THE SURVIVAL BENEFIT AND COST-EFFECTIVENESS OF A PANCREATIC CANCER EARLY-DETECTION STRATEGY FOR A TARGETED POPULATION OF NEW-ONSET DIABETES PATIENTS

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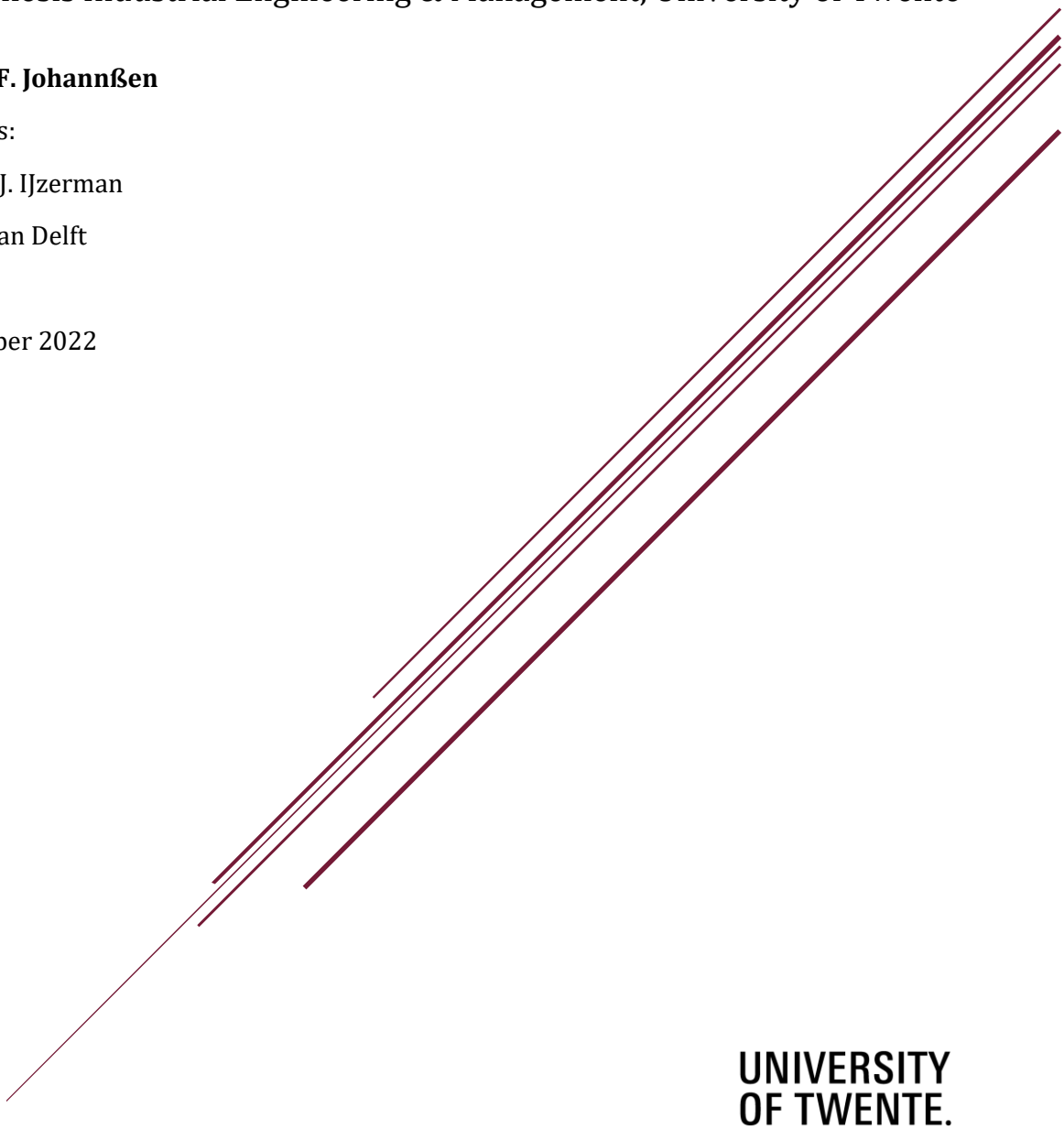

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Master thesis report

The survival benefit and cost-effectiveness of a pancreatic cancer early detection strategy for a targeted population of new-onset diabetes patients

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Abstract

Background Pancreatic cancer (PC) is the fourth deadliest cancer in the United States. However, because of its low incidence, screening for asymptomatic, early-stage PC in the general population is not recommended and surveillance is restricted to individuals with inherited risk factors. In recent years, a growing body of evidence suggests that also high-risk individuals (HRIs) among a new-onset diabetes (NOD) population should be tested for PC. This thesis evaluates a targeted early detection (TED) strategy where a population of NOD patients aged ≥50 years, enriched by the "Enriching New-Onset Diabetes for Pancreatic Cancer" (END-PAC) prediction model in combination with a biomarker panel of serum IL-1Ra and adiponectin levels, undergoes one-time diagnostic tests for PC. The research questions of this thesis are whether the TED strategy is cost-effective compared to the current standard of care (SoC) of no early testing and if it results in improved clinical benefits for PC patients in the NOD population.

Methods An integrated decision tree and Markov cohort model was built in RStudio based on U.S. clinical guidelines. A deterministic analysis (DA) with fixed parameters, probabilistic sensitivity analysis (PSA) with 5,000 simulation runs and scenario analyses were performed. Parameter estimates and distributions for demographics, transition probabilities, costs and health utilities were derived from online databases and published studies. Costs and clinical benefits, measured in terms of life-years (LYs) and quality-adjusted life years (QALYs) gained, are tracked over a lifetime horizon and discounted at 3% per year. Cost-effectiveness is measured in terms of the incremental cost-effectiveness ratio (ICER) and results are presented in 2022 U.S. dollars.

Results Across the entire NOD population, the TED strategy resulted in additional costs of $28,742 and $51,875 per LY and QALY gained, respectively in the DA. However, 0.004 LYs gained (1.5 days) and 0.002 QALYs gained (< 1 day) are a marginal difference, suggesting no clinically relevant benefit across the overall NOD population. The results are confirmed by the PSA, as the TED strategy was cost-effective compared to the SoC at a $100,000 WTP threshold in 99% of the simulation runs, but the clinical benefit never exceeded 0.0055 QALYs (2 days). The scenario analysis suggests LYs gained increasing linearly to the PC incidence in the initial model population as well as a disproportional decreasing (relative) decay of the ICER. However, with the TED strategy, the share of resectable PC cases increases by 11% resulting in clinically relevant 0.44 LYs gained (163 days) and 0.22 QALYs gained (80 days) among PC cases in the NOD population. Again, the results are confirmed by the PSA.

Discussion & Conclusion The main reason for marginal differences between the TED and SoC strategy across the NOD population was the small PC incidence in the initial model population. In addition, the relatively low sensitivity of the combined enrichment tests resulted in more than 50% of PC cases not being diagnosed early in the TED strategy. As a result, the two-tier enrichment of the NOD population does not indicate improved outcomes in comparison to a similar analysis where only the END-PAC model has been used. While the TED strategy is cost-effective compared to the current SoC at a $100,000 WTP threshold, the ICER is not a suitable measure given the low clinical benefit. While the TED strategy yielded clinically relevant benefits among PC patients, the impact on long-term survival (≥ 5 years) is small. Improved treatment options are required to allow more patients to undergo resection surgery and improve the survival outlook afterwards. Also, standardized model frameworks and international collaborations could make future research more meaningful and comparable.

Foreword

The completion of this master thesis report marks not only the finalization of my Industrial Engineering & Management degree at University of Twente, but also the end of my student days. Over the last seven years, I had the opportunity to study at three different universities, make important experiences and meet extraordinary people who impacted my journey and made me who I am today. A few of those people, I want to point out in particular.

My student journey started at Augsburg University. I am sincerely grateful for the friends I made there, especially everyone from the „Wingx Club“, who made me feel home in Augsburg right from the beginning and keep inspiring me with their achievements until today. Also, I want to thank Prof. Dr. Jens Brunner as well as my bachelor thesis supervisors Dr. Jan Schoenfelder and Dr. Sebastian Kohl. Working at the Chair for Health Care Operations/ Health Information Management and writing my thesis in the field has provided me with a clear direction for my further studies as well as a vision of the impact I want to make afterwards.

Further, I want to thank Stefan Seitz for seeing potential in me and enabling me for a first internship at EY, which would further bolster my confidence in my own skills and interest to work in an international environment.

My two years at the University of Twente have been an intensive experience and despite many restrictions due to COVID-19, I am leaving with great memories. I want to give special credits to „Arriba“, the UT‘s basketball association, for their great efforts to integrate new (international) students into Enschede‘s student life. A big part of my studies was this master thesis. I thank my supervisors Prof. Dr. Maarten IJzerman and Freek van Delft for their continuous guidance throughout the last year, while also keeping me challenged to improve my work. The result is a master thesis which not only allowed me to deep dive and get involved into current cancer research, but also enabled me to apply and improve many of the skills and knowledge I have learned during my studies.

I also want to thank Frank, Ernest, Matt and Marina for their individual support and contributions to my study success. Finally, I want to thank my parents for their unconditional love and support throughout my whole life.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	American Cancer Society
AD	age dependent
AJCC	American Joint Committee on Cancer
AMA	American Medical Association
ASCO	American Society of Clinical Oncology
AUC	area under the curve
BRCA2	Breast Cancer gene 2
BRPC	borderline resectable pancreatic cancer
CA	carbohydrate antigen
CAPS	International Cancer of the Pancreas Screening
cc	cubic centimeters
CDC	Centers for Disease Control and Prevention
CDF	cumulative density function
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A
CDLFS	Clinical Diagnostic Laboratory Fee Schedule
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curves
CET	cost-effectiveness threshold
cfDNA	cell-free DNA
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CP	chronic pancreatitis
CPT	Current Procedural Terminology
CT	computed tomography
DA	Deterministic analysis
DAM	decision analytical model
DES	discrete event simulation
DM	diabetes mellitus
DTMs	decision tree models
ECOG	Eastern Cooperative Oncology Group
EDI	Early Detection Initiative
END-PAC	Enriching New-Onset Diabetes for Pancreatic Cancer
EoL	end-of-life
EUS	endoscopic ultrasonography
EUS-FNA	endoscopic ultrasonography with fine-needle aspiration
FBG	fasting blood glucose
FDA	U.S. Food and Drug Administration
FN	false negative
FP	false positive
HbA1c	hemoglobin A1c

Abbreviation	Definition
HRIs	high-risk individuals
IA	immunoassay
IARC	International Agency for Research on Cancer
ICER	incremental cost-effectiveness ratio
IDF	International Diabetes Federation
IL-1Ra	interleukin-1 receptor antagonist
LAPC	locally advanced pancreatic cancer
LSDM	long-standing diabetes mellitus
LY	life years
MCMs	Markov cohort models
mOS	mean overall survival
MPC	metastatic pancreatic cancer
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	United Kingdom's National Health Service
NIH	National Institutes of Health
NOD	new-onset diabetes
NPF	The National Pancreas Foundation
NPV	negative predictive value
OS	overall survival
PALB2	Partner and localizer of BRCA2,
PC	pancreatic cancer
PD	pancreaticoduodenectomy
PDAC	pancreatic ductal adenocarcinoma
PET/CT	positron emission tomography
PFS	Physician Fee Schedule
PJS	Peutz-Jeghers syndrome
PPV	positive predictive value
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-years
QoL	quality of life
RBG	random blood glucose
RPC	resectable pancreatic cancer
RR	relative risk
SEER	Surveillance, Epidemiology, and End Results
SoC	standard-of-care
STK11	serine/threonine kinase 11
T2DM	type 2 diabetes mellitus
T3cDM	type 3c diabetes mellitus
TD	time dependent

Abbreviation	Definition
TED	targeted early detection
THIN	The Health Improvement Network
TN	true negative
TNM	tumor/node/metastases
tnormal	truncated normal distribution
TP	true positive
TSP-1	thrombospondin-1
WHO	World Health Organization

1. INTRODUCTION & BACKGROUND

Located in the posterior portion of the upper abdomen, behind the stomach and across the spine, the pancreas is a large gland with a weight of about 100g and a length of 14-25 cm (Beger et al., 2018, p. 52). It is surrounded by the liver, gallbladder, spleen, bile ducts and small intestine, which is wrapped along its wide end (Fig. 1-1) (NCCN, 2021b). The liver produces bile during the removal of waste from blood, a fluid that helps to digest food. The gallbladder stores the bile, before the common bile duct runs it into the main pancreatic duct. From there, bile and enzymes empty into the duodenum, the first part of the small intestine, which absorbs food nutrients. The two main functions of the pancreas are the production of insulin and glucagon to control the amount of blood sugar (glucose), as well as pancreatic enzymes that help to digest food in the small intestine.

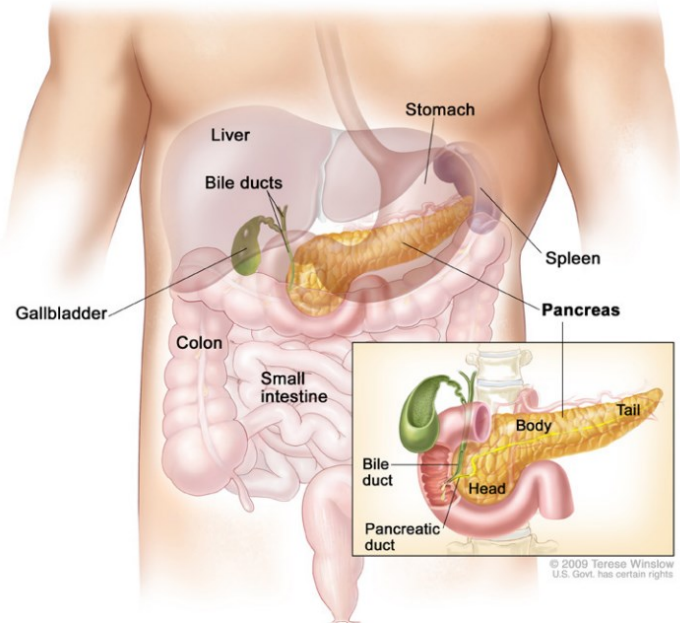

Fig. 1-1. Schematic depiction of the pancreas' location in the abdomen (NCCN, 2021b)

The various parts of the pancreas are referred to as head, body, and tail (Fig. 1-1). The head boarders the "C-shaped" portion of the duodenum in the right upper quadrant of the abdomen (Beger et al., 2018). The tail reaches into the hilum of the spleen in the left upper quadrant.

Common disorders of the pancreas include diabetes, pancreatitis, or pancreatic cancer (PC). The following sections present some background knowledge derived from literature. Section 1.1 explains characteristics of the disease. Section 1.2 presents the burden of PC in the United States. Section 1.3 presents the current guidelines for PC management. Finally, Section 1.4 elaborates on efforts towards an early stage pancreatic cancer diagnosis.

1.1. Characterization of pancreatic cancer

The next three subsections characterize PC. Section 1.1.1 describes the pathology of PC. Section 1.1.2 describes its different clinical stages. Section 1.1.3 describes the pre-diagnostic progression of the disease.

1.1.1. Pathology

Pancreatic cancer starts in exocrine or endocrine cells of the pancreas. While the endocrine cells produce hormones which are released into the bloodstream, exocrine cells secrete enzymes into the small intestine that help to digest food (NCCN, 2021b).

Around 95% of PCs start in the exocrine cells that line small tubes, called ducts, of the pancreas (Rawla et al., 2019). The predominant type is *pancreatic ductal adenocarcinoma* (PDAC) and accounts for 85-90% of all PCs alone. Other exocrine PCs include *squamous cell carcinoma*, formed purely by squamous cells, *adenosquamous carcinoma* with characteristics of both PDAC and squamous cell carcinoma, and *colloid carcinoma*, which originates in a benign cyst called intraductal papillary mucinous neoplasm. These variants have a different molecular signature and differ in terms of prognosis.

However, the clinical presentation of the different variants is indistinguishable and the treatment options for the rarer variants are poorly understood (Majumdar et al., 2019). Hence, standard treatment guidelines are only published for PDAC.

The rarer cancer originated in endocrine tissue of the pancreas is *pancreatic neuroendocrine tumor (PanNET)*, accounting for less than 5% of cases (Rawla et al., 2019). PanNETs are growing slower than PDACs and have higher 5- and 15-year overall survival (OS) rates. Also, their diagnosis and disease management differ from PDACs (Gao et al., 2020).

An estimated 60-70% of PCs originate in the head of the pancreas, 20-25% in the body and 10-20% in the tail (Gress et al., 2017).

Given the predominance of PDAC compared to other types, it is used interchangeably with “pancreatic cancer” (PC) in this report.

1.1.2. Clinical stages

Accurate PC staging is crucial for making treatment decisions, selecting patients for clinical trials, and determining prognosis (Kulkarni et al., 2020). The American Joint Committee on Cancer (AJCC) has developed the tumor/node/metastases (TNM) system for solid tumor staging. The group published its first edition of the Manual for Staging of Cancer in 1977, which gets updated every few years with updates and new schemes for additional cancer sites (NCI, 2022a).

The three categories, T, N and M, all together describe the tumor extend. “T” is defined by the “size and/or contiguous extension of the primary tumor”. “N” is defined by the absence or presence of regional lymph nodes. “M” is defined by the absence or presence of distant metastases (Gress et al., 2017). Criteria for the different categories are defined separately for cancers in “different anatomic locations and/or for different histologic types”. Combining the three categories’ factors results in a cancer stage. Patients within a stage group generally have similar outcomes, even though their burden of disease may vary. Stages are numerated by Roman numerals from I to IV and are associated with an increasing extend of disease and generally worsening prognosis. Stage I generally indicates smaller

cancers or those that are less invasive without regional disease or nodes. Stage II and III define cases with increasing tumor or nodal extent, and Stage IV those with metastases at diagnosis. In addition, Stage 0 denotes carcinoma in the original location ("in situ") with generally no potential of metastases. Depending on the cancer side, stages are further divided into subgroups indicated by capital letters, such as A and B, to provide more refined prognostic information. A tabular summary of the different category factors for PC is provided in the Appendix (Fig. A- 1), together with an overview of the prognostic groups depending on the three categories (Fig. A-2).

TMN staging, in parts, requires postsurgical pathologic evaluation of resected tumors. However, in clinical practice most PC patients do not receive surgery. Therefore, the TNM system is not used as much for PC as for other cancers. Instead, institutions use a classification system based mainly on results of presurgical imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) (NCCN, 2021b). This system classifies the tumor into one of four distinct categories, based on whether it can be resected by surgery and where it has spread (ASCO, 2021b). The distinct categories are presented in the following paragraphs.

Resectable pancreatic cancer (RPC)
The cancer can be removed by surgery, potentially after additional neoadjuvant treatment (ASCO, 2021b). It is crucial that the tumor has not grown into arteries or veins in the area, e.g. celiac axis, superior mesenteric artery, or common hepatic artery. Also, there must be no evidence of metastases, either in nearby lymph nodes or distant organs.

Borderline resectable pancreatic cancer (BRPC)
The cancer has spread to nearby blood vessels, however, might still be removable completely by surgery (ASCO, 2021b). The concept BRPC is relatively new, with its first definition published in 2009 after emerging data that vein resection with negative margins is associated with equivalent survival to pancreaticoduodenectomy (PD), also called Whipple procedure, a common resection surgery (Lopez et al., 2014).

