Early-Stage Cost-Effectiveness Analyses of New Health Care Technologies

By ©**Shweta Mital**

Thesis submitted to the School of Graduate Studies in

partial fulfillment of the requirements for the degree of

Doctor of Philosophy

within the

School of Pharmacy, Memorial University of Newfoundland

February 2021

St. John's, Newfoundland and Labrador, Canada

Abstract

With the rapid pace of technological innovation in health care alongside rising health care costs, policymakers need to decide which innovations are worth adopting from an economic perspective. Cost-effectiveness analyses – especially those conducted at an early stage of the life cycle of a technology -- are useful tools to identify technologies which can yield better patient outcomes that justify the costs of these technologies.

In this thesis, I provide the first evidence on cost-effectiveness of four new health care technologies. In chapter 2, I investigate the cost-effectiveness of Teplizumab, the first-ever drug to prevent or delay onset of Type 1 diabetes. A market price for this drug has not yet been established and there exist differences in the drug's efficacy based on genetic and antibody characteristics of patients. Thus, in this study, I identify price ranges within which the drug will be cost-effective for different patient groups. In chapter 3, I examine the cost-effectiveness of a novel, but highly controversial, weight loss technique – aspiration therapy – versus bariatric surgery. I find that even though aspiration therapy is not cost-effective versus bariatric surgery, it is cost-effective for patients who do not have access to bariatric surgery. In chapter 4, I assess the cost-effectiveness of using Elipse – the first procedureless intragastric balloon – as a substitute or complement to bariatric surgery for treatment of obesity, and find that providing Elipse prior to sleeve gastrectomy is the most cost-effective treatment approach. In chapter 5, I examine the cost-effectiveness of using artificial intelligence (AI) or polygenic risk scores (PRS) to risk-stratify women aged between 40 and 49 years for mammography screening and find that AI-based screening is

cost-effective compared with PRS-based screening and screening based exclusively on existing guidelines by the United States Preventive Services Task Force, the American College of Obstetricians and Gynecologists and the American College of Radiology.

These four studies can serve to inform decision-making by manufacturers, policymakers, clinicians and other stakeholders with regard to these emerging technologies.

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor and mentor, Dr. Hai Nguyen, for giving me the opportunity to pursue this PhD and providing relentless guidance, mentorship and motivation throughout. I will forever be indebted to you for all the knowledge that you have imparted to me and for nurturing the researcher within me.

I would also like to thank Dr. Stephen Bornstein for being on my supervisory committee and providing me valuable guidance. Special thanks to the Dean of School of Pharmacy, Dr. Shawn Bugden, for encouraging my research work in the annual School of Pharmacy Research Day presentations.

I also wish to express my thanks to authors of the Sheffield Type 1 Diabetes Policy Model and the University of Wisconsin Breast Cancer Epidemiology Simulation Model for allowing me to adapt their models to the context of my study (this permission by these authors, however, does not imply that they endorse the studies in this thesis).

Finally, the completion of this thesis would not have been possible without the support of my family. I am extremely grateful to my parents and my brother for their unwavering support in my academic pursuits and for providing inspiration and encouragement throughout the course of my studies.

Chapter 2 is a post-peer-review, pre-copyedit version of an article published in *PharmacoEconomics* (reprinted in this thesis by permission from [Springer Nature

Customer Service Centre GmbH]: [Springer Nature] [PharmacoEconomics Vol 38: 1359-1372] [(Cost-Effectiveness of Teplizumab for Prevention of Type 1 Diabetes among Different Target Patient Groups (doi:10.1007/s40273-020-00962-y), Mital, S., Nguyen, H.V.), [Copyright©] (2020)).

Chapter 3 contains a non-final version of an article published in final form in the *American Journal of Gastroenterology: (Mital, Shweta; Nguyen, Hai V. Incremental Cost-Effectiveness of Aspiration Therapy vs Bariatric Surgery and No Treatment for Morbid Obesity, The American Journal of Gastroenterology: September 2019 - Volume 114 - Issue 9 - p 1470-1477 doi: 10.14309/ajg.0000000000000359)* and a response to the letter to editor for this article which is a non-final version of an article published in final form in the *American Journal of Gastroenterology: (Mital, Shweta; Nguyen, Hai V. Response to Jirapinyo et al., The American Journal of Gastroenterology: March 2020 - Volume 115 - Issue 3 - p 482-483 doi: 10.14309/ajg.0000000000000541).*

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

AI	Artificial Intelligence
ACOG	American College of Obstetricians and Gynecologists
ACR	American College of Radiology
AFT	Accelerated Failure Time
AUC	Area Under the Receiver Operating Characteristic Curve
BMI	Body Mass Index
BCSC	Breast Cancer Surveillance Consortium
CISNET	Cancer Intervention and Surveillance Modeling Network
CVD	Cardiovascular
ESRD	End-stage renal disease
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Perfect Information
EWL	Excess Weight Loss
FDA	Food and Drug Administration
HDL	High Density Lipoprotein
HLA	Human Leukocyte Antigen
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan Meier

LYG	Life Year Gained
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
PIGB	Procedure-less Intragastric Balloon
PRIME	PRIority MEdicines
PRS	Polygenic Risk Scores
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard deviation
SNP	Single Nucleotide Polymorphisms
USPSTF	US Preventive Services Task Force
UWBCS	University of Wisconsin Breast Cancer Epidemiology Simulation model
VOI	Value of information
WTP	Willingness to Pay

Chapter 1 : Introduction and Overview

1.1 Technological innovation and rising health care costs

"As an economist who studies health care, I find it hard to know whether to welcome or fear new technology."

Jonathan S. Skinner, 2013 (1)

The 21st century has ushered in an era of rapid technological innovation[1] in health care. Recent estimates indicate that the global private sector alone spends nearly US$160 billion annually on health care research and development (R&D) (2). A prime example of the scale and speed of innovation can be appreciated from the fact that the time and cost to sequence the human genome – a task believed extremely arduous in the 1980s (3) -- have fallen from 13 years and US$1 billion in 2003 to 2 hours and US$1,000 in 2019 (4). Besides next generation sequencing, other examples of breakthrough innovations include point-of-care diagnostics that allow convenient and timely diagnostic testing, stem cell therapy to treat otherwise fatal diseases, digital innovations like biosensors and trackers for real-time patient monitoring, and artificial intelligence and robotics that improve speed and accuracy in screening and treatment (5,6).

Even though some new health technologies may improve health outcomes, technological innovation has been indicted as a key contributor to rising health care costs (7). In the US, for instance, it is estimated that 40-50% of the annual increase in health care spending is

[1] In this thesis, I follow World Health Organization (WHO)'s definition of health technologies which encompasses "*devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives*" (2). Meanwhile, following the Canadian Advisory Panel on Healthcare Innovation, innovation refers to "*activities that generate value in terms of quality and safety of care, administrative efficiency, the patient experience and patient outcomes*" (3).

due to new, expensive health care technologies (8). The cost impact of new technologies depends on several factors such as whether the technology substitutes or complements existing care, leads to changes in the care delivery process or extends life expectancy and thus prolongs health care consumption (9). Nevertheless, limited health care budgets necessitate that policymakers account for these cost impacts, alongside other considerations, when making adoption and reimbursement decisions.

To make evidence-based decisions, reimbursement agencies in some countries (such as UK, Canada, Australia (10) and most recently, Japan (11)) incorporate economic evaluations into reimbursement and coverage decisions for new pharmaceutical products. However, not all countries do. The hesitance to using economic evidence in coverage decisions in the US is a key example (12). Even where economic evaluations are required for reimbursement approval, long turnaround times, technicality of reports, use of inappropriate health-related quality of life data, etc. often imply that real-time evidence that aligns with policymakers' needs and priorities is not available (13–15). Furthermore, health technology assessment (HTA) processes for medical devices are not as streamlined as for pharmaceuticals. For instance, in Canada, many funding decisions for medical devices are made by hospital administrators in the absence of formal HTA evidence (16). Manufacturers are not required to supply HTA information and even though some provinces conduct ad-hoc assessments, hospitals may choose not to follow recommendations based on these assessments (16).

The fallout of this lack of evidence-based decision making is that, amidst growing pressures to fund new technologies, policymakers are unable to appropriately weed out low-value from high-value innovations. As a result, adoption of health technologies is plagued by both over-utilization of low-value technologies and under-utilization of high-value technologies.

1.2 Early-stage cost-effectiveness analyses as tools to harness the innovation potential

1.2.1 Early-stage cost-effectiveness analyses: The concept

Cost-effectiveness analyses[2] –especially those conducted at early stages of a technology's life cycle -- can serve as useful tools to aid decisions relating to product development, adoption, reimbursement and further evidence generation for new health technologies. Cost-effectiveness analyses compare costs and outcomes of two or more interventions to determine whether incremental costs of adopting a new intervention justify the additional benefits (17). The goal of these analyses is to maximize health outcomes given the health care budget (18).

Early-stage HTA is a broader concept that includes not only cost-effectiveness analyses but also other methods such as headroom analyses, methods to elicit stakeholder preferences, multicriteria decision analyses, etc. (19). Different definitions of early-stage HTA have been used in the literature. Most recently, IJzerman *et al*. defined early-stage HTA as "*all methods used to inform industry and other stakeholders about the potential*

[2] For a description of cost-effectiveness analyses, please refer to Appendix A1.1

value of new medical products in development, including methods to quantify and manage uncertainty" (19). This definition of early-stage HTA can, nevertheless, be extended analogously to early-stage cost-effectiveness analyses.

Combining this definition by IJzerman *et al.* (19) with phases of product development outlined by Grutters *et al*. (20), early-stage cost-effectiveness analyses thus refers to cost-effectiveness analyses of technologies conducted during the stages of conceptualization of product idea, product development and clinical research until the technology receives regulatory approval (i.e., until the Phase III clinical trial stage for drugs or the pre-market launch stage for devices) as shown in Figure 1.1. It is noted, however, that while IJzerman *et al.*'s definition of early HTA also includes technologies in the early stages of clinical use that have received regulatory approval, whether these technologies can still be classified as early is debatable (20). Therefore, for the purposes of this thesis, only analyses of technologies that have not yet received regulatory approval are classified as 'early-stage'.

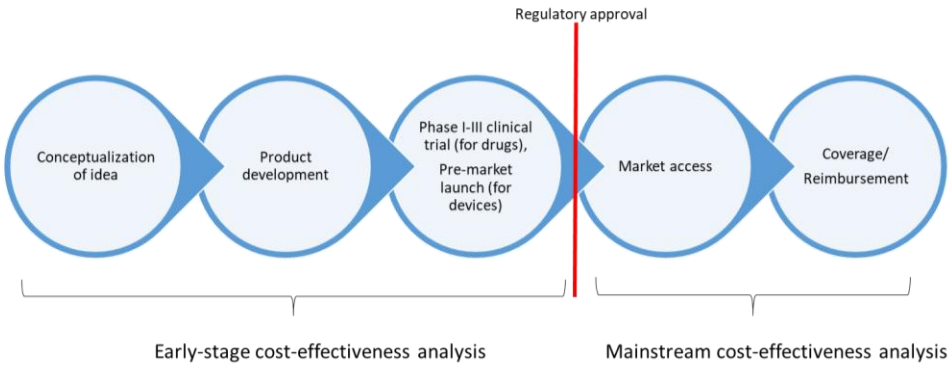


Figure 1.1: Early-stage cost-effectiveness analysis by stage of product development

1.2.2 Uses of early-stage cost-effectiveness analyses

Early-stage cost-effectiveness analyses can serve several purposes:

i) Informing product research and development (R&D) and pricing: Lack of early collaboration and dialogue with policymakers precludes inventors of new technologies from knowing which products will meet the demands of the health system (21), creating uncertainty for the manufacturer regarding future licensing and reimbursement at a time when considerable investment in product R&D has already been made. Early-stage cost-effectiveness analyses can aid manufacturers' decision-making in terms of stop/go decisions, identifying potentially successful technologies that will be of value to the health system and their predicted future demand, identifying the most efficient research designs to collect needed clinical evidence and informing pricing decisions and strategies for market access and reimbursement (21–23). Such estimations can limit future uncertainty for manufacturers (21–23).

ii) Early signals on potentially high-value technologies: Early-stage cost-effectiveness analyses can provide early signals to decision makers on potential high-value technologies and, thereby, help to inform public spending decisions for health technology R&D as well as speed up adoption of these technologies by informing later reimbursement and formulary decisions (23). This idea is akin to *horizon scanning* in which novel and emerging technologies that are not yet approved, but which have a potential to meet unmet health care needs, are identified and assessed (24). Notably, even though cost analyses are

commonly performed, cost-effectiveness analyses are not currently included in horizon scanning exercises (23).

iii) Identification of cost-effective care pathways: Even though new health technologies invariably increase health care costs, their cost-effectiveness depends on how they are positioned in the clinical pathway (25). Early-stage cost-effectiveness models offer the opportunity to directly compare cost-effectiveness of alternative ways of positioning new innovations within the clinical care pathway. Thus, while a new technology may not be cost-effective compared with existing alternatives, it may still be valuable if, for instance, it is offered as an add-on to existing treatments or provided only to specific patient subgroups. Knowledge of exactly how a new technology can best add value to existing care can help guide its future adoption.

iv) Timely decision-making for newly emerging technologies: As IJzerman et al. suggest, early cost-effectiveness analyses and simulation modelling can be useful in the context of personalized medicine technologies which are characterized by a rapid rate of development, dynamic and complex treatment strategies, and where standard approaches to evidence generation (e.g., randomized controlled trials) may not be viable (19). Examples of such technologies include genetic technologies and artificial intelligence.

1.2.3 Uncertainty in early-stage cost-effectiveness analyses

Uncertainty is inherent in all cost-effectiveness analyses and arises on several accounts including uncertainty in parameter estimates used to populate the model, methodological choices and model structure (26,27). However, given the immaturity in evidence base at

early stages of a technology's development, uncertainty is particularly pronounced in early-stage cost-effectiveness analyses: the technology may not yet have been examined in clinical trials (if in conceptualization of idea/product development stage) or studied in only a small, select group of patients, long-term intervention effects are unknown and real-world effectiveness of an intervention may differ from that observed in clinical trials (28).

While uncertainty in early-stage cost-effectiveness analyses is inevitable, uncertainty that poses a risk of making wrong decisions (i.e., 'decision uncertainty') represents a challenge in decision-making for new technologies (26,28). For manufacturers, this decision uncertainty could mean inappropriate stop-go, product portfolio and pricing decisions. Meanwhile, where early-stage cost-effectiveness analyses inform future adoption and coverage decisions, such uncertainty could result in providing access to an inefficient technology or denying access to a technology that could in fact generate positive net health benefits.

Wrong decisions can impose irreversible costs on stakeholders (as depicted in Figure 1.2 below). For instance, for manufacturers, investment in technologies that turn out to be cost-ineffective based on evidence generated at later stages of product development (and are thus not covered) can mean substantial capital losses. For reimbursement agencies and decision makers, wrong decisions can result in sunk costs in terms of investment in technology, personnel training, etc. (27). Further, approval of a technology for coverage based on existing evidence eliminates the incentives for manufacturers to engage in further evidence development (27). For patients, negative health outcomes can ensue both in case of lack of or delayed access to effective technologies 'wrongly' deemed cost-ineffective

based on existing evidence or from access to technologies deemed cost-effective based on current information but with potential to result in negative health outcomes.

Uncertainty analyses, therefore, have a critical role in early-stage cost-effectiveness analyses. For manufacturers, value of information (VOI) analyses[3] performed within a Value Engineered Translation framework have been recommended (29,30). These analyses can help identify areas for further evidence generation and the most efficient research designs to collect such evidence with a goal to meet future regulatory and reimbursement criteria (30).

For reimbursement agencies and decision-makers, coverage with evidence development and patient access schemes (such as 'Only with Research' and 'Only in Research' schemes) are potential solutions to address decision uncertainty wherein patients get timely access to new technologies while additional evidence is generated to inform future decisions and re-appraisals (27,28). As these schemes allow manufacturers and reimbursement agencies to share risks associated with decision uncertainty, it is important to appropriately characterize patterns of uncertainty inherent in risk sharing arrangements. Analyses using net benefit probability maps, which depict the distribution of uncertainty over time and uncertainty around when an investment in a new technology would break even, can be useful tools for this purpose (28). Further, VOI analyses can help determine what additional evidence must be collected within these schemes, whether the value of this additional

[3] For a description of value of information analyses, please refer to Appendix A1.1

evidence justifies the additional cost of its collection and the most efficient research designs to use to gather this evidence (27,28,30).

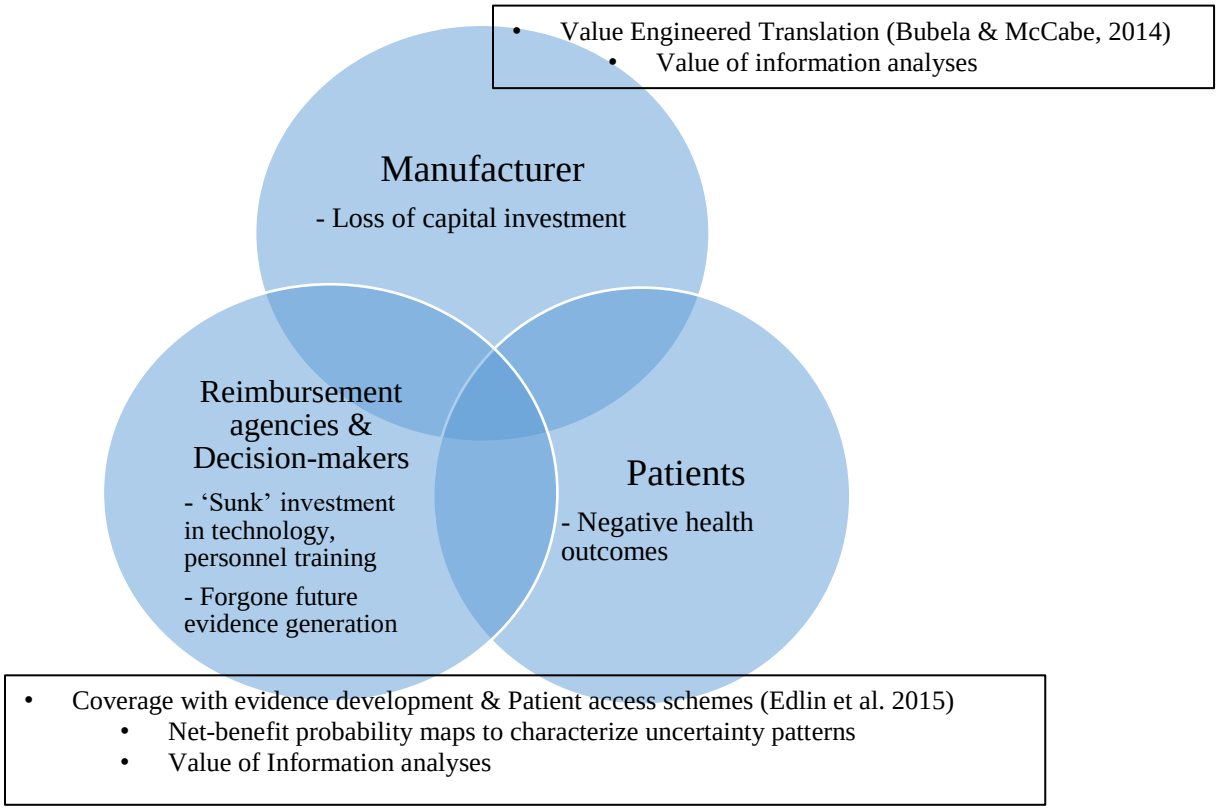


Figure 1.2: Costs of decision uncertainty to different stakeholders and role of uncertainty analyses

1.2.4 Characterization of heterogeneity in early-stage cost-effectiveness analyses

The Second Panel on Cost-Effectiveness in Health and Medicine recently recommended including patient heterogeneity within cost-effectiveness analyses in general (31). However, in most cost-effectiveness analyses, heterogeneity is often not considered which can be explained by factors such as inadequate availability of clinical evidence on patient subgroups, lack of credibility of subgroup-level findings due to small patient populations

and equity considerations for decision-making (32,33). Patient heterogeneity can arise on several accounts including demographic factors, treatment effects, patients' disease history and severity of illness, factors related to health-care delivery and patients' preferences for alternative treatments (34).

Characterization of heterogeneity in cost-effectiveness analyses for decision-making is important (arguably more so than in clinical effectiveness analyses) because restricting provision of a new intervention only to patients for whom it is cost-effective (vs existing interventions) ensures that gain in health exceeds that displaced elsewhere in the health system; that is, resource allocation can be made more efficient (34). Potential benefits of considering heterogeneity within early-stage cost-effectiveness analyses include: (i) facilitating differential price setting by manufacturers based on expected value of their innovation for different patient subgroups; (ii) informing future reimbursement decision-making; and (iii) gaining insights on the value of additional evidence on variability across individual patients or subgroups (32,35). These benefits, however, need to be balanced against the often limited and uncertain evidence base at the individual/subgroup level for technologies in early stages of development.

Several frameworks have been developed to incorporate heterogeneity within cost-effectiveness analyses. These can broadly be classified into three categories based on the level of stratification and decision-making as described below: (i) patient subgroup level; (ii) individual patient level; and, (iii) population level with implicit consideration of heterogeneity.

In the first category, Hoch et al. suggested using standard regression methods within a net-benefit framework where interaction terms between the new intervention and patient subgroups are used to examine the marginal cost-effectiveness of the intervention at the subgroup level (36). Meanwhile, Coyle et al. suggested stratifying cost-effectiveness analyses by patient subgroups to identify 'efficient limited use criteria' whereby a new technology is reimbursed only for patients with positive net benefits (37). Importantly, their framework allowed accounting for losses due to equity-efficiency trade-offs and non-adherence to limited use criteria observed in real practice (37). Espinoza et al. further expanded this framework to identify the most appropriate criteria to define subgroups and the optimal level of stratification (32). Further, they introduced the concept of 'dynamic value of heterogeneity' which refers to the value of additional research to resolve uncertainty in subgroup-specific evidence (32).

While the above frameworks focused on subgroups of patients, Basu and Meltzer examined the gains from individualized decision-making whereby cost-effectiveness of treatments is assessed at the individual patient level, after accounting for differences in individual preferences and attributes that influence the net health benefit from an intervention (35). By contrast, Kim and Basu emphasized the need to account for heterogeneity within population-level decision making (as opposed to individualized decision making) (38). They suggest a framework to estimate the value of alternative policies (instead of alternative interventions) that induce differential adoption of the intervention across patient subgroups (38).

1.3 Thesis Objective

The objective of this thesis is to contribute to the literature on early-stage cost-effectiveness analyses by providing the first evidence on cost-effectiveness of four new health care technologies that are in the early stages of their life cycle. The goal is to provide rigorous evidence that can help inform decision-making by manufacturers, policymakers, clinicians and other stakeholders.

1.4 Thesis Outline

This thesis follows the manuscript style. Chapters 2-5 contain cost-effectiveness analyses of each of the four innovations. These are briefly outlined below. A graphical depiction of the position of these four innovations within the early-stage cost-effectiveness framework is shown in Figure 1.3 below.

In **Chapter 2,** I conduct an early-stage cost-effectiveness analysis of a new drug, Teplizumab, for prevention of Type 1 diabetes. Teplizumab is the first-ever drug that, after over 30 years of research, has been recently shown to prevent or delay onset of Type 1 Diabetes in at-risk patients in a Phase II clinical trial (39). Findings from this trial were published recently in the *New England Journal of Medicine* (39). Teplizumab has been accorded 'breakthrough therapy' designation by the US Food and Drug Administration (FDA) (40). Furthermore, as a biologic drug, it is anticipated to be expensive when it arrives on the market (expected in 2021) (41). As such, policymakers, payers and the manufacturer of Teplizumab will face the challenge of choosing a price for this drug that

can maximize access to Teplizumab for at-risk patients while ensuring budget sustainability for payers and commercial viability for the manufacturer.

In this study, I combine headroom-type threshold analyses with rigorous economic modelling to identify price ranges for which this drug will be cost-effective for different target patient groups. As such, findings from this study can be used to inform value-based pricing and reimbursement for this drug. The manuscript has been published in *PharmacoEconomics*.

In **Chapter 3**, I provide the first evidence on the cost-effectiveness of a newly invented weight loss device, aspiration therapy, relative to bariatric surgery and no treatment for morbid obesity. Aspiration therapy is less invasive, reversible and cheaper than bariatric surgery. Even though the product is past the clinical research stage and has been recently approved by FDA and Health Canada, this product is still within the early stages of its life cycle, especially as its regulatory approvals have been subject to considerable debate with critics demanding a revocation of these approvals on the grounds that the therapy may lead to bulimia and binge eating disorders (42). Owing to this controversy, clinical acceptability and availability of this treatment is extremely limited and its further adoption into clinical practice is unclear.

This manuscript was published in the *American Journal of Gastroenterology*. It gathered attention of clinicians at the Brigham and Children's Hospital in the US who wrote a letter to the editor. A response to their letter has also been published in the *American Journal of Gastroenterology*.

Chapter 4 examines the cost-effectiveness of the first-ever procedure-less intragastric balloon (Elipse™). The process for pre-market approval of Elipse by the FDA is ongoing (43). Unlike previous intragastric balloons, Elipse does not require endoscopy for insertion or removal. Further, even though its weight loss effects are lower and temporary compared with bariatric surgery, it is less costly and entails lower risk of complications. These features make it attractive as a stand-alone treatment or as an add-on to bariatric surgery. However, as yet, no study has compared the cost-effectiveness of these alternative strategies of including Elipse (and intragastric balloons, more broadly) into the care pathway.

In **Chapter 5,** I examine the cost-effectiveness of using an emerging technology that is still in development -- Artificial Intelligence (AI) -- to risk-stratify women aged between 40 and 49 years for breast cancer screening. There is a lack of consensus in existing guidelines over appropriate breast cancer screening strategies, especially for women in the 40 to 49 age group. Professional societies such as the American College of Obstetricians and Gynecologists and American College of Radiology recommend annual screening for all women starting at age 40 (44) while the US Preventive Services Task Force recommendation to screen women aged between 40 and 49 years without family history is only a grade C recommendation (i.e., the net benefit of screening in this group is small) (45,46). A recent study showed that Artificial Intelligence (AI) can be used to predict breast cancer risk (47). The accuracy of AI-based risk prediction estimated in this study is even higher than that reported previously for and Polygenic Risk Scores (PRS) (48). Using AI or PRS to identify and target screening at high-risk patients can be cost-effective compared

with screening based on existing guidelines. To date, however, no study has compared these AI-based, PRS-based and guideline-based screening approaches. The study in this chapter fills this gap.

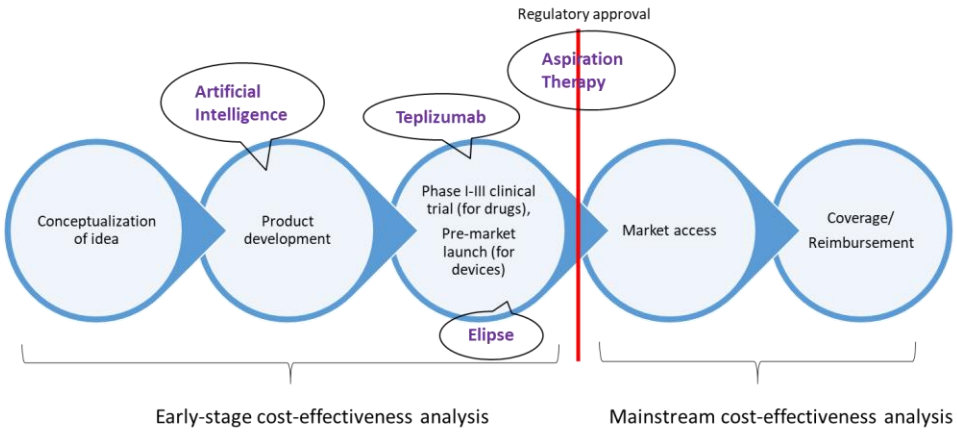


Figure 1.3: Position of innovations in the early-stage cost-effectiveness framework

Chapter 6 summarizes the key findings of my studies and highlights how these early-stage cost-effectiveness analyses can serve to inform decision-making for these new interventions. It also details the challenges and limitations in the 4 studies in Chapters 2-5 and measures taken to overcome them.

1.5 Existing literature

Literature review indicated no existing evidence on the cost-effectiveness of the 4 technologies under consideration in Chapter 2-5. Nevertheless, in what follows, I provide

a brief overview of the existing literature relevant to each chapter, along with the gaps in this literature.

1.5.1 Cost-effectiveness of interventions for Type 1 diabetes

Existing cost-effectiveness analyses relating to Type 1 diabetes have examined alternative insulin types (e.g., long-acting vs. intermediate acting insulin (49)), and mechanisms of glucose monitoring (50) and insulin delivery (e.g., continuous subcutaneous insulin infusion vs. multiple daily injections (51)) among patients with Type 1 diabetes. Recent studies have also examined cost-effectiveness of screening programs for pre-symptomatic Type 1 diabetes patients (52). Most of these studies have utilized rigorous, previously validated microsimulation models such as the CORE Diabetes Model (53) or the Sheffield Type 1 Diabetes Policy Model (54).

Yet, in the absence of an effective prevention strategy for Type 1 diabetes thus far, these studies have focused only on screening and treatment interventions.

1.5.2 Cost-effectiveness of weight loss interventions

There exists a vast literature on cost-effectiveness of different bariatric surgery procedures (gastric bypass, gastric banding, sleeve gastrectomy) in different patient populations varying by geography, age and co-morbidity status (e.g., (55–60)). In these studies, bariatric surgery is compared with usual care (such as lifestyle interventions or conventional diabetes management for diabetes patients). Other studies have compared cost-effectiveness of weight loss drugs with lifestyle interventions and no treatment (61,62). Markov model is, by far, the most commonly employed modeling technique.

There are, however, two key gaps in this literature. First, most existing studies compare alternative approaches of the same treatment type (such as alternative types of bariatric surgery or alternative weight loss drugs (e.g., (56,57,63)) or compare a treatment with standard care (e.g., bariatric surgery versus usual care (64)). While one recent analysis compared different non-surgical treatments such as pharmacotherapy and one intragastric balloon (Orbera) (65), it did not consider bariatric surgery which is known to be more effective than these interventions (66). Second, existing studies do not assess cost-effectiveness of combinations of different treatments. As a result, as new weight loss procedures enter the market, the existing literature does not sufficiently inform decision-makers on optimal care pathways for obese patients -- for instance, triaging patients across treatments or providing a procedure as a bridge to another.

1.5.3 Cost-effectiveness of breast cancer screening and AI-based risk prediction

The extensive, long-standing literature on cost-effectiveness of breast cancer screening has primarily focused on comparing alternative starting ages and frequencies of screening in different populations, as well as different modalities of breast imaging such as digital mammography, tomosynthesis, ultrasound, magnetic resonance imaging (MRI), or combinations thereof (67–78).

A key limitation of these studies, however, is that these studies do not account for the newly emerging technologies, such as AI and PRS, which can capture heterogeneity in patient risk and thereby optimally target breast cancer screening. While a few recent studies have accounted for risk stratification in their cost-effectiveness analyses (75–78), these studies

have mostly relied on traditional predictors such as breast density, family history, childbearing and menstrual history, etc., which are often less accurate than these newer technologies in predicting breast cancer risk (47). Only one study (Pashayan *et al*. (79)) has examined cost-effectiveness of PRS-based risk stratified mammography screening versus screening all women within a specific age group or no screening. However, Pashayan *et al*. employed a simplified life table approach to estimating costs and effectiveness instead of rigorous modeling approaches. Their approach did not allow them to account for critical parameters -- such as variation in treatment costs and utility losses associated with different cancer stages – that can be influenced by better targeted screening.

More generally, previous studies have demonstrated diverse potential applications of AI in various sub-fields of medicine – from image interpretation in radiology to assessing embryo quality for in vitro fertilization and interpretation in genomics (80). Yet, evidence on cost-effectiveness of using AI in healthcare is limited (81), especially in the medical imaging domain where potential for leveraging AI powered solutions is enormous. To my knowledge, previous studies have only performed economic evaluations of using artificial intelligence to read fundus photographs to detect diabetic retinopathy compared with human grading (82,83).

Consequently, the economic base to guide policymakers on adoption of this emerging technology is extremely thin. In particular, no evidence exists on the cost-effectiveness of AI versus PRS for risk stratification.

1.5.4 Early-stage cost-effectiveness analyses of new health technologies

Several literature reviews have examined the development of the literature on early stage cost-effectiveness analyses (and early-stage HTA more broadly) over time. These studies have sought to inform the uses to which early-stage assessments can be employed (23,84), methods used and the underlying challenges (19,22,85–87), and more recently, the role of clinicians in these early assessments (88). With regard to the purpose of these assessments, Hartz and John reviewed economic assessments that used early-stage data to highlight the role these evaluations can play in decision making by the industry (84) and by public health policymakers (23), respectively. For industry, they highlighted the benefits of early-stage assessments for preliminary market assessment, portfolio management, informing go/no-go decisions, decisions on future trial design and future pricing policies (84). However, they noted that empirical studies did not clearly state their purpose in most instances (84). For policymaking, they suggested that these assessments could guide diffusion, adoption and reimbursement of new technologies as well as public sponsorship of new technologies (23). Nevertheless, the actual use of current evidence on early assessments in policymaking was difficult to determine (23).

In terms of methods, IJzerman and Steuten (2011) used a theoretical framework based on product development stages, clinical case analyses and decision contexts and reviewed the various techniques that have been used and/or proposed for early-stage HTA (22). These methods were further iterated by Markiewicz et al. (2014) in the context of medical devices and include headroom analyses, cost-effectiveness/cost-benefit/cost-utility analyses, multi-criteria decision analyses, value of information analyses, roadmapping processes,

real options analyses, return on investment analyses, Bayesian modelling and discrete choice experiments (22,85). However, Markiewicz et al. noted the existence of multiple frameworks and the need for a standardized, agreed-upon framework that integrates these different methods to enhance the value of early assessments (85). Not surprisingly, the biggest challenge noted across these reviews is decision uncertainty due to uncertainty in evidence base during early phases of a product's development (22,85). Belief elicitation, multi-criteria decision analyses, scenario analyses and Delphi panels are some methods suggested to address this challenge (22).

More recently, in 2017, two further scoping reviews encompassing studies relating to a broad range of technologies and HTA methods were conducted. Fasterholdt et al. reviewed 24 early-stage assessments of new health care technologies published between 1996 and 2015 (87) while IJzerman et al. included 22 studies published between 2013 and 2017 (19). A common finding across both these reviews was that the majority of reviewed studies used health economic modelling approaches and headroom analyses (19,87). Furthermore, uncertainty was addressed mostly using sensitivity and scenario analyses (19,87), although IJzerman et al. also noted the use of belief elicitation methods by some studies as a tool to reduce uncertainty (19). IJzerman et al concluded that methods that combine systems engineering approaches (including multicriteria decision analyses and optimization analyses) with health economic approaches need to be developed to better address uncertainty (19).

To examine the most recent trends and developments in this literature, I conducted an updated scoping review of early-stage economic analyses published between January 2017

and February 2021. This time period was chosen as studies published prior to 2017 have already been covered by the seminal review by IJzerman et al. in 2017 and other previous reviews mentioned above (1 review study was conducted after 2017 but the focus of this review was narrower as it included only early-stage evaluations of medical devices (88)).

A systematic search was performed using a combination of keywords and MeSH terms across 3 databases: PubMed, Scopus and EconLit. The full list of search terms used for each database are provided in Appendix A1.2. Studies were included if these were published between January 1, 2017 and February 8, 2021. Given the focus of this thesis on early-stage cost-effectiveness and headroom analyses, the review focused on early-stage assessments that used one or more types of cost-effectiveness/cost-utility/cost-benefit analyses and/or headroom analyses. Studies were included if they examined a technology that was in the early stages of its lifecycle, i.e., had not yet been approved (for the specific indication) in the country where the analysis was performed. Where regulatory approval was granted in the same year as the publication of the study, a study was included only if its publication date was before the date of regulatory approval. Furthermore, a technology that was approved only with conditions of clinical governance, additional research or audit, was still considered early stage and was thus included. Only English language articles were included. Review and methodological studies were excluded as were studies that did not involve any technology, such as rehabilitation programs, food-labelling initiatives etc. Publications of regulatory/reimbursement appraisal reports were excluded.

The search yielded 1149 unique articles and 9 articles were obtained from other sources including citation pearling of included studies. After screening based on titles and abstracts

and assessing full texts for eligibility, 38 articles were included in the review (Appendix A1.3). A detailed description of these studies is provided in Appendix A1.4.

Several key findings emerge from this review. First, majority of the reviewed studies related to medical tests, devices and procedures; less than one-quarter (8 out of 38) of all studies were early assessments of drugs. This relative lack of early-stage evaluations for drugs (relative to other technologies) may reflect the current paradigm in which health technology assessments for drugs are performed mostly at the reimbursement stage, after the drug has obtained regulatory approval. However, it also highlights an area where the potential of early-stage economic evaluations can be more fully exploited, especially as number of expensive drugs (especially biologics) continue to rise (89) and countries (for example, Canada (90)) increasingly shift towards pricing based on pharmacoeconomic value thresholds.

Second, in 18 of the 38 studies, the technology had not reached the clinical trial/pre-market launch stage. In most of these instances, the purpose of the study was therefore to inform further product development and investment, especially in terms of identifying cost and efficacy targets to achieve for the product to be cost-effective. As such, headroom analyses were commonly employed, either alone or in combination with cost-effectiveness/cost-utility analyses. However, as was also observed in previous reviews (84,87), it is worth noting that the decision context and purpose of conducting the assessment as well as the exact stage of development were not clearly stated in all studies.

Third, where stated, the perspective adopted in the early-stage evaluations was that of the payer, health system or the societal perspective. This choice of perspective reflects the fact that, even where the immediate goal of (very) early-stage assessments was to inform further product development and investment, the overarching objective was to ensure that the 'fourth hurdle' to market access could be overcome.

