive surgery	
Minimally invasive versus open	
Robotic versus laparoscopic partial	
Distal pancreatectomy	
Pancreatic remnant	
Stapler versus hand-sewn stump closure	
Reinforced staplers	
Anastomosis	✓
Autologous coverage	✓
Sealants	✓
Endoscopic intervention to prevent pancreatic fistula	
Drainage	
Intra-abdominal drainage versus no drainage	
Early versus late removal of intra-abdominal drainage	
Type of drainage	
Surgical aspects	
Spleen management	
Radical antegrade modular pancreatosplenectomy versus standard	
Celiac axis resection	
Energy device dissection	
Minimally invasive surgery	
Minimally invasive versus open	
Robotic versus laparoscopic	
Pancreatitis	
Acute	
Surgical management	
Chronic	
Duodenum-preserving pancreatic head resection versus partial pancreatoduodenectomy	✓
Time point of surgery	
Other surgical techniques	
Modifications of duodenum-preserving pancreatic head resections	
Endoscopic versus surgical management	

**Table II (continued)**

	Living meta-analysis
Palliative measures	
Palliative pancreatic surgery	✓
Trauma	
Pancreatic trauma	
Various perioperative interventions	
Prevention of surgical site infection	
Interventions to improve recovery	✓
Pain management	
Perfusion management	✓
Frozen section analysis	
Other interventions to improve outcome	
Pharmaceutical cotreatment	
Somatostatin analogues	✓
Corticosteroids	
Pancreatic enzyme replacement	
Erythromycin for gastric emptying	
Proton pump inhibitor	
Glucose control	
Nutrition	
Enriched versus standard diet	✓
Route of nutrition	✓
Pro/synbiotics	✓
Time point and duration of nutritional support	
Minimally invasive surgery	
3-D pancreatic surgery	
Other surgical aspects	
No-touch isolation technique	
Vascular resection	
Treatment of complications	
Resection versus nonsurgical management of pancreatic neuroendocrine tumors	
Volume-outcome relationship	
Multivisceral resection	
Parenchyma-sparing resection	
Total versus partial pancreatoduodenectomy	
Resection of duodenal carcinoma	

3-D, 3-dimensional; ISGPS, International Study Group of Pancreatic Surgery.

The ISGPS Evidence Map of Pancreatic Surgery offers the perfect springboard for such an approach. By its application, funding bodies may objectively assess which research projects would fill existing gaps of knowledge, thus enabling them to prioritize funding.

Second, the evidence map is a valuable resource for planning new clinical trials. Its structure enables researchers to easily view the current state of research and permits them the opportunity to identify specific areas that warrant meaningful research. Key data for estimated effect sizes can be taken directly from the living meta-analyses and can serve as the basis for sample size calculations. Moreover, references derived from high-quality research on the effectiveness and safety of different surgical procedures are needed during the writing stage. Thanks to the pooled outcomes estimates, hard comparators can be provided with a 99% CI as a benchmark. These, along with the living meta-analyses, enable the ISGPS Evidence Map of Pancreatic Surgery to serve as a comprehensive source of robust data when writing trial proposals or publications.

Additionally, this endeavor supports writing synoptic evidence, ie, reviews and evidence-based patient information. Scientists are provided with a quick overview of existing SRs, which can help them to focus on novel research questions and to prevent redundant publications. The map will also be an important comparative tool for future literature searches, data extraction, and critical appraisal. Again, the aspect of benchmarking is addressed and fulfilled here.

Furthermore, clinicians and patients alike can obtain a rapid overview of existing treatments and their comparative effectiveness. Unlike fixed guidelines, clinicians can interpret the literature

themselves, for individual patients and clinical situations, which again follows the evidence-based medicine approach. Finally, this project can inspire other researchers to create similar maps for their particular fields of research.