Locally advanced cancer (LAPC)
LAPC is generally unresectable due to extensive vascular involvement and consequently high chances of positive margins, although the cancer is still nonmetastatic (van Veldhuisen et al., 2019). However, other types of surgery might still be performed to prevent or relieve associated symptoms or problems, instead of trying to cure the disease (ACS, 2017).

Metastatic cancer (MPC)
The cancer has spread beyond the area of the pancreas and to other organs, such as the liver, lungs, or distant parts of the abdomen (ASCO, 2021b). It is unresectable and any surgery performed only aims at relieving symptoms (ACS, 2017).

1.1.3. Pre-diagnostic progression

The progression of PC starts with the first evidence of detectable cancer, followed by an asymptomatic but potentially detectable phase (lead time), and ends at clinical cancer diagnosis (Kamisawa et al., 2016). In most cases PC becomes symptomatic, and therefore diagnosed, in the presence of advanced, unresectable disease.

Knowing the duration of the lead time allows to determine if early detection, when the cancer is still asymptomatic, is even feasible. In an approach to answer this question, scientists collected tissue samples during rapid autopsies of seven patients who recently died from MPC (Yachida et al., 2010).

Sequencing the genomes of metastases' cell DNA, the scientists found that similar mutations were present in both the primary tumor site as well as the areas of metastasis. Also, they found that these mutations were present in the primary tumor site years before metastases became clinically evident. Using mathematic modelling, the scientists conservatively estimated an average of 11.7 years before cancer cells develop into a high-grade lesion, followed by another 6.8 years of cancer growth until the first cell has metastatic potential. The findings are supported by a retrospective review of pre-diagnostic CT scans suggesting that the transition from resectable to unresectable disease occurs only over a period of approximately 6 months before diagnosis (Chari, 2007). Together, these outcomes suggest that there is a broad time window for early-stage PC detection, as cancer cell growth is slow in the first years and metastases only occur comparatively shortly before symptomatic diagnosis.

On the other hand, according to study findings by Yu et al. (2015), patients with advanced T3 or T4 tumors were on average only 13-14 months older at the time of diagnosis than patients with T1 tumors. This finding indicates that while the pre-diagnostic phase is long in theory, a problem in practice could be that once PC becomes detectable by current diagnostic tests, its growth and progression to more advanced stage disease is rapid.

1.2. Pancreatic cancer statistics in the United States

The National Cancer Institute (NCI), a part of the U.S. Department of Health and Human Services, estimates a total of 60,430 new PC cases in the United States for 2021, accounting for 3.2% of all new cancer cases (NCI, 2022b). At the same time, the number of PC deaths is estimated at 48,220, accounting for 7.9% of all cancer deaths in the country. Hence, while PC is relatively rare, with only the eleventh highest incidence across cancer types, it is the fourth-deadliest type. In addition, both, the (age-adjusted) incidence and mortality rates were still increasing with rates of 0.4% and 0.2% per year, respectively, in between 2009 and 2019. As a result of the persistent trend, PC is expected to be the second or third deadliest cancer type by 2030 (Lambert et al., 2019).

The 5-year survival strongly depends on the cancer stage at diagnosis. Based on data from the Surveillance, Epidemiology, and End Results (SEER) database between 2011 and 2017, the NCI reports a 5-year relative survival rate of 42% among individuals with a localized tumor (RPCs) (NCI, 2022b). Among patients with regional cancer (BRPCs and LAPCs), the 5-year relative survival rate reduces to 14% and becomes as small as 3% across patients with a distant, metastasized, disease (MPC). At the same time, only 11% of cancers were diagnosed at a localized stage, 30% at a regional stage and 52% at a distant stage. In the remaining 7% of cases the cancer stage was unknown. Overall, this results in an average 5-year relative survival rate of only 11.5%.

Further, according to SEER data from 2014 to 2018, PC is slightly more common in men than women, with incidences of 0.015% and 0.012%, respectively. Across both sexes the (age-adjusted) incidence was 0.013%. In comparison, the incidence was 0.041% (3-fold higher) for lung and bronchus cancer and 0.128% (10-fold higher) for female breast cancer in the same period. Also, the cancer incidence is higher in older adults. Ninety percent of patients are 55 years or older at diagnosis, with a median age of 70 years. Given the low 5-year survival rate after diagnosis, the death rates are similar to the incidence rates. Based on SEER data from 2015 to 2019, 0.011% U.S.-Americans die from PC every year, with a median age of 72 years.

1.3. Guidelines for pancreatic cancer diagnosis and management

This section presents the current guidelines for PC diagnosis as well as disease management and follow-up by the National Comprehensive Cancer Network (NCCN). The NCCN is a "not-for-profit alliance of 31 leading cancer centers devoted to patient care, research, and education" (NCCN, 2022a). The NCCN updates its guidelines at least annually, based on reviews of clinical cancer experts, a literature review by the staff and external submission requests (NCCN, 2022b). Proposed updates are discussed during panel meetings, whose members include representatives of the member institutions, a patient advocate, and a primary care physician. In the subsequent subsections, guidelines are divided into diagnosis (Subsection 1.3.1) and disease management (Subsection 1.3.2)

1.3.1. Diagnosis

Diagnostic tests for PC are performed if patients present disease-specific symptoms, such as weight loss, jaundice, floating stools, pain, dyspepsia, nausea vomiting or pancreatitis (NCCN, 2021a). Besides confirming the disease, especially the distinction between resectable and unresectable disease is essential at diagnosis, to identify eligible patients for resection surgery with a curative intend.

The only established tumor biomarker for PC is carbohydrate antigen (CA) 19-9, which, however, has a poor positive predictive value (PPV) of around 72% and 0.9% in symptomatic and asymptomatic patients, respectively. Biomarker development for PC is particularly difficult, as tumors are highly heterogeneous, both within and between individuals (Pereira et al., 2020). Therefore, imaging is the primary mean for diagnosis and staging. The most common techniques are endoscopic ultrasonography (EUS), CT and MRI (Kanji & Gallinger, 2013). The techniques are briefly presented in the subsequent paragraphs, followed by the NCCN guidelines for PC diagnosis.

Endoscopic ultrasonography (EUS)
An ultrasound uses sound waves to create a picture of the internal organs. For an EUS, a gastroenterologist passes a thin light tube through the patient's mouth and stomach and down into the small intestine from where pictures of the pancreas are taken (ASCO, 2021a). The patient is usually under sedation during the procedure. EUS is considered the most sensitive method for detecting neoplasia, abnormal cell growth, in the pancreas (Canto et al., 2012). The technique can be used in combination with fine-needle aspiration (EUS-FNA), a biopsy to obtain a tissue sample and confirm diagnosis. However, EUS results highly depend on operator skills and the modality is not available in all facilities (Singhi et al., 2019).

Computed tomography (CT)
A CT scan takes pictures of the inside of the body, using X-rays taken from different angles. A computer combines these pictures into a detailed multi-dimensional typically 3-dimensional or more) scan image that shows any abnormalities or tumors (ASCO, 2021a). Typically, patients receive a special dye, called contrast medium, to provide better detail on the image, either intravenous or as a pill or liquid to swallow. It can be combined with positron emission tomography (PET/CT), allowing for monitoring metabolic response, making it optimal in evaluation of different kinds of treatment and in detecting suspected recurrence (Wang et al., 2014).

Magnetic resonance imaging (MRI)
An MRI uses magnetic fields to produce detailed images of the body (ASCO, 2021a). Similar to the CT technique, patients take in a contrast medium to obtain a clearer picture. Pancreas protocol MRI with contrast has the advantage that, unlike CT, it does not depend on ionizing radiation for image

acquisition and also provides a better soft-tissue resolution (Singhi et al., 2019). However, it is less standardized than CT and not as widely available. Also, costs are higher compared to CT and patients might experience claustrophobia inside the machine.

NCCN recommendations

The diagnostic process should start with a CT scan of the abdomen, chest, and pelvis, further referred to as pancreas protocol CT (NCCN, 2021a). In addition, other imaging modalities such as EUS and MRI are appropriate under certain clinical conditions. The role of EUS in staging is complementary to pancreas protocol CT, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes. Imaging should be followed by liver function tests and baseline CA19-9 level measurement. While its PPV is low for diagnosing PC, increased CA19-9 levels can differentiate PC from other inflammatory conditions of the pancreas. If the diagnosis is confirmed, additionally Germline testing should be performed. Based on the findings, a multidisciplinary panel with experts on among others, surgery, diagnostic imaging, and interventional endoscopy, should stage the cancer to one of the four clinical stages presented in Section 1.1.2.

1.3.2. Disease management

The following paragraphs provide an overview about current treatment and potential follow-up care per diagnosed cancer stage, based on the 2021 NCCN guidelines (NCCN, 2021a).

Metastatic pancreatic cancer

The primary goals of treating MPC are palliation and lengthened survival. Survival benefits are usually limited to patients with a good performance status (PS), grade 0 or 1, based on the Eastern Cooperative Oncology Group (ECOG) classification (Fig. A-3), good biliary drainage, and adequate nutritional intake. These patients are recommended to receive systemic therapy, e.g., in form of combination therapy with 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) or gemcitabine mono- or combination therapy. Patients with poor PS generally receive palliative and best supportive care and only in some cases single-agent chemo- or radiotherapy. For patients who respond well to initial therapy, a chemotherapy holiday is appropriate, or a maintenance therapy during the treatment-free interval prior to disease progression. Recommended forms of maintenance therapy include continuation of systemic therapy, dropping the most toxic agents, or administering different agents. After progression, second-line treatment with a wide range of chemotherapy options is possible, if patients maintain a good PS.

Locally advanced pancreatic cancer

As for metastatic disease, the aim of treating LAPC are palliation and lengthened survival, and options include systemic therapy or best supportive care and single-agent chemotherapy or palliative RT depending on PS. In case of a “significant response” to chemotherapy and/or radiation, surgical resection can be considered. Though cases are rare, these patients have similar survival rates than patients initially diagnosed with RPC.

Resectable and borderline resectable pancreatic cancer

PC tumor resection requires surgery aiming at removing the primary tumor as well as regional lymph nodes. However, while this is the only form of potentially curative treatment, surgery is only curative in less than 20% of cases. On a positive note, the mortality across different surgery procedures is below 5% in experienced centers, according to recent studies, which is acceptably low. Experienced

centers perform at least 15 resection surgeries per year. Patients eligible for surgery should have ruled out peritoneal liver and distant lymph node metastases as well as distant disease.

PC tumor resection requires surgery aiming at removing the primary tumor as well as regional lymph nodes. Patients with cancers of the pancreas' head and uncinate usually undergo a PD, removing the head of the pancreas. For patients with cancers of the pancreas' body and tail, a distal pancreatectomy with splenectomy is preferred, where the surgeon removes the pancreas tail, body and spleen. If the cancer is present at multiple sides within the pancreas, a total pancreatectomy is required, where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen and nearby lymph nodes.

The different types of surgery show the same efficacy, with similar mortalities, hospital stay duration and rates of reoperation. However, a total pancreatectomy lowers the long-term perceived QoL due to insufficient pancreatic endocrine and exocrine function making it a rare choice for resection surgeries (Yang et al., 2019).

The curative intend of surgery is determined by the probability of obtaining negative (R0) resection margins. A borderline resectable lesion is characterized by a higher chance of incomplete (R1) resection. Patients with BRPC are not good candidates for resection surgery, however, potentially eligible after neoadjuvant therapy with the aim to downsize the tumor to a size where a R0 resection is more likely. Practices vary about chemotherapy and chemoradiation for therapy. Other factors in consideration when deciding whether a patient should undergo surgery are comorbidities, PS, and frailty, which should be discussed during a multidisciplinary review.

CT and MRI have been shown to underestimate pancreatic tumor size by 4.3 and 5.8 mm, respectively, compared to the final surgical pathology. Therefore, tumors that have been staged to be RPC or BRPC might turn out to be unresectable during surgery (Olecki et al., 2021). In that case, the panel recommends biopsy to confirm the cancer, if not previously performed.

Even after R0 resections, however, PC recures in approximately 80% of cases. Also, approximately 70% of recurrent cancers are in a locally advanced or metastatic stage, but even if in a local stage the survival outlook is poor (Moletta et al., 2019). Therefore, to reduce the likelihood of recurrence, adjuvant therapy is recommended following resection. However, there is no established definite standard therapy at this time since multiple studies came to different conclusions regarding preferred treatment. Options include chemotherapy alone with gemcitabine, 5-FU/leucovorin, gemcitabine/capecitabine, or continuous infusion 5-FU. In case of disease recurrence after resection, clinical trials are the preferred treatment option. In case of a poor PS, patients only receive palliative and best supportive care. If the PS is good, recurrence therapy should be considered, however, without any curative intend. Recurrence therapy can include another surgical resection in case of a local (pancreas-only) recurrence, chemoradiation in patients with local disease recurrence in the pancreatic bed or systemic chemotherapy.

1.4. Efforts towards early-stage pancreatic cancer diagnosis

In this section current screening and surveillance guidelines for early PC detection are introduced. Subsection 1.4.1 defines and distinguishes the two terms. Subsection 1.4.2 reports on current guidelines. Subsection 1.4.3 lists additional considerations for designing early detection strategies. Finally, Subsection 1.4.4 provides an outline for the remainder of this thesis.

1.4.1. Screening vs. surveillance

Diagnosing PC at a local and potentially resectable stage requires examining asymptomatic individuals. Two relevant concepts in this regard are *screening* and *surveillance*. According to the definition by Steele (2018), screening can be defined as the process of actively approaching large numbers of asymptomatic individuals, most of whom without the disease at question, and either perform direct diagnostic tests or identify HRIs who then are recommended to undergo diagnostic interventions. Surveillance describes testing individuals who are already known to have a (very) high-risk condition. Hence, unlike screening, surveillance does not involve pro-actively identifying HRIs from within an average risk population. However, tests for screening and surveillance can be identical. If test results during screening or surveillance indicate a possible illness, diagnostic tests are performed to obtain a definite diagnosis. In the case of cancer care this includes staging the disease. For the remainder of this thesis, thus, the term "testing" is used rather than "screening" or "surveillance" if an intervention is suitable for both concepts.

1.4.2. Recommendations for surveillance of high-risk individuals

Approximately 90% of PC cases are sporadic, meaning they do not occur in patients with familial conditions or premalignant pancreatic cysts (Chari et al., 2015). However, due to its relatively low incidence and the absence of biomarkers, screening potentially results in high potential of false-positive (FP) test results. Therefore, screening the average risk population for sporadic PC is not recommended (Poruk et al., 2013).

Five U.S. academic medical centers with pancreatic tumor registries and multidisciplinary PC screening programs formed the American Cancer of the Pancreas Screening (CAPS) Consortium providing PC screening and surveillance guidelines (Canto et al., 2012). The CAPS consortium defines HRIs as those who have a five-fold increased relative risk (RR) of PC compared to the general population or an at least 5% lifetime risk (Goggins et al., 2020). This HRI definition includes persons with at least one first-degree and one second-degree relative who developed pancreatic cancer, who have a lifetime risk of about 8%. Also, individuals with germline mutations in cancer susceptibility genes, such as CDKN2A or STK11 (Peutz-Jegher syndrome) are HRIs. Carriers of mutations in ATM, BRCA2 and PALB2 are HRIs if they have at least one blood relative with PC, as well as hereditary pancreatitis patients.

The CAPS Consortium recommends that HRIs undergo regular surveillance starting at age 50 or when they are 10 years younger than their youngest relative at PC-onset (Goggins et al., 2020). A baseline (initial) PC test should include EUS and MRI due to their high sensitivity for the detection of small, sub-centimeter cysts and lower risk profile, since patients are not exposed to radiation unlike in a CT scan. In addition, fasting blood glucose and/or HbA1c levels should be measured. If the initial screening test detects concerning abnormalities, an EUS-FNA and or CT scan should be performed. If the abnormality is confirmed and malignancy suspected, an individual decision must be made, ideally by a multidisciplinary team, about whether to resect the lesion surgically. The decision should consider the gene mutation status, family history, operative risk, comorbidities, life expectancy and compliance with surveillance of the patient. If no concerning abnormalities are found at the baseline screening, follow-up testing should be performed every 12 months. If concerning abnormalities were detected but malignancy is not suspicioned after confirmatory testing, follow-up testing should be performed every 3 or 6 months, if a solid or cystic lesion was found, respectively. MRI and EUS should be alternated as follow-up tests, with no consensus about if and how to alternate. A decision flow-chart for the management of pancreatic abnormalities found during surveillance is added to the

Appendix (Fig. A-4). The CAPS consortium also recommends "additional investigation" if new-onset diabetes (NOD) is diagnosed in HRIs (Goggins et al., 2020). The relationship between diabetes mellitus (DM) and PC is the central element of this thesis' research question which will be developed in Chapter 2.

1.4.3. Considerations for early cancer detection strategies

This subsection describes three different possible downsides of early cancer detection strategies, that must be considered when forming a decision about implementing interventions.

Lead-time bias

Lead-time bias occurs when screening or surveillance detects a cancer earlier than a "regular" symptomatic diagnosis, but the earlier diagnosis does not change the course of the disease (NCI, 2018). As a result, patients undergoing screening, for example, have a higher expected survival time because they are diagnosed earlier, but eventually still die at the same age or even earlier compared to when not receiving screening.

Overdiagnosis

According to Brodersen et al. (2018), overdiagnosis can be divided into two major causes: overdetection and overdefinition of disease. Overdetection means that early-detection strategies are more likely to pick up slower growing, less aggressive cancers. These cancers might never cause harm in a patient's lifetime, thus would not require treatment. In the case of PC, it is a problem that other pancreatic lesions with variable malignant potential, such as mucinous pancreatic cysts are commonly discovered during screening protocols. These cysts can cause a pancreatectomy, surgery to remove all or parts of the pancreas, due to fear that they progress into cancer. (Srivastava et al., 2019) Overdefinition describes lowering the threshold for a risk factor without evidence of clinical benefit for the patients. In the context of PC this could for mean lowering the RR for defining HRIs who should undergo regular surveillance. Overdiagnosis is also different from overtreatment, which describes ineffective treatment for a correctly diagnosed disease. Therefore, overdiagnosis often causes overtreatment, though not always.

False positives (FPs)

FPs are abnormal results that turn out not to be diseases after further investigation. This is different from overdiagnosis, where patients meet the current criteria for pathological disease (Brodersen et al., 2018).

FPs are common in cancer screening tests, where even tests with a high sensitivity wrongly diagnose a high number of people in larger asymptomatic populations. While patients receive unnecessary follow-up tests or even treatment, a major concern is the psychological distress of dealing with the FP diagnosis.

1.4.4. Outline of the report

Chapter 2 (Research problem) will introduce NOD as a potential early indicator for sporadic PC and suggest a new targeted early detection strategy based on a literature study. Further, a model framework will be introduced to compare the new strategy to the standard of care (SoC). Eventually, the exact research problem is defined. Chapter 3 (Materials & Methods) describes the model design, utilized data sources and performed analyses. Chapter 4 (Results) presents the results of the analyses for the research questions. Chapter 5 (Discussion) reflects on the findings, compares them to findings

from other authors, describes study limitations and provides recommendations for future research. Finally, Chapter 6 (Conclusion) states the main findings and recommendation

2. RESEARCH PROBLEM

In this chapter the research problem for this thesis is developed, based on the background information introduced in Chapter 1. Section 2.1 explains the relationship between PC and NOD. Section 2.2 presents a targeted early detection (TED) strategy among NOD patients based on a review of current literature. Section 2.3 introduces economic evaluation as a technique to compare the TED strategy to the current SoC. Section 2.4 states the final study intentions. Finally, Section 2.5 summarizes and concludes Chapter 1 and Chapter 2.