Fourth, as observed in earlier reviews (19,87), deterministic and probabilistic sensitivity analyses continue to be the mainstay of uncertainty analyses performed in early-stage evaluations. Only 6 of the 38 studies used VOI analyses. Further, only 2 studies used expert elicitation to obtain an estimate of the technology's efficacy and one study used scenario drafting. Several studies relied only on assumptions with regard to efficacy estimates. Thus, there is further scope for integration of VOI analyses and belief elicitation approaches alongside cost-effectiveness and headroom analyses.

Fifth, most early-stage evaluations have not captured patient heterogeneity. Only 9 studies considered some form of heterogeneity at the patient subgroup level. Newer methods proposed to integrate heterogeneity within economic evaluations such as individual patient level analyses and methods that account for differences in technology adoption across different patient subgroups have not been used.

Finally, 14 of the 38 studies have been performed in Netherlands and 9 in the UK. Such concentration to a limited set of countries highlights the need to communicate the role and value of early-stage evaluations to stakeholders in other countries.

1.6 Thesis Contributions

In addition to contributing the first evidence on the cost-effectiveness of the four new interventions as well as adding to the literature on early-stage cost-effectiveness analyses, each study in this thesis also makes several other contributions. These are outlined below and summarized in Box 1.1.

1.6.1 Contributions to medical literature

Cost-effectiveness in Type 1 Diabetes prevention

The study in Chapter 2 is the first cost-effectiveness analysis of Teplizumab – a breakthrough intervention to prevent Type 1 diabetes. With over 100,000 adolescents diagnosed with Type 1 diabetes annually worldwide, a rapid rate of annual increase in Type 1 diabetes incidence of 3% (91), as well as the associated risks of serious complications that pose a significant economic burden, the decision on who gets access to this breakthrough innovation and at what price will be critical from a health economic perspective.

Cost-effectiveness of bariatric surgery versus non-surgical interventions

The studies in Chapters 3 and 4 represent one of the first comparisons of cost-effectiveness of bariatric surgery with endoscopic weight loss procedures and intra-gastric balloon therapy, respectively. Furthermore, the study in Chapter 4 is the first cost-effectiveness analysis to compare the use of intra-gastric balloon therapy as a substitute or adjunct to bariatric surgery in morbidly obese patients. With limited access to and uptake of bariatric

surgery both in US and Canada (92,93), these analyses can help inform clinicians, policymakers and payers on cost-effective approaches to deliver weight loss treatments.

Cost-effectiveness of AI technology in medicine

The study in Chapter 5 contributes to the limited literature on cost-effectiveness of AI applications in medicine. In particular, it is the first study to examine the cost-effectiveness of using AI in the field of radiology. A further novelty of this study is that it is the first to directly compare cost-effectiveness of AI-based vs. PRS-based risk stratification in medicine. Given the increasing shift towards individualized health care, both these technologies will see widespread (and possibly competing) applications throughout medicine. Although their cost-effectiveness will vary depending on application, a general understanding of their relative cost-effectiveness will be useful to guide future adoption and coverage of these continuously-evolving technologies.

1.6.2 Contributions to HTA literature

Integration of genetic heterogeneity within early-stage cost-effectiveness analyses

The study in Chapter 3 is among the first studies to integrate genetic heterogeneity within early-stage cost-effectiveness analyses to determine price ranges of drugs that would render them cost-effective. This analysis, can therefore, not only guide value-based provision and reimbursement for a given price of Teplizumab (when it arrives on the market) but can also inform price-volume negotiations as well as differential pricing for different target patient groups. More generally, the framework of this study can be easily adapted to inform value-based pricing of other drugs whose treatment effects are genetically determined.

Contribution to the growing literature on value of information analyses

Given the limited evidence on efficacy of new technologies considered, in Chapter 6, I conduct value of information (VOI) analyses to quantify the expected benefit of eliminating uncertainty in the cost-effectiveness analyses for Teplizumab and Elipse intragastric balloon. These VOI analyses contribute to the growing literature on VOI analyses and can enable decision makers to assess the expected net gain in terms of benefits of additional evidence that reduces uncertainty versus the losses in health outcomes due to delayed adoption of these novel interventions (94).

Box 1.1: Contributions by thesis chapter

Chapter 2

- First cost-effectiveness analysis in Type 1 diabetes prevention.
- Incorporation of genetic heterogeneity in treatment effects within early-stage cost-effectiveness analyses to inform drug pricing and reimbursement.

Chapter 3

- First cost-effectiveness analysis to compare bariatric surgery with a non-surgical, endoscopic weight loss procedure.

Chapter 4

- First study to compare use of intragastric balloon therapy as a substitute or adjunct to bariatric surgery.

Chapter 5

- First cost-effectiveness analysis of using AI in the field of radiology
- First cost-effectiveness analysis of AI and PRS as alternative risk prediction tools in medicine.

Chapter 2 : Cost-Effectiveness of Teplizumab for Different Target Patient Groups

This is a post-peer-review, pre-copyedit version of an article published in *PharmacoEconomics*: *Mital, S., Nguyen, H.V. Cost Effectiveness of Teplizumab for Prevention of Type 1 Diabetes Among Different Target Patient Groups. PharmacoEconomics 38, 1359–1372 (2020). doi:10.1007/s40273-020-00962-y.*

The final authenticated version is available online at: https://link.springer.com/article/10.1007/s40273-020-00962-y

Abstract

Objective: Teplizumab is the first-ever drug recently shown to prevent or delay Type 1 diabetes onset in at-risk individuals, especially in those with certain genetic and antibody characteristics. However, its potentially high price may pose challenges for coverage and reimbursement for payers and policymakers. Thus, it is critical to investigate the cost-effectiveness of this drug for different target individuals.

Research Design and Methods: Using Markov microsimulation modelling, we compared cost-effectiveness of 5 options for choosing target individuals (i.e., all at-risk individuals, individuals without Human Leukocyte Antigen (HLA)-DR3 *or* with HLA-DR4 allele, individuals without HLA-DR3 *and* with HLA-DR4 allele, individuals with anti-Zinc Transporter 8 (ZnT8) antibody negative and no provision at all) at different possible prices of Teplizumab. Effectiveness was measured by quality-adjusted life-years. Costs were estimated from health system perspective.

Results: If the price of Teplizumab therapy is below US$48,900, treating all at-risk individuals is cost-effective. However, it will be cost-effective to treat only individuals without HLA-DR3 *or* with HLA-DR4 alleles for prices between US$48,900 and US$58,200, only individuals both without HLA-DR3 *and* with HLA-DR4 alleles for prices between US$58,200 and US$88,300, and only individuals with negative ZnT8 antibody status for prices between US$88,300 and US$193,700.

Conclusions: Cost-effective provision of Teplizumab to target individuals depends on the price of Teplizumab and genetic and the antibody characteristics of treated individuals. As

the drug makes its way to the market, findings from this study will help inform policymakers and payers on cost-effective ways to provide this innovative but expensive drug to at-risk individuals.

2.1 Introduction

Type 1 diabetes is an auto-immune disorder that occurs due to the destruction of insulin-producing beta cells in the islet of Langerhans region of the pancreas (95). The disease affects nearly 1.25 million children and adults in the United States (US) (96). Furthermore, first-degree relatives of Type 1 diabetes patients have a 15-fold increase in risk of developing Type 1 diabetes themselves (97). Treatment for Type 1 diabetes involves lifelong dependence on external insulin, which not only causes the inconvenience of daily insulin jabs but also imposes severe economic burden on patients and health care systems. In the US, annual health care costs attributed to Type 1 diabetes were estimated at over US$14.4 billion (98). In particular, rising insulin costs (99) have induced patients to ration insulin use, use less-effective and harder-to-manage forms of insulin, or even travel to countries such as Canada, Mexico and European nations to purchase insulin at a cheaper cost (100,101).

Recently, a Phase II clinical trial showed that *Teplizumab* -- an Fc receptor–nonbinding anti-CD3 monoclonal antibody -- can reduce loss of beta cell function and thus prevent or at least delay onset of Type 1 diabetes among at-risk relatives of Type 1 diabetes patients (39). It is delivered as a one-time, 14-day course of treatment, administered intravenously in an outpatient setting (39). Median delay of Type 1 diabetes onset observed in the Phase II trial was two years and particularly, for individuals with anti–zinc transporter 8 (ZnT8) antibody--negative, Human Leukocyte Antigen (HLA)-DR3--negative or HLA-DR4—positive, the median delay was nearly 4 years (39). As the first drug that can prevent or delay onset of Type 1 diabetes, Teplizumab has received ‘breakthrough therapy’

designation from the US Food and Drug Administration in August 2019 (40) and 'PRIority MEdicines (PRIME)' designation from the European Medical Agency in October 2019 (102), with an expected market launch date in 2021 (40).

Although Teplizumab holds considerable promise for improved health outcomes, better quality of life, and reduction of downstream health care costs (especially insulin costs) for individuals at-risk of developing Type 1 diabetes, there are some indications that this biologic drug may even cost over US$100,000 per patient (41). Such high cost will pose challenges for policymakers and insurers in terms of coverage and reimbursement. If the drug's price is excessively high, it may not be possible to reimburse the drug's cost for all at-risk individuals. In such case, access to this drug may need to be restricted to individuals who are more likely to respond to the drug. Even so, there may be a need to choose among several groups of at-risk individuals because the drug is more effective in individuals without HLA-DR3 allele, with HLA-DR4 allele or with negative ZnT8 antibodies (39).

The objective of this study is to assess the cost-effectiveness of providing Teplizumab to different groups of at-risk individuals at different possible prices of the drug. This economic analysis can help shed light on specific group(s) of individuals for whom Teplizumab offers highest value at a certain price of the drug. Such information is especially important at this early-stage of the drug's development as it can help inform payers' early planning efforts and their choices with respect to coverage and reimbursement as well as manufacturer's pricing of the drug when it enters the market (19,103,104).

2.2 Research Design and Methods

2.2.1 Choice of target patient groups for Teplizumab

We estimated cost-effectiveness of 5 different options with respect to choice of target groups for the drug. These include providing Teplizumab to each of 4 different groups of at-risk individuals (described below) and no provision of Teplizumab at all (i.e., the usual care) (Figure A2.1, Appendix 2).

Although choice of target groups could be made based on their risk of Type 1 diabetes development and/or likelihood of drug response, the drug may not be as effective for high-risk individuals with more severe autoimmune response (39). Consequently, our choice of different target groups was driven by likelihood of drug response determined by: (i) genetic characteristics (HLA-DR allele status); and, (ii) possible extent of autoimmune response (ZnT8 antibody status).

Specifically, the first target group included all at-risk relatives of Type 1 diabetes patients. The next two groups focused on individuals with HLA-DR alleles that best predict drug response. Group 2 included individuals with *at-least one of the two* favorable HLA-markers (namely, those without HLA-DR3 allele *or* with HLA-DR4 allele *or* both), accounting for 76% of all at-risk individuals in the Phase II trial(39). In group 3, we further restricted access to the drug to only those *both* without HLA-DR3 *and* with HLA-DR4, which would predict highest response to the drug among the four HLA-DR3/DR4 combinations. This group accounted for 54% of group 2 (and for 41% of all individuals at risk (39)).

Group 4 comprised of individuals who tested negative for ZnT8 antibodies (regardless of their HLA-DR allele status). This group represented 26% of all individuals at risk (39). Individuals with negative ZnT8 antibodies were found to have the highest response to the drug, likely due to less severe immune-mediated islet cell destruction (39). While other antibodies (such as glutamic acid decarboxylase 65, islet antigen 2, and islet-cell autoantibody) are also associated with Type 1 diabetes, no difference in drug response was associated with the presence of these antibodies (39). Thus, these antibodies were not considered.

2.2.2 Model structure

We developed a hybrid decision tree/Markov microsimulation model to estimate the cost and effectiveness of each of the 5 options for provision of the drug. The decision tree component of the model captured genetic and antibody testing and administration of Teplizumab (Figure 2.1). Genetic testing involved genotyping the HLA-DR antigen while antibody testing comprised of islet-cell antibody test (specifically, the ZnT8 antibody test). The microsimulation component, which was adapted from the Sheffield Type 1 Diabetes Policy Model (54), simulated the progression of at-risk individuals from pre-type 1 diabetes to Type 1 diabetes and eventually to diabetes-related complications. Details of the Sheffield Type 1 Diabetes Policy Model have been published elsewhere (54).

In the microsimulation component, all at-risk individuals started in the pre-type 1 diabetes state. In each year, they faced risk of developing Type 1 diabetes; risk of developing Type 1 diabetes was lower in individuals receiving Teplizumab relative to those not receiving

the drug. Once an individual developed Type 1 diabetes, s/he faced risk of diabetes-related complications including microvascular complications (neuropathy, nephropathy and retinopathy), macrovascular complications (myocardial infarction, stroke, revascularization and angina), diabetic ketoacidosis and hypoglycemia (54). Patients faced mortality risks from cardiovascular events and end-stage renal disease as well as from causes unrelated to diabetes (54). The analysis was conducted from a health care system's perspective. Cycle length was one year, and lifetime horizon was used. All analyses were performed using TreeAge 2019 v2.1 (105).

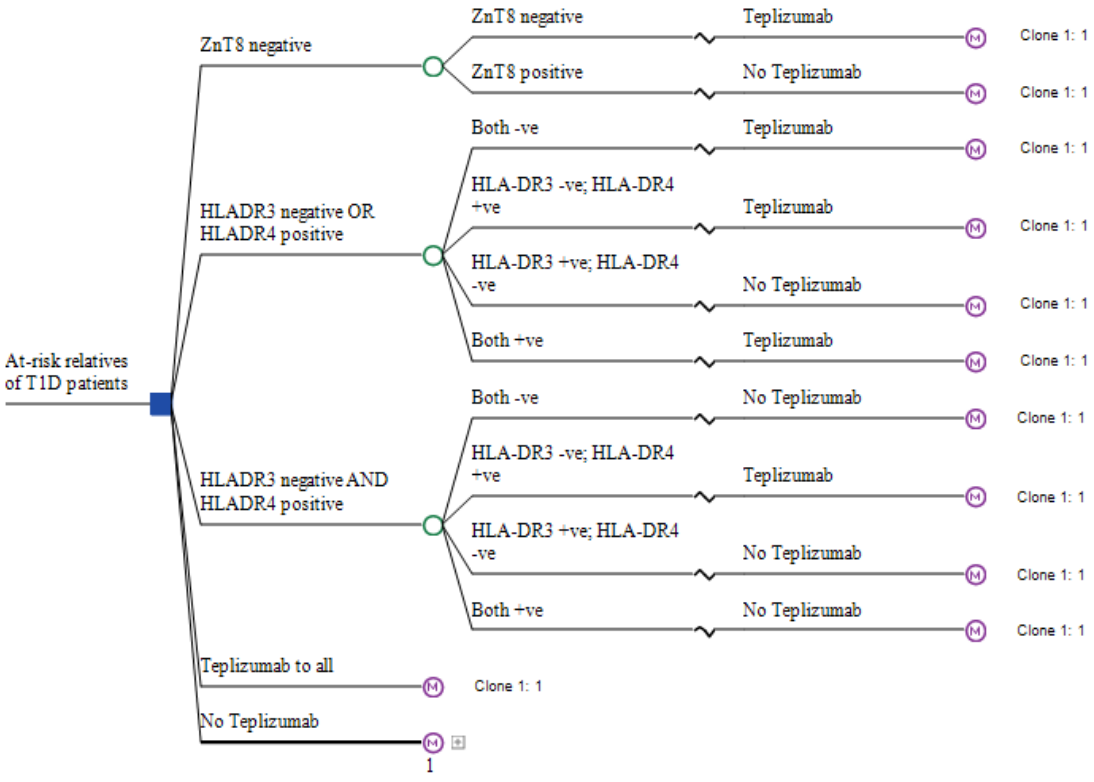


Figure 2.1: Decision Tree

Notes: T1D: Type 1 Diabetes; HLA-DR3: Human Leukocyte Antigen DR3; HLA-DR4: Human Leukocyte Antigen DR4; ZnT8: Zinc Transporter 8

2.2.3 Study Cohort

We simulated a hypothetical cohort of 10,000 individuals at risk of developing Type 1 diabetes who were aged 8-49 years, were relatives of Type 1 diabetes patients and met the criteria for being at high risk for Type 1 diabetes development as defined in the Phase II clinical trial of Teplizumab (39). To mirror the age distribution of the study cohort in this trial, we assumed that 66% of the cohort was aged below 18 years. Within the 8-17 and 18-49 age groups, distribution of individuals mirrored the age distribution of the US population in 2018 (106). The full set of demographic and clinical characteristics assumed for the hypothetical patient cohort are provided in Table A2.1 in Appendix 2.

2.2.4 Model inputs

Model inputs are described below and presented in Table 2.1.

Teplizumab efficacy and risk of developing Type 1 diabetes

Data on the efficacy of Teplizumab in delaying Type 1 diabetes onset were from the Phase II clinical trial (39) and were available for all individuals at risk and separately for groups of individuals defined by their HLA-DR3 status, HLA-DR4 status and ZnT8 antibody status. These efficacy data were presented in the form of Kaplan Meier (KM) curves that showed time-to-Type 1 diabetes over the trial period. We converted these time-to-Type 1 diabetes event data to annual risk of developing Type 1 diabetes for use in our Markov model. We proceeded in 2 steps. First, as we did not have access to raw individual patient data that were used to generate the KM curves, we reconstructed the raw data by digitizing the KM survival curve (107,108). Second, we applied survival modelling techniques to

convert these reconstructed raw data to annual risk of developing Type 1 diabetes (109,110). Further details of these two steps are provided in Appendix A2.3.

We note that annual risk of developing Type 1 diabetes described above could only be obtained separately for HLA-DR3 positive, HLA-DR3 negative, HLA-DR4 positive and HLA-DR4 negative subgroups. To use these risk estimates in our model where groups of at-risk individuals were defined by *combinations* of HLA-DR3 and HLA-DR4 statuses, we assumed that annual risk of developing Type 1 diabetes for each specific combination was an average of the Type 1 diabetes risks for the respective HLA-DR3 and HLA-DR4 statuses (values are shown in Table 2.1). We tested the robustness of our results to this assumption in the sensitivity analyses below.

Transition probabilities after occurrence of Type 1 diabetes

Probabilities of developing diabetes-related complications and progression through these complications were based on the Sheffield Type 1 Diabetes Policy Model (54). Risk of mortality from causes unrelated to diabetes was age- and sex-specific, and was obtained from the (latest available) 2017 US life tables (111).

Adverse effects from Teplizumab

Rash and lymphopenia were the main complications associated with Teplizumab (39). However, in the Phase II trial, rash resolved spontaneously and even though lymphopenia resolved in a maximum of 105 days, differences in rates of infection (a consequence of

lymphopenia) between patients receiving Teplizumab and placebo were not statistically significant (39). Thus, our model did not include Teplizumab-induced complications.

Costs

Cost of each option included cost of HLA-DR or ZnT8 tests (if applicable), cost of treatment with Teplizumab (if applicable), and annual health care costs depending on diabetes status and existence of diabetes complications. Cost of treatment with Teplizumab consisted of cost of the drug and cost of 14 outpatient visits (39). Costs of outpatient visits as well as cost of ZnT8 antibody and HLA-DR tests were obtained from Center for Medicare and Medicaid's 2019 Clinical Diagnostic Laboratory Fee Schedule (112). Annual health care costs of pre-type 1 diabetes were based on annual age-specific medical costs of prediabetes observed in the US (113). Costs of diabetes (without complications) comprised of annual costs of insulin treatment (which were dependent on body weight) (114) and cost of two physician visits per year. Costs of managing diabetes related complications, on average, were based on those used in a recent, high-quality published study (114). All costs were converted to 2019 US dollars using the consumer price index inflation calculator of the US Bureau of Labor Statistics (115) and discounted at 3.5% per year (116).

Effectiveness

Effectiveness was measured in terms of Quality Adjusted Life Years (QALYs) that captured a person's life expectancy adjusted by his/her health-related quality of life called utility. Utility was specific to diabetes status (namely, pre-type 1 diabetes or diabetes) and

was higher for children (age <=18) compared with adults (age>18). Utility values for children and adults with pre-type 1 diabetes were based on previously reported quality of life assessments of 12-18 year olds and adults with prediabetes, respectively (117,118). For patients with diabetes, utility values were obtained from Lee *et al*. (119) which elicited utilities from over 400 children and adults with Type 1 diabetes in the US. For patients who experienced diabetes-related complications, we applied utility decrements for each complication to the utility value for diabetes; these disutility values were sourced from the published literature (54,120). All utility values were discounted at 3.5% per year (116).

Table 2.1: Model Inputs

Variable	Value	Source
Probabilities		
Prevalence of ZnT8 antibody markers & HLA-DR alleles		
Zinc Transporter 8 antibody negative	0.263 (0.066)	(39)
HLA-DR3 negative, HLA-DR4 negative	0.107 (0.011)	(39)
HLA-DR3 negative, HLA-DR4 positive	0.413 (0.041)	(39)
HLA-DR3 positive, HLA-DR4 negative	0.24 (0.024)	(39)
Probability of developing diabetes		
No Teplizumab	0.305	Calculated based on KM survival curves in (39)
Teplizumab to all	0.147	
HLA-DR3 negative (with Teplizumab)	0.105	
HLA-DR3 negative (without Teplizumab)	0.379	
HLA-DR3 positive (with Teplizumab)	0.250	
HLA-DR3 positive (without Teplizumab)	0.224	
HLA-DR4 negative (with Teplizumab)	0.251	
HLA-DR4 negative (without Teplizumab)	0.166	
HLA-DR4 positive (with Teplizumab)	0.126	
HLA-DR4 positive (without Teplizumab)	0.400	
ZnT8 negative (with Teplizumab)	0.100	
ZnT8 negative (without Teplizumab)	0.595	
ZnT8 positive (with Teplizumab)	0.175	
ZnT8 positive (without Teplizumab)	0.259	
HLA-DR3 negative/HLA-DR4 negative (with Teplizumab)	0.178 (0.045)	Authors' calculations
HLA-DR3 negative/HLA-DR4 negative (without Teplizumab)	0.272 (0.068)	

HLA-DR3 negative/HLA-DR4 positive (with Teplizumab)	0.116 (0.029)			
HLA-DR3 negative/HLA-DR4 positive (without Teplizumab)	0.389 (0.097)			
HLA-DR3 positive/HLA-DR4 negative (with Teplizumab)	0.251 (0.063)			
HLA-DR3 positive/HLA-DR4 negative (without Teplizumab)	0.195 (0.049)			
HLA-DR3 positive/HLA-DR4 positive (with Teplizumab)	0.188 (0.047)			
HLA-DR3 positive/HLA-DR4 positive (without Teplizumab)	0.312 (0.078)			
Annual transition probabilities				
Healthy to Neuropathy*	0.0083			(54)
Healthy to Amputation	0.0003 (0.00008)			(54)
Neuropathy to Amputation	0.0154 (0.004)			(54)
Healthy to Microalbuminuria*	0.0179			(54)
Healthy to Macroalbuminuria*	0.00042			(54)
Healthy to ESRD	0.00 (0.00)			(121)
Microalbuminuria to Macroalbuminuria*	0.018			(54)
Macroalbuminuria to ESRD^	0.0042 (0.001) – 0.074 (0.019)			(121)
Death from Microalbuminuria due to ESRD	0.0004 (0.0001)			(54)
Death from Macroalbuminuria due to ESRD	0.007 (0.0018)			(54)
Death from ESRD	0.0884 (0.022)			(54)
Healthy to Background Retinopathy*	0.0028			(54)
Healthy to Proliferative Retinopathy*	0.00023			(54)
Healthy to Macular Edema*	0.00086			(54)
Healthy to Blindness	0.0000019 (4.7e-7)			(54)
Background Retinopathy to Proliferative Retinopathy*	0.0106			(54)
Background Retinopathy to Macular Edema*	0.0368			(54)
Background Retinopathy to Blindness	0.0001 (2.5e-5)			(54)
Proliferative Retinopathy to Blindness	0.0038 (0.0009)			(54)
Macular Edema to Blindness	0.0016 (0.0004)			(54)
Probabilities in case of CVD event†				
Angina	0.28 (0.07)			(54)
Stroke	0.07 (0.018)			(54)
Myocardial Infarction	0.53			(54)
Revascularization	0.12 (0.03)			(54)
Death from Revascularization in year of event	0.057 (0.014)			(54)
Death from Stroke in year of event	0.24(0.06)			(122)
Death from Myocardial infarction in year of event		Males	Females	(123)
	<=39 years	0.038 (0.01)	0.125 (0.03)	
	40-49	0.051 (0.01)	0.111 (0.03)	
	50-59	0.092 (0.02)	0.140 (0.04)	
	60-69	0.175 (0.04)	0.209 (0.05)	

	70-79	0.318 (0.08)	0.326 (0.08)	
	80-89	0.481 (0.12)	0.467 (0.12)	
	>=90	0.672 (0.17)	0.645 (0.16)	
Costs (in US$)				
Zinc Transporter 8 antibody test	23.57 (5.89)			(112)
HLA-DR test	106.14 (26.54)			(112)
Diabetic Ketoacidosis	16,863.33 (4,215.83)			(114)
Hypoglycemia	1498.32 (374.58)			(114)
Angina	9,340.02 (2,335,01)			(114)
Myocardial Infarction	47,078.79 (11,769.70)			(114)
Stroke event	62344.89 (15,586.22)			(114)
Revascularization	19,057.14 (4,764.29)			(114)
Amputation	59,979.21 (14,994.80)			(114)
Annual costs				
Pre-type 1 diabetes	Age <45: 342.06 (85.52); Age 45-64: 487.17 (121.79); Age >=65: 849.96 (212.49)			(113)
Diabetes with no complication[#]	5332.24+36.17*weight+229.42			(114)
Myocardial Infarction	2,602.31 (650.58)			(114)
Stroke	20806.88 (5,201.72)			(114)
Angina	4,044.23 (1,011.06)			(114)
Revascularization	2,001.60 (500.4)			(114)
Background Retinopathy	10,287.50 (2,571.88)			(114)
Proliferative Retinopathy	14865.38 (3,716.35)			(114)
Macular Edema	9,306.52 (2,326.63)			(114)
Blindness	5,079.51 (1,269.88)			(114)
Neuropathy	1,555.02 (388.76)			(114)
Amputation	2,110.38 (527.60)			(114)
Microalbuminuria	23.43 (5.86)			(114)
Macroalbuminuria	34.48 (8.62)			(114)
ESRD	117,736.97 (29,434.24)			(114)
Utilities				
Pre-type 1 diabetes	Age <=18: 0.91 (0.14) Age >18: 0.9 (0.23)			(117,118)
Diabetes with no complication	Age <=18: 0.89 (0.12) Age >18: 0.85 (0.17)			(119)
Angina	-0.09 (0.023)			(54)
Blindness	-0.208 (0.052)			(54)
ESRD	-0.023 (0.006)			(54)
Revascularization	-0.058 (0.015)			(54)
Hypoglycemia	-0.005 (0.001)			(120)
Diabetic Ketoacidosis	-0.001 (0.0003)			(120)
Macroalbuminuria	-0.017 (0.004)			(54)
Myocardial Infarction	-0.058 (0.015)			(54)
Neuropathy	-0.055 (0.014)			(54)

Amputation	-0.116 (0.029)	(54)
Stroke	-0.018 (0.004)	(54)

CVD: Cardiovascular; ESRD: End-stage renal disease; ZnT8: Zinc-transporter 8; HLA- Human Leukocyte Antigen

Standard deviations used for probabilistic sensitivity analyses are reported in parentheses.

* Value varies based on HbA1c. Coefficients of risk equations in (54) varied assuming standard deviation equal to 25% of mean value, except for probability of transition from microalbuminuria to macroalbuminuria for which standard deviation is assumed to be 5% of mean value.

^ Varies based on age.

Cost includes average cost of testing and equipment for insulin use (Mean (SD): US$5332.24 (US$1333)), cost of insulin which varies by age, gender and weight (Mean (SD): US$36.17 (US$9.04)) and cost of 2 outpatient visits per year (Mean (SD): US$114.71 (US$28.68) per visit).

† Probability of CVD event is determined based on age, duration of diabetes, TC, HDL cholesterol, systolic blood pressure, smoking status, macroalbuminuria and history of CVD events. Distribution of HDL cholesterol, systolic blood pressure and smoking status obtained from (114). For example, for a male patient aged 40 years who is not a smoker, having Type 1 diabetes for 30 years, HbA1c level of 7.6%, HDL of 53 mg/dl, TC of 166 mg/dl, SBP of 124 mmHg, previous history of macroalbuminuria but no previous CVD event, annual probability of having a macrovascular CVD event is 0.04. Similarly, for a patient with the same characteristics but with a previous CVD event, this probability increases to 0.11.

2.2.5 Threshold analysis and the Incremental Cost Effectiveness Ratio

We used threshold analyses to determine the price ranges of Teplizumab within which providing Teplizumab to a specific group of at-risk individuals would be cost-effective. Provision of the drug to a patient group was considered to be cost-effective relative to another if the Incremental Cost Effectiveness Ratio (ICER) (calculated as difference in two patient groups' costs divided by difference in two groups' QALYs) was lower than the willingness-to-pay (WTP) threshold of US$100,000 per QALY (124).

We conducted several scenario and sensitivity analyses to examine the robustness of our results. First, we conducted two-way sensitivity analyses in which we varied values of key inputs (cost of insulin and cost of managing diabetes complications) along with the price of Teplizumab (125). This analysis shed light on how cost-effectiveness of Teplizumab for a certain group of at-risk individuals varied for different possible combinations of cost of

Teplizumab and other health care system costs. As possible diabetes-related complications were several and varied, we used cost of managing ketoacidosis as a proxy for diabetes complications-related health care costs. Second, instead of using a lifetime horizon, we used a 10-year horizon. This shorter time horizon may be more relevant for third party payers while still sufficiently long to capture the benefits of delayed onset of Type 1 diabetes. Third, as Type 1 diabetes is primarily a juvenile onset condition and benefits of delaying onset are particularly pronounced for children (39), we narrowed the study cohort's age range to 8-17 years.

Next, instead of extrapolating risks of developing diabetes beyond the 5 year duration based on reconstructed data from KM survival curves, we considered two alternative scenarios: (i) both treated and untreated individuals in the model, who are Type 1 diabetes-free at the end of 5 years, develop Type 1 diabetes after year 5; and, (ii) risk of Type 1 diabetes onset becomes zero for individuals treated with Teplizumab who do not develop Type 1 diabetes at the end of 5 years while all individuals who do not receive Teplizumab develop Type 1 diabetes at end of 5 years. Further, our base case analysis conservatively used the average of two individual risks of Type 1 diabetes associated with HLA-DR3 and HLA-DR4 alleles as the risk of Type 1 diabetes onset in individuals with combinations of HLA-DR3 and HLA-DR4 alleles. To examine how our results are sensitive to this assumption, we used the lower value of the two individual risks of Type 1 diabetes onset instead, which implies a higher efficacy of the drug for individuals with these alleles.

Lastly, to address parameter uncertainty, we: (i) used disutility values for hypoglycemia and diabetic ketoacidosis from alternative sources; (ii) performed conventional one-way sensitivity analyses in which we varied key costs and utilities over a reasonably large range of +/-25% of base case values (125); and (iii) conducted probabilistic sensitivity analyses (PSA) in which we assigned distributions to input parameters and performed 100 second-order Monte Carlo simulations. In the PSA, we used standard deviations derived from the literature where available. Where unavailable, these were assumed to be 25% of base case values of parameters (126,127). Two exceptions were the prevalence of HLA-DR3 and HLA-DR4 allele combinations and probability of transition from microalbuminuria to macroalbuminuria for which we assumed standard deviation of 10% and 5%, respectively, to prevent the probabilities from exceeding 1. For one-way sensitivity analyses and PSA, we assumed that mean price of Teplizumab is US$100,000.

2.2.6 Model validation

While the microsimulation component of our model was adapted from an already validated model, we further assessed the validity of our model following the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool (128) and guidelines of the International Society for Pharmacoeconomics and Outcomes Research (129). First, to ensure face validity, one health economist independently developed the model. The model structure, assumptions, analyses and results were then evaluated by a senior health economist. Next, we conducted trace analysis for internal and external validation. Specifically, we first compared the modelled proportion of patients who

develop Type 1 diabetes after 5 years with proportions observed in the Phase II trial (i.e., dependent validation) for two patient groups (Teplizumab to all at-risk and no treatment). We further compared these modelled proportions for the no treatment group with the 5-year risk of Type 1 diabetes observed in the Diabetes Prevention Trial (DPT-1) -- a large, US-based multi-center randomized controlled trial (i.e., independent validation) (130). As this study is the first cost-effectiveness analysis of an intervention to prevent or delay Type 1 diabetes, cross validation could not be performed.

2.3 Results

2.3.1 Base case analysis

Base case results are presented in Table 2.2. The table shows that, as price of Teplizumab increases, the group of individuals for whom Teplizumab is cost-effective becomes smaller. Specifically, if Teplizumab is priced at or below US$19,600, giving Teplizumab to all individuals at-risk of developing Type 1 diabetes will be dominant (i.e., cost saving and more effective). If it is priced above US$19,600 but below US$48,900, giving Teplizumab to all at-risk individuals will entail higher costs compared with other patient groups but would also yield maximum QALYs, so that giving Teplizumab to all at-risk individuals will still be cost-effective (at a WTP threshold of US$100,000/QALY). However, if price of Teplizumab exceeds US$48,900, it will no longer be cost-effective to provide Teplizumab to all at-risk individuals. In this scenario, if price ranges between US$48,900 and US$58,200, it will be cost-effective to provide the drug only to individuals who are HLA-DR3 negative *or* HLA-DR4 positive (or both). If it is priced between

US$58,200 and US$88,300, treating only individuals with both HLA-DR3 negative *and* HLA-DR4 positive will be cost-effective. If the price is even higher -- between US$88,300 and US$193,700 -- only individuals with negative ZnT8 antibody markers could be provided the drug for it to be cost-effective. Finally, treatment with Teplizumab will not be cost-effective for any patient group we considered if its price exceeds US$193,700.

Table 2.2: Optimal options for different price ranges of Teplizumab

Price range	Optimal option	Result for optimal option relative to other options
$1 - $19,598	Teplizumab to all at-risk	Dominant
$19,598 - $48,956	Teplizumab to all at-risk	Cost-effective
$48,956 - $58,235	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$58,235 - $88,325	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$88,325 - $193,779	ZnT8 negative	Cost-effective
>$193,779	No Teplizumab	

Notes: All costs are in 2019 US dollars (US$). This base case analysis is based on a lifetime horizon. HLA-DR3: Human Leukocyte Antigen DR3; HLA-DR4: Human Leukocyte Antigen DR4; ZnT8: Zinc Transporter 8

To put a comparison of strategies into perspective, in Table 2.3, we present results for one potential price of Teplizumab, namely, US$100,000. At this price, providing Teplizumab to patients with negative ZnT8 antibody markers costs US$1,203 more than the least costly alternative of no treatment, but also yields 0.26 greater QALYs over a patient's lifetime. The resulting ICER of US$4,647 is much lower than the conventional WTP threshold of US$100,000 per QALY. While providing Teplizumab to successively broader patient groups generates higher QALYs than providing only to those with ZnT8 negative, these additional QALYs are insufficient to justify the additional costs; ICERs for the HLA-DR3

negative and HLA-DR4 positive, HLA-DR3 negative or HLA-DR4 positive and Teplizumab to all at-risk groups exceed the US$100,000 per QALY WTP threshold.

Table 2.3: Cost effectiveness results if Teplizumab is priced at US$100,000

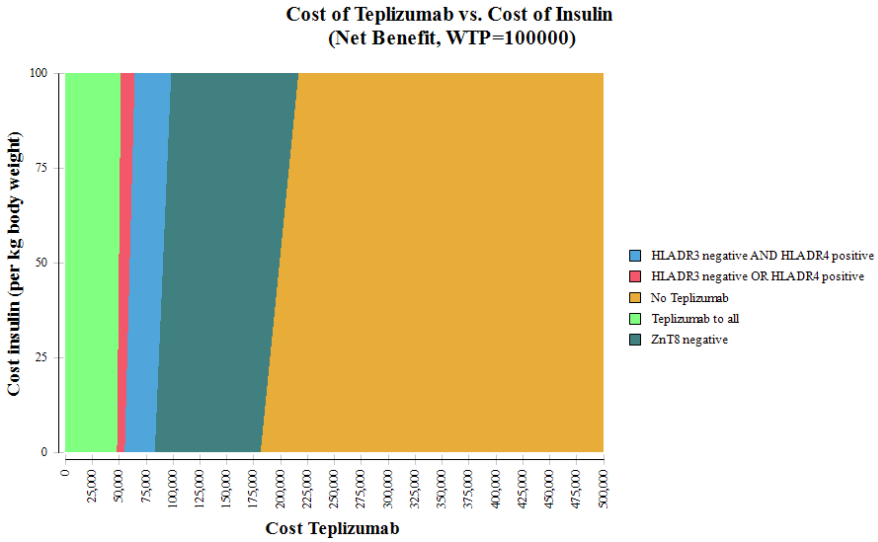
Strategy	Cost (US$)	Incremental Costs (US$)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER (US$/QALY)
No Teplizumab	360,904		18.72		
ZnT8 negative	362,107	1,203	18.98	0.26	4,647
HLA-DR3 negative and HLA-DR4 positive	373,265	11,158	19.07	0.09	119,702
HLA-DR3 negative or HLA-DR4 positive	399,666	26,401	19.19	0.12	217,871
Teplizumab to all at-risk	418,846	19,180	19.26	0.07	271,793

All costs are in 2019 US dollars (US$). ICER = incremental cost-effectiveness ratio. This base case analysis is based on a lifetime horizon.

