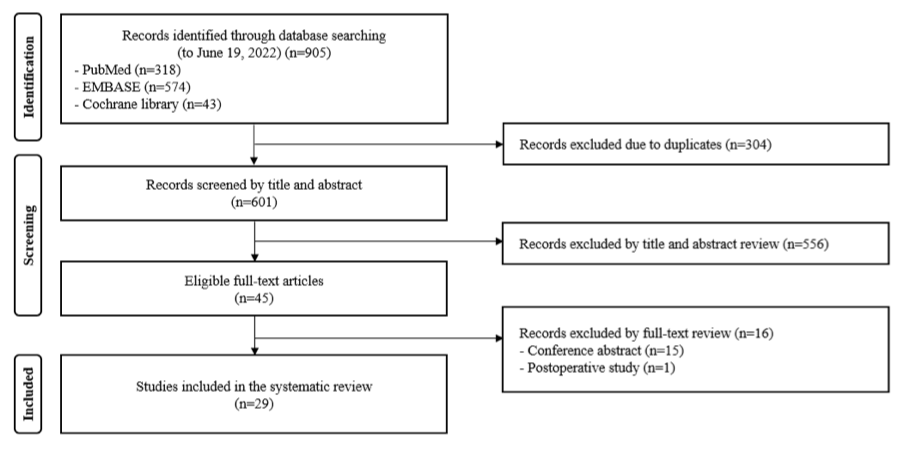


**Figure 1.** Conceptual diagram for the review of economic evaluation studies on the management of pancreatic cystic neoplasms. CEA, cost-effectiveness analysis; CBA, cost-benefit analysis; QALY, quality-adjusted life year.

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**Figure 2.** PRISMA chart of study selection

**A screenshot of a video game

Description automatically generated with medium confidence**

**Figure 3A.** Quality assessment according to CHEERS 2022 checklist. FR, fully reported; PR, partially reported; NR, not reported; NA, not applicable.

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**Figure 3B.** Scores according to CHEERS 2022 checklist

**Table 1.** Inclusion criteria and exclusion criteria

|  |  |
| --- | --- |
| Inclusion criteria | |
| Source of information | All published studies that are accessible publicly and/or can be retrieved through Seoul National University Library |
| Time frame | All studies till June 19th, 2022 |
| Language | All language |
| Study population | Adult population, focus on elderly as defined |
| Types of interventions | All types of interventions for screening and patient management (during the screening and follow-up periods) related to PCN |
| Types of economic evaluations | All economic evaluations  - Cost-effectiveness analysis  - Cost-benefit analysis  - Cost-minimization analysis  - Cost-utility analysis  - Model-based studies that do not include cost estimates |
| Types of outcomes considered | Unit costs of intervention, effectiveness measures, cost-effectiveness outcomes, cost-utility analysis outcomes |
| Types of studies | Model-based studies, cohort and observational studies |
| Types of articles | Original research, communication, research letter which are peer-reviewed, grey literature including pre-print text |
|  |  |
| Exclusion criteria | |
| 1. Clinical/cohort studies comparing only clinical benefits of different strategies with clinical/epidemiological outcomes without model-based approaches | |
| 2. Considering different types of surgery or therapy for the treatment of pancreatic cancer | |
| 3. Review articles, clinical guideline articles | |

**Table 2.** Main characteristics of studies included in the review

| **Study** | **Model type** | **Perspective** | **Country** | **Base year (currency)** | **Annual discount rate** | **Population** | **Strategy** | **Outcome** | **Main finding** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Economic evaluation studies** | | | | | | | | | |
| **Cost effectiveness analysis** | | | | | | | | | |
| Faccioli et al., 2022 | Decision tree | Society | Italy | 2006 (EUR) | NR | Hypothetical cohort: BD-IPMN patients, asymptomatic, without worrisome features and risks or malignant progression | CEUS, IAP 2017, Italian consensus guideline | Incremental cost per QALY gained | CEUS: dominant strategy |
| Schwartz et al., 2022 | Decision tree + Markov model | NR | US | 2020 (USD) | 3% | Hypothetical cohort: new-onset diabetes, age ≥50 years | 1 or 2 CT screening, no screening | Life year, QALY, ICER, direct cost | CT: cost-effective |
| Wang et al., 2021 | Markov model | Healthcare sector | US | 2020 (USD) | 3% | Hypothetical cohort: new-onset diabetes, ≥50 years old (modeled from 89,881 individuals in THIN cohort) | Single MRI/MRCP then EUS-FNA, no screening | Incremental cost per QALY gained | Risk-tailored PDAC early detection: cost-effectiveness with a minimum predicted 3-year PDAC risk of 1% to 2% |
| Kumar et al, 2021 | Decision tree | Third-party payer | US | 2018 (USD) | 3% | High-risk individuals (modeled from 8 previous studies and CAPS5 data) | No screening, single EUS at age of 55 years old | QALY, ICER | Index EUS is cost-effective when lifetime PDAC >10.8% or life expectancy after resection >16 years, and if missed, lesion rates≤5% |
| Lobo et al., 2020 | Markov model | NR | US | NR (USD) | NR | Hypothetical cohort: 55 years old | IAP 2017, AGA 2015 | Cancer death, surgical death, all-cause death, missed cancer, number of surgeries, cost, QALY | Overall mortality: similar between 2 guidelines More intensive surveillance strategy: fewer missed cancers, but more surgical deaths and higher cost |
| Kowada et al., 2020 | Decision tree + Markov model | Healthcare sector | Japan | 2018 (USD) | 3% | Hypothetical cohort: 50 years old, familial high-risk (3 PC patients in 1 or 2 relatives) | Abdominal US, MRI, EUS, CT, PET, no screening | Incremental cost per QALY gained | Abdominal US: most cost-effective |
| Sharib et al., 2020 | Markov model | NR | US | 2018 (USD) | 3% | Hypothetical cohort: 60 years old, asymptomatic, 2.5 cm solitary PCN | Do nothing, immediate surgery, surveillance (IAP 2017) | ICER, lifetime cost, QALY | Surveillance: not cost-effective and may increase mortality owing to overtreatment of low-grade cysts |
| Corral et al., 2019 | Markov model | Third-party payer | US | 2017 (USD) | 3% | Hypothetical cohort: 40 years old, asymptomatic, high-risk genetic mutation | No screening, EUS, MRI | Incremental cost per QALY gained | MRI: most cost-effective in moderate risk cases EUS: most cost-effective in high-risk cases |
| Aronsson et al., 2018 | Markov model | NR | Sweden | 2017 (EUR) | 3% | Hypothetical cohort: 65 years old, BD-IPMN, low risk (without worrisome and high-risk stigmata features) | Watchful waiting, initial surveillance (EUS then MRI), partial pancreatomy, total pancreatomy | Incremental cost per QALY gained | Initial surveillance (EUS then MRI): most cost-effective |
| Joergensen et al., 2016 | NA | NR | Denmark | 2015 (USD) | 4% | Hereditary pancreatitis patients and 1st degree relatives of familial PC patients | No screening, EUS + CA19-9 | Incremental cost per QALY gained | EUS + CA19-9: cost-effectiveness at WTP level of $50,000 per QALY |
| Das et al., 2015 | Decision tree + Markov model | Society | US | 2012 (USD) | 3% | Hypothetical cohort: asymptomatic, 3 cm solitary PCN, ASA score III | Wait-and-watch, resect if operable, EUS-FNA + CEA + cytology, EUS-FNA + CEA + cytology + IMP | ICER, net health benefit, relative risk, number needed to treat, cost | EUS-FNA + CEA + cytology + IMP: most cost-effective |
| Ghatnekar et al., 2013 | Probabilistic decision-analytic cohort model | Society | Sweden | 2011 (EUR) | NR | PC patients | Screening, wait-and-see | Cost, life-year gained, QALY, ICER | Results were sensitive according to the PC incidence |
| Huang et al., 2010 | Markov model | Society | US | 2008 (USD) | 3% | Hypothetical cohort: 60 years old, BD-IPMN in the head of pancreas | Surveillance, no surveillance, surgery | Incremental cost per QALY gained | Surveillance: 88% patient within budget at WTP level of $50,000 per QALY gained |
| Das et al., 2009 | Decision tree + Markov model | Third-party payer | US | 2007 (USD) | 3% | Hypothetical cohort: 65 years old, ASA score III, 3 cm, incidental cystic lesion in pancreas tail | Wait-and-watch, resect if operable, EUS-FNA + resect if operable | ICER, net health benefit, relative risk, number needed to treat, cost | EUS-FNA + resect if operable: most cost-effectiveness |
| Rubenstein et al., 2007 | Markov model | Third-party payer | US | 2005 (USD) | 3% | Hypothetical cohort: 45 years old male, 1st-degree relative of PC patients | Do nothing, resection (PTP), EUS, EUS-FNA | Life year, QALY, Incidence, Mortality, Cost, ICER | Do nothing: most effective |
| Rulyak et al., 2003 | Decision tree | Third-party payer | US | 2000 (USD) | 3% | Hypothetical cohort: 50 years old, high risk (familial pancreatic cancer kindreds) | EUS/ERCP, no screening | Cost, life-years, ICER | Screening with EUS/ERCP increase patient life expectancy |
| **Cost benefit analysis** | | | | | | | | | |
| Bicu et al., 2021 | Decision tree + Markov model | US healthcare system | Germany | NR (USD) | 3% | Hypothetical cohort: IPMN patients | CT/MRI, addition of 18F-FDG-PET/CT | Cost, QALY, malignancy | 18F-FDG-PET/CT: beneficial in health care system |
| **Cost minimization analysis** | | | | | | | | | |
| Morelli et al., 2019 | NA | NR | Italy | NR (EUR) | NR | Non-surgical PCN patients | US-restricted MRI, European evidenced-based MRI | Cost, PCN incidence | Abdominal US surveillance: delay and reduce numbers of second level examinations and thus reduce costs |
| Rosenkrantz et al., 2018 | NA | NR | US | 2018 (EUR) | 3% | Pancreatic cyst patients | Radiologists' recommendations, ACR recommendations | Cost | Costs between 2 strategies did not significantly differ |
| Bruenderman et al., 2015 | NA | NR | US | 2013 (USD) | NR | High-risk PC population | MRI, MRCP | Costs per year of life added | MRI/MRCP in high-risk population |
| Lim et al., 2005 | NA | NR | US | NR (USD) | NR | Patients operatively treated for presumed PCN | Management algorithm (CT, MRI, US, EUS, ERCP, FNA, cystic fluid analysis) | Cost, test accuracy (to differentiate benign from premalignant and malignant cysts) | Management algorithm based on presenting symptoms, radiographic findings, and cyst fluid CEA |
| **Non-economic evaluation studies** | | | | | | | | | |
| Han et al., 2021 | Markov-based nomogram | NA | Republic of Korea |  |  | IPMN patients | Surgery vs. surveillance | Life year, QALY | Surgery for high-risk of malignancy individuals |
| Koopmann et al., 2021 | Microsimulation model | NA | Netherlands |  |  | Hypothetical cohort: high-risk individuals | Screening, surveillance, resection (6 scenarios) | Life year gained, interval cancers, number needed to screen, number needed to surveillance, number needed to treat to prevent cancer death | Screening reduces PC mortality in all modeled scenarios. Natural disease course and PC risk determines the effectiveness of screening. |
| Peters et al., 2018 | Markov model | NA | US |  |  | Hypothetical cohort: pancreatic intraepithelial neoplasia | NA | Progression probabilities from PanIN to PDAC | PanIN 3 detection and treatment: provide a maximum, average life expectancy gain of 40 days |
| Hu et al., 2018 | Markov model | NA | US |  |  | Hypothetical cohort: 65 years old, incidental BD-IPMN with worrisome features | Early resection, long-term surveillance | discounted QALY | Early resection: yield higher QALY than surveillance |
| Cucchetti et al., 2016 | Markov model | NA | Italy |  |  | PC patients | 3 scenarios: reduction of 20%, 30%, 50% in stages III/IV | Life expectancy, proportion of surviving, number needed to screen | Screening high-risk individuals could be effective in the presence of a stage migration to stage I and/or in improving both surgical and non-surgical patients |
| Pandharipande et al., 2015 | Markov model | NA | US |  |  | Hypothetical cohort: 50 years old, risk-stratified | One-time MRI/MRCP screening | PDAC incidence, mortality, life year gained | Screening for entire population is not effective |
| Pandharipande et al., 2015 | Markov model | NA | US |  |  | Hypothetical cohort: 20 years old, BRCA2 mutation carriers | One-time screening at age 50, annual MRI screening at age 50 until age 80 | Life expectancy | Screening may be ineffective unless additional indicators of elevated risk (2 or more FDRs) are present |
| Weinberg et al., 2010 | Markov-based nomogram | NA | US |  |  | Hypothetical cohort: 65-85 years, asymptomatic pancreatic cysts (0.5-3 cm in head of pancreas | Pancreaticoduodenectomy, CT/MRI, EUS (+/- FNA), do nothing | Life year, QALY | Considering overall survival: surgery for lesions ≥2cm Considering quality-adjusted survival: surgery for lesions ≥3cm |

NA, not applicable; NR, not reported; US, United States; EUR, euro; USD, US dollar; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; THIN, The Health Improvement Network; CAPS, Cancer of the Pancreas Screening; PC, pancreatic cancer; PCN, pancreatic cystic neoplasm; ASA, American Society of Anesthesiologists; BRCA, breast cancer gene; CEUS, contrast-based endoscopic ultrasound; IAP, International Association of Pancreatology; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; AGA, American Gastroenterological Association; PET, positron emission tomography; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; IMP, integrated molecular pathology; PTP, prophylactic total pancreatectomy; ERCP, endoscopic retrograde cholangiopancreatography; 18F-FDG-PET, flourine-18 fluorodeoxyglucose positron emission tomography; ACR, American College of Radiology; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PanIN, intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; WTP, willingness to pay; FDR, first-degree relative.

**Table 3.** Incremental cost-effectiveness ratios management strategies comparing to no screening and surveillance in economic evaluation studies

| **Strategy** | | | **Comparator (No screening and surveillance)** | | | **ICER** | **Study** | **Subgroup** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cost** | **Effectiveness** |  | **Cost** | **Effectiveness** |
| **Guideline-based** | | | | | | | | |
| IAP 2017 | $ 244,800 | 10.86 QALYs |  | $ 126,776 | 10.17 QALYs | 171,143 $/QALY | Sharib et al., 2020 | - |
| Surveillance (IAP 2006 guideline) | $ 226,474 | 11.123 QALYs |  | $ 222,593 | 10.930 QALYs | 20,096 $/QALY | Huang et al., 2010 | - |
| **CT-based** | | | | | | | | |
| Risk-based screening (CT 1 or 2 times) | $ 248,148 | 1.0958 QALYs |  | $ 225,461 | 0.5465 QALYs | 41,302 $/QALY \* | Schwartz et al., 2022 |  |
| **MRI-based** | | | | | | | | |
| Single MRI/MRCP then EUS/FNA | $ 203,790.80~  203,894.66 | 9.9782~9.9788 QALYs |  | $ 203,786.52 | 9.9780 QALYs | 47,948.20~290,131.74 $/QALY | Wang et al., 2021 | 3-year PDAC risk of 0.5~3% |
| Annual MRI-based | $ 27,617~  66.639 | 20.0~21.5 QALYs |  | $ 54,741~  110,441 | 14.8~19.5 QALYs | Dominant  7,847 $/QALY | Corral et al., 2019 | High risk of PC (RR>20, RR=5-20) |
| MRI-based surveillance every 3 years | $ 17,162 | 21.5 QALYs |  | $ 54,741 | 19.5 QALYs | Dominant | Corral et al., 2019 | High risk of PC (RR=5-20) |
| MRI/MRCP every 6 months (and CA19-9 with abnormal findings) | $ 26,374.80 | x + 23.1~41.3 LYs |  | - | x | 638.62~1,141.77 $/LY | Bruenderman et al., 2015 | Familial/Hereditary disease† |
| MRI/MRCP every 6 months (and CA19-9 with abnormal findings) | $ 3,956.22 | x + 11.1 LYs |  | - | x | 356.42 $/LY | Bruenderman et al., 2015 | New-onset diabetes (aged ≥50 years) |
| **EUS-based** | | | | | | | | |
| Single EUS | $ 19,448 | 21.21 QALYs |  | $ 6,221 | 21.05 QALYs | 82,669 $/QALY | Kumar et al, 2021 | - |
| Annual EUS-based | $ 47,750~  64,875 | 20.6~21.2 QALYs |  | $ 54,741~  110,441 | 14.8~19.5 QALYs | Dominant  13,200 $/QALY | Corral et al., 2019 | High risk of PC (RR>20, RR=5-20) |
| EUS-based surveillance every 3 years | $ 25,099 | 21.4 QALYs |  | $ 54,741 | 19.5 QALYs | 84,020 $/QALY | Corral et al., 2019 | High risk of PC (RR=5-20) |
| 6-month EUS then annual MRI) | € 26,305 | 9.31 QALYs |  | € 12,624 | 8.88 QALYs | 31,682 €/QALY | Aronsson et al., 2018 |  |
| Annual EUS + CA19-9 | $ 265,797 | x + 5.3 QALYs |  | - | x | 50,329 $/ QALY | Joergensen et al., 2016 |  |
| Single EUS/FNA + cytology + CEA | $ 25,841 | 11.22 QALYs |  | $ 19,251 | 10.36 QALYs | 6,590 $/QALY | Das et al., 2015 |  |
| Single EUS/FNA + cytology + CEA + IMP | $19,373 | 12.33 QALYs |  | $ 19,251 | 10.36 QALYs | 62 $/QALY | Das et al., 2015 |  |
| EUS/FNA (on suspicious mass lesion only) | $ 42,521 | 17.94 QALYs |  | $ 2,983 | 18.57 QALYs | Dominated | Rubenstein et al., 2007 |  |
| Annual EUS | $ 186,089 | 14.54 QALYs |  | $ 2,983 | 18.57 QALYs | Dominated | Rubenstein et al., 2007 |  |
| Single EUS/ERCP | $ 26,237.35 | 17.58 LYs |  | $ 40,376.63 | 17.20 LYs | Dominant | Rulyak et al., 2003 |  |
| Screening | € 561 | 8.07 QALYs |  | € 114 | 8.04 QALYs | 13,466 €/QALY | Ghatnekar et al., 2013 |  |
| **Resection-based** | | | | | | | | |
| Immediate surgery | $ 283,231 | 11.24 QALYs |  | $ 126,776 | 10.17 QALYs | 146,903 $/QALY | Sharib et al., 2020 |  |
| Partial pancreatomy | € 47,635 | 9.00 QALYs |  | € 12,624 | 8.88 QALYs | 278,696 €/QALY | Aronsson et al., 2018 |  |
| Total pancreatomy | € 86,653 | 9.32 QALYs |  | € 12,624 | 8.88 QALYs | 167,731 €/QALY | Aronsson et al., 2018 |  |
| Resect if operable | $ 32,393 | 9.95 QALYs |  | $ 19,251 | 10.36 QALYs | Dominated | Das et al., 2015 |  |
| Surgery | $ 246,493 | 11.274 QALYs |  | $ 222,593 | 10.930 QALYs | 132,436 $/QALY | Huang et al., 2010 |  |
| Resection (PTP) | $ 199,911 | 14.28 QALYs |  | $ 2,983 | 18.57 QALYs | Dominated | Rubenstein et al., 2007 |  |

\* Incremental cost-effectiveness ratios were calculated based on cost and effectiveness of strategies in original studies.

† Peutz-Jeghers syndrome (aged ≥30 years), Hereditary pancreatitis (aged ≥45 years), Familial PC and p-16 Leiden carriers (aged ≥50 years)

Dominated: the strategy listed is less effective and more expensive than the compared strategy.

Dominant: the strategy listed is more effective and less expensive than the compared strategy.

IAP, International Association of Pancreatology; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; IMP, integrated molecular pathology; ERCP, endoscopic retrograde cholangiopancreatography; PTP, prophylactic total pancreatectomy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; LY, life year; PDAC, pancreatic ductal adenocarcinoma; RR, relative risk; PC, pancreatic cancer.