2.1. New-onset diabetes as an early indicator of pancreatic cancer

Already today, DM is one of the most prevalent diseases worldwide, with an ever-increasing incidence. It was the ninth leading cause of death worldwide in 2019 and is a major cause for even more severe diseases such as blindness, kidney failure and heart attacks (Loke, 2021). As of 2019, the year for which the most recent estimates are available, 37.3 million US-Americans or 11.3% of the population had diagnosed DM (CDC, 2022). Its incidence was around 1.4 million new cases (0.59%). Like in the case of PC, the risk of diabetes onset is higher in older adults. While the estimated incidence is 0.32% in the age group of 18 to 44-year-old's, it is 1.01% for 45 to 64-year-olds and 0.58% across individuals of age 65 or older (CDC, 2022) .

The most common aetiological types of DM are type 1 (T1DM) and type 2 (T2DM). T1DM indicates processes of pancreatic islet beta-cell destruction, an autoimmune reaction, leaving individuals with no residual insulin production. The more common T2DM is characterized by disorders of insulin action and secretion, inhibiting its efficient use in the body (Alberti & Zimmet, 1998). Among US adults, with diagnosed DM, T1DM and T2DM account for 5.6% and 91.2% of cases respectively (CDC, 2022).

While French clinicians discovered the association between DM and PC already in the 19th century (Green et al., 1958), the multidirectional relationship between both diseases is still subject to ongoing research (Sah et al., 2013). Long-standing DM (LSDM) likely poses a risk for PC, due to the chronic exposure to hyperglycemia (elaborated blood sugar levels), higher insulin concentration and insulin resistance (Dankner et al., 2018). However, the strength of this association is moderate. On the other hand, there are other less common types of DM next to T1DM and T2DM, including diabetes secondary to pancreatic disease. This type of DM is sometimes referred to as T3cDM. While the most common cause of T3cDM is pancreatitis, it can also be caused by PC (Hart et al., 2021). Therefore, also NOD can be an early sign of PC (Dankner et al., 2018). Due to its rarity, T3cDM is often misdiagnosed as T2DM (Oldfield et al., 2022).

Dankner et al. (2018) observed a 15- and 14-fold greater risk for detecting PC during the first year after diagnosing DM in adult women and men, respectively, which dropped during the second year to 5.4-fold and 3.5-fold, respectively, and stabilized around 3-fold for the rest of the 11-year follow-up period, compared to a nondiabetic population in an Israeli population-based sample including 2,186,196 adult woman and men. The extraordinary increased probability of PC detection within three years after NOD diagnosis has also been reported by Chari et al. (2005) in a population-based study including 2,152 NOD patients of age 50 years or older, with a reported three-year PC incidence of 0.85% which translates into a 6-8-fold increased RR compared to the general population. The

findings were similar in a subsequent confirmatory study in the same setting, with 0.90% of NOD patients developing PC within 3 years of DM onset (Sharma, Kandlakunta, et al., 2018).

While the prevalence of DM in PC ranges from 4-20% in studies relying on medical records, it ranges from 45-65% in studies where fasting blood glucose (FBG) levels were screened via oral glucose tolerance testing (Singhi et al., 2019). These findings are supported by a multi-state registry study including 512 newly diagnosed PC cases (Pannala et al., 2008). Applying American Diabetes Association criteria, 47% of the participants had DM (FBG ≥126 mg/dl), 38% impaired fasting glucose (FBG between 100–125 mg/dl) and only 14% normal fasting glucose (FBG ≤99 mg/dl). Additional studies support the hypothesis that DM is a manifestation of PC, since PC-caused insulin resistance and beta cell dysfunction resolved with tumor resection (Singhi et al., 2019). Interestingly, in these studies, also FBG levels decreased despite removal of a third of the pancreas.

However, while DM is common across PC patients, a PC prevalence of less than 1% among NOD patients is still not high enough to make early-detection strategies in this risk-stratified population cost-effective (Chari et al., 2005; Hart et al., 2011; Mizuno et al., 2013). Thus, further enriching the population of NOD patients is required to increase the cancer risk in the tested population. In risk-stratified testing individualized risk assessment may inform testing intensity/interval, starting age, imaging modality used, or even decisions not to perform tests (Clift et al., 2022). As risk-stratification can be relevant for screening tests as well as diagnostic tests, its combination with either of the two is referred to as an "targeted early detection" (TED) strategy for the remainder of this thesis.

Regarding the time course of hyperglycemia in pre-diagnostic PC, Sharma, Smyrk, et al. (2018) suggest that relative hyperglycemia (mean FBG in PC cases higher than mean FBG in nondiabetic, age- and sex-matched controls) significantly occurred 36 to 30 months prior to PC diagnosis, rapidly increases with decreasing lead time, and crosses the DM threshold 12 to 6 months prior to diagnosis (Fig. 2-1). Also, the study shows that FBG levels start rising when tumors are 1-2 cc in size and cross the DM threshold at around 12cc, when there is still a good chance that the tumor is resectable (Singhi et al., 2019).

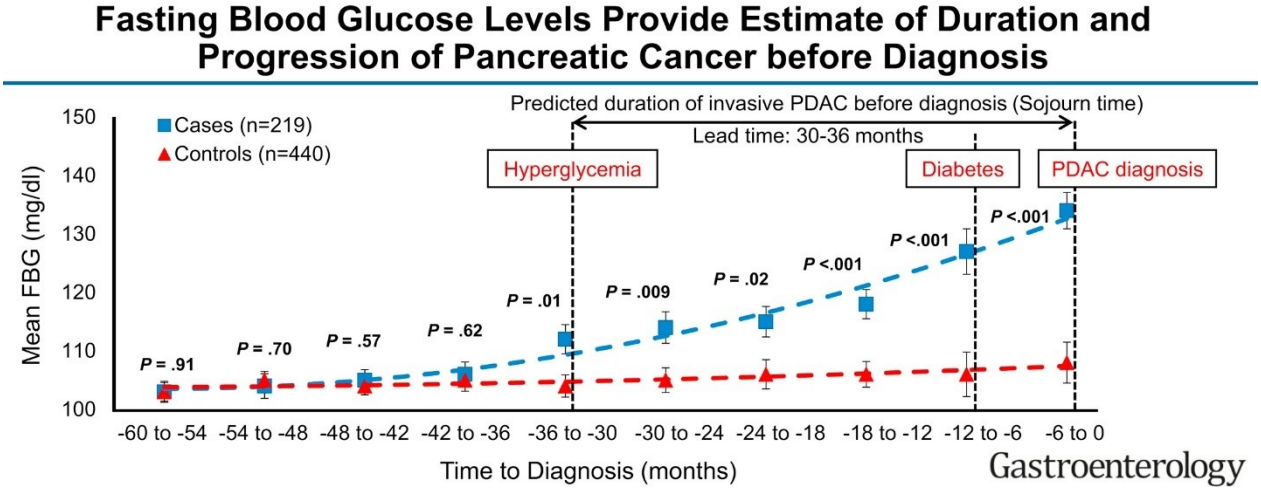

Fig. 2-1. Fasting blood glucose levels prior to the diagnosis of PC (cases) compared to an age- and gender-matched control group (controls) (Sharma, Smyrk, et al., 2018)

In conclusion, there is compelling evidence, that DM is an additional risk-factor for PC, and NOD a possible indicator of early-stage, asymptomatic PC at the same time. However, while DM is common

in PC patients, the incidence of DM is still so much higher that it would not be beneficial to screen all NOD patients for PC. Therefore, further enrichment of the NOD population by additional PC risk-factors is required to make TED strategies considerable.

2.2. Targeting a high-risk new-onset diabetes population for pancreatic cancer testing

While the findings of increased PC incidence among NOD patients within the first 3 years after diagnosis presented in Section 2.1 are yet to be validated in larger studies and other settings, even if confirmed, the reported incidences will likely not be high enough to classify all NOD patients as HRIs and start PC surveillance as described in Section 1.4.2.

A method to improve the benefit-harm balance of early cancer detection is risk stratification. Identifying HRIs within a chosen population for targeted testing rather than performing such an intervention across the entire population can reduce the number of false positive results and overdiagnosis (Knoppers et al., 2021).

The following Subsection 2.2.1 first presents possibilities of enriching the NOD population for PC testing found in literature. Then, Subsection 2.2.2 describes a developed early-detection strategy which will be further analyzed in this thesis.

2.2.1. Literature review about enriching the new-onset diabetes population for pancreatic cancer testing

For enriching the NOD population for PC testing, clinical risk prediction models or biomarkers are suitable (Singhi et al., 2019). The following paragraphs presents existing models and biomarker tests for that purpose.

Clinical prediction models

Clinical prediction models are an "explicit, empirical approach to estimate probabilities of disease or an outcome of disease" (Steyerberg, 2019). They combine multiple characteristics (e.g., related to the patient, disease, or treatment) to predict a diagnostic or prognostic outcome. Typically, a limited number of 2 to 20 predictors is considered. By separating those at low versus those at high risk, prediction models support targeting treatment at high-risk patients. Therefore, prediction models are a direct tool for personalized medicine, a form of medicine that seeks to improve stratification and timing of health care.

As of today, two prediction models for identifying NOD patients with a high-risk of PC have been published. The Health Improvement Network (THIN) database UK model included 109,385 physician-diagnosed NOD patients and the final model includes demographic, behavioral, and clinical variables (Singhi et al., 2019). In its initial study, the model identified a population with a 5% risk of PC diagnosis within 3-years among NOD patients with 11% sensitivity and 99.7% specificity (AUC 0.82) (Gallo et al., 2021). However, the overall 3-year PC incidence of 0.4% across the enriched population is significantly lower than in studies using glycemic-defined NOD, despite a 4-fold enrichment, and too low to warrant further study (Sharma, Kandlakunta, et al., 2018).

Another clinical model is the "Enriching New-Onset Diabetes for Pancreatic Cancer" (END-PAC) model (Sharma, Kandlakunta, et al., 2018). The model only includes 3 factorized parameters: age, change in blood glucose, and weight loss. As already described in Section 1.2, age is a strong factor for an individual's PC risk, as 90% of patients are 55 years or older at the time of diagnosis. Also, as

reported in Section 2.1, according to recent study findings, T3cDM patients have a significant reduction in body weight after diagnosis, as well as higher reaching FBG levels compared to T2DM patients. Unlike in the THIN model, the END-PAC model utilizes the glycemic definition of NOD (FBG ≥ 126 mg/dL, HbA1c ≥ 6.5% or RBG ≥ 200 mg/dL). Patients are considered to have NOD if they have at least two measured diabetic parameters, had at least one non-diabetic parameter three to eighteen months prior to diabetes diagnosis and do not have any anti-diabetic medication history. Patients are divided into three risk groups based on the resulting sum-score: low (score ≤ 0), intermediate (score 1-2), and high (score ≥ 3). The model is solely meant for enriching the NOD population. Patients above a designated cutoff score still need confirmation testing with imaging protocols to be diagnosed with PC. A listing of the categories and associated scores is provided in the Appendix ().

The initial validation study of the END-PAC model included 1096 NOD patients. Its sensitivity was 78%, the specificity 85%, the PPV 3.6% and the negative predictive value (NPV) 48% for a cutoff score of ≥ 3. A high END-PAC score in patients who did not have PC (FPs) was explained for by recent steroid use or different malignancy. An END-PAC score ≤ 0 (in 49% of cases) meant that patients had an extremely low risk for being diagnosed with PC in the subsequent 3 years (<0.1%). 75% of patients in the discovery cohort who were diagnosed with PC at least 6 months after diabetes onset were classified as high-risk by the model.

In a subsequent larger study, including 13,947 NOD patients, the END-PAC model has been evaluated in a racially and ethnically more diverse setting (Chen et al., 2021). In this setting, the PPV (of developing PC within the next 3 years) and sensitivity were 2.0% and 63%, which is lower than in the initial study (3.6% and 78%). Further, the authors conclude that glycemic parameters prior to diabetes onset are often not available in clinical practice and thus suggest a model with relaxed glycemic criteria, based solely on a single HbA1c test.

In another subsequent retrospective case-control study by Khan et al. (2021), the END-PAC model has been validated utilizing the less restrictive definition of diabetes suggested by Chen et al. (2021). The study included patients from TrinetX, a global health research network that links healthcare organizations. Out of 1,288,858 patients in the database who had an HbA1c > 6.5% preceded by an HbA1c ≤ 6.5%, 107,305 met the glycemic diabetes criteria described above and 6,302 had all elements needed to compute a complete END-PAC score, as well as at least 4 years of annual outpatient clinic appointments after diabetes diagnosis. It is important to highlight that the study also confirmed that HbA1c values are more widely available than FBG levels. There were 8,245,405 total HbA1C values in this dataset compared to only 493,482 FBG values. In this study, the PPV for a cutoff-score of ≥ 3 was 1.9%, similar to the result by Chen et al. (2021). However, the optimal cutoff-score, calculated by its Youden index, was ≥ 2, resulting in a PPV of 1.7%, a sensitivity of 56% and a specificity of 75%. However, in this case, 25% of the analyzed NOD population would require follow-up imaging, which is still disproportionate given the low incidence of PC compared to NOD. A solution could be to reduce the burden of FP results and further enrich this cohort by subsequential secondary serological testing with a biomarker.

Biomarker tests

The U.S. Food and Drug Administration (FDA) defines a biomarker as a "defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" (FDA, 2021). Examples of biomarkers include everything from pulse and blood pressure through basic chemistries to more complex laboratory tests of blood and other tissues (Strimbu & Tavel, 2010). In the context of cancer risk

stratification, breast cancer genes 1 and 2 (BRCA1/2) are an example of an approved susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer (FDA, 2016).

In terms of enriching the NOD population, while there are no biomarkers for early PC detection available, a suitable biomarker needs to be able to at least distinguish T2DM from T3cDM. While there is no such biomarker identified yet, there are several lines of evidence suggesting that T3cDM is caused not so much by local effects of tumor infiltration, as by remote effects impairing glucose metabolism. Therefore many groups are actively investigating the possibility of identifying a unique serologic marker of T3cDM (Chari, 2007).

In a cohort study, the protein thrombospondin-1 (TSP-1) distinguished T3cDM from long-term T2DM, but not from NOD (Jenkinson et al., 2016). Other immune signatures including GM-CSF, IL-31, RANTES, resistin, FasL, and ICAM1 were shown to separate subjects with T3cDM from T2DM with high accuracy (AUC 0.96). However, the studies included patients with LSDM as well as NOD and the sample size was statistically small. Recently, a proteomic analysis of DM patients identified a panel of 11 proteins, which, in combination with CA19-9, resulted in an AUC of 0.85 (Hart et al., 2021). The two serum proteins galectin-3 and S100AP were identified as potential mediators as well, although their diagnostic performance equals separating patients by their weight change (loss vs. gain).

In another cohort study, levels of circulating adiponectin, a protein hormone, were elevated in T3cDM patients compared to those with NOD ($p < 0.005$) (Oldfield et al., 2022). In the same study, interleukin-1 receptor antagonist (IL-1Ra), another protein, was found to be elevated in T3cDM patients ($p < 0.0001$). Interestingly, two independent subsets of pre-diagnostic study samples, also showed that IL-1Ra levels were significantly upregulated up to 12 months prior to PC diagnosis ($p = 0.03$ and 0.02) which would make it a potential marker for early-detection. Combining both markers for distinguishing T3cDM from NOD in a panel test yielded an AUC of 0.91 with an optimal sensitivity and specificity of 83.7% and 100.0%, respectively. The diagnostic accuracy is based on predicted probabilities from a multivariable logistic regression analysis. The model coefficients and corresponding formula to derive the probability of T3cDM from the panel is presented in the Appendix (Formula C-1).

2.2.2. Targeted early detection strategy

Based on the literature review presented in the previous section, a targeted early detection (TED) strategy has been developed for PC testing in a subset of the NOD population utilizing the "Define, Enrich, Find" paradigm introduced by Singhi et al. (2019). First, the NOD population with a higher-than-average PC risk is clearly defined. Second, the steps for enriching the NOD population further to identify a subset of HRIs are described. Finally, the proposed modalities to find PC in the asymptomatic HRIs are explained.

The TED is presented in Figure Fig. 2-2 and compared to the current SoC, which is *no* surveillance of NOD patients without additional inherited risk factors. Accordingly, patients in the SoC are either diagnosed with PC at symptom onset or never develop PC.

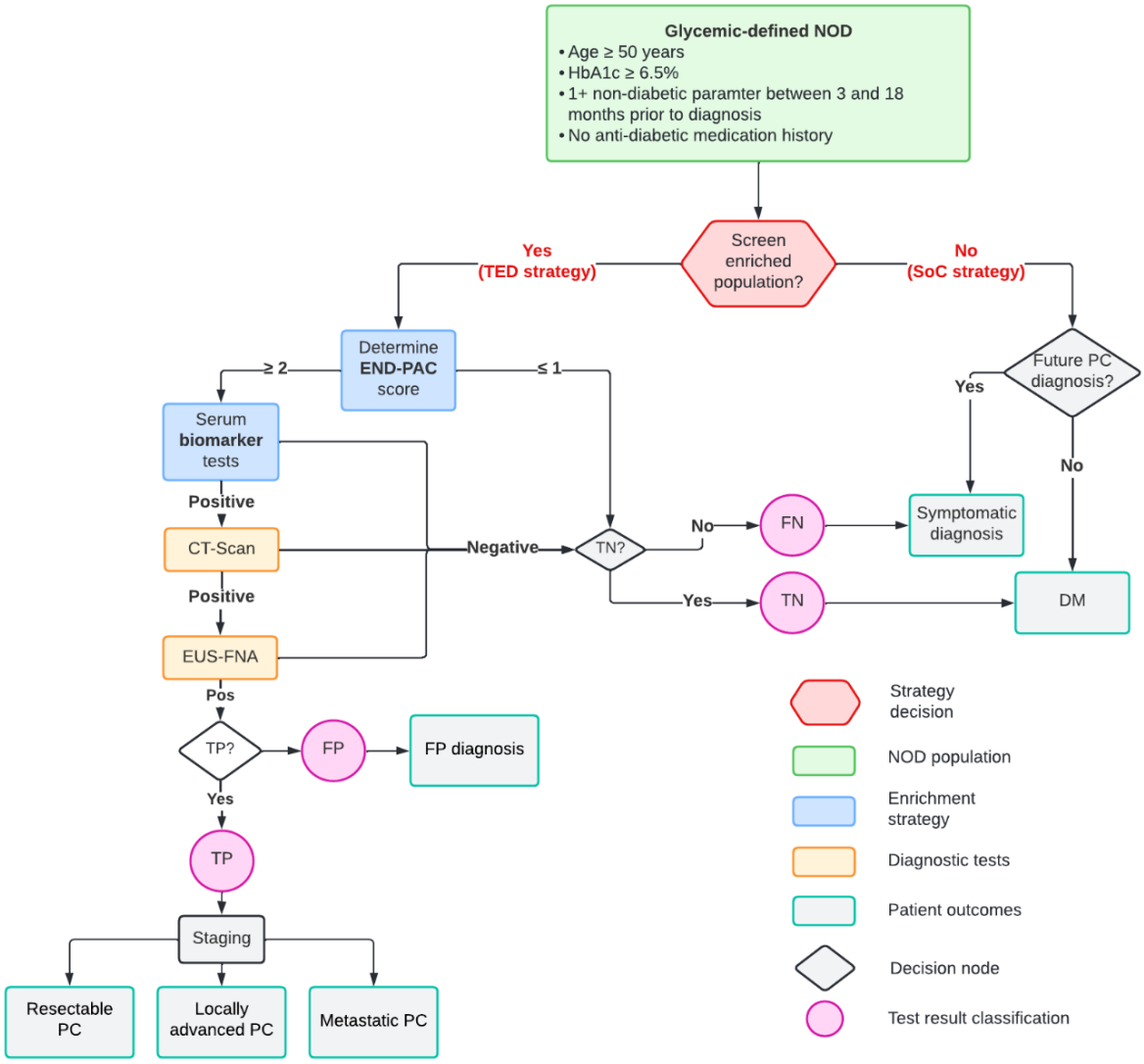

Fig. 2-2. Flow-chart representing the current SoC and proposed TED strategy as well as possible patient outcomes

Step 1: Definition of the new-onset diabetes population

The initial higher-than-average NOD population is defined by criteria of the most recent END-PAC model validation study by Khan et al. (2021) presented in the following subsection. All individuals who meet *all of* the following criteria are included:

- An HbA1c > 6.5% was preceded by at least one HbA1c < 6.5% in the past 6-24 months. The date the HbA1c > 6.5% was obtained was defined as the index date.
- No HbA1c > 6.5% before the index date.
- No exposure to anti-diabetic medications occurred up until three months before the index date.
- No history of pancreatic cancer before the index date.
- Age ≥ 50 years at the index date.