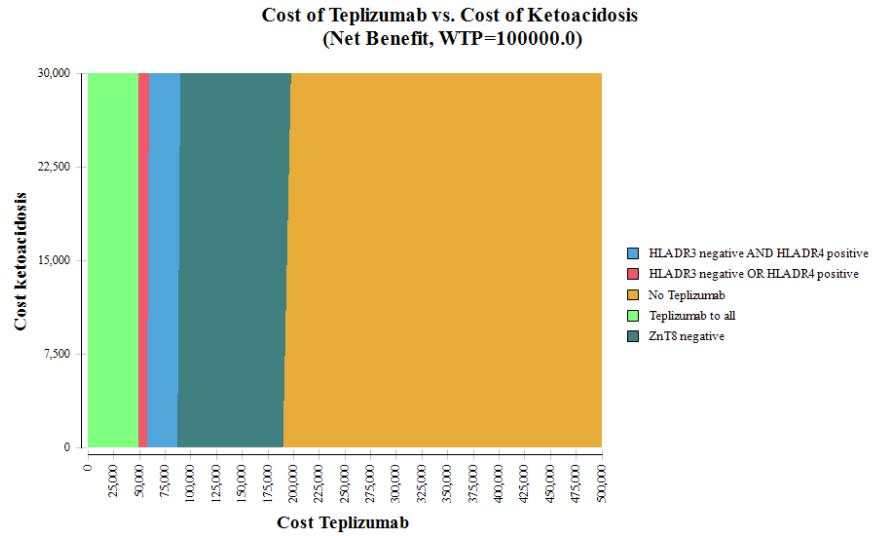
2.3.2 Scenario and sensitivity analyses

Figure 2.2 presents the results of the two-way sensitivity analyses. These figures show the different combinations of cost of diabetes management (cost of insulin in Figure 2.2(a) and cost of ketoacidosis management in Figure 2.2(b)) and price of Teplizumab together with the corresponding cost-effectiveness of the five patient groups. The graphs depict a trade-off between cost of diabetes management, price of Teplizumab and extent of treatment coverage. If cost of diabetes management is high (and assuming all other parameters are held constant), it is cost-effective to provide Teplizumab to the same patient group at a higher price or to expand treatment access to a broader patient group at the same price. For example, at a price of US$90,000, it will be cost-effective to provide Teplizumab to

individuals who have 'HLA-DR3 negative *and* HLA-DR4 positive' if diabetes management costs are high but only to a smaller group of individuals with negative ZnT8 antibody if diabetes management costs are low.



(a) Cost of Teplizumab vs. Cost of Insulin



(b) Cost of Teplizumab vs. Cost of Ketoacidosis

Figure 2.2: Two-way sensitivity analysis

Notes: HLA-DR3: Human Leukocyte Antigen DR3; HLA-DR4: Human Leukocyte Antigen DR4; ZnT8: Zinc Transporter 8

Further results of scenario and sensitivity analyses are presented in Table 2.4. Panel A shows that for a 10-year time horizon, price thresholds for Teplizumab to be cost-effective are substantially lower than those for a lifetime horizon. This is because the benefits of delayed onset of Type 1 diabetes accrue over a shorter time period. Meanwhile, as utility losses due to diabetes are lower for children compared with adults, price thresholds that render each patient group cost-effective are also slightly lower for children aged 8-17 years than when the sample also includes adults (Panel B). For instance, Teplizumab to all at-risk children will be cost-effective if it is priced below US$34,800 compared with US$48,900 when the sample also includes adults.

Panel C contains price thresholds and cost-effective treatment groups under the assumptions that all at-risk individuals who have not developed Type 1 diabetes by 5 years will do so after 5 years. As expected, price thresholds are lower relative to the base case. Meanwhile, Panel D shows that if the drug could 'completely cure' individuals who do not develop Type 1 diabetes during the first 5 years, it would be cost-effective to treat all at-risk individuals even if Teplizumab is priced as high as US$284,500.

When we used the lower value of the two risks of Type 1 diabetes onset for HLA-DR3 and HLA-DR4 alleles, treating individuals with at least one of the favorable HLA-DR markers will be cost-effective for a price of up to US$72,800. Compared with US$58,200 found in the base case (Panel E), this higher price threshold for cost effectiveness makes sense because the lower value (instead of the average value) of the two risks of Type 1 diabetes onset implies higher efficacy of the drug for individuals with favorable HLA-DR markers,

and hence, allows the manufacturer to charge a higher price for the drug while still retaining its cost-effectiveness.

The price thresholds obtained using alternative disutility values for diabetic ketoacidosis and hypoglycemia were very similar to those in our base case analysis (Table A2.4, Appendix 2), indicating that our results were robust to the choice of disutility values used for these adverse events.

The results from one-way sensitivity analyses conducted assuming a mean price of US$100,000 for Teplizumab are presented in the Tornado diagrams in Figure A2.4 (Appendix 2). These figures show that annual health care costs of diabetes and cost of treating end-stage renal disease (Figure A2.4(a)) as well as utility values for diabetes and pre-type 1 diabetes health states (Figure A2.4(b)) affect ICER the most. However, for all values of the health care costs and except for very low utility for diabetes or very high utility for pre-type 1 diabetes, treating only patients with 'ZnT8 negative' -- the target patient group identified in the base case -- remains cost-effective or dominant. The results from the PSA also indicate that at the WTP threshold of US$100,000 per QALY gained, giving Teplizumab to those who are ZnT8 negative is cost-effective in the highest number of iterations, namely, 29% (Figure A2.5, Appendix 2).

Table 2.4: Sensitivity analyses

Price range	Optimal option	Result for optimal option relative to other options
A: 10-year time horizon		
$1 - $6,858	Teplizumab to all at-risk	Dominant
$6,858 - $11,825	Teplizumab to all at-risk	Cost-effective
$11,825 - $19,002	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$19,002 - $30,012	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$30,012 - $57,752	ZnT8 negative	Cost-effective
>$57,752	No Teplizumab	
B: Sample of only children aged 8-17 years		
$1 - $17,339	Teplizumab to all at-risk	Dominant
$17,339 - $34,876	Teplizumab to all at-risk	Cost-effective
$34,876 - $58,451	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$58,451 - $88,633	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$88,633 - $210,602	ZnT8 negative	Cost-effective
>$210,602	No Teplizumab	
C: All patients develop Type 1 diabetes at end of 5 years		
$1 - $1,039	Teplizumab to all at-risk	Dominant
$1,039 - $26,734	Teplizumab to all at-risk	Cost-effective
$26,734 - $29,019	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$29,019 - $29,636	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$29,636 - $74,155	ZnT8 negative	Cost-effective
>$74,155	No Teplizumab	
D: Zero risk of Type 1 diabetes onset after 5 years		
$1 - $134,197	Teplizumab to all at-risk	Dominant
$134,197 - $284,475	Teplizumab to all at-risk	Cost-effective
$284,475- $330,284	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$330,284 - $444,890	ZnT8 negative	Cost-effective
>$444,890	No Teplizumab	
E: Minimum of the risks of Type 1 diabetes onset among HLA-DR3 and HLA-DR4 alleles		
$1 - $34,994	HLA-DR3 negative or HLA-DR4 positive	Dominant
$34,994 - $72,871	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$72,871 - $220,142	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
>$220,142	No Teplizumab	

Notes: All costs are in 2019 US dollars (US$). HLA-DR3: Human Leukocyte Antigen DR3; HLA-DR4: Human Leukocyte Antigen DR4; ZnT8: Zinc Transporter 8

2.3.3 Model validation

Results of the trace analysis indicated that, in our model, 76% and 46% of patients in the no treatment and Teplizumab to all-at risk groups, respectively, developed Type 1 diabetes at the end of 5 years. These proportions were similar to those observed in the Phase II trial (72% and 43%, respectively). Further, the proportion for the no treatment group was slightly higher than that the 5-year risk observed among patients in the DPT-1 trial conducted between 1994 and 2003 (76% vs. 65%) (130). This difference, however, may be explained by the rising incidence of Type 1 diabetes over time (131).

2.4 Discussion

Our study is the first to identify different target groups of at-risk individuals for cost-effective provision of Teplizumab at different possible prices of the drug. Our analysis suggests that Teplizumab will be a cost-effective treatment for all at-risk individuals if it is priced below US$48,900. For prices up to US$58,200, it is cost-effective to treat individuals with HLA-DR3 negative or HLA-DR4 positive alleles, comprising 76% of all at-risk individuals. However, if price exceeds US$58,200, only individuals with both HLA-DR3 negative and HLA-DR4 positive accounting for 41% of at-risk individuals can be treated (if the price is less than US$88,300) or only those with ZnT8 antibody negative (accounting for 26% of at risk individuals) can be treated if the price is less than US$193,700.

As this drug makes its way to the market, our findings from this early stage economic evaluation can help inform early planning and future decisions on pricing and reimbursement for both payers and manufacturers of Teplizumab. For payers, the findings can help identify which group of at-risk individuals would be cost-effective to offer Teplizumab at a certain price of Teplizumab. For Teplizumab's manufacturers, while profit motive will be the main driver of drug pricing, it will also be important not to set prices that are considered excessive. Payers and agencies in charge of monitoring and regulating drug prices are increasingly utilizing cost-effectiveness analyses to determine optimal prices of brand-name drugs. For instance, in the latest amendment to Canada's Patented Medicine Prices Review Board regulations, Health Canada proposed to use cost-utility analyses to determine if a pharmaceutical price is excessive (132).

Though we used US data in this study, our general framework can be adapted by stakeholders to their own clinical and policy contexts. For example, our sensitivity analyses additionally considered various scenarios (such as alternative costs of insulin and management of diabetes-related complications, shorter time horizons and treatment for only children).

Our study has several limitations. First, data on efficacy of Teplizumab was only available for a 5-year time period. Thus, the extent to which Teplizumab can delay Type 1 diabetes onset in the long-run remains to be seen. We conducted extensive sensitivity analyses under alternative long-run scenarios. Nonetheless, future research that uses long-term outcome data could offer further insights when such data becomes available. Second, data on efficacy of the drug among individuals with different combinations of HLA-DR3 and

HLA-DR4 alleles were not available. Thus, we had to assume that the risk of developing Type 1 diabetes among these individuals was an average of the Type 1 diabetes risks for the patient subsets with each individual marker. However, we conducted sensitivity analyses around this assumption and results supported the validity of our base case results. Third, probabilities of most microvascular complications in the Sheffield Type 1 Diabetes Policy model are dependent only on HbA1c level. To the extent that such risks increase with age and duration of diabetes, these risks may also be overestimated in our model. However, we varied these probabilities in the PSA, and our results continued to hold. Finally, as our study relied on data from a Phase II clinical trial, the limitations of this trial extended to our study. In particular, the number of patients and timing of exposure to the intervention in the trial were limited. Nevertheless, we believe there is considerable value in conducting an early stage cost-effectiveness analysis of this important drug instead of waiting for more complete data. Furthermore, as the drug enters the market and further real-world outcome data becomes available, the model developed in this paper can be easily used to update the cost-effectiveness of this drug.

2.5 Conclusion

We showed that cost-effective provision of Teplizumab varies depending on price of Teplizumab and genetic and/or antibody characteristics of treated patients. If the price of the drug turns out to be above US$100,000 as current indications suggest (41), it will only be cost-effective to give the drug to 26% of patients at risk. Meanwhile, if the price is below US$58,200, it will be cost-effective to give the drug to at least 76% of all at-risk individuals. Given the high clinical relevance of this drug, these findings highlight the

potential challenge for the manufacturer and payers to arrive at a price that can maximize access to the drug for at-risk individuals while ensuring sustainable budget for the payer and healthy profits for the manufacturer.

Co-authorship Statement

The candidate has co-authored this paper with her supervisor, Dr. Hai Nguyen. The candidate conceptualized the research idea, conducted data analyses and was the primary contributor to manuscript preparation. The paper has been published in *PharmacoEconomics*.

Cite: Mital, S., Nguyen, H.V. Cost Effectiveness of Teplizumab for Prevention of Type 1 Diabetes Among Different Target Patient Groups. *PharmacoEconomics* 38, 1359–1372 (2020). doi:10.1007/s40273-020-00962-y.

Available at: https://link.springer.com/article/10.1007/s40273-020-00962-y

Chapter 3 : Incremental Cost Effectiveness of Aspiration Therapy versus Bariatric Surgery and No Treatment for Morbid Obesity

This chapter contains non-final versions of articles published in final form in the American Journal of Gastroenterology*:*

(i) *Mital, Shweta; Nguyen, Hai V. Incremental Cost-Effectiveness of Aspiration Therapy vs Bariatric Surgery and No Treatment for Morbid Obesity, The American Journal of Gastroenterology: September 2019 - Volume 114 - Issue 9 - p 1470-1477 doi: 10.14309/ajg.0000000000000359.* The published article is available at: *https://journals.lww.com/ajg/Abstract/2019/09000/Incremental_Cost_Effectiveness_of_Aspiration.15.aspx?Ppt=Article%7Cajg:2019:09000:00015%7C10.14309/ajg.0000000000000359%7C*

and

(ii) *Mital, Shweta; Nguyen, Hai V. Response to Jirapinyo et al., The American Journal of Gastroenterology: March 2020 - Volume 115 - Issue 3 - p 482-483 doi: 10.14309/ajg.0000000000000541.*

The published article is available at: *https://journals.lww.com/ajg/Citation/2020/03000/Response_to_Jirapinyo_et_al_.24.aspx*

In compliance with publisher's agreement to password protect the above articles, only links to the above articles published in the American Journal of Gastroenterology are being provided here.

Chapter 4 : Cost-Effectiveness of Procedure-less Intragastric Balloon Therapy as Substitute or Complement to Bariatric Surgery

To be submitted

Abstract

Objective: To compare the incremental cost-effectiveness of a procedure-less intragastric balloon (PIGB) as a substitute or complement to bariatric surgery.

Background: The first procedure-less intragastric balloon (Elipse™) does not require endoscopy for insertion or removal. Although weight loss effects of PIGB are lower than bariatric surgery, it involves smaller treatment costs and greater convenience than bariatric surgery. These features render it attractive as a stand-alone treatment or as an add-on to bariatric surgery. The cost-effectiveness of such alternative uses of PIGB has, however, not been established.

Methods: We developed a microsimulation model to compare the incremental cost-effectiveness of six treatment strategies: PIGB, gastric bypass or sleeve gastrectomy as stand-alone treatments, PIGB as a bridge to gastric bypass or sleeve gastrectomy, and no treatment.

Results: Despite being more costly upfront, adding PIGB as a bridge to bariatric surgery is less costly and more effective than bariatric surgery alone as it helps to achieve a lower post-operative BMI. Of the six strategies, PIGB as a bridge to sleeve gastrectomy is the most cost-effective with an ICER of US$4,619 per QALY. While PIGB alone is not cost-effective compared with bariatric surgery alone or when PIGB is used as a bridge to bariatric surgery, it is cost-effective compared with no treatment with an ICER of US$89,096 per QALY.

Conclusions: Given its low treatment costs and ability to generate modest weight loss, providing PIGB treatment to patients prior to bariatric surgery can both improve health outcomes and lower health care costs compared with direct provision of bariatric surgery.

4.1 Introduction

Bariatric surgery is the most effective and cost-effective treatment for obesity compared with non-surgical alternatives (55–57,64,133,134). However, access to bariatric surgery in the United States (US) is extremely limited owing to financial and insurance constraints and shortage of bariatric surgeons; only 0.5% of eligible patients in the US have access to bariatric surgery each year (93).

Intragastric balloon therapy – which involves placing gas- or saline-filled balloon inside the stomach -- is an alternative procedure that can induce temporary weight loss (135). This technique has recently gained popularity after the US Food and Drug Administration (FDA) approved two intragastric balloon devices: Orbera® (liquid-filled balloon) in 2015 and Obalon® (gas-filled balloon) in 2016 (136). A recent innovation in the field of intragastric balloons is the Elipse™ balloon (137), which is unique in that it is the first procedure-less intragastric balloon (PIGB). Unlike previous intragastric balloons, PIGB does not require endoscopy for either insertion or removal (137). Consequently, treatment costs and risk of complications with PIGB are lower. It also offers greater patient convenience compared with other weight loss procedures. While Allurion Technologies has submitted an application for pre-market approval of Elipse™ by the US FDA (43), Elipse™ has not yet been approved by the FDA and is considered an investigational device in the US (138). However, it is currently being used in over 30 other countries worldwide (139).

In addition to being used as stand-alone treatment to achieve modest weight loss in non-severely obese patients, recent studies have also examined use of intragastric balloons as a potential bridge to bariatric surgery to achieve pre-operative weight loss among severely obese patients (140). PIGB – with its low treatment costs and greater patient convenience – represents an attractive option for this purpose.

The objective of this study is to establish the cost-effectiveness of PIGB compared with the two most commonly performed bariatric surgeries (i.e., gastric bypass and sleeve gastrectomy) and no treatment among morbidly obese patients. In addition to a direct comparison of cost-effectiveness of these treatments, we examine two hybrid strategies in which PIGB is offered as a first-line treatment prior to gastric bypass or sleeve gastrectomy. To our knowledge, this study is the first to examine the cost-effectiveness of an intragastric balloon device as a stand-alone and as an add-on treatment to bariatric surgery.

4.2 Methods

4.2.1 Procedure-less intragastric balloons and their characteristics

The procedure-less intragastric balloon (Elipse™, Allurion Technologies, Natick, MA, USA) is delivered using a swallowable capsule (141). Upon reaching the stomach, the balloon is filled using a delivery catheter and the catheter is then withdrawn (141). The procedure is thus non-invasive and does not involve sedation. Within the stomach, the balloon works by occupying stomach capacity, inducing satiety and thereby reducing food intake (141). The balloon stays in the stomach for 4 months after which a release valve opens and the balloon is excreted naturally (141).

PIGB offers several advantages compared with bariatric surgery. First, as it is non-invasive, intervention costs of PIGB are lower than bariatric surgery (142). Second, adverse events with PIGB are less likely and in most cases of a major complication, the balloon can be endoscopically removed (143). Moreover, unlike bariatric surgery, existing studies of PIGB have not reported any mortality associated with the intervention (143,144).

As with other intragastric balloons, however, a key limitation of PIGB is that it generates lower weight loss than bariatric surgery. For instance, percentage of body weight lost on average with PIGB was 14% after 1 episode of treatment (lasting 4 months) (143) compared with 32% in 1-2 years after gastric bypass (145). Furthermore, while long-term evidence on weight loss effects of PIGB is lacking, limited evidence (at 12 months after treatment initiation) suggests that patients regain weight after balloon removal (144).

4.2.2 Treatment strategies

We estimated the cost-effectiveness of 6 strategies for weight loss. The first three strategies involved PIGB ('PIGB -only, hereafter), gastric bypass ('gastric bypass-only, hereafter) or sleeve gastrectomy ('sleeve gastrectomy-only', hereafter) as stand-alone treatment for all patients, respectively. In the next two strategies, PIGB was provided as first-line treatment to all patients. Patients who remained morbidly obese after PIGB treatment underwent gastric bypass or sleeve gastrectomy immediately ('PIGB + gastric bypass' and 'PIGB + sleeve gastrectomy', hereafter); those whose BMI fell below 35 kg/m^2 after PIGB treatment did not receive bariatric surgery immediately but did so once their BMI reached 35kg/m^2

due to weight regain following PIGB treatment. Finally, the sixth strategy involved no weight loss treatment.

4.2.3 Model structure and study cohort

We developed a microsimulation model to compare the costs and quality-adjusted life years (QALYs) of the 6 strategies. This individual patient-level microsimulation model allowed us to capture variation in weight loss effects across patients which in turn, influenced the timing of switch to bariatric surgery (if any) in the two hybrid strategies as described below. We simulated 10,000 adults aged 18-74 years with class 2 or class 3 obesity (i.e., BMI >=35 kg/m^2). We considered only patients with BMI>=35 kg/ m^2 as bariatric surgery is primarily recommended for this BMI range (146). The proportion of patients with class 2 obesity (35<=BMI<40) versus class 3 obesity (BMI>=40) was 56% versus 44%, respectively, following patterns of obesity prevalence among US adults (147). The analysis was conducted from the health system perspective. Cycle length was set at 4 months to match the length of an episode of PIGB treatment, and a lifetime horizon was used.

The microsimulation model accounted for patients' transition across 5 health states (Not Obese (BMI <30), Obese 1 (30<=BMI<35), Obese 2 (35<=BMI<40), Obese 3 (BMI>=40) and Death). Transitions across these health states have been depicted elsewhere (148). Patients entered the model in the Obese 2 or Obese 3 health states. All patients underwent treatment (with PIGB, gastric bypass or sleeve gastrectomy depending on strategy) in the first cycle. After the first cycle, patients in the PIGB -only and gastric bypass/sleeve

gastrectomy-only strategies transitioned across health states depending on extent of weight loss achieved by PIGB or surgery. Meanwhile, patients in the hybrid strategy who were still eligible for bariatric surgery (i.e., had BMI>=35 kg/m^2) underwent surgery. During the PIGB treatment, patients faced risk of major or minor complications. Major complications required balloon removal. Some patients could also experience early balloon deflation and expulsion. Those undergoing bariatric surgery faced risk of surgery-related mortality as well as the risk of short and long-term minor and major complications.

We estimated costs from the health system perspective. Effectiveness was measured in terms of QALYs that captured patients' length of life weighted by their health-related quality of life (or utility).

4.2.4 Model inputs

Model inputs are presented in Table 4.1 and detailed below.

Weight loss effects

Weight loss effects at the end of 4 months of PIGB treatment were obtained from Ienca et al. (2020), a global multi-center study of 1770 patients (143). While several studies have examined weight loss effects of PIGB, we chose this study for two reasons: (i) it included a substantial western European patient population which would most closely resemble the US population; (ii) it reported weight loss following PIGB treatment for different BMI groups (<30, 30-40 and >40 kg/m^2), allowing us to obtain weight loss effects specific to morbid obesity. However, Ienca et al. did not report weight loss or regain beyond treatment

cessation at 4 months. Thus, for patients who achieved BMI<35 kg/m^2 after PIGB treatment (and therefore, were not immediately eligible for bariatric surgery), we assumed weight regain per cycle of 7% of the initial weight loss at the end of 4 months. This rate of weight regain was based on meta-analytic estimates that included studies with follow-up period of up to 12 months (144). Further, for patients in the PIGB-only strategy who experienced early expulsion of balloon or major complications requiring removal of PIGB, we assumed annual BMI increase of 0.175kg/m^2 (similar to that for an average obese individual not undergoing treatment (149); this magnitude corresponds to 0.5%- 0.3% increase per year over initial BMI of 35-55kg/m^2).

Weight loss effects for bariatric surgery were obtained from Alsumali et al., a recent cost-effectiveness analysis that presented long-term weight loss effects for gastric bypass (up to 10 years post-surgery) and sleeve gastrectomy (up to 8 years post-surgery) (56). As only yearly weight loss effects were available for bariatric surgery, we linearly interpolated weight loss effects for each 4-month period to match the 4-month cycle length in our model. Beyond 10 years, we followed the literature in assuming that BMI remains constant at the level achieved in year 10 (56,57).

Complications and mortality risks

Patients treated with PIGB could experience one of 3 types of complications during treatment: (i) early deflation and expulsion of balloon not requiring clinical intervention; (ii) major complications (such as balloon intolerance, small bowel obstruction, esophagitis, pancreatitis and gastric perforation) requiring endoscopic or laparoscopic removal of

PIGB; and, (iii) minor complications (such as gastric dilation) (143). Probabilities of these complications were obtained from Ienca et al. (143).

Patients undergoing bariatric surgery faced the risk of short and long-term major and minor complications. Short-term complications could occur in the first 30 days while long-term complications could occur in years 1 to 5 post-surgery. We obtained the probability of these complications from a recent, high quality randomized controlled trial (RCT) (150).

Patients in all strategies faced risk of mortality specific to their age and BMI. We obtained age-specific risk of mortality from the latest available US life tables (111) and applied BMI-specific hazard ratios to it (151). Patients undergoing bariatric surgery also faced risk of surgery-related mortality up to 1 year post-surgery (152). There was no risk of death associated with PIGB (143).

Costs

Costs of each strategy included cost of intervention and follow-up, general BMI-specific health care costs, and cost of managing complications (if any). Costs of PIGB included cost of the device, 6 physician visits (1 visit each pre-intervention, on the day of balloon placement and in each month during treatment) and cost of medications (143). Costs of bariatric surgery included cost of the surgical procedure, cost of follow-up visits (5 visits in year 1, 3 visits in year 2 and 2 visits year 3 onwards for gastric bypass and 5 visits in year 1, 2 visits in year 2 and 1 visit year 3 onwards for sleeve gastrectomy (153)) and cost of dietary supplementation. These costs, along with the general BMI-specific health care

costs, were obtained from the published literature (56). All costs were estimated in 2020 US dollars and discounted at 3.5% per year (116).

Utility

Utility values were age and BMI specific and were obtained from Alsumali *et al* who estimated EQ-5D scores based on data from the US Medical Expenditure Panel Survey (56). Our model also captured disutility related to the intervention and its complications. Specifically, following existing literature, we assumed that disutility associated with bariatric surgery and its major complications lasted for 6 weeks while disutility from any minor complications lasted for 4 weeks (57). As PIGB is non-invasive and its complications are less severe than bariatric surgery, we assumed that disutility from balloon placement was half that of bariatric surgery and lasted only 1 week. Further, disutility from complications of PIGB was half that due to bariatric surgery and lasted 4 weeks for a major complication and 1 week for a minor complication. We varied these disutilities in the one-way sensitivity analyses (described below). All utility values were discounted at 3.5% per year (116).

Table 4.1: Model Inputs

Variable	PIGB	Gastric Bypass	Sleeve Gastrectomy	Source
Percent Total Weight Loss				
Month 4	14.4% (4.9%) for Obese 2; 14.7% (4.2%) for Obese 3			(143)
Month 120		30.6% (7.7%)	22.3% (5.6%)	(56)
Mortality Hazard Rates				
Not Obese	1.83 (age 18-29); 0.72 (age 30-44); 1.08 (age 45-64); 0.89 (age >65)			(151)
Obese 1	1.77 (age 18-29); 1.18 (age 30-44); 1.27 (age 45-64); 0.92 (age >65)			
Obese 2	1.68 (age 18-29); 1.69 (age 30-44); 2.30 (age 45-64); 1.10 (age >65)			
Obese 3	4.91 (age 18-29); 1.48 (age 30-44); 1.86 (age 45-64); 1.27 (age >65)			

Probabilities				
Proportion of patients starting in Obese 2 state	0.56			(147)
Proportion of patients starting in Obese 3 state	0.44			
Procedure related mortality (short term)	0	0.0038 (9.5E-4)	0.0029 (7.25E-4)	(143,152)
Procedure related mortality (long term)	0	0.0072 (0.0018)	0.0034 (8.5E-4)	
Early deflation	0.006 (0.002)	n/a	n/a	(143)
Major complication (0-30 days)	0.036 (0.009)	0.094 (0.024)	0.058 (0.015)	(143,150)
Minor complication (0-30 days)	0.0006 (1.5E-4)	0.171 (0.043)	0.074 (0.019)	
Major complication (years1-5)	n/a	0.151 (0.038)	0.083 (0.021)	(150)
Minor complication (years1-5)	n/a	0.109 (0.027)	0.107 (0.027)	
Costs (in US$)				
Intervention[1]	5,550	30,235 (5,033)	26,328 (6,248)	(56)
Follow up visits[2]		805, 483, 322	805, 322, 161	(56,143)
Dietary supplements (annual)		100 (25)		(56)
Complications[*]				
Major complication (0-30 days)	2,695 (674)[3]	49,458 (12,364)		(56)
Minor complication (0-30 days)	161 (40)[3]	1,517 (379)		
Major complication (years 1-5)	n/a	54,454 (13,614)		
Minor complication (years 1-5)	n/a	951 (238)		
Health care costs (per year) by health state:				
Not Obese	4,152 (1,038)			(56)
Obese 1	4,881			
Obese 2	5,744			
Obese 3	6,997			
Utilities				
BMI Specific Utilities				
Not Obese	0.91 (age 18-30); 0.89 (age 31-40); 0.86 (age 41-50); 0.83 (age 51-60); 0.81 (age 61-70); 0.79 (age >=71)			(56)
Obese 1	0.89 (age 18-30); 0.86 (age 31-40); 0.82 (age 41-50); 0.80 (age 51-60); 0.79 (age 61-70); 0.76 (age >=71)			
Obese 2	0.88 (age 18-30); 0.83 (age 31-40); 0.79 (age 41-50); 0.77 (age 51-60); 0.76 (age 61-70); 0.74 (age >=71)			
Obese 3	0.84 (age 18-30); 0.82 (age 31-40); 0.75 (age 41-50); 0.73 (age 51-60); 0.71 (age 61-70); 0.69 (age >=71)			
Disutility				
Intervention related disutility	0.002 (1.4E-4)	0.025 (0.002)		(57)
Major complication	0.014 (7.7E-4)	0.042 (0.002)		
Minor complication	0.001 (7.2E-5)	0.008 (5.8E-4)		

Values are Mean (SD). Standard deviations (SD) were obtained from the published literature where available. Where unavailable, SD was assumed equal to 25% of the mean value. Costs are measured in 2020 US dollars.
[1]Total cost of PIGB includes cost of balloon (US$4,050 (SD: US$1,012) calculated as £2800 (142) converted to USD @ 1 GBP= 1.3897 USD as on January 18, 2018 (154) and adjusted for inflation), 6 physician visits (1 before balloon placement, 1 on day of balloon placement, 1 each in months 1-4) @ US$161 (SD: US$40) per visit (56), one dose of aprepitant 125 mg (@ US$90.73 per unit (155)) + Ondansetron (9 tablets @ US$5.79 per unit (156)) + 2 doses of aprepitant 80 mg (US$61.81 per unit (155)) + daily proton pump inhibitor starting 14 days before treatment (134 days x US$2 per unit (157)) (143).

[2]Follow-up visits are based on the following schedule: 5 visits in year 1, 3 visits in year 2 and 2 visits per year beyond year 2 for gastric bypass and 5 visits in year 1, 2 visits in year 2 and 1 visit per year beyond year 2 for sleeve gastrectomy (153). Each follow-up visit costs US$161 (56).
[3] Cost of major complication with PIGB is assumed to be the weighted average of treatment with endoscopy costing US$1,082 (158) and laparoscopy costing US$26,328 (assumed equal to cost of laparoscopic sleeve gastrectomy procedure), where weights are based on proportion of complications treated with endoscopy vs. laparoscopy in Ienca et al. (143). Cost of minor complication with PIGB is assumed to be the cost of one physician visit.

4.2.5 Cost effectiveness analysis

We estimated the total costs and QALYs of the six strategies. We removed any strategies that were dominated in a simple sense (i.e., strategies that cost more while yielding fewer QALYs). We then estimated the Incremental Cost Effectiveness Ratio (ICER) as the ratio of the difference in total costs to the difference in total QALYs gained between two strategies and removed any strategies that were extended dominated (i.e., had a higher ICER than a more effective strategy). Among the remaining strategies, a strategy was considered cost-effective relative to another strategy if the ICER was lower than the conventional willingness-to-pay threshold of US$100,000 per QALY.

We conducted several additional analyses. First, to address parameter uncertainty, we conducted conventional one-way sensitivity analyses in which we varied all costs and utilities in a range of ±25% of base case values (125), and probabilistic sensitivity analyses (PSA) in which we assigned distributions to input parameters and performed 1,000 Monte Carlo simulations. Second, we examined robustness of our results to changes in magnitude of 4-month weight loss of PIGB. In this analysis, we used meta-analytic estimates of weight loss after PIGB treatment from Vantanasiri et al. (144), which are slightly lower than the estimates from Ienca et al. used in the base case analysis (i.e., 12.75% vs. 14.4%-14.7%).

Third, while no deaths have been reported in PIGB studies, the FDA has recently alerted to the risk of mortality from other liquid-filled intragastric balloons that was reported after the approval of those balloons (159). Therefore, in this analysis, we considered the hypothetical possibility of a small mortality risk of 0.025% from PIGB similar to that observed for other balloons (160).

Fourth, we conducted additional sensitivity analyses to examine alternative long-term weight dynamics after PIGB and bariatric surgery. Long-term weight regain after PIGB treatment is not yet known. Therefore, in the first of these analyses, we varied the magnitude of weight regain after PIGB treatment between 0% (i.e., no weight regain) and 14% (twice that used in the base case analysis). In the second analysis, we used long-term weight loss data for bariatric surgery from a recent, large, multi-center randomized clinical trial which compared weight loss after gastric bypass and sleeve gastrectomy (150). For gastric bypass, total percent weight loss at the end of 5 years in this trial was lower than weight loss at the end of 10 years reported in Alsumali et al. (27% vs. 31%). However, weight loss for sleeve gastrectomy was slightly higher (22.8% vs. 22.3%). All analyses were conducted using TreeAge Pro 2019 v2.1 (105).

4.3 Results

4.3.1 Base case analysis

Table 4.2 presents the results of the base case cost-effectiveness analysis. There are three key findings. First, adding PIGB as a bridge to bariatric surgery is less costly and more effective than bariatric surgery alone (Panel A). Specifically, 'PIGB + sleeve gastrectomy'

dominates sleeve gastrectomy only, and 'PIGB + gastric bypass' dominates gastric bypass only. This finding is explained by the fact that even though adding PIGB treatment increases upfront procedure costs, eventual weight loss is greater than without PIGB treatment which lowers downstream health care costs and improves quality of life.

Second, among all six strategies, the 'PIGB + sleeve gastrectomy' is the most cost-effective strategy (Panel B). 'PIGB + sleeve gastrectomy' costs US$10,084 more than no treatment (US$128,045 vs. US$117,961), but it also yields 2.18 additional QALYs. The resulting ICER is US$4,619 per QALY gained which is much lower than the WTP threshold of US$100,000 per QALY. Meanwhile, 'PIGB + gastric bypass' generates 0.06 additional QALYs compared with 'PIGB + sleeve gastrectomy'. However, it is also more costly (US$137,576 vs. US$128,045) due to higher procedure costs and greater risk of complications with gastric bypass. As a result, 'PIGB + gastric bypass' is not cost effective relative to 'PIGB + sleeve gastrectomy' with an ICER of US$163,491 per QALY that exceeds the WTP threshold of US$100,000 per QALY.

Finally, Panel C shows that if only compared with no treatment, PIGB costs US$6,920 more and generates 0.08 additional QALYs, generating an ICER of US$89,096 per QALY gained. This ICER is lower than the WTP threshold of US$100,000 per QALY, suggesting that PIGB treatment alone is cost-effective relative to no treatment.

Table 4.2: Incremental Cost Effectiveness Results, Base case

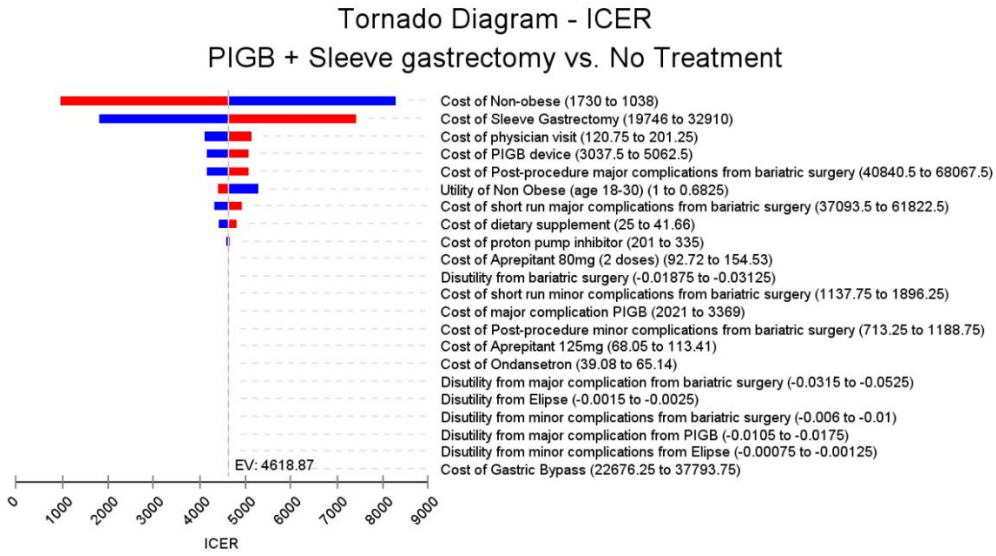
Strategy	Cost (US$)	Incremental Costs (US$)	Effectiveness	Incremental Effectiveness	ICER (US$/QALY)
Panel A: All strategies					
No treatment	117,961	-	13.48	-	-
PIGB only	124,880	6,920	13.56	0.08	Ext. dominated
PIGB + Sleeve Gastrectomy	128,045	3,165	15.66	2.11	1,503
Sleeve Gastrectomy only	130,678	2,633	15.25	-0.41	Dominated
PIGB + Gastric Bypass	137,576	9,531	15.72	0.06	163,491
Gastric Bypass only	138,242	667	15.46	-0.26	Dominated
Panel B: Undominated strategies					
No treatment	117,961	-	13.48	-	-
PIGB + Sleeve Gastrectomy	128,045	10,084	15.66	2.18	4,619
PIGB + Gastric Bypass	137,576	9,531	15.72	0.06	163,491
Panel C: PIGB only vs. No treatment					
No treatment	117,961	-	13.48	-	-
PIGB only	124,880	6,920	13.56	0.08	89,096

All costs are in 2020 US dollars (US$). ICER = incremental cost-effectiveness ratio.

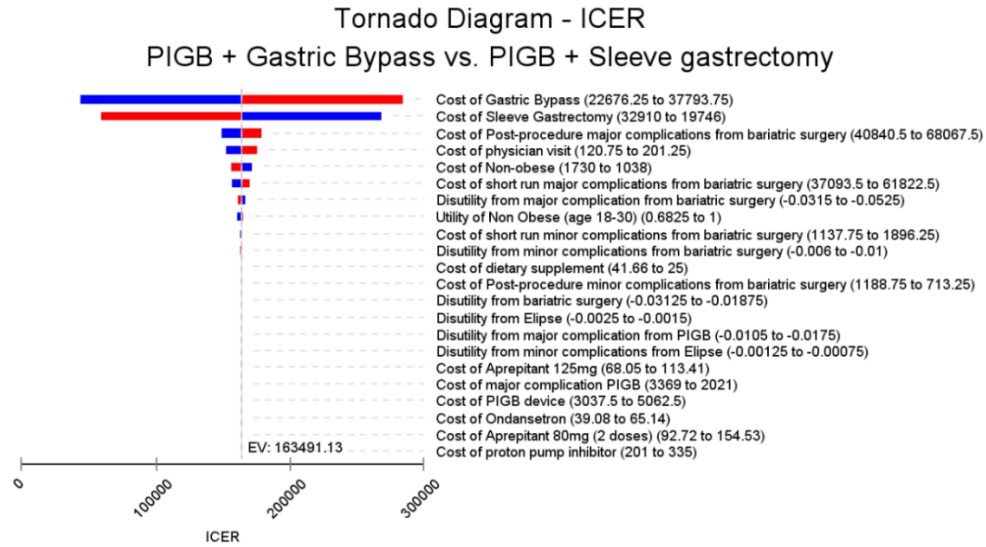
4.3.2 Sensitivity analysis

Results of the one-way sensitivity analyses are presented in Tornado diagrams in Figure 4.1. Figure 4.1 (a) shows that the 'PIGB + sleeve gastrectomy' strategy remained cost-effective relative to no treatment for all values of costs and utilities in the range of +/- 25% of base case values. Furthermore, except for very low cost of gastric bypass or very high cost of sleeve gastrectomy, the 'PIGB + gastric bypass' strategy remained not cost-effective relative to the 'PIGB + sleeve gastrectomy' (Figure 4.1(b)). Cost-effectiveness

acceptability curves from the PSA indicate that at the cost-effectiveness threshold of US$100,000 per QALY, 'PIGB + sleeve gastrectomy' is cost-effective in 70% of iterations (Figure 4.2).



(a) Elipse + Sleeve gastrectomy vs. No Treatment



(b) Elipse + Gastric bypass vs. Elipse + Sleeve gastrectomy

Figure 4.1: Tornado diagram

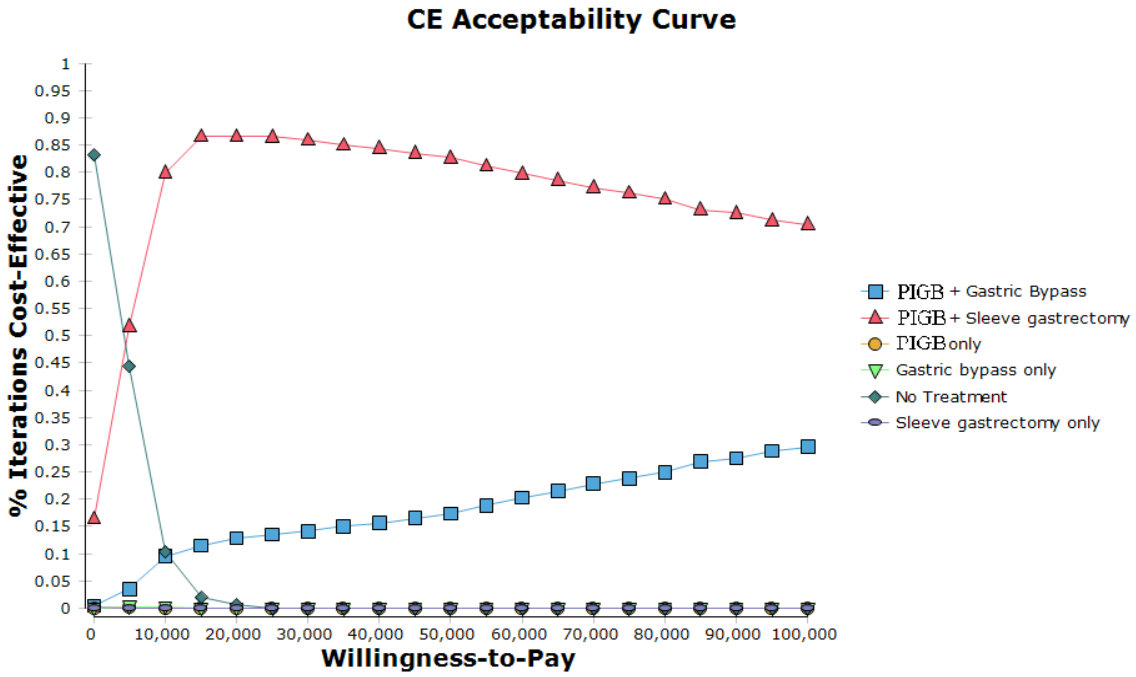


Figure 4.2: Cost-effectiveness acceptability curve

Table 4.3 shows the results of the additional sensitivity analyses. We obtained similar results to the base case even when we used meta-analytic estimates for weight loss effects of PIGB instead of estimates from Ienca et al. (Panel A). The results were also robust when we allowed for mortality due to PIGB (Panel B) and used alternative data for weight loss effects for bariatric surgery (Panel C).

Table 4.3: Incremental Cost Effectiveness Results, Sensitivity Analyses

Strategy	Cost (US$)	Incremental Costs (US$)	Effectiveness	Incremental Effectiveness	ICER (US$/QALY)
Panel A: Meta-analytic estimates for weight loss from PIGB					
No treatment	117,961	-	13.48	-	-
PIGB + Sleeve Gastrectomy	129,080	11,119	15.62	2.14	5,190
PIGB + Gastric Bypass	138,406	9,327	15.69	0.07	137,651
Panel B: Allowance for PIGB -related death					
No treatment	117,961	-	13.48	-	-
PIGB + Sleeve Gastrectomy	127,128	9,167	15.55	2.07	4,438
PIGB + Gastric Bypass	136,908	9,780	15.63	0.08	124,285
Panel C: Alternative weight loss effects for bariatric surgery					
No treatment	117,961	-	13.48	-	-
PIGB + Sleeve Gastrectomy	128,112	10,151	15.69	2.21	4,591
PIGB + Gastric Bypass	138,219	10,107	15.71	0.02	597,356

All costs are in 2020 US dollars (US$). ICER = incremental cost-effectiveness ratio. Dominated strategies are excluded. In Panel A, total percent weight loss effects (Mean (SD)) for PIGB is 12.75% (3.2%) for patients in both Obese 2 and Obese 3 categories.

Further, when we varied the extent of weight regain after PIGB treatment between no weight regain and regain of 14% of weight loss per cycle, the 'PIGB + sleeve gastrectomy' was the most cost-effective unless weight regain was very small (smaller than 1.5% in each 4-month period; Figure 4.3). Overall, these sensitivity analyses indicate the robustness of our base case results.

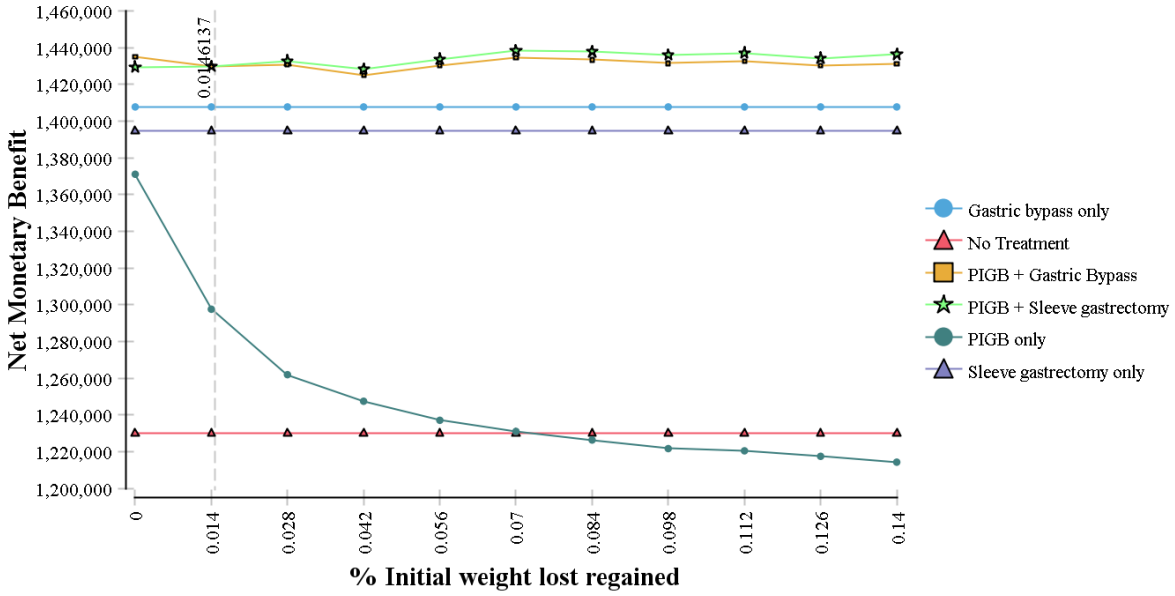


Figure 4.3: Net monetary benefit for different percentages of weight regain

4.4 Discussion

In this study, we provided the first assessment of the incremental cost-effectiveness of PIGB as a substitute or complement to bariatric surgery. We found that using PIGB as an add-on treatment before bariatric surgery is both less costly and more effective than bariatric surgery alone. In particular, treatment with PIGB followed by sleeve gastrectomy is the most cost-effective. Also, although PIGB alone is not cost effective versus bariatric surgery, it is a cost-effective treatment option compared with no treatment.

Our findings have several implications for policy and clinical practice. First, contrary to expectations that an add-on treatment to already expensive bariatric surgery would further increase health care costs, our results show that using PIGB as an add-on treatment *reduces*

total costs and improves health outcomes compared with bariatric surgery alone, owing to a lower post-operative BMI. Consequently, as decision-makers look for ways to curb rising health care costs, incorporating PIGB prior to bariatric surgery within the clinical care pathway could represent an attractive treatment option in the future.

Second, PIGB as a bridge therapy can be especially valuable for patients as it helps to achieve a lower BMI post-bariatric surgery. This is corroborated by findings from previous studies which suggest a positive correlation between pre-operative and post-operative weight loss(161). Furthermore, intragastric balloon treatment can help allay fears and concerns of a more restrictive surgical procedure for some patients and ease their path towards bariatric surgery(162).

Third, even though weight loss effects of PIGB are modest and likely temporary, our results indicate that treatment with PIGB alone is still cost-effective for patients who lack access to bariatric surgery. Further, treatment with PIGB is non-invasive and reversible. Thus, it is likely to be of interest to patients who do not have bariatric surgery due to lack of insurance, fear of surgery-related risks or concerns over long-term weight regain after bariatric surgery(93).

Our study has a number of limitations. First, data on weight loss from PIGB were available for a maximum duration of 12 months after treatment initiation. Thus, our analysis assumed that patients regain weight at a fixed percentage of initial weight loss every 4-months period. However, we conducted sensitivity analyses to account for this data limitation, and our conclusions continued to hold. Second, our study relied on non-RCT data for weight

loss effects of PIGB as RCT data was not available. In addition, no study has directly compared weight loss from PIGB with that from bariatric surgery so that weight loss effects for these treatments had to be obtained from separate studies. Future studies that utilize longer-term weight loss data for PIGB from RCTs (when such data becomes available) will be useful. Third, while our study highlights the economic value of PIGB as a bridge therapy to bariatric surgery, these findings are based exclusively on economic modelling using data from observational studies; no clinical studies have examined such use of PIGBs specifically prior to bariatric surgery. Although previous studies have indicated the feasibility of using intragastric balloons prior to bariatric surgery, further clinical evidence on the use of PIGB prior to bariatric surgery will be useful. Value of information analyses can be used to quantify the value of this additional research and the most efficient research design to collect such evidence (94).

In conclusion, findings from this study suggest that offering PIGB as a first-line treatment to all obese patients prior to bariatric surgery is cost-effective compared with bariatric surgery or PIGB alone. Given the potential economic value of this use of PIGB, future clinical trials examining the use of PIGBs as bridge therapy to bariatric surgery will be useful.

Co-authorship Statement

The candidate has co-authored this paper with her supervisor, Dr. Hai Nguyen. The candidate conceptualized the research idea, conducted data analyses and was the primary contributor to manuscript preparation.

Chapter 5 : Cost-Effectiveness of Using Artificial Intelligence and Polygenic Risk Score to Guide Breast Cancer Screening

To be submitted

Abstract

Background: There exists widespread debate on appropriate breast cancer screening strategies for women aged between 40 and 49 years. Thus, current guidelines for mammography screening in this age group vary widely across agencies. Artificial intelligence (AI) and polygenic risk scores (PRS) are new methods of risk prediction, with AI shown to be more accurate than PRS. However, cost-effectiveness of AI-based vs PRS-based vs guideline-based screening is not established.

Methods: We compared the cost-effectiveness of four alternative strategies of mammography screening for breast cancer. The first two strategies, i.e., AI-based and PRS-based strategies, used AI reading of index mammograms and genetic risk profile, respectively to guide screening for women aged 40-49 (with screening beyond age 50 following existing guidelines). The other two strategies exclusively followed existing guidelines, namely, the United States Preventive Services Task Force (USPSTF) and American College of Obstetricians and Gynecologists/American College of Radiology (ACOG/ACR) guidelines. The analysis was conducted from a health care system perspective and lifetime horizon was used.

Results: AI-based screening was cost-effective compared with PRS-based screening and USPSTF guideline-based screening, with an incremental cost-effectiveness ratio of US$23,133 per QALY gained. It also cost US$156 million (per 100,000 women) less and generated 1,755 additional QALYs (per 100,000 women) than ACOG guideline-based screening. Compared with USPSTF guidelines that recommend screening based on family

history, AI-based screening can reduce missed or delayed diagnoses as more high-risk women are accurately identified and screened. At the same time, it can help alleviate existing concerns about both over-diagnoses and false-positive diagnoses inherent in ACOG/ACR guidelines that recommend annual screening for all women.

Conclusions: Although AI and PRS technologies are still in their nascent stages, findings from this study provide useful first insights to inform policymakers on the potential value of using these technologies to optimize breast cancer screening practices in the future.

5.1 Introduction

There is widespread debate among clinicians and researchers globally over what constitutes appropriate breast cancer screening, especially for women younger than age 50 (163). Consequently, existing guidelines on mammography screening for breast cancer vary widely, even within a country. In the United States (US), the American College of Obstetricians and Gynecologists (ACOG) and the American College of Radiology (ACR) recommend annual mammography starting at age 40 for all women (44). Meanwhile, the most recent US Preventive Services Task Force (USPSTF) guidelines recommend biennial mammography between ages 50 to 74 years for women without family history of breast cancer while indicating that women with family history may benefit from starting screening between ages 40 and 49 (44). In Canada, breast cancer experts have challenged the Canadian Preventive Task Force which recommends against breast cancer screening for women aged between 40 and 49 years who are not at high risk, arguing that these recommendations are "outdated and dangerous" and have called for annual screening of all women above age 40 (164).

Cost-effectiveness analyses can inform this debate by estimating and comparing the costs and effectiveness of alternative screening strategies to identify the most cost-effective screening strategy. However, despite several cost-effectiveness analyses of alternative screening intervals and starting ages for mammography screening associated with current screening guidelines (67,69), the results remain inconclusive. Earlier studies have found starting screening at age 50 to be cost-effective (67), which lends support to the existing

USPSTF guidelines while more recent cost-effectiveness analyses point to the value of extending screening to women younger than age 50 (69) as recommended by ACOG/ACR.

A key limitation of existing guidelines is that these do not fully account for heterogeneity in women's risk of breast cancer. For instance, while risk assessment tools may consider family history or breast density as risk factors, these tools do not consider the full set of genetic markers now known to be associated with breast cancer. Furthermore, breast density measurements are also subject to radiologists' assessment and discernment. From an economic perspective, a more rigorous risk stratification can enable focusing health care resources on screening women with high risk while avoiding unnecessary screening and follow-up costs for those with low risk.

Two new risk prediction tools have recently emerged, namely polygenic risk score (PRS) and artificial intelligence (AI). PRSs estimate a woman's risk of breast cancer based on susceptibility loci identified through genome wide association studies (165). AI-based risk prediction models, in contrast, identify discriminative image patterns from full-field mammograms to categorize a woman's risk of developing breast cancer in the future (47).

To date, there is very little evidence on the cost-effectiveness of using these new risk stratification tools to aid breast cancer screening. Only one study has examined the cost-effectiveness of PRS-based risk stratified mammography screening versus screening all women aged between 50 and 69 years and no screening for breast cancer. This study found that offering mammography screening only to women above the 70^{th} percentile of the PRS-based risk distribution is cost-effective relative to screening all women aged between 50

and 69 years and no screening (79). Notably, no study has compared the cost-effectiveness of risk-stratified mammography screening using AI-based risk prediction versus PRS-based risk prediction. Our study fills this evidence gap.

In this study, we examine the cost-effectiveness of using AI or PRS to guide mammography screening for breast cancer compared with screening based exclusively on existing USPSTF guidelines (which recommend mammography screening based on family history) or ACOG/ACR guidelines (which recommend annual mammography screening for all women). As most of the debate over breast cancer screening centers on screening for women aged between 40 and 49 years and as data on predictive ability of AI has been validated only in the short-term (47), we focus on using AI or PRS to guide screening only among women in the 40 to 49 years age group, with screening for older women based on existing USPSTF or ACOG/ACR guidelines.

5.2 Methods

5.2.1 Study Cohort and Risk of Breast Cancer

Our model simulated 100,000 white women aged 40 years with no previous history of breast cancer. Each woman had an underlying risk of developing breast cancer based on the most recent risk distribution estimated for US white females using a comprehensive set of genetic and other non-modifiable and modifiable breast cancer risk factors (166). As criteria for who is considered ‘high risk’ for screening purposes differ across guidelines, we conservatively defined ‘true’ high risk women as those with an underlying risk of breast cancer equal to or higher than 1.1 times the average risk in the population of 40 year old

women (relative risk (RR) of 1.1 or higher). This RR threshold of 1.1 was chosen because, based on the latest report of the American Cancer Society, it can capture a broad range of factors known for increasing risk of breast cancer, including family history of breast cancer, personal history of breast or ovarian cancer, reproductive risk factors, genetic variations, dense breast on mammography, history of chest radiation, etc. (167). With this RR threshold, 43% of our hypothetical study cohort was classified as 'true' high risk, while the remaining 57% of the cohort was classified as 'true' low risk.

5.2.2 Screening strategies

We compared four alternative screening strategies which are presented graphically in Figure 5.1. In all four strategies, screening started at age 40 and ceased at age 74. The first strategy involved risk stratification based on AI reading of an index mammogram ('AI-based', hereafter). All women underwent an index mammogram at age 40, which was interpreted using AI to predict risk of breast cancer. Women predicted to have high risk underwent annual digital mammography starting at age 40 while those predicted to have low risk were not screened. This screening pattern continued until age 49. Beyond age 50, screening followed the USPSTF guideline, as described below. We considered the scenario where screening beyond age 50 was based on ACOG/ACR guidelines in a sensitivity analysis.

In the second strategy, screening pathways were the same as in the first strategy; however, risk stratification was performed using PRS instead of AI ('PRS-based', hereafter). All

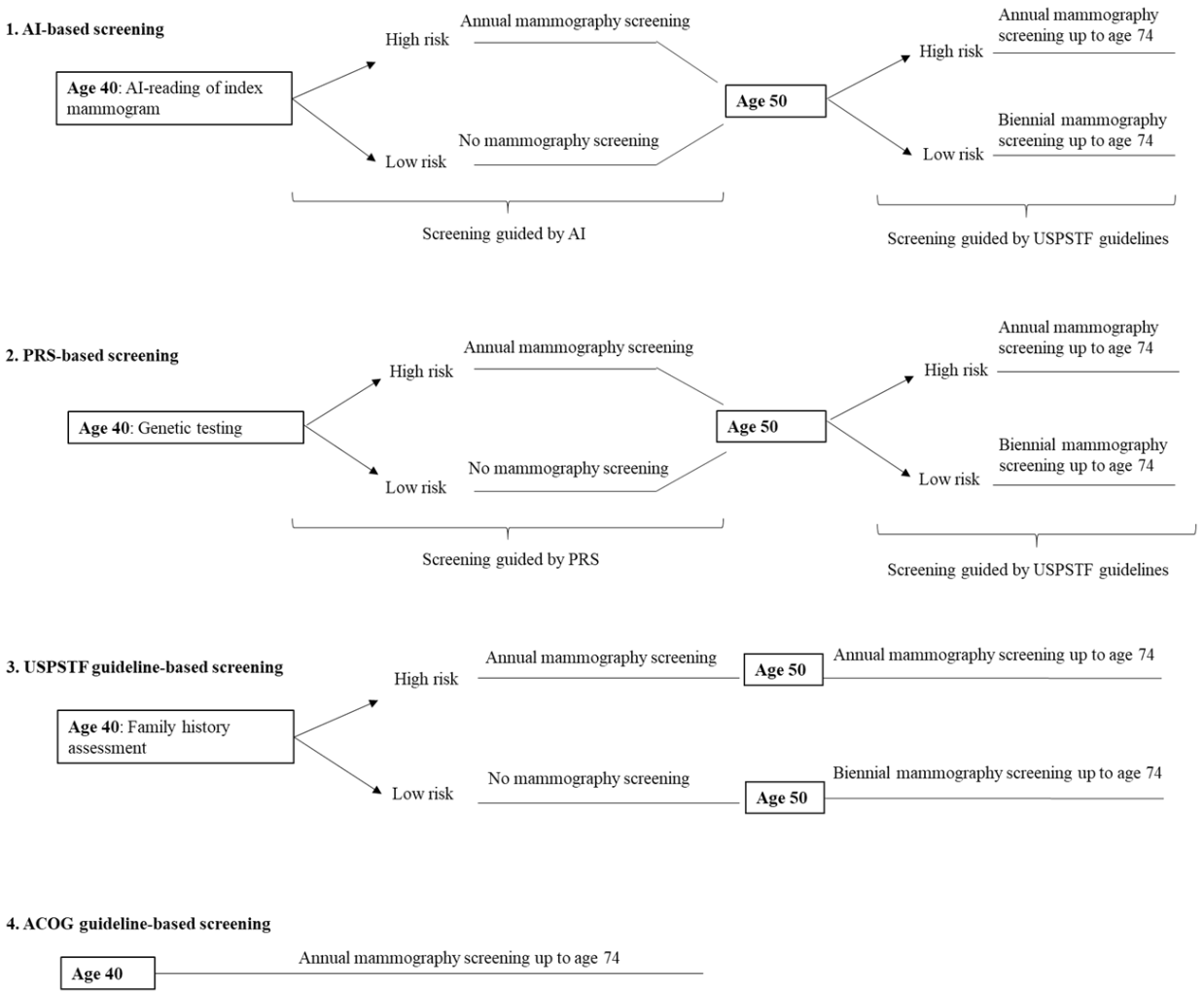
women underwent genetic testing at age 40 in which 76 single nucleotide polymorphisms (SNPs) known to be associated with breast cancer were genotyped (48).

The third strategy followed the current USPSTF guidelines ('USPSTF guideline-based', hereafter). For women older than age 50, the guidelines recommend biennial screening for women without family history (45). The USPSTF guidelines indicate that women with family history may benefit from starting screening before age 50 (44) but do not specify frequency of screening for these women. Given that most other screening guidelines recommend annual screening for high-risk women (44), we considered that women with family history underwent annual mammography. For women aged between 40 and 49 years, the USPSTF recommendation to screen women without family history is only a grade C recommendation (i.e., the net benefit of screening in this group is small) (45,46). Therefore, in our model, women younger than age 50 without family history were not screened. Meanwhile, similar to older women, women with family history underwent annual mammography.

In the fourth strategy, all women (regardless of risk level) underwent annual digital mammography starting at age 40 as recommended by ACOG and ACR ('ACOG guideline-based', hereafter).

The four strategies, thus, differed in the proportion of women subjected to aggressive screening. ACOG guideline-based screening was the most aggressive as all women, including those at low risk, were screened annually starting at age 40. By contrast, in the remaining 3 strategies, low-risk women younger than age 50 were not screened and those

aged over 50 were screened only biennially. While screening frequencies were the same in the AI-based, PRS-based and USPSTF guideline-based strategies, these strategies differed in their accuracy of risk prediction for women aged between 40 and 49 which in turn determined the proportion of women screened prior to age 50.



Note: 'High risk' and 'Low risk' refer to estimated high-risk and low-risk women, respectively.

Figure 5.1: Screening strategies

5.2.3 Model structure

We developed a hybrid decision tree/Markov microsimulation model to estimate the cost and effectiveness of the four screening strategies. This model structure allowed us to rigorously capture both the accuracy of risk prediction and the natural history, screening and treatment of breast cancer. The analysis was conducted from a health care system's perspective. Cycle length was one year and lifetime horizon was used.

Figure 5.2 shows the decision tree component of the model which captured risk prediction and stratification at age 40 based on AI, PRS or family history (for USPSTF guideline-based screening). Women entering the model had an underlying high or low risk of breast cancer. Depending on risk-stratification strategy, AI, PRS or family history were used to predict this underlying risk; the extent to which the estimated risk category matched the underlying risk category was determined by the accuracy of each method (described below).

The microsimulation component, which was adapted from the Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Cancer Working Group's University of Wisconsin Breast Cancer Epidemiology Simulation model (UWBCS) (168–170), simulated the natural history, screening, diagnosis and treatment for breast cancer. Details of the UWBCS model have been published elsewhere (168–170).

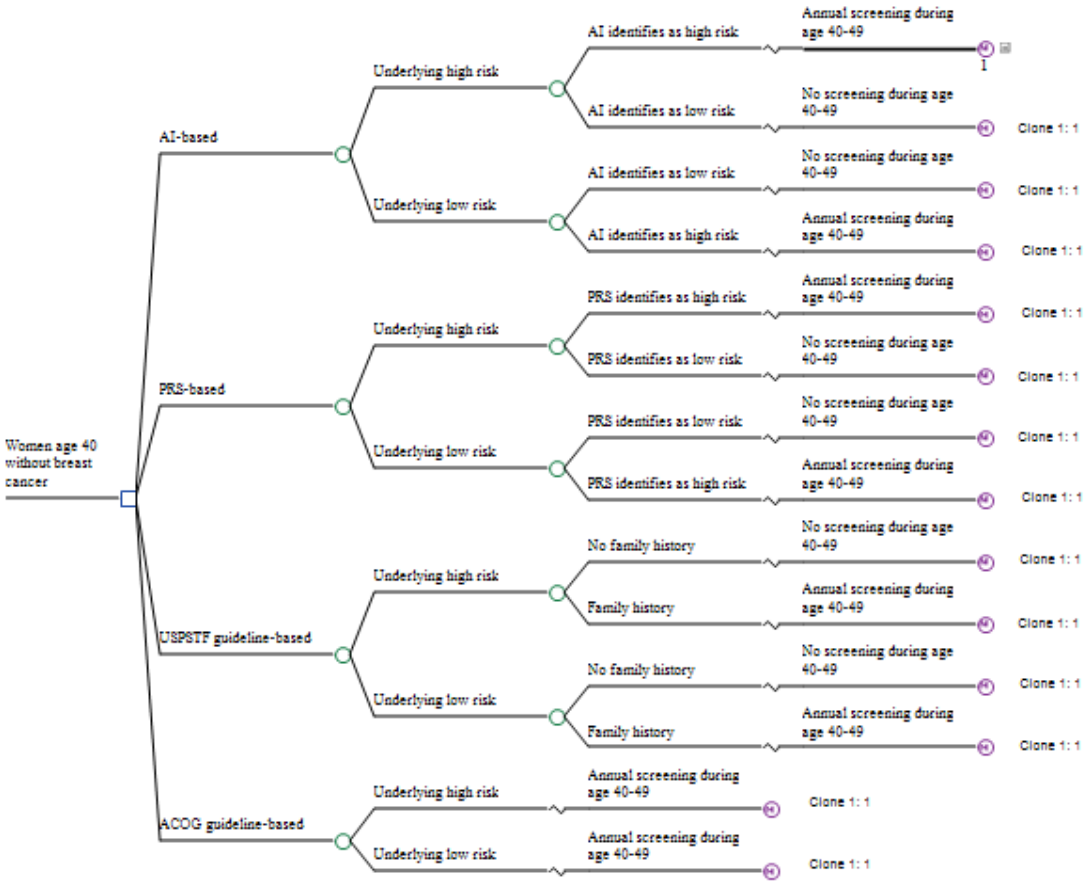


Figure 5.2: Decision Tree

5.2.4 Model Inputs

Inputs used in our model are presented in Table 5.1 and described below.

Accuracy of risk prediction

The key determinant of costs and effectiveness of each screening strategy was the accuracy of risk prediction. Higher accuracy of risk prediction implied that fewer women with underlying high-risk were incorrectly predicted to be at low risk, resulting in timely

diagnosis and treatment of cancer for high-risk women. It also meant that fewer low-risk women were incorrectly predicted to be at high risk, leading to reduction in screening and fewer false-positive diagnoses and over-diagnosed cases (i.e., additional screen-detected cases which would not have been detected in the absence of screening (171)).

In our model, accuracy of prediction of breast cancer risk using AI and PRS was measured using area under the receiver operating characteristic curve (AUC) obtained from published studies (47,48). As real-world clinical decisions will also likely utilize information on other demographic and personal risk factors (such as weight, family history, breast density) in addition to AI or PRS, we used AUC values for models based on both AI or PRS and other risk factors. Using data from digital screening mammograms read by deep learning algorithms (AI), information on other demographic and personal risk factors and breast cancer outcomes from tumor registries, Yala et al. estimated an AUC of 0.71 for white females in the US (47). This study was chosen owing to its large study sample of patients seen in the US (over 31,000 patients in the training dataset and over 3,900 patients in the test set) (47). Meanwhile, AUC for PRS was obtained from Vachon et al., a recent, high-quality study that estimated the AUC for PRS combined with other risk factors for a large study sample primarily consisting of American women (48). Vachon et al. estimated an AUC of 0.69 for a model that combined PRSs developed based on 76 SNPs and information from the Breast Cancer Surveillance Consortium (BCSC) five-year risk-prediction model (48). We followed a previously published method to simulate distributions of RR estimated using AI or PRS using these AUC values (172,173). The correlation between underlying 'true' RR and RR estimated using AI or PRS was assumed

equal to the respective AUC. Women with estimated RR of 1.1 or higher were then classified as high risk while those with estimated RR below 1.1 as low risk. We note that as AUC of both AI and PRS is below 1, not all 'true' high risk women will be correctly classified as such.

In the USPSTF guideline-based screening strategy, risk prediction was based on family history. As women with an underlying low risk will not have a family history of breast cancer, all low-risk women will be correctly classified as such. Among high-risk women, we assumed that 37% will be correctly classified. This proportion was calculated as the share of US women with first-degree family history of breast cancer (16% (174,175)) among high-risk women (43% of our study cohort).

Incidence and progression of breast cancer and mortality risk

A patient's likelihood of developing breast cancer was estimated by multiplying age-specific annual breast cancer incidence rates per 100,000 population among white women in the US (176) (adjusted for increase in incidence rates due to screening (177)) with a woman's 'true' RR (166). Detection of cancer through screening depended on screening frequency and sensitivity of mammography; the latter depended on patient age and was obtained from the published literature (178). Once detected, all patients received treatment (chemotherapy, radiation therapy and/or surgery (lumpectomy or mastectomy)); type of treatment was dependent on cancer stage and age at diagnosis (68). Patients with estrogen-receptor positive status also received adjuvant therapy with tamoxifen for 5 years (68). Probability of treatment success depended on patient's age and stage of cancer at diagnosis

as well as estrogen-receptor status (170). If treatment was unsuccessful, patients experienced cancer progression and faced risk of breast cancer mortality once cancer reached the distant metastases stage (170). All patients faced risk of mortality from competing causes; this mortality risk was age-specific, and was obtained from the (latest available) 2017 US life tables (111).

Costs

Cost of each strategy included cost of risk prediction (index mammogram read by AI technology or genetic testing as applicable), cost of screening with digital mammogram (if any), and cost of breast cancer treatment determined by the stage at cancer diagnosis (treatment costs were lower for cancers detected at an earlier stage). Cost of genetic test for the PRS-based strategy was the cost of OncoArray test in US laboratories (179). While cost of AI-based risk prediction in clinical practice is not yet available, calculations by European Society of Radiology suggest fixed costs of €60,000 (US$65,300) in addition to an annual cost of €20,000 (US$21,770) for the software license (180). Assuming equipment is amortized in 10 years, and with 8,695 mammogram facilities in the US (181) serving nearly two million women aged 40 years (182), cost of AI reading of each mammogram amounts to ~US$112. We varied cost of AI reading per mammogram over a wide range (up to US$500) in the sensitivity analyses.

Cost of mammogram was obtained from Center for Medicare and Medicaid's 2020 Physician Fee Schedule (183). Cost of diagnostic work-up following a positive diagnosis

and cost of treatment of breast cancer were obtained from the published literature (68,70). All costs were estimated in 2020 US dollars and discounted at 3.5% per year (116).

Effectiveness

Effectiveness was measured in terms of Quality Adjusted Life Years (QALYs) that captured a person's life expectancy adjusted by his/her health-related quality of life called utility. Screening entailed disutility of 0.006 QALYs for one week and diagnostic workup following a positive diagnosis involved disutility of 0.105 QALYs for five weeks (70). Utilities were age-specific and utility values according to patients' cancer stage were applied once cancer was detected and treatment initiated (72). For patients who were successfully treated and were not in distant metastases stage, stage-specific utility was applied until two years after diagnosis after which utility was equal to that for a healthy individual (72). All utility values were discounted at 3.5% per year (116).

Table 5.1: Model Inputs

Variable	Value	Source
Risk prediction		
AI (AUC)	0.71	(47)
PRS (AUC)	0.69	(48)
Family history (proportion correctly identified as high risk)	0.37	Authors' calculation based on (174,175)
Probabilities		
Hyper-aggressive regional cancer	0.01	(168)
Hyper-aggressive distant cancer	0.02	
Limited Malignant Potential tumors	0.42	
Clinical Surfacing (annual probability)	0.06 – 1 (tumor diameter 1cm to 8 cm)	(170)
Treatment success	0.025 – 0.99 (dependent on age and stage at diagnosis and ER status)	(170)
Tumor growth rate	Gamma (0.12, 0.012)	(168)
ER positive	0.65 – 0.83 (depending on age)	(170)
Sensitivity and specificity of mammography		

Sensitivity	0.824 (age 40-49); 0.805 (age 50-59); 0.899 (age 60-69); 0.86 (age 70-74)	(178)
Specificity	0.88 (age 40-49); 0.909 (age 50-59); 0.921 (age 60-69); 0.928 (age 70-74)	
Costs (in US$)		
AI	112	(180), Author's calculation
OncoArray genetic test	115	(179)
Mammography	152.19	(183)
Additional diagnostic costs (true positive diagnosis)		
Age 40-49	2490.97	(70)
Age 50-64	2337.39	
Age 65-74	2350.36	
Additional diagnostic costs (false positive diagnosis)		
Age 40-49	260.81	(70)
Age 50-64	309.13	
Age 65-74	309.97	
Treatment costs		
In situ, initial cost	11543.32; 10328.77	(68)
In situ, continuing cost	0	
In situ, terminal cost	44428.05	
Localized, initial cost	24545.89; 16547.88	
Localized, continuing cost	1349.14; 822.23; 793.55; 1001.76; 710.69; 678.82	
Localized, terminal cost	50804.05	
Regional, initial cost	50339.97; 33784.12	
Regional, continuing cost	6253.84; 4230.13; 3993.77; 3566.19; 2546.37; 2164.46	
Regional, terminal cost	57584.79	
Distant, initial cost	56534.28; 43643.09	
Distant, continuing cost	24728.52; 22107.79; 21290.87; 18775.32; 13867.43; 14283.86	
Distant, terminal cost	75002.48	
Tamoxifen (5 years)	1519.11	(68)
Utilities		
Disutility from screening	0.006 for 1 week	(70)
Disutility from additional diagnosis	0.105 for 5 weeks	
Health state		
Healthy	0.59-0.829 (depending on age)	(72)
In situ & Localized	0.531-0.746 (depending on age)	
Regional	0.442 – 0.622 (depending on age)	
Distant	0.354 – 0.497 (depending on age)	

Notes: All costs are in 2020 US dollars (US$). Calculations by European Society of Radiology suggest fixed costs of €60,000 (US$65,300 @ €1=US$1.08 (184)) in addition to €20,000 (US$21,770) annually for the software license (180). Assuming equipment is amortized in 10 years, and with 8,695 mammogram facilities in the US (181) serving over 2 million women aged 40 years (182), cost of AI reading of each mammogram amounts to ~US$112. Initial treatment costs for each stage are for age<70 and age>=70, respectively, calculated as the weighted average of costs of different breast cancer treatments with proportion of patients receiving each type of treatment as the weight (68). Continuing treatment costs for each stage are for 1 to 5 and >=6 years after the year of diagnosis, respectively.

5.2.5 Cost effectiveness analysis

We estimated the costs and QALYs of the four strategies. A strategy was considered cost-effective relative to another strategy if the Incremental Cost Effectiveness Ratio (ICER), calculated as the difference between the overall costs of the two strategies divided by the difference between the total QALYs gained, was lower than the conventional willingness-to-pay threshold (WTP) of US$100,000 per QALY. Meanwhile, a strategy was dominated if it was both more costly and less effective than the other strategy or extended dominated if it achieved fewer total QALYs than a more costly strategy at a higher incremental cost per QALY (i.e., its ICER relative to the next less costly strategy was higher than the ICER of a more effective strategy) (185).

In addition to the conventional sensitivity analyses of varying values of key costs and utilities in one-way sensitivity analyses and addressing parameter uncertainty using probabilistic sensitivity analyses (PSA), we conducted several additional sensitivity and scenario analyses. First, our base case analysis used AUC for AI for all white women, both pre- and post-menopausal. As women entering our model are aged 40 years and thus likely pre-menopausal, in this analysis, we simulated a distribution of estimated RR using a higher AUC (0.79) specific to pre-menopausal women (this AUC for pre-menopausal women is, however, not race-specific) (47). Estimated risk for PRS was the same as in the base case as menopausal status is unlikely to affect accuracy of PRS. Second, to capture differences in accuracy of AI and PRS technologies themselves, we examined the scenario where risk prediction is performed exclusively using AI or PRS, i.e., without considering demographic and personal risk factors. Thus, in this analysis, AUC value was 0.69 for AI

(47) and 0.63 for PRS (165). Third, we considered the scenario where screening beyond age 50 in the AI-based and PRS-based screening strategies followed ACOG/ACR guidelines (instead of USPSTF guidelines), i.e., all women were screened annually after age 50. Finally, we considered the scenario where women identified as low-risk by AI or PRS are also offered screening between ages 40 and 49 (albeit at lower frequency than high-risk women) instead of not being screened at all. Specifically, similar to the USPSTF guidelines for women aged above 50 without family history, these low-risk women were screened biennially. All analyses were performed using TreeAge Pro 2019 v2.1 (105).

5.3 Results

5.3.1 Base case analysis

Base case cost-effectiveness results are presented in Table 5.2. Panel A shows that, among the four strategies, AI-based screening is the most cost-effective. AI-based and PRS-based screening cost more than USPSTF guideline-based screening (US$49.4 million and US$39.5 million per 100,000 women more, respectively) but also yield 2,136 and 1,676 additional QALYs (per 100,000 women), respectively. While PRS-based screening is cost-effective relative to USPSTF guideline based screening (ICER: US$23,572 per QALY gained is lower than the conventional WTP threshold of US$100,000 per QALY gained), it achieves fewer QALYs at a higher cost per QALY compared with AI-based screening, and is thus extended dominated. After excluding the PRS-based screening strategy, the resulting ICER of AI-based screening compared with USPSTF guideline-based screening is US$23,133 per QALY gained which is lower than the conventional WTP threshold of

US$100,000 per QALY gained (Panel B). Meanwhile, AI-based screening dominates ACOG guideline-based screening. Total lifetime costs of AI-based screening are US$155.8 million (per 100,000 women) lower than ACOG guideline-based and it also generates 1,755 higher QALYs (per 100,000 women).

Table 5.2: Incremental Cost Effectiveness Results, Base Case

Strategy	Cost (in 1000 US$)	Incremental Costs (in 1000 US$)	Effectiveness (in QALYs)	Incremental Effectiveness (in QALYs)	ICER (US$/QALY)
Panel A: All strategies					
USPSTF guideline-based	257,858		1,643,776		
PRS-based	297,373	39,516	1,645,453	1,676	Ext. dominated
AI-based	307,276	9,903	1,645,913	460	21,534
ACOG guideline-based	463,163	155,886	1,644,158	-1,755	Dominated
Panel B: Excluding dominated strategies					
USPSTF guideline-based	257,858		1,643,776		
AI-based	307,276	49,419	1,645,913	2,136	23,133

All costs are in 2020 US dollars (US$). Costs and effectiveness are calculated per 100,000 women. ICER = incremental cost-effectiveness ratio.

The cost-effectiveness of AI-based screening compared with USPSTF guideline-based screening is explained by the higher accuracy of AI in identifying high-risk women compared with family history. Specifically, AI correctly classifies 61% of true high-risk women as such, compared with 37% with family history (Table 5.3). Consequently, even though mammography screening costs increase when screening is guided by AI instead of family history as more women are screened during ages 40 to 49, more high-risk women benefit from this screening which is reflected in fewer breast cancer deaths (2.6% vs. 2.7% of cases).

Meanwhile, the lower costs and higher effectiveness of AI-based screening relative to ACOG guideline-based screening arise as a result of targeted screening. Even though breast cancer deaths increase as not all women are screened during age 40-49 (and low-risk women are screened only biennially beyond age 50), this reduction in screening results in nearly 40% fewer over-diagnoses (2,920 per 100,000 women vs 4,692 per 100,000 women) and over 50% fewer false-positive diagnoses (141,537 per 100,000 women vs 292,133 per 100,000 women). Thus, AI-based screening saves screening costs, cost of additional diagnostic work-up for false-positive diagnoses and downstream treatment costs for over-diagnosed cases. At the same time, it also reduces disutility arising from screening, additional diagnostic work-up (for false-positive diagnoses) and treatment (for over-diagnosed cases).

Table 5.3: Breast Cancer Outcomes by Strategy

Strategy	No. (%) of true high risk women classified as high risk	No. (%) of true low risk women classified as low risk	No (%) of breast cancer deaths	No. (%) of over-diagnosed cases (per 100,000 women)	No. of False positive diagnoses (per 100,000 women)
USPSTF guideline-based	15,961 (36.7)	56,530 (100)	323 (2.7)	2,920	122,242
PRS-based	26,099 (60.0)	49,511 (87.6)	299 (2.5)	3,033	141,565
AI-based	26,520 (61.0)	50,017 (88.5)	316 (2.6)	2,920	141,537
ACOG guideline-based	---	---	255 (1.9)	4,692	292,133

Percentage of breast cancer deaths is calculated as the proportion of breast cancers detected that result in death due to cancer. In each strategy, 'no. of over-diagnosed cases' are calculated as: modelled number of cases detected – number of cases that would be detected in the absence of screening. 'No. of False positive diagnoses' refers to total number of false positive diagnoses among all mammograms performed during the lifetimes of 100,000 women. As specificity of each mammogram is <100%, a woman can have more than one false-positive diagnosis in her lifetime.

While AI-based risk prediction is more costly than genetic testing, its higher accuracy justifies the higher cost: 61% vs 60% high-risk women and 88.5% vs 87.6% of low risk women are correctly classified with AI and PRS, respectively. The lower accuracy of PRS implies that more low-risk women incorrectly undergo annual screening between ages 40 and 49 compared with AI-based screening, leading to higher over-diagnoses (3.033 vs 2.920 per 100,000 women) and false-positive diagnoses (141,565 vs 141,537 per 100,000 women).

5.3.2 Sensitivity and scenario analyses

Results from one-way sensitivity analyses presented in tornado diagrams in Figure 5.3 indicate that the ICER is most sensitive to age- and stage-specific utilities. Nevertheless, for all values of costs and utilities in the ±25% range, AI-based screening remains cost-effective. In particular, it remains the most cost-effective screening strategy as long as cost of AI reading is below US$472 per mammogram (Figure 5.4). The cost-effectiveness acceptability curve (Figure 5.5) shows that, at the WTP threshold of US$100,000/QALY, AI-based screening is cost-effective in 94% of iterations.

Table 5.4 presents results from additional sensitivity and scenario analyses. Our results were very similar to the base case analysis even when we used AUC values for AI-based risk prediction that were specific to pre-menopausal women (Panel A) and when risk prediction was based exclusively on AI or PRS (Panel B). AI-based screening also continued to dominate ACOG guideline-based screening in the model where screening beyond age 50 in the AI-based and PRS-based screening strategies followed ACOG/ACR

guidelines (Panel C). This finding highlights the cost savings and improvement in QALYs arising from targeted screening specifically in the 40 to 49 age group (as effect of differences across USPSTF and ACOG/ACR guidelines beyond age 50 in the base case analysis is nullified). Finally, even though total lifetime costs of AI-based and PRS-based screening were higher if low-risk women in these strategies were offered biennial screening between ages 40 and 49 years (instead of not being screened), AI-based screening still remained the most cost-effective screening strategy (Panel D).

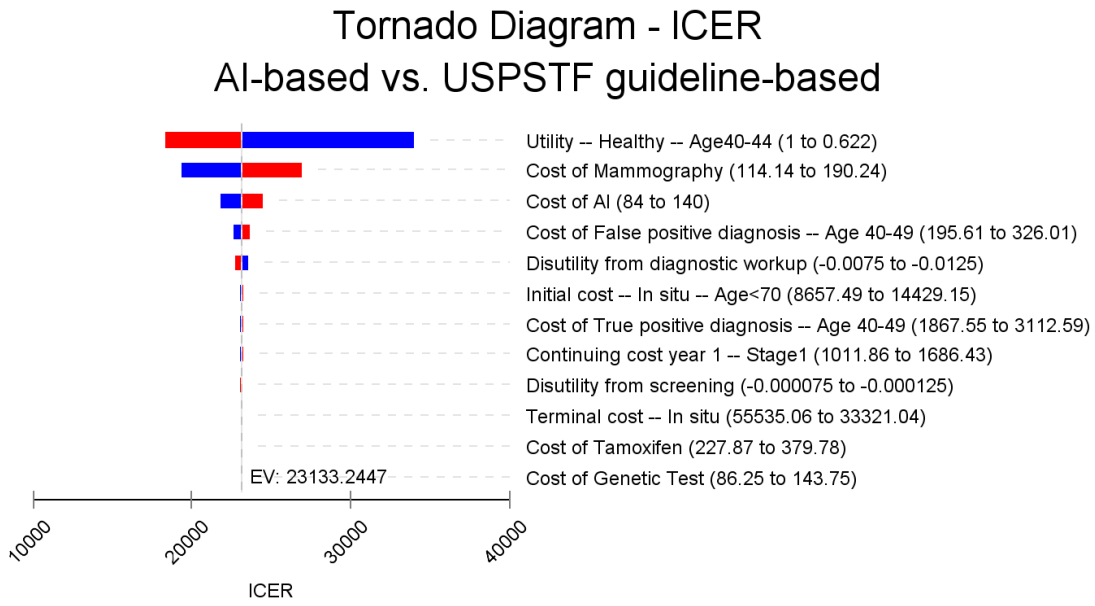


Figure 5.3: Tornado diagram

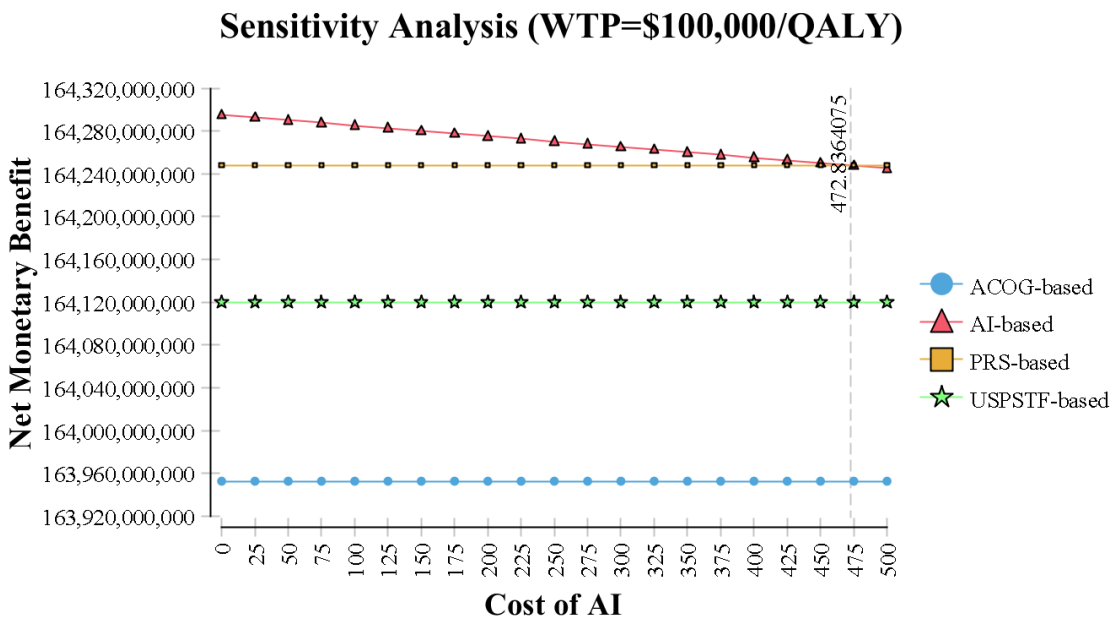


Figure 5.4: Threshold analysis for cost of AI

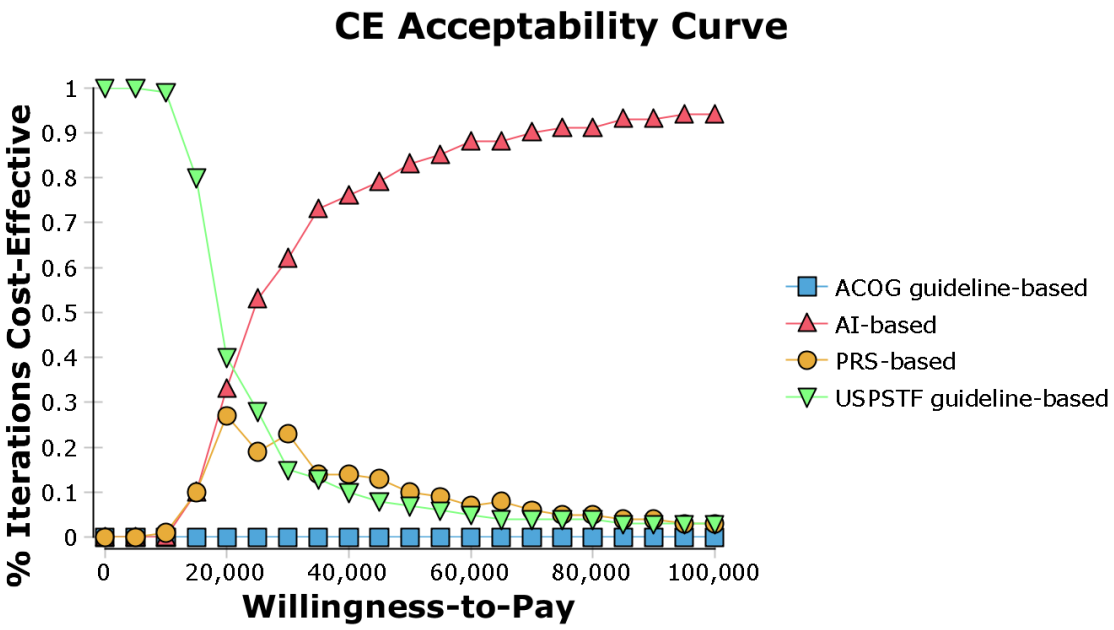


Figure 5.5: Cost effectiveness acceptability curve

Table 5.4: Incremental Cost Effectiveness Results, Sensitivity and Scenario Analyses

Strategy	Cost (in 1000 US$)	Incremental Costs (in 1000 US$)	Effectiveness (in QALYs)	Incremental Effectiveness (in QALYs)	ICER (US$/QALY)
Panel A: AUC for premenopausal women for AI					
USPSTF guideline-based	257,858		1,643,776		
PRS-based	297,843	39,985	1,645,659	1,882	21,242
AI-based	307,135	9,292	1,645,991	332	28,005
ACOG guideline-based	463,163	156,028	1,644,158	-1,832	Dominated
Panel B: AUC for AI and PRS without inclusion of other risk factors					
USPSTF guideline-based	257,858		1,643,776		
PRS-based	296,448	38,590	1,645,492	1,715	Ext. dominated
AI-based	306,732	48,874	1,646,021	2,245	21,772
ACOG guideline-based	463,163	156,431	1,644,158	-1,863	Dominated
Panel C: ACOG guideline beyond age 50 in AI and PRS strategies					
USPSTF guideline-based	257,858		1,643,776		
PRS-based	373,549	115,691	1,644,624	847	Ext. dominated
AI-based	382,993	125,135	1,645,054	1,278	97,922
ACOG guideline-based	463,163	80,169	1,644,158	-896	Dominated
Panel D: Biennial screening for low-risk in AI and PRS strategies					
USPSTF guideline-based	257,858		1,643,776		
PRS-based	348,282	90,424	1,644,782	1,005	89,968
AI-based	359,721	11,439	1,644,900	118	96,931
ACOG guideline-based	463,163	103,442	1,644,158	-741	Dominated

All costs are in 2020 US dollars (US$). Costs and effectiveness are calculated per 100,000 women. ICER = incremental cost-effectiveness ratio. In Panels B and C, PRS-based strategy is extended dominated. Hence, incremental costs, incremental effectiveness and ICER for AI-based strategy are calculated with reference to USPSTF guideline-based strategy.

5.4 Discussion

This study estimated the cost-effectiveness of AI-based or PRS-based risk stratification to guide breast cancer screening for women aged between 40 and 49 years (with screening beyond age 50 based on existing guidelines) compared with screening based exclusively on existing guidelines. We found that AI-based screening is the most cost-effective screening strategy. It is cost-effective compared with both PRS-based screening and screening based on family history (as recommended by USPSTF) with an ICER of US$23,133 per QALY gained. Furthermore, it costs less and is more effective relative to screening all women annually (as recommended by ACOG/ACR).

As AI and PRS are still emerging technologies, findings from this early stage evaluation will provide useful first insights to policymakers on the economic value of adopting these technologies as well as inform the debate over appropriate breast cancer screening practices for women aged between 40 and 49 years. Specifically, our results highlight that using AI or PRS to risk-stratify women and targeting mammography screening at women identified as high-risk can help alleviate existing concerns about missed or delayed diagnosis as more high-risk women are accurately identified and subjected to screening compared with existing USPSTF guidelines. At the same time, it can also reduce over-diagnoses and false-positive diagnoses that arise by screening all women over age 40.

This study is the first cost-effectiveness analysis to compare the use of two emerging technologies, namely AI and PRS for risk stratification. Given the increasing shift towards individualized care and the widespread potential for leveraging AI powered solutions to

overcome the limitations of human discernment, both these technologies will likely see widespread (and possibly competing) applications throughout medicine. Oncology will be a particularly consequential venue where benefits to risk-stratified and personalized care can offer significant economic benefits. Even though we used US data in this study, our general framework can be easily adapted by stakeholders to conduct economic evaluations of these competing technologies within their own clinical and policy context. In particular, both AI and PRS are still in nascent stages and their use in health care provision is continuously evolving. As their accuracy improves in the future, our framework can be utilized to update the cost-effectiveness of these important risk-stratification strategies.

Our study has several limitations. First, randomized controlled trials that directly compare AI with PRS or existing screening criteria are lacking and thus, data on efficacy of AI and PRS had to be obtained from different studies. We note that the demographic and personal risk factors considered in addition to AI and PRS were slightly different in the two studies. Nonetheless, we conducted sensitivity analyses that excluded these other risk factors and obtained similar results. Second, cost of using AI for breast cancer risk prediction in clinical practice is not yet known and was not available from existing literature. Therefore, for our analysis, we had to rely on cost estimates from the European Society of Radiology (180) to estimate this cost. Nevertheless, we varied the cost of AI in one-way sensitivity analyses and our results continued to hold for all costs of AI as high as US$472 per mammogram. Third, in our model, AI was used to guide breast cancer screening over a 10-year duration (i.e., between ages 40 and 49) while existing data could validate the accuracy of AI-based risk prediction only for five years post risk-assessment (47). However, these

existing data provide suggestive evidence that AI is able to detect features associated with long-term risk (47). As deep learning models improve in the future and long-term data become available, future studies could re-examine the cost-effectiveness of using AI to guide breast cancer screening compared with PRS-based or guideline-based screening. Fourth, our model did not account for mastectomy or other invasive risk reducing procedures that may be undertaken by high-risk women. If these procedures are considered, AI-based screening will further prevent unnecessary downstream costs and enhance quality of life of patients. Finally, due to lack of data, we could not account for variations in accuracy of AI-based or PRS-based risk stratification along different points of the risk distribution nor could we consider another possible screening strategy that combines AI-based and PRS-based risk stratification. Cost-effectiveness of this potential strategy should be examined in future research.

To conclude, this study finds that using AI to risk-stratify women for breast cancer screening between ages 40 and 49 (followed by screening based on existing guidelines beyond age 50) is cost-effective compared with PRS-based screening and screening based exclusively on existing USPSTF and ACOG/ACR guidelines. Compared with USPSTF guidelines that recommend family history-based screening, AI-based screening can reduce the possibility of missed or delayed diagnosis as more high-risk women are accurately identified and screened. At the same time, it can help alleviate existing concerns about over-diagnoses and false-positive diagnoses inherent in ACOG/ACR guidelines that recommend annual screening for all women.

Co-authorship Statement

The candidate has co-authored this paper with her supervisor, Dr. Hai Nguyen. The candidate is the first author. She conceptualized the research idea, conducted data analyses and was the primary contributor to manuscript preparation.

Chapter 6 : Summary and Future Directions

6.1 Key findings

In **Chapter 2**, I assessed the cost-effectiveness of providing Teplizumab to different target patient groups at different possible prices of the drug. I found that if the price of the drug turns out to be above US$100,000 as current indications suggest (41), it will be cost-effective to give the drug to just about a quarter of at-risk individuals. Meanwhile, if the price is below US$58,200, it will be cost-effective to give the drug to at least 76% of all at-risk individuals.

In **Chapter 3**, I examined the cost-effectiveness of aspiration therapy relative to gastric bypass and sleeve gastrectomy as well as no treatment. I found that, over a lifetime horizon, aspiration therapy is dominated by bariatric surgery, that is, it costs more while yielding fewer QALYs. However, as access to bariatric surgery remains difficult, aspiration therapy can be a cost-effective treatment compared with no treatment.

In **Chapter 4**, I compared the cost-effectiveness of Elipse intragastric balloon as a stand-alone or as an add-on treatment to bariatric surgery with bariatric surgery alone. I found that despite being more costly upfront, providing Elipse treatment prior to bariatric surgery results in lower lifetime costs and higher QALYs than directly performing bariatric surgery. In particular, Elipse as an add-on to sleeve gastrectomy was found to be most cost-effective among the strategies considered with an ICER of US$4,619 per QALY. Further, even though treatment with Elipse alone is not cost-effective compared with bariatric surgery alone or when used as an add-on to bariatric surgery, it is cost-effective compared with no treatment with an ICER of US$89,096 per QALY gained.

In **Chapter 5**, I found that AI-guided risk-stratified breast cancer screening between ages 40 and 49 years costs less and is more effective relative to screening all women annually (as recommended by ACOG/ACR). It is also cost-effective compared with screening based on PRS or family history (as recommended by USPSTF) with an ICER of US$23,133 per QALY gained.

6.2 Challenges and limitations

6.2.1 Data uncertainty

"It's always too early until, unfortunately, it's suddenly too late."

-Buxton's law of technological evaluation, 1987 (186)

As with all early-stage cost-effectiveness analyses (19,23), a key challenge in the analyses in this thesis was the inherent data uncertainty and lack of a strong evidence base on the effectiveness of the innovations. As shown in Figure 6.1, data uncertainty arose on 4 accounts.

First, for interventions considered in Chapters 3, 4 and 5, direct head-to-head comparisons on effectiveness were not available from a single study. That is, no study has compared breast cancer outcomes from AI-based vs PRS-based screening vs screening based on existing USPSTF or ACOG/ACR guidelines. There also exists no study that directly compares the accuracy of risk prediction using AI and PRS. Similarly, no clinical trials have directly compared effectiveness of Elipse and bariatric surgery. Although a clinical trial to compare aspiration therapy with bariatric surgery has been conducted (187), its

results were not available at the time that cost-effectiveness analysis in Chapter 3 was conducted.

Second, while RCTs are considered the 'gold standard' for data on effectiveness of interventions, suitable RCT-based evidence was not available for the interventions considered in Chapters 3 (aspiration therapy), 4 (Elipse intragastric balloon) and 5 (AI-based breast cancer screening),. While 4-year results of an RCT of aspiration therapy have been published more recently (188), only 1 year results were available at the time the cost-effectiveness analysis in Chapter 3 was performed (66,189). Given this very short time period, the cost-effectiveness analysis had to rely on evidence from observational studies.

Third, as the technologies considered in this thesis are still in their nascent stages, data on long-term health outcomes of these interventions are not available. For example, long-term (such as 10-15 year) weight loss effects of aspiration therapy and Elipse are unknown. Accuracy of AI-based risk prediction of breast cancer has also been validated for only up to 5 years post risk-assessment. Similarly, efficacy of Teplizumab in delaying Type 1 diabetes has been assessed for only a 5-year time period.

Fourth, the Phase II trial for Teplizumab largely comprised of white individuals who were first-degree relatives of Type 1 diabetes patients (39). The effectiveness of this drug in other patient populations remains to be seen.

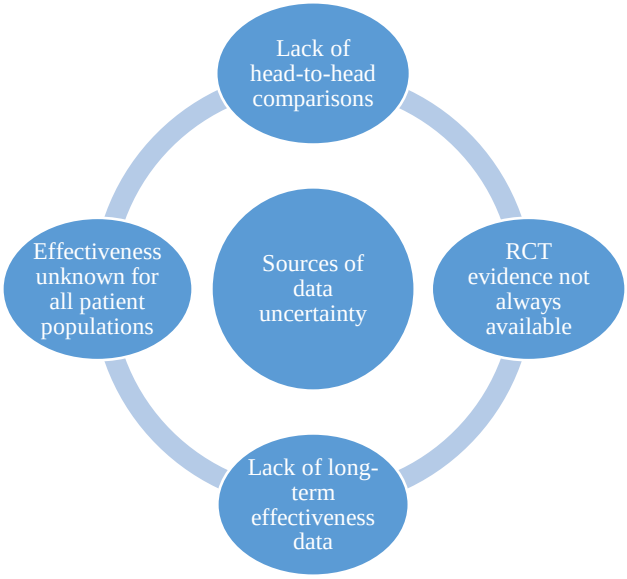


Figure 6.1: Sources of data uncertainty in the foregoing studies

6.2.2 Choice of discount rate

All analyses in this thesis rely on a discount rate of 3.5% per annum. This rate is recommended by the National Institute for Health and Care Excellence (NICE) based UK Treasury's estimate of the social time preference rate for consumption (190), and is similar to recommendations by other countries (the Washington Panel: 3% for US; Germany: 3%; France: 4%) (191). Meanwhile, CADTH recommends a lower discount rate of 1.5% (127). There also exists considerable debate around differential discounting of costs and health outcomes (191).

Existing literature in this area suggests that the choice of a discount rate depends on several factors including social objectives (i.e., to maximize present value of health or present consumption value of health) and constraints on health budgets (190–192). Social

objectives determine whether real interest rates or the social rate of time preference for consumption form the basis of discount rates as well as the need to account for growth in consumption value of health over time (191,192). Constraints on health budgets imply the existence of opportunity costs of adopting a new technology in terms of health forgone (i.e. the existence of a cost-effectiveness threshold) and the need to adjust for growth in this threshold over time (191). These studies conclude that the appropriate discount rate should be lower than 3.5%, both as it is higher than observed interest rates (192,193) and as consumption value of health is expected to grow over time (190).

To the extent that appropriate discount rates may be lower than 3.5% and may potentially be lower for health outcomes than for costs, the choice of 3.5% discount rate in the 4 analyses may bias against technologies that cost more upfront but yield health benefits over time (such as bariatric surgery or Teplizumab) (193). Nevertheless, as identified by previous studies, further research is needed on several components used to estimate the discount rate including obtaining empirical estimates of growth in cost-effectiveness threshold and consumption value of health (191,194).

6.2.3 Combination of health-related quality of life values derived from multiple instruments

Owing to limitations in data availability, in Chapters 2 and 5, health-related quality of life data derived from different multi-attribute utility instruments had to be combined. In Chapter 2, following the Sheffield Type 1 Diabetes Policy Model (54), disutilities from Type 1 diabetes complications were obtained from a study that used the Self-Administered

Quality of Well Being index. However, utility scores for children and adults with pre-Type 1 diabetes or Type 1 diabetes had to be sourced from studies that used the Health Utilities Index and the HRQOL-15D instruments. Similarly, in Chapter 5, quality of life weights for healthy and cancer health states were based on EQ-5D scores which use time-tradeoff valuations while disutility from screening and diagnostic work up were obtained from a study that used the visual analog scale. To the extent that utility values derived using different generic, multiattribute utility instruments vary due to differences in descriptive systems and measurement scales used by each instrument (195), and utility scores obtained using the visual analog scale are systematically lower than those obtained using the time-tradeoff approach (196), the utility values across different health states may not be perfectly comparable. As utility values derived from similar instruments are collected in future studies, cost-effectiveness of these technologies may be re-examined.

6.2.4 Commercial viability for manufacturer

While the study in Chapter 2 identified price ranges in which provision of Teplizumab to different target patient groups will be cost-effective, it does not shed light on whether these price ranges will be commercially viable for the manufacturer. Return on investment analyses conducted from the manufacturer's perspective which use these price ranges as inputs can answer this question. Nevertheless, given the focus of this thesis on early-stage cost-effectiveness analyses within a translational context, these return on investment analyses have not been considered here and may be a subject for future research.

6.2.5 Cost-effectiveness in later phases of health care technology's life-cycle

While the 4 early-stage cost-effectiveness analyses in this thesis provided the best possible current estimates on cost-effectiveness of the technologies considered which can help inform adoption and coverage decisions of these technologies, it will be important to monitor whether the anticipated health system and population health benefits of these technologies are actually achieved and to re-assess the cost-effectiveness of these technologies over time. Life cycle HTA approaches that involve iterative evaluations throughout the life cycle of the technology will be necessary to identify and prevent inefficient uses of these technologies and to guide subsequent disinvestment decisions should these technologies fail to achieve anticipated benefits (197,198). In this regard, the rigorous economic models and general frameworks developed in this thesis can be adapted to conduct these iterative evaluations.

6.3 Solutions to overcome challenges due to data uncertainty

First, to overcome the limitation that data on effectiveness of different interventions had to be sourced from different studies, I tried to ensure comparability of data (and study populations) across studies to the extent possible. For example, data on effectiveness of bariatric surgery in Chapter 3 were sourced from a meta-analysis in which the study population was comparable (in terms of age, sex and pre-treatment BMI) to that in the study for aspiration therapy. Second, to overcome the lack of availability of long-term evidence on effectiveness of interventions, I conducted a rich set of sensitivity and scenario analyses. For instance, I considered alternative scenarios for the efficacy of Teplizumab beyond 5 years, namely that all treated and untreated individuals develop Type 1 diabetes

after year 5, or that risk of Type 1 diabetes onset becomes zero for treated individuals. Similarly, for cost-effectiveness analyses of aspiration therapy and Elipse, I considered alternative long-term weight trajectories. In this regard, I note that in addition to the sensitivity analyses in Chapter 3, I conducted several further sensitivity analyses which were published in response to the letter to editor by Jirapinyo et al. (199) (provided in Appendix 3.6).

Third, unlike several previous early-stage cost-effectiveness analyses, the models developed in each of the 4 studies were rigorous and comprehensive. In particular, to comprehensively capture disease progression and treatment, the microsimulation components of the models in Chapters 2 and 5 were adapted from well-known previously validated models for Type 1 diabetes and breast cancer, respectively. Thus, as further data on effectiveness of the 4 interventions in other patient populations and policy contexts is generated in the future, the models in these studies can be used to repeat these cost-effectiveness analyses for different populations and contexts.

6.4 Value of information analyses

In addition to the sensitivity analyses conducted to capture the effects of data uncertainty, in this section, I also conducted VOI analyses to quantify the consequences of decision-making based on current evidence. Given the computational burden inherent in VOI analyses, I conducted these analyses for two interventions -- Teplizumab and Elipse intragastric balloon -- as examples.

6.4.1 VOI analyses for Teplizumab

For Teplizumab, the largest source of uncertainty lies in the drug's effect estimates in the phase II trial. Therefore, I conducted two types of VOI analyses. First, I conducted an expected value of perfect information (EVPI) analysis to quantify the expected benefit of eliminating uncertainty in a broad set of parameters. In this analysis, I assumed drug price of US$100,000 and an annual beneficiary population of 16,356 patients who are ZnT8 negative (based on 26.3% prevalence of ZnT8 negative, annual Type 1 diabetes incidence of 22.9 per 100,000 population (200) and population size of ~272 million aged <65 years in the US in 2020 (201)). I then applied a discount rate of 3.5% per annum and assumed that benefits of research accrue for 7 years (length of orphan drug exclusivity period in the US (202)) to estimate the EVPI at the population level. Next, I conducted expected value of partial perfect information (EVPPI) analysis to quantify the benefit of eliminating uncertainty specifically in the drug's effect estimates. This latter analysis can guide researchers on the net monetary benefit of generating further evidence on the efficacy of this drug (94). EVPPI analysis was performed using three-level Monte Carlo simulation with 50 iterations in the outer-most loop which sampled distributions for probabilities of drug efficacy, 100 iterations in the second loop which sampled distributions for all other parameters and 10,000 iterations for the inner-most first-order microsimulation.

These VOI analyses indicate that at the WTP threshold of US$100,000 per QALY, expected net monetary benefit of eliminating uncertainty in all model parameters (EVPI) is US$33,644 per person (Figure 6.2 below) or US$3.9 billion for the entire population. The expected net monetary benefit of eliminating uncertainty in evidence on efficacy of

Teplizumab (EVPPI) is US$17,491 per patient or US$2 billion for the entire population (Figure 6.3 below).

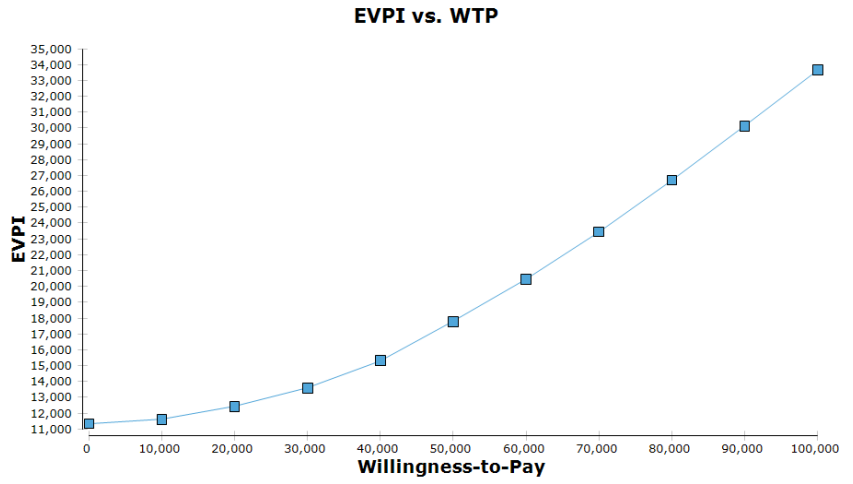


Figure 6.2: Expected Value of Perfect Information vs. Willingness-to-Pay Threshold for Teplizumab

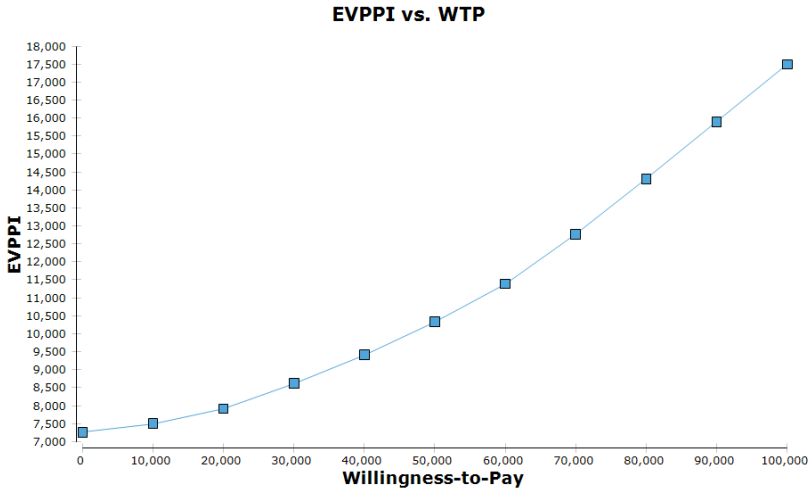


Figure 6.3: Expected Value of Perfect Partial Information vs. Willingness-to-Pay Threshold for Teplizumab

6.4.2 VOI analyses for Elipse intragastric balloon

EVPI and EVPPI analyses for Elipse intragastric balloon were similar to the above analyses for Teplizumab but with two differences. First, the annual beneficiary population was assumed to be 456,000 patients (based on ~23 million patients eligible for bariatric surgery in 2017 (203) and assuming patients live with obesity for about 50 years on average[4]). Second, benefits of research were assumed to accrue for 20 years (length of patent in the US (202)).

The EVPI analysis indicates that at the WTP threshold of US$100,000 per QALY, expected net monetary benefit of eliminating uncertainty in all model parameters is US$1,624 per person (Figure 6.4 below) or US$11.2 billion for the entire population. The EVPPI analysis shows that the expected net monetary benefit of eliminating uncertainty in evidence on weight loss effects of Elipse is US$966 per patient or US$6.7 billion for the entire population (Figure 6.5 below).

[4] Obesity duration of 50 years was assumed based on average life expectancy of ~78 years in the US (204), the assumption that 10 years of life are lost due to obesity (previous studies show that years of life lost due to obesity vary between 1 year and 20 years depending on age, sex, race and BMI level (205)) and the starting age of our study cohort of 18 years.

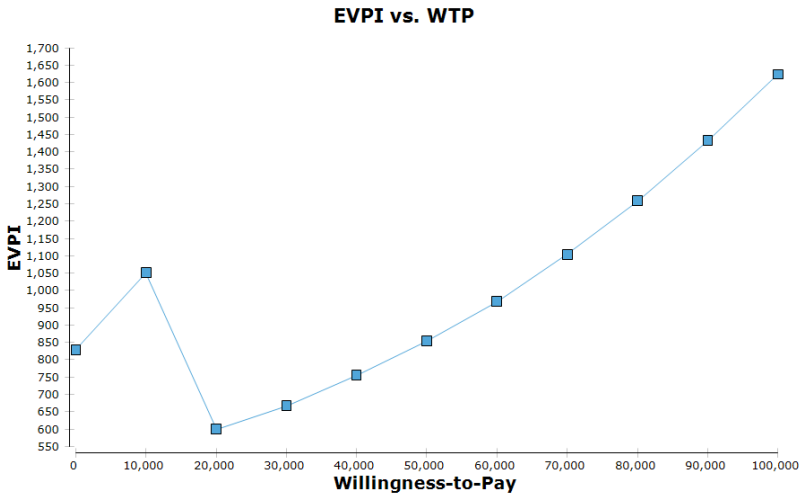


Figure 6.4: Expected Value of Perfect Information vs. Willingness-to-Pay Threshold for Elipse intragastric balloon

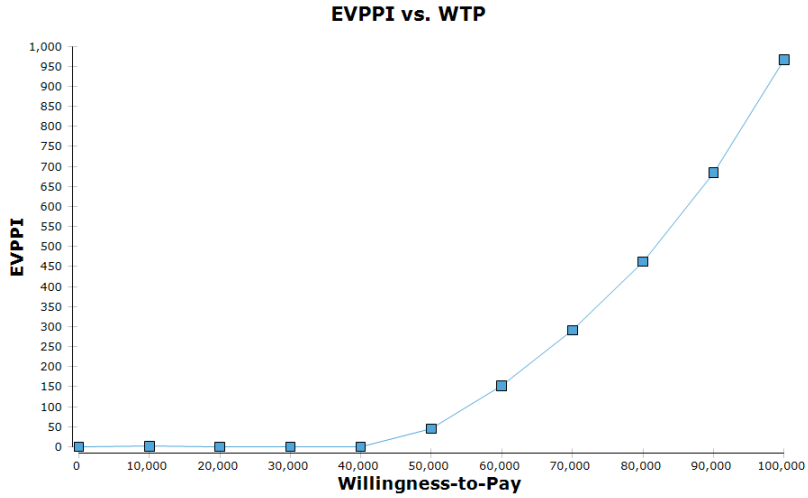


Figure 6.5: Expected Value of Perfect Partial Information vs. Willingness-to-Pay Threshold for Elipse intragastric balloon

6.5 Role of the foregoing studies in informing decision-making and directions for future research

In this section, I detail how findings in each of the four studies in this thesis can help inform decisions by manufacturers, policymakers, clinicians and other stakeholders for the 4 technologies studied. However, I note that the technologies studied are still in early stages with inherent uncertainty in the evidence base. Therefore, decision makers will need to balance the benefits of providing patients with early access to these technologies which could potentially improve patients' health outcomes (e.g., prevention of Type 1 diabetes, timely treatment for obesity or timely diagnosis and treatment of breast cancer) with the risk that the technology could potentially lead to overall negative patient health outcomes (either directly from harms of an intervention unknown at an early stage or in terms of opportunity costs from health care displaced elsewhere in the system). At the same time, further clinical evidence will need to be generated. I detail these implications for each study below.

6.5.1 Cost-effectiveness of Teplizumab

The cost-effectiveness analysis of Teplizumab provides early indications to manufacturers and policymakers on the potential value of this drug at different prices for different patient subgroups. These findings can help inform future pricing and coverage decisions. Specifically, the price ranges estimated for different patient subgroups can help decision-makers' formulation of 'efficient limited use criteria' and/or price-negotiations with manufacturers. Nevertheless, as this drug is still in development and evidence on efficacy at the patient subgroup level is based on small sample sizes, there is value in collecting

further evidence on the drug's efficacy for different subgroups (as indicated by VOI analyses in the previous section). To balance this need for further evidence with providing patients' early access to this clinically important innovation, coverage with evidence development schemes will be useful after this drug receives regulatory approval. Further, expected value of sample information and expected net present value of sampling information analyses will be needed to identify the most efficient research design to collect the additional evidence (30,94).

6.5.2 Cost-effectiveness of aspiration therapy

The cost-effectiveness analysis of aspiration therapy versus bariatric surgery highlights the economic value of a technology that is highly controversial and despite regulatory approval is neither universally available nor universally accepted among clinicians. It is also not covered by most insurance providers (206). Findings from this study will highlight to clinicians, health care payers and decision-makers the economic value of offering this technology to patients who lack access to bariatric surgery. These findings can, therefore help promote greater uptake of this intervention in a cost-effective way as well as inform its coverage decisions, especially in jurisdictions such as the US and Canada where access to bariatric surgery is particularly low. At the same time, further clinical evidence on its potential side-effects (such as bulimia) and long-term weight loss effects will need to be generated alongside developing an understanding of patients' preferences and choices (207) for aspiration therapy. This additional evidence can then be factored into future cost-effectiveness analyses.

6.5.3 Cost-effectiveness of PIGB

The cost-effectiveness analysis of PIGB will provide clinicians and decision makers with timely evidence on a potential cost-effective utilization of the PIGB technology within clinical care, both as it is being introduced in the US and in countries where it has already been adopted. Nevertheless, this analysis is based on non-RCT evidence on PIGB efficacy, and future clinical studies (preferably RCTs) that specifically examine the efficacy of PIGB prior to bariatric surgery will be valuable to reduce the uncertainty in evidence. Expected value of sample information and expected net present value of sampling information methods could be employed to identify the most suitable trial design.

6.5.4 Cost-effectiveness of AI

The lack of sufficient evidence to fast-track adoption of some of the newly emerging technologies into clinical practice has been recognized. Khoury and Mensah recently remarked in the context of integration of PRS into clinical practice: "*Let's Do the Science First and Follow the Evidence Wherever it Takes Us!"* (208)**.** The cost-effectiveness analysis of AI-based versus PRS-based risk stratified breast cancer screening will therefore provide early insights to policymakers into the potential economic value of using these technologies to optimize breast cancer screening. Even though AI and PRS may not be subject to reimbursement and coverage HTA assessments in the same way as drugs and devices, findings from this study can help encourage greater acceptance and timely adoption of these rapidly evolving technologies by hospital administrators, radiology centers and other decision-makers. Yet, AI and PRS are still in early development stages

such that the negative consequences of relying on these technologies to guide breast cancer screening may not be fully appreciable. Thus, further clinical trials to compare the accuracy of these technologies vs existing guidelines will provide useful insights. Coverage with evidence development and patient access schemes could provide incentives for the private sector to develop and profitably market these technologies.

6.6 Conclusion

Cost-effectiveness analyses have long been recommended to guide adoption and reimbursement decision-making for new technologies. Nevertheless, these analyses are most often performed later in the life cycle of technologies. Cost-effectiveness analyses conducted at early stages of a technology's life cycle can be particularly useful to guide stakeholders on potential cost-effective innovations that can generate higher value in health care.

This thesis contributed early-stage cost-effectiveness evidence of 4 new health care technologies with high clinical relevance. Findings from these analyses will help to inform decision-making by manufacturers, policymakers, clinicians and other stakeholders for these technologies.

Chapter 7 : Appendices

Appendix 1: Appendix to Chapter 1

A1.1. Types of analyses in the thesis

Analysis	Description	Reference
Cost-effectiveness analyses	Cost-effectiveness analyses compare the costs and health outcomes of two or more interventions. If an intervention costs less and generates better health outcomes vs another intervention, it is said to be dominant. If it is both more costly and more effective, it is considered cost-effective relative to the other intervention if the incremental cost effectiveness ratio, calculated as the difference between the overall costs of the two strategies divided by the difference between the total QALYs gained, is lower than the willingness-to-pay threshold. In the analyses in this thesis, a threshold of US$100,000 per QALY following suggestions by Neumann et al. (124). In all 4 cost-effectiveness analyses in this thesis, I used the health care system perspective to estimate costs, as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and CADTH (127,209). Thus, all medical costs borne by third-party payers or patients were considered (209).	(17,210)
Value of information analyses	Value of information analyses quantify the value of collecting further evidence on key parameters to reduce uncertainty in resource allocation decisions. This value can then be compared with the cost of conducting research to collect this additional evidence.	(94,211)

A1.2. Search terms used for literature review

Database: Pubmed

(technology[MH] OR technolog*[Title/Abstract] OR device*[MH] OR device*[Title/Abstract] OR innovation[Title/Abstract] OR test*[Title/Abstract] OR diagnostic*[Title/Abstract] OR biomarker*[Title/Abstract] OR drug*[Title/Abstract] OR pharmaceutical*[Title/Abstract] OR treatment*[Title/Abstract] OR therap*[Title/Abstract] OR intervention[Title/Abstract] OR screen*[Title/Abstract])

AND

(((cost benefit[MH] OR cost benefit[Title/Abstract] OR cost effectiveness[Title/Abstract] OR cost-benefit[Title/Abstract] OR cost-effectiveness [Title/Abstract] OR cost-effective[Title/Abstract] OR cost effective[Title/Abstract] OR cost utility[Title/Abstract] OR cost-utility[Title/Abstract] OR economic evaluation[Title/Abstract] OR quality adjusted life year[MH] OR quality adjusted life year*[Title/Abstract] OR QALY*[Title/Abstract] OR ((model*[Title/Abstract]) AND (health economic[Title/Abstract] OR economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract])) OR decision tree[MH] OR decision tree*[Title/Abstract] OR decision-analytic[Title/Abstract] OR state transition[Title/Abstract] OR markov[Title/Abstract] OR ((discrete-event*[Title/Abstract] OR individual*[Title/Abstract] OR patient-level*[Title/Abstract]) AND (simulation*[Title/Abstract])) OR partitioned-survival*[Title/Abstract]) AND (early-stage[Title/Abstract] OR early stage[Title/Abstract] OR early[Title/Abstract])) OR (headroom[Title/Abstract] OR headroom analysis[Title/Abstract]))

AND

(product develop*[Title/Abstract] OR develop*[Title/Abstract] OR R&D[Title/Abstract] OR ((trial[Title/Abstract]) AND (“Phase 1”[Title/Abstract] OR “Phase 2”[Title/Abstract] OR “Phase 3”[Title/Abstract] OR “Phase I” [Title/Abstract] OR “Phase II” [Title/Abstract] OR “Phase III” [Title/Abstract])) OR pre-market[Title/Abstract] OR premarket[Title/Abstract] OR emerging[Title/Abstract] OR innovation[Title/Abstract] OR novel[Title/Abstract] OR hypothetical[Title/Abstract] OR exploratory[Title/Abstract] OR (regulatory[Title/Abstract] AND approval[Title/Abstract]))

Filters: 2017-2021, Language English, Article type: Journal article

Database: Scopus

ALL((technolog* OR device* OR innovation OR test* OR diagnostic* OR biomarker* OR drug* OR pharmaceutical* OR treatment* OR therap* OR intervention OR screen*))

AND

ALL(((cost benefit OR cost effectiveness OR cost-benefit OR cost-effectiveness OR cost-effective OR cost effective OR cost utility OR cost-utility OR (economic W/2 evaluation) OR quality adjusted life year* OR QALY* OR (model* W/5 ((health W/2 economic) OR economic* OR pharmacoeconomic*)) OR (decision W/3 (analy* OR tree*)) OR state transition OR markov OR ((discrete-event* OR individual* OR patient-level*) W/3 (simulation*)) OR partitioned-survival*) AND (early-stage OR (early W/3 stage) OR early)) OR (headroom))

AND

ALL((product develop* OR develop* OR R&D OR (trial* W/5 ("Phase 1" OR "Phase 2" OR "Phase 3" OR "Phase I" OR "Phase II" OR "Phase III")) OR pre-market OR premarket OR emerging OR innovation OR novel OR hypothetical OR exploratory OR (regulat*W/4 approv*)))

AND (LIMIT-TO (PUBYEAR,2021) OR LIMIT-TO (PUBYEAR,2020) OR LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017)) AND (LIMIT-TO (LANGUAGE,"English"))

Database: Econlit

AB,TI(technolog* OR device* OR innovation OR test* OR diagnostic* OR biomarker* OR drug* OR pharmaceutical* OR treatment* OR therap* OR intervention OR screen*)

AND

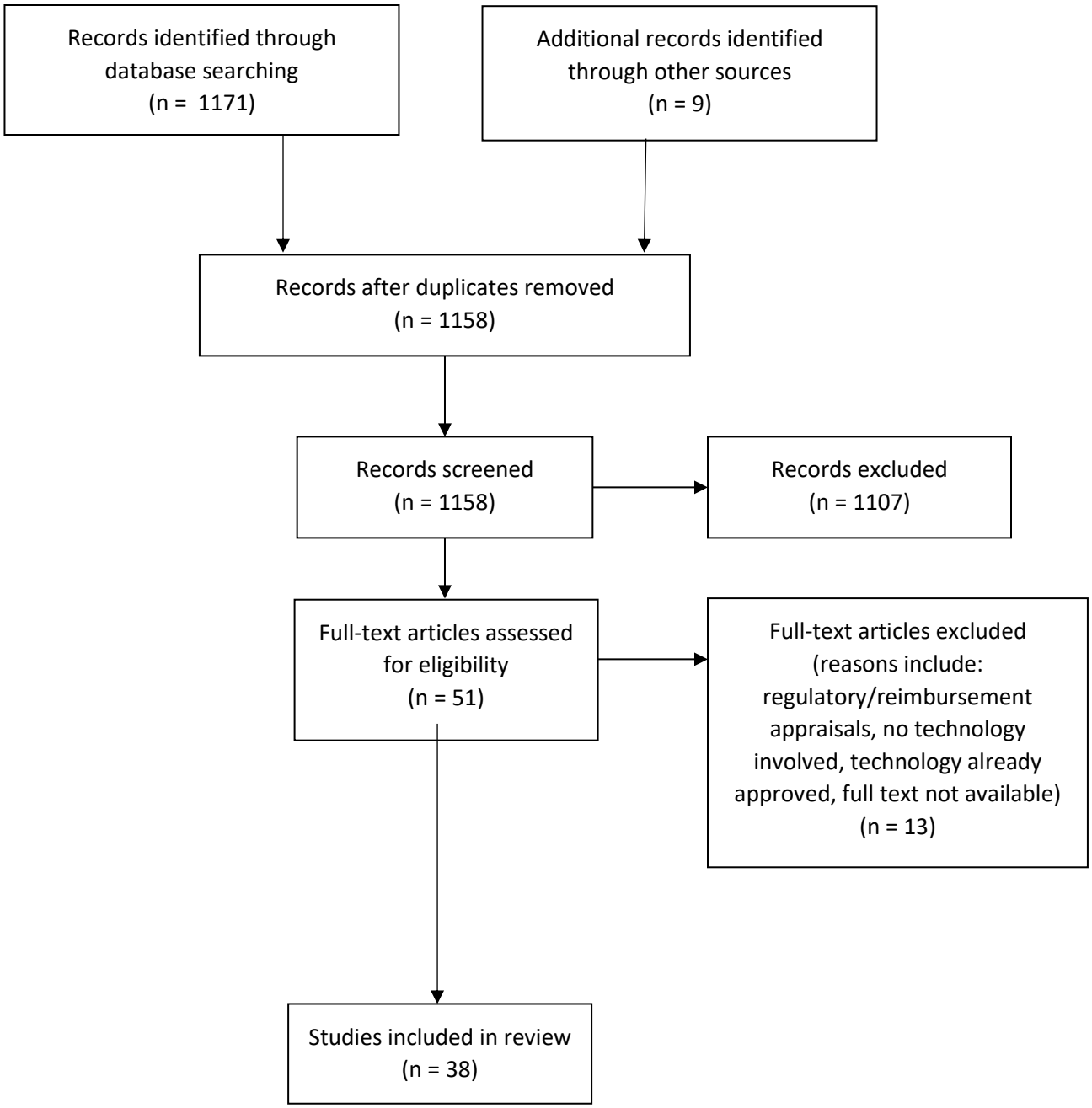
AB,TI(((cost benefit OR cost effectiveness OR cost-benefit OR cost-effectiveness OR cost-effective OR cost effective OR cost utility OR cost-utility OR (economic NEAR/2 evaluation) OR quality adjusted life year* OR QALY* OR (model* NEAR/5 ((health NEAR/2 economic) OR economic* OR pharmacoeconomic*)) OR (decision NEAR/3 (analy* OR tree*)) OR state transition OR markov OR ((discrete-event* OR individual* OR patient-level*) NEAR/3 (simulation*)) OR partitioned-survival*) AND (early-stage OR (early NEAR/3 stage) OR early)) OR (headroom))

AND

AB,TI((product develop* OR develop* OR R&D OR (trial* NEAR/5 ("Phase 1" OR "Phase 2" OR "Phase 3" OR "Phase I" OR "Phase II" OR "Phase III")) OR pre-market OR premarket OR emerging OR innovation OR novel OR hypothetical OR exploratory OR (regulat*NEAR/4 approv*)))

LIMITS: English language, 2017-2020, Academic journals

A1.3. PRISMA flow diagram for literature search



A1.4. Description of studies included in scoping review

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
1.	Adamson et al. 2017 (212)	HIV vaccines co-administered with pre-exposure prophylaxis	Clinical trial	Inform further research	USA	Cost-utility/Markov model	Clinical studies	Healthcare payer	DSA, PSA, Scenario analyses	Subgroup level (by risk)
2.	Geenen et al. 2017 (213)	Pharmacogenomic test for ACEi induced angioedema risk	Conceptualization of idea	Identify test sensitivity, specificity, cost targets	Netherlands	Headroom/ Decision tree	N/A	Health system	DSA, PSA	Subgroup level (by risk)
3.	Hummelink et al. 2017 (214)	Virtual surgical planning in deep inferior epigastric perforator flap breast reconstruction surgery	Conceptualization of idea	Inform decision on product development	Netherlands	Headroom/Decision tree	N/A	Not stated	Scenario analyses	No
4.	Khoudigian-Sinani et al. 2017 (215)	Biomarker for detection of oral cancer	Pre-market	Inform future adoption	Canada	Cost-effectiveness/ Decision tree	Clinicians' belief elicitation	Private payer and patient	DSA, PSA	Subgroup level (by dysplasia severity)
5.	Kip et al. 2017 (216)	Point-of-care troponin test for acute coronary syndrome	Product development	Not clearly stated	Netherlands	Cost-utility/Patient level simulation	Clinical studies	Not stated	PSA, VOI	No
6.	Knuttel et al. 2017 (217)	Magnetic resonance-guided high intensity focused ultrasound (MR-	Product development	Not clearly stated	Netherlands	Cost-minimization/ Decision tree	Assumption	Not stated	DSA, Scenario analyses	No

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
		HIFU) ablation for breast cancer								
7.	Nimwegen et al. 2017 (218)	Diagnostic test for complex pediatric neurology	Conceptualization of idea/ Illustrative	Illustrative	Netherlands	Headroom	N/A	Not stated	No	No
8.	Wan et al. 2017 (219)	Nivolumab for Renal Cell Carcinoma	Clinical trial	Inform future pricing/policy decisions	China*	Cost-utility/ Markov model	Clinical studies	Payer	DSA, PSA	No
9.	Windt et al. 2017 (220)	Single stage tissue engineering procedure for cartilage repair	Clinical trial	Identify key cost/utility targets	Netherlands	Headroom, cost-utility/Decision tree	Assumption	Societal	DSA	No
10.	Wong et al. 2017 (221)	15-gene expression signature to guide chemotherapy in non-small cell lung cancer	Clinical trial	Not clearly stated	Canada	Cost-effectiveness, cost-utility/Decision tree	Clinical studies	Health care system	DSA	Subgroup level (by risk)
11.	Graaf et al. 2018 (222)	Biomarkers for cardiovascular disease risk in Type 2 diabetes	Conceptualization of idea	Inform product development and investment	Netherlands	Headroom	Biomarker discovery research	Not stated	DSA	No
12.	Retel et al. 2018	Tumor infiltrating lymphocyte treatment for melanoma	Clinical trial	Facilitate evidence-based decisions for payers; estimate value	Netherlands	Cost-utility/Markov model	Clinical studies	Health care	DSA, PSA, VOI, Scenario analyses	No

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
				of further research						
13.	Schlemm et al. 2018 (223)	Real-time acute ischaemic stroke detection devices	Conceptualization of idea	Inform product development and investment	UK	Headroom/Conditional probabilistic model	Assumption	Societal	DSA	Subgroup level (by demographic, risk, socio-geographic factors)
14.	Sutton et al. 2018 (224)	Diagnostic test for bladder cancer	Product development	Inform further evidence generation	UK	Cost-utility/Markov model	Biomarker discovery research	Health care provider	DSA, PSA, VOI	No
15.	Velickovic et al. 2018 (225)	Tissue engineered bovine tissue pericardium scaffold for congenital heart defects	Clinical trial	Not clearly stated	UK	Cost-utility/Markov model	Clinical studies	Payer	DSA, PSA	No
16.	Vilsboll et al. 2018 (226)	Cell based therapies for female stress urinary incontinence	Clinical trial	Not clearly stated	Denmark	Cost-utility/Decision tree	Clinical studies	Healthcare sector	DSA	No
17.	Vogelaar et al. 2018 (227)	Biomarkers for colorectal cancer detection	Conceptualization of idea	Identify test sensitivity, specificity, cost targets	Netherlands, USA	Headroom/ microsimulation	N/A	Modified societal	DSA, Scenario analyses	No

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
18.	Wallner et al. 2018 (228)	Stem cell-derived Transplant therapy for Type 1 diabetes	Clinical trial	Identify circumstances for cost-effectiveness	Canada	Headroom, cost-utility/Markov model	Assumption	Healthcare provider	VOI, Scenario analyses	No
19.	Abel et al. 2019 (229)	Test to guide treatment for COPD	Product development	Inform further development	UK	Cost-utility/Decision tree+ Markov model	Manufacturer	Health system	DSA, PSA, Scenario analyses	No
20.	Buisman et al. 2019 (230)	Imaging test for carotid endarterectomy	Conceptualization of idea	Not clearly stated	Netherlands	Cost-utility/Decision tree	N/A	Societal	PSA	Subgroup level (by sex and age)
21.	Kluytmans et al. 2019 (231)	Biomarker for primary aldosteronism	Conceptualization of idea	Identify test sensitivity, specificity, cost targets	Netherlands	Headroom/Markov model	N/A	Societal	DSA, PSA	No
22.	Mital et al. 2019 (148)	Aspiration therapy for weight loss	Regulatory approval controversial	Inform adoption and coverage	USA	Cost-utility/Markov model	Clinical studies	Health system	DSA, PSA, Scenario analyses	No
23.	Vreman et al. 2019 (232)	Acalabrutinib for relapsed chronic lymphocytic leukaemia	Clinical trial	Inform early reimbursement decision-making	UK	Cost-utility/Partitioned survival model	Clinical studies	Health service	DSA, PSA, Scenario analyses	No
24.	Wang et al. 2019 (233)	Monotherapy for treatment resistant depression	Conceptualization of idea/Product development	Inform investment in treatment provision for treatment resistant depression	UK	Cost-utility/Decision tree+ Markov model	Assumption	Payer	DSA, PSA, Scenario analyses	No

S. No	Study	Interventions	Stage of development[†]	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
25.	Wenker et al. 2019 (234)	Interventional MRI for pulmonary vein isolation for atrial fibrillation	Conceptualization of idea/Product development[^]	Inform clinical effectiveness targets	Netherlands	Headroom/Decision tree	N/A	Not stated	PSA	No
26.	Bakker et al. 2020 (235)	Real time analytics for mechanical ventilation	Product development	Inform further product development and clinical trials	Greece	Headroom, cost-utility/Decision tree + Markov model	Clinical studies	Payer	DSA, PSA, Scenario analyses	No
27.	Frempong et al. 2020 (236)	Diagnostic test for typhoid	Conceptualization of idea	Inform future research & development	Ghana	Headroom, cost-utility/Decision tree	N/A	Health service	PSA, VOI	No
28.	Guinan et al. 2020 (237)	Polygenic risk score to predict nephropathy	Clinical trial	Inform implementation	Canada	Cost-utility/Markov model	Clinical studies	Health system & societal	DSA, PSA	No
29.	Huygens et al. 2020 (238)	Tissue engineered heart valves	Product development	Inform further product development	Netherlands	Headroom, cost-utility, budget impact/ Discrete event simulation	Assumption	Societal	PSA, VOI, Scenario analyses	Subgroup level (by age)
30.	Lindenberg et al. 2020 (239)	Tumor infiltrating lymphocyte treatment for melanoma	Clinical trial	Inform adoption decisions	Netherlands	Cost-utility, Scenario drafting/Markov model	Clinical studies + Assumptions	Health care	DSA, PSA, Scenario analyses	No
31.	Magee et al. 2020 (240)	Radiofrequency ablation for gastric antral vascular ectasia	Approval with conditions[#]	Not clearly stated	UK	Cost-utility/Markov model	Expert eliciation	Health Service & Personal social service	PSA, Scenario analyses	No

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
32.	Mandavia et al. 2020 (241)	Therapeutics for hearing loss	Product development/ Clinical trial	Inform product development and future decision making	UK	Headroom/Decision tree + Markov model	N/A	Health service	DSA, PSA, Scenario analyses	Subgroup level (by age)
33.	Mital et al. 2020 (242)	Teplizumab for type 1 diabetes	Clinical trial	Inform manufacturer's pricing and payers' future coverage decisions	USA	Headroom, cost-utility/Microsimulation	Clinical studies	Health system	DSA, PSA, Scenario analyses	Subgroup level (by genetic, antibody characteristics)
34.	Schneider et al. 2020 (243)	Multi-mRNA host response test for acute respiratory tract infections and sepsis	Pre-market	Not clearly stated	US	Cost impact/ Decision tree	Previous modeling/ statistical analyses of genetic data	Payer	DSA	Subgroup level (by true bacterial/viral infection status, mortality risk)
35.	Shi et al. 2020 (244)	Panitumumab as additional second line therapy for metastatic colorectal cancer	Pre-regulatory approval	Inform future pricing/policy decisions	China	Cost-utility/ Markov model	Clinical studies	Health care	DSA, PSA	No
36.	Steffen et al. 2020 (245)	Diagnostic tests for tuberculosis	Pre-market	Inform adoption in public health system	Brazil	Cost-utility/ Markov model	Clinical studies	Health care system	DSA, PSA	No
37.	Wallace et al. 2020 (246)	Vaginal CO_2 laser therapy for genitourinary syndrome of menopause-associated dyspareunia	Clinical trial	Inform future coverage decisions	USA	Cost-utility/Decision tree	Clinical studies	Not stated	DSA	No

S. No	Study	Interventions	Stage of development†	Purpose	Country	Analysis/Model type	Source of efficacy data	Perspective	Uncertainty analysis	Characterization of heterogeneity
38.	Willems et al. 2020 (247)	Drug for hidradenitis suppurativa	Product development	Identify cost, effects targets; understand drivers of cost-effectiveness	UK	Headroom, cost-utility/Markov model	Assumption	Health Service & Personal social service	DSA, Scenario analyses	No

† Stage of development in country where analysis undertaken.

*The analysis was done for both US and China. However, Nivolumab was already approved in the US at the time of the study. Hence, description of the US analyses is excluded.

^ Interventional MRI is in clinical use for other procedures but not for cardiac ablation.

As per NICE guidelines, this procedure can only be performed "with special arrangements for clinical governance, consent and audit or research" due to limited evidence on clinical efficacy (248).

Appendix 2: Appendix to Chapter 2

A2.1: Description of target patient groups

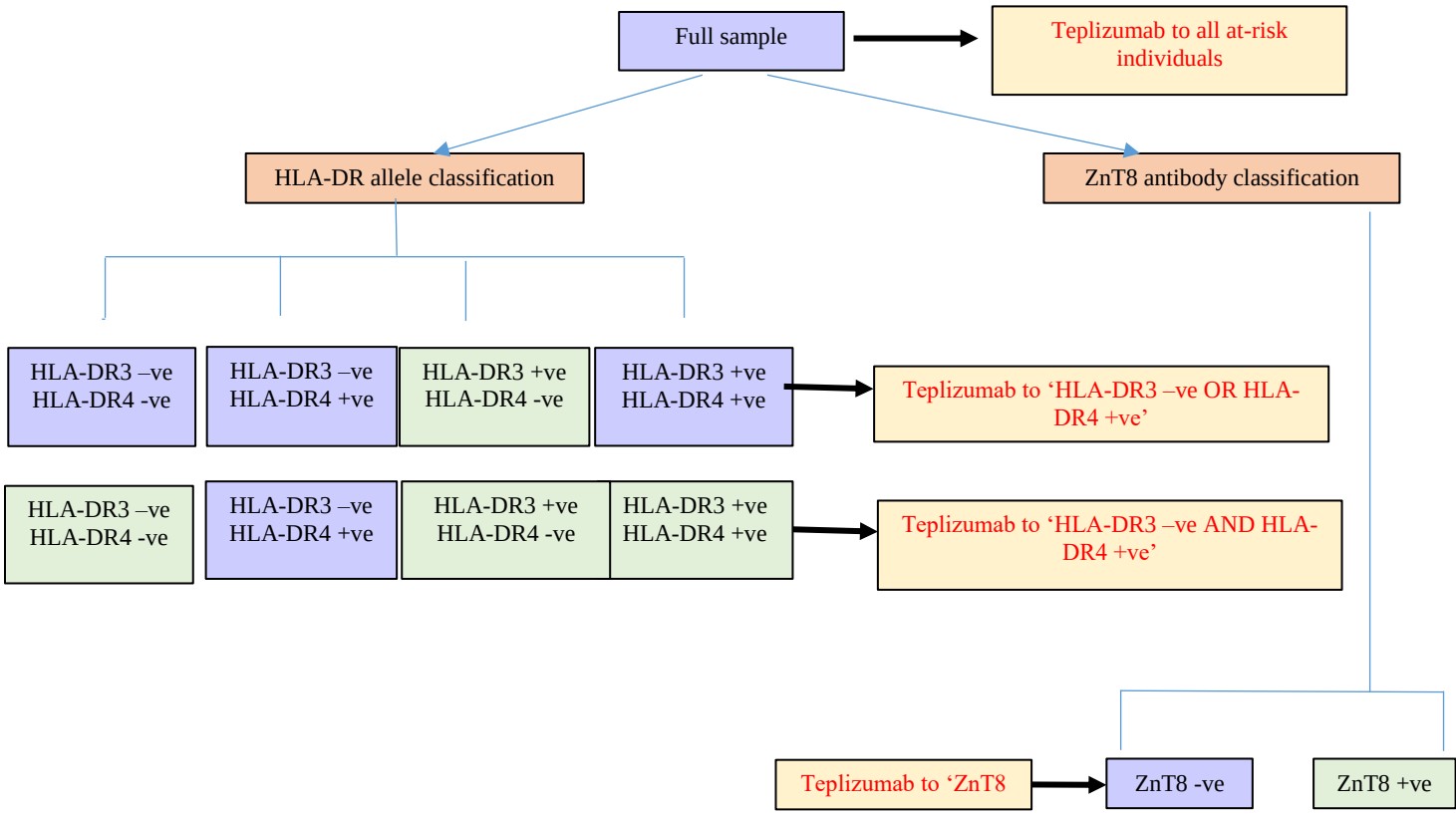


Figure A2.1: Treated groups by treatment options

Note: Treatment options are shown in yellow boxes. Purple boxes depict treated groups and green boxes depict untreated groups for each option.

Appendix A2.2: Characteristics of simulated patients

Table A2.1: Patient characteristics used in microsimulation

Variable	Value	Distribution	Source
Initial age	8-49 years	n/a	(106)
Male	0.51	Binomial	(106)
HbA1c (%)	7.6 (1.5) Range: 5-12	Truncated normal	(114)
Body weight	Dependent on age and sex	n/a	(249)
Total cholesterol (mg/dl)	*If age<20*: 159 (27) Range: 100-300 *If age>=20*: 166 (29) Range: 100-300	Truncated normal	(114)
HDL (mg/dl)	*If age<20*: 56 (13) Range: 30-85 *If age>=20*: 53 (15) Range: 30-85	Truncated normal	(114)
Systolic blood pressure	*If age<20*: 99 (12) Range: 85-145 *If age>=20*: 124 (10) Range: 90-180	Truncated normal	(114)
Smoker	*If age<=12*, 0; *If age>12 & age<14*, 0.022; *If age>=14 & age<18*, 0.08; *If age>=18 & age<25*, 0.147; *If age>=25 & age<45*, 0.206; *If age>=45 & age<65*, 0.193; *If age>=65*, 0.101	Binomial	(114)

Note: Numbers are Mean(SD), unless stated otherwise. HbA1c level applicable after patient develops Type 1 diabetes.

Appendix A2.3: Choice of time-to-event distribution for estimation of probability of developing Type 1 diabetes

We estimated probability of developing Type 1 diabetes for the full sample of patients in the Phase II trial (39) and for each of the 6 groups defined by HLA-DR3, HLA-DR4 and ZnT8 antibody statuses (namely, HLA-DR3 negative, HLA-DR3 positive, HLA-DR4 negative, HLA-DR4 positive, ZnT8 negative and ZnT8 positive). For each sample, we first reconstructed individual patient data on the following four parameters by digitizing the KM survival curve using WebPlotDigitizer (107), and using information on number of patients at risk at each 6-month interval and total number of events (where available) as reported by Herold et al. (39): (i) number of patients diagnosed with diabetes, (ii) time at which each patient was diagnosed with diabetes, (iii) number of patients censored, and (iv) time at which each patient was censored.

Next, we tested the proportional hazards assumption using the global proportional hazards test. We found that the assumption was met in all samples except HLA-DR4 negative (Table A1.2). However, log cumulative hazard plots for treated and control groups were not parallel for any sample and even crossed each other in some samples (Figure A1.2).

Consequently we fitted four Accelerated Failure Time (AFT) models -- exponential, Weibull, log normal and log logistic models(109). For samples for which hazard plots did not cross each other, we fitted AFT models with a treatment covariate while for samples where the plots crossed, individual AFT models for each treatment group were used.

Among the four distributions that were fit, we chose the distribution for which model parameters were significant and which had the lowest Aikaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) (109,110). In Table A1.3, we show the AIC/BIC for models with significant parameters. The chosen distribution is reported in *italics*. As can be seen from the table, exponential distribution was chosen for all target patient groups.

For most groups, exponential distribution had the lowest AIC/BIC. For the full sample and HLA-DR4 positive groups, AIC for exponential distribution was higher than for log-logistic distribution while BIC was lower. In these cases, we used a graphical analysis of Cox-Snell residuals to determine the optimal distribution. As shown in Figure A1.3, for both cases, hazard function followed the diagonal line more closely with the exponential distribution compared with log-logistic distribution, suggesting better fit with observed data with the exponential distribution. Thus, exponential distribution was chosen for the full sample and HLA-DR4 positive groups.

For HLA-DR3 positive and HLA-DR4 negative groups that were treated with Teplizumab, Weibull distribution had the lowest AIC/BIC, followed by log-logistic and log-normal distributions. However, annual probability of developing Type 1 diabetes estimated from all 3 distributions increased by age. This pattern is unrealistic in the context of Type 1 diabetes which is primarily a juvenile onset condition. Consequently, owing to clinical implausibility of extrapolated values, we chose exponential distribution for these groups as well. Finally, clinical implausibility of extrapolated values was also observed for the ZnT8 negative and ZnT8 positive groups that were treated with Teplizumab. Consequently,

exponential distribution was chosen over Weibull, log-logistic and log-normal distributions for these groups as well.

Finally, we calculated the annual probability of developing Type 1 diabetes for each patient sample using exponential distributions.

Table A2.2: Results of Global Proportional Hazards Test, by target patient group

Patient subgroup	Chi 2	P value
Full sample	2.33	0.1271
HLA-DR3 negative	1.87	0.1717
HLA-DR3 positive	2.66	0.1030
HLA-DR4 negative	5.41	0.02
HLA-DR4 positive	0.05	0.8263
ZnT8 negative	0.05	0.8224
ZnT8 positive	0.60	0.4399

Table A2.3: AIC/BIC for fitted distributions with significant parameters, by target patient group

Patient subgroup	Model Type	Distribution	Ll(null)	Ll(model)	AIC	BIC
Full sample	AFT with treated covariate	*Exponential*	*-91.73*	*-88.14*	*180.28*	*184.94*
		Log-logistic	-91.88	-86.44	178.88	185.87
HLA-DR3 negative	AFT with treated covariate	*Exponential*	*-49.12*	*-43.54*	*91.07*	*94.40*
		Log-logistic	-49.39	-42.63	91.27	96.26
HLA-DR3 positive (without Teplizumab)	Individual AFT	*Exponential*	*-20.03*	*-20.03*	*42.05*	*42.76*
HLA-DR3 positive (with Teplizumab)	Individual AFT	Weibull	-14.13	-14.13	32.25	34.03
		Exponential	*-17.93*	*-17.93*	*37.86*	*38.75*
		Log-logistic		-14.24	32.48	34.26
		Log-normal		-14.34	32.67	34.45
HLA-DR4 negative (without Teplizumab)	Individual AFT	*Exponential*	*-14.86*	*-14.86*	*31.71*	*32.11*
HLA-DR4 negative (with Teplizumab)	Individual AFT	Weibull	-11.63	-11.63	27.25	28.53
		Exponential	*-13.88*	*-13.88*	*29.76*	*30.40*
		Log-logistic		-11.87	27.74	29.02
HLA-DR4 positive	AFT with treated covariate	*Exponential*	*-58.30*	*-52.31*	*108.62*	*112.32*
		Log-logistic	-58.78	-51.16	108.31	113.86
ZnT8 negative (without Teplizumab)	Individual AFT	*Exponential*	*-10.30*	*-10.30*	*22.61*	*22.69*
ZnT8 negative (with Teplizumab)	Individual AFT	Weibull	-6.07	-6.07	16.14	17.11
		Exponential	*-9.76*	*-9.76*	*21.53*	*22.02*
		Log-logistic		-6.39	16.78	17.75
		Log-normal		-6.64	17.29	18.26
ZnT8 positive (without Teplizumab)	Individual AFT	*Exponential*	*-35.24*	*-35.24*	*72.48*	*73.66*
ZnT8 positive (with Teplizumab)	Individual AFT	Weibull	-27.40	-27.40	58.79	61.72
		Exponential	*-29.84*	*-29.84*	*61.69*	*63.15*
		Log-logistic		-26.31	56.62	59.56

Figure A2.2: Log cumulative hazard plots, by target patient group

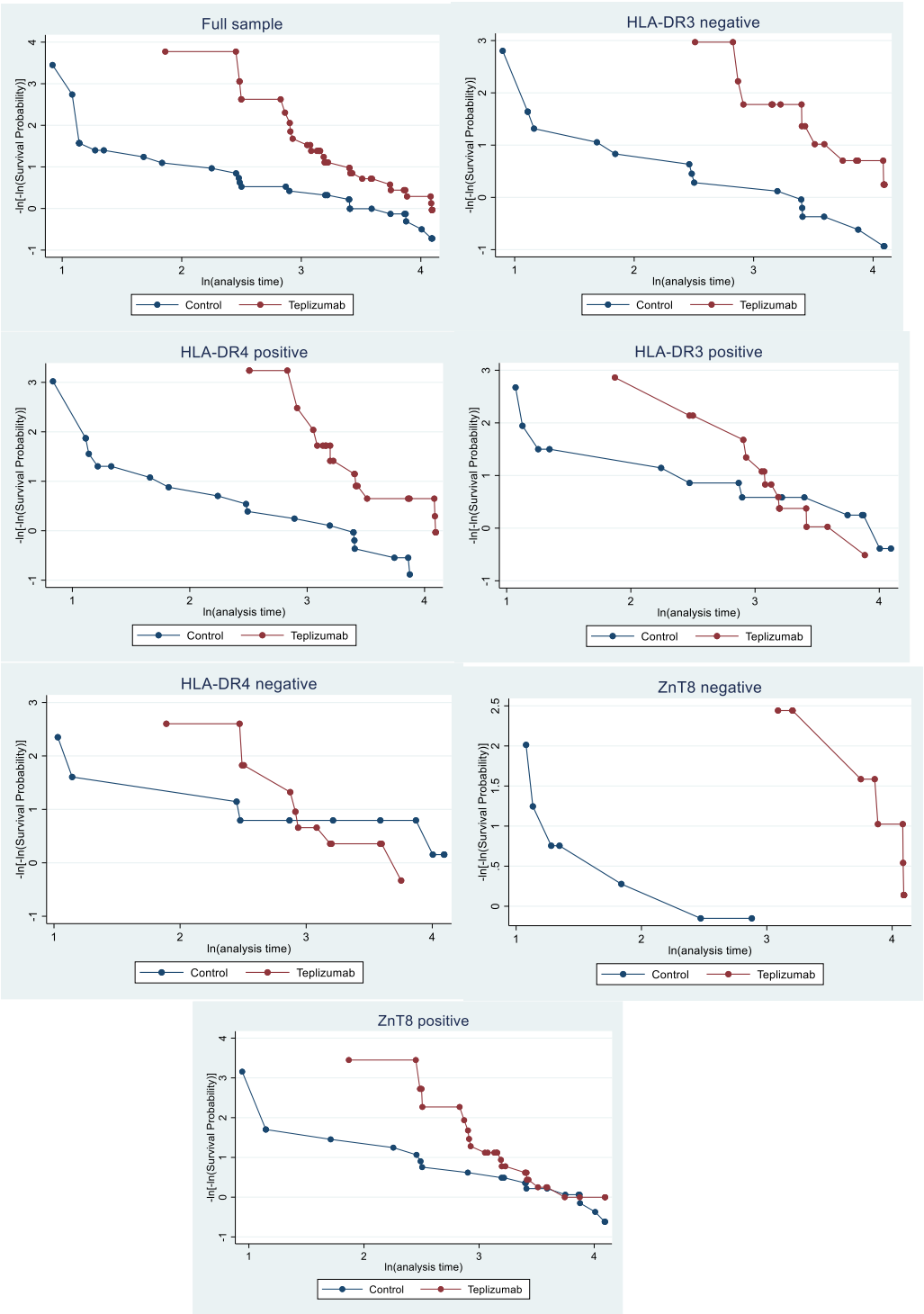
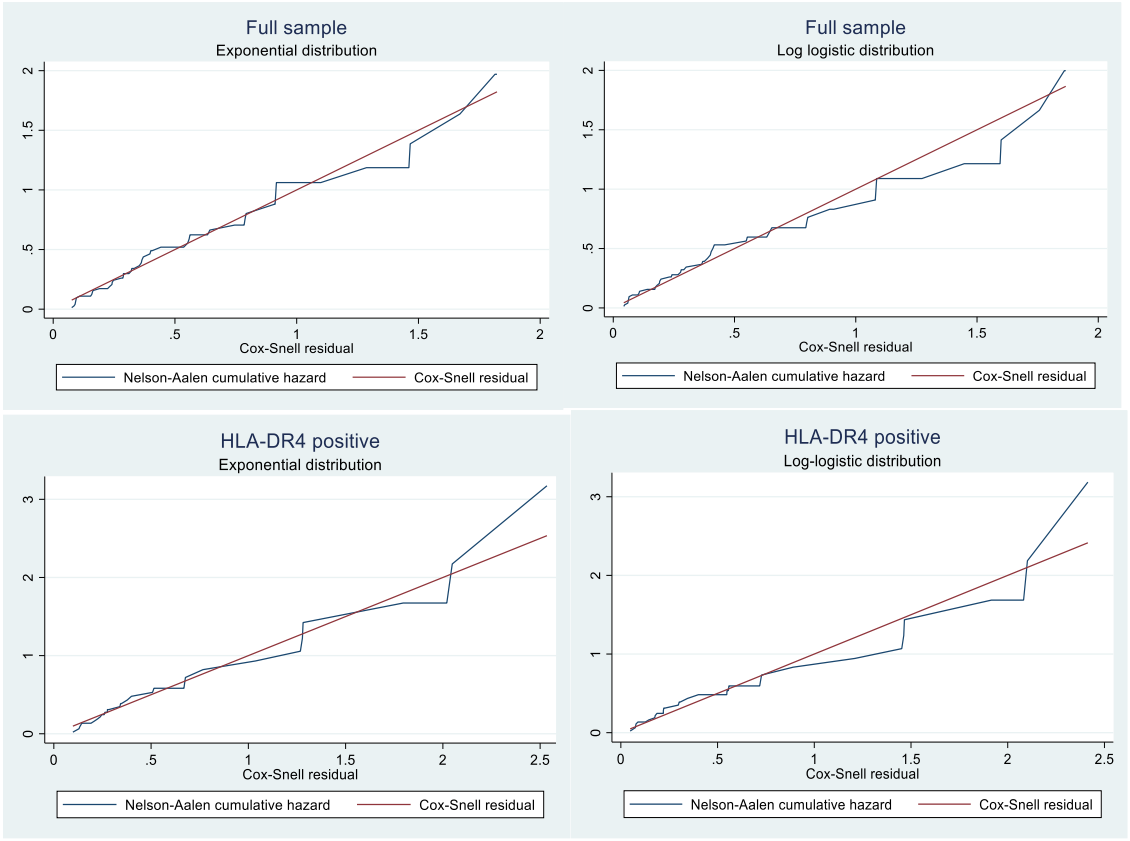


Figure A2.3: Analysis of Cox-Snell residuals for fitted distributions, for Full Sample and HLA-DR4 positive patient groups



Appendix A2.4: Additional sensitivity analyses

Figure A2.4: Tornado diagrams

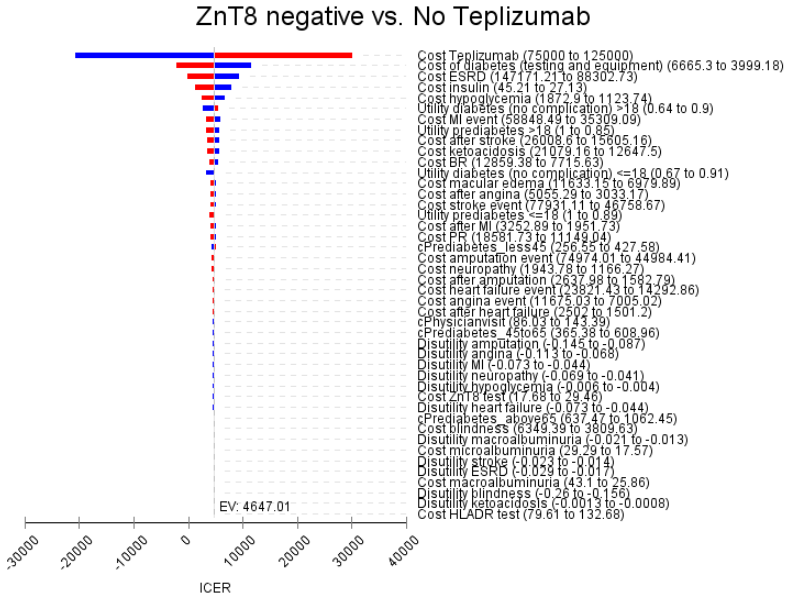


Figure A2.4(a)

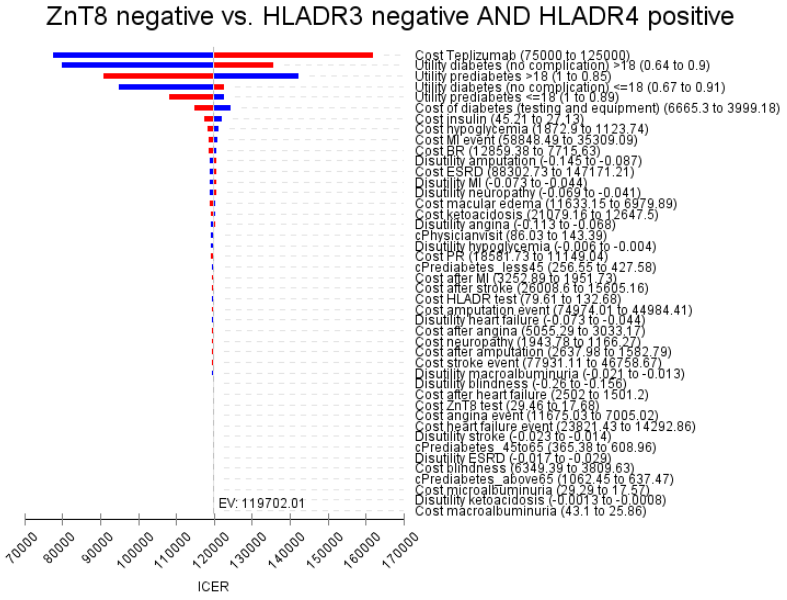


Figure A2.4(b)

Figure A2.5: Cost-effectiveness acceptability curve

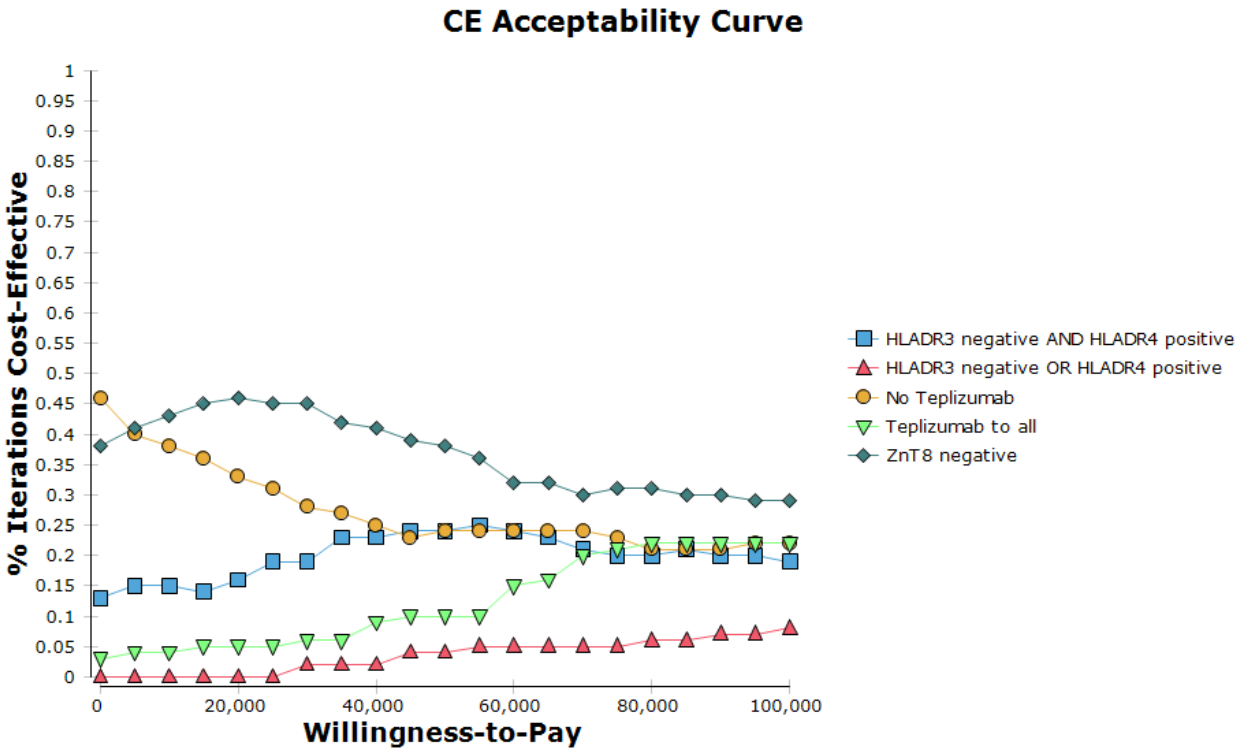


Table A2.4: Sensitivity analysis using alternative disutility values for diabetic ketoacidosis and hypoglycemia

Price range	Optimal option	Result for optimal option relative to other options
$1 - $19,598	Teplizumab to all at-risk	Dominant
$19,598 - $48,802	Teplizumab to all at-risk	Cost-effective
$48,802 - $57,862	HLA-DR3 negative or HLA-DR4 positive	Cost-effective
$57,862 - $87,713	HLA-DR3 negative and HLA-DR4 positive	Cost-effective
$87,713 - $192,342	ZnT8 negative	Cost-effective
>$192,342	No Teplizumab	

Notes: All costs are in 2019 US dollars (US$). HLA-DR3: Human Leukocyte Antigen DR3; HLA-DR4: Human Leukocyte Antigen DR4; ZnT8: Zinc Transporter 8

Appendix 3: Appendix to Chapter 3

A3.1 Description of types of bariatric surgeries

(i) Gastric bypass: It involves creating and connecting a small pouch from the upper part of the stomach directly with the small intestine; i.e., parts of the stomach and intestines are 'bypassed' (250,251).

(ii) Sleeve gastrectomy: It involves creating a tubular pouch from the stomach and nearly 80% of the stomach is removed (250,251).

Both surgeries work by (i) reducing stomach volume which limits food intake; and (ii) affecting satiety via hormonal effects (250,251). While gastric bypass is more complex than sleeve gastrectomy and may be performed as an open procedure, sleeve gastrectomy is performed laparoscopically. However, sleeve gastrectomy is irreversible. Meanwhile, sleeve gastrectomy results in more rapid weight loss than gastric bypass and involves lower risk of complications than gastric bypass (56,250,251).

References

1. Skinner J. The Costly Paradox of Health-Care Technology | MIT Technology Review [Internet]. 2013;[cited 2020 Jun 15] Available from: https://www.technologyreview.com/2013/09/05/252307/the-costly-paradox-of-health-care-technology/

2. West DM, Villasenor J, Schneider J. Private Sector Investment in Global Health R&D [Internet]. 2017;[cited 2020 Jul 19] Available from: https://www.brookings.edu/research/private-sector-investment-in-global-health-rd/

3. Hood L, Rowen L. The Human Genome Project: big science transforms biology and medicine [Internet]. Genome Medicine 2013;5:79.[cited 2020 Jul 19] Available from: https://doi.org/10.1186/gm483

4. Cabral A. The Computer Science behind DNA Sequencing [Internet]. 2019;[cited 2020 Jul 19] Available from: http://sitn.hms.harvard.edu/flash/2019/the-computer-science-behind-dna-sequencing/

5. Deloitte. Top 10 health care innovations: Achieving more for less [Internet]. 2016;[cited 2020 Jul 19] Available from: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-top-10-health-care-innovations-web-friendly.pdf

6. Cox L. The Top 10 Medical Advances of the Decade [Internet]. 2009;[cited 2020 Jul 19] Available from: https://www.medpagetoday.com/infectiousdisease/publichealth/17594

7. Neumann PJ, Weinstein MC. The diffusion of new technology: costs and benefits to health care. The changing economics of medical technology 1991;2:21–34.

8. Clemens M. Council Post: Technology And Rising Health Care Costs [Internet]. Forbes [cited 2020 Jun 15] Available from: https://www.forbes.com/sites/forbestechcouncil/2017/10/26/technology-and-rising-health-care-costs/

9. Sorenson C, Drummond M, Khan BB. Medical technology as a key driver of rising health expenditure: disentangling the relationship. ClinicoEconomics and outcomes research: CEOR 2013;5:223.

10. Torbica A, Fornaro G, Tarricone R, Drummond MF. Do Social Values and Institutional Context Shape the Use of Economic Evaluation in Reimbursement Decisions? An Empirical Analysis [Internet]. Value in Health 2020;23:17–24.[cited 2020 Aug 29] Available from: http://www.sciencedirect.com/science/article/pii/S1098301519351770

11. Hasegawa M, Komoto S, Shiroiwa T, Fukuda T. Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System [Internet]. Value in Health 2020;23:43–51.[cited 2020 Aug 29] Available from: https://www.valueinhealthjournal.com/article/S1098-3015(19)35170-8/abstract

12. Neumann PJ. Why don't Americans use cost-effectiveness analysis. Am J Manag Care 2004;10:308–312.

13. Naylor D, Girard F, Mintz J, Fraser N, Jenkins T, Power C. Unleashing innovation: excellent healthcare for Canada. Report of the Advisory Panel on Healthcare Innovation. 2015.

14. MacNeil M, Koch M, Kuspinar A, Juzwishin D, Lehoux P, Stolee P. Enabling health technology innovation in Canada: Barriers and facilitators in policy and regulatory processes. Health Policy 2019;123:203–214.

15. Raymakers AJN, Regier DA, Peacock SJ. Health-related quality of life in oncology drug reimbursement submissions in Canada: A review of submissions to the pan-Canadian Oncology Drug Review [Internet]. Cancer 2020;126:148–155.[cited 2020 Oct 19] Available from: https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/cncr.32455

16. Husereau D, Arshoff L, Bhimani S, Allen N. Medical device and diagnostic pricing and reimbursement in Canada. Edmonton (AB): Institute of Health Economics 2015;

17. Centers for Disease Control and Prevention. Cost-Effectiveness Analysis [Internet]. 2019;[cited 2020 Aug 28] Available from: https://www.cdc.gov/policy/polaris/economics/cost-effectiveness.html

18. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost-effectiveness analysis in healthcare. Oxford University Press; 2011.

19. IJzerman MJ, Koffijberg H, Fenwick E, Krahn M. Emerging use of early health technology assessment in medical product development: a scoping review of the literature. Pharmacoeconomics 2017;35:727–740.

20. Grutters JP, Govers T, Nijboer J, Tummers M, Van Der Wilt GJ, Rovers MM. Problems and promises of health technologies: the role of early health economic modeling. International journal of health policy and management 2019;8:575.

21. Tu HAT, Han D, Pechlivanoglou P, Miller F, Rac V, Chin W, Tricco AC, Paulden M, Bielecki J, Krahn M. Early economic evaluation of emerging health technologies: protocol of a systematic review. Systematic reviews 2014;3:81.

22. Ijzerman MJ, Steuten LM. Early assessment of medical technologies to inform product development and market access. Applied health economics and health policy 2011;9:331–347.

23. Hartz S, John J. Public health policy decisions on medical innovations: What role can early economic evaluation play? Health Policy 2009;89:184–192.

24. Canadian Agency for Drugs and Technologies in Health. Horizon scanning process [Internet]. 2015;[cited 2020 Jun 25] Available from: https://www.cadth.ca/sites/default/files/externalprocesses_horizonscanningprogram.pdf

25. Reckers-Droog V, Federici C, Brouwer W, Drummond M. Challenges with coverage with evidence development schemes for medical devices: A systematic review. Health Policy and Technology 2020;

26. Edlin R, McCabe C, Hulme C, Hall P, Wright J. Uncertainty, Probabilistic Analysis and Outputs from Cost Effectiveness Analyses. In: Cost Effectiveness Modelling for Health Technology Assessment. Springer; 2015. p. 59–76.

27. Claxton K. Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics 2008;26:781–798.

28. Edlin R, McCabe C, Hulme C, Hall P, Wright J. Investing in Health Care, Research and the Value of Information. In: Cost Effectiveness Modelling for Health Technology Assessment. Springer; 2015. p. 177–198.

29. Bubela T, McCabe C. Value-engineered translation: developing biotherapeutics that align with health-system needs. The American journal of managed care 2014;20:E3–E3.

30. Edlin R, McCabe C, Hulme C, Hall P, Wright J. Value of Information in Health Technology Regulation and Reimbursement. In: Cost Effectiveness Modelling for Health Technology Assessment. Springer; 2015. p. 199–208.

31. Sanders GD, Neumann PJ, Basu A, Ganiats T, De Vos MA, Bos AP, Plötz F, Willems DL, Waldman HB, Ackerman M. Recommendations for conduct,

methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;

32. Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. Medical Decision Making 2014;34:951–964.

33. Lavelle TA, Kent DM, Lundquist CM, Thorat T, Cohen JT, Wong JB, Olchanski N, Neumann PJ. Patient variability seldom assessed in cost-effectiveness studies. Medical Decision Making 2018;38:487–494.

34. Sculpher M. Subgroups and Heterogeneity in Cost-Effectiveness Analysis [Internet]. Pharmacoeconomics 2008;26:799–806.[cited 2021 Feb 1] Available from: https://doi.org/10.2165/00019053-200826090-00009

35. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. Medical Decision Making 2007;27:112–127.

36. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health economics 2002;11:415–430.

37. Coyle D, Buxton MJ, O'Brien BJ. Stratified cost-effectiveness analysis: a framework for establishing efficient limited use criteria. Health economics 2003;12:421–427.

38. Kim DD, Basu A. New metrics for economic evaluation in the presence of heterogeneity: focusing on evaluating policy alternatives rather than treatment alternatives. Medical Decision Making 2017;37:930–941.

39. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, Gitelman SE, Gottlieb PA, Krischer JP, Linsley PS. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. New England Journal of Medicine 2019;381:603–613.

40. Dolgin E. Anti-CD3 drug keeps diabetes at bay. Nature biotechnology 2019;

41. Reuters. Experimental drug delays type 1 diabetes onset in mid-stage trial [Internet]. Reuters 2019;[cited 2020 Jan 1] Available from: https://www.reuters.com/article/us-health-diabetes-tepzlizumab-idUSKCN1TA0P8

42. Reuters. Critics of weight-loss device urge U.S. regulator to reverse approval [Internet]. 2016;[cited 2018 Oct 27] Available from: https://www.reuters.com/article/us-health-weight-loss-device-obesity-idUSKCN10727Z

43. Business wire. Allurion Technologies Announces Submission of US Premarket Approval (PMA) Application for its Flagship Elipse® Gastric Balloon [Internet]. 2020;[cited 2020 Aug 15] Available from: https://www.businesswire.com/news/home/20200407005041/en/Allurion-Technologies-Announces-Submission-Premarket-Approval-PMA

44. Centers for Disease Control and Prevention. Breast Cancer Screening Guidelines for Women [Internet]. 2016;Available from: https://www.cdc.gov/cancer/breast/pdf/BreastCancerScreeningGuidelines.pdf

45. United States Preventive Services Taskforce. Breast Cancer: Screening [Internet]. 2016;[cited 2020 Apr 5] Available from: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening

46. United States Preventive Services Taskforce. Grade definitions [Internet]. [cited 2020 Oct 15] Available from: https://epss.ahrq.gov/ePSS/gradedef.jsp

47. Yala A, Lehman C, Schuster T, Portnoi T, Barzilay R. A deep learning mammography-based model for improved breast cancer risk prediction. Radiology 2019;292:60–66.

48. Vachon CM, Pankratz VS, Scott CG, Haeberle L, Ziv E, Jensen MR, Brandt KR, Whaley DH, Olson JE, Heusinger K. The contributions of breast density and common genetic variation to breast cancer risk. Journal of the National Cancer Institute 2015;107:dju397.

49. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W, Harrington A, Wilson C, Tsouros S, Soobiah C, Yu CH, Hutton B, Hoch JS, Hemmelgarn BR, Moher D, Majumdar SR, Straus SE. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients

with type 1 diabetes: systematic review and network meta-analysis [Internet]. BMJ 2014;349[cited 2020 Jul 6] Available from: https://www.bmj.com/content/349/bmj.g5459

50. Bilir SP, Hellmund R, Wehler B, Li H, Munakata J, Lamotte M. Cost-effectiveness analysis of a flash glucose monitoring system for patients with type 1 diabetes receiving intensive insulin treatment in Sweden. European endocrinology 2018;14:73.

51. Roze S, Smith-Palmer J, Valentine W, Portu S de, Nørgaard K, Pickup JC. Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections of insulin in Type 1 diabetes: a systematic review [Internet]. Diabetic Medicine 2015;32:1415–1424.[cited 2020 Jul 6] Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/dme.12792

52. McQueen RB, Rasmussen CG, Waugh K, Frohnert BI, Steck AK, Yu L, Baxter J, Rewers M. Cost and Cost-Effectiveness of Large-Scale Screening for Type 1 Diabetes in Colorado. Diabetes Care 2020;

53. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and costeffectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Current medical research and opinion 2004;20:S5–S26.

54. Thokala P, Kruger J, Brennan A, Basarir H, Duenas A, Pandor A, Gillett M, Elliott J, Heller S. Assessing the cost-effectiveness of Type 1 diabetes interventions: the Sheffield Type 1 Diabetes Policy Model. Diabetic Medicine 2014;31:477–486.

55. Salem L, Devlin A, Sullivan SD, Flum DR. Cost-effectiveness analysis of laparoscopic gastric bypass, adjustable gastric banding, and nonoperative weight loss interventions. Surgery for Obesity and Related Diseases 2008;4:26–32.

56. Alsumali A, Eguale T, Bairdain S, Samnaliev M. Cost-effectiveness analysis of bariatric surgery for morbid obesity. Obesity surgery 2018;1–12.

57. Campbell J, McGarry LA, Shikora SA, Hale BC, Lee JT, Weinstein MC. Cost-effectiveness of laparoscopic gastric banding and bypass for morbid obesity. The American journal of managed care 2010;16:e174-87.

58. Panca M, Viner RM, White B, Pandya T, Melo H, Adamo M, Batterham R, Christie D, Kinra S, Morris S. Cost-effectiveness of bariatric surgery in adolescents with severe obesity in the UK. Clinical obesity 2018;8:105–113.

59. Keating CL, Dixon JB, Moodie ML, Peeters A, Bulfone L, Maglianno DJ, O'brien PE. Cost-effectiveness of surgically induced weight loss for the management of type 2 diabetes: modelled lifetime analysis. Diabetes care 2009;

60. Hoerger TJ, Zhang P, Segel JE, Kahn HS, Barker LE, Couper S. Cost-effectiveness of bariatric surgery for severely obese adults with diabetes. Diabetes care 2010;33:1933–1939.

61. Foxcroft DR, Milne R. Orlistat for the treatment of obesity: rapid review and cost-effectiveness model. obesity reviews 2000;1:121–126.

62. Finkelstein EA, Kruger E, Karnawat S. Cost-effectiveness analysis of Qsymia for weight loss. Pharmacoeconomics 2015;33:699–706.

63. Lee M, Lauren BN, Zhan T, Choi J, Klebanoff M, Abu Dayyeh B, Taveras EM, Corey K, Kaplan L, Hur C. The cost-effectiveness of pharmacotherapy and lifestyle intervention in the treatment of obesity. Obesity Science & Practice 2020;6:162–170.

64. James R, Salton RI, Byrnes JM, Scuffham PA. Cost-utility analysis for bariatric surgery compared with usual care for the treatment of obesity in Australia. Surgery for Obesity and Related Diseases 2017;13:2012–2020.

65. Finkelstein EA, Verghese NR. Incremental cost-effectiveness of evidence-based non-surgical weight loss strategies. Clinical obesity 2019;9:e12294.

66. Sullivan S, Stein R, Jonnalagadda S, Mullady D, Edmundowicz S. Aspiration Therapy Leads to Weight Loss in Obese Subjects: A Pilot Study [Internet]. Gastroenterology 2013;145:1245-1252.e5.[cited 2018 Oct 13] Available from: https://www.gastrojournal.org/article/S0016-5085(13)01276-6/fulltext

67. Mittmann N, Stout NK, Lee P, Tosteson AN, Trentham-Dietz A, Alagoz O, Yaffe MJ. Total cost-effectiveness of mammography screening strategies. Health reports 2015;26:16.

68. Shih Y-CT, Dong W, Xu Y, Shen Y. Assessing the cost-effectiveness of updated breast cancer screening guidelines for average-risk women. Value in Health 2019;22:185–193.

69. Mittmann N, Stout NK, Tosteson AN, Trentham-Dietz A, Alagoz O, Yaffe MJ. Cost-effectiveness of mammography from a publicly funded health care system perspective. CMAJ open 2018;6:E77.

70. Stout NK, Lee SJ, Schechter CB, Kerlikowske K, Alagoz O, Berry D, Buist DS, Cevik M, Chisholm G, De Koning HJ. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. JNCI: Journal of the National Cancer Institute 2014;106

71. Gocgun Y, Banjevic D, Taghipour S, Montgomery N, Harvey BJ, Jardine AKS, Miller AB. Cost-effectiveness of breast cancer screening policies using simulation. The breast 2015;24:440–448.

72. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. Journal of the National Cancer Institute 2006;98:774–782.

73. Sprague BL, Stout NK, Schechter C, Van Ravesteyn NT, Cevik M, Alagoz O, Lee CI, Van Den Broek JJ, Miglioretti DL, Mandelblatt JS. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. Annals of internal medicine 2015;162:157–166.

74. Lee CI, Cevik M, Alagoz O, Sprague BL, Tosteson AN, Miglioretti DL, Kerlikowske K, Stout NK, Jarvik JG, Ramsey SD. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. Radiology 2015;274:772–780.

75. Vilaprinyo E, Forne C, Carles M, Sala M, Pla R, Castells X, Domingo L, Rue M. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. PloS one 2014;9:e86858.

76. Trentham-Dietz A, Kerlikowske K, Stout NK, Miglioretti DL, Schechter CB, Ergun MA, Van Den Broek JJ, Alagoz O, Sprague BL, Van Ravesteyn NT. Tailoring breast cancer screening intervals by breast density and risk for women aged 50 years or older: collaborative modeling of screening outcomes. Annals of internal medicine 2016;165:700–712.

77. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Annals of internal medicine 2011;155:10–20.

78. Gray E, Donten A, Karssemeijer N, Gils C van, Evans DG, Astley S, Payne K. Evaluation of a stratified national breast screening program in the United Kingdom: an early model-based cost-effectiveness analysis. Value in Health 2017;20:1100–1109.

79. Pashayan N, Morris S, Gilbert FJ, Pharoah PD. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. JAMA oncology 2018;4:1504–1510.

80. Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. BMC medicine 2019;17:195.

81. Wolff J, Pauling J, Keck A, Baumbach J. The Economic Impact of Artificial Intelligence in Health Care: Systematic Review. Journal of Medical Internet Research 2020;22:e16866.

82. Xie Y, Nguyen QD, Hamzah H, Lim G, Bellemo V, Gunasekeran DV, Yip MY, Lee XQ, Hsu W, Lee ML. Artificial intelligence for teleophthalmology-based diabetic retinopathy screening in a national programme: an economic analysis modelling study. The Lancet Digital Health 2020;

83. Wolf RM, Channa R, Abramoff MD, Lehmann HP. Cost-effectiveness of Autonomous Point-of-Care Diabetic Retinopathy Screening for Pediatric Patients With Diabetes. JAMA ophthalmology 2020;138:1063–1069.

84. Hartz S, John J. Contribution of economic evaluation to decision making in early phases of product development: a methodological and empirical review. International Journal of Technology Assessment in Health Care 2008;24:465–472.

85. Markiewicz K, Van Til JA, IJzerman MJ. Medical devices early assessment methods: systematic literature review. Int J Technol Assess Health Care 2014;30:137–146.

86. Steuten LM, Ramsey SD. Improving early cycle economic evaluation of diagnostic technologies. Expert review of pharmacoeconomics & outcomes research 2014;14:491–498.

87. Fasterholdt I, Krahn M, Kidholm K, Yderstræde KB, Pedersen KM. Review of early assessment models of innovative medical technologies. Health Policy 2017;121:870–879.

88. Smith V, Warty R, Nair A, Krishnan S, Sursas JA, Silva Costa F da, Vollenhoven B, Wallace EM. Defining the clinician's role in early health technology assessment during medical device innovation - a systematic review. BMC Health Serv Res 2019;19:514.

89. Fraser Institute. BLOG: Mandatory switching of biologic drugs—beware of potential side-effects [Internet]. 2020;[cited 2021 Feb 17] Available from: https://www.fraserinstitute.org/blogs/mandatory-switching-of-biologic-drugs-beware-of-potential-side-effects

90. Balijepalli C, Gullapalli L, Druyts E, Yan K, Desai K, Barakat S, Locklin J. Can Standard Health Technology Assessment Approaches Help Guide the Price of Orphan Drugs in Canada? A Review of Submissions to the Canadian Agency for

Drugs and Technologies in Health Common Drug Review [Internet]. Clinicoecon Outcomes Res 2020;12:445–457.[cited 2021 Feb 17] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7455764/

91. Patterson CC, Karuranga S, Salpea P, Saeedi P, Dahlquist G, Soltesz G, Ogle GD. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice 2019;157:107842.

92. Canadian Obesity Network. Report Card on Access to Obesity Treatments for Adults in Canada 2017 [Internet]. 2017;[cited 2018 Oct 13] Available from: https://obesitycanada.ca/wp-content/uploads/2017/07/Report-Card-Full-Version-PDF.pdf

93. Liu N, Funk LM. Bariatric Surgery Trends in the U.S.: 1% is the Loneliest Number. Annals of Surgery 2020;271:210–211.[cited 2020 Jul 5]

94. Fenwick E, Steuten L, Knies S, Ghabri S, Basu A, Murray JF, Koffijberg H (Erik), Strong M, Schmidler GDS, Rothery C. Value of Information Analysis for Research Decisions—An Introduction: Report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force [Internet]. Value in Health 2020;23:139–150.[cited 2020 Jul 23] Available from: https://www.valueinhealthjournal.com/article/S1098-3015(20)30027-9/abstract

95. Klinke DJ. Extent of Beta Cell Destruction Is Important but Insufficient to Predict the Onset of Type 1 Diabetes Mellitus [Internet]. PLoS One 2008;3[cited 2019 Dec 21] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2147725/

96. Statistics About Diabetes | ADA [Internet]. [cited 2019 Nov 21] Available from: https://www.diabetes.org/resources/statistics/statistics-about-diabetes

97. Chiang JL, Kirkman MS, Laffel LM, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes care 2014;37:2034–2054.

98. Tao B, Pietropaolo M, Atkinson M, Schatz D, Taylor D. Estimating the cost of type 1 diabetes in the US: a propensity score matching method. PLoS One 2010;5:e11501.

99. Hua X, Carvalho N, Tew M, Huang ES, Herman WH, Clarke P. Expenditures and prices of antihyperglycemic medications in the United States: 2002-2013. Jama 2016;315:1400–1402.

100. Families Cross Borders in Search for Affordable Insulin [Internet]. [cited 2019 Nov 21] Available from: https://www.webmd.com/diabetes/news/20190718/spiking-insulin-costs-put-patients-in-brutal-bind

101. Diabetes and insulin costs: Diabetics struggle as drug prices soar [Internet]. [cited 2019 Nov 21] Available from: https://www.usatoday.com/in-depth/news/50-

states/2019/03/21/diabetes-insulin-costs-diabetics-drug-prices-increase/3196757002/

102. Provention Bio Announces PRV-031 (Teplizumab) Granted PRIME Designation by the European Medicines Agency [Internet]. [cited 2019 Nov 21] Available from: https://www.prnewswire.com/news-releases/provention-bio-announces-prv-031-teplizumab-granted-prime-designation-by-the-european-medicines-agency-300944591.html

103. World Health Organization. Drugs and Money - Prices, Affordability and Cost Containment [Internet]. 2003;[cited 2019 Dec 21] Available from: https://apps.who.int/medicinedocs/en/d/Js4912e/

104. Craig A-M, Kennedy L. Health economic considerations for early drug discovery [Internet]. 2019;[cited 2019 Dec 21] Available from: https://www.ddw-online.com/drug-discovery/p148533-health-economic-considerations-for-early-drug-discovery.html

105. TreeAge Software. TreeAge Pro 2020, R2 [Internet]. 2020;[cited 2020 Aug 17] Available from: https://www.treeage.com/software-downloads/treeage-pro-2020-r2-healthcare/

106. US Census Bureau. National Population by Characteristics: 2010-2018 [Internet]. The United States Census Bureau 2019;[cited 2019 Dec 21] Available from:

https://www.census.gov/data/tables/time-series/demo/popest/2010s-national-detail.html

107. WebPlotDigitizer v4.2 [Internet]. 2019;[cited 2019 Dec 21] Available from: https://automeris.io/WebPlotDigitizer/

108. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology 2012;12:9.

109. Diaby V, Adunlin G, Montero AJ. Survival modeling for the estimation of transition probabilities in model-based economic evaluations in the absence of individual patient data: a tutorial. Pharmacoeconomics 2014;32:101–108.

110. Haines P, Tremblay G, Briggs A. A criterion-based approach for the systematic and transparent extrapolation of clinical trial survival data. Journal of Health Economics and Outcomes Research 2015;2:147–160.

