The value of medical 3D Printing

Hope versus Hype

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WOORD VOORAF

Toen ik in 2006 startte aan de Universiteit Gent had ik niet kunnen voorspellen dat ik de titel van ‘doctor’, PhD, zou mogen dragen. Het was een lang en vooral intensief parcour, dat ontzettend veel doorzetting vergde, maar waar ik nu bijzonder trots op terugkijk.

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Zoals reeds kort aangehaald werd ik ontzettend goed onthaalt in het topteam gezondheidseconomie. Mijn ‘bureaumies’ waren steeds een bron van motivatie, hulp en ambiance. Ik kon steeds bij jullie terecht met vragen en zelden heb ik mij verveeld. Ik ben blij dat ik er ook goede vrienden aan overhield.

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ABREVIATION LIST

3D	Three-dimentional
AM	Additive Manufacturing
ASDr	Atrial Septal Defect repair
ASO	Arterial Switch Operation
BCPA	Bidirectional cavopulmonary (Glenn) anastomosis
CAD	Computer-Aided Design
CAM	Computer-Aided Manufacturing
CAVCr	Complete Atrioventricular Canal Defect repair
CCG	Custom Cutting Guide
CHD	Congenital Heart Disease
CT	Computed Tomography
CTAC	Custom Three-flanged Acetabular Component
DICOM	Digital Imaging and Communications in Medicine
EBM	Electron beam melding
EQ-5D	EuroQoL 5 Dimensions QoL
FDA	US Food and Drug Administration
FDM	Fused Deposition Modelling
GDP	Gross Domestic Product
ICER	Incremental Cost-Effectiveness Ratio
LoS	Lenght of Stay
MRI	Magnetic Resonance Imaging
NHS	UK National Health Service
NICE	UK National Institute of Health and Care Excellence
NO	Norwood operation
OR	Operation Room
P4P	Pay for Performance
PET	Positron Emition Tomography
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RP	Rapid prototyping
SF-36	36-Item Short Form Survey
SL	Stereolithography
SLS	Selective Laser Sintering
SPECT	Single Photon Emission Computed Tomography
Tar	Truncus Arteriosus repair
TCPC	Total Cavopulmonary Connection
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
TOFr	Tetralogy of Fallot repair
VSDr	Ventricular Septal Defect repair

NEDERLANDSTALIGE SAMENVATTING

Medisch 3D printen kent een toenemende integratie in de huidige gezondheidszorg. Op heden werden de verhoopte medische voordelen, geassocieerd met de patiënt specifieke aanpak, nog niet afgewogen ten opzichte van de geanticipeerde additionele kosten dat deze technologie met zich mee brengt.

Gezondheid economische evaluaties gaan na of een medische technologie genoeg gezondheid genereert aan een aanvaardbare kost. Hierbij wordt afgetoetst of het waardevol is om deze technologie op te nemen in de reguliere gezondheidszorgen en die dus ook te vergoeden. Gezondheid economische evaluaties geven waardevolle informatie over de potentiele waard van de nieuwe technologie, dit zowel aan de gezondheidsmedewerkers die het zullen gebruiken, het ziekenhuismanagement dat erin zal investeren en de overheden of andere gezondheidsinstellingen die eveneens de kost zullen dragen.

Om een beeld te hebben van de huidige adoptiegraad van medisch 3D printen werd een literatuurstudie gevoerd op Pubmed, Embase en Web of Science. Artikels gepubliceerd tot en met december 2015, met minimaal 3 patiënten werden in de systematische literatuurstudie opgenomen. Zij werden geanalyseerd op een gestandaardiseerde manier met betrekking tot hun gebruik, uitkomsten en implicaties. Ons onderzoek toonde aan dat de literatuur rond medisch 3D printen een exponentiele groei kende sinds 2009, een trend dat nog steeds actueel is. Uit ons onderzoek bleek dat 45% van de publicaties gerelateerd waren met orthopedische chirurgie en 24% met mond, kaak en aangezichtschirurgie. De technologie wordt voornamelijk gebruikt om anatomische modellen en patiënt specifieke geleiders te maken als hulpmiddelen voor operaties.