Step 2: Enrichment of new-onset diabetes population for high-risk individuals
While there are promising clinical prediction models and biomarkers for enriching the NOD population for PC early-detection testing, the high incidence of DM compared to the low incidence of PC and the resulting high number of FPs from any individual tests is a major drawback. To reduce this problem, the use of filters using increasingly invasive (and costly) interventions has been advocated (P. A. Hart et al., 2021) and is also applied here.

NOD patients are first divided into a high and low risk population by applying the END-PAC model presented in the previous subsection with a cut-off score of ≥ 2, meaning that patients with a score greater equal 2 are considered being of higher-risk of PC. The decision for the cut-off value is based on findings in the most recent model validation study by Khan et al. (2021). As a second filter, the subset of patients with predicted high PC risk undergoes a liquid biopsy to obtain serum levels of the proteins IL-1Ra and adiponectin. Individuals who again have a predicted high-risk of PC from the combined analyses of the two biomarker levels are considered to be HRIs who should be tested further.

Step 3: Testing for pancreatic cancer in asymptomatic high-risk individuals
The combination of the two enrichment interventions has a high combined sensitivity and specificity. Therefore, the assumption is made that it can replace the suggested baseline MRI and EUS imaging tests suggested by the CAPS Consortium for the surveillance of HRIs (Section 1.4.2). Instead, the HRIs directly undergo diagnostic testing based on the NCCN guidelines (Section 1.3.1). Patients first receive a pancreas protocol CT. If abnormalities are found, a subsequent EUS-FNA is performed to confirm the diagnosis and correctly stage the disease to one of the clinical stages listed in Section 1.1.2.

The tests are only performed once, in contrast to the CAPS Consortiums' recommendations for HRI surveillance. This decision is based on the key difference in between testing HRIs among a NOD population and the surveillance of patients with inherited risk factors, as in the first case the diabetes is assumed to be a *consequence* of asymptomatic, but detectable PC. At the same time, most T3cDM cases in the SoC are diagnosed with PC within one year after diabetes onset, making early-stage PC detection during longer surveillance unlikely.

2.3. Economic evaluation of targeted early pancreatic cancer detection

The FDA is regarded as a kind of "gatekeeper" for the evaluation of new health interventions in the United States, as its approval e.g., of a new test ensures safety and efficacy which then translates into effectiveness (Ransohoff, 2021). The term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made based on clinical efficacy and other data (FDA, 1998). In order for the FDA to approve an intervention, it generally needs to show a *clinical benefit.* "Clinical benefit is a favorable effect on a meaningful aspect of how a patient feels (e.g. symptom relief), functions (e.g., improved mobility) or survives as a result of treatment" (Lee, 2015). Therefore, a clinical benefit can only be achieved if a treatment is effective in changing a certain health outcome.

However, also the *economic evaluation* of a test becomes increasingly important, especially in cancer care, which accounts for approximately 5% of health care spending in the United States, a share which is expected to further increase. Therefore, the ASCO recommends the economic evaluation of new interventions, to ensure that all Americans have access to high-quality, cost-effective care (Meropol et al., 2009).

Briggs (2011, p. 2) defines economic evaluation in health care as the comparison of alternative options in terms of their costs and consequences. Options include interventions, such as an early cancer detection strategy. Costs include all tangible resources, e.g., clinical and other staff, capital equipment, buildings and drugs, but also non-health service resources such as time of patients and their families. Consequences represent all effects of the options other than those on resources. Generally, they focus on changes in individual's health, but can also include other effects, such as information provision and reassurance. Economic evaluations are strictly comparative.

The following subsections define cost-effectiveness analysis (Subsection 2.3.1) and decision analysis (Subsection 2.3.2) in the context of economic evaluation and describe how they can be applied to compare the proposed TED strategy to the current SoC. Further, Subsection 2.3.3 describes model type selection for economic evaluation with decision analytical modelling.

2.3.1. Cost-effectiveness analysis in economic evaluation

Cost-effectiveness analysis (CEA) is the most common form of economic evaluation in the fields of medicine and public health (Tengs, 2004). According to Tengs (2004), in a CEA, incremental cost and effectiveness of an intervention are calculated relative to a comparator resulting in a ratio. The numerator of the ratio is generally direct costs, often from the societal perspective. Most frequently, the denominator (effectiveness) are life-years (LYs) saved or quality-adjusted life-years (QALYs). LYs are saved when an intervention reduces the risk of premature death, e.g., absolutely increases the live time of a patient. QALYs, on the other hand, are the equivalent of one life year in full health, combining health status and survival in one index. Therefore, patients' health is divided into multiple states. Health states might be acute health problems such as pneumonia or injury, chronic diseases such as AIDS or depression, or side effects such as pain or nausea. Analysts specify numerical utilities for each health state, often between 0 (e.g., death) and 1 (e.g., perfect health). The utilities are then multiplied by the time an individual spends in the respective health state. Utilities are assessed with techniques such as the rating scale, time tradeoff, standard gamble or using health status instruments such as the Health Utilities Index, Quality of Well Being Scale, or EQ-5D. In some cases, the analysis is referred to as "cost-utility analysis", instead of CEA, if effectiveness is measured in QALYs. The "U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine" recommends the use of QALYs over LYs as the preferred measure of effectiveness, as they capture morbidity as well as mortality. This allows for factoring in for example a gradual health decline as the disease progresses or side effects of treatment. On the other hand, there are no established standards of how to measure utility, and values can vary a lot even in analyses of the same disease.

Standard cost-effectiveness decision rules involve relating differences in costs between options under comparison to differences in benefits (Briggs, 2011, pp. 3-4). A simplified decision rule is the incremental cost-effectiveness ratio (ICER), which is the additional costs per extra unit of effect (e.g. QALY) from the more effective treatment. The ICER can be compared to other interventions or a cost effectiveness threshold (CET). The CET is defined as the maximum cost per health outcome that a health system is willing to pay (Grosse, 2008). One concept to justify the CET, is the willingness-to-pay (WTP) of an individual. This is the amount an individual is willing to spend for a certain health gain in terms of quality and lengths of life (McDougall et al., 2020). It is commonly obtained from interviews where participants are in hypothetical scenario of demanding a good or service and is used to construct the value of a QALY (Martín-Fernández et al., 2014). The standard WTP threshold for cancer care in the Unites States is $100,000 (Hunt et al., 2009).

There are several requirements for any economic evaluation seeking to inform decision makers (Briggs, 2011, pp. 6-8). First, all relevant evidence must be considered. Second, an economic evaluation should compare all options which are feasible in practice. Third, the time horizon is required to be long enough to reflect on all key differences between options in terms of costs and effects. Finally, an economic evaluation must show how uncertainty in the available evidence translate into decision uncertainty.

An economic evaluation in form of a CEA is an appropriate method to compare the TED strategy for PC proposed in Section 2.2.2 to the current SoC to form a decision if the former positively impacts patients' LYs and QALYs at acceptable costs. However, a remaining challenge are the requirements for a CEA, especially the uncertainty of evidence.

2.3.2. Decision analysis in economic evaluation

Decision analysis is a systematic approach to decision making under uncertainty (Briggs, 2011, p. 6). Therefore, it is an analytic tool that works complementary to a CEA. A decision analytical model (DAM) uses mathematical relationships to define a series of possible consequences from different model inputs. Each consequence has an assigned probability, cost, and effect. Therefore, it allows for modelling the expected costs and effects, variability and uncertainty associated with decisions.

The use of DAMs for decision making in health care is growing, as it helps to fulfill the requirements listed in the previous subsection (Briggs, 2011, p. 7). It allows to set up a decision analytical framework synthesizing evidence from multiple different sources and compare options over an appropriate time horizon.

Next to DAMs, also trial-based economic evaluations are common. In this case, a clinical trial provides the sole evidence on resource use and health effects for the evaluation (Briggs, 2011, pp. 8-9). While randomized controlled trials are an important way to obtain *some* evidence, they often fall short to meet all the requirements for a CEA. For example, the follow-up time of trials is often not long enough to compare all consequences, such as potential mortality effects. Also trials often fail to include all relevant evidence and compare all options.

For the CEA of the TED strategy in comparison to the SoC, a DAM is the best choice, as setting up an appropriate clinical trial would have limitations. As PC is a very rare disease, its prevalence is usually small even in larger study populations. Likewise, the heterogeneity of the disease leads to different outcomes in different settings. Therefore, it would be hard to justify a single trial as sole evidence. Also, if LYs-saved are the outcome of interest, the follow-up time of a trial will most likely not be sufficient to analyze the full life-expectancy.

2.3.3. Model type selection for economic evaluations with decision analytical modelling

The following paragraphs present possible model types for a DAM and existing CEAs with DAMs in the context of early PC detection.

Model type comparisons

The most common DAM types in economic evaluations are *discrete event simulations* (DES), *Markov cohort models* (MCMs) and *decision tree models (DTMs)* (Brennan et al., 2006).

DTMs outline decisions, the probability or fraction of various outcomes and the valuation of each outcome (e.g., QALYs, cost or net benefits) (Brennan et al., 2006). The decision's mean value is

computed through "rollback" by summing the probability of each outcome with its value. While this makes decision tree models a good choice for untimed models, the technique gets more complicated if a recursive process is considered over a longer time horizon, as the nodes and branches of the tree increase exponentially (Sun & Faunce, 2008).

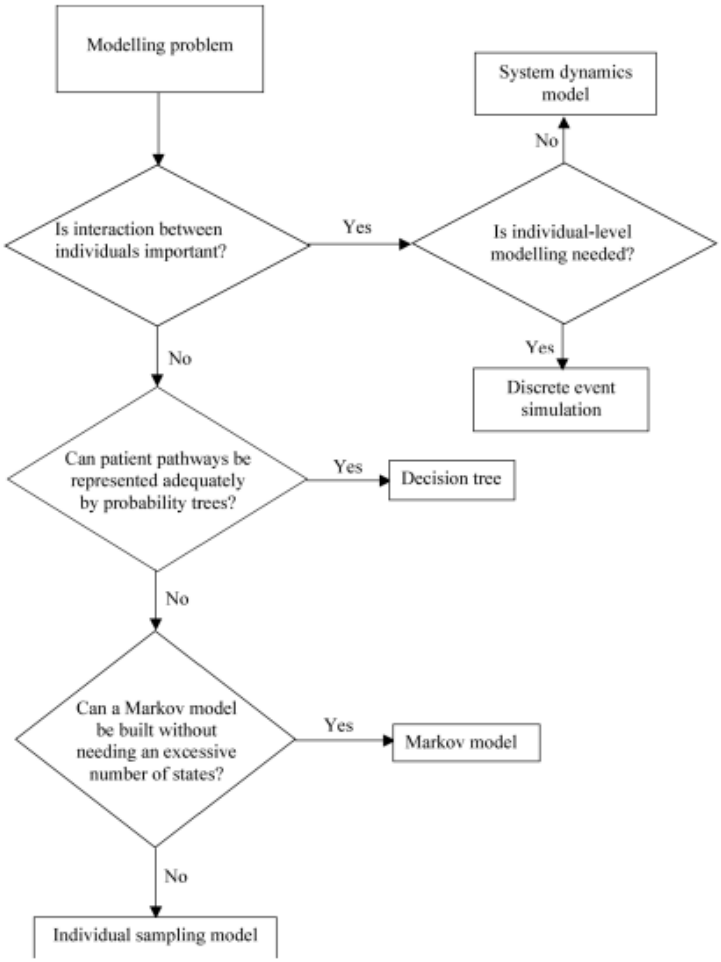

Fig. 2-3 Flowchart for selecting an appropriate model type (Barton, 2004)

If only a repeated set of outcomes is possible, a MCM is a good alternative to a DTM (Brennan et al., 2006). In an MCM, the disease of interest is "divided into discrete states of progression". After a pre-defined time-interval ("cycle time"), individuals transfer between states based on predefined probabilities. These states have attached (incremental) health utilities and costs that are accumulated during the model's time horizon. Ultimately, the model needs an "absorbing state" that individuals cannot leave (e.g. death) (Sun & Faunce, 2008). The underlying principle of a MCM is the Markov property which states that the "upon knowing the value of the process at the *m*th step, its values after the *m*th step do not depend on its values before the *m*th step" (Grimmett, 2001, p. 73). The state transitions, which are called a Markov process, are *time-homogenous* if the transition probabilities do not change over time, and *time-inhomogeneous* otherwise.

A DES tracks patients individually in the model, making it possible to take a patient's history into account, such as the time since a past event (Briggs, 2011, p. 59). A DES can be similar to a MCM with a discrete number of states, time periods and transition probabilities, just that the DES is structured around how long an individual remains in a state rather than the transition probability to another state. However, DES can require more data, e.g. about patient characteristics if their history is used to model future prognosis.

In a case study, comparing the performance of a MCM to a DES for modelling two possible treatments of breast cancer patients, Karnon (2003) found similar results across both model types. However, the author concluded that a slight benefit of DES with regards to model flexibility in adapting to different forms of input data does not make up for its more time-consuming developing and evaluating process. The author finds that the increased flexibility of DES is only useful when applied to a large proportion of the model. However, in another comparison by Simpson et al. (2009) between a MCM and a DES to model outcomes in HIV, the DES model achieved a slightly predictive advantage for clinical outcomes, provided more outcome details and had a better long-term (5-year) predictive validity. The authors conclude that the DES is superior, because of its higher face validity due to its natural modelling of disease progression and easier possibilities to perform a sensitivity analysis. Also, they found that the DES model is better in "isolating long-term implications of small but important differences in crucial input data".

Barton (2004) developed a framework for selecting an appropriate model type, which received much attention in literature (Fig. 2-3). A key decision in their framework is the question, whether individuals in the model must be regarded independently. The authors also emphasize to keep the model as simple as possible, making it easy to understand and validate. However, simpler models not always require less data, as in this case often (weighted) averages of multiple possible conditions must be considered to keep the model accurate.

Modelling approaches for early PC detection strategies

There are numerous examples of economic evaluations with DAM for early PC testing strategies in literature.

Kumar et al. (2021) computed the cost-effectiveness of EUS as a screening test for the surveillances of HRIs compared to no screening with a DTM. The model divides patients by their screening test results and whether they will ever develop PC. Therefore, it covers a lifetime horizon, while not modelling time-progression explicitly.

Corral et al. (2019) developed a MCM as well to assess the cost-effectiveness of two surveillance strategies for HRIs involving EUS and MRI, respectively, to no screening among HRIs. True positive PC cases are divided into states of local, regional or metastatic disease and costs and utilities are modelled until death. However, in this study, HRIs are defined by the CAPS Consortium's recommendations, not including NOD patients.

Ghatnekar et al. (2013) developed a framework to identify and analyze under which conditions a PC early detection strategy including an unspecified biomarker would be cost effective compared to no testing. They designed a MCM to estimate the difference in cost and QALYs for a hypothetical model population. Individuals with a TP diagnosis enter a PC care module with the health states "Resectable", "Locally Advanced" or "Metastatic". Patients either stay in their respective health state or move to the absorbing "Death" state in annual cycles. Likewise, patients who are not tested, as well as FN cases remain in a "wait-and-see" state before they are diagnosed with one of the PC stages or

die from another cause. The author's calculations showed that the cost-effectiveness depended on the PC incidence within the population and that certain risk groups, such as NOD patients could be screened at acceptable costs.

Wang et al. (2021) constructed a combined DTM and MCM to assess the CEA of a "risk-tailored early detection strategy targeting high-risk NOD patients". Their proposed early-detection strategy is similar to the TED strategy presented in Section 2.2.2. In a DTM, a NOD population including individuals of age 50 or older is first enriched by the THIN prediction model. The high-risk group receives diagnostic testing with abdominal MRI. Individuals with positive findings further underwent EUS-FNA. Afterwards, individuals entered a MCM with the four states "DM", "PC", "Missed PC" and "Death, a 3-month cycle length and a lifetime horizon. Their conclusions are that testing HRIs among a NOD population with a minimum predicted 3-year PC risk of 1-2% may be cost effective.

In a similar modelling approach, Schwartz et al. (2021) performed a CEA of testing for PC in a population of NOD patients enriched by the END-PAC model presented in Section 2.2.1. The strategy consists of testing all patients with an END-PAC score ≥ 0 by a contrast CT. Health states of PC patients are resectable and unresectable pre-progressive disease, as well as death. Patients with undiagnosed PC can be alive without PC, alive with PC or death. State transitions are tracked in monthly cycles with subgroup-specific transition probabilities. The model framework was used to calculate the deterministic and probabilistic estimates of life-years, QALYs, and direct medical expenditures over a lifetime horizon in each of the screening strategies. According to the model results, the enriched testing strategy would be cost effective at a $100,000 WTP threshold. A sensitivity analysis was performed on the most influential inputs on the costs per QALY gained across the whole NOD cohort for risk-based screening. The result was that the "percentage of screen-detected cases that are resectable" had by far the highest impact on the costs per QALY. However, according to additional threshold analyses, not before the percentage falls below 25% would costs per QALY-gained exceed 100,000$.

2.4. Study intention

Subsection 2.4.1 describes the action and knowledge problem faced in this thesis. Subsection 2.4.2 describes the research questions and objective and Subsection 2.4.3 its scope.

2.4.1. Problem formulation

A clear action problem is the high share of PC cases diagnosed at an unresectable stage, resulting in a short mean survival time after diagnosis. Therefore, a TED strategy has been developed, aiming to detect more resectable PC cases among a NOD population (Section 2.2.2). However, it is unclear if this strategy leads to improved outcomes for the whole NOD population as well as the subset of PC cases in the population. These are the knowledge problems for this thesis.

2.4.2. Study objective and research questions

The aim of this thesis is to investigate how risk stratification of a NOD population by a TED strategy translates into LYs and QALYs gained compared to the SoC.

Thus, the two main research questions for this study are the following:

1.) Is the risk-stratification of a NOD population by the END-PAC model in combination with serum IL-1Ra and adiponectin levels and subsequent diagnostic testing of HRIs **cost-effective** compared to the SoC (no TED strategy) **for the overall NOD population?**

2.) Does the risk-stratification of a NOD population by the END-PAC model in combination with serum IL-1Ra and adiponectin levels and subsequent diagnostic testing of HRIs yield a **clinical benefit** compared to the SoC (no TED strategy) **for PC cases in the NOD population?**

2.4.3. Scope of the research

In this study, we will evaluate possible changes in the diagnostic pathway by enriching the population of asymptomatic NOD patients for one-time PC testing. Other parts of the clinical pathway will remain as suggested by current clinical guidelines presented in Section 1.3 and potentially simplified and generalized in the model.