In conclusion, the ISGPS Evidence Map of Pancreatic Surgery, which is freely accessible via [www.evidencemap.surgery](http://www.evidencemap.surgery) and as a mobile phone app, provides a regularly updated overview of the available literature displayed in an intuitive fashion. Clinical decision-making and evidence-based patient information are supported by the primary data provided, as well as by living meta-analyses. Researchers can use the systematic literature search and processed data for their own projects, and funding bodies can base their research priorities on evidence gaps that the map uncovers.

### Funding/Support

This work was supported by the Heidelberg Foundation for Surgery (Heidelberger Stiftung Chirurgie, [www.stiftung-chirurgie.de](http://www.stiftung-chirurgie.de)), Heidelberg, Germany. The Heidelberg Foundation for Surgery is a nonprofit organization and is not involved in the planning or conducting of this study.

### Conflict of interest/Disclosure

None of the authors has a secondary interest (as defined by the International Committee of Medical Journal Editors guidelines) that might inappropriately influence their contribution to this work.

### Acknowledgments

The introduction and the methods section are based on a protocol,<sup>6</sup> which was published under a Creative Commons license (<http://creativecommons.org/licenses/by/4.0>). The presented study is part of the doctoral thesis of Ömer Meydan. This paper was edited for language by Elizabeth Corrao-Billeter.

### References

- Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387(10031):1957–1966.
- Schnelldorfer T, Ware AL, Sarr MG, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? *Ann Surg*. 2008;247:456–462.
- Sánchez-Velázquez P, Muller X, Malleo G, et al. Benchmarks in pancreatic surgery: A novel tool for unbiased outcome comparisons. *Ann Surg*. 2019;270:211–218.
- Hüttner FJ, Capdeville L, Pianka F, et al. Systematic review of the quantity and quality of randomized clinical trials in pancreatic surgery. *Br J Surg*. 2019;106:23–31.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341.
- Probst P, Hüttner FJ, Meydan Ö, et al. Evidence map of pancreatic surgery: protocol for a living systematic review and meta-analysis. *BMJ Open*. 2019;9:e032353.
- Goossen K, Tenckhoff S, Probst P, et al. Optimal literature search for systematic reviews in surgery. *Langenbecks Arch Surg*. 2018;403:119–129.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
- Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6*; 2019. <http://handbook.cochrane.org>. Accessed April 11, 2020.
- Bassi C, Marchegiani G, Dervenis C, et al, and the International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery*. 2017;161:584–591.
- Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142:761–768.
- Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): An International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. 2007;142:20–25.
- Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. 2011;149:680–688.
- Besselink MG, van Rijssen LB, Bassi C, et al, and the International Study Group on Pancreatic Surgery. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. *Surgery*. 2017;161:365–372.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
- Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258:1–7.
- Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial; 2019. <https://training.cochrane.org/handbook/current/chapter-08>. Accessed April 11, 2020.
- Probst P, Zschke S, Heger P, et al. Evidence-based recommendations for blinding in surgical trials. *Langenbecks Arch Surg*. 2019;404:273–284.
- Probst P, Knebel P, Grummich K, et al. Industry bias in randomized controlled trials in general and abdominal surgery: An empirical study. *Ann Surg*. 2016;264:87–92.
- R Development Core Team. *R: A language and environment for statistical computing*; 2008. <http://www.R-project.org>. Accessed on June 13, 2019.
- Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
- Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443–3457.
- Guyatt GH, Oxman AD, Vist GE, et al, and the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
- McMaster University. *GRADEpro guideline development tool*; 2015. <http://grade.pro.org/>. Accessed on June 13, 2019.
- Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Q*. 2016;94:485–514.
- Elliott JH, Synnot A, Turner T, et al. and the Living Systematic Review Network. Living systematic review: 1. Introduction—the why, what, when, and how. *J Clin Epidemiol*. 2017;91:23–30.
- Sutton AJ. Not enough I say! Expand the remit of living systematic reviews to inform future research. *J Clin Epidemiol*. 2017;91:54–55.
- Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The global evidence mapping initiative: scoping research in broad topic areas. *BMC Med Res Methodol*. 2011;11:92.
- Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Syst Rev*. 2016;5:28.