Op basis van dit onderzoek kunnen wij 3D printen onderverdelen in 4 niveaus. Het eerste niveau is hierbij de anatomische modellen. Wanneer we de chirurgische planning verder willen overzetten naar de operatiezaal komen wij bij het tweede niveau, de patiënt specifieke geleiders. Voor erg complexe casussen kunnen patiënten voordeel halen uit het gebruik van 3D geprinte implantaten. Het printen van levende weefsels en organen kan als laatste niveau beschouwd worden. Ondanks het potentieel van deze 4de laag werd dit niet verder bestudeerd in deze thesis.

Anatomische modellen worden reeds veelvuldig gebruikt als hulpmiddel voor de chirurgische planning van hart operaties bij kinderen met aangeboren hartaandoeningen. Wij onderzochten de gezondheid economische waarde van deze modellen vanuit een het perspectief van de gezondheidzorg door middel van een Markov model op 15 jaar, en dit voor 8 verschillende operaties. De gegevens werden verzameld uit literatuurstudies met medische en economische data en aangevuld met expert advies waar de wetenschappelijke data niet beschikbaar was. De analyse toonde een incrementele kost die varieert tussen -366€ (95% betrouwbaarheidsinterval: -2,595€; 1,049€) voor een ‘Norwood operatie’ tot 1,485€ (95% betrouwbaarheidsinterval: 1,206€; 1,792€) voor het herstel van een artriaal septum defect. De studie toonde tevens aan dat een incrementeel gezondheids voordeel bestaat gaande van een verwaarloosbaar voordeel bij het herstel van een atriaal septum defect tot 0.54 kwaliteitsvolle levensjaren (QALY) (95% betrouwbaarheidsinterval: 0.06; 1.43) bij een truncus arteriosus herstel. Hieruit concludeerden wij dat anatomische modellen voornamelijk kosteneffectief zullen zijn bij complexe operaties, wanneer falen vaker voor komt en geassocieerd is met forse verliezen in gezondheid. De toegevoegde gezondheid economische waarde van deze modellen zal lager zijn wanneer de operatie minder complex is. Hoewel de resultaten preliminair zijn en deels afhankelijk zijn van de mening van experten kunnen we toch een eerste richting geven met betrekking tot de toepassingen met een gunstig gezondheid economisch profiel. Bij de juiste indicatie kunnen deze modellen erg waardevol zijn.

Uit he tweede niveau, werd de meest gebruikte toepassing van 3D geprinte chirurgische hulpmiddelen onderzocht. Patiënt specifieke zaaggeleiders voor totale knie prothesen hebben reeds hun intrede gemaakt in de klinische praktijk ondanks dat de literatuur omtrent hun klinische waarde eerder ambigu is. Verschillende meta analyses onderzochten het klinisch voordeel maar konden geen voordeel aantonen ten opzichte van de normale zaaggeleiders. Om een grotere groep aan patiënten te kunnen onderzoeken maakten wij gebruik van het Belgische register voor heup en knie prothesen. Wij onderzochten hierbij 112,070 primaire totale knieprothesen waarvan 5,735 (5.13%) met patiënt specifieke zaaggeleiders. Hierbij vonden wij geen grote verschillen in het profiel van de 2 groepen, met uitzondering van de fixatie van het implantaat. Een overlevingsanalyse, met correctie voor de fixatiemethode van het implantaat en de ervaring van de chirurg, gaf hierbij een wedsverhouding van 0.696 [betrouwbaarheidsinterval: 0.558; 0.868] in het voordeel van de patiënt specifieke zaaggeleiders. Dit betekent dat het risico op revisiechirurgie beduidend lager met de nieuwe technologie. Om de gezondheid economische implicaties te onderzoeken werd een Markov model opgesteld met een tijdsduur van 5 jaar. De data voor het model was afkomstig uit het register en uit de literatuur. Het model gaf een incrementele kost-effectiviteitsratio van €4,541 per QALY voor een 68 jarige patiënt, wanneer geen kost in rekening werd gebracht voor de beeldvorming dat noodzakelijk is om het hulpmiddel te maken. CT-scan gebaseerde hulpmiddelen hadden een incrementele kost-effectiviteitsratio van €28,839 en MRI gebaseerde hulpmiddelen hadden een incrementele kost-effectiviteitsratio van €52,735. Men kan dus aannemen dat deze hulpmiddelen gemiddeld gezien kosten effectief zullen zijn zolang de prijs van het hulpstuk, inclusief deze van de beeldvorming, beperkt blijft tot maximaal €587. Dit rekening houdende met een limiet van €40,000 per QALY, wat gangbaar is in België. De 'eenwegs' sensitiviteitsanalyse geeft aan dat de revisiegraad, de prijs van het hulpstuk en de prijs van de revisie chirurgie de belangrijkste impact hebben op de kosteneffectiviteit. De probabilistische sensitiviteitsanalyse toont aan de 59% van de gevallen kosteneffectief zijn indien de kost van beeldvorming niet wordt meegerekend. Voor respectievelijk CT-gebaseerde en MRI gebaseerde guides is dit 51.71% en 45% als de kost van beeldvorming wel in rekening wordt gebracht. Deze hulpmiddelen hebben ook in mond, kaak en aangezichtschirurgie hun intrede gemaakt. Preliminaire resultaten geven hierbij aan dat de operatietijd kan verkort worden en dat de esthetische uitkomst wordt verbeterd. Dit toont reeds aan dat deze hulpmiddelen mogelijks een voordeel hebben voor zowel de patiënt als het ziekenhuis.