The research is conducted for an U.S. setting, with regards to clinical guidelines, costs, and incidences. The absolute U.S. PC incidence, as of 2020, was the second highest worldwide (IARC, 2020). Likewise, the incidence of diagnosed DM, is among the highest worldwide, both in absolute and relative numbers (IDF, 2021).

2.5. Summary and conclusions

PC, while rare, is one of the deadliest cancer types. Today, resection surgery is the only curative treatment available for the disease. However, most patients are already in an unresectable cancer stage at symptom onset. Also, surveillance by regular imaging tests is restricted to asymptomatic individuals with certain inherited high-risk factors for PC.

A potential early sign of PC is NOD. However, the PC risk among NOD patients is too low to justify surveillance of all patients. Instead, a TED strategy has been developed to offer one-time diagnostic tests to a risk-stratified NOD population. For risk stratification, HRIs are first identified by the END-PAC prediction model. Subsequently, serum levels of two biomarkers (IL-1Ra + adiponectin) are measured across HRIs to confirm the selection. HRIs receive a one-time CT scan and confirmatory EUS-FNA for PC diagnosis and staging.

The TED strategy will be analyzed by its effectiveness in improving the survival outlook for PC cases and its cost-effectiveness compared to the current SoC. A DAM will be designed to compare both alternatives. Existing DAMs for CEAs in the context of early PC have been identified and serve as a reference to choose an appropriate model type.

Chapter 3 discusses the modelling approach and data sources for this research.

3. MATERIALS & METHODS

Section 3.1 presents the model design. In Section 3.2 the different types of analyses to be performed with the model are motivated. Section 3.3 provides an overview of data sources for the required model inputs. Section 3.4 presents the obtained model outputs.

3.1. Model design

An integrated DTM and MCM has been constructed. Subsection 3.3.1 describes the model type selection. Subsection 3.1.1 and Section 3.1.2 provide specifics about the DTM and MCM, respectively.

3.1.1. Model type selection

For the CEA with a DAM, an integrated DTM and MCM has been constructed. The model was built in RStudio (Version 1.3.1093). While the DTM components are implemented in *Base-R*, the *heemod* package was used for building the MCM.

The decision about a suitable model type was made based on the definitions in the framework by Barton (2004), presented in Section 2.3.3. As no interaction between individuals in the model needs to be considered, neither a system dynamics model nor a DES are required. For the intervention itself, patient pathways can be represented adequately by a probability tree, as it takes place in a short time frame. Therefore, a DTM is suitable to model the direct outcomes of the intervention and assign shares of the initial population to different health states. However, to model transitions between health states as well as costs, LYs and QALYs over a lifetime horizon, a DTM would become very complex with many nodes and branches. At the same time, the number of required health states is small enough to allow for an MCM, rather than an individual sampling model.

3.1.2. Decision tree model

A DTM is applied to model the initial distribution of patients across different health states for both, the SoC, as well as the TED strategy (see Fig. 2-2 in Section 2.2.2). An important modelling choice is that time-progression is neglected in the DTM, because of the underlying assumption that all tests of the TED strategy happen in a time span of only a couple of weeks, which is short compared to the lifetime horizon of the MCM. Hence, time progression and utilities are not tracked in the DTM. Also, patients are assumed not to die during the TED procedures. Clinical probabilities and costs associated with each model node are pre-defined and presented in Section 3.3.

3.1.3. Markov cohort model

After the NOD population is assigned to one of, depending on the strategy, up to 6 initial health states in the DTM, patients enter the MCM for tracking the clinical and economic outcomes over a lifetime horizon. Patients cycle across the predefined health states in annual cycles (Fig. 3-1). As individuals in the model population are at least 50 years of age, the number of cycles is set to 50 to cover the expected lifetime of almost all individuals in the model. Individuals that reach the age of 99 in the model will transition to “Death” in the next cycle.

Patients in the “Metastatic PC at diagnosis”, “Locally Advanced PC at diagnosis” or “DM” state remain in their respective state in each cycle or transfer to the “Death” state. Patients in the “Resectable PC at diagnosis” stage undergo a resection surgery, which is assumed to be a distal pancreatectomy, as a

one-time event. If successful and given a survival of the first treatment year, patients transfer to the "Resected PC" state. Patients in the "Missed PC" state are treated like DM patients (without PC) for one year, with the same costs and utilities, before being diagnosed with resectable, locally advanced, or metastatic PC and transition to the respective state. It is assumed that all FP results in the model are resectable cancers. Hence, patients in the "FP diagnosis" stage are assumed to undergo resection surgery with the respective costs and utility, before moving to the "DM" state in the next cycle, granted survival of the first year.

Also, half-cycle correction is applied in the model by taking the average of the patient numbers at the beginning and end of each cycle, to simulate the state membership (and associated costs and utilities) in the middle of each cycle, where transitions occur on average in reality (Naimark et al., 2008).

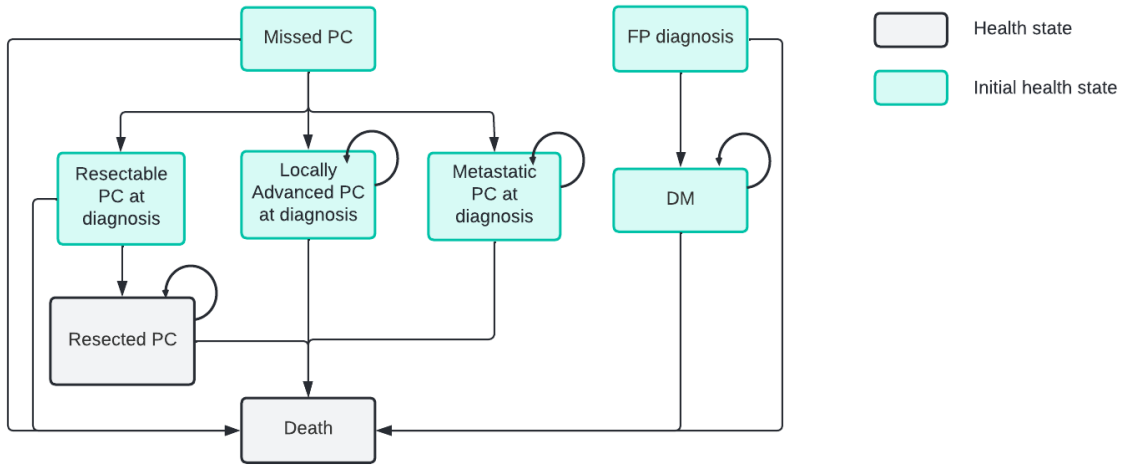

Fig. 3-1. Schematic representation of the Markov cohort model

3.2. Types of analyses

Using the same model framework with different inputs, two different analyses were performed separately for both research questions.

First, a *deterministic analysis (DA)* was conducted using the expected value for each input parameter. Second, a *probabilistic sensitivity analysis (PSA)* was performed to account for the joint uncertainty of multiple input parameters and its implications for decision uncertainty. Finally, a *scenario analysis* has been conducted to test the effect of different PC incidences in the initial model population on LYs gained with the TED strategy and the associated ICER.

3.3. Data sources

All input parameters for the base case analysis as well as the PSA are listed in Tab. 3-1, together with the respective references. The methodology for finding and selecting data is explained in three subsections, divided into demographics and clinical probabilities, costs and utilities.

Tab. 3-1. Base case estimates and PSA inputs used in the DTM and MCM. [TD = (model) time-dependent; AD = age-dependent]

Description	Reference	DA estimate	PSA input
US Population			
US population of age 50+ (million)	US Census Bureau (2021)	98.04	Not varied in PSA
Median age of NOD patients	Sharma, Kandlakunta, et al. (2018)	66	tnormal (mean = 66, sd =10.1, lower = 50, upper =100)
Median age of PC patients with NOD	Sharma, Kandlakunta, et al. (2018)	72	tnormal (mean = 72, sd =9.3, lower = 50, upper =100)
Annual incidence rates			
DM incidence rate among individuals of age 50+	CDC (2022)	0.84%	Not varied in PSA
3-year PC incidence rate among NOD patients	Sharma, Kandlakunta, et al. (2018)	0.82%	beta (α=95.2, β=11,519.9)
Sensitivities & Specificities			
Sensitivity of END-PAC model (cutoff-score ≥ 2)	Khan et al. (2021)	56.0%	beta (α=26.88, β=21.12)
Specificity of END-PAC model (cutoff-score ≥ 2)	Khan et al. (2021)	75.0%	beta (α=4654.5, β=1551.5)
Sensitivity of biomarkers (IL-1Ra + adiponectin)	Oldfield et al. (2022)	83.7%	beta (α=31, β=6)
Specificity of Biomarker (IL-1Ra + adiponectin)	Oldfield et al. (2022)	100.0%	beta (α=12, β=0)
Sensitivity of CT scan	Toft et al. (2017)	90.0%	beta (α=733.5, β=81.5)
Specificity of CT scan	Toft et al. (2017)	87.0%	beta (α=455.0, β=68.0)
Sensitivity of EUS-FNA	Banafea et al. (2016)	90.8%	beta (α=2485.0, β=276.0)
Specificity of EUS-FNA	Banafea et al. (2016)	96.5%	beta (α=2664.0, β=96.6)
PC stage distribution			
Stage *without* early detection strategy	Schwartz et al. (2021)		
Resectable PC		10.0%	beta (α=38.3, β=344.8)
Locally Advanced PC		30.0%	Calculated
Metastatic PC		60.0%	beta (α=20.0, β=18.4)
Stage *with* early detection strategy	Schwartz et al. (2021)		

Description	Reference	DA estimate	PSA input
Resectable PC		40.0%	beta (α=25.2, β=37.8)
Locally Advanced PC		50.0%	Calculated
Metastatic PC		10.0%	beta (α=38.3, β=344.8)
Transition probabilities			
Prob. of death after resection surgery	Gillen et al. (2010)	5.3%	beta (α=233.0, β=4161.0)
Prob. of death from RPC	SEER (2022)	TD	Not varied in PSA
Prob. of death from LAPC	SEER (2022)	TD	Not varied in PSA
Prob of death from MPC	SEER (2022)	TD	Not varied in PSA
Prob of death with T2DM	Wright et al. (2016)	AD	Not varied in PSA
Prob. of PC recurrence after resection surgery	Moletta et al. (2019)	80.0%	Not varied in PSA
Prob. of progressive LAPC	van Veldhuisen et al. (2019)	30.0%	Not varied in PSA
Costs			
Annual discount rate	Paulden et al. (2017)	3.0%	Not varied in PSA
Early-detection strategy			
END-PAC score (CPT G0439)	CMS (2022b)	$132.54	Not varied in PSA
Biomarker test			
Blood draw (CPT 36415)	CMS (2022a)	$3.00	Not varied in PSA
IL-1Ra IA (CPT 83520)	CMS (2022a)	$17.27	Not varied in PSA
Adiponectin IA (CPT 83520)	CMS (2022a)	$17.27	Not varied in PSA
CT scan			
Abdomen & pelvis (CPT 74177)	CMS (2022b)	$333.26	Not varied in PSA
Chest (CPT 71260)	CMS (2022b)	$178.91	Not varied in PSA
EUS-FNA (CPT 43242)	CMS (2022b)	$266.12	Not varied in PSA
Costs of surgery after FP diagnosis	Kumar et al. (2021)	$19,935.12	triangular (mode = 19935.12 min= 17942, max =21929.12)
T2DM care	Wang et al. (2021)	$4401.67	triangular (mode = 4401.67, min= 3744.98, max =5060.49)
Stage of disease	Mariotto et al. (2020)		
Resectable at diagnosis		TD	Not varied in PSA
Resected		TD	Not varied in PSA
LAPC at diagnosis		TD	Not varied in PSA
MPC at diagnosis		TD	Not varied in PSA

Description	Reference	DA estimate	PSA input
Quality of Life			
Annual discount rate	Paulden et al. (2017)	3.0%	Not varied in PSA
Utility of T2DM	Wang et al. (2021)	0.82	triangular (mode = 0.82, min = 0.77, max = 0.92)
Utility per PC stage			
RPC	Schwartz et al. (2021)		
Surgery to 6 months post-surgery		0.78	beta (α=5141.1, β=1450.1)
6 months post-surgery onwards		0.80	beta (α=14.4, β=3.6)
LAPC	Wang et al. (2021)	0.732	triangular (mode = 0.732, min = 0.549, max = 0.915)
MPC	Wang et al. (2021)	0.72	triangular (mode = 0.72, min = 0.540, max = 0.90)
Death	Assumption	0	Not varied in PSA

3.3.1. Demographics and clinical probabilities

The data for the model populations' demographics and clinical probabilities can be divided into two categories, time-homogeneous and time-inhomogeneous. All model inputs for the DTM are time-homogeneous, which is trivial since no time-progression is assumed for this part. Also, most inputs for the MCM are time-homogeneous.

Preferably, model inputs were derived from online databases or other published reports from U.S. agencies. This is the case for estimates about the current U.S. population and DM incidence. Other estimates were derived from study results published in literature. This includes the PC incidence among NOD patients, the sensitivity and specificity of all tests performed as well as the PC stage distribution at diagnosis with and without an early detection strategy. In most cases this data was obtained from the existing CEAs for early PC detection presented in Section 2.3.3. In case different values for the same parameter were available, one estimate was selected, with a preference for pooled estimates from large meta-analyses. If no or multiple meta-analyses were available for estimating the same parameter, the number of patients enrolled in a single study as well as the date of publication were considered to select a study.

As model parameters are estimated, they are subject to uncertainty as to their true value, which is accounted for in the PSA (Briggs, 2011, p. 61). If the estimate ($\bar{p}$) is derived from a study with a discrete number of patients n, it can be seen as the proportion of r events of interest out of n independent experiments. Therefore, a standard approach is to recognize that the underlying data for a parameter estimate follows a binomial distribution ($binomial(\bar{p}, n)$).(Briggs, 2011, p. 82) For example, the sensitivity of a test ($\bar{p}$) can be estimated based on a study with n individuals with a TP or FN test result, where the events of interest are the TP test results (r). The discrete binomial distribution has a special relationship to the continuous *beta distribution*, called conjugacy, which makes it especially suitable to represent parameter uncertainty in a model. The beta distribution is constraint on the interval 0-1 and is characterized by two parameters, α and β. Fitting the beta

distribution for binominal data is straightforward, by setting α equal the number of events of interest ($\alpha = r$) and β to the number of "failures" ($\beta = n - r$).

Fitting a beta distribution to binomial data for a PSA has the limitation that parameters are assumed to be independent (Briggs, 2011, p. 95). This assumption, however, is not true for the sensitivity and specificity of the same test. A higher test sensitivity (e.g., by reducing the cutoff-score of the END-PAC model) will result in a lower test specificity and vice versa. It is possible though to correlate parameters if the covariance structure is known (Briggs, 2011, pp. 95-96). Therefore, a multivariate normal distribution is fitted for the test's sensitivity and specificity, using the covariance matrix obtained from a series of values for different cutoff-scores. By drawing a random number from the distribution and taking it as an input for returning values of cumulative density functions (CDFs) for the sensitivity and specificity, respectively, which can then be used as quantile inputs again to return values of the original beta distributions adjusted for parameter correlation.

Next to time-homogeneous parameters, some inputs are time dependent (TD), hence changing during the model's time horizon. This is the case for the probability of dying in the respective cancer stages, as the probability decreases successively over the years (Tab. B-1). An important modelling assumption is that patients who are diagnosed earlier through the TED strategy experience the same probability of death in the first year like patients in the "Missed PC" state who are assumed to be diagnosed a year later due to symptom onset. This choice adjusts the outcomes for the lead time bias explained in Section 1.4.3, as the bias can also lead to underestimation of early-detection benefits in health economic models if mortality rates after diagnoses are applied earlier to the respective population than to a population with later symptomatic diagnosis.

Finally, also the probability of dying from T2DM is time dependent. All patients receive an initial age, according to a fitted (truncated) normal distribution, which is a difference between patients (*heterogeneity*) added to the model. The initial age increases in each cycle and likewise the probability of death is recalculated. The probability is also added to the probability of death for PC patients caused by their respective cancer stage. To distinguish this approach including heterogenic patient characteristics from the time-inhomogeneity introduced before, it is labeled "age dependent" (AD). The probabilities of death with T2DM in the different age groups are added to the Appendix (Tab. B-2).

3.3.2. Costs

The CEA considers a health payer's perspective. Costs associated with the individual tests which are part of the proposed early-detection strategy are derived from the 2022 CMS Physician Fee Schedule (PFS) or Clinical Diagnostic Laboratory Fee Schedule (CDLFS). The PFS is used by the CMS to reimburse physician services, and national payment averages can be accessed through an online lookup tool. Likewise, The CDLFS lists the CMS reimbursements for laboratory services. Both types of services are coded with unique "Current Procedural Terminology" (CPT) codes (AMA, 2022). While costs of diagnostic tests used in the strategy (CT and EUS-FNA) could be directly derived from the PFS, assumptions were made for selecting suitable CPT codes for the not yet covered enrichment tests. The costs of obtaining the ENDPAC score are set equal to the reimbursement for an annual "wellness" visit and the costs of performing biomarker tests to the reimbursement for an immunoassay (IA) listed in the CDLFS.

The annual costs for the different MCM stages are derived from literature and incorporate the most frequent treatment choices emphasized in Section 1.3.2, such as surgery, best supportive care,

chemotherapy and chemoradiation. Estimates are standardized to 2022 U.S. dollars by assuming an annual inflation of 3% which is also used within the model to discount future costs. For the PSA, beta distributions were fitted for the costs estimates or triangular distributions if only the mean and range of possible average costs had been reported.

All costs in the model are time-homogeneous, except for the costs of the states representing different PC stages. These vary not just by cancer stage but also phase of care. For each stage, higher costs occur during the initial 12 months after diagnosis followed by constant costs in the "continuing" phase (Mariotto et al., 2020). Costs associated with the EOL phase, the final 12 months of treatment, are not explicitly modelled. The estimates are added to the appendix (Tab. B-3). As the values are derived from a SEER database, they remain unvaried in the PSA.

3.3.3. Quality of Life (QoL)

Health state utility estimates, in the form of relative QoL per year, were derived from literature. A utility score of 0 represents the value of death, and 1 represents the value of perfect health. Like costs, the values are discounted by 3% per year based on current guidelines. Also, like for costs, beta or triangular distributions were fitted as stochastic inputs for the PSA. To account for likely PC recurrence after resection surgery, the utility in the "Resected PC" state is adjusted for the likelihood of recurrence.

3.4. Model outputs

The model framework was applied to perform a CEA, with LYs as well as QALYs as measurements of health outcome. The results are reported separately for the overall NOD population and the PC cases among the population.

For the PSA, 5,000 simulation runs were performed. A cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are plotted to visualize the results using the *hesim* package in R. Survival of PC patients is plotted by a Kaplan-Meier estimator using the *survival* package.

4. RESULTS

Section 4.1 presents the results of the CEA for the overall NOD population in the model. Section 4.2 presents the results of clinical benefit for PC cases in the NOD population.

4.1. Cost-effectiveness analysis for the overall new-onset diabetes population

The following subsections show the results of the DA (4.1.1), PSA (4.1.2) and scenario analysis (4.1.3).

4.1.1. Deterministic analysis for the overall new-onset diabetes population

Tab. 4-1. Results of the deterministic analysis for the overall NOD population

Strategy	LYs	QALYs	Cost	Cost per LY gained	Cost per QALY gained
TED	15.785	9.856	$54,265	$28,742	$51,875
SoC	15.781	9.854	$54,161		
Difference	0.004	0.002	$104		

Tab. 4-1 shows the results of the deterministic CEA analysis for the overall NOD population. We see that the TED strategy is associated with increased LYs, QALYs and cost, although the outcome difference is marginal in comparison to the SoC. An expected difference of 0.004 LYs equals only around 1.5 additional days of survival and the difference in QALYs is even lower. However, also the difference in cost is low. Therefore, while the ICER for the cost per LY gained as well as the cost per QALY gained suggest that the TED strategy is cost-effective compared to the SoC at a $100,000 WTP threshold, the clinical benefit is so small that it does not have any clinical relevance.

4.1.2. Probabilistic sensitivity analysis for the overall new-onset diabetes population

Tab. 4-2. PSA outcomes for LYs and QALYs per strategy for the overall NOD population

Outcome	Mean	SD	Min	Max
LYs				
SoC	15.781	0.0104	15.738	15.813
TED	15.786	0.0100	15.746	15.817
QALYs				
SoC	10.049	0.3689	9.279	11.051
TED	10.051	0.3689	9.278	11.054

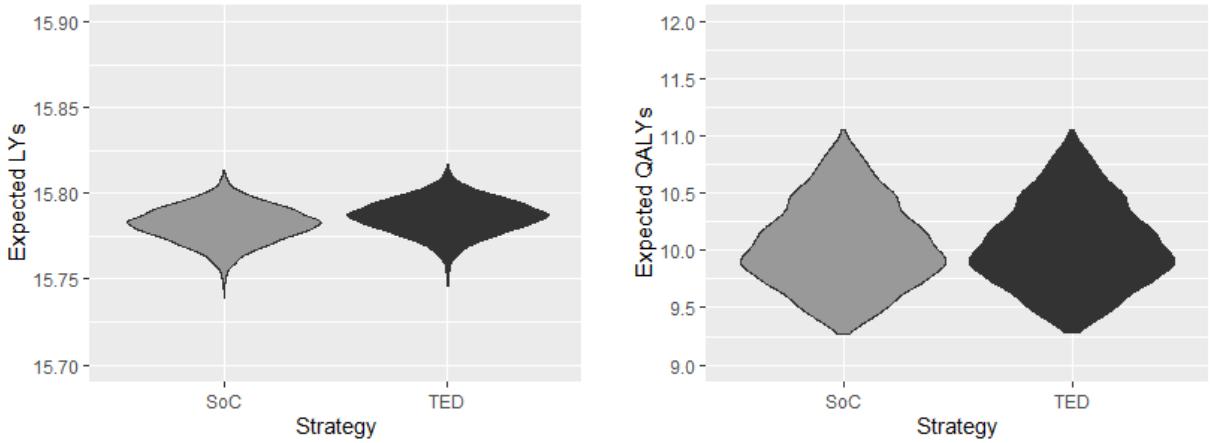

Fig. 4-1. Violin plots of LYs per strategy (left) and QALYs per strategy (right) for overall NOD population

Tab. 4-2 lists the results of the PSA, separately for both strategies and health outcome measures, including the respective mean, standard deviation, minimum and maximum. The results are also visualized in a violin plot (Fig. 4-1). The mean expected LYs of the NOD population in the model are 15.768 years in the SoC compared to 15.781 years in the TED strategy, a difference of below 5 days. While the means are similar, the SD is very small. In terms of QALYs, the means are 10.051 QALYs and 10.049 QALYs with the TED and SoC strategy, respectively, a difference of below 1 day. While the means are similar again, the standard deviation is larger than across LYs. Therefore, the PSA confirms the results of the DA that the improvement of average LYs as well as QALYs by the TED strategy is not clinically significant.

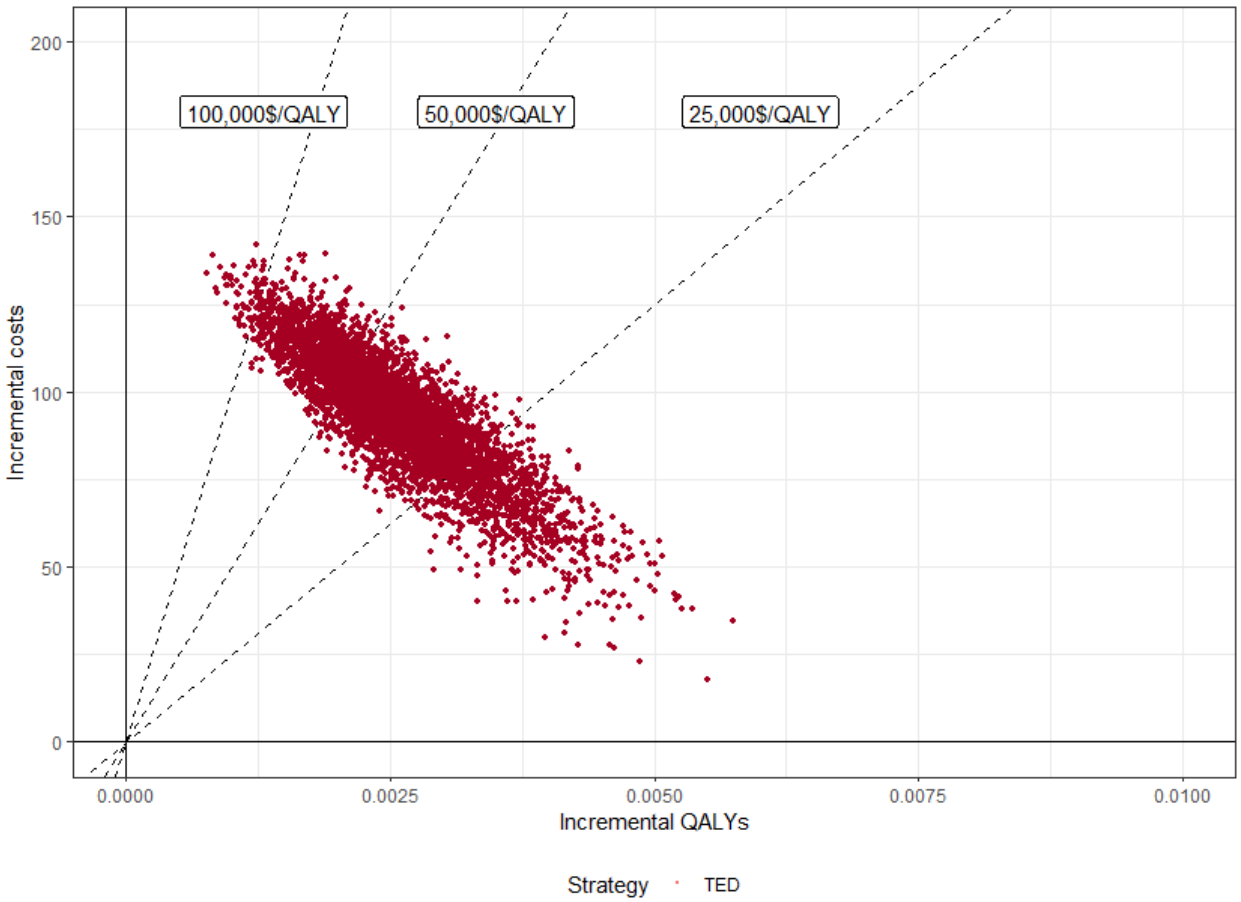

Fig. 4-2. CEP of 5000 simulation runs for the incremental added costs and QALYs of the TED strategy. Dotted lines represent different WTP thresholds

Fig. 4-2 shows the resulting incremental added costs and QALYs of the TED strategy per simulation run in a CEP, including three different WTP thresholds for orientation. The majority of individual ICER results falls in between the $25,000/QALY and $100,000/QALY threshold. Also, we see that all outcomes lie in the upper right quadrant of the CEP, indicating that the TED strategy resulted in higher costs but also higher QALYs in each simulation run. Outliers occur in the favorable direction of higher QALYs for lower costs and in the unfavorable direction of fewer QALYs for higher costs. Drivers for the first case are a high difference in the PC stage distribution at diagnosis (a high increase of RPC cases and a high decrease of MPC cases in the TED strategy), a high PC incidence in the NOD population, as well as a high sensitivity of the END-PAC model. Vice versa, drivers for the second case are a low additional share of RPC cases at diagnosis, a low share of reduced MPC cases at diagnosis and a low sensitivity of the END-PAC model.

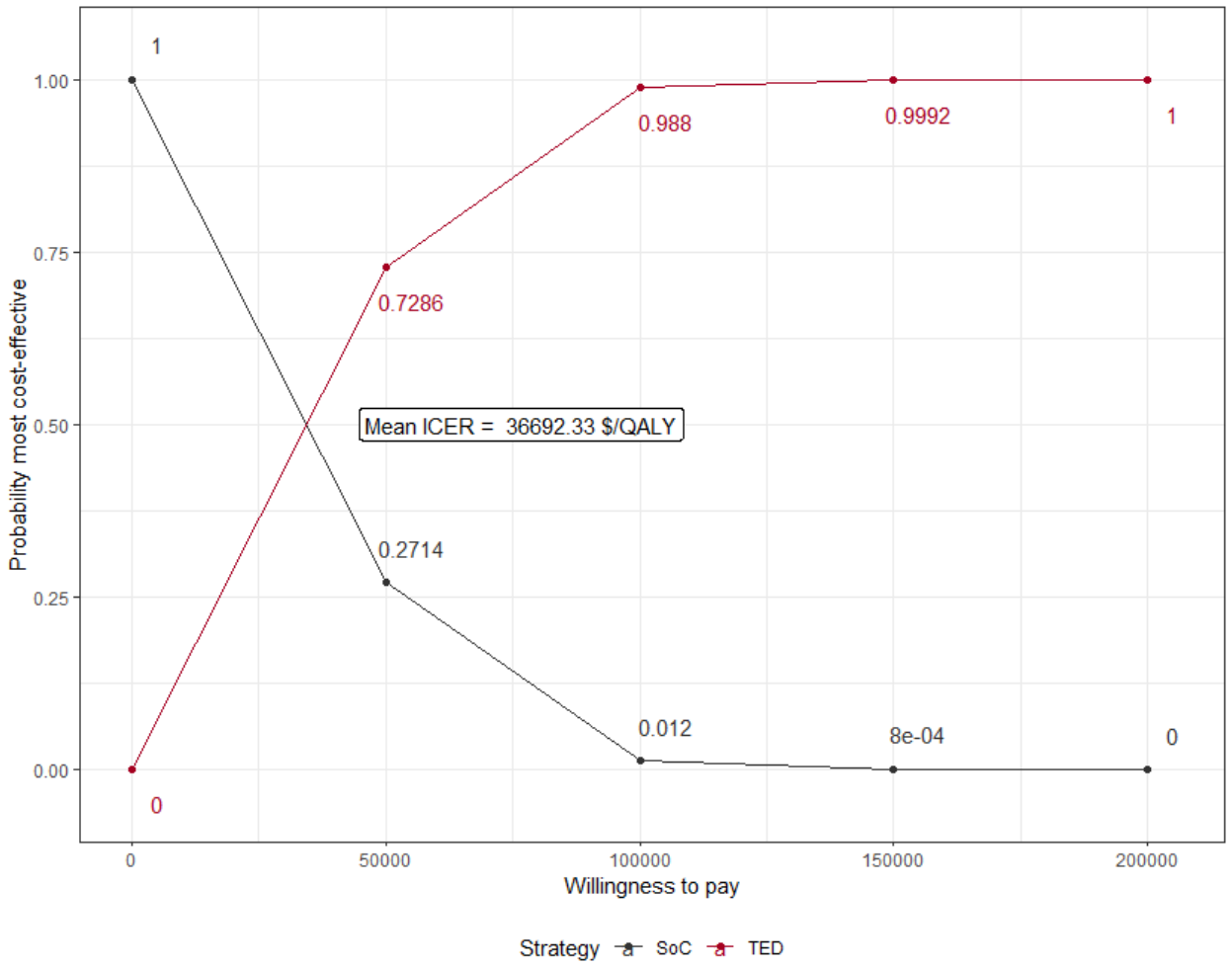

Fig. 4-3. CEAC of the TED compared to the SoC strategy based on PSA results

Fig. 4-3 displays the probabilities of cost-effectiveness of the TED and SoC strategy, respectively, based on the PSA results. We observe a mean ICER of $36,692/QALY. Also, given the parameter uncertainty in the PSA, there is a 98.8% chance that that the additional costs of the TED strategy compared with the SoC is less than $100,000 per QALY. However, this is *not* equivalent to saying that the TED strategy has a 98.9% chance of costing less than $100,000 per QALY.

4.1.3. Scenario analysis for the overall new-onset diabetes population

This scenario analysis explores the effects of the PC incidence in the NOD population on the clinical benefits in terms of LYs gained by the TED strategy as well as the cost-effectiveness in terms of ICER compared to the SoC. Therefore, the DA results presented in Section 4.1.1 are compared to fixed PC incidence estimates.

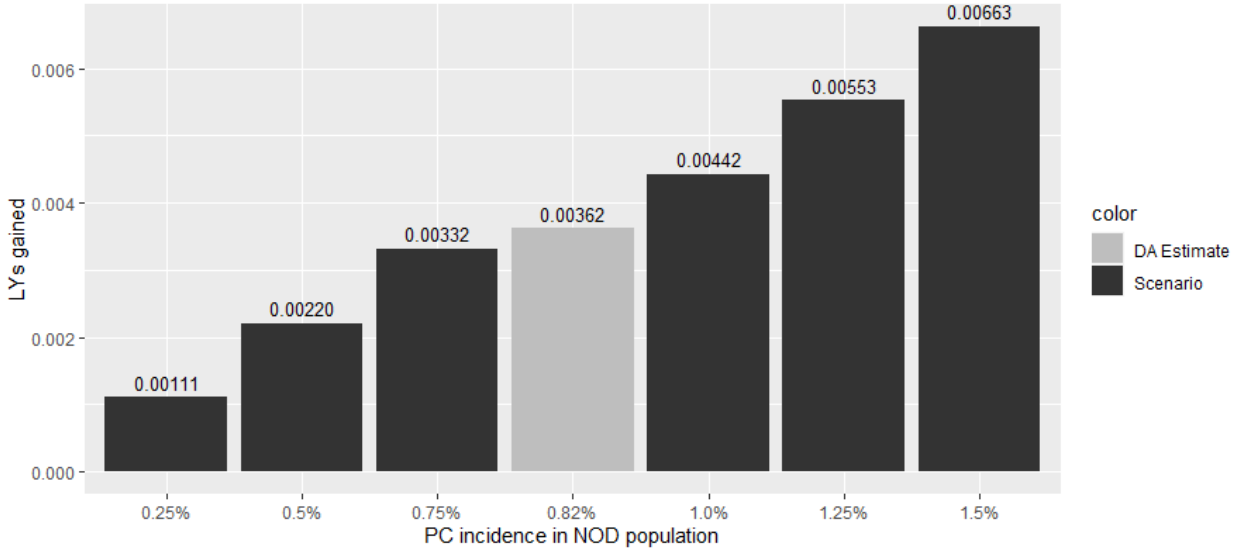

Fig. 4-4. LYs gained for different PC incidence estimates in the NOD population in a DA setting

Fig. 4-4 shows the LYs gained by the TED strategy for different PC incidence estimates in the NOD population. The effect of an increasing incidence is almost perfectly linear. An increase of incidence by 0.25% is associated with around 0.0011 LYs gained on average, which equals around 0.4 days. Therefore, even if the current DA estimate of the PC incidence (0.82%) would increase to 1.5%, the LYs gained are low, with an average of just 0.00663 (2.42 days). Even for a PC incidence of 5% and 10%, the LYs gained would be only 0.02209 (8.10 days) and 0.04417 (16.12 days), respectively (not in the figure). Hence, we cannot conclude that the LYs gained become clinically relevant in the range of tested incidences.

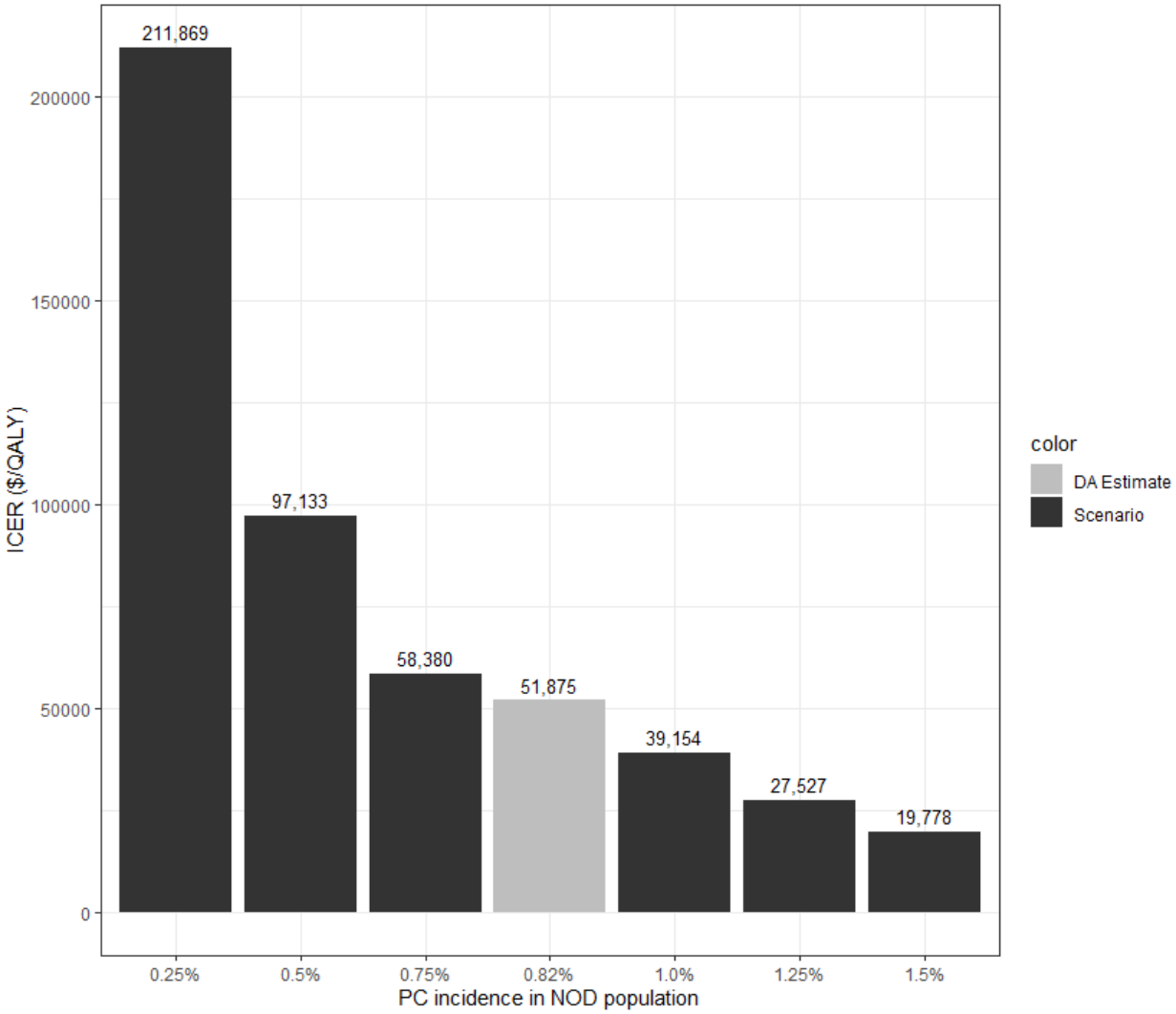

Fig. 4-5. ICER for different PC incidence estimates in the NOD population in a DA setting

Fig. 4-5 shows the cost-effectiveness in terms of costs per QALY gained by the TED strategy for the different PC incidences. The results indicate that an increased PC incidence in the initial model population leads to a disproportional (relative) decay of the ICER. The ICER reduction decreases by around 50% per 0.25% increase of the PC incidence. If, for example, the PC incidence increases from 0.25% to 0.50%, the ICER reduces by around 54%, while an increase from 1.25% to 1.50% with the same step size only reduces the ICER by around 28%.

For even higher PC incidences of 5% or 10%, the ICER becomes negative with values of $-7,285/QALY and $-13,085/QALY, respectively (not in this figure). Hence, while the clinical benefit in terms of LYs gained remains marginal even for high PC incidences, we observe that the TED could lead to cost savings compared to the SoC.

4.2. Clinical benefit for pancreatic cancer cases in the new-onset diabetes population

This section presents the results of the DA (Section 4.2.1) and PSA (Section 4.2.2) for only the PC cases in the NOD population.

4.2.1. Deterministic analysis for pancreatic cancer cases in the new-onset diabetes population

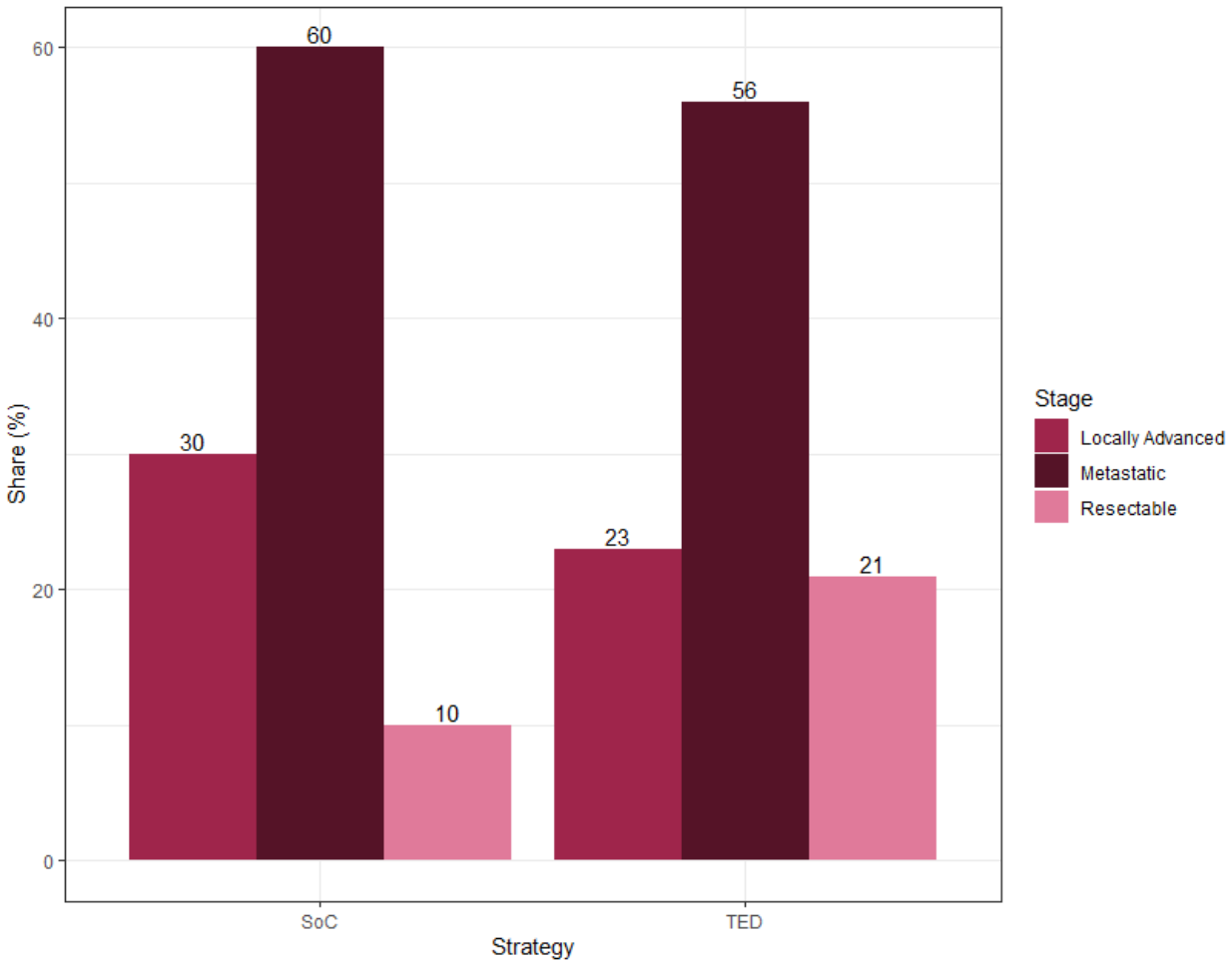

Fig. 4-6. Relative PC stage distribution at diagnosis in the SoC and TED strategy

Fig. 4-6 shows the relative PC stage at diagnosis. While the share of LAPC and MPC patients is reduced with the TED strategy (e.g., 4% and 7%, respectively), the share of RPC cases is more than doubled (10% to 21%).

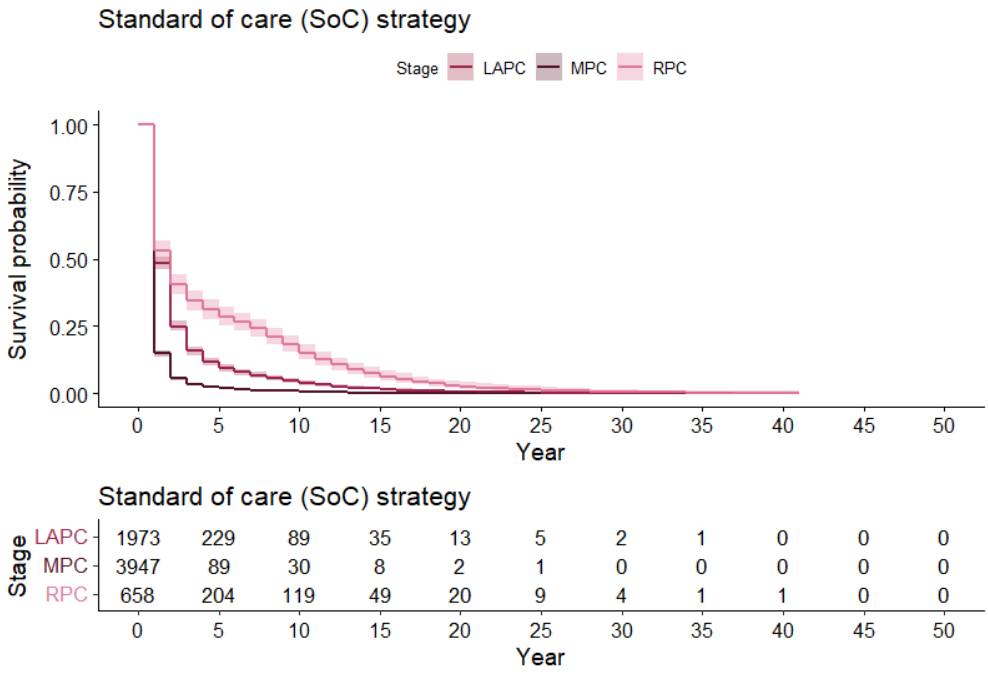

Fig. 4-7. Kaplan-Meier estimator of survival per PC stage at diagnosis in SoC strategy

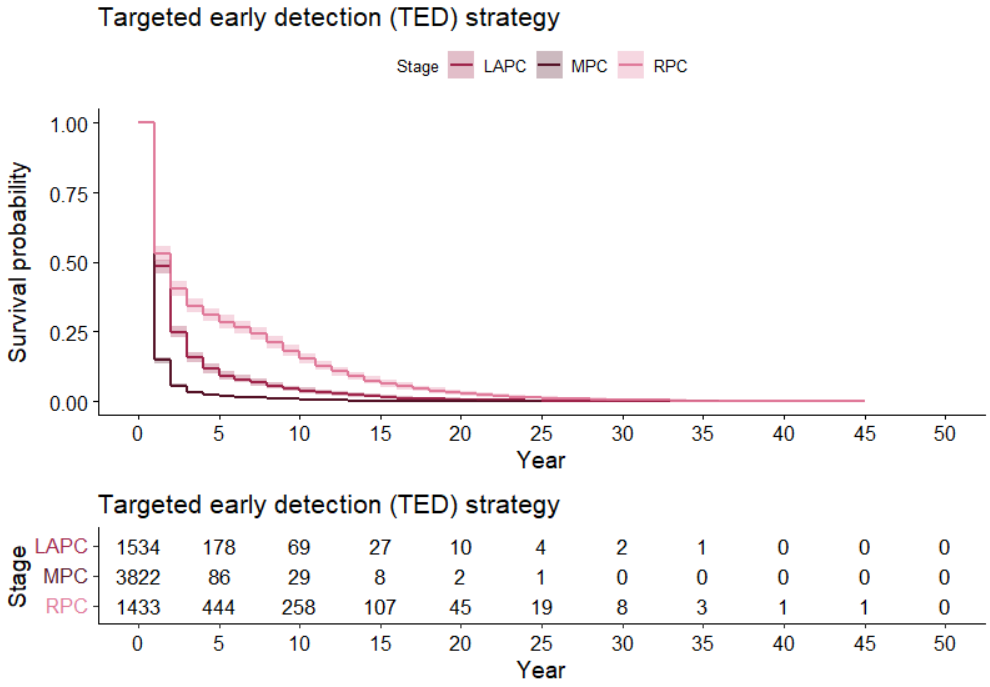

Fig. 4-8. Kaplan-Meier estimator of survival per PC stage at diagnosis in TED strategy

Fig. 4-7 and Fig. 4-8 present the survival time of PC patients per cancer stage at diagnosis in the SoC and TED strategy, respectively. For accurate comparison, Year 0 in this analysis is the year of cancer diagnosis in the respective strategy. The total number of PC cases in the TED strategy is higher than in the SoC strategy (6789 vs. 6578), because all PC cases in the SoC are diagnosed one year later in

the model. During this year, a number of patients dies of non-cancer causes. As the probability of death in the model does only depend on the cancer stage and patient's age, but not on the detection (TED or SoC strategy) the relative decrease of survival probabilities is similar. However, in absolute numbers, after 5 years, a total of 186 additional patients are alive in the TED strategy (SoC: 522 vs. TED: 708). After 10 years the number reduces to 118 cases (SoC: 238 vs. TED: 356) and after 15 years to 50 (SoC: 92 vs. TED: 142).

Tab. 4-3. Results of the deterministic analysis for the PC cases in the NOD population

Strategy	**LYs**	**QALYs**
TED	4.40	2.71
SoC	3.96	2.93
Difference	0.44	0.22

Tab. 4-3 shows the results of LYs and QALYs per strategy. We see that the TED strategy is associated with increased expected LYs and QALYs. The TED strategy leads to additional 0.44 LYs, equal to around 163 days, and additional 0.22 QALYs, equal to around 80 days.

4.2.2. Probabilistic sensitivity analysis for pancreatic cancer cases in the new-onset diabetes population

Tab. 4-4. PSA outcomes for LYs and QALYs per strategy for PC cases in the NOD population

Outcome	Mean	SD	Min	Max
LYs				
SoC	3.53	0.0992	3.17	3.90
TED	4.08	0.1416	3.51	4.61
QALYs				
SoC	2.40	0.1577	1.92	2.89
TED	2.71	0.1901	2.10	3.38

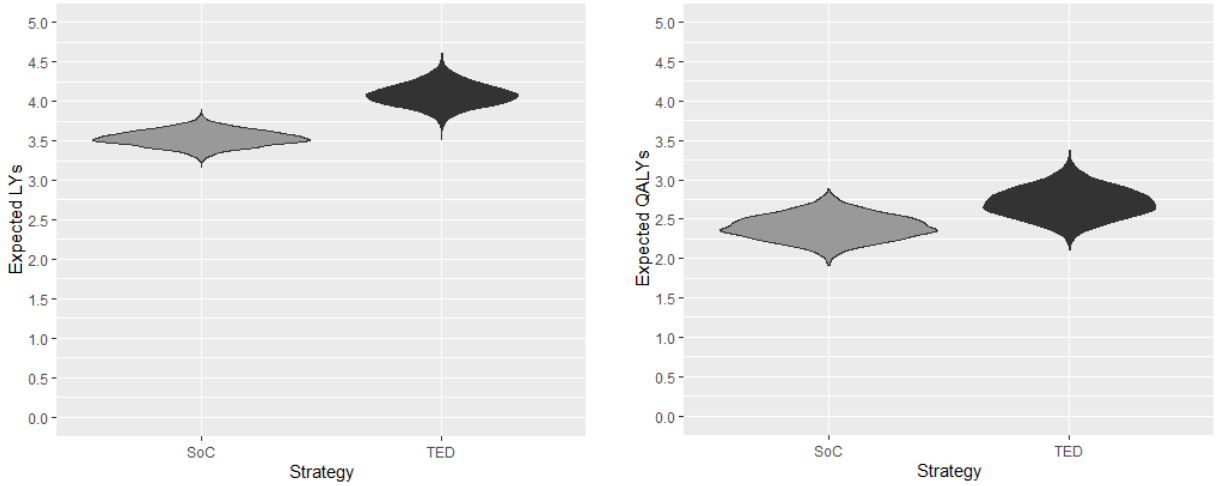

Fig. 4-9. Violin plots of LYs per strategy (left) and QALYs per strategy (right) among PC patients in the NOD population

Tab. 4-4 and Fig. 4-9 show the PSA outcomes in expected LYs and QALYs for the respective strategy. The mean expected LYs after diagnosis of PC patients in the NOD population are 4.08 years in the TED compared to 3.53 years in the SoC strategy, a difference of 0.55 years (201 days). In terms of QALYs, the means are 2.71 QALYs and 2.40 QALYs in the TED and SoC strategy, respectively, a difference of 0.31 years (113 days). Given the poor survival outlook for PC patients, this improvement is likely to be clinically relevant.

5. DISCUSSION

Section 5.1 discusses the CEA results for the overall NOD population. Section 5.2 discusses the clinical benefit results for the PC cases in the population. Lastly, Section 5.3 discusses limitations of this study.

5.1. Cost-effectiveness of the targeted early detection strategy among the new-onset diabetes population

While the TED strategy is cost-effective compared to the SoC in the DA setting, the incremental costs, and benefits, both in terms of LYs and QALYs gained, are very small. The reason for the small differences in between strategies is the low number of PC cases in the NOD population. There are 827,793 NOD patients in the initial model population, among whom only 6,789 do have PC. Therefore, for most of the population the same costs and effects occur in both strategies. In the CEA of the END-PAC model by Schwartz et al. (2021) presented in Section 2.3.3, the results of cost per LY and QALY gained are higher than in this analysis ($53,421/LY gained; $65,076/QALY gained), although the stage distributions at diagnosis (for the TED and SoC strategy), PC incidence in the model population, and some health state utilities were adopted and thus are similar in both analyses. Their results indicate a greater gain of LYs and QALYs in the "screening strategy" compared to a "no screening strategy", although the absolute expectations per strategy are lower. At the same time, however, their computed average additional costs are higher ($293 vs. $104). The difference in LYs can be explained by the different mean initial age of individuals in both analyses. In the model by Schwartz et al. (2021), the average age was 72 years across the NOD population, while in this model the average age was 66 years. Also, higher costs occur, because patient liabilities are included in their estimates, while this analysis only accounts for Medicare claims. However, the overall outcomes in both analyses, cost-effectiveness at a $100,000 WTP threshold and relatively small additional costs and benefits through early detection, are similar.

Next to the low share of PC cases in the initial NOD population (0.83% in the DA), also the proportion of the NOD population characterized as high-risk for diagnostic testing is low (0.38% in the DA). While the enrichment tests do have a great combined specificity, leading to a 100% PC cases in the enriched population, also most PC cases are not captured due to comparable low sensitivity of the tests. According to the findings of the CEA by Wang et al. (2021) presented in Section 2.3.3, already a lower risk threshold of only 1-2% could be cost-effective at a $100,000 WTP threshold, which would be achieved by only applying the END-PAC model for risk stratification, like in the analysis by Schwartz et al. (2021).

The outcome that the TED strategy is cost-effective at a threshold of $100,000 is confirmed by the results of the PSA analysis. In terms of health outcomes, the only differences occur due to different stage distributions at diagnosis, however with neglectable clinical benefits. The small standard deviation of LYs among both strategies indicates that varying all the uncertain parameters in the model has little impact on the overall survival compared the actual number of PC cases (of all stages) in the model population. While we observe that the impact of uncertainty on QALYs is larger, the difference of the mean in between strategies becomes even smaller. A reason for that is that the utilities of living with DM and all PC stages do not differ much in the model.

Regarding cost-effectiveness, we see that the mean ICER of the PSA outcomes is smaller than in the DA ($36,692 vs. $51,875). This indicates that the chosen distributions to represent parameter uncertainty overall tend to take on values resulting in more favorable results in terms of costs and health outcomes. The visualization of the CEAC (Fig. 4-3) shows that the proportion of simulations resulting in an ICER < WTP is constantly increasing with rising WTP thresholds, cutting the y-axis at 0 and converging to 1. This is accurate, as all simulation outcomes lie in the upper right quadrant of the CEP (Fig. 4-2). Also, we may assume that the curves represent the probability that the respective strategy is cost-effective for a given threshold, as a Bayesian framework is applied where multiple parameters are set as random variables drawn from a distribution function (Fenwick et al., 2004). The fact that the incremental costs and QALYs were higher in each simulation run show two things: First, the cost savings among PC patients diagnosed in earlier disease stages did *never* make up the additional costs for earlier detection in the PSA. Second, though small, on average patients *always* had incremental QALYs with the TED strategy in comparison to the SoC in the PSA.

The linear relationship between the PC incidence and LYs gained observed in the scenario analysis confirms the (small) clinical benefit of the TED strategy. As the number of PC cases increases in the scenarios, more cases are detected early by the TED strategy, which is associated with a higher chance of RPC at diagnosis and longer survival. Also, the observed disproportional relationship of the PC incidence and ICER outcome (approximately halving of ICER decrease per 0.25% increase of PC incidence) is reasonable, as a lower incidence reduces the number of PC patients in the model with *saved* costs and added benefit through the TED strategy, while at the same time increasing the number of patients with *added* costs and no change in QALYs (through unnecessary testing). While the exact relationship might differ for every disease, the finding underlines the importance of ensuring a sufficient prevalence of targeted disease in any early-detection initiative.

The estimated U.S. crude PC incidence rate for 2020 was 17.1 per 100,000 persons (IARC, 2020) and the DM prevalence 13.6% for 2021 (IDF, 2021). However, other large high-income countries had even higher PC incidence rates of 35.0 (Japan), 25.7 (Germany) and 23.4 (Italy) (IARC, 2020). Likewise, the DM prevalence in these countries is comparable to the United States (11.8% in Japan, 10.0% in Germany and 11.8% in Italy (IDF, 2021). Therefore, higher PC incidence rates among NOD patients in these countries are likely, and especially in Japan an incidence around 1.5%, considered in the scenario analysis, is realistic. Thus, while a comparison of the clinical pathways for PC patients across different countries is outside the scope of this research, the TED strategy is expected to result in equal or higher clinical benefits and relative ICER improvements in healthcare systems of the countries mentioned above.

5.2. Clinical benefit of targeted early detection strategy for pancreatic cancer patients in the new-onset diabetes population

Regarding the cancer stage at diagnosis of PC cases in the NOD population, we can observe a considerable increased share of RPC in the TED strategy compared to the SoS (21% vs. 10%) in the DA. While this result indicates that the TED strategy causes a positive stage shift, the share of RPC is way below the 40% of PCs that are set to be resectable upon early detection in the analysis. This shows that there is still great number of "Missed PC" cases in the TED strategy, who only get diagnosed at the same time as they would have without TED. Also, the difference in total number of PC cases at diagnosis (211) indicate an overtreatment rate of 3.1% (211/6789). These patients would have died before symptomatic diagnosis. The increasing alignment of the overall absolute survival in both

strategies over the model's time horizon is realistic, as with increasing patient age the probability of a non-cancer-caused death grows.

In terms of health outcomes, we observe that the average benefit is considerably higher than across the overall NOD population, which underlines the clinical benefit of early-stage PC detection. However, the average benefits remain small, both LYs and QALYs, so that we cannot derive long-term benefits for PC patients. The outcomes are similar in the analysis by Schwartz et al. (2021), with 0.67 and 0.54 added LYs and QALYs, respectively.

In the PSA, the deviation of LYs and QALYs around the mean is similar across strategies. In terms of LYs, the standard deviation is larger in both strategies compared to the deviation among the overall NOD population. The higher deviation is connected to the uncertainty of PC stage distribution at diagnosis in both strategies. In terms of QALYs, interestingly, the standard deviation is lower compared to the overall NOD population for both strategies. This shows that the impact of the uncertain QoL for DM patients is larger than the uncertainty of QoL in the different PC stages.

5.3. Limitations

Section 5.3.1 discusses limitations of the TED strategy. Section 5.3.2 discusses limitations of the DAM.

5.3.1. Limitations of the targeted early detection strategy

The arrangement of interventions in the TED strategy is solely based on intermediate findings and data of published studies. However, the small PC prevalence in studies of all phases in the clinical pathway in combination with the heterogenous disease characteristics has led to different results for similar interventions in different settings.

While the END-PAC model has been validated twice in different settings, both studies were retrospective, hence removing a large share of patients due to missing data. For example, in the study by Chen et al. (2021), 46% of PC cases had no required abnormal glycemic test available. Therefore, the prevalence of PC in the NOD population and the model's sensitivity and specificity are uncertain. The model is currently assessed in an ongoing prospective trial ("Early Detection Initiative") including an estimated 12,500 participants. The estimated primary completion date is in 2030. (Chari et al., 2022) However, even if the study confirms the model's efficacy, its data requirements remain an issue in real-life. Another challenge is that diabetes is often only clinically diagnosed years after its onset, largely reducing its predictive value for PC. (Sharma, Kandlakunta, et al., 2018)

A limitation of the incorporated biomarker panel is that the underlying study was small (43 T3cDM and 32 T2DM cases, respectively) and all patients in the cohorts came from a single center (Oldfield et al., 2022). Also, T3cDM can indicate other malfunctions of the pancreas next to PC. (Gallo et al., 2021) In general, the majority of T3cDM cases are caused by chronic pancreatitis (CP), while only 8-31% are caused by PC. However, as the average age of CP patients was lower than the age of PC patients among DM cases in the biomarker study (52 years vs. 71.5 years), we may expect that the preceding END-PAC model excludes most of the CP cases in the population. However, CA19-9 might be an additional biomarker suitable to discriminate PC from other CP. Hence, while adding CA19-9 to the biomarker panel did not improve its diagnostic performance in the initial study, it might be worth further consideration (Oldfield et al., 2022).

Regarding the diagnostic tests in the TED strategy, a strong limitation is the uncertain performance of imaging tests for asymptomatic PC. In a retrospective cohort study, only 46% of patients who were

later diagnosed with PC by a CT scan, had abnormal scans 6-12 months prior to diagnosis and the share decreases to only 16% in the 24-36 months interval (Singh et al., 2020). Accordingly, the test's sensitivity likely will be lower than the sensitivity for symptomatic disease used in this thesis.

Next to the limitations for the individual tests of the TED strategy, there are also general legal and ethical challenges associated with risk-stratified early-detection programs. Data protection laws might hinder the collection of rich datasets and efficient international data sharing required to build comprehensive prediction models, which also account for human genetic diversity (Knoppers et al., 2021). Equitable access to the TED can be a challenge, as the required specialized staff and technological infrastructure could be lacking in rural areas. In addition, if a TED strategy falls within the oversight of medical device regulation, it would impose additional costs and formal requirements to obtain approval, which could discourage the introduction interventions.

5.3.2. Limitations of the decision analytical model

It is important to highlight that the DAM in this thesis was designed to compare two strategies in terms of costs and effects. The absolute results of LYs, QALYs and costs can be misleading due to the performed lead-time adjustment to make the TED and SoC strategy comparable. Also, potential disutility during the enrichment and diagnosis stage are excluded from the model. For example, the EUS-FNA for cancer staging can cause adverse events such as bleeding, perforation, pancreatitis or even death. Also, psychological distress from an (intermediate) FP result was disregarded in this study. While the combination of tests works well to enrich the NOD population for eventual diagnostic testing, individuals might be considered high-risk from the END-PAC model without being diagnosed with PC eventually. However, disutility in both cases is assumed to be of short duration or very rare and thus to not have a big impact on the results. Also, EoL costs for patients in the respective cancer stage as well as with DM are not incorporated in the model. While costs estimates are available (see Mariotto et al., 2020), the MCM does not allow to predict the time-until-death of an individual in the model.

In addition, while the role of parameter uncertainty has already been explained, there are a number of structual uncertainties in the DAM. First, one limitation of the MCM is that state transitions only occur on an annual basis. While the applied half-cycle correction leads to a more realistic representation of events which might happen in between these transition times (e.g. death), the problem remains for health states which do not last for a whole cycle length (e.g. resection surgery). A trade-off has been made here to utilize more accurate available survival and cost data on an annual basis. Second, the number of possible states for PC patients in the model, does not adequately represent the complexity of the disease and the likely changing utility during its course, e.g. due to progression. Again, however, these limitations are not expected to influence the results much in a comparison, especially as all health state utilties other than dead were relatively high and close to each other.

Another limitation lies in the interpretation of the clinical relevance of the observed differences in the model as accepted values are missing (Ranganathan et al., 2015). Therefore conclusions about clinical relevance of results could only be assumed.

5.4. Recommendations for future research

The main risk factors for sporadic PC identified today are cigarette smoking, DM, a high body mass index, alcohol consumption and pancreatitis (Klein, 2021). However, there are other factors that

require further research. For example, studies have demonstrated that patients with allergies, such as hay fever and animal allergies have a reduced risk of PC and improved survival (Gandini et al., 2005). Also, in an analysis of a large-scale case control study, patients with PC were often regularly exposed to pesticides, asbestos, and chlorinated hydrocarbons (Antwi et al., 2015). Also, a better understanding of the role of genetics could yield survival gains. For example, over 90% of PCs harbor a KRAS gene mutation, which appears to occur very early in pancreatic carcinogenesis (Singh & Chaudhary, 2015). Tests which can detect rare mutant genes e.g., in duodenal juice and stool of patients could lead to earlier PC detection or differentiation of PC from CP.

As the results suggest, the impact of early detection on clinical benefit is limited by available treatment options. Advances for example in *neoadjuvant therapy* could increase the number of resectable tumors and reduce the risk of cancer recurrence after resection. The survival benefit of neoadjuvant therapy has already been reported for gastric cancer and is widely accepted for resectable rectal cancer, as up to 50-60% of patients are downstaged (Oba et al., 2020). While definite conclusions about the survival benefit of neoadjuvant therapy for PC are lacking, in recent meta-analyses resectability rates after neoadjuvant therapy ranged in between 66 to 89% (Singh & Chaudhary, 2015). Another strong predictor for PC survival is *adjuvant chemotherapy*. Statistically significant improved survival after surgery with adjuvant therapy compared to no adjuvant therapy could be demonstrated in at least two trials and improved regimes could further improve survival in the future, for example by further exploring the role of additional radiotherapy (Singh & Chaudhary, 2015). Also, improvements of the *surgical procedures* for PC resection could improve patient outcomes. Total pancreatectomy is a procedure where more tissue is removed, minimizing the chance of recurrence. Improving the QoL for patients after total pancreatectomy, which today is associated with increased surgical mortality and morbidity could increase its appropriateness. The same is the case for extended lymphadenectomy, a procedure to remove lymph nodes which can be performed in addition to a pancreatoduodenectomy (Singh & Chaudhary, 2015). PC spread to the lymph nodes is associated with a median survival of <17 months compared with 5-year survival rates of up to 38 % in patients without lymph node involvement. However, as of today, the procedure is contested, because of increased risk of morbidities. Another hindrance for margin-negative resection is the presence of vascular involvement, e.g., in the superior mesenteric vein and artery. While technically complex with morbidity imposed to patients, vascular resection as part of regional pancreatectomy and reconstruction of a short segment of the portal vein or superior mesenteric vein could increase the number of patients who can undergo curative resection and therefore provide a survival benefit. Another driver for clinical benefit is surgery in *high-volume centers*, which study results associate with reduced postoperative mortality rates as well as increased overall survival (Singh & Chaudhary, 2015). The definition of high-volume centers is ambiguous. The NCCN defines it at centers with at least 15-20 annual PC resections (NCCN, 2021a).

6. CONCLUSION

The objective of this master's thesis was to evaluate an early-detection strategy for PC and investigate 1.) its cost-effectiveness among a targeted NOD population compared to the current SoC and 2.) its clinical benefit for PC cases in the NOD population compared to the current SoC. Therefore, a DAM framework was designed, accounting for a wide range of uncertain parameters.

The results indicate that while the TED strategy is technically cost-effective compared to the SoC at a $100,000 WTP threshold among a NOD population including individuals of age 50 years or older and with glycemic-defined DM, the clinical benefit is not meaningful, and costs are not lower. Therefore, it is not useful to form a decision based on the ICER. Among only PC patients in the NOD populations, however, the gain of LYs and QALYs is likely to be clinically relevant. Hence, we may also conclude that detecting PC earlier among patients with NOD does have a positive impact for those concerned. In addition, the results showed that adding a biomarker test to the enrichment strategy did not lead to much different clinical benefits compared to existing analyses where only a prediction model has been used.

A key take-away from this thesis is that the positive outcomes of early-stage PC detection in terms of LYs and QALYs gained are strongly limited by available treatment options. Improvements of (neo)adjuvant therapy as well as reduced morbidity and mortality of complicated surgical procedures could allow more patients to undergo resection surgery and improve the survival outlook afterwards. In addition, population-based interventions aiming at smoking cessation and prevention of obesity and DM could also reduce the burden of PC, by lowering its incidence in the first place.

Also, while there are many DAMs for the economic evaluation of PC interventions available, the frameworks and underlying data varies a lot, even for comparable analyses. While there always will be variety of findings across smaller studies, international collaborations, and data exchange as well as standardized model frameworks could make future research more meaningful and comparable.

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APPENDIX A: FIGURES

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Fig. A- 1. American Joint Commitee on Cancer AJCC TNM Staging of Pancreatic Cancer (Kakar et al., 2017)

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Fig. A-2. AJCC Prognostic Groups for pancreatic cancer (NCCN, 2021b)

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Fig. A-3. ECOG Performance Status Scale (Oken et al., 1982)

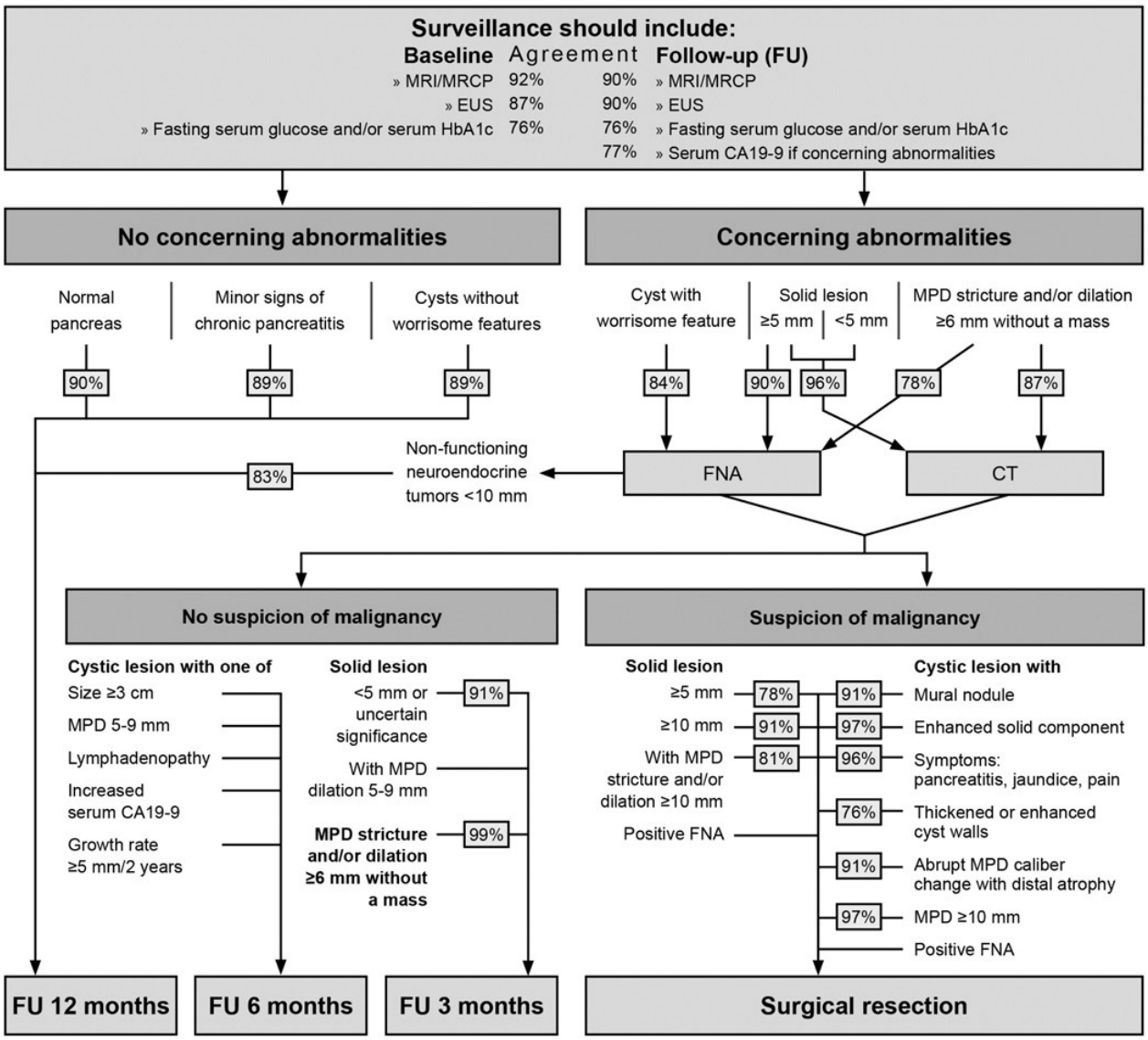

Fig. A-4. Decision flow-chart for the management of pancreatic abnormalities found during surveillance. EUS, endoscopic ultrasound; FNA, fine-needle aspiration; MPD, main pancreatic duct; MRCP, magnetic retrograde cholangiopancreatography. (Goggins et al., 2020)

Blood Glucose (BG) Categories		Δ BG Category Score (NOD-1y) (A)
BG range (mg/dl)	**Score**	**Score Range**
BG category at −1 years		1–4
<100	1	
100–109	2	
110–125	3	
BG category at glycemically-defined new-onset diabetes		
126–160	4	
>160	5	
Δ Weight Categories		**Δ Weight score (B)**
Δ Weight (kg)	Score	Score Range
≤ −6.0	+6	−6 to +6
−5.9 to −4.0	+4	
−3.9 to −2.0	+2	
−1.9 to +1.9	0	
+2.0 to +3.9	−2	
+4.0 to +5.9	−4	
≥ +6.0	−6	
Age (years) at glycemically-defined new-onset diabetes		**Age score (C)**
Age range	Score	Score Range
≤59	−1	−1 to +1
60 to 69	0	
≥70	+1	
Total Score		**A + B + C**

Abbreviations: BG, blood glucose; NOD, new-onset diabetes

Fig. A- 5. END-PAC score parameters (Sharma, Kandlakunta, et al., 2018)

APPENDIX B: TABLES

Tab. B-1. Model-time dependent clinical probabilities used in the MCM (SEER, 2022)

Description	Year								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10+**
Prob of death with RPC at diagnosis (%)	43.8	20.8	10.3	4.8	3.2	2.7	3.4	1.7	4.5
Prob of death with LAPC at diagnosis (%)	48.5	45.4	32.4	21.1	15.3	11.0	8.0	7.7	5.6
Prob of death with MPC at diagnosis (%)	82.1	59.8	37.5	24.4	17.6	14.3	8.3	13.6	11.1

Tab. B-2. Probability of death with T2DM across different age groups (Wright et al., 2016)

Description	Age (Years)						
	50-54	55-59	60-64	65-69	70-74	75-79	80+
Prob of death with T2DM (%)	0.7	0.9	1.4	2.0	3.1	4.8	11.6

Tab. B-3. Estimated costs (in estimated 2022 thousand U.S. dollars) per PC stage that is used as a state in the MCM and number of years in the respective state. (Mariotto et al., 2020)

Costs (in 2022 thousand U.S. dollars)	**Phase**	
	Initial	**Cont.**
Costs of RPC	79.8	11.4
Costs of LAPC	121.7	18.5
Costs of MPC	101.1	33.6

APPENDIX C: FORMULAS

Formula C-1: Reconstructed calculation of T3cDM probability depending on serum adiponectin and IL-1Ra levels by fitted logistic regression model bases on data from Oldfield (2022)

$$p(T3cDM)_{pred} = \frac{exp(\ OR_{intercept} + OR_{adiponectin} * SL_{adiponectin} + \ OR_{IL-1Ra} * SL_{IL-1Ra}}{(1 + \ exp(\ OR_{intercept} + OR_{adiponectin} * SL_{adiponectin} + \ OR_{IL-1Ra} * SL_{IL-1Ra})}$$

$$with:$$

$$p(T3cDM)_{pred} = \ predicted\ probability\ of\ T3cDM$$

$$\mathrm{OR_{intercept}} = \text{Odds ratio of intercept} = -4.201$$

$$\mathrm{OR_{adiponectin}} = \text{Odds ratio of serum adiponectin} = 0.279$$

$$\mathrm{OR_{IL-1Ra}} = \text{Odds ratio of serum IL} - 1\text{Ra} = 0.019$$

$$SL_{adiponectin} = \ sample\ \text{adiponectin}\ level\ measurement\ (\mu g/mL)$$

$$SL_{IL-1Ra} = \ sample\ \ IL-1Ra\ level\ measurement\ (\mu g/mL)$$