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Chancen und Limitationen früher gesundheitsökonomischer Evaluation zur Unterstützung der Translation medizinischer Innovationen aus dem Bereich der regenerativen Medizin

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Abkürzungsverzeichnis

BIP	Bruttoinlandsprodukt
GBA	Gemeinsamer Bundesausschuss
GBP	Great Britain Pound
GÖE	Gesundheitsökonomische Evaluation
GKV	Gesetzliche Krankenversicherung
HM	Headroom Method
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IKER	Inkrementelle Kosten-Effektivitäts Relation
NHS	National Health System
NICE	National Institute for Health and Clinical Excellence
QALY	Quality Adjusted Life Year
SGB	Sozialgesetzbuch

Zusammenfassung

Die Erkenntnisse medizinischer Forschung haben maßgeblich dazu beigetragen die öffentliche Gesundheit in den Industrienationen im letzten Jahrhundert signifikant zu verbessern. Hierfür ist es gelungen, grundlegende Ergebnisse aus dem Forschungslabor in Anwendungen zur tatsächlichen Verbesserung der öffentlichen Gesundheit zu „übersetzen“. Ein Prozess, der unter dem Terminus „Translation“ in die wissenschaftliche Literatur eingegangen ist.

Die regenerative Medizin ist ein relativ neues medizinisches Forschungsfeld, welches untersucht, inwieweit die Heilung von Krankheiten durch die Wiederherstellung der Funktion von Zellen, Geweben oder Organen erreicht werden kann. Bisher haben sich nicht alle Erwartungen, die in regenerativmedizinische Ansätze gesetzt worden sind, erfüllt, da die Translation für viele Entdeckungen nicht erfolgreich abgeschlossen werden konnte. Ein Grund dafür wird in der mangelnden Berücksichtigung der Anforderungen nationaler Gesundheitssysteme hinsichtlich der Wirtschaftlichkeit neuer Technologien durch die Entdecker gesehen.

Auf Grund knapper Ressourcen im deutschen Gesundheitswesen gewinnen gesundheitsökonomische Analysen neuer medizinischer Technologien bei der Translation zunehmend an Bedeutung. Für Arzneimittel beispielsweise ist Evidenz über die Wirtschaftlichkeit, nach dem Nachweis der Qualität, Wirksamkeit und Sicherheit, die vierte regulatorische Hürde auf dem Weg zur Erstattung durch die Kostenträger. Die gesundheitsökonomische Evaluation hat sich dabei als das Mittel der Wahl zur Erfassung von Kosten und Nutzen etabliert, da sie einen systematischen Vergleich der ökonomischen und medizinischen Auswirkungen verschiedener Therapieoptionen erlaubt.

Zur erfolgreichen Verbreitung neuer Therapien im Gesundheitssystem wäre es für deren Entdecker nützlich, möglichst frühzeitig bei ihren Entscheidungen auf gesundheitsökonomische Daten zurückgreifen zu können. Sie erlauben eine erste Einschätzung der Erstattungswahrscheinlichkeit und somit des kommerziellen Potenzials. Außerdem können durch die Daten gewonnene Erkenntnisse noch kostengünstig bei der Produktentwicklung berücksichtigt werden. Klinische und ökonomische Daten stehen in frühen Phasen der Technologieentwicklung jedoch meist nicht in ausreichendem Umfang zur Verfügung. Ein wichtiges Werkzeug vergleichender gesundheitsökonomischer Evaluationen ist daher die entscheidungsanalytische Modellierung, welche es ermöglicht, ein komplexes System realitätsnah darzustellen und, auf Grundlage der besten, verfügbaren Evidenz, die Auswirkungen verschiedener Handlungsalternativen auf dieses System abzuschätzen.

Ziel der vorliegenden Arbeit ist es, die frühzeitige Nutzbarkeit gesundheitsökonomischer Modelle zur Unterstützung der Translation medizinischer Innovationen aus dem Gebiet der regenerativen Medizin empirisch zu erforschen. Hierfür werden Fallstudien aus zwei Indikationsgebieten hinzugezogen, für die jeweils ein entscheidungsanalytisches Kosten-Nutzwert-Modell programmiert wird. Im ersten Aufsatz werden die generelle Machbarkeit sowie Chancen und Limitationen der Modellierung im Kontext einer Innovation zur Behandlung von Knorpelschäden des Knies untersucht. Im zweiten Aufsatz werden diese Erkenntnisse auf ein Fallbeispiel aus dem Bereich der Behandlung von Komplikationen in Folge der Prostatektomie angewendet.

Eine frühe Modellierung erwies sich im Fall der ausgewählten Innovationen als machbar. Es konnten für beide Fallstudien auf Grundlage der Modelle Schlussfolgerungen für die weitere Produktentwicklung gezogen werden, beispielsweise durch die Identifikation von Patientengruppen, die in besonderem Maße von der Innovation profitieren. Den Limitationen der Modellierung aufgrund der Ergebnisunsicherheit des Modells im ersten Fallbeispiel, konnte im zweiten Fallbeispiel teilweise durch eine genauere Erfassung dieser Unsicherheit entgegengewirkt werden.

Summary

The findings of medical research have significantly contributed to improving public health in the last century in the developed world. This has been made possible by the successful translation of results from basic research into applications that generate an actual impact on public health outcomes. Quite suitable the term “translation” has been coined for this development process from bench to bedside.

Regenerative medicine is a relatively new field of medical research, which explores the possibility of curing diseases by restoring the original functioning of cells, tissues or organs. Up till today not all expectations that have been set in regenerative medicine could be realized because for many discoveries the translation has not been successfully completed. The lack of consideration for the requirements of national health care systems concerning the ratio of costs to benefits of new technologies has been identified as one of the reasons for this result.

Due to scarce resources in the German health care system economic considerations for the adoption of new medical technologies are becoming increasingly important during the translational process. Drugs for example have to provide favorable evidence about costs and benefits in order to be covered by sickness funds. Health economic evaluation has established as the method of choice for assessing costs and benefits of new technologies. It allows a systematic comparison of the economic and medical effects of various treatment options.

For the successful diffusion of new therapies in the health care system, it would be desirable for developers to have access to health economic data as early as possible in order to inform their decision making. On the basis of such data a first assessment can be made of the likelihood of a positive coverage decision and hence the commercials potential of the technology. Furthermore product modifications to improve cost-effectiveness can still be implemented at low costs in early phases of product development. Sufficient clinical and economic data are however frequently not available in the early stages of technology development. For this decision-analytic models are an important tool of comparative health economic evaluation. They represent complex systems as realistically as possible and estimate the effects of different decision alternatives on this system based on the best evidence available.

This thesis intends to investigate empirically the usability of decision-analytic health economic models to support the translation of medical innovations in the field of regenerative medicine. For this purpose decision-analytic cost-utility models are programmed for two case studies from different indications. The first article assesses the general feasibility as well as opportunities and limitations of early modeling in the context of an innovation for the treatment of cartilage defects of the knee. In the second

article, these findings are applied to a case study of an innovation that deals with the treatment of negative side-effects as a result of prostatectomy.

Early modeling proved to be feasible for both of the selected innovations. It was possible to draw conclusions for further product development for both case studies based on the models, for example by identifying groups of patients who particularly benefit from the innovation. The first case study revealed limited power of conclusions drawn due to the uncertainty of the results of the model. This was partially counteracted by a more accurate detection of this uncertainty in the second case study.

1. Allgemeine Einleitung

He that will not apply new remedies must expect new evils: for time is the greatest innovator.

Francis Bacon (1561-1626), engl. Staatsmann u. Philosoph

Innovationen, wie die Entdeckung neuer Wirkstoff-Familien zur Bekämpfung von bakteriellen Infektionen oder die Entwicklung neuer medizintechnischer und chirurgischer Verfahren, haben dazu beigetragen die Lebenserwartung und Lebensqualität im Verlauf des 20. Jahrhunderts beträchtlich steigen zu lassen [1]. Gleichzeitig entstanden in den Ländern der westlichen Welt neue medizinische Herausforderungen, beispielsweise durch den Anstieg von Herz-Kreislauf-Erkrankungen und Krebsneuerkrankungen [2]. Die medizinische Forschung begegnet diesen Entwicklungen durch die Identifikation von Wirkmechanismen und darauf basierenden therapeutischen Ansätzen. Ein vielversprechendes und innovatives Forschungsfeld ist der Bereich der regenerativen Medizin, die es zum Ziel hat, menschliche Zellen, Gewebe und Organe zu ersetzen oder zu regenerieren, um deren ursprüngliche Funktion wiederherzustellen [3].

Medizinische Entdeckungen können Patienten aber nur dann zu Gute kommen, wenn die Weiterentwicklung vom Labor in die reale Patientenversorgung erreicht wird. Ein Prozess, der im Rahmen der translationalen Medizin in zwei Abschnitte eingeteilt wird [4, 5]. In der ersten Phase gilt es, die Übersetzung von identifizierten Wirkmechanismen in die Anwendung am Menschen im Rahmen klinischer Studien zu erreichen. Damit sich diese Investitionen für den Hersteller rentieren und Patienten unabhängig von der individuellen Zahlungsfähigkeit von kostspieligen medizinischen Innovationen profitieren können, ist in der zweiten Phase die Aufnahme in den Leistungskatalog der gesetzlichen Krankenversicherungen bzw. des nationalen Gesundheitssystems wünschenswert, um eine Verbesserung der öffentlichen Gesundheit zu erreichen [6, 7].

Aufgrund begrenzter Ressourcen können jedoch nicht alle medizinischen Technologien[1] durch die Kostenträger finanziert werden [8, 9]. Die ökonomische Evaluation ist eine etablierte wissenschaftliche Methode zur Erfassung von Kosten und Nutzen von Handlungsalternativen und wird seit Langem zur Entscheidungsfindung bei der Frage von Allokation öffentlicher Mittel als Kriterium hinzugezogen [10]. Sie hat auch ihren Eingang in die Gesundheitspolitik gefunden und ist in vielen Gesundheitssystemen ein Kriterium für die Entscheidung über Kostenübernahme sowie Erstattungshöhe [11-14].

Da im Rahmen der ersten Phase der Translation oft bereits sehr hohe Kosten für Forschung und Entwicklung entstehen können, ist in der Literatur der Einsatz von gesundheitsökonomischen Methoden zu einem frühen Zeitpunkt, vor Beginn der klinischen Studien, diskutiert worden, um die Wahrscheinlichkeit einer erfolgreichen Kommerzialisierung zu erhöhen [15-17]. Die Notwendigkeit einer frühzeitigen Fokussierung auf die Phase Zwei der Translation ist explizit für den Bereich der regenerativen Medizin gefordert worden, in dem die mangelnde Berücksichtigung des Verhältnisses von Kosten und Nutzen zum Scheitern einer Vielzahl neuer Technologien beigetragen hat [18]. Aufgrund des Defizits publizierter empirischer Arbeiten, wird im Rahmen der vorliegenden Arbeit anhand von zwei Fallbeispielen untersucht, welchen Beitrag die gesundheitsökonomische Evaluation bereits während der präklinischen Entwicklung zur Unterstützung der Translation von Innovationen aus dem Bereich der regenerativen Medizin vom Labor in die Patientenversorgung leisten kann [11].

1.1 Erstattungsentscheidung als vierte Hürde des Marktzugangs

Verschiedene Faktoren, wie die gestiegene Lebenserwartung und der rasche technologische Fortschritt, haben die Gesundheitsausgaben in Industrieländern stark ansteigen lassen [19-21]. So wuchsen die Ausgaben für Gesundheit in Deutschland zwischen 1993 und 2008 mit einer konstanten durchschnittlichen Wachstumsrate von 2,2 Prozent, während die volkswirtschaftliche Produktivität, ausgedrückt als Bruttoinlandsprodukt (BIP) pro Kopf, im selben Zeitraum lediglich um 1,5 Prozent

[1] Technologie ist in diesem Kontext weit zu verstehen und impliziert Arzneimittel, Medizinprodukte, Heilmittel, Hilfsmittel sowie Operationen und Methoden

anstieg [21]. Da die dem Kostenträger zur Verfügung stehende Geldmenge begrenzt ist, ergibt sich das Entscheidungsproblem, welche medizinischen Innovationen in die Regelversorgung der gesetzliche Krankenversicherung (GKV) aufgenommen werden sollen [10]. In vielen entwickelten Gesundheitssystemen wurden aus diesem Grund Institutionen geschaffen, welche im Rahmen eines formalisierten Prozesses über die Erstattung neuer Gesundheitstechnologien entscheiden bzw. dem entsprechenden politischen Entscheidungsträger Empfehlungen aussprechen [22]. In der Literatur werden diese Einrichtungen auch als „Vierte Hürde" des Marktzugangs beschrieben [6, 23]. Diese Bezeichnung trägt dem Fakt Rechnung, dass die Erstattungsentscheidung für Arzneimittel erst nach dem gelungenen Nachweis der Qualität, Wirksamkeit und Sicherheit erfolgt. Für das erfolgreiche Überwinden der vierten Hürde wird üblicherweise gefordert, zusätzlich zum klinischen Nutzen auch die Kosteneffektivität einer neuen Technologie zu dokumentieren [24].

Das National Institute of Health and Clinical Excellence (NICE) des National Health Service (NHS) in England wird oft als Referenz für eine besonders weit entwickelte vierte Hürde genannt [25, 26]. Es bewertet seit 1999 regelmäßig das Kosten-Nutzen-Verhältnis neuer medizinischer Technologien mit Hilfe von gesundheitsökonomischen Evaluationen. Anhand des Ergebnisses empfiehlt es unter Hinzunahme weiterer Faktoren dem NHS die Leistungsaufnahme oder den Leistungsausschluss. Im Rahmen der Selbstverwaltung des deutschen Gesundheitssystems entscheidet der Gemeinsame Bundesausschuss (GBA) über die Aufnahme neuer Leistungen in den Leistungskatalog der gesetzlichen Krankenversicherungen. Die gesetzliche Grundlage für die Entscheidung wird hierbei durch das fünfte Buch des Sozialgesetzbuchs (SGB) vorgegeben und inkludiert die Forderung des Nachweises der Wirtschaftlichkeit der neuen Leistung (§ 12 SGB V). Die Bedeutung der vierten Hürde manifestierte sich in Deutschland 2004 mit der Gründung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG). Das IQWIG unterstützt die Entscheidung des GBAs durch die Erstellung wissenschaftlicher Studien, die den aktuellen Wissenstand hinsichtlich des Nutzens und Schadens neuer Technologien widergeben (§ 139a-c SGB V). Neben der evidenzbasierten Bewertung des Nutzens, kann das IQWIG seit 2007 außerdem durch den GBA beauftragt werden, das Kosten-Nutzen-Verhältnis für die Bewertung neuer Arzneimittel zu ermitteln (§ 35b SGB V). Die Konkretisierung der Umsetzung erfolgte

2009 mit der Veröffentlichung des Methodenpapiers „Allgemeine Methoden zur Bewertung des Verhältnisses von Kosten und Nutzen“, welches das adäquate Vorgehen für das Durchführen einer gesundheitsökonomischen Evaluation aus der Sicht des deutschen GKV-Systems darstellt [27]. Es ist davon auszugehen, dass die Kosten-Nutzen-Bewertung weiter an Bedeutung gewinnen wird und auch in anderen Versorgungsbereichen, wie beispielsweise Medizinprodukten angewendet wird.[2]

1.2 Gesundheitsökonomische Evaluation

Die gesundheitsökonomische Evaluation (GÖE) ist das Mittel der Wahl zum Vergleich medizinischer Interventionen hinsichtlich ihrer Kosten und ihres Nutzens [28]. Das Ergebnis dieser Wirtschaftlichkeitsuntersuchung hängt dabei auch von der Methodik ab, mit der Kosten und Nutzen erhoben werden sowie der Datengrundlage der Evaluation [29]. Eine wichtige Entscheidung ist deshalb die Wahl der Perspektive, aus der die Evaluation durchgeführt wird. Grundsätzlich kann eine Evaluation z.B. aus der Perspektive der Gesellschaft, der Sozialversicherung, einer einzelnen Krankenkasse oder auch eines Krankenhauses durchgeführt werden [28]. Während aus der Sicht eines Krankenhauses lediglich die dort anfallenden Kosten eine Rolle spielen und in die Evaluation einfließen, ist es das Ziel der gesellschaftlichen Perspektive alle bewerteten Ressourcenverbräuche zu erfassen, unabhängig davon, wer sie trägt [29]. Die gesellschaftliche Perspektive betrachtet dementsprechend auch indirekte Kosten, wie beispielsweise den Produktivitätsverlust durch krankheitsbedingten Arbeitsausfall. Die gesundheitsökonomischen Richtlinien für die Wahl der Perspektive sind international unterschiedlich. Es wird argumentiert, dass letztlich kein Entscheidungsträger eine gesellschaftliche Perspektive einnimmt, da diese jeweils Partikularinteressen vertreten [29]. Mit Hinblick auf die Erstattungsentscheidung ist es aus Sicht eines Innovators sinnvoll, die Perspektive der jeweiligen vierten Hürde als relevanten Entscheidungsträger für die Aufnahme neuer Leistungen in die Regelversorgung einzunehmen. Für den deutschen Versorgungskontext empfiehlt das IQWiG die

[2] Vgl.: http://www.strategieprozess-medizintechnik.de/studien (zuletzt abgerufen am 03.03.2015)

Perspektive der Versichertengesellschaft der GKV oder eine gesellschaftliche Perspektive einzunehmen [27].

Während es verschiedene Formen der gesundheitsökonomischen Evaluation gibt, haben sich die Kosten-Effektivitäts-Analyse und die Kosten-Nutzwert-Analyse als am häufigsten genutzte Typen etabliert [25]. Sie unterscheiden sich hinsichtlich der Einheiten mittels welcher der Nutzen erfasst wird [30]. Bei der Kosten-Effektivitäts-Analyse wird der Nutzen in klinischen Einheiten, wie gewonnene Lebensjahre oder vermiedene Komplikationen, gemessen [31]. Bei der Kosten-Nutzwert-Analyse hingegen wird das Ergebnis in qualitätsadjustierten Lebensjahren (QALY) ausgedrückt, wobei die zu erwarteten Lebensjahre mit einem Faktor gewichtet werden, der die Lebensqualität in diesem Zeitraum wiederspiegelt. Die Kosten-Nutzwert-Analyse erlaubt so auch die Vergleichbarkeit über unterschiedliche Indikationsgebiete hinweg.

Das Ergebnis der Kosten-Nutzen-Analyse wird üblicherweise als inkrementelles Kosten-Nutzen-Verhältnis (IKER) der neuen Technologie im Vergleich zum Behandlungsstandard ausgedrückt und dann mit Hinblick auf einen definierten Schwellenwert, der Zahlungsbereitschaft, bewertet [8]. In Deutschland gibt es keinen expliziten indikationsübergreifenden Schwellenwert. Stattdessen wird gegenwärtig über das vom IQWIG vorgeschlagene Effizienzgrenzenkonzept diskutiert, welches eine indikationsspezifische Zahlungsbereitschaft vorschlägt, die sich am IKER des gegenwärtigen Behandlungsstandards orientiert [32]. Das englische NICE hingegen erstattet regelmäßig Technologien mit einem IKER < 20,000 £ / QALY. Für Interventionen mit einem IKER zwischen 20,000 £ und 30,000 £ pro QALY gilt ein schwächerer Schwellenwert, bei dem in Abhängigkeit vom jeweiligen Entscheidungskontext verschiedene weitere Kriterien die Aufnahme oder Ablehnung begünstigen können [33, 34]. Für Interventionen mit einem IKER > GBP 30,000 müssen sehr starke Gründe vorliegen, damit die Erstattung nicht abgelehnt wird. Neben der (Un-)Sicherheit der Modellergebnisse oder dem Vorliegen einer lebensverlängernden Behandlung zum Lebensende ist der Grad der Innovation ein Kriterium für die Akzeptanz eines höheren Schwellenwerts.

1.3 Frühe gesundheitsökonomische Evaluation

Die Kosten für Forschung und Entwicklung medizinischer Innovationen können sehr hoch sein. Für den Bereich der weilweiten Arzneimittelentwicklung zum Beispiel werden Zahlen zwischen 92 $ Millionen und 884 $ Millionen berichtet [35].[3] Die exakte wissenschaftliche Erfassung der Kosten ist nicht trivial und die Frage nach den geeigneten Methoden und Daten wird in der Literatur kontrovers diskutiert [35]. In jedem Fall kann davon ausgegangen werden, dass ein großer Teil der Kosten während des ersten Schritts der Translation ab klinischen Studien der Phase I anfällt [36, 37]. Während die Ausfallrate aus technischen Gründen in jeder weiteren Phase abnimmt, werden Entwicklungsprojekte teilweise erst in der späten Phase III aus ökonomischen Gründen, z.B. wegen zu geringer Wirksamkeit für eine profitable Kommerzialisierung, abgebrochen [16]. Publizierte Forschungsergebnisse legen nahe, dass eine Verlagerung von 5% aller Projektabbrüche von der Phase III in Phase I die Kosten der Entwicklung um 7,1% reduzieren könnte [38]. Hinzu kommen diejenigen Projekte, welche im zweiten Schritt der Translation an der vierten Hürde scheitern und kommerziell nicht erfolgreich genug sind, damit sich die Kosten der Forschung und Entwicklung amortisieren.

Für eine effizientere Allokation privater und öffentlicher Investitionen wäre es deshalb wünschenswert, bereits während der Entwicklungsphase strategische Entscheidungen unter Hinzunahme ökonomischer Daten treffen zu können. Hierfür ist von verschiedenen Autoren der Einsatz gesundheitsökonomischer Evaluationen zu einem frühen Zeitpunkt vorgeschlagen worden [39-42]. Früh bezieht sich dabei auf die Tatsache, dass gesundheitsökonomische Evaluationen üblicherweise erst nach Erhalt der Marktzulassung für das Überwinden der vierten Hürde erstellt werden. Dementsprechend definieren Markiewicz et al. frühe Evaluationen als diejenigen, welche zwischen dem Zeitpunkt des Entstehens der Produktidee und klinischen Studien durchgeführt werden [43].

Hieraus ergeben sich besondere Herausforderungen an die GÖE, da üblicherweise zu diesem frühen Zeitpunkt noch keine belastbaren Daten hinsichtlich der Wirksamkeit

[3] Ohne Einbezug der Opportunitätskosten

oder gar langfristiger Auswirkungen vorliegen. Somit besteht große Unsicherheit über entscheidende Parameter des IKERs. In der Gesundheitsökonomie hat sich für derartige Situation der Einsatz entscheidungsanalytischer Modelle als „systematischer, expliziter und quantitativer Ansatz zur Entscheidungsfindung unter Unsicherheit“ etabliert [44]. Sie bieten die Möglichkeit, unter Hinzunahme der besten verfügbaren Evidenz, das Entscheidungsproblem unter Unsicherheit zu strukturieren und somit die Entscheidungsfindung zu unterstützen [30, 45]. Hierfür werden Daten aus verschiedenen Quellen identifiziert und nach den Kriterien der evidenzbasierten Medizin bewertet [30]. Die synthetisierten und aufbereiteten Daten werden in das Modell integriert, um den IKER über den für die Problemstellung angemessenen Zeitraum zu projizieren. Ein wichtiger Teil der Arbeit mit entscheidungsanalytischen Modellen liegt dann in der Analyse der Folgen der zu Grunde liegenden Unsicherheit auf die Modellergebnisse und deren Quantifizierung [46]. In einem deterministischen Modell sind die Modellparameter fix und die Unsicherheit kann im Rahmen von Sensitivitätsanalysen durch die gezielte Variation einzelner Parameter sichtbar gemacht werden. Bei stochastischen Modellen dagegen werden die Modellparameter als Häufigkeitsverteilungen in das Modell integriert und die Unsicherheit kann durch gleichzeitige, zufällige Ziehung aus den Verteilungen, z.B. mittels Monte Carlo Simulation erfasst werden. Häufig verwendete Typen entscheidungsanalytischer Modelle sind Entscheidungsbaummodelle und Markovmodelle. Während sich der erste Modelltyp vor allem für weniger komplexe Entscheidungssituationen eignet, lassen sich in einem Markovmodell eine Vielzahl von Gesundheitszuständen mit zeitabhängigen Wahrscheinlichkeiten modellieren [47]. Grundsätzlich ist der Einsatz beider Modelltypen im Kontext der frühen gesundheitsökonomischen Evaluation von Technologien aus dem Bereich der regenerativen Medizin denkbar.

1.4 Frühe gesundheitsökonomische Evaluation und regenerative Medizin

Die Entwicklung der regenerativen Medizin hat ihren Ursprung in der Mitte der 70er Jahre des letzten Jahrtausends und markiert mit dem Ziel menschliche Zellen, Gewebe und Organe zu ersetzen oder zu regenerieren einen Paradigmenwechsel in der

modernen Medizin [48]. Der regenerativen Medizin wird zugetraut als vierte Säule neben konventionellen Pharmazeutika (niedermolekulare Verbindungen), Biopharmazeutika (rekombinante Proteine) und Medizinprodukten neue Behandlungsmethoden hervorzubringen, mit denen Krankheitsbilder behandelt werden können, für die es momentan keine oder nur unzureichend effektive Therapien gibt [49, 50]. So haben die großen Pharmaunternehmen in den letzten Jahren verstärkt in innovative Unternehmen aus dem Bereich der zellbasierten Therapie investiert, die u.a. neue Ansätze zur Therapie von Volkskrankheiten wie Diabetes entwickeln [51].

Die großen Hoffnungen, die auf der regenerativen Medizin ruhen, spiegeln sich auch in durch Bundesmittel geförderten Forschungsprogrammen wie dem Projekt „Regenerative Medizin in der Region Neckar-Alb“ (REGiNA) wieder, im Rahmen dessen die vorliegende Forschungsarbeit erstellt wurde.[4] Dass die Gesundheitsökonomie als Teilprojekt in diesem Forschungscluster vertreten war, trägt dem Ruf verschiedener Autoren Rechnung, Entwicklungen aus dem Bereich der regenerativen Medizin frühzeitig hinsichtlich ihres kommerziellen Potenzials zu evaluieren [18, 52]. Die geforderte Fokussierung auf die zweite Phase der Translation ist ein Ergebnis der Erfahrungen aus der ersten Dekade des neuen Jahrtausends, in dem viele Innovationen aus dem Bereich der regenerativen Medizin gescheitert sind, weil es nicht gelang Produkte mit einem ausreichendem, messbaren Nutzen für Patienten zu für die Kostenträger akzeptablen Kosten in die Versorgung zu tragen [53, 54]. Eine frühzeitige Orientierung an den Anforderungen der Kostenträger während der Produktentwicklung ist im Bereich der regenerativen Medizin auch deshalb besonders wichtig, da die regulatorischen Anforderungen sich noch entwickeln und das rechtzeitige Wissen um eine Veränderung den optimalen Einsatz von Ressourcen erlauben. So kann das Risiko für ein kommerzielles Scheitern des Produkts reduziert werden [55, 56].

McAteer et al. waren die ersten, welche die Methoden der gesundheitsökonomischen Evaluation für die Einschätzung des kommerziellen Potenzials von Entwicklungen aus der regenerativen Medizin mit der sogenannten „Headroom Method“ (HM) angewendet haben [18]. Bei der HM wird der Kostenspielraum einer neuen Technologie auf der Grundlage von Annahmen über die zusätzliche Effektivität und der Zahlungsbereitschaft

[4] Vgl.: http://www.gesundheitsforschung-bmbf.de/de/2269.php#REGINA (zuletzt abgerufen am 12.04.2015)

eines Entscheidungsträgers hierfür getroffen. Wenn λ die Zahlungsbereitschaft für zusätzliche Effektivität repräsentiert (z.B. GBP 30,000/QALY), so lässt sich die HM-Bedingung über eine einfach Umstellung der IKER-Formel ableiten:

$$\lambda \geq \Delta \text{ Kosten} / \Delta \text{ QALY}$$

$$\Leftrightarrow$$

$$\lambda * \Delta \text{ QALY} \geq \Delta \text{ Kosten}$$

Aus der Formelumstellung wird deutlich, dass die HM nur eine grobe Einschätzung über den tatsächlichen Kostenspielraum geben kann, da lediglich die monetarisierten Gesundheitsgewinne als Obergrenze angenommen werden. Das Vorgehen unterstellt, dass keine Wechselwirkungen zwischen Gesundheitsgewinn und Kosten der Versorgung besteht. Der zusätzliche Nutzen resultiert nur aus dem Gesundheitsgewinn. Realiter ist es aber plausibel, dass sich eine Verbesserung des medizinischen Nutzens (z.B. schnellere Heilung) auch in einer Reduktion der Kosten (z.B. weniger Krankenhaustage) wiederspiegelt. Aus diesem Grund wäre es für eine genauere Quantifizierung des Mehrwerts einer neuen Technologie wünschenswert, auch die Auswirkungen einer Effektivitätssteigerung auf die Ressourcenverbräuche in die Berechnung zu inkludieren. Dies gilt in besonderem Maße für Innovationen aus der regenerativen Medizin, da sie die Wiederherstellung des Urzustands anstreben und somit ggf. nach einmaliger Behandlung keine Behandlungskosten mehr anfallen, wie es z.B. bei lebenslanger Behandlung von Knorpeldefekten der Fall ist.

1.5 Zielsetzung und Inhalt der Dissertation

Das Ziel dieser Dissertation ist es, einen Beitrag zur Forschung über die Nutzung früher gesundheitsökonomischer Evaluationen bei der Translation von Innovationen zu leisten und den Stand der wissenschaftlichen Literatur um eine empirische Arbeit zu ergänzen. In den Aufsätzen wird anhand von zwei Fallbeispielen der Frage nachgegangen, inwieweit der Einsatz früher gesundheitsökonomischer Evaluationen für Innovationen aus dem Bereich der regenerativen Medizin machbar ist und welche Chancen und Limitationen hinsichtlich der Unterstützung des Translationsprozesses hierdurch bestehen. In Anlehnung an die HM wird hierfür der Zusatznutzen von zwei Produkten

im Entwicklungsstadium auf der Grundlage von Annahmen über die zusätzliche Effektivität der Technologie bestimmt. Ausgangspunkt ist dabei die Wirtschaftlichkeit des gegenwärtigen Behandlungsstandards. Die Analyse wird um die bewerteten Ressourcenverbräuche erweitert und für ein Fallbeispiel als Entscheidungsbaummodell und das andere Fallbeispiel als Markovmodell programmiert.

Bei den Fallbeispielen handelt es sich um Innovationen aus dem Indikationsgebiet Knorpelschaden des Knies sowie erektile Dysfunktion/Inkontinenz als Folge der operativen Behandlung des Prostatakarzinoms. Isolierte Knorpelschäden des Knies treten bei jüngeren Menschen meist als Folge von Sportverletzungen auf und verursachen zunächst Schmerzen bei Belastung. Langfristig kann sich der Defekt zu einer generalisierten Arthrose entwickeln und den Einsatz einer Knieendoprothese erforderlich machen. Um dies zu verhindern, wurden Ansätze aus der regenerativen Medizin entwickelt, die es zum Ziel haben, den Knorpel zu regenerieren. Innovation 1 stellt eine Verbesserung dieser existenten Behandlungsoption durch ein neuartiges Verfahren zur Zellzucht dar.

Innovation 2 ist ein Gel, mit dem die Entwickler beabsichtigen, die natürliche Regeneration von Nerven nach deren Schädigung durch einen operativen Eingriff zu fördern. Im konkreten Fall wird die Regeneration der *nervi cavernosi* intendiert, die nach der operativen Entfernung der Prostata auf Grund eines Prostatakarzinoms (PCa) häufig geschädigt sind, was zu den Komplikationen erektile Dysfunktion und Harninkontinenz führt. Die Modellierung der Fallbeispiele erfolgt in unterschiedlichem Detaillierungsgrad, um den divergierenden Zielsetzungen der beiden Aufsätze gerecht zu werden.

Der Fokus des ersten Aufsatzes in Kapitel 2 liegt auf der grundsätzlichen Darstellung der Machbarkeit der angewendeten Methode im Kontext der regenerativen Medizin und den gewonnenen Erkenntnissen hinsichtlich der Nutzbarkeit des Modells für Entscheidungen während der Produktentwicklung. Außerdem sollte das Modell möglichst schnell als Entscheidungshilfe verfügbar sein. Dazu wurde ein deterministisches Entscheidungsbaummodell des Behandlungsstandards für Knorpelschäden des Knies in Microsoft Excel © programmiert und die neue Technologie als Szenario modelliert. Das Indikationsgebiet Knorpelschäden des Knies

eignet sich besonders gut als Fallbeispiel, weil die Effekte der neuen Therapie sich erst langfristig manifestieren, was für den Ansatz einer entscheidungsanalytischen Modellierung spricht. In diesem ersten Fallbeispiel werden die verschiedenen Aspekte der Nutzbarkeit früher Modelle, jenseits der Vorbereitung der Erstattungsentscheidung, deutlich. So kann beispielsweise auf der Grundlage von modellbasierten Kalkulationen wertbasierter Preise, den Fallzahlen und der Wettbewerbssituation eine Umsatzschätzung vorgenommen und somit das kommerzielle Potenzial eingeschätzt werden. Ferner generiert die Synthese der klinischen Evidenz ein Verständnis über Studienlage, was eine effiziente Planung zukünftiger klinischer Studien ermöglicht. Im vorliegenden Fall zeichnete sich die klinische Evidenz durch eine große Heterogenität hinsichtlich der Endpunkte, der Studiendesigns und betrachteten Zeiträume aus, was zu Unsicherheit der Modellergebnisse führt.

Das Ziel des zweiten Aufsatzes in Kapitel 3 ist es deswegen, neben der Erfassung der Wirtschaftlichkeit, eine möglichst genaue Quantifizierung der Unsicherheit durch eine stochastische Modellierung zu erreichen. Hierfür wurde ein vollständig probabilistisches Markovmodell mit der Modellierungssoftware TreeAge © programmiert. Für eine exakte Erfassung der Nutzendimension wurden nicht nur Krankheitsspezifische Nutzwerte verwendet, sondern zusätzlich auch der altersbedingten Veränderung der Lebensqualität Rechnung getragen. Die Wirtschaftlichkeitsuntersuchung hat bei diesem Fallbeispiel einen großen Stellenwert, da es mit der aktiven Überwachung des PCa eine Behandlungsalternative gibt, welche die Komplikationen der Operation vermeidet und somit die Innovation ggf. redundant macht. Die stochastische Analyse der Unsicherheit zeigt, dass aktive Überwachung im Standardszenario in 56% der Simulationen die überlegene Therapieoption ist. Dieses Ergebnis legt nahe, dass die individuelle Risikoaversion der Patienten ein maßgeblicher Faktor für die Wahl der optimalen Therapie darstellt.

In Kapitel 4 werden, aufbauend auf den Ergebnissen der Modellierung des zweiten Aufsatzes sowie den Erkenntnissen des ersten Aufsatzes, Konsequenzen hinsichtlich der Anforderungen an die Produktentwicklung gezogen, welche im Rahmen des Abschlussberichts des Forschungsprojekts berichtet werden. So wurden auf Grundlage von Annahmen über die Zahlungsbereitschaft des Kostenträgers Mindestanforderungen

an die zusätzliche Effektivität der neuen Technologie berechnet. Es zeigte sich, dass bei einer Zahlungsbereitschaft von € 100,000 / QALY eine Reduktion der Nebenwirkungen Inkontinenz und Erektile Dysfunktion von jeweils mindestens 20% notwendig wäre, um einen Preisaufschlag zu rechtfertigen. Eine wichtige Erkenntnis war die Identifikation einer Subgruppe der Prostatakrebspatienten, für welche die neue Technologie eher zu Kosteneinsparungen für das Gesundheitssystem führt, da in diesem Fall aktive Überwachung keine Therapieoption darstellt. In dieser Kohorte von Patienten mit lokal fortgeschrittenem Karzinom würde dem Modell gemäß bereits eine marginale Reduktion von Nebenwirkungen einen Preisaufschlag für die Innovation erlauben, ohne zusätzliche Kosten für das Gesundheitssystem zu verursachen. Dies gilt auch für Patienten, bei denen aktive Überwachung zwar eine Therapieoption ist, die aber aufgrund ihrer Risikoneigung und der bestehenden Unsicherheit eher operiert werden sollten. Bei der Weiterentwicklung scheint folglich eine Fokussierung, z.B. der klinischen Studiendesigns, auf diese Patientengruppen ratsam.

Die Forschungsergebnisse haben gezeigt, dass eine frühe Modellierung die Translation von Innovationen aus dem Bereich der regenerativen Medizin durch eine Quantifizierung der kommerziellen Erfolgschancen und die Identifikation vielversprechender Entwicklungsrichtungen unterstützen kann. Limitationen bestehen auf Grund der Unsicherheit der Modellergebnisse und der Entwicklung der regulatorischen Rahmenbedingungen. Während der Modellunsicherheit zum Teil durch eine stochastische Modellierung begegnet werden kann, ist gegenwärtig noch unklar welche Rolle die gesundheitsökonomische Evaluation bei der Erstattungs- und Vergütungsentscheidung im Bereich der regenerativen Medizin in Deutschland spielen wird.

Der Promovend (FK) war maßgeblich an der Konzeption der in diese kumulative Dissertation eingehenden Publikationen beteiligt und hat die methodische Umsetzung weitgehend selbst festgelegt. Fachliche Unterstützung für statistische und medizinische Detailfragen wurde von den genannten Ko-Autoren geleistet. Alle Artikel wurden in Fachzeitschriften und mit Erstautorenschaft des Promovenden veröffentlicht.

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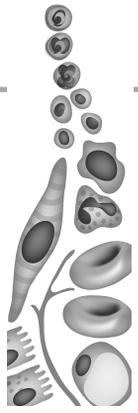
2. Early Evaluation and value-based pricing of regenerative medicine technologies



Early evaluation and value-based pricing of regenerative medicine technologies

Since the first pioneering scientists explored the potential of using human cells for therapeutic purposes the branch of regenerative medicine has evolved to become a mature industry. The focus has switched from 'what can be done' to 'what can be commercialized'. Timely health economic evaluation supports successful marketing by establishing the value of a product from a healthcare system perspective. This article reports results from a research project on early health economic evaluation in collaboration with developers, clinicians and manufacturers. We present an approach to determine an early value-based price for a new treatment of cartilage defects of the knee from the area of regenerative medicine. Examples of using evaluation results for the purpose of business planning, market entry, preparing the coverage decision and managed entry are discussed.

KEYWORDS: business planning ■ commercialization ■ early evaluation ■ innovation management ■ market access ■ pricing ■ reimbursement

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The need to establish value

The successful translation of regenerative medicine research into commercially viable products has been identified as key objective of today's regenerative medicine industry [1]. Among the many factors determining commercial success of a new therapy, such as evidence of a favorable efficacy and safety profile, and available marketing budgets, the coverage decision is an important driver as it allows access to a broad market [2]. This is because – unlike in the self-payer market – individual inability to pay does not negatively affect demand for covered technologies. Hence, a positive reimbursement decision increases the technology's potential sales, as regenerative medicine therapies, such as some cell-based therapies, can be too expensive for being paid out of pocket [3]. Also, complex manufacturing protocols are thought to cause high manufacturing costs [2]. Moreover, the lack of established regulatory frameworks may cause additional expenditures during the development phase through the repeated need of producing evidence [4]. Consequently, coverage will be particularly desirable for regenerative medicine technologies. In the past, it was sufficient for manufacturers of health technologies to gain market authorization by demonstrating a product's quality, safety and efficacy. Subsequently, they would be included into the catalog of services of most national health services or statutory health insurances [5]. Meanwhile, rapid technological advances and aging societies have caused healthcare expenditures to grow faster than economic productivity in many high-income countries (Figure 1). Consequently, healthcare payers have become more conscious about costs. Discount agreements for high-volume drugs and profit and price controls on manufacturers are means to reduce the financial burden to healthcare systems, as expenditures for drugs alone account for approximately 16% of total health expenditures on Organisation for Economic Co-operation and Development average [101]. Not surprisingly, commercial reasons are now a major cause of attrition during development [6]. Additionally, there is a recent trend to limit funding to the degree that technologies deliver value for money [7]. Under such a policy, the price tag that manufacturers can put on their products and still gain coverage is bound to the relationship between health benefit created and the costs of care. A value-based approach may benefit regenerative medicine technologies that may incur high costs but also high benefit by restoring health rather than offering symptomatic or even palliative treatment [8]. Mason and Dunnhill showed the potential value gains regenerative medicine could generate for the treatment of chronic diseases in general [3]. Using the example of cartilage defects of the knee we provide a detailed value analysis for a single treatment using the methods of health economic evaluation (HEE). HEE is an established tool used to inform decision-makers about the value proposition of medical innovations and is practiced in numerous countries.

Regenerative Medicine

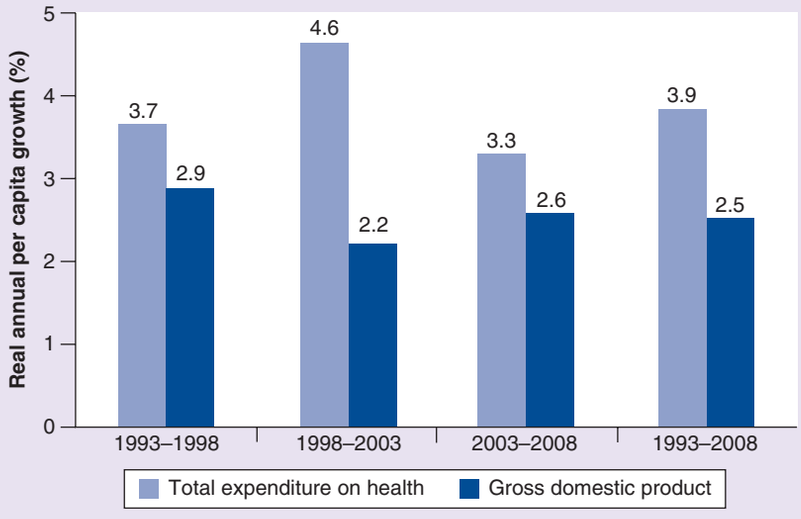

Figure 1. Gross domestic product growth of 36 Organisation for Economic Co-operation and Development countries in comparison with growth in healthcare expenditures.
Data taken from [101].

Thought up and first applied systematically in the Australian and Canadian public health systems, nowadays the UK is probably the best known for most rigorously integrating economic evaluations into its coverage decisions [9]. As the coverage decision takes place after the assessment of quality, safety and efficacy, these institutions have been termed the fourth hurdle of market access [5]. From a company perspective, it would be desirable to be able to assess before or early in the development phase, that is, Phase 0–II clinical trials, whether and at what price a new technology will be likely to meet cost–effectiveness requirements [10,11]. A transparent mechanism that links additional value to price enables an enterprise to estimate different pricing scenarios at an early stage [12]. Since capital requirements increase with each phase, such considerations may be undertaken as soon as indicators about effectiveness are available [2]. Taking account of further factors such as estimates of market size, this information can be used to prioritize resource allocation between competing internal research and development projects, or to inform the go/no go decision [13–15].

Value-based pricing in healthcare

The notion of value-based pricing (VBP) is to set a price based on the perceived benefit to customers rather than benchmarks such as production costs or competitor prices alone. The value-based price (V) can be expressed as [16]: $V = R \pm D$. The differential value (D) stands for the monetized additional value that the product generates and represents the price premium that may be charged on top of the reference price of the best alternative (R). Consequently, under a VBP approach, identifying and quantifying differential value are essential steps. In the context of healthcare, one main driver of value is the additional health benefit that a new product generates compared with standard treatment. However, a mere analysis of benefits is not sufficient to capture value: differential value may be negative if the costs associated with the increased therapeutic benefit exceed the payers' WTP. Also, a new technology may not improve outcomes but may deliver the same health outcomes at lower costs. Differential value can thus be determined within the methodological framework of HEE, which routinely addresses the question of how much more an additional unit of health outcome costs compared with standard treatment [17]. Depending on the data source, different study types of HEE can be distinguished (Table 1). Decision-analytic modeling is most suited to the assessment of cost–effectiveness in the development phase, as usually only limited data regarding the new technology are available at this early stage. A practice-oriented approach to simple early-stage modeling consists of four main steps: developing a model structure; determination of health benefits; identification, quantification and valuing of resource usage; and programming the model.

Table 1. Different types of health economic evaluation studies.

Data source	Advantage	Disadvantage
Decision-analytic models (e.g., literature and assumptions)	Easily adaptable to decision problem, early availability	Uncertainty of results
Health economic data collected alongside clinical trials	High internal validity of clinical studies	Results are potentially not transferable to the reality of service provision
Retrospective analysis of observational data from health service provision	Takes into account the reality of service provision	Prone to different biases (e.g., selection bias)

Box 1. Model structure for the treatment of cartilage defects of the knee.

An exploratory search in the relevant databases yielded several published models for cartilage defects of the knee (SUPPLEMENTARY TABLE 5). For this case study of early modeling, the model is based on the most recently published model by Gerlier *et al.* [29]. Isolated cartilage lesions are a challenging indication as they have no capacity for spontaneous healing. Crucial clinical implications of the treatment may be distinguished into short-term and long-term events. In the short term, treatment of the defect can lead to an improvement in symptoms or not (success or failure). Furthermore, complications might arise that require reoperation. In the long term, degenerative moderate osteoarthritis may develop, which can be treated with conservative measures. Severe forms of the disease result in the need for joint replacement. Information about the treatment path can be represented graphically by a structure as displayed in FIGURE 2; see TABLE 2 for treatment options. After deciding on a treatment option, the course of cartilage cure is thus determined by treatment-specific probabilities for health events

Developing a model structure

In order to capture as many value-relevant aspects as possible in the model, it is essential to thoroughly understand the course of the disease and translate it into a structure that contains all the central events. For known conditions, HEEs are frequently already available in the literature upon which further work can build (BOX 1, FIGURE 2 & TABLE 2).

Alternatively, the treatment path can be constructed on the grounds of treatment guidelines by medical societies and interviews with clinicians and other experts. For the value comparison of the innovation with existing therapies,

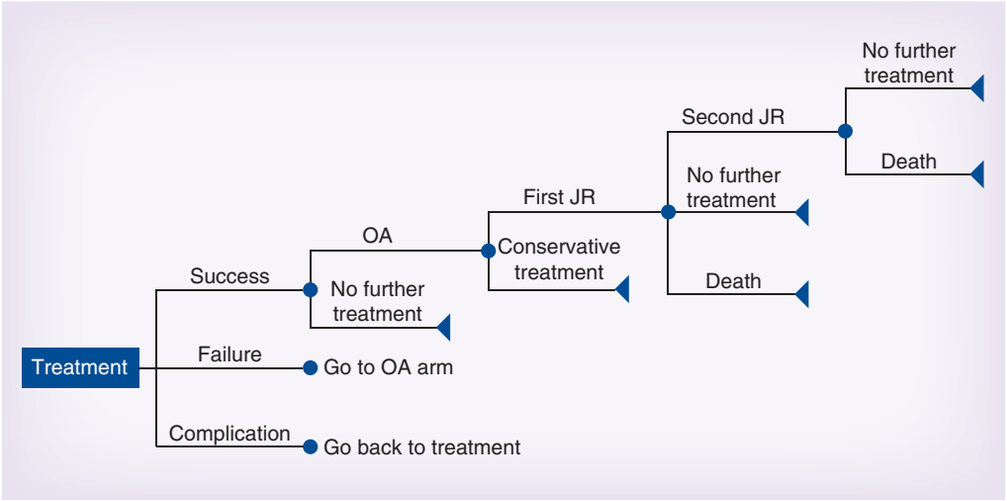

Figure 2. Treatment path of cartilage defects. The box represents a point of active decision (in this case for one treatment option, see TABLE 2); circles indicate that the future path is driven by chance; triangles represent a final state.
JR: Joint replacement; OA: Osteoarthritis.

Table 2. Treatment options for cartilage defects.

Method	Description
Microfracture	Penetration of subchondral bone layer permits influx of mesenchymal stem cells and other cells with regenerative capabilities, subsequently forming a repair tissue in the defect area
Mosaicplasty	Intact cartilage plugs are taken from a less-weight-bearing zone and transplanted into the defect area
Autologous chondrocyte implantation	A cartilage sample is extracted and the isolated chondrocytes are cultivated in a laboratory. During a second operation, the cells are reimplanted using a membrane, such as a collagen matrix, to cover the cell suspension. An older (first-generation) method used a periostal flat as a cover
Matrix-associated autologous chondrocyte implantation	In the laboratory, cultivated chondrocytes are seeded into a matrix scaffold for attachment prior to implantation

Box 2. Health benefits arising from treatment of cartilage defects.

The central health effects of cartilage defects arise from decreased health-related quality of life resulting from low functionality of the knee. A key surrogate parameter in the cure of cartilage defects is the kind of cartilage formed: hyaline-like cartilage leads to permanent treatment success, whereas fibrocartilage harbors the risk of treatment failure and long-term problems [30]. A stable linear correlation between functioning of the knee and utility score has been shown by Gerlier *et al.* [29]. Hence, the capacity of a treatment method to produce a more hyaline-like cartilage (Table 3) determines the probability of spending a lifetime in a health state with low, medium or high functionality of the knee (Table 4)

the same principles of evidence-based medicine apply as for the determination of clinical effectiveness [18]. Therefore, high-quality clinical studies on key model parameters are desirable. Randomized clinical trials or meta-analyses may be identified through systematic literature searches of respective databases (Supplementary Tables 1 & 2; see online at www.futuremedicine.com/doi/suppl/10.2217/rme.13.69).

Determination of health benefits

The relevant health outcomes are ideally measured in terms of patient-relevant end points and may differ according to the national context of the decision problem. For example, a national health authority may pay particular attention to medical end points such as life years gained. In this case, the mortality associated with different treatment options is an adequate measure of effects. This type of HEE using natural units of health outcomes is known as cost–effectiveness analysis. Health may also be considered as a multidimensional construct in which physical, mental and social capabilities interact with each other and affect perceived health-related quality of life. Under such a premise, a subgroup, cost–utility analysis, embodies a more suitable measure of cost–effectiveness. Parameters influencing quality of life can be surveyed and translated into a health-related quality of life index. These are captured in standard instruments for measuring health-related quality of life such as the EQ-5D questionnaire, which captures dimensions such as 'mobility' and 'pain or discomfort' as well as emotional dimensions such as 'anxiety' [19]. Weighting the time spent in alternative health states using such an index yields quality-adjusted life years (QALYs), which is a frequently used outcome measure in HEE and a required standard for evaluations submitted to NICE in the UK. High-quality evidence on health outcomes – especially on long-term outcomes – is often not available at an early point of time. In this case assumptions need to be made on the basis of surrogate parameters in decision analytical models (Box 2, Table 3 & Table 4). However, these surrogate parameters may not necessarily represent an improvement in health outcomes considered acceptable by fourth-hurdle agencies. One way to address such uncertainty is the formulation of managed entry agreements with third-party payers such as coverage with evidence development schemes [20].

In order to translate health outcomes into a monetary value a willingness-to-pay (WTP) threshold needs to be applied. The definition of such a threshold may differ depending on the value judgments of a society. For example, from the perspective of a health provider with a fixed budget for maximizing health, it can be argued that the threshold ideally reflects the opportunity costs of funding that technology,

Table 3. Effectiveness of standard treatments.

Standard treatments	Tissues (%)		Treatment result (%)		Reoperation (%)	Ref.
	Hyaline-like cartilage	*Fibrocartilage*	*Treatment success*	*Treatment failure*		
MF	14.29	85.71	75.00	25.00	2.50	[32,33]
MP	0.00	100.00	69.05	30.95	10.00	[34,35]
ACI-P	22.22	77.78	77.50	22.50	5.00	[32,33]
ACI-C	28.57	71.43	59.09	40.91	9.09	[36]
M-ACI	27.27	72.73	72.34	27.66	10.64	[36]

ACI-C: Collagen matrix cover autologous chondrocyte implantation; ACI-P: Periostal flap cover autologous chondrocyte implantation; M-ACI: Matrix-associated autologous chondrocyte implantation; MF: Microfracture; MP: Mosaicplasty.

that is, the price of a health gain of alternative technologies forgone. This is the value perspective favored by NICE, which applies the estimated productivity of other National Health Service activities as a WTP threshold [17]. In Germany, alternative approaches to determining the value of innovative products are presently being explored. Rather than stating a single threshold per unit of health outcome, the current suggestion aims to determine indication-specific WTP thresholds that take into account the explicit context of each disease. Under this approach – labeled the efficiency frontier concept – the cost–effectiveness of the standard of care serves as measure of WTP. However, this approach faces substantial criticism among the health economics community and, at the moment, it is still unclear how it will be translated into practice.

Identification, quantification & valuing of resource usage

Analyzing a technology's costs involves the three steps of: identifying all relevant resource consumptions associated with the use of a technology; measuring the amount of resources consumed in physical units; and valuing the resources appropriately. Costs considered generally include the immediate costs of treatment as well as downstream costs of disease management across all areas of health provision. For example, the assessment of resource usage for joint replacement requires taking into account the costs accumulating for rehabilitation, follow-up treatment, potential replacement surgery and medication. Hence, potential savings by not having to treat owing to the application of a regenerative technology are included into the calculation. A technology's costs can differ substantially depending on which perspective is chosen (e.g., healthcare provider or health insurance provider). The broadest perspective of costs is the society perspective, which accounts for all costs including productivity losses (Table 5, Box 3, Table 6 & Table 7) [21].

Table 4. Utility weights in different health states.

Health state	Utility score
Low functionality	0.690
Medium functionality	0.760
High functionality	0.835

Data taken from [31].

International guidelines for HEE differ on the perspective to be taken: while all strongly recommend the inclusion of direct medical costs, only some ask for a societal perspective, which is theoretically favored from a scientific point of view [22]. For countries operating diagnosis-related group systems (e.g., the USA, Germany and the UK), it is often useful to investigate codes of indications and applicable procedures. International classification systems such as the WHO International Classification of Diseases and International Classification of Procedures in Medicine are frequently adapted to country-specific needs, resulting in national systems such as International Statistical Classification of Diseases and Related Health Problems (ICD) ICD-10-GM and Operationen und Prozedurenschlüssel (OPS; equivalent to the International Classification of Procedures in Medicine) in Germany [23]. National grouping tools and compensation catalogs permit the pricing of in-patient measures on the basis of indication, procedure code combinations and patient characteristics. Other resources can be valued in accordance with market prices and national price lists for out-patient treatments.

Table 5. Costs and operationalization depending on perspective of assessment.

Perspective	Sectors affected	Parameter	Operationalization
Healthcare payer	Health sector	Direct medical costs (covered)	Surgery, hospitalization, out-patient follow-up care, opium plasters, walking aids, physiotherapy, rehabilitation
Individual	Health sector, patient/ family, other sectors	Direct medical costs (out of pocket), direct nonmedical costs (not covered)	Copayments for opium plasters and other health services not covered, and chauffeur services, household help, waiting time
Society	Productivity of all sectors	Indirect costs (in addition to all direct medical costs, nonmedical costs, costs to other social services)	Loss of production due to inability to earn an income/death

Box 3. Costs of care for the treatment of cartilage defects of the knee.

For the present case study the perspective of the German statutory health insurance was taken. Hence, all direct medical costs incurred by the healthcare payer, as well as the individual patient, were considered. This includes costs for in-patient treatments, out-patient treatments, pharmaceuticals, and aids and remedies. Resource usage was identified and quantified by national treatment guidelines and interviews with general and specialist practitioners. For an overview of relevant resource usage please refer to Tables 6 & 7

Programming the model

Once the perspective of the analysis is established and the relevant data have been gathered, a model can be programmed in standard desktop software such as Microsoft® Excel. A simple deterministic health economic model aggregates all discounted costs and health effects accumulated through the arms of the decision tree (Box 4 & Table 8).

The early model catches the value

The results of the HEE can be depicted in an efficiency plot (Figure 3). Microfracture has been identified as the reference treatment. The current care provision includes two methods that are dominated or extensively dominated. The innovation under evaluation is a new method of cell cultivation, which is necessary for matrix-associated autologous chondrocyte implantation (M-ACI) treatment. The process of cell cultivation is crucial for the results as it determines the amount of hyaline-like cartilage and hence the accumulated costs and QALYs generated. Because no reliable data are available at such an early stage, estimates of accumulated costs and QALYs are based on effectiveness scenarios of the innovation with regard to its capability of generating hyaline cartilage. Differential value can then be projected by using model results to calculate D = WTP * ΔEffects + ΔCosts. As

Table 6. Costs of surgical treatments.

Item	Code	Price/unit (€)	Quantity (p.a.) if applicable	Value (€)
Short term				
ACI-P/ACI-C, in-patient	DRG I108F I108D	4748 6624	0.8 0.2	5123
M-ACI, in-patient	DRG I108F I108D ZE† 126	7337 9213 2589	0.8 0.2	7712
Arthroscopy‡, in-patient	DRG I24Z	1675	0.1	167
Arthroscopy‡, out-patient	GOP 31142, 31503, 31614, 31615 and 31822	424	0.9	382
MF/MP, in-patient	DRG I18 A I18 B	1897 2460	0.72 0.18	1808
MF/MP, out-patient	GOP 31143, 31504, 31616, 31617 and 31823	587	0.1	59
Long term				
First JR	DRG I44 A I44B	7196 8983	0.8 0.2	7554
Second JR	DRG I43 A I43 B	9481 13,204	0.8 0.2	10,226
Revision JR	DRG I44 A I44B	7196 8983	0.8 0.2	7554

†Additional reimbursment for cell cultivation.
‡Necessary for all autologous chondrocyte implantation procedures in order to extract cells for cultivation.
ACI-C: Collagen matrix cover autologous chondrocyte implantation; ACI-P: Periostal flap cover autologous chondrocyte implantation; DRG: Diagnosis-related group; GOP: Fee schedule position ('Gebührenordnungsposition'); JR: Joint replacement; M-ACI: Matrix-associated autologous chondrocyte implantation; MF: Microfracture; MP: Mosaicplasty; p.a.: Per annum; ZE: Additional reimbursement ('Zusatzentgelt').

Table 7. Costs of nonsurgical treatments.

Item	Code	Price/unit (€)	Quantity (p.a.) if applicable	Value (€)
Pre-OA				
GP visit	GOP 03111	31	2	62
Specialist visit	GOP 18211, 18310	40	1	40
Imaging (MRT)	GOP 34450	120	1	120
Physiotherapy	EX2	25	18	450
Opium plaster		36	10	360
Paracetamol (acetaminophen) + codeine		15	10	150
With OA				
OA treatment	Direct medical costs (GP/specialist, hospitalization, medication)			1148

EX2: Catalog of remedies and aids for injuries and illnesses of the extremities; GOP: Fee schedule position ('Gebührenordnungsposition'); MRT: Magnetic resonance tomography: p.a.: Per annum; OA: Osteoarthritis.

the ideal value proposition from a payer's point of view is more benefits at lower or no more costs, a first analysis uses a WTP benchmark of WTP = 0€/QALY, that is, determining a price premium at which the innovation would be cost saving. For example, if the new method produced 20% additional hyaline-like cartilage compared with traditional M-ACI it could be charged at a price premium of €786 and still reduce overall costs (Figure 4). Further analysis may elicit the value proposition from the perspective of a healthcare system with a defined WTP threshold for an additional unit of health outcome (Table 9). As the German WTP concept has not been established as a standard method we additionally applied the threshold of £30,000 (~€50,000) used by NICE to value health benefits. Value-based prices of the new technology based on the WTP thresholds of the UK and Germany are displayed in Figure 5. Value-based prices considered cost-effective by Institute for Quality and Efficiency in Health Care (IQWiG) and NICE depend on the additional effectiveness of the innovation. Evidence from decision-analytic modeling hence allows a translational change in perspective from the scope of the laboratory to the viewpoint of healthcare decision-makers as assumptions about effectiveness are translated into potential value added. Once a model structure has been

Box 4. Evaluation of costs and benefits of different treatments.

Being successfully treated with microfracture implies a 14.29% chance of having generated hyaline cartilage 2 years after treatment. Assuming a constant development from low to high functionality and yearly calculation cycles the health effects are calculated as duration (years) × functionality utility score (see Table 4) × probability. Therefore, in the first year: 1 × 0.760 (medium functionality utility score) × 0.1429 = 0.1086 quality-adjusted life years (QALYs); in the second year: 1 × 0.835 (high functionality utility score) × 0.1429 = 0.1193 QALYs in year 2. Discounting allows to determine the present value (PV) of future cash flows (CFs) applying a discount factor, r, for each time period, t:

$$PV = \frac{CF}{(1+r)^{\tau}}$$

Discounting with 3% yields the following QALYs for the first 2 years of this arm of the decision tree:

$$\frac{0.1064}{(1+0.03)^{1}} + \frac{0.1176}{(1+0.03)^{2}} = 0.22$$

Resource usage in the same time period includes costs of surgery, GP visits, and physiotherapy and pain medication, and add up to €1329 in the same manner. Conducting this calculation for all arms over the complete time horizon results in the overall QALYs and costs generated for each treatment method as displayed in Table 8 (for a detailed calculation please refer to Supplementary File)

Table 8. Results of health economic evaluation.

Dimension	Treatment				
	MF	*MP*	*ACI-P*	*ACI-C*	*M-ACI*
Costs (€)	13,445	17,774	19,082	18,713	21,204
ΔCosts (€)	NA	4329	5638	5269	7759
QALYs	19.66	19.47	19.76	19.79	19.8
ΔQALYs	NA	-0.19	0.1	0.13	0.14

ACI-C: Collagen matrix cover autologous chondrocyte implantation; ACI-P: Periostal flap cover autologous chondrocyte implantation; M-ACI: Matrix-associated autologous chondrocyte implantation; MF: Microfracture; MP: Mosaicplasty; NA: Not applicable; QALY: Quality-adjusted life year.

established, a variety of analyses can be conducted that help in understanding the potential value proposition any regenerative medicine technology. The results of HEE can thereby be used differently at different stages of product development.

Business planning

Combining VBP results with internal limitations such as the costs structure yields a bandwidth of viable prices from a company's perspective [16]. Furthermore, the research carried out in the execution of a HEE produces many spillovers that are part of basic business planning (Table 10). Knowledge of disease codes and compensation schemes, for example, allows an estimation of historical and current market size as national health statistics are frequently organized according to this metric. Differentiation by procedure codes also enables the innovator to get an idea about the market structure and market shares of competing treatments. In the case at hand for example, official statistics on hospital data indicate approximately 1400 M-ACI procedures per year for Germany (Supplementary Table 3). In combination with the results of the value-based price analysis, revenue projections for the innovation under different scenarios can be obtained. Business planning based on such methodologically soundly derived numbers may facilitate the acquisition of external financing from private and public funds. As collaborations with established companies may often be desirable and these companies frequently use HEE for the assessment of projects, the model provides a basis for negotiations [3,10].

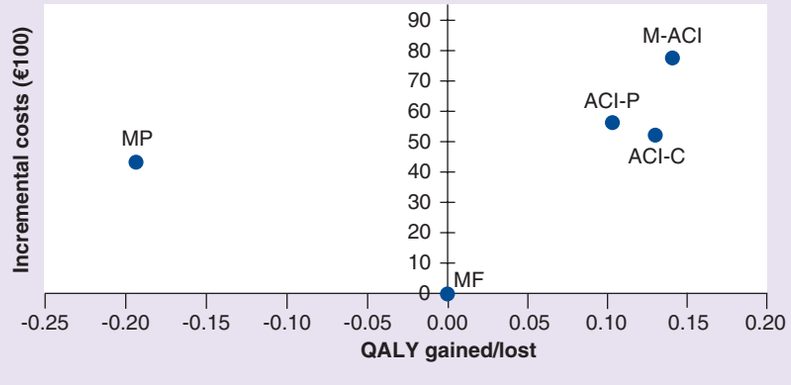

Figure 3. Results of the health economic evaluation.
ACI-C: Collagen matrix cover autologous chondrocyte implantation; ACI-P: Periostal flap cover autologous chondrocyte implantation; M-ACI: Matrix-associated autologous chondrocyte implantation; MF: Microfracture; MP: Mosaicplasty; QALY: Quality-adjusted life year.

Positioning for market entry

Running the model with effectiveness data from patient subgroups (e.g., age or sex) could reveal that the differential value for one cohort is significantly higher than for the average patient. Such types of information are particularly valuable for manufacturers with a restricted production capacity – as is usually the case for young and highly innovative enterprises from the area of regenerative medicine – in order to position the product in a profit-maximizing manner. Also, it allows entering the healthcare market at a segment where the chances of success are higher. As a consequence, the focus of development and the final positioning of the product may be framed around this insight.

Preparation of national coverage decision

The classical use of HEE is national coverage decisions for new pharmaceuticals. In some countries – namely Sweden, Australia and Canada – evidence of cost–effectiveness is already used to determine a reimbursable price that is acceptable for fourth hurdles prior to product launch [13]. Other countries – such as the UK – currently debate about the introduction of such a mechanism, which has become known as *ex ante* VBP [17]. Early modeling can help manufacturers to prepare for these decisions, particularly if novel regenerative technologies fall under mechanisms for drug reimbursement. The early model provides a template where evidence from clinical trials conducted later in development can be integrated as soon as it is available. Early synthesis of evidence-based data also helps to identify relevant end points and potential difficulties in demonstrating cost–effectiveness. In the case at hand, for example, a closer look at existing randomized clinical trials (Supplementary Table 1) exposed great heterogeneity in patient populations, measures

of end points, and duration of trials. Addressing these issues at an early point in collaboration with fourth-hurdle agencies allows optimizing the design of upcoming clinical trials and increasing the chances of commercial success [24]. Due to the lack of an established regulatory framework such dialog is likely to prove particularly fertile for regenerative medicine technologies as it may help to reduce uncertainty about regulatory pathways and upcoming costs [4].

Managed entry agreements

Changing the perspective of assessment can provide further information on value potentials so far unconsidered. The intervention's cost–effectiveness from the perspective of a health service provider such as a hospital may differ substantially from that of national health services. If an innovation can incur cost-savings at a healthcare provider level, they are a good starting point for contract negotiations with healthcare providers or regional payers, even if no new reimbursement rate for the new intervention is created at a national level. Besides negotiating fixed prices, contract negotiations can also be used to mitigate the payer's or provider's uncertainty about the manufacturer's value proposition: managed entry agreements allow manufacturers to turn the value proposition established by the early model into a value guarantee, as payment can be bound to measures of the value added [25]. This is particularly relevant in countries that provide full coverage at the time of product launch and subsequently review reimbursement rates by the means of HEE based on evidence from clinical trials or routine data (i.e., *ex post* VBP) [26]. The modeling exercise helps to understand the care pathways and associated reimbursement codes that can serve as a basis for the evidence used by such agreements.

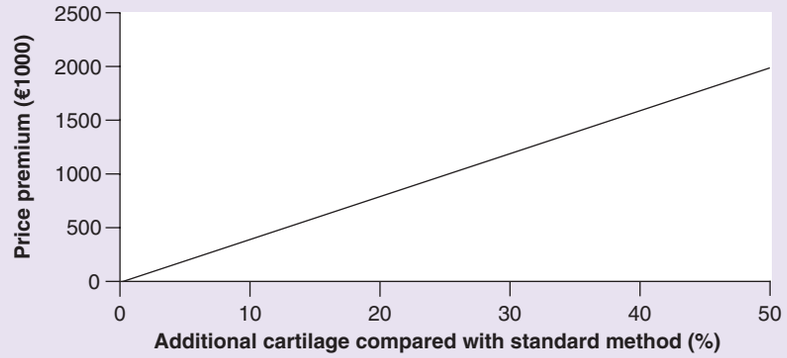

Figure 4. Price premium at which innovation is cost saving depending on the additional effectiveness of the innovation.

Crystal balls are breakable

Results of early VBP analysis must be seen as preliminary as they are still tainted with uncertainty (for limitations and major assumptions of the HEE see Supplementary Note). In our case study for example, the body of evidence on effectiveness parameters for treatments methods is of mediocre quality [27]. Furthermore, there are no long-term studies available investigating the effect of treatments on osteoarthritis. This parameter uncertainty is characteristic for new technologies and should be scrutinized further via deterministic or probabilistic sensitivity analysis (Supplementary Figure 1 & Supplementary Table 4) [9]. There is the tendency of innovators to assume the most optimistic effectiveness scenarios. VBP of the innovation should be presented assuming a wide range of scenarios (Figures 4 & 5) including the case of no effectiveness improvement. This way the influence of uncertainty of effectiveness on VBP is made transparent. Structural uncertainty should be minimized by validating the model structure with physicians and scientists and can be addressed by exploring the impact of different structural assumptions on the results.

Table 9. Value perspectives of the UK and Germany.

Country (institution)	Preferred outcome measure	Costs considered	Willingness to pay	Ref.
Germany (IQWiG)	Mortality, morbidity, health-related quality of life	Direct medical and nonmedical; indirect costs optional	Indication dependent (efficiency frontier), not stated	[102]
UK (NICE)	Quality-adjusted life years	Direct medical (covered) relevant to NHS and personal social services; nonmedical costs optional	~GB£20,000–£30,000/quality-adjusted life years	[103]

IQWiG: Institute for Quality and Efficiency in Health Care; NHS: National Health Service.

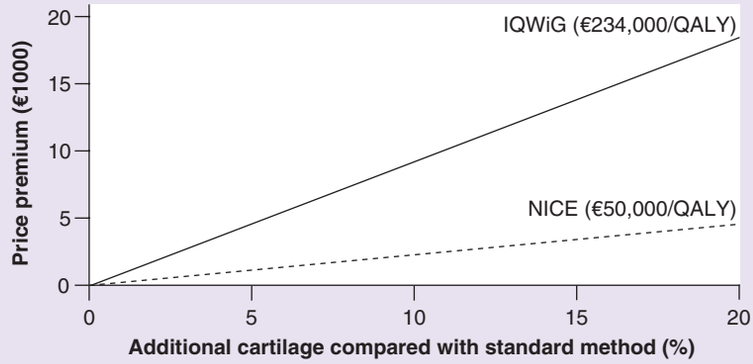

Figure 5. Value-based prices considered cost-effective by Institute for Quality and Efficiency in Health Care and NICE depending on the additional effectiveness of the innovation.
IQWiG: Institute for Quality and Efficiency in Health Care; QALY: Quality-adjusted life year.

Generally, the valuation must always take place in the context of the disease in question. Decision-making frequently becomes more complex when aspects such as severity (e.g., priority for life-saving interventions) have to be considered. These additional ethical concerns are often very specific to the technologies under consideration and are typically included in the payer's overall assessment of value as well as overall budget impact and wider societal benefits. Adopting a multicriteria decision-making framework theoretically allows for the systematic inclusion of such additional criteria [28]. More practically, additional value considerations may be included qualitatively at such an early phase of product development to prepare a case for a particularly high price, for example, in the case of a treatment of an orphan condition. Furthermore, early models are faced with a dynamic competitive environment. The HEE therefore needs to be updated as new treatment options, effectiveness data or price information becomes relevant, which can easily be included in the framework. As new comparators enter the scene, the effects on value-based prices can be studied *ex ante* by means of scenario analyses.

Future perspective

The high-value potential of many new regenerative technologies has been demonstrated in a general manner [3]. Due to financial pressures of healthcare payers, it will be of increasing importance to establish this value for specifically new products entering healthcare systems, based on sound HEEs. Early evaluations will hence continue to be established as a means of communication with internal and external stakeholders: during the research and development phase to inform business planning; at market entry to optimize product positioning; for coverage decisions to establish value for money; and as a starting point for managed entry agreements.

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No writing assistance was utilized in the production of this manuscript.

Table 10. Overview of spillovers generated by an early health economic evaluation.

Research topic	Knowledge required	Understanding supported	Sources
Baseline epidemiology	Incidence, prevalence, number of cases (expected)	Market size, market growth disease impact	Official health statistics (WHO, national health reports)
Standard treatment	Existing therapies, structure of healthcare provision across sectors	Market structure, channels of distribution, competitor situation	Treatment guidelines, insurer reports, existing health economic evaluation models (National Health Service DARE, PubMed)
Effectiveness	End points used, quality of evidence, data on competitors' value proposition	Strength and weaknesses of innovation, design of clinical studies, critical aspects in dialog with fourth hurdles	Literature research (PubMed, Google Scholar™, Cochrane reviews)
Costs	Compensation schemes, prices of competitor products	Application for representation, market segments, market shares	Compensation catalogs (e.g., diagnosis-related group), market prices

Executive summary

The need to establish value

- Cost coverage by third-party payers will be an important driver of commercial success for many regenerative medicine technologies.
- Due to rising healthcare costs value for money is becoming an increasingly important determinant for a positive coverage decision in many healthcare systems.

Value-based pricing in healthcare

- Decision-analytic modeling offers a methodologically sound approach to assess the value potential and prepare successful market access.
- Our report demonstrates how simple models can be constructed and in what way the results may be utilized.

The early model catches the value

- Scenario-based analysis allow scrutinization of the value proposition and identification of attractive markets.
- The model serves as means of communication with internal and external stakeholders, and facilitates dialog with investor and fourth-hurdle agencies.

Crystal balls are breakable

- Value projections are subject to uncertainty due to the early stage of product development, which should be taken account for by excessive sensitivity analysis.
- Besides cost–effectiveness there are additional sources of value that should be considered in the overall assessment.

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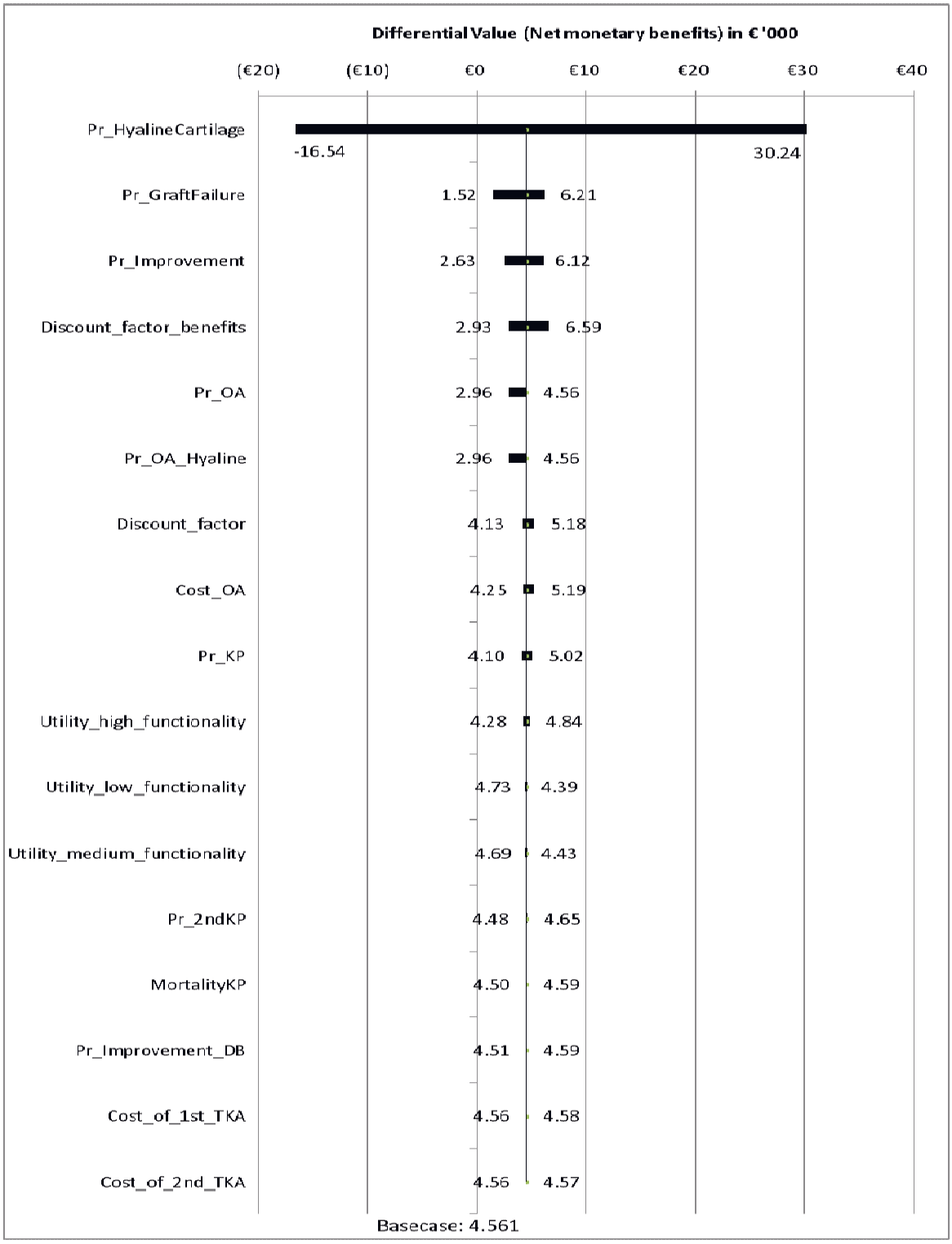
Supplements

Supplementary Figure 1: Tornado diagram of most influential parameters on value based
price



For cost-effectiveness analyses submitted to bodies like NICE it is standard to analyze uncertainty by means of a probabilistic sensitivity analysis: parameters are incorporated in the model as probability distributions and simulation techniques are used to arrive at a distribution of net benefits rather than fixed estimates. This was omitted here, because given the early stage, the aim of modeling was to generate benchmarks rather than to systematically assess the joint uncertainty of all parameters. Also, structural uncertainty is likely to be more relevant than parameter uncertainty at this stage. The differential value analysis is based on the NICE willingness to pay threshold of € 50,000. Differential value is calculated in relation to the best alternative which is standard M-ACI. It is assumed that the new method produces 20% more hyaline-like (i.e. 33%) cartilage than the one used in standard M-ACI. Subsequently all effectiveness parameters as well as all methodological parameters are varied. For input value see Supplementary Table 1.

Supplementary Table 1: Values used for sensitivity analysis

Parameter (Pr_ = probability)	**Value Deterministic**	**Value Min**	**Value Max**	**Sources of Min/Max Values**
Pr_HyalineCartilage	0.273	0.060	0.610	Clopper Pearson Intervals
Pr_GraftFailure (i.e. need for re-operation)	0.106	0.035	0.231	Clopper Pearson Intervals
Pr_Improvement (i.e. treatment success)	0.723	0.574	0.844	Clopper Pearson Intervals
Discount_factor_benefits	0.030	0.000	0.060	Gerlier et al. 2010
Pr_OA (i.e. developing OA with fibrocartilage)	1.000	0.000	1.000	Gerlier et al. 2010
Pr_OA_Hyaline (i.e. developing OA even with hyaline-like cartilage)	0.000	0.000	0.500	Gerlier et al. 2010
Discount_factor_costs	0.030	0.000	0.060	Gerlier et al. 2010
Cost_OA	€ 1,148	€ 574	€ 2,296	Weights severe/normal
Pr_JR	0.500	0.250	0.750	50% Variation
Utility_high_functionality	0.835	0.826	0.844	95% Confidence Intervals
Utility_low_functionality	0.690	0.681	0.699	95% Confidence Intervals
Utility_medium_functionality	0.760	0.749	0.771	95% Confidence Intervals
Pr_2ndJR	0.250	0.100	0.400	Wildner 2000
MortalityJR	0.007	0.002	0.009	Gerlier et al. 2010
Pr_Improvement_DB (i.e. treatment success after shaving)	0.570	0.000	0.824	Clopper Pearson Intervals
Cost_of_1st_TKA	€ 7,554	€ 7,196	€ 8,983	Weights severe/normal
Cost_of_2nd_TKA	€ 10,226	€ 9,481	€ 13,204	Weights severe/normal

Supplementary Table 2: Number of cases per treatment option in Germany

Method	***OPS-Code***	***# 2009***
M-ACI	*OPS 5-801.kh & 5-812.hh*	*1.442*
ACI	*OPS 5-801.ch & 5-812.ah*	*1.164*
MF	*OPS 5-801.hh & 5-812.fh*	*30.035*
MP	*OPS 5-801.3h & 5-812.3h*	*1.075*

Source: German Federal Statistical Office (Destatis); DRG statistics 2009

Supplementary Table 3: Overview of health economic studies

Source	Treatment options	Time / Country	Costs / Perspective	Type of evaluation	Results
Clar 2005 [1]	MF, ACI, MP	50 years / United Kingdom	Direct Medical/ Payer	Cost-utility / Decision analytic model	ICER : £3.617 / QALY (ACI vs. MF, best case)
Gerlier et al. 2010 [2]	MF, CC ACI-C	40 years / Belgium	Direct Medical/ Payer	Cost-utility / Decision analytic model	ICER : € 16.299 / QALY
Wildner 2000 [3]	MF, ACI, MP, Periostal transplantation (PT), conservative (C)	46 years / Germany	Direct Medical/ Payer	Cost-effectiveness / Decision analytic model	MF dominates MP, PT and C; ICER of ACI to MF: DM 9.032
Derret 2005 [4]	ACI, MP	2 years / United Kingdom	Direct Medical/ Hospital	Cost-utility	ICER : £16.349 / QALY
Minas 1998 [5]	ACI	1 year / United States	Direct Medical/ Hospital	Cost-utility	ICER : $ 6.791 / QALY
Lindahl 2001 [6]	ACI	20 years / Sweden	Direct Medical and indirect/ hospital and society	Cost study	Ø costs post-OP decrease by $ 88.146

Supplementary Table 4: Overview of clinical studies

Reference	Treatments	Study Design	N	Functional Outcome	Histological Outcome	Time in months
Knutsen 2004 [7]	MF, ACI-P	RCT	80	VAS, Lysholm, SF-36 PCS, Tegner	Biopsy - Expert opinion, polarized light	12, 24
Knutsen 2005 [8]	MF, ACI-P	RCT	80	Lysholm, SF-36 PCS, Tegner, ICRS form		24, 60
Bartlett 2005 [9]	M-ACI, ACI-C	RCT	91	Modified Cincinatti, Stanmore functional rating system, VAS	Biopsy - Expert staining, ICRS grade of repair	6, 12
Bentley 2003 [10]	MP, ACI-C/P	RCT	100	Modified Cincinatti, Stanmore functional rating system	Biopsy - expert, polarized light, ICRS grade of repair, Nature of cartilage	
Marcacci 2007 [11]	MP	Case Series	30	ICRS form, Tegner, IKDC	MRI/MOCART	84

Supplementary Table 5: Parameters long term

Parameter	Probability	Reference
Joint replacement with OA, 20 years post OP	0,50	Gerlier et al. 2010 [2], Clar 2005 [1]
Revision OP	0,03	knhttp://www.bqs-institut.de/
JR replacement, 10 years post 1st JR	0,25	Wildner 2000 [3]
Mortality due to JR surgery	0,07	Gerlier et al. 2010 [2]
OA with fibrocartilage after 15 years	1,00	Gerlier et al. 2010 [2], Clar 2005 [1]
OA with hyaline-like cartilage after 15 years	0,00	Gerlier et al. 2010 [2]

Supplementary Note:
Limitations of the economic model

The model structure is based on published models and has been adapted to the German context in dialogue with clinicians and practitioners. Nonetheless it cannot be representative for all institutions. There is no binding treatment algorithm and treatment pathways may differ across institutions. Costs estimation for the treatment of OA was based on an Austrian cost study and could differ to German Cost structures. However several other European studies suggest similar annual costs *[2]*. Furthermore sensitivity analysis showed that costs for OA only have marginal influence on cost-effectiveness. Quantities for out-patient services as well the weights for severe/simple cases have been elicited via expert interviews and may be subjected to institutional bias. We investigated variations by scenario analysis and no major effect on the results could be observed. Resource usage before surgery was assumed to be equally distributed across all treatment methods and hence omitted from analysis. Treatment unspecific health outcomes have been applied as evidence on quality of life is sparse for patients treated with respective technologies. The only published data was found in the publication by *Gerlier et al. (2010) [2]* who based their utility scores on data collected alongside a clinical trial investigating effectiveness of a special version of ACI and MF [12]. Since the ACI technology considered in this study is not relevant in the German context we decided to apply utility scores related to the functioning of the knee rather than these treatment specific scores. However since the proportions of utility weights across health states are similar to the ones of *Gerlier et al. (2010) [2],* scenario analysis using their utility weights did not fundamentally change the results.

Major assumptions

Treatment options are compared to microfracture with respect to additional costs and QALYs produced. The study population consists of male and female patients aged 32 years with symptomatic, isolated cartilage defects and no contra indications. On the basis of the German average life expectancy for this population the model's time horizon is 47 years -

https://www.destatis.de/EN/FactsFigures/SocietyState/Population/Deaths/CurrentLifeExpectancy.html. Cost and benefits are discounted at 3% according to the recommendations for health economic evaluation by IQWIG - https://www.iqwig.de/download/General_Methods_for_the_Assessment_of_the_Relation_of_Benefits_to_Costs.pdf . The analysis is performed from the perspective of German statutory health insurance. For in patient treatments the statutory health insurance pays a case specific lump sum based on the German diagnose related groups (G-DRG). The applicable codes have been researched via the official G-DRG literature and grouper tools - http://www.dimdi.de/static/en/index.html - and were validated by clinical experts. Codes (GOP) and prices for out-patient services of general practitioners (GP) and Specialists were deduced from the German price catalogue of out-patient care - http://www.kbv.de/9897.html. For procedures that could be undertaken in-patient as well as out-patient weightings have been applied according to expert statements. The same applies for DRGs with differing degrees of severity due to patient characteristics such as comorbidities. In the year after any surgical intervention all patients have one follow up visit at the GP. Furthermore they are entitled to physiotherapy according to the catalogue of therapeutic measures - http://www.gkv-spitzenverband.de/upload/Heilmittel-Richtlinie_(Zweiter_Teil_-_Heilmittel-Katalog)_770.pdf - for the relevant indication. Prices for physiotherapy are based on market prices which have been researched by telephone interviews of which a mean value was calculated. Treatment failures are treated for medium pain pharmaceutically with analgesics and codeine. In the year of cartilage smoothing and re-operations one GP visit with MRT diagnostics is assumed. Cartilage smoothing is undertaken within the scope of a arthroscopy. Patients with failed smoothing subsequently consult their GP in 2 quarters per year. In case of complications strong pain medication like opium plasters is necessary. Amounts and prices were taken from expert statements and the German drug registry - http://www.rote-liste.de/ - . Co-payments by patients are included as out of pocket payments. Patients developing OA consult their GP in 2 quarters per year 5 years prior to entering the status OA. In the year before entering the state OA a specialist is consulted. The average costs p.a. for OA treatment were taken from a recent Austrian cost study by *Wagner 2011 [13]* and include direct medical costs covered by health insurers as well as out of pocket payments, which amount for almost half of the total costs.

Supplementary Literature

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3. The cost-utility of open prostatectomy compared with active surveillance in early localized prostate cancer

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RESEARCH ARTICLE Open Access

The cost-utility of open prostatectomy compared with active surveillance in early localised prostate cancer

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Abstract

Background: There is an on-going debate about whether to perform surgery on early stage localised prostate cancer and risk the common long term side effects such as urinary incontinence and erectile dysfunction. Alternatively these patients could be closely monitored and treated only in case of disease progression (active surveillance). The aim of this paper is to develop a decision-analytic model comparing the cost-utility of active surveillance (AS) and radical prostatectomy (PE) for a cohort of 65 year old men with newly diagnosed low risk prostate cancer.

Methods: A Markov model comparing PE and AS over a lifetime horizon was programmed in TreeAge from a German societal perspective. Comparative disease specific mortality was obtained from the Scandinavian Prostate Cancer Group trial. Direct costs were identified via national treatment guidelines and expert interviews covering in-patient, out-patient, medication, aids and remedies as well as out of pocket payments. Utility values were used as factor weights for age specific quality of life values of the German population. Uncertainty was assessed deterministically and probabilistically.

Results: With quality adjustment, AS was the dominant strategy compared with initial treatment. In the base case, it was associated with an additional 0.04 quality adjusted life years (7.60 QALYs vs. 7.56 QALYs) and a cost reduction of €6,883 per patient (2011 prices). Considering only life-years gained, PE was more effective with an incremental cost-effectiveness ratio of €96,420/life year gained. Sensitivity analysis showed that the probability of developing metastases under AS and utility weights under AS are a major sources of uncertainty. A Monte Carlo simulation revealed that AS was more likely to be cost-effective even under very high willingness to pay thresholds.

Conclusion: AS is likely to be a cost-saving treatment strategy for some patients with early stage localised prostate cancer. However, cost-effectiveness is dependent on patients' valuation of health states. Better predictability of tumour progression and modified reimbursement practice would support widespread use of AS in the context of the German health care system. More research is necessary in order to reliably quantify the health benefits compared with initial treatment and account for patient preferences.

Keywords: Economic evaluation, Cost-utility analysis, Cost-effectiveness, Prostate cancer, Active surveillance, Decision analysis, Early evaluation

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Background

Prostate cancer (PC) – ICD code C.61 'Malignant neoplasm of the prostate' following ICD-10-GM classification – is the second most frequent cancer among males in economically developed countries and the most common cancer in Germany, accounting for 14% and 25% of total new cancer cases respectively [1]. Since 1990, the number of new cases has risen by over 50%, amounting to more than 80,000 new diagnoses in Germany in 2010 [2]. The increase in PC incidence has been related to improved means of early diagnosis, especially through prostate-specific antigen (PSA) testing [3]. Prostatectomy (PE) is the first line treatment option for early stage PC. PE is considered the gold standard in urology because other options such as radiotherapy (RT) cannot guarantee complete elimination of tumour cells in the prostate [4,5]. It is also the only treatment for which there exists favourable high quality clinical evidence [6,7]. Accordingly, the German Federal Joint Committee ('Gemeinsamer Bundesausschuss', GBA) decided that PE is the preferred treatment option for early stage PC in low risk patients because of the lack of prospective, randomised evidence for RT [6].

Because most carcinomas are thought to have a protracted natural history and more than 85% of patients are older than 65 years at the time of diagnosis, most patients die with the disease and not of it [8,9]. This is especially true for carcinomas that exhibit a low risk profile, i.e. a low PSA value, no histological conspicuity suggested by an indicator such as the Gleason score and confinement to the prostate. For such men, the risk of over-treatment is associated with negative health impacts resulting from the adverse effects of prostatectomy [10,11]. Postoperative rates of incontinence (IC) or erectile dysfunction (ED) of 97% and 72%, respectively, have been reported within 90 days of PE [12]. Despite the fact that some patients recover in the long term, these adverse effects (AE) significantly reduce health related quality of life [13].

As a consequence, observing strategies have been proposed as an alternative to initial treatment [11,14]. Watchful waiting (WW) is a strategy from the pre-PSA test era for patients with limited life expectancy. WW implies no intention to initiate curative treatment. In case of symptomatic disease progression, only palliative treatment is offered to patients, and a survival benefit of primary treatment with PE over WW has been documented in a prospective, randomised controlled trial (RCT) [7,15]. Active surveillance (AS), on the other hand, describes a policy of close monitoring for patients with a life expectancy >15 years. In cases of disease progression, curative treatment is triggered.

There exists no evidence from RCTs for AS [16]. Because AS implies close monitoring and curative treatment when necessary, it can reasonably be assumed that an AS strategy is more effective in avoiding PC specific death than WW. In fact, some evidence suggests that there is no difference in PC death to be expected between AS and PE [17]. The aim of this article was to develop a Markov model for the evaluation of AS as an alternative strategy to PE for the treatment of early stage, localised prostate cancer in the context of the German health care system. Owing to the lack of evidence for AS, we had to base our analysis on reasonable assumptions which we then challenged using extensive sensitivity analyses.

Methods

Evaluation

A decision analytic cost-utility model was developed following the standard of the CHEERS checklist, a general guideline on decision-analytic modelling [18]. It was performed from the perspective of the citizens insured by German Statutory Health Insurance (SHI), which is recommended by the German Institute for Quality and Efficiency in Health Care (IQWIG) and includes costs for SHI and out of pocket payments [19]. The study population consisted of men newly diagnosed with low risk PC, no other severe comorbidities and a life expectancy of >15 years. Low risk PC is characterised by a PSA value ≤10 ng/ml, Gleason score ≤6 and tumour stage ≤T2a [11].

Men enter the model at the age of 65 years, which corresponds to the mean age of the cohort in the underlying clinical study. A Markov model was chosen to represent this cohort's course of disease through different states over time. Quarter-yearly transition cycles were assumed because significant changes in tumour states could occur after 90 days and long term adverse effects could be apparent. In order to capture the full range of costs and effects, we applied a lifetime horizon of 35 years, assuming an age limit of 100 years.

Health outcomes were measured in quality adjusted life years (QALYs), as quality of life is a central aspect in the decision whether to treat or not. All costs (€) were adjusted to 2011 values. Both health outcomes and costs were discounted by 3%, and the half-cycle correction was applied. The model was implemented in TreeAge Pro 2012.

Interventions/model structure

The German Association for Urology has published guidelines for the treatment of PC that include AS. According to these, AS involves 3-monthly determinations of PSA value and digital rectal examinations (DRE) in the first 2 years after diagnosis and bi-annually thereafter [5]. Additionally, a biopsy should be taken in the first year and every 3 years after. Treatment can be triggered

by an indication of local progression through any of these parameters as well as patient choice. Patients aged ≤72 years are treated by open radical PE; older patients receive RT. A recent review revealed no RCTs comparing the effectiveness of RT and PE with respect to PC mortality [20]. Conservatively, it was assumed that RT and PE have the same disease related outcomes. Downstream treatments such as treatment of adverse effects, prostate hyperplasia and advanced disease were assumed not to have an influence on the difference in mortality between AS and PE. Despite close monitoring, rapidly growing tumours might progress unnoticed under AS and develop metastases prior to treatment [21,22]. Complications occurring within 30 days of PE include rectal injury, wound infection, haemorrhage requiring blood transfusion, deep vein thrombosis and myocardial infarctions [23]. Short term adverse effects such as ED and/or IC are characterised by occurrence and resolution within 90 days after surgery. Long term adverse effects persist after 90 days and can be cured only by surgical intervention. In cases of local recurrence after initial PE, RT is the primary treatment option [5]. As with PE, the adverse effects of RT can be divided into short term and long term effects. In addition to IC and ED, bowel problems (BP) such as abdominal pain, bloating and diarrhoea may develop [24]. Local recurrence is a prerequisite for developing metastatic disease after initial treatment. Once metastases have developed, there is no chance of cure and patients will eventually die of prostate cancer (Figure 1) [25].

Utilities

Baseline utilities

Age-adjusted utility values from the general population provide a reasonable approximation when condition specific baseline data are not available [26]. Health state specific utilities were thus applied as a multiplicative factor to average, age-adjusted utilities from the German male population. The latter are based on a representative study among German citizens (n = 2,049) surveying the EQ-5D items in the years 2006-2011 [27]. Based on these data, the functional relationship between mean EQ-5D utilities and age was estimated with a generalised

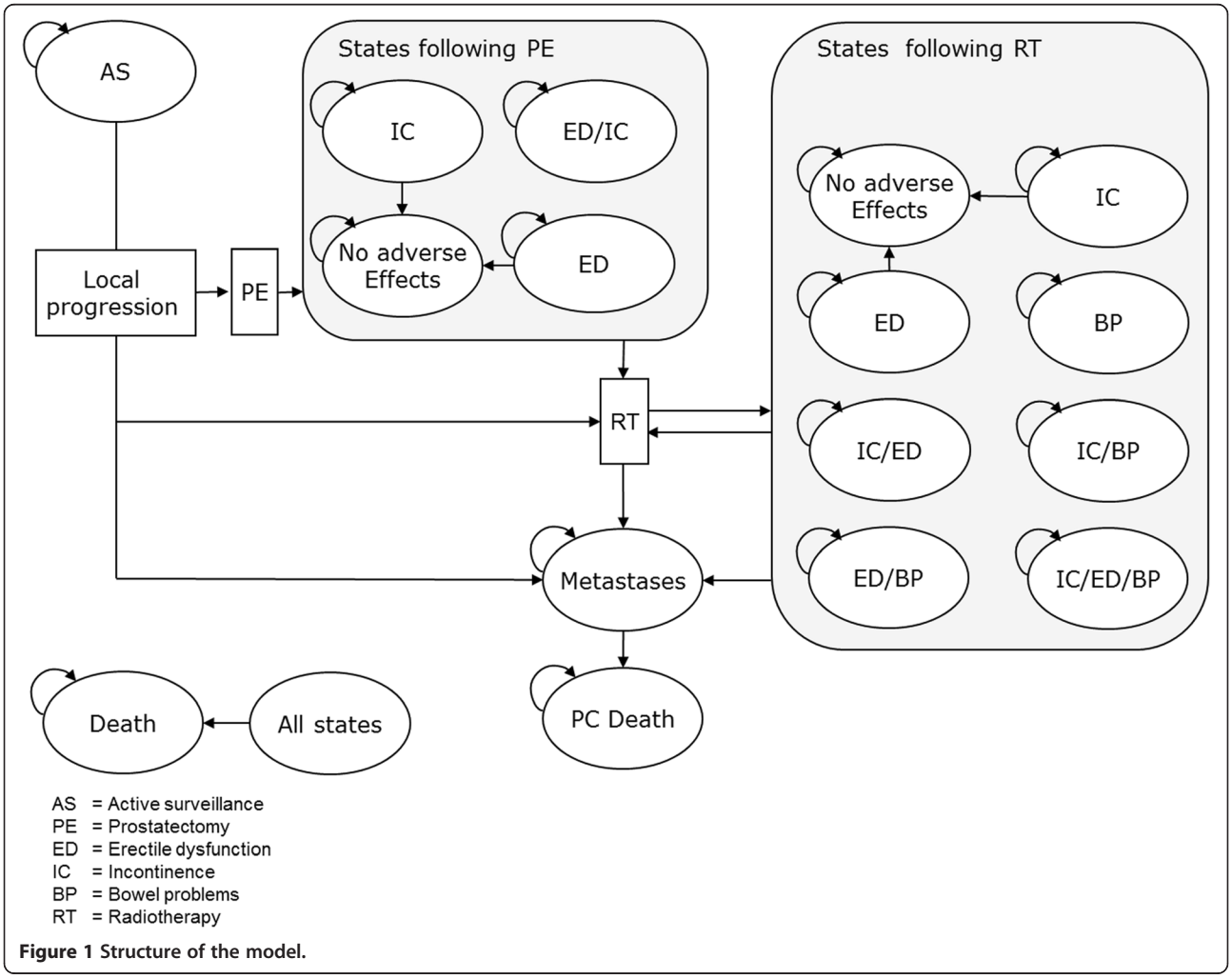

Figure 1 Structure of the model.

additive regression model using cubic regression splines (Figure 2) [25].

Health state specific utilities

We identified five studies that reported utility weights for relevant health states. Two of these presented implausible or inconsistent results because combined adverse effects were valued more highly than single ones or utility weights >1 were possible, respectively [28,29]. One recent study reported values depending on age and socio-economic status, which could not be adequately combined with our baseline utilities [30]. Stewart et al. provide mean utilities for postoperative health states from a cohort of 162 men [31]. These values compare well with the results of Sommers et al. [32]. Stewart et al. additionally reported utility values for treatment states and combined adverse events, such as ED and IC. Utility values for combined adverse events were surveyed as separate health states so no combination method had to be applied. Furthermore, the quality of life effects of conservative, i.e. non-surgical, downstream treatments such as incontinence pads were already incorporated in the description of health states. We therefore decided to use their preference-based set of utilities elicited by the standard gamble method. Following Liu et al. and the results of the meta-analysis by Bremner et al., we assumed that life under AS has the same utility as life after treatment without side effects [28,33] (Table 1).

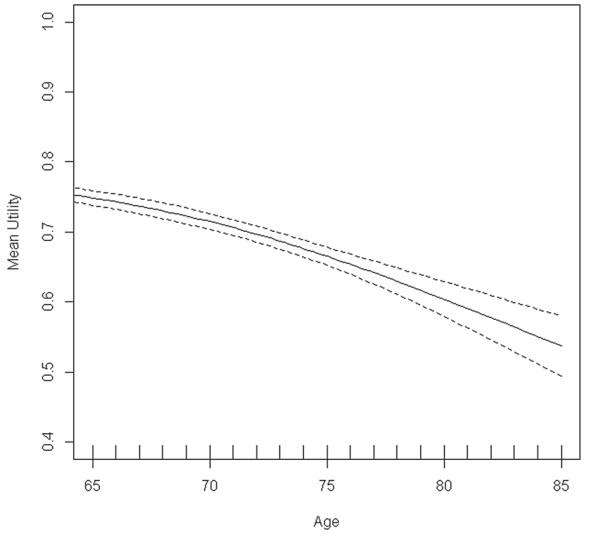

Figure 2 Age adjusted baseline utility German population.

Table 1 Utility weights of relevant health states

State	Expected value	SE	95% CI	Source
During AS	0.99	0.05	1; 0.9	Bremner [28], Liu [33], own calculation
Urinary difficulty during AS	0.89	0.024	0.91; 0.85	Steward 2005
During PE treatment	0.67	0.041	0.75; 0.59	Steward 2005
During radiotherapy	0.73	0.045	0.82; 0.64	Steward 2005
Post treatment no adverse effects	0.99	0.05	1; 0.9	Bremner [28], Liu [33], own calculation
Post treatment IC	0.83	0.022	0.87; 0.79	Steward 2005
Post treatment ED	0.89	0.013	0.92; 0.86	Steward 2005
Post treatment BP	0.71	0.021	0.75; 0.67	Steward 2005
Post treatment IC, ED	0.79	0.033	0.86; 0.72	Steward 2005
Post treatment IC, BP	0.70	0.036	0.77; 0.63	Steward 2005
Post treatment ED, BP	0.57	0.039	0.65; 0.49	Steward 2005
Post treatment IC, ED, BP	0.45	0.044	0.54; 0.36	Steward 2005
Metastatic disease	0.25	0.015	0.28; 0.22	Steward 2005

AS = Active surveillance.
PE = Prostatectomy.
IC = Incontinence.
ED = Erectile Dysfunction.
BP = Bowel Problems.

Costs

Following the perspective of citizens insured by German SHI, all direct medical costs incurred by the SHI as well as by individual patients were included [19]. Indirect costs were neglected as the study population has passed retirement age. Equally, post hospital rehabilitation was not considered as it is typically covered by pension funds. Resource usage was identified and quantified through literature research and treatment recommendations from the Association of German Urologists. Out-patient unit prices are based on the physician's fee catalogue 2011 (0.035048 cents/point) [34]. In-patient unit prices are based on diagnosis related group (DRG) weights from the German DRG catalogue and the federal base rate for 2011 of €2,963 [35]. For the pricing of pharmaceuticals, we referred to the German formulary 2011 [36]. Remedies and other aids were valued according to market prices investigated using internet research as well as telephone interviews.

Primary treatments

In the German DRG system, re-hospitalisations within 30 days are coded as one case. Hence, the costs of PE with and without complications are reflected by the respective DRGs (Table 2). Postoperative monitoring takes place on an out-patient basis (Table 3). Physicians can bring to account a maximum of four patient visits per

Table 2 In-patient costs of prostatectomy

In-patient treatment	DRG	Total costs (€)
Prostatectomy	M01B	6,886
Complications	M01A	9,526

annum. AS implies determination of PSA values, DRE and regular biopsies (Table 4). Despite preventive antibiotics, biopsy may cause urosepsis which requires hospitalization [37]. Furthermore, symptoms of benign prostate hyperplasia can develop in patients under AS. We assumed that initially half these patients are treated with alpha-1 adrenergic antagonists (Tamsulosin) and the other half with 5-alpha-reductase inhibitors (Finasteride). Patients experiencing worsening of symptoms of urinary difficulty require surgical intervention with transurethral resection of the prostate (TURP) (Table 5). RT is undertaken by a specialist practitioner. Curative treatment entails two target volumes with a maximum of 72 gray, which is equivalent to 40 times 1.8 gray (Table 6).

Adverse effects

The numbers of general practitioner (GP) and specialist practitioner (SP) consultations due to diagnosis of erectile dysfunction were derived from a costing study by Wilson et al. [38]. We estimated consumption of remedies and aids based on the assumption that 70% of patients would make use of phosphodiesterase (PDE) inhibitor and 10% of cavernous injections, SKAT/MUSE or a vacuum pump respectively (Table 7). Symptomatic treatment of IC is achieved through the use of pads in the majority of patients (90%). We assumed an equal distribution of strong, medium and low pads and an average use of three pads/day. Diapers or permanent catheters are necessary in 5% of all patients (Table 8). Costs of managing BP were based on a publication by Hummel et al. [20].

Metastases

Metastatic stage is characterised by two phases. At first, cancer is responsive to treatment with luteinizing hormone-releasing hormone (LHRH) agonists which delay progression. Following treatment guidelines, we assumed a dose of 11.5 mg every 3 months. Eventually, patients will become refractory and require chemotherapy. Chemotherapy implies treatment with 142.5 mg of Docetaxel and 5 mg of Prednisolone every 3 weeks. Additionally, around 70% of all refractory patients will develop bone metastases which are treated with zoledronic acid and RT (Table 9) [39]. Radiation therapy assumes a target volume of 35 gray, i.e. 14 times 2.5 gray.

Table 3 Out-patient costs of prostatectomy

Item	Quantity p.a.			Price/unit (€)	Total costs p.a. (€)		
Follow-up year	*< 2*	*2-4*	*> 4*		*< 2*	*2-4*	*> 4*
PSA value	4	2	1	4.8	19.20	9.60	4.80
Consultation fee	4	2	1	1.75	7.00	3.5	1.75
Treatment fee > 60 yrs	4	2	1	21.20	84.80	42.40	21.20
Insuree lump sum	4	2	1	9.11	36.45	18.22	9.11

PSA = Prostate Specific Antigen.

Table 4 Out-patient costs of active surveillance

Item	Quantity p.a.			Price/unit (€)	Total costs p.a. (€)		
AS year	*1*	*2*	*> 2*		*1*	*2*	*> 2*
DRE	4	4	2		Included in lump sum		
PSA value	4	4	2	4.80	19.20	19.20	9.60
Biopsy	1	0.33	0.33	18.58	18.58	6.19	6.19
Consultation fee	4	4	1	1.75	7.01	7.01	1.75
Treatment fee > 60 yrs	4	4	2	21.20	84.82	84.82	42.41
Insuree lump sum	4	4	2	9.11	36.45	36.45	18.22
Medication							
Antibiotics (preventive)	0.5	0.16	0.16	16	8.00	2.64	2.64
Sum					**174.05**	**156.33**	**80.84**

DRE = Digital Rectal Examination.
PSA = Prostate Specific Antigen.

Probabilities

Mortality

No RCTs comparing disease related mortality of PE and AS could be found in the literature [16]. One American and one Scandinavian RCT were identified comparing WW and initial treatment [7,40]. The 10-year results of the American study (PIVOT) reported overall PC death of 5.8% and 8.4% in the PE and observation arms respectively [40]. This corresponds to a relative risk (RR) of 0.69 which is more favourable towards WW than the results of the Scandinavian Prostate Cancer Group (SPCG). The difference in results is likely to be because the PIVOT cohort represented a population with less advanced disease [40]. However the PIVOT sample also included a large number of African Americans (>30%) who have been shown to suffer from an increased risk of developing and dying from PC [41,42]. In order to avoid country specific bias, we chose to use the SPCG data, which represent the European population more realistically. The SPCG trial found that PE significantly reduced the risk of PC death 15 years after diagnosis with a RR = 0.62, 95% confidence interval (CI) 0.44, 0.87. RR over the time period was estimated by the authors using Cox proportional hazard models. However, the study

Table 5 Costs other

Item	DRG	Quantity p.a.	Price/unit (€)	Total costs p.a. (€)
In-patient treatment				
Surgical				
Prosthesis*	M03C, ZE 58	1	10238.03	
Sphincter*	M01B, ZE 10	0.5	6393.77	3196.14
Sling*	L06A, ZE139	0.5	3677.58	1388.79
Treatment of urosepsis	T60E	1	3075.59	
TURP	M02A	1	3768.93	
Out-patient treatment				
BPS medication				
Finasteride (5 mg, N3)		1.825	139.88	255.28
Tamsulosin (0.4 mg, N3)		1.825	96.43	175.98

*not covered by statutory health insurance (out of pocket).
BPS = Benign prostate syndrome.
TURP = Transurethral resection of the prostate.

population (n = 695, mean age 64.7 years) included men with more advanced disease, i.e. PSA value <50, tumour stage ≤ T2 and Gleason score ≤10. Furthermore, patients in the WW group were only treated palliatively in case of disease progression [43]. Following Pearson et al. in the base case, we thus assumed that only half the treatment benefit of PE would be maintained when compared with AS corresponding to a RR of 0.81. This also makes our base case results comparable to the study by Hayes et al. who assume that AS would be 25% more effective than WW, implying a RR of 0.82. We calibrated the transition probability of developing metastases prior to treatment under AS on the basis of the RR of PC mortality after 15 years of 0.81 and the other model parameters. This was based on the assumptions that the additional risk of PC death under AS is constituted by silent progression to metastatic disease and that metastatic PC is a state of terminal illness [4,22,44]. Background mortality was based on the life table of the German Federal Statistical Office 2011 [2].

Table 6 Out-patient costs of radiotherapy

Item	EBM*	Quantity p.a	Price/unit (€)	Total costs p.a. (€)
Consultation fee	25011	1	61.86	61.86
CT Planning	34360	1	38.38	38.38
Radiation plans	25342	2	247.44	247.44
Lump sum/radiation field	40840	15	140	2100
Radiation	25321	40	35.22	1408.93
>2 fields	25322	40	6.48	259.36
3D-planning	25232	40	9.46	378.52
Sum				**4741.92**

*EBM = 'Einheitlicher Bewertungsmaßstab', i.e. position in the catalogue of reimbursed out-patient services.

State transition probabilities

We identified a recent systematic review and meta-analysis of studies comparing the benefits and harms of AS and PE for the population in question as best available evidence [45]. If necessary, annual probabilities were translated into quarter-yearly probabilities via conversion to rates [46]. Transition probabilities from short

Table 7 Costs of managing erectile dysfunction

Item	EBM	Quantity p.a	Price/unit (€)	Total costs p.a. (€)
Treatment of symptoms				
Out-patient				
Specialist practitioner				
Consultation fee	1436	1	1.75	1.75
Treatment fee > 60 yrs	26212	1	21.20	21.20
Insuree lump sum	1320	1	9.11	9.11
General practitioner				
Consultation fee	1436	2	1.75	3.50
Treatment fee > 60 yrs	3112	2	35.75	71.50
Insuree lump sum	3111	2	15.77	31.54
Remedies and aids*				
Sildenafil		8.75	44	385
Cavernous injection		2.5	36.62	91.55
(SKAT, MUSE)		2.5	33.19	82.98
Vacuum pump		0.05	301.76	2.66
Ring		4	17	68.00
Sum				**768.80**

*not covered by statutory health insurance (out of pocket).

Table 8 Costs of managing incontinence

Item	Quantity p.a	Price/unit (€)	Total costs p.a. (€)
Treatment of symptoms			
Out-patient			
Specialist practitioner			
Consultation fee	1	1.75	1.75
Treatment fee > 60 yrs	1	21.20	21.20
Insuree lump sum	1	9.11	9.11
General practitioner			
Consultation fee	2	1.75	3.50
Treatment fee > 60 yrs	2	35.75	71.50
Insuree lump sum	2	15.77	31.54
Remedies and aids			
Pads	983	0.36	350.53
Diapers (20 × 20)	19	0.56	10.3
Net trousers for pads/diapers	0.95	10	9.5
Physiotherapy (Pelvic floor)	12	15	180
Balloon catheter	0.6	21.18	12.7
Bed bag sterile	6.1	2.51	15.3
Leg bag sterile	6.1	4.51	27.4
Sum			**744.34**

Table 9 Costs of managing metastatic disease

	Quantity p.a	Price/unit (€)	Total costs p.a. (€)
Responsive			
Out-patient			
Specialist practitioner	4	See above	128.28
Medication			
LHRH Agonist leuprorelin	4	415	1,660
Refractory			
Medication			
Docetaxel	17.3	1768	30,645.3
Prednisolon	0.87	10.6	9.2
Bone metastases			
Out-patient			
Radiation	14	See Table 5	1,484.06
In-patient			
Bone scan	0.7	1629.65	1,140.76
Medication			
Zoledron acid	12	367.98	4,415.76

LHRH = Luteinizing Hormone-Releasing Hormone.

to long term AE could be calculated from the quotient of the probabilities of long term AE and short term AE, i.e. P(transition short term to long term AE) = P(AE long term)/P(AE short term). For transitions to states with combined AE, statistical independence was presumed except in the case of IC. Here, it was assumed that 80% of patients experiencing IC would also experience ED. For an overview of transition probabilities, please refer to Table 10.

Analysis

Sensitivity analysis

Univariate sensitivity analysis was conducted for all parameters to analyse their isolated impact on cost-effectiveness. For transition probabilities and utilities, input values were varied within the 95% confidence interval. The probability of developing metastases under AS was varied between assuming no difference in disease related mortality compared with PE (i.e. RR =1) and the full treatment effect found in the SPCG trial (i.e. RR = 0.62). Costs for in-patient treatments were varied by running the model with DRG rates resulting from maximum and minimum days of hospitalisation resulting from treatment. All other cost variables were tested by assuming half and double the central estimate. The 10 variables with the highest impact on model uncertainty are presented in a tornado diagram (Figure 3). Given that there exists no explicit cost-effectiveness threshold for Germany, net benefits were calculated with the frequently quoted willingness to pay (WTP) threshold of €50,000, which was chosen for illustration only to incorporate impacts on both effects and costs [49,50]. Based on the tornado analysis, we report threshold values for variables that changed strategy rankings. Key assumptions of the model were varied to test the robustness of the base case results. First, we considered alternative time horizons of 5, 15 and 30 years. Furthermore, we tested the influence of applying alternative discount rates, where both costs and benefits were discounted at the same rate. Following German recommendations, the discount rate was varied between using values of 0%, 5%, 7% and 10% [19,51].

Probabilistic analysis

Multivariate probabilistic sensitivity analysis was conducted to assess overall model uncertainty. For this purpose, values were simultaneously and randomly drawn in second order Monte Carlo simulation. Beta distributions were adopted for probabilities and utilities and gamma distributions for costs. The distribution parameters were derived from the model parameter's expected value and standard error (Tables 1, 10 and 11). In the case of costs, the standard error (SE) was calculated based on the range applied for deterministic sensitivity

Table 10 Transition probabilities

State	Event	Expected value	SE	Source*
AS	Progression of Gleason Score	0.0263	0.007	
	Other Progression (DRE/PSA)	0.0268	0.007	
	Choosing treatment	0.018	0.005	
	Developing metastatic prostate cancer under active surveillance	0.0023	0.000425	Bill-Axelson [7]; own calculation
	Infection due to biopsy	0.02	0.0075	Cambell-Walsh Urology
	Develop benign prostate hyperplasia	Age dependent		Andersson 2004 [48]
	Transurethral resection of the prostate due to benign prostate hyperplasia	0.000462	-	Andersson 2004; own calculation
Treatment	Perioperative death	0.0044	0.00001	
	Major complication during surgery	0.0472	0.0168	
	Urethral stricture	0.0344	0.002	
Post PE	Incontinence and erectile dysfunction short term	0.37	0.0467	
	Erectile dysfunction short term	0.39	0.0384	
	Incontinence short term	0.09	0.0113	
	Keep incontinence and erectile dysfunction long term	0.27	0.0338	
	Keep incontinence long term	0.28	0.035	
	Keep erectile dysfunction long term	0.89	0.0831	
	Disease recurrence	0.00875	0.0032	
	Progression from recurrence to metastatic disease	0.0127	0.0047	Horwitz 2005 [49]
	Death due to prostate cancer after development of metastatic state during hormonal therapy	0.022	0.0225	Alibhai [44]
Post RT	Incontinence short term	0.3	0.0835	
	Bowel problems short term	0.18	0.0506	
	Bowel problems and incontinence short term	0.054	0.0068	
	Keep incontinence long term	0.16	0.02	
	Keep bowel problems long term	0.152	0.019	
	Erectile dysfunction long term	0.064	0.016	
	Keep incontinence and bowel problems long term	0.148	0.0148	
IC	Sphincter/sling surgery	0.05	0.0075	
ED	Prosthesis surgery	0.02	0.0003	
Death	Death due to other reasons	Age dependent	-	

*If not stated otherwise: [45].
AS = Active Surveillance, ED = Erectile Dysfunction.
DRE = Digital Rectal Examination, IC = Incontinence.
PSA = Prostate Specific Antigen.
PE = Prostatectomy.
RT = Radiotherapy.

analysis as follows: SE = (Max value−Min value)/4. The probabilistic sensitivity analysis was based on 1,000 replications, and the results are presented as a cost-effectiveness acceptability curve (CEAC) and as a scatter plot on the cost-effectiveness plane.

Validation

For the sake of cross validation a structured literature search was performed in the databases PubMed, NHS Centre for Reviews and Dissemination as well as Google Scholar to compare our results with existing economic cost-utility models of AS and PE. First we looked for existing reviews of economic evaluations using the (Mesh-) terms 'review', 'prostatic neoplasm' and 'economics'. After screening titles and abstracts for the terms 'model', 'evaluation', 'cost(s) ', 'utility', 'quality of life', 'effectiveness' and 'benefit' we analysed full texts. In a second step we searched for economic evaluations using the (Mesh-) terms 'prostatic neoplasm' and 'economics'. Face validity of the model structure and major model assumptions was undertaken within our modelling team (FK, BS) and with our clinical expert (RW). Furthermore, we

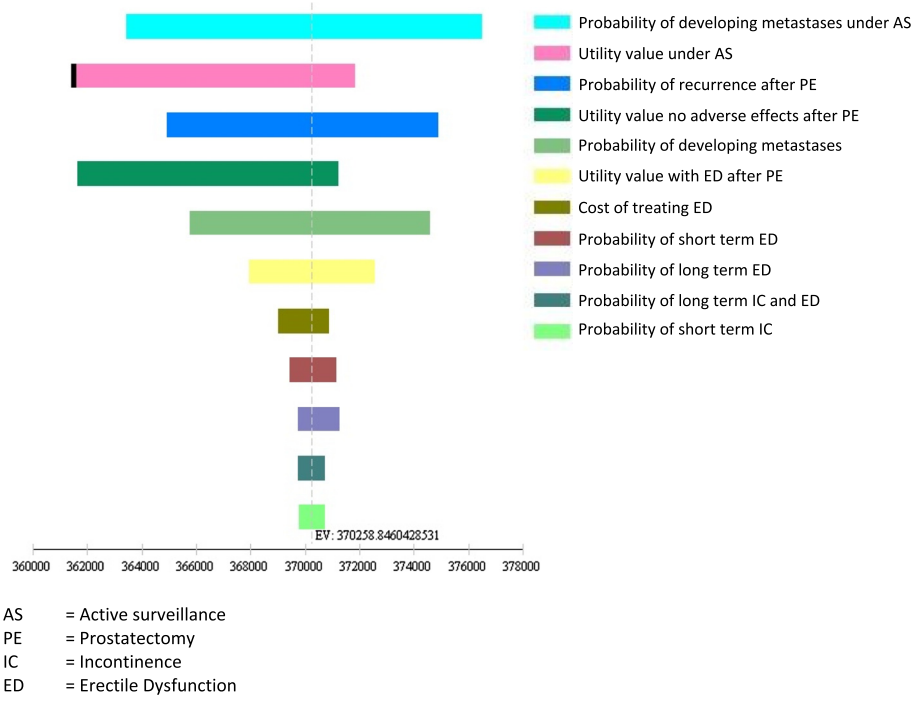

Figure 3 Tornado diagram (Net Benefits in €).

compared model results with clinical data from the American PIVOT trial for the purpose of external validation.

Results

Base case

Expected, discounted life expectancy was 12.07 years under AS and 12.15 years with initial surgery if not adjusted for quality of life. This was associated with discounted costs of €16,468 for PE and €9,585 for AS. Treatment with PE therefore generated an additional 0.08 life years and caused additional costs of €6,883, corresponding to an incremental cost-effectiveness ratio (ICER) of €96,420 /life year gained. Some 48% or €7,935 of overall costs were caused by initial treatment in the PE arm. Treatment costs resulting from PE or RT amounted to €3,463 in the AS arm, accounting for 36% of all costs. Costs for AS only amounted to €2,178, making up 22% of total costs. After adjusting for quality of life, effects decreased to 7.60 QALYs under AS and 7.56 QALYs with initial surgery. So AS dominated initial treatment, causing higher effects (+0.04) and lower costs (−€6,883) in the base case. The lifetime risk of PC death was 11.49% under AS and 10.92% in the PE cohort.

Table 11 Parameters for probabilistic sensitivity analysis of costs

Costs item	Expected value in €*	SE
Prostatectomy	6,886	843.75
Conservative treatment of incontinence	186	23.25
Conservative treatment of erectile dysfunction	192	24.03
Radiotherapy	4,742	592.75
Treatment of metastases	447	55.88
Surgical treatment of urosepsis	3,796	384.50
Treatment prostate hyperplasia	108	13.50
Transurethral resection of the prostate	3,769	86.25
Surgical treatment of incontinence	2,292	286.50
Surgical treatment of erectile dysfunction	10,238	1,279.75
Treatment of refractory metastases	7,663.75	957.97
Treatment of bone metastases	1,760.25	220.03

*Quarter yearly except for surgical procedures.

Sensitivity analysis

AS dominated initial surgery in all time perspectives. Because the average health of the population as well as the share of people under AS decreases over time, the benefit of avoiding postoperative AE is most influential in the first years after diagnosis. As the share of people under AS decreases and PC mortality increases, this effect is temporarily compensated for between years 3 and 15. After this, rapidly increasing other cause mortality limits the relative influence of additional PC mortality, which correspondingly puts more weight on patients still under AS. With increasing values for the discount rate, the

Table 12 Results of sensitivity analysis

Parameter	Value	Costs (€)			Effects (QALY)			ICER (€/QALY)
		PE	AS	Difference	PE	AS	Difference	
Base case	Time horizon 5	11,355	4,080	−7,275	2.971	3.019	−0.048	Dominated
	Time horizon 15	15,011	8,263	−6,748	6.454	6.467	−0.013	Dominated
	Time horizon 30	16,444	9,564	−6,880	7.545	7.567	−0.022	Dominated
Discount rate	0%	19,013	12,201	−6,811	9.778	9.800	−0.022	Dominated
	5%	15,291	8,346	−6,945	6.525	6.549	−0.025	Dominated
	7%	14,386	7,376	−7,010	5.713	5.739	−0.027	Dominated
	10%	13,376	6,270	−7,106	4.794	4.824	−0.029	Dominated

amount of QALY gains and cost savings decreased, but AS remained the dominant strategy for all discount rates between 0% and 10% (Table 12). Figure 3 depicts the results of the univariate sensitivity analyses in the form of a tornado diagram that displays the effect of the uncertainty associated with individual parameter values on the net monetary benefits of AS for a WTP of €50,000. The utility weight for patients under AS and the probability of developing metastases under AS have the highest impact on model results. Probabilities of recurrence after PE and developing metastases as well as the utility weight for no AE after PE are almost equally influential variables. Threshold analysis revealed that seven of the most influential variables changed the strategy ranking when varied within their 95% confidence intervals (Table 13). The probability of developing metastases under AS proved to be particularly influential. The strategy ranking changed at a threshold value of P = 0.0025 corresponding to a RR of prostate cancer death of 0.76. Additionally we performed a threshold analysis for the proportion of patients under AS crossing over to curative treatment. This proportion is driven by the probability of disease progressing for any reason (i.e. Gleason score or DRE + PSA) and men electing treatment without signs of progression. In the base case this corresponds to an annual crossover probability of $P_{crossover}$ = 0.071 and 61% of patients under AS being treated. PE strategy became more effective than AS at a threshold value of $P_{crossover}$ = 0.149 with 81% of AS patients crossing over to radical treatment.

Table 13 Results of threshold analysis

Variable	Base case value	Threshold value
Probability of developing metastases under AS	0.0023	0.0025
Probability of PC recurrence after PE	0.00875	0.00772
Utility value after PE with no adverse effects	0.99	1
Utility value under AS	0.99	0.98
Probability of developing metastases after recurrence	0.0127	0.0113
Utility value after PE with ED	0.89	0.91
Costs of treatment of ED	768.8	None
Probability of short term ED	0.77	0.73
Probability of long term ED	0.89	0.79
Probability of long term ED and IC	0.27	None
Probability of short term IC	0.47	None

AS = Active Surveillance.
PC = Prostate Cancer.
PE = Prostatectomy.
IC = Incontinence.
ED = Erectile Dysfunction.

Probabilistic sensitivity analysis

Probabilistic analysis resulted in mean discounted costs of €16,415 (95% CI €13,664, €19,339) for PE and €9,564 (95% CI €8,535, €10,735) for the AS strategy. Mean QALYs amounted to 7.58 (95% CI 7.06, 7.93) and 7.60 (95% CI 7.07, 7.83) for PE and AS respectively. Figure 4 shows a scatter plot of ICERs for 1,000 repetitions. AS was the more effective strategy in 56% of all realisations, and it was always associated with lower costs. Figure 5 shows the corresponding CEAC for AS. Even at very high WTP thresholds, the probability of AS being the more effective strategy is more than 50%.

Validation

Two decision-analytic models could be identified that compared the effectiveness of AS and PE for the treatment of early stage prostate cancer in terms of QALYs generated [29,33], and one other cost-utility study was found [52]. All these studies were undertaken from an American perspective. The models published by Hayes et al. both indicate that more QALYs are generated under AS than with initial PE (11.07 vs. 10.23 and 8.85 vs. 7.95) [29,52]. The study by Liu et al. reports a smaller QALY advantage for a comparable cohort of men. In their study, AS was associated with an additional 0.05 QALYs [33]. The smaller difference in QALYs is likely to be related to the fact that Hayes et al. assume that utility

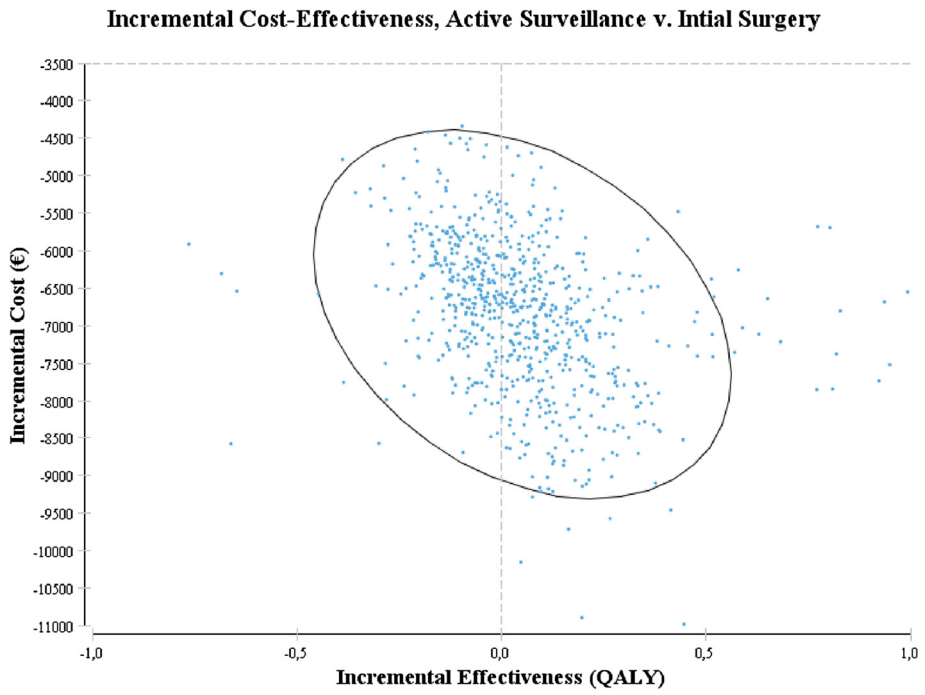

Figure 4 Scatter plot.

under AS is higher than after PE with no adverse effects. Liu et al. assume equal utility in both states. Our study reports a smaller overall amount of QALYs because the age related decline in quality of life is also considered. The only cost-utility study identified also found AS to be a cost-saving strategy from the perspective of US Medicare [52]. This corresponds to a recent study by Keegan et al. showing that AS is a cost-saving treatment option when compared with immediate treatment in the context of the US healthcare system [53]. Face validation resulted in model adaptations with respect to development and treatment of AEs, length of transition cycles as well as assumptions concerning resource utilisation. For the sake of external validation, we ran the model with the RR of PC death derived from the PIVOT trial. Ceteris paribus this resulted in the same strategy ranking with additional 0.01 QALYs gained in the AS arm (7.61).

Discussion

We present the first cost-utility study assessing the cost-effectiveness of AS and PE in a European context. Our analysis demonstrated that AS is a cost-saving treatment strategy for men aged 65 years with low risk, early stage carcinoma. AS generates more QALYs at lower costs

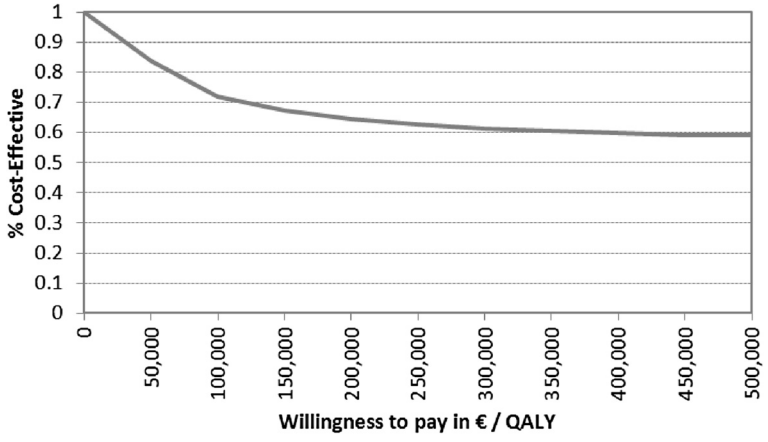

Figure 5 Cost-effectiveness acceptability curve for active surveillance.

than treatment with PE in this cohort. The difference in life expectancy was small as other cause mortality accounted for most deaths and limited the influence of treatment specific differences of PC death. Sensitivity to changes in the discount rate and time horizons was low and did not change strategy rankings.

Despite these results, PE is currently widely applied. As the calculation of costs shows, this may be because the current reimbursement rates in Germany set incentives in favour of PE rather than the AS strategy. For example, the restricted ambulatory reimbursement for AS conflicts with the increased patient need for information and counselling. Also, hospitals cannot charge for preventive services and patients are not charged co-payments if they choose the more costly service.

The wide spread of effectiveness results shown in the scatter plot (Figure 4) illustrates that the results are associated with considerable uncertainty surrounding key effectiveness and outcome parameters. Sensitivity analysis revealed that the results are highly sensitive to varying the probability of developing metastases under AS. This reflects the uncertainty concerning the precision of early stage diagnosis and the associated uncertainty in comparative effectiveness between AS and PE. The risk of under-staging, i.e. wrongly diagnosing an aggressive tumour as low risk, due to the limited predictive power of current diagnostic tools is a challenge for current urological research [54]. It has been shown that more than 25% of tumours may be wrongly diagnosed as insignificant in clinical practice [55,56]. Better diagnostic methods for identifying particularly aggressive tumours, e.g. by new molecular markers, analysis of DNA ploidy or CYP3A4 genotype [57], would increase the effectiveness of AS on account of the reduced number of PC deaths due to under staging [54].

Given the currently available staging methods, despite identical clinical parameters, the optimal therapy recommendation may differ depending on the patient's trade-off between quantity and quality of life and personal risk appetite [32]. Some patients may prefer the avoidance of AEs at the cost of increased risk of dying from PC. Others might not be willing to carry this risk and, at the same time, not consider AEs such as ED as a significant loss of quality of life. For such patients, PE may be a treatment strategy that is considered comparatively expensive but still cost-effective by a number of health care payers. This is highlighted by the fact that, if the lifetime spent in different health states is not adjusted for quality of life, PE is associated with an ICER of €96,420/QALY compared with AS. Also, postoperative rates of IC and ED - the main drivers of QALY advantage under AS–may differ considerably depending on the experience of the surgeon and the overall PE volume of the institution [58,59].

Although consideration of individual patient preference and local setting is an important issue in clinical practice, our study aimed to investigate the cost-utility of AS from a broader health care systems perspective. One of the strengths of our model is the use of age adjusted, population specific utilities in addition to health state specific utility weights. Although this methodology has been demanded by health economists, it is hardly applied in health economic evaluations [60]. Utilities can have a big influence on model results, and disregarding the utility level of the general population overestimates the amount of QALYs generated. Especially in an elderly study population, the effects of age dependent decline in mean utility can significantly influence QALY gains.

Our study is the first evaluation that systematically includes costs for PC management in a European country in the decision analysis. Prices for health services in European countries can differ substantially from those in the US and affect the transferability of results of economic evaluations [61]. The costs quoted for the PSA test in the US evaluation, for example, were almost 80% higher than in Germany, and the costs for PE were over 20% higher (based on an exchange rate of $0.75/€).

Limitations

A limitation of this study is the restricted quality of evidence concerning disease specific outcomes of treatments. We based our study on the RR of dying from PC from an RCT comparing WW with PE. WW describes a different strategy from AS and is more likely to favour PE as a treatment option. We tried to take account of this by conservatively assuming only half the treatment benefit being maintained under AS and performing wide range sensitivity analysis. We did not include all possible treatment options in our model. There is no conclusive comparative evidence available for alternative treatment options such as brachytherapy or intensity modulated radiation therapy [20,62]. Finally, we assumed that surgical treatment of benign prostate syndrome under AS did not affect the probability of disease progression, which might not be realistic. However, as a reduction in the probability of disease progression would favour AS, this corresponds with our conservative modelling approach.

Conclusion

The model results indicate that the difference in overall health outcomes between AS and PE is small. On average, approximately one month of life is gained by having immediate surgery; when QALYs are considered, about two additional weeks of life spent in perfect health can be gained by choosing AS. Given the cost difference, the cost-utility analysis replaces the clinical ambiguity with a more solid conclusion that AS may offer better value for money, given the assumptions and perspective of this

analysis. In conflict with these results, current reimbursement practise in Germany sets incentives in favour of PE rather than the AS strategy. This study may serve as a starting point to analyse the costs and incentives associated with existing reimbursement patterns in comparison with alternative arrangements.

The model results are subject to substantial uncertainty so that they must be handled with caution. This confirms the importance of ongoing clinical studies, such as the HAROW study in Germany [63] and the German RCT PREFERE [64], that will improve the evidence base in future years. The model needs to be updated as soon as new data from these studies are available. Appropriate staging and risk prediction, which allows the differentiation of high and low risk tumours, plays an important role in decisions about the optimal clinical strategy. Therefore, further research is needed to allow for a better stratification of invasive interventions to high risk patients. This cost-utility analysis can be used for early evaluation of the potential impact of different newly evolving diagnostic strategies on the costs and effects of PC management to inform further research and development [65].

This study revealed that whether PE is considered effective depends not only on clinical data but also on patient preferences about the role of quality of life in decision making. Existing evaluations are typically based on estimates of mean utility gains, which are insensitive to this aspect of benefit. Further research is necessary to better determine the appropriate role of preferences in existing evaluation frameworks. Finally, there is a need for further research on decision aids that make such information accessible to PC patients. Traditional approaches to informing the decision have been shown to understate the importance of postoperative AEs [66]. Ideally, these aspects could be combined so that an analysis of existing incentives and the integration of information from improved biomarker based risk prediction, valuations of health states and cost-effectiveness would lead to new models of fully personalised and cost-effective prostate cancer care.

Competing interests

The authors declare that they have no financial or non-financial competing interests.

Authors'contributions

FK programmed the model and drafted the manuscript. RW developed the model structure and provided medical expertise concerning various aspect of urologic health care provision. BS provided statistical expertise for parameter synthesis and analysis. WR conceived the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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4. Appendix

4.1 Auszug aus dem Abschlussbericht: S. 36

Das Prostatakarzinom stellt bei Männern die häufigste Krebsform dar. Die deshalb durchgeführte operative Entfernung der Prostata führt häufig zur Verletzung von Nerven und damit zu erektiler Dysfunktion (Impotenz) und Inkontinenz (Verlust der Harnkontrolle). Aufbauend auf Arbeiten der Projektpartner in den Bereichen Prostatatherapie und Nervenimplantat-Entwicklung soll im Rahmen des TP 15 ein neuartiges Therapiekonzept etabliert werden durch ein in situ formbares, resorbierbares Hydrogel, welches regenerierenden Nervenfasern als Wachstumsmatrix dient. Das Hydrogel basiert auf einer Lösung aus einer biologischen Matrixkomponente, die erst direkt während der Operation polymerisiert wird und sich damit jeder Form anpasst. Ziel ist die Reduktion von Komplikationen durch die Förderung der Regeneration peripherer Nerven [8]. Auf diese Weise können einerseits Kosteneinsparungen durch vermiedene Behandlungskosten von Komplikationen erzielt werden und andererseits die Lebensqualität der Prostatakrebspatienten erhöht werden.

Eine erste Analyse der gesundheitsökonomischen Literatur zur Einschätzung der Kosten und Effekte der Komplikationen ergab, dass potenziell beträchtliche Einsparungen möglich sind. So kommt eine Studie für den englischen Versorgungskontext zu dem Schluss, dass die jährliche Kosten für die Behandlung von ED aus Sicht der NHS bei £ 297 p.a. liegen [40]. Eine weitere Studie, welche die Kostenlast für die Behandlung der IK untersucht, kommt zu dem Schluss, dass die Kosten zwischen £ 378 und £ 556 p.a. für die NHS und zwischen £ 832 und £ 1667 p.a für die Patienten liegen. Eine Recherche der Lebensqualität über die Datenbank des Tufts Medical Center ergab signifikante Gesundheitsabschläge für bei Gesundheitszustände (IK = 0,83; ED = 0,89).

4.2 Auszug aus dem Abschlussbericht: S. 52 - 57

Das Modell der Machbarkeitsstudie wurde nach dem Workshop um die Behandlungsalternative active surveillance (AS) erweitert. Diese stellt einen direkten Wettbewerber für die Kohorte der Prostatakrebspatienten mit niedrigem Risikoprofil dar. Im Rahmen der AS wird das Karzinom mittels regelmäßiger Untersuchungen überwacht und die Operation erst bei Tumorprogress durchgeführt. Ziel ist es, auf diese Weise eine möglicherweise unnötige Operation und deren Konsequenzen (IK und ED) zu verzögern bzw. komplett zu vermeiden.

Die Modellstruktur wurde somit um diverse Zustände erweitert. In der Folge erwies sich ein Markov Modells adäquater als ein Entscheidungsbaummodell und die Programmierung des deterministischen und des probabilistischen Modells erfolgte in TreeAge 2013 ©. Das Modell erstreckt sich über die gesamte Restlebenszeit der Kohorte 65jähriger Männer, die mit Prostatakrebs eines niedrigen Risikoprofils diagnostiziert wurden. Übergangswahrscheinlichkeiten konnten auf Grundlage des RCTs der *Scandinavian Prostate Cancer Group* und einer meta-Analyse berechnet werden. Direkte medizinische Kosten wurden mit Hilfe von Experten sowie Leitlinien erfasst und auf Grundlage des EBM Katalogs, der DRG-Gewichte und Marktpreise für das Jahr 2011 bewertet. Gesundheitseffekte wurden in qualitätsadjustierte Lebensjahre (QALYs) gemessen. Altersspezifische Durchschnittswerte der deutschen, männlichen Bevölkerung wurden hierfür mit krankheitsspezifischen Werten gewichtet. Kosten und Effekte wurden mit 3% diskontiert und die Ergebnisse im Rahmen von deterministischer und probabilistischer Sensitivitätsanalyse auf Robustheit getestet.

Im Basisszenario dominiert die AS. Die Strategie generiert 0.02 zusätzliche QALYs (7.59 vs 7.57) bei einer Kostenreduktion von € 7.275 gegenüber Prostatektomie (PE). Bei Verzicht auf die Qualitätsadjustierung erweist sich PE als wirksamer mit einer IKER von € 96,420/QALY. Die Sensitivitätsanalyse zeigte, dass die Wahrscheinlichkeit Metastasen unter AS zu entwickeln sowie die Nutzwertgewichte unter AS und nach PE wesentliche Quellen der Ergebnisunsicherheit darstellen. Modellrechnungen mit alternativen Zeithorizonten (5,15 bzw. 30 Jahre) oder Diskontsätzen (0%, 5%, 7%, 10%) zeigten keinen Einfluss auf die Richtung des Ergebnisses. Die Monte Carlo Analyse zeigte, dass AS in 56% der 1000 Simulationen effektiver war.

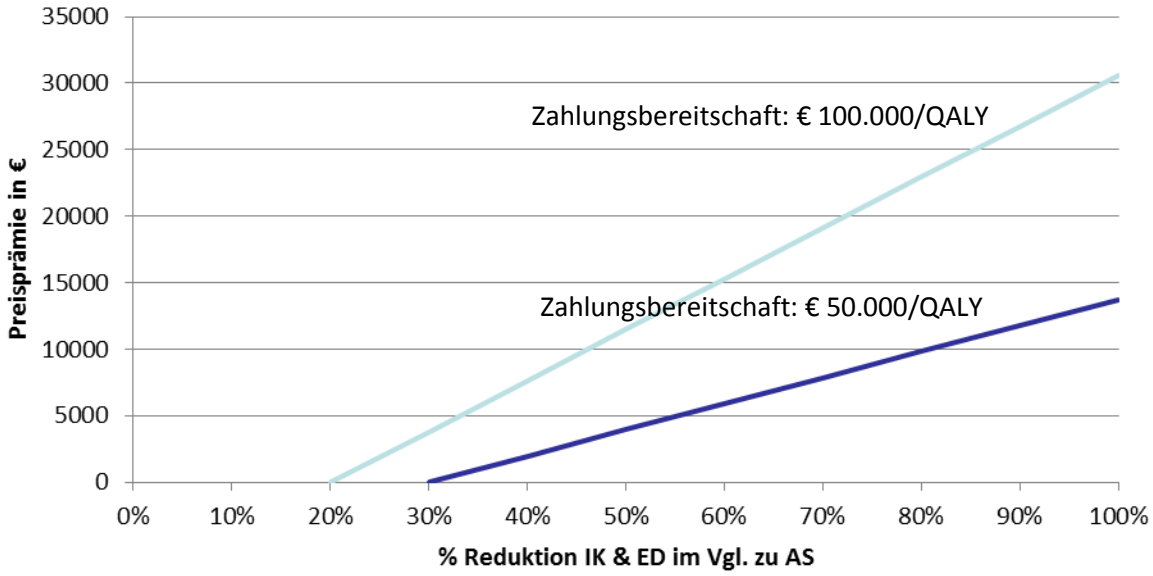
Die Ergebnisse hängen stark von den Patientenpräferenzen hinsichtlich Qualität und Quantität der Lebenszeit ab. Auf Grund des Risikos unbemerkter Tumorprogression ist die Lebenserwartung mit PE höher. Für risikoaverse Patienten, welche die Nebenwirkungen nicht als großen Verlust der Lebensqualität empfinden, kann PE die bessere Behandlungsoption sein.

Eine Limitation dieser Studie ist die begrenzte Qualität der Daten zur krankheitsspezifischen Mortalität, welche auf einem einzigen RCT basiert, der PE mit *Watchful Waiting* vergleicht, welches eine etwas andere Strategie als AS ist.

Das entscheidungsanalytische Modell wurde in der ebenfalls Thompson-ISI gelisteten, referierten wissenschaftlichen Fachzeitschrift BMC Health Services Research veröffentlicht [53]. Active Surveillance erwies sich im Rahmen der Modellierung als kostensparende Strategie im Vergleich zur Prostataektomie. Die Strategie ist also mit mehr qualitätsadjustierten Lebensjahren und geringeren Kosten assoziiert. Gleichzeitig ist die krankheitsspezifische Mortalität bei der Behandlung mit Active Surveillance geringer, sodass die Patientenpräferenzen eine große Rolle für die Wahl der optimalen Strategie spielen. Für Patienten, die verlängerter Lebenszeit einen höheren Stellenwert einräumen als der verbleibenden Lebensqualität, kann Prostatektomie eine kosteneffektive Strategie sein. Für diese Patientenkohorte wurden wertbasierte Preise für die Innovation geschätzt.

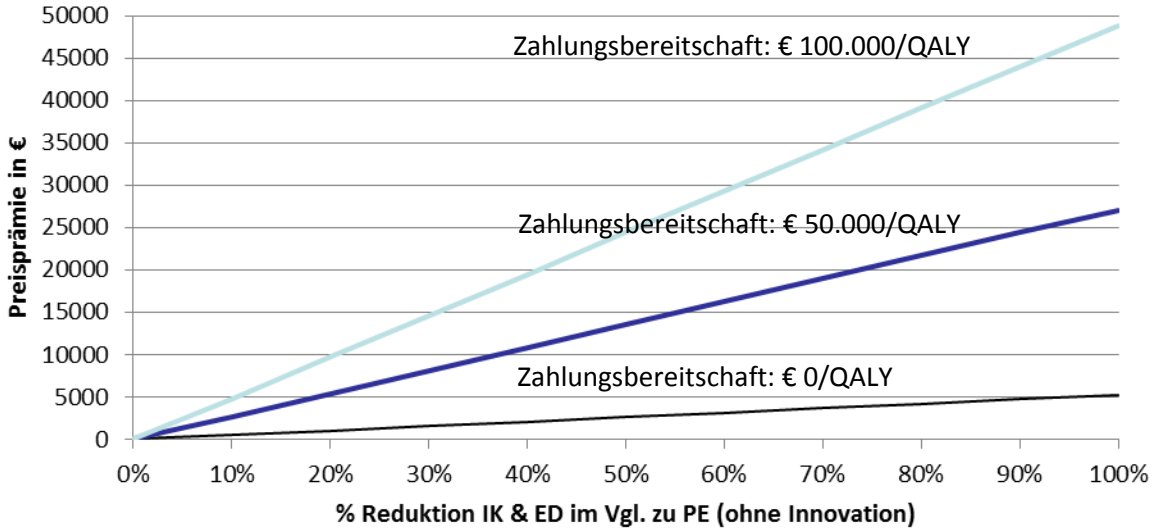
Auf Grund der Tatsache, dass die Strategie AS sich als kostensparend im Vergleich zur Prostatektomie darstellt, wurde die Strategie PE + Hydrogel selbst unter der Annahme, dass das gemeinsame Auftreten von IK und ED um 100% verringert wurde, nicht kostensparend. Unter der Annahme einer Zahlungsbereitschaft von € 50.000/QALY wäre eine Reduktion der Nebenwirkung um mindestens 30% notwendig, um aus Sicht des Modells einen positiven Preisaufschlag rechtfertigen zu können. Bei einer Zahlungsbereitschaft von € 100.000/QALY genügte bereits eine Reduktion um 20% (siehe Abbildung 12)

Abbildung 12: Obergrenzen für wertbasierte Preise in Abhängigkeit der Reduktion von Nebenwirkungen IK und ED bei AS als Behandlungsalternative



In einem weiteren Szenario wurden WBP für den Fall berechnet, dass AS keine Behandlungsalternative darstellt. Dies ist der Fall, wenn das Prostatakarzinom lokal fortgeschritten ist. In Diesem Fall gibt es lediglich die Option PE sowie PE + Hydrogel. Die resultierenden WBP in Abhängigkeit der Reduktion von Komplikationen sind in Abbildung 13 dargestellt.

Abbildung 13: Obergrenzen für wertbasierte Preise in Abhängigkeit der Reduktion von Nebenwirkungen IK und ED, wenn AS keine Behandlungsalternative darstellt



In diesem Szenario ergäben sich wesentlich höhere WBP bereits bei geringer Reduktion von Komplikationen.

Informationswertanalyse

Weitere Information ist für die Entscheider wertvoll, wenn die Möglichkeit besteht, dass auf Grundlage der gegenwärtigen Evidenz eine falsche Entscheidung getroffen werden könnte. Dies ist der Fall, wenn der zu erwartende Mehrwert positiv ist, die Verteilung der Ergebnisse jedoch negative Werte beinhaltet. Der Erwartungswert der perfekten Information (Expected Value of Perfect Information = EVPI) ist die Differenz zwischen dem erwarteten Mehrwert (Net benefit), der erreicht werden könnte, wenn alle Unsicherheit aufgelöst ist und dem erwarteten Mehrwert auf Basis der Evidenz, die zur Verfügung steht [54]. Der Nettonutzen ergibt sich aus dem Produkt der gewonnenen Outcome-Einheiten (QALYs) und der Zahlungsbereitschaft (λ) des Entscheidungsträgers pro zusätzlicher Einheit, abzüglich der Kosten für die Behandlung (NB=QALY × λ–Kosten).

$EVPI = E_\theta max_j\, NetBenefit\,(j, \theta) - \; max_j\, E_\theta max_j\, NetBenefit\,(j, \theta)$ [55]

Der EVPI kann aus den Ergebnissen der Monte-Carlo-Simulation berechnet werden und erlaubt den Vergleich mit den potenziellen Kosten die für eine Gewinnung weiterer Informationen notwendig wären. Die probabilistische Modellierung erlaubt außerdem

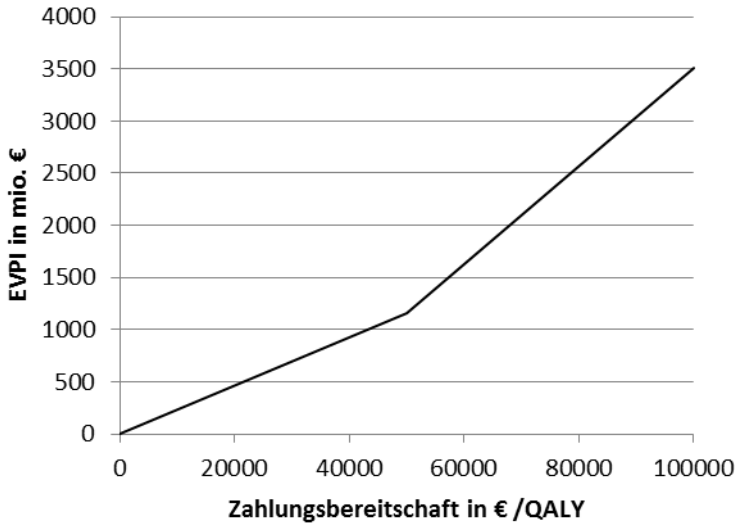
Informationswertanalysen, die indizieren, für welche Parameter (-gruppen) sich weitere Forschungen zur Reduktion der Parameterunsicherheit besonders lohnen, indem der EVPI für einzelne Parameter oder Parametergruppen berechnet wird (Expected Value of Partial Perfect Information = EVPPI). In beiden Fällen wird schließlich über alle Personen, die von einer Veränderung der Informationslage während der betrachteten Zeitspanne betroffen sind, aufsummiert.

Im Basisfall wurde eine Zahlungsbereitschaft von λ = € 50.000 pro QALY angenommen und eine Monte-Carlo-Simulation mit 10.000 Wiederholungen in TreeAge 2013 durchgeführt. Die Berechnungen wurden auf Grundlage der Prostatektomie - Fallzahlen der Krankenhausstatistik durchgeführt (2010 = 28,383). Die Berechnung geht weiter von einem Zeithorizont von 10 Jahren aus (d.h., dass die Evidenz für 10 Jahre relevant bleibt und danach eine neue Entscheidung zu treffen ist, beispielsweise wegen neu hinzugekommener Behandlungen) und setzt einen Diskontsatz von 3% für zukünftige Kosten und Effekte an. Dadurch ergibt sich dadurch ein Bevölkerungsmultiplikator in Höhe von 249.376, mit dem der EVPI pro Patient zu multiplizieren ist.

Die Ergebnisse zeigen, dass weitere Forschung potenziell einen großen Nutzen stiften könnte: der Populations-EVPI beträgt unter den getroffenen Annahmen € 304 Mio. Die Parametergruppe mit dem höchsten partiellen EVPI war Unsicherheit über die Wahrscheinlichkeit, Metastasen zu entwickeln, die auch die Prostata-Sterblichkeit im Modell bestimmt. Für diese Parametergruppe ergab sich ein Expected Value of Partial Perfect Information (EVPPI) von € 23 Mio.. Die Parametergruppe mit dem zweithöchsten EVPPI war die der Nutzwerte mit einem EVPPI von € 16 Mio. Größten Einfluss auf die gesamten erwarteten Kosten der Unsicherheit hat im Modell die Unsicherheit über die Prostatakrebsmortalität, die durch die Prostatektomie reduziert werden soll. Dieser wichtigen Frage wird derzeit auch bereits in groß angelegten klinischen Studien nachgegangen, deren Wert durch dieses Modell bestätigt wird. Zweitgrößten Einfluss hat die Unsicherheit über die Bewertung der Lebensqualität. Die Kosten spielen eine vergleichsweise geringe Rolle, da aus dem Modell sehr klar hervorgeht, dass Active Surveillance Kosten einspart.

Grundsätzlich sind verschiedene Annahmen zum Populationsmultiplikator denkbar, mit einem unbegrenzten Zeithorizont als Obergrenze [56]. Im Falle dieses Modells beträgt der Multiplikator mit unbegrenztem Zeithorizont 946.100. Um dem Einfluss des Schwellenwerts λ auf den Informationswert Rechnung zu tragen, werden die Ergebnisse für die zur Berechnung der WBP angewendete Schwellenwerte in Abbildung 14 präsentiert. Dabei wird der PEVPI mit unbegrenztem Zeithorizont ermittelt.

Abbildung 14: EVPI in Abhängigkeit von der Zahlungsbereitschaft für Gesundheit (i.e. €/QALY)



4.3 Auszug aus dem Abschlussbericht: Literaturverzeichnis

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Curriculum Vitae

Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

Chancen und Limitationen früher gesundheitsökonomischer Evaluation zur Unterstützung der Translation medizinischer Innovationen aus dem Bereich der regenerativen Medizin

selbstständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

_____ _____

Ort, Datum Unterschrift Doktorand

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