Het derde niveau dat geïdentificeerd werd integreert de chirurgische planning maximaal door het maken van patiënt specifieke implantaten. We onderzochten de kosteneffectiviteit van 3D geprinte heup implantaten voor patiënten met een discontinuïteit in het bekken. Wij gebruikten hiervoor een Markov model over 10 jaar met een interval van 6 maanden en vergeleken het 3D geprint implantaat met een niet-3D geprint alternatief. De data werd gehaald uit de literatuur en bezorgt door een grote Belgische mutualiteit. De uitkomst van dit model gaf aan dat het nieuwe 3D geprinte implantaat meer kwaliteitsvolle levensjaren opbrengt tegen een lagere kost dan het alternatief. Voor een 65 jarige patiënt levert het implantaat gemiddeld gezien 0.05 additionele QALY's en een kostenreductie van €1,265 op. Wij merkten hier tevens op dat het voordeel groter was bij jonge patiënten dan bij oudere patiënten. De kans op een her operatie en de gezondheidstoestand na de eerste operatie waren de belangrijkste determinanten van het model. Een Monte-Carlo simulatie toonde aan dat het 3D geprinte implantaat kosteneffectief is in 90% van de patiënten jonger dan 85jaar en in 88% van de patiënten ouder dan 85 jaar, vergeleken met het niet 3D-gesprint alternatief. In België zou het gebruik van dergelijk implantaat voor deze specifieke patiëntenpopulatie een kostenreductie van €20,500 opleveren op jaarbasis.

Tijdens het literatuuronderzoek merkten wij duidelijk een positievere en enthousiastere tendens bij de eerste onderzoeken in vergelijking met de onderzoeken van een latere datum. Dit toont aan dat ook wetenschappelijke literatuur een invloed ondervindt van de hype van de nieuwe technologie.

Waarde kan erg verschillen afhankelijk van het perspectief waaruit je onderzoekt. Ook immateriële voordelen, zoals een beter imago voor het ziekenhuis en de arts door het gebruik van de nieuwe technologie kunnen eveneens doorwegen in de beslissing tot implementatie. Innovaties die zowel de efficiëntie van het ziekenhuis en de patiënt ten goede komen zullen in de toekomst, met de invoering van een meer uitkomst-gebaseerde vergoeding van de gezondheidszorg, steeds aantrekkelijker worden.

3D printen kan ook lokaal gebeuren in het ziekenhuis. Tegenwoordig zijn de anatomische modellen en guides dat in de ziekenhuizen geprint worden van een vergelijkbare kwaliteit als de industriële prints en vaak aan een lagere kost. De adoptie van de technologie kan hierdoor versneld worden.

Bij het onderzoeken van innovaties was één probleem erg aanwezig: de afwezigheid van robuuste data. Enkel in de studie rond de 3D geprinte zaaggeleiders konden wij een dataset aanspreken van uitstekende kwaliteit. Terugbetaling van medische innovaties is steeds een pijnpunt geweest, net omwille van de gebrekkige data om hun voordeel aan te tonen. Wij benadrukken dus het belang van het koppelen van een vroegtijdige terugbetaling aan het genereren van data op een systematische wijze. Dit zal de adoptie vergemakkelijken en versnellen doordat preliminaire analyses mogelijk worden. Hierdoor kan de financiering gekanaliseerd worden naar innovaties waar het grootste potentieel ligt op gezondheid economisch vlak.