111. Centers for Disease Control and Prevention. US Life Tables [Internet]. 2019;[cited 2019 Dec 21] Available from: https://www.cdc.gov/nchs/products/life_tables.htm

112. Centers for Medicare and Medicaid Services. Clinical Laboratory Fee Schedule Files [Internet]. 2019;[cited 2019 Dec 21] Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files

113. Dall TM, Yang W, Gillespie K, Mocarski M, Byrne E, Cintina I, Beronja K, Semilla AP, Iacobucci W, Hogan PF. The Economic Burden of Elevated Blood Glucose Levels in 2017: Diagnosed and Undiagnosed Diabetes, Gestational Diabetes, and Prediabetes. Diabetes care 2019;dc181226.

114. GoodSmith MS, Skandari MR, Huang ES, Naylor RN. The Impact of Biomarker Screening and Cascade Genetic Testing on the Cost-Effectiveness of MODY Genetic Testing. Diabetes Care 2019;42:2247–2255.

115. US Bureau of Labor Statistics. CPI Inflation Calculator [Internet]. [cited 2020 Aug 17] Available from: https://www.bls.gov/data/inflation_calculator.htm

116. NICE. Guide to the methods of technology appraisal 2013 | Guidance and guidelines [Internet]. 2013;[cited 2018 Oct 14] Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword

117. Makrilakis K, Liatis S, Tsiakou A, Stathi C, Papachristoforou E, Perrea D, Katsilambros N, Kontodimopoulos N, Niakas D. Comparison of health-related quality of Life (HRQOL) among patients with pre-diabetes, diabetes and normal glucose tolerance, using the 15D-HRQOL questionnaire in Greece: the DEPLAN study. BMC endocrine disorders 2018;18:32.

118. Rhodes ET, Goran MI, Lieu TA, Lustig RH, Prosser LA, Songer TJ, Weigensberg MJ, Weinstock RS, Gonzalez T, Rawluk K, Zoghbi RM, Ludwig DS, Laffel LM. Health-Related Quality of Life in Adolescents With or at Risk for Type 2 Diabetes

Mellitus [Internet]. J Pediatr 2012;160:911–917.[cited 2020 Jul 21] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4793715/

119. Lee JM, Rhee K, O'Grady MJ, Basu A, Winn A, John P, Meltzer DO, Kollman C, Laffel LM, Lawrence JM. Health utilities for children and adults with type 1 diabetes. Medical care 2011;49:924.

120. Wan W, Skandari MR, Minc A, Nathan AG, Winn A, Zarei P, O'Grady M, Huang ES. Cost-effectiveness of continuous glucose monitoring for adults with type 1 diabetes compared with self-monitoring of blood glucose: the DIAMOND randomized trial. Diabetes Care 2018;41:1227–1234.

121. Johnson SR, Carter HE, Leo P, Hollingworth SA, Davis EA, Jones TW, Conwell LS, Harris M, Brown MA, Graves N. Cost-effectiveness analysis of routine screening using massively parallel sequencing for maturity-onset diabetes of the young in a pediatric diabetes cohort: reduced health system costs and improved patient quality of life. Diabetes care 2019;42:69–76.

122. Hägg-Holmberg S, Thorn LM, Forsblom CM, Gordin D, Elonen N, Harjutsalo V, Liebkind R, Putaala J, Tatlisumak T, Groop P-H. Prognosis and its predictors after incident stroke in patients with type 1 diabetes. Diabetes Care 2017;40:1394–1400.

123. Brophy S, Cooksey R, Gravenor MB, Weston C, Macey SM, John G, Williams R, Lyons RA. Population based absolute and relative survival to 1 year of people with

diabetes following a myocardial infarction: a cohort study using hospital admissions data. BMC public health 2010;10:338.

124. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. New England Journal of Medicine 2014;371:796–797.

125. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. OUP Oxford; 2006.

126. Miquel-Cases A, Retèl VP, Harten WH van, Steuten LM. Decisions on further research for predictive biomarkers of high-dose alkylating chemotherapy in triple-negative breast cancer: a value of information analysis. Value in health 2016;19:419–430.

127. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the Economic Evaluation of Health Technologies: Canada . CADTH; 2017 [Internet]. 2017;Available from: https://www.cadth.ca/sites/default/files/pdf/economic_guidelines_worked_example.pdf

128. Vemer P, Corro Ramos I, Voorn GAK van, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users [Internet]. PharmacoEconomics 2016;34:349–361.[cited 2020 Aug 17] Available from: http://link.springer.com/10.1007/s40273-015-0327-2

129. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. Medical Decision Making 2012;32:733–743.

130. Diabetes Prevention Trial–Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. New England Journal of Medicine 2002;346:1685–1691.

131. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. New England Journal of Medicine 2017;376:1419–1429.

132. Patented Medicine Prices Review Board. PMPRB Steering Committee on Modernization of Price Review Process Guidelines - Final Report [Internet]. 2019;[cited 2019 Dec 23] Available from: http://pmprb-cepmb.gc.ca

133. Borisenko O, Mann O, Duprée A. Cost-utility analysis of bariatric surgery compared with conventional medical management in Germany: a decision analytic modeling. BMC surgery 2017;17:87.

134. Mäklin S, Malmivaara A, Linna M, Victorzon M, Koivukangas V, Sintonen H. Cost–utility of bariatric surgery for morbid obesity in Finland. British Journal of Surgery 2011;98:1422–1429.

135. UpToDate. Intragastric balloon therapy for weight loss [Internet]. 2020;[cited 2020 Aug 14] Available from: https://www.uptodate.com/contents/intragastric-balloon-therapy-for-weight-loss

136. Shahnazarian V, Ramai D, Sarkar A. Endoscopic bariatric therapies for treating obesity: a learning curve for gastroenterologists. Translational gastroenterology and hepatology 2019;4

137. Allurion. Elipse™ Balloon Weight Loss Program [Internet]. 2020;[cited 2020 Aug 15] Available from: https://allurion.com/en

138. About Allurion [Internet]. Allurion - Elipse™ Balloon Weight Loss Program [cited 2020 Aug 15] Available from: https://allurion.com/en-us

139. Business wire. Allurion Expands into Asia with Launch of the Elipse® Gastric Balloon Weight Loss Program [Internet]. 2020;[cited 2020 Aug 15] Available from: https://www.businesswire.com/news/home/20200728005010/en/Allurion-Expands-Asia-Launch-Elipse%C2%AE-Gastric-Balloon

140. Ball W, Raza SS, Loy J, Riera M, Pattar J, Adjepong S, Rink J. Effectiveness of intra-gastric balloon as a bridge to definitive surgery in the super obese. Obesity Surgery 2019;29:1932–1936.

141. Allurion. Instructions for Use Elipse™ Gastric Balloon System [Internet]. [cited 2020 Aug 15] Available from: https://allurion.com/sites/default/files/2020-03/CS113-

08_ART_1%20Instructions%20for%20Use%20%28IFU%29%2C%20Elipse%20System%2C%20Booklet_1.pdf

142. The Sun. Susanna Reid's shock at "huge" weight-loss BALLOON that inflates in your tummy [Internet]. 2018;[cited 2020 Aug 15] Available from: https://www.thesun.co.uk/fabulous/5369276/good-morning-britain-susanna-reid-weight-loss-balloon/

143. Ienca R, Al Jarallah M, Caballero A, Giardiello C, Rosa M, Kolmer S, Sebbag H, Hansoulle J, Quartararo G, Zouaghi SAS. The Procedureless Elipse Gastric Balloon Program: Multicenter Experience in 1770 Consecutive Patients. Obesity surgery 2020;1–9.

144. Vantanasiri K, Matar R, Beran A, Jaruvongvanich V. The Efficacy and Safety of a Procedureless Gastric Balloon for Weight Loss: a Systematic Review and Meta-Analysis. Obesity Surgery 2020;1–6.

145. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B. Effects of bariatric surgery on mortality in Swedish obese subjects. New England journal of medicine 2007;357:741–752.

146. American Society for Metabolic and Bariatric Surgery. Who is a Candidate for Bariatric Surgery? [Internet]. 2020;[cited 2020 Aug 3] Available from: https://asmbs.org/patients/who-is-a-candidate-for-bariatric-surgery

147. CDC. Health, United States: Table 058: Normal weight, overweight, and obesity among adults aged 20 and over, by selected characteristics: United States, selected years 1988–1994 through 2013–2016 [Internet]. 2018;[cited 2018 Oct 20] Available from: https://www.cdc.gov/nchs/hus/contents2017.htm

148. Mital S, Nguyen HV. Incremental Cost-Effectiveness of Aspiration Therapy vs Bariatric Surgery and No Treatment for Morbid Obesity. American Journal of Gastroenterology 2019;114:1470–1477.

149. Lyratzopoulos G, McElduff P, Heller RF, Hanily M, Lewis PS. Mid-term Body Mass Index increase among obese and non-obese individuals in middle life and deprivation status: a cohort study. BMC Public Health 2005;5:32.

150. Salminen P, Helmiö M, Ovaska J, Juuti A, Leivonen M, Peromaa-Haavisto P, Hurme S, Soinio M, Nuutila P, Victorzon M. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. Jama 2018;319:241–254.

151. Borrell LN, Samuel L. Body Mass Index Categories and Mortality Risk in US Adults: The Effect of Overweight and Obesity on Advancing Death [Internet]. Am J Public Health 2014;104:512–519.[cited 2019 Apr 2] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3953803/

152. Chang S-H, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA surgery 2014;149:275–287.

153. Clinical Practice Guidelines for the Support of the Bariatric Surgery Patient | ASMBS [Internet]. American Society for Metabolic and Bariatric Surgery 2013;[cited 2019 Mar 27] Available from: https://asmbs.org/resources/clinical-practice-guidelines-for-the-perioperative-nutritional-metabolic-and-nonsurgical-support-of-the-bariatric-surgery-patient

154. Exchange rates.org. British Pounds (GBP) to US Dollars (USD) Rates for 1/18/2018 [Internet]. 2018;[cited 2020 Aug 16] Available from: https://www.exchange-rates.org/Rate/GBP/USD/1-18-2018

155. Drugs.com. Aprepitant Prices, Coupons & Patient Assistance Programs [Internet]. 2020;[cited 2020 Aug 16] Available from: https://www.drugs.com/price-guide/aprepitant

156. Drugs.com. Ondansetron Prices, Coupons & Patient Assistance Programs [Internet]. 2020;[cited 2020 Aug 16] Available from: https://www.drugs.com/price-guide/ondansetron

157. Drugs.com. Lansoprazole Prices, Coupons & Patient Assistance Programs [Internet]. 2020;[cited 2020 Aug 16] Available from: https://www.drugs.com/price-guide/lansoprazole

158. Saumoy M, Schneider Y, Shen N, Kahaleh M, Sharaiha RZ, Shah SC. Cost effectiveness of gastric cancer screening according to race and ethnicity. Gastroenterology 2018;155:648–660.

159. Food and Drug Administration. UPDATE: Potential Risks with Liquid-filled Intragastric Balloons - Letter to Health Care Providers [Internet]. 2020;[cited 2020 Aug 15] Available from: https://www.fda.gov/medical-devices/letters-health-care-providers/update-potential-risks-liquid-filled-intragastric-balloons-letter-health-care-providers-0

160. Apollo Endosurgery, Inc. Orbera®Intragastric Balloon System Patient Information Booklet [Internet]. Available from: https://www.orbera.com/resource/us_orbera_code/pdfs/orbera-patient-information-US.pdf

161. Ochner CN, Dambkowski CL, Yeomans BL, Teixeira J, Pi-Sunyer FX. Pre-bariatric surgery weight loss requirements and the effect of preoperative weight loss on postoperative outcome. International Journal of Obesity 2012;36:1380–1387.

162. Melissas J, Mouzas J, Filis D, Daskalakis M, Matrella E, Papadakis JA, Sevrisarianos N, Charalambides D. The intragastric balloon–smoothing the path to bariatric surgery. Obesity surgery 2006;16:897–902.

163. CBS News. The high cost of breast cancer “false positives” [Internet]. 2015;[cited 2020 Apr 5] Available from: https://www.cbsnews.com/news/the-cost-of-breast-cancer-false-positives/

164. Global News. New breast cancer screening guidelines are outdated and dangerous, experts say [Internet]. 2019;[cited 2020 Apr 4] Available from: https://globalnews.ca/news/4898068/breast-cancer-screening-guidelines-backlash/

165. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, Tyrer JP, Chen T-H, Wang Q, Bolla MK. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. The American Journal of Human Genetics 2019;104:21–34.

166. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, Schumacher FR, Anderson WF, Check D, Chattopadhyay S. Breast cancer risk from modifiable and nonmodifiable risk factors among white women in the United States. JAMA oncology 2016;2:1295–1302.

167. American Cancer Society. Breast Cancer Facts & Figures 2019-2020 [Internet]. Atlanta: American Cancer Society, Inc. 2019;Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf

168. Alagoz O, Ergun MA, Cevik M, Sprague BL, Fryback DG, Gangnon RE, Hampton JM, Stout NK, Trentham-Dietz A. The University of Wisconsin breast cancer epidemiology simulation model: an update. Medical decision making 2018;38:99S-111S.

169. Fryback DG, Stout NK, Rosenberg MA, Trentham-Dietz A, Kuruchittham V, Remington PL. Chapter 7: The Wisconsin breast cancer epidemiology simulation model. JNCI Monographs 2006;2006:37–47.

170. University of Wisconsin CISNET. CISNET Model Profile [Internet]. 2013;[cited 2020 May 23] Available from: https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_BREAST_UWISC_001_07232013_58567.pdf#pagemode=bookmarks

171. National Cancer Institute. Q&A: What is Cancer Overdiagnosis? [Internet]. 2016;[cited 2020 Oct 16] Available from: https://prevention.cancer.gov/news-and-events/news/qa-what-cancer

172. Naber SK, Kundu S, Kuntz KM, Dotson WD, Williams MS, Zauber AG, Calonge N, Zallen DT, Ganiats TG, Webber EM, Goddard KAB, Henrikson NB, Ballegooijen M van, Janssens ACJW, Lansdorp-Vogelaar I. Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk: Current Status and Future Potential [Internet]. JNCI Cancer Spectr 2020;4[cited 2020 Aug 27] Available from: https://academic.oup.com/jncics/article/4/1/pkz086/5586982

173. Kundu S, Kers JG, Janssens ACJ. Constructing hypothetical risk data from the area under the ROC curve: modelling distributions of polygenic risk. PloS one 2016;11:e0152359.

174. Shiyanbola OO, Arao RF, Miglioretti DL, Sprague BL, Hampton JM, Stout NK, Kerlikowske K, Braithwaite D, Buist DS, Egan KM. Emerging trends in family history of breast cancer and associated risk. Cancer Epidemiology and Prevention Biomarkers 2017;26:1753–1760.

175. Ahern TP, Sprague BL, Bissell MCS, Miglioretti DL, Buist DSM, Braithwaite D, Kerlikowske K. Family History of Breast Cancer, Breast Density, and Breast Cancer Risk in a U.S. Breast Cancer Screening Population [Internet]. Cancer Epidemiol Biomarkers Prev 2017;26:938–944.[cited 2020 Aug 27] Available from: https://cebp.aacrjournals.org/content/26/6/938

176. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Breast Cancer SEER Incidence Rates by Age at Diagnosis, 2013-2017 [Internet]. 2020;Available from: https://seer.cancer.gov/explorer/application.html

177. Gangnon RE, Sprague BL, Stout NK, Alagoz O, Weedon-Fekjær H, Holford TR, Trentham-Dietz A. The contribution of mammography screening to breast cancer incidence trends in the United States: an updated age–period–cohort model. Cancer Epidemiology and Prevention Biomarkers 2015;24:905–912.

178. Kerlikowske K, Hubbard RA, Miglioretti DL, Geller BM, Yankaskas BC, Lehman CD, Taplin SH, Sickles EA. Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. Annals of internal medicine 2011;155:493–502.

179. Iowa Institute of Human Genetics. Microarrays and Fees [Internet]. 2020;[cited 2020 Apr 4] Available from: https://medicine.uiowa.edu/humangenetics/research/genomics-division/microarray/microarrays-and-fees

180. European Society of Radiology. The cost of AI in radiology: is it really worth it? [Internet]. 2019;[cited 2020 Apr 4] Available from: https://ai.myesr.org/healthcare/the-cost-of-ai-in-radiology-is-it-really-worth-it/

181. US Food and Drug Administration. MQSA National Statistics [Internet]. 2020;[cited 2020 Apr 4] Available from: https://www.fda.gov/radiation-emitting-products/mqsa-insights/mqsa-national-statistics

182. US Census Bureau. 2018 Population Estimates by Age, Sex, Race and Hispanic Origin [Internet]. 2019;[cited 2020 Apr 4] Available from: https://www.census.gov/newsroom/press-kits/2019/detailed-estimates.html

183. Centers for Medicare and Medicaid Services. Physician Fee Schedule Search [Internet]. 2020;[cited 2020 Apr 4] Available from: https://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx

184. Exchange rates.org. Euros (EUR) to US Dollars (USD) Rates for 2/26/2020 [Internet]. 2020;Available from: https://www.exchange-rates.org/Rate/EUR/USD/2-26-2020

185. US Department of Veteran Affairs. HERC: Cost-Effectiveness Analysis [Internet]. 2020;[cited 2020 Oct 14] Available from: https://www.herc.research.va.gov/include/page.asp?id=cost-effectiveness-analysis

186. Buxton MJ. Problems in the economic appraisal of new health technology: the evaluation of heart transplants in the UK. Economic appraisal of health technology in the European Community. Oxford: Oxford Medical Publications 1987;103–118.

187. US National Library of Medicine. Gastric Bypass Procedure and AspireAssist Aspiration Therapy System for the Treatment of Morbid Obesity, Observational Study Over 5 Years [Internet]. 2018;[cited 2020 Jul 6] Available from: https://clinicaltrials.gov/ct2/show/NCT02142257

188. Thompson CC, Dayyeh BKA, Kushnir V, Kushner RF, Jirapinyo P, Schorr AB, Aronne LJ, Amaro A, Jaffe DL, Schulman AR. Aspiration therapy for the treatment of obesity: 4-year results of a multicenter randomized controlled trial. Surgery for Obesity and Related Diseases 2019;15:1348–1354.

189. Thompson CC, Dayyeh BKA, Kushner R, Sullivan S, Schorr AB, Amaro A, Apovian CM, Fullum T, Zarrinpar A, Jensen MD. Percutaneous gastrostomy

device for the treatment of class II and class III obesity: results of a randomized controlled trial. The American journal of gastroenterology 2017;112:447.

190. Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health economics 2011;20:2–15.

191. Paulden M, Galvanni V, Chakraborty S, Kudinga B, McCabe C. Discounting and the evaluation of health care programs [Internet]. 2016;Available from: https://www.cadth.ca/sites/default/files/pdf/CP0008_Economic_Evaluation_Guidelines_Discount_Rate_Report.pdf

192. Paulden M, Claxton K. Budget allocation and the revealed social rate of time preference for health. Health economics 2012;21:612–618.

193. Paulden M, O'Mahony JF, McCabe C. Discounting the recommendations of the second panel on cost-effectiveness in health and medicine. Pharmacoeconomics 2017;35:5–13.

194. Attema AE, Brouwer WB, Claxton K. Discounting in economic evaluations. Pharmacoeconomics 2018;36:745–758.

195. Richardson J, Iezzi A, Khan MA. Why do multi-attribute utility instruments produce different utilities: the relative importance of the descriptive systems, scale and 'micro-utility'effects. Quality of Life Research 2015;24:2045–2053.

196. De Haes J, Koning HJ de, Oortmarssen GJ van, Agt HM van, Bruyn AE de, Maas PJ van der. The impact of a breast cancer screening programme on quality-adjusted life-years. International journal of cancer 1991;49:538–544.

197. Bryan S, Mitton C, Donaldson C. Breaking the Addiction to Technology Adoption [Internet]. Health Economics 2014;23:379–383.[cited 2020 Oct 19] Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/hec.3034

198. Scotland G, Bryan S. Why Do Health Economists Promote Technology Adoption Rather Than the Search for Efficiency? A Proposal for a Change in Our Approach to Economic Evaluation in Health Care [Internet]. Med Decis Making 2017;37:139–147.[cited 2020 Oct 19] Available from: https://doi.org/10.1177/0272989X16653397

199. Mital S, Nguyen HV. Response to Jirapinyo et al. American Journal of Gastroenterology 2020;115:482–483.

200. Rogers MA, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC medicine 2017;15:199.

201. US Census Bureau. Age and Sex Composition in the United States: 2019 [Internet]. 2020;[cited 2020 Jul 31] Available from: https://www.census.gov/data/tables/2019/demo/age-and-sex/2019-age-sex-composition.html

202. FDA Center for Drug Evaluation and Research. Frequently Asked Questions on Patents and Exclusivity [Internet]. 2020;[cited 2020 Jul 31] Available from: https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity

203. American Society for Metabolic and Bariatric Surgery. New Study Finds Most Bariatric Surgeries Performed in Northeast, and Fewest in South Where Obesity Rates are Highest, and Economies are Weakest [Internet]. 2018;[cited 2020 Oct 6] Available from: https://asmbs.org/articles/new-study-finds-most-bariatric-surgeries-performed-in-northeast-and-fewest-in-south-where-obesity-rates-are-highest-and-economies-are-weakest

204. Centers for Disease Control and Prevention. Life Expectancy [Internet]. 2020;[cited 2020 Oct 11] Available from: https://www.cdc.gov/nchs/fastats/life-expectancy.htm

205. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. Jama 2003;289:187–193.

206. Aspire Bariatrics. AspireAssist Weight Loss Procedure - Insurance Options [Internet]. AspireAssist Non-Surgical Weight Loss Procedure 2017;[cited 2018 Oct 20] Available from: https://www.aspirebariatrics.com/access/

207. Kohli-Lynch CN, Briggs AH. Heterogeneity in Cost-Effectiveness Analysis. In: Oxford Research Encyclopedia of Economics and Finance. 2019.

208. Centers for Disease Control and Prevention. Is it Time to Integrate Polygenic Risk Scores into Clinical Practice? Let's Do the Science First and Follow the Evidence Wherever it Takes Us! [Internet]. 2019;[cited 2020 Jun 19] Available from: https://blogs.cdc.gov/genomics/2019/06/03/is-it-time/

209. Garrison LP, Pauly MV, Willke RJ, Neumann PJ. An Overview of Value, Perspective, and Decision Context—A Health Economics Approach: An ISPOR Special Task Force Report [2] [Internet]. Value in Health 2018;21:124–130.[cited 2019 Mar 17] Available from: https://linkinghub.elsevier.com/retrieve/pii/S1098301517338913

210. York Health Economics Consortium. Cost-Effectiveness Analysis [Internet]. 2016;[cited 2021 Jan 29] Available from: http://yhec.co.uk/glossary/cost-effectiveness-analysis/

211. York Health Economics Consortium. Value of Information Analysis [Internet]. 2016;[cited 2021 Jan 29] Available from: http://yhec.co.uk/glossary/value-of-information-analysis/

212. Adamson BJS, Carlson JJ, Kublin JG, Garrison LP. The potential cost-effectiveness of pre-exposure prophylaxis combined with HIV vaccines in the united states [Internet]. Vaccines 2017;5Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-

85024383928&doi=10.3390%2fvaccines5020013&partnerID=40&md5=63fb2a30718e31d9f67f2004c6a4da29

213. Geenen JW, Baranova EV, Asselbergs FW, Boer A de, Vreman RA, Palmer CN, Maitland-van der Zee AH, Hövels AM. Early health technology assessments in pharmacogenomics: a case example in cardiovascular drugs. Pharmacogenomics 2017;18:1143–1153.

214. Hummelink S, Gerrits JGW, Schultze Kool LJ, Ulrich DJO, Rovers MM, Grutters JPC. The merits of decision modelling in the earliest stages of the IDEAL framework: An innovative case in DIEP flap breast reconstructions [Internet]. Journal of Plastic, Reconstructive and Aesthetic Surgery 2017;70:1696–1701.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85028645755&doi=10.1016%2fj.bjps.2017.07.011&partnerID=40&md5=e5cb0b937b146efb49ced4e2aedd5fc1

215. Khoudigian-Sinani S, Blackhouse G, Levine M, Thabane L, O'reilly D. The premarket assessment of the cost-effectiveness of a predictive technology "Straticyte™" for the early detection of oral cancer: a decision analytic model. Health economics review 2017;7:35.

216. Kip MMA, Koffijberg H, Moesker MJ, IJzerman MJ, Kusters R. The cost-utility of point-of-care troponin testing to diagnose acute coronary syndrome in primary care [Internet]. BMC Cardiovascular Disorders 2017;17Available from:

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85026649122&doi=10.1186%2fs12872-017-0647-6&partnerID=40&md5=9e000a6c6e9ea9aa5bc69f1891329a96

217. Knuttel FM, Huijsse SEM, Feenstra TL, Moonen CTW, Bosch MAAJ van den, Buskens E, Greuter MJW, Bock GH de. Early health technology assessment of magnetic resonance-guided high intensity focused ultrasound ablation for the treatment of early-stage breast cancer [Internet]. Journal of Therapeutic Ultrasound 2017;5Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85026504180&doi=10.1186%2fs40349-017-0101-3&partnerID=40&md5=6114ab9b13d492acef8324fa753cb7bc

218. Van Nimwegen KJM, Lilford RJ, Van Der Wilt GJ, Grutters JPC. Headroom beyond the quality- adjusted life-year: The case of complex pediatric neurology [Internet]. International Journal of Technology Assessment in Health Care 2017;33:5–10.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85019658211&doi=10.1017%2fS0266462317000046&partnerID=40&md5=e0a2d3b958dcd690b871ce4383bb5ed7

219. Wan XM, Peng LB, Ma JA, Li YJ. Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and C hinese perspectives. Cancer 2017;123:2634–2641.

220. Windt TS de, Sorel JC, Vonk LA, Kip MMA, Ijzerman MJ, Saris DBF. Early health economic modelling of single-stage cartilage repair. Guiding implementation of technologies in regenerative medicine [Internet]. Journal of Tissue Engineering and Regenerative Medicine 2017;11:2950–2959.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85032486776&doi=10.1002%2fterm.2197&partnerID=40&md5=4fee2d305201c463c9290a73aff6bedf

221. Wong KM, Ding K, Li S, Bradbury P, Tsao M-S, Der SD, Shepherd FA, Chung C, Ng R, Seymour L, Leighl NB. A Cost-Effectiveness Analysis of Using the JBR.10-Based 15-Gene Expression Signature to Guide Adjuvant Chemotherapy in Early Stage Non-Small-Cell Lung Cancer. Clin Lung Cancer 2017;18:e41–e47.

222. Graaf G de, Postmus D, Westerink J, Buskens E. The early economic evaluation of novel biomarkers to accelerate their translation into clinical applications. Cost Eff Resour Alloc 2018;16:23.

223. Schlemm L. Disability Adjusted Life Years due to Ischaemic Stroke Preventable by Real-Time Stroke Detection-A Cost-Utility Analysis of Hypothetical Stroke Detection Devices. Front Neurol 2018;9:814.

224. Sutton AJ, Lamont JV, Evans RM, Williamson K, O'Rourke D, Duggan B, Sagoo GS, Reid CN, Ruddock MW. An early analysis of the cost-effectiveness of a diagnostic classifier for risk stratification of haematuria patients (DCRSHP)

compared to flexible cystoscopy in the diagnosis of bladder cancer. PloS one 2018;13:e0202796.

225. Veličković VM, Borisenko O, Svensson M, Spelman T, Siebert U. Congenital heart defect repair with ADAPT tissue engineered pericardium scaffold: An early-stage health economic model [Internet]. PLoS ONE 2018;13Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85053908884&doi=10.1371%2fjournal.pone.0204643&partnerID=40&md5=b64fa6b3f321089fb970980ecc9934b8

226. Vilsbøll AW, Mouritsen JM, Jensen LP, Bødker N, Holst AW, Pennisi CP, Ehlers L. Cell-based therapy for the treatment of female stress urinary incontinence: an early cost–effectiveness analysis. Regenerative medicine 2018;13:321–330.

227. Lansdorp-Vogelaar I, Goede SL, Bosch LJW, Melotte V, Carvalho B, Engeland M van, Meijer GA, Koning HJ de, Ballegooijen M van. Cost-effectiveness of High-performance Biomarker Tests vs Fecal Immunochemical Test for Noninvasive Colorectal Cancer Screening. Clin Gastroenterol Hepatol 2018;16:504-512.e11.

228. Wallner K, Pedroza RG, Awotwe I, Piret JM, Senior PA, Shapiro AMJ, McCabe C. Stem cells and beta cell replacement therapy: a prospective health technology assessment study. BMC Endocr Disord 2018;18:6.

229. Abel L, Shinkins B, Smith A, Sutton AJ, Sagoo GS, Uchegbu I, Allen AJ, Graziadio S, Moloney E, Yang Y. Early economic evaluation of diagnostic

technologies: experiences of the NIHR diagnostic evidence co-operatives. Medical Decision Making 2019;39:857–866.

230. Buisman LR, Rijnsburger AJ, Lugt A van der, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Cost-effectiveness of novel imaging tests to select patients for carotid endarterectomy. Health Policy and Technology 2019;8:111–117.

231. Kluytmans A, Deinum J, Jenniskens K, Van Herwaarden AE, Gloerich J, Van Gool AJ, Van Der Wilt GJ, Grutters JPC. Clinical biomarker innovation: When is it worthwhile? [Internet]. Clinical Chemistry and Laboratory Medicine 2019;Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85069667274&doi=10.1515%2fcclm-2019-0098&partnerID=40&md5=21be50cf690ad7f5af77b1700d5d20bb

232. Vreman RA, Geenen JW, Hövels AM, Goettsch WG, Leufkens HG, Al MJ. Phase I/II Clinical Trial-Based Early Economic Evaluation of Acalabrutinib for Relapsed Chronic Lymphocytic Leukaemia. Applied health economics and health policy 2019;17:883–893.

233. Wang S-T, Anderson IM, Mitchell D, Johnson SJ, Shiozawa A. Cost-effectiveness model for a hypothetical monotherapy vs standard of care in adult patients with treatment-resistant depression [Internet]. ClinicoEconomics and Outcomes Research 2019;11:257–270.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-

85072813608&doi=10.2147%2fCEOR.S181718&partnerID=40&md5=890309b080e5630696d72b866bb47206

234. Wenker S, Lieshout C van, Frederix G, Heijden J van der, Loh P, Chamuleau SAJ, Slochteren F van. MRI-guided pulmonary vein isolation for atrial fibrillation: what is good enough? An early health technology assessment. Open Heart 2019;6:e001014.

235. Bakker L, Vaporidi K, Aarts J, Redekop W. The potential of real-time analytics to improve care for mechanically ventilated patients in the intensive care unit: an early economic evaluation [Internet]. Cost Effectiveness and Resource Allocation 2020;18Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85097363742&doi=10.1186%2fs12962-020-00254-4&partnerID=40&md5=41c167fff21ebf006753bd0bb1982313

236. Frempong SN, Sutton AJ, Davenport C, Barton P. Early Economic Evaluation to Identify the Necessary Test Characteristics of a New Typhoid Test to be Cost Effective in Ghana. PharmacoEconomics-open 2020;4:143–157.

237. Guinan K, Beauchemin C, Tremblay J, Chalmers J, Woodward M, Tahir MR, Hamet P, Lachaine J. Economic Evaluation of a New Polygenic Risk Score to Predict Nephropathy in Adult Patients With Type 2 Diabetes [Internet]. Canadian Journal of Diabetes 2020;Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-

85092047130&doi=10.1016%2fj.jcjd.2020.06.010&partnerID=40&md5=53e7b072e61304246d641aeb3804126b

238. Huygens SA, Ramos IC, Bouten CV, Kluin J, Chiu ST, Grunkemeier GL, Takkenberg JJ, Rutten-van Mölken MP. Early cost-utility analysis of tissue-engineered heart valves compared to bioprostheses in the aortic position in elderly patients. The European Journal of Health Economics 2020;1–16.

239. Lindenberg M, Retèl V, Rohaan M, Berg J van den, Haanen J, Harten W van. Evaluating different adoption scenarios for TIL-therapy and the influence on its (early) cost-effectiveness. BMC Cancer 2020;20:712.

240. Magee C, Graham D, Leonard C, McMaster J, Davies H, Skotchko M, Lovat L, Murray C, Mealing S, Smart H, Haidry R. The cost-effectiveness of radiofrequency ablation for treating patients with gastric antral vascular ectasia refractory to first line endoscopic therapy [Internet]. Current Medical Research and Opinion 2020;36:977–983.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85083897422&doi=10.1080%2f03007995.2020.1747997&partnerID=40&md5=a2b94a5731e6daa282e06fba36f90441

241. Mandavia R, Horstink YM, Grutters JPC, Landry E, May C, Rovers M, Schilder AGM, Scholte M. The Potential Added Value of Novel Hearing Therapeutics: An

Early Health Economic Model for Hearing Loss. Otol Neurotol 2020;41:1033–1041.

242. Mital S, Nguyen HV. Cost Effectiveness of Teplizumab for Prevention of Type 1 Diabetes Among Different Target Patient Groups [Internet]. PharmacoEconomics 2020;38:1359–1372.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85091392087&doi=10.1007%2fs40273-020-00962-y&partnerID=40&md5=1ab52a4d93d719bd880f56c65c61d94e

243. Schneider JE, Romanowsky J, Schuetz P, Stojanovic I, Cheng HK, Liesenfeld O, Buturovic L, Sweeney TE. Cost Impact Model of a Novel Multi-mRNA Host Response Assay for Diagnosis and Risk Assessment of Acute Respiratory Tract Infections and Sepsis in the Emergency Department. J Health Econ Outcomes Res 2020;7:24–34.

244. Shi Y, Wan X, Tan C, Li J, Peng L. Model-Based Cost-Effectiveness Analysis of Panitumumab Plus FOLFIRI for the Second-Line Treatment of Patients with Wild-Type Ras Metastatic Colorectal Cancer [Internet]. Advances in Therapy 2020;37:847–859.Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85077598001&doi=10.1007%2fs12325-019-01214-y&partnerID=40&md5=5800a78cc59c8b8fe1a304c619649eca

245. Steffen RE, Pinto M, Kritski A, Trajman A. Cost-effectiveness of newer technologies for the diagnosis of Mycobacterium tuberculosis infection in Brazilian people living with HIV [Internet]. Scientific Reports 2020;10Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85097511209&doi=10.1038%2fs41598-020-78737-w&partnerID=40&md5=0f364a3d43659370f6c08e84026bcdfc

246. Wallace SL, St Martin B, Lee K, Sokol ER. A cost-effectiveness analysis of vaginal carbon dioxide laser therapy compared with standard medical therapies for genitourinary syndrome of menopause-associated dyspareunia. Am J Obstet Gynecol 2020;223:890.e1-890.e12.

247. Willems D, Charokopou M, Evers SMAA, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020;1–9.

248. National Institute for Health and Care Excellence. Recommendations | Radiofrequency ablation for gastric antral vascular ectasia | Guidance [Internet]. 2015;[cited 2021 Feb 16] Available from: https://www.nice.org.uk/guidance/ipg520/chapter/1-Recommendations

249. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults; United States, 2011-2014. 2016;

250. Penn Medicine. Gastric Sleeve or Gastric Bypass: What's the Difference? [Internet]. 2020;[cited 2021 Jan 24] Available from: https://www.pennmedicine.org/updates/blogs/metabolic-and-bariatric-surgery-blog/2013/march/gastric-sleeve-or-gastric-bypass-whats-the-difference

251. American Society for Metabolic and Bariatric Surgery. Bariatric Surgery Procedures [Internet]. 2021;[cited 2021 Jan 24] Available from: https://asmbs.org/patients/bariatric-surgery-procedures

252. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in health 2013;16:231–250.

253. The EQUATOR Network. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement [Internet]. 2020;[cited 2021 Feb 16] Available from: https://www.equator-network.org/reporting-guidelines/cheers/

CHEERS Checklists

These checklists are based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (252) and obtained from (253).

Checklist for Chapter 2

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The ISPOR CHEERS Task Force Report, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Chapter 2 Title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract to Chapter 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Section 2.1
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Section 2.2.1 & 2.2.3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Section 2.1 & 2.2.1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Section 2.2.2
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Section 2.2.1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Section 2.2.2
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Section 2.2.4 (Costs, Effectiveness)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Section 2.2.4
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Section 2.2.4

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Section 2.2.4 (Effectiveness)
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Section 2.2.4 (Costs)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Section 2.2.4 (Costs)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Section 2.2.2; Figure 2.1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Section 2.2.2 & 2.2.4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Section 2.2.4 & 2.2.5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2.1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Section 2.3.1; Table 2.3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Not applicable

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Section 2.3.2
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Captured by comparator strategies
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Section 2.4
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	No funding received
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

Checklist for Chapter 4

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The ISPOR CHEERS Task Force Report, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Chapter 4 Title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract to Chapter 4
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Section 4.1
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Section 4.2.3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Section 4.1 & 4.2.1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Section 4.2.3 & Appendix A1.1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Section 4.2.2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Section 4.2.3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Section 4.2.4 (Costs, Utility)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Section 4.2.4
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Section 4.2.4
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Section 4.2.4 (Utility)
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Section 4.2.4 (Costs)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Section 4.2.4 (Costs)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Section 4.2.3
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Section 4.2.4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Section 4.2.5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 4.1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Section 4.3.1; Table 4.2
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Section 4.3.2; Table 4.3
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Section 4.4
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	No funding received
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

Checklist for Chapter 5

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Chapter 5 Title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract to Chapter 5
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Section 5.1
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Section 5.2.1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Section 5.1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Section 5.2.3 & Appendix A1.1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Section 5.2.2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Section 5.2.3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Section 5.2.4 (Costs, Effectiveness)
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Section 5.2.4
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Section 5.2.4
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Section 5.2.4 (Costs)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Section 5.2.4 (Costs)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Section 5.2.3
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Section 5.2.4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Section 5.2.5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 5.1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Section 5.3.1; Table 5.2
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	Not applicable
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Section 5.3.2; Table 5.4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Inherent in risk stratification
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Section 5.4
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	No funding received
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.