SUMMARY IN ENGLISH

As many innovations, medical 3D-printing is increasingly drawing attention in the healthcare sector. To date, the estimated health benefits related to the tailored approach have not been balanced with the anticipated additional costs of the technology.

Health economic evaluations analyze whether a technology brings sufficient value to the general health at an acceptable cost and is worthwhile to be adopted and financially covered by healthcare systems. They provide valuable information to assess their value for physicians that are envisioning to use the technology, government or healthcare agencies that are in charge of paying the interventions using the new technology and hospital management looking to invest in new technologies.

To evaluate current adoption, a systematic literature review was conducted using the Web of Science, PubMed, and Embase incorporating literature up to December 2015. 227 papers on 3D printing applications on humans with more than 3 cases were retained for further analysis. Papers retained after the full-text review were analyzed in detail using an evidence table to report relevant study characteristics and outcomes. Based on commonly reported outcomes in the literature, we included the following variables: impact on operation room (OR) time or treatment time, level of accuracy of the printed part, impact on exposure to radiation, clinical outcome, cost, and cost-effectiveness. We could see an exponential growth in publications gaining momentum from 2009 onwards. This trend had not stopped to date. Our search showed that published results on 3D printing most often concern surgical guides and models for surgical planning. 45% of the publications were related to orthopedics and 24% to maxillofacial surgery.

Medical 3D printing can be split in multiple levels. Anatomic models can be considered the first level while custom printed guides take it a step further in bringing the surgical plan into the operation room and can be considered the second level. In some cases, patients can benefit from having an even more customized solution. Custom 3D printed implants are therefore considered to be the third layer. At last, bioprinting can be considered as the final level. While bioprinting might revolutionize medicine in the future, it is not quite there yet today and is not considered in detail in this thesis.

As an already well adopted application of 3D printed anatomic models we evaluated the potential cost-effectiveness of 3D printed anatomic models used as a tool for surgical planning of congenital heart diseases from a health care payer perspective. To analyze this application decision tree and subsequent Markov model with a 15-year time horizon was constructed and analyzed for nine cardiovascular surgeries. Epidemiological, clinical and economic data were derived from databases. Literature was reviewed to provide most of the input data but experts had to be consulted to close data gaps. A scenario, one-way, threshold and probabilistic sensitivity analysis captured methodological and parameter uncertainty. The analysis showed an incremental costs of using anatomical models ranging from -366€ (95% credibility interval: -2,595€; 1,049€) in the Norwood operation to 1,485€ (95% CI: 1,206€; 1,792€) in atrial septal defect repair. Furthermore, the incremental health benefits ranged from negligible in atrial septal defect repair to 0.54 Quality Adjusted Life Years (95% CI: 0.06; 1.43) in truncus arteriosus repair. We could therefore conclude that the use of 3D printed anatomic models are likely to be cost-effective in complex operations, but have a less favorable profile when the complexity of the operation is lower. While the results of this study have to be interpreted with caution, as expert opinion has been used to fill in the gaps, it gives a first glance at where we are likely to find the highest value for anatomic models for surgical planning. With the right indication, these models thus provide a clinical advantage at an acceptable cost.

In line with our levels, we analyzed the most used application of 3d printed custom cutting guides, being cutting guides for total knee arthroplasty. Despite being already well incorporated into the clinical practice the literature on its health economic value has been ambiguous. Multiple meta-analyses have been performed to evaluate its potential benefits but failed to show convincing evidence to routinely support its use. We therefore approached the matter differently, using registry data, to analyze the use of these custom guides in Belgium, its effect on revision surgery and its health-economic implications. We analyzed the data of the Belgian Arthoplasty Register (BAR) up to May 2020 incorporating 112,070 procedures of which 5,735 (5.13%) with custom cutting guides but could not find major differences in the descriptive statistics between the group with custom guides and the group with conventional guides, expect for fixation type. A survival analysis with revision surgery as outcome was ran to analyze the impact of using the custom cutting guides. The survival analysis showed an odds ratio of 0.696 [CI: 0.558, 0.868] for revision within 5 years in the advantage of custom guides when incorporating corrections for fixation and surgical experience, indicating the custom guides do provide a health benefit for primary knee arthroplasty. To assess the health economic impact of using these guides in primary TKA, a Markov model with a duration of 5 years was built. Utilities and costs were found through literature review and through communication with the manufacturers. Only direct medical costs were incorporated in the model. Transition probabilities were derived from the BAR. The price of CCG was found to vary between €375 and €400. The model revealed an ICER of €4,541 per QALY gained with CCG for an average 68 year old person, when no additional cost of imaging to make the guide was included. CT-based guides resulted in an ICER of €28,839 while MRI-based guides had an ICER of €52,735. On average, guides can be a cost-effective strategy at a cut-off of €40,000 if the total price, including all costs, does not exceed €587. Deterministic sensitivity analysis showed the revision rate, cost of the guide and cost of revision to be the most important factors influencing the ICER. Probabilistic sensitivity analysis showed 59% of the cases without imaging cost to be cost-effective. For CT-based and MRI-based CCG respectively, 51.74% and 45% of the observations were considered cost-effective. 3D printed surgical guides are also commonly used in maxillofacial surgery, where the surgical time and esthetics can highly benefit from it. The latter being in the advantage of both the hospital and the patient.

The third level of medical 3D printing integrates the surgical planning into 3D printed custom implants. We therefore analyzed the cost-effectiveness of a 3D printed acetabular cup for revision hip arthroplasty in patients with an acetabular discontinuity. We analyzed non-3D printed custom acetabular implant with the 3D printed alternative using a Markov model on a 10-year time horizon with cycle lengths of 6 months. The input data was obtained through a systematic literature search and provided by a large social security agency. The analysis was performed from a societal perspective. Based on the outcomes of our model, the 3D printed implant provided more health at a lower cost than its closest alternative. In the base case of a 65 year old person, a 0.05 QALY gain was found with a reduced cost of €1,265. The advantage of using the 3D printed implant was found to be greater if a patient is younger. The re-revision rates of both types of implants and the utility of having a successful revision surgery have the highest impact on costs and effects. A Monte Carlo simulation showed aMace to be a cost-effective strategy in 90% of simulations for younger patients and in 88% of simulations for patients above 85 years old. In Belgium it would imply a cost reduction of €20,500 on an annual basis. This analysis proves again that 3D printing can be cost-effective when selecting the right patient.

During our search for relevant literature we could clearly see the high enthusiasm and expectations in the first publications. This was often followed by less positive and more realistic results when the hype slowed down.

Furthermore, while we considered the health economic value from a (public healthcare) payer perspective the value can be different from other perspectives. Amongst the stated advantages of medical 3D printing we often found reduction in OR time or a reduced need for surgical trays. Both a benefit for the hospital. Furthermore, using an innovative technology might lead to competitive advantages in terms of marketing or even the quality of the delivered health. With the upcoming shift in medical remunerations focused on performances rather than procedures, using technologies that improve both health and in-hospital efficiency can become even more attractive.

‘In-house’ 3D printing has become more popular in recent years and results have become close to that of industrial prints. The often reduced price of in-house printing compared to the commercial prints might speed up the adoption and even shift the cost- effectiveness threshold down.

While analyzing this technology, one problem was found to be common. The lack of structured data to allow a solid analysis has been the main driver of uncertainty. Only the case of custom cutting guides for total knee arthroplasty was based on solid quantitative data compared to single studies in the other analyses. Getting reimbursement of innovative technologies has always been a difficult process, especially since the health benefit can’t be quantified. We therefore heavily advocate to incorporated a mandatory standardized data collection with the preliminary reimbursement of new technologies. This will facilitate the adoption of promising technologies as data analysis can be performed early on, guiding the financing towards innovations that show the potential to bring the most value for money.

Chapter 1

General introduction.

Introduction

We all believe, or at least want to believe, that new technologies will sort all problems and therefore often want to adopt it as soon as possible. The same is true for medical 3D printing. In the begin days a magnitude of promising articles were published (1). We could see reports on 3D printed tissues and were already dreaming about printing a new meniscus or even a new leg. Custom implants and guides were the solution to many problems by delivering a patient specific solution and greatly improving health outcomes, and all of this was published before the technology had proven anything. Additionally no one had mentioned the costs, which often tend to be higher for the innovation than the current standard (1). After the initial magnitude of positive reports came a wave of disillusionment on its potential, even leading to some repellence of the technology (2). With the technology getting more mature we start to question the cost-effectiveness. 'Does it actually provide enough health to cover its premium price?'

This cycle is common in innovations and often referred as the hype cycle (3). Innovations are often associated with a heavily exaggerated potential in the short term, followed by a steep disillusion underestimating its value on the long term. In orthopedics, this trend was also noticeable for surgical navigation (4). It was thought to solve many accuracy problems but failed to deliver in the short term leading to a massive disappointment. To date we do see valuable applications, eg in orthognathic surgery. The same can be seen in the evolution of 3D printing and more recently we even see this same high enthusiasm toward robotics (5).

Combining aspects and insights of medicine and (health)-economics, this thesis intends to give the reader a glance on the (potential) value of medical 3D printing. It tries to bring balance between its advantages and its cost and gives insights towards what could be done to improve the adoption and valuation of medical innovations.

This thesis is built upon three major parts. In the first part (Chapter 1) a general introduction on (medical) 3D printing and basics of health-economics is given, to ease the understanding of further chapters. Furthermore, an outline is given to understand de flow of this thesis. The second part consists of 4 scientific publications (Chapter 2-5) on specific applications of medical 3D printing. At last (Chapter 6), a general conclusion is given in the final part.

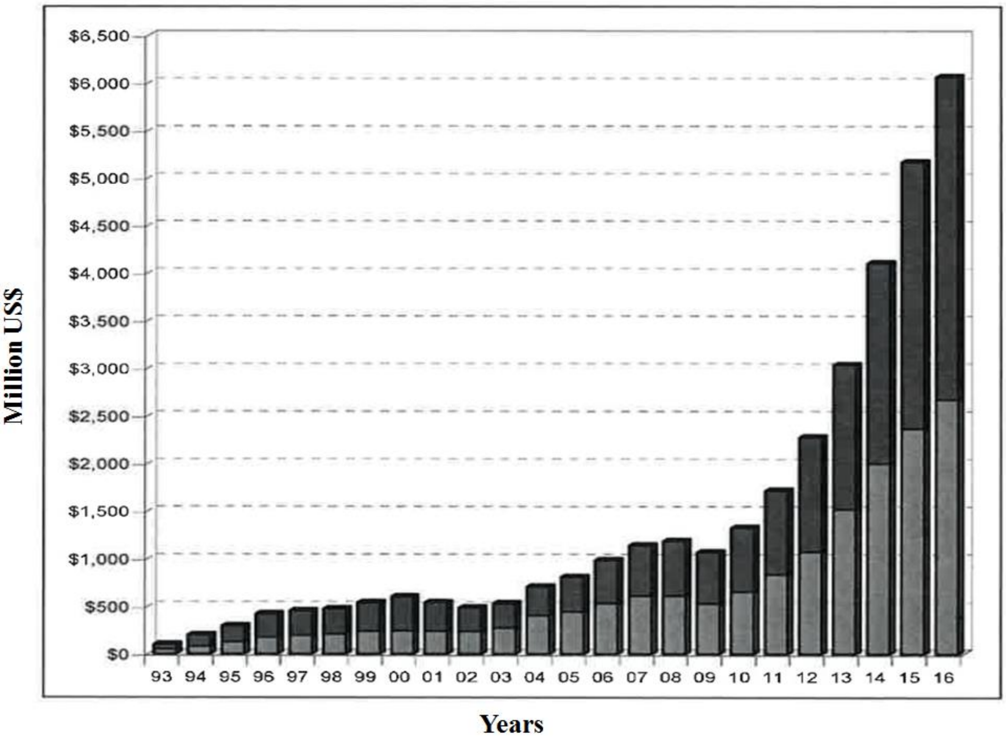
A general introduction to 3D printing

1.1. History and market

At the end of the 20th century, 3D printing first saw light. In 1981, Hideo Kodama, a Japanese researcher came with the idea to print three-dimensional plastic objects (6). Although the Japanese publication was the first describing 3D printing, Charles Hull is most often considered the father of 3D printing. Hull was the first to successfully file a patent on 3D printing in the United States in 1984 and founded his company '3D Systems' (7). The invention of 3D printing has had a major influence on the way single items and complex items are produced to date. Instead of subtracting material to get the desired shape of the object, material is added to result in the final object, hence the synonym to 3D printing: additive manufacturing (AM) (8). Even though it has been around for 30 years, the big industrial adoption and mainstream knowledge only came around 10 years ago (9).

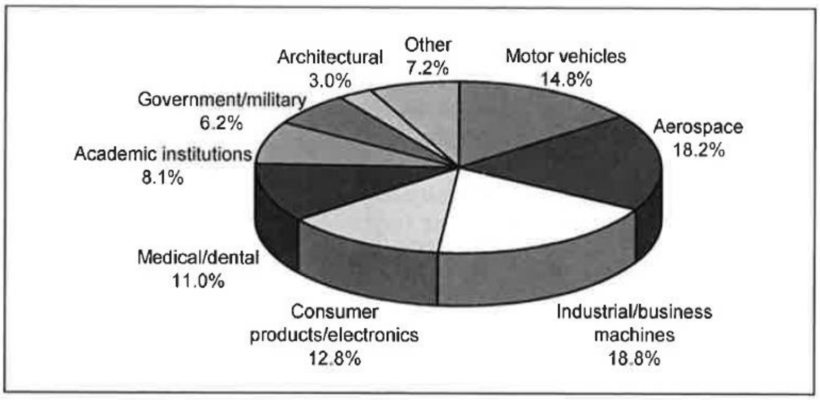
In 2016, 3D printing represented a 6.063 billion dollar industry, a growth of 17.4% compared to 2015. The market is growing rapidly and forecasted to be worth 26 billion dollars by 2022 (9).

Figure 1.1: Industry growth of 3D printing in million $. From Wohlers 2017 (9).



3D printing is used for a wide range of applications, ranging from medical applications, aerospace engineering, automobile prototyping to the future usage in bioprinting (10, 11).

Figure 1.2: General use of 3D printing per field. From Wohlers 2017 (9).



Belgium has been one of the pioneers in 3D printing with leading 3D printing companies as Materialise NV founded in 1990. This allowed Belgian clinicians to endorse the 3D printing technology. For instance, in 2011 at the University Hospital of Ghent, Belgium, 3D printing was used to prepare one of the most complex facial transplants ever performed. Shortly after, the university of Hasselt printed a patient-specific porous titanium prosthetic jaw implant that allowed bone ingrowth, and performed the first surgery in the world on a 83-year-old woman (12).

3D printing has revolutionized the way we prototype and produce custom equipment as moulds don't need to be produced anymore (13). This explains 3D-printing's other synonym; 'rapid prototyping' (RP) . The often cited advantage situates itself in the automobile industry where the cost of prototyping has experienced a steep decline since the introduction of 3D printing. At the moment 3D printing does not intend to replace all current manufacturing techniques; it is a new way of producing physical goods that could not have been produced before or could not have been made with the same precision (13, 14). Originally, low-volume productions of specific products were manufactured through 3D printing, as for example printing pieces of the Boeing airplanes (15). To date, manufacturing is the fastest growing segment of 3D. Major brands, e.g. Nike, have adopted the technology. The fabrication of functional parts accounts for 1/3 of the AM market and is expected to increase in years to come. (9)

3D printing can be used in almost all industries and has been used by many. Other than for prototyping and production, 3D printing has the potential to produce spare parts on demand and replace large inventories, especially when the parts are difficult to mass-produce, when the inventory cost is unreasonably high or when the demand is rare (14). This application has also been investigated by the US military to produce spare parts on location (16). In a more creative field 3D printing has been adopted by cooks, who print highly fashionable dishes, or artists that make art pieces with their printer. More recently, 3D printing has been widely used to make adapted pieces to modify the use of non-medical equipment to medical equipment. A great example of this was the use of full-face snorkel masks as to allow positive pressure ventilation on patients, or to be used as protective devices against viral particles during the Covid-19 pandemic (17-19).

As briefly mentioned above, major clothing brands, like Nike, joined the 3D printing market, not only for prototyping, but also for the production of some of their top-level sneakers (9).

3D printing has multiple advantages compared to standard manufacturing techniques. Holmström et al. (2010) summed the benefits of using the technology (14):

- No tooling is needed, with exception of the tools needed to remove supportive struts, which significantly reduces production ramp-up time and expense.
- Small production batches are feasible and economical.
- Design changes are easy and quick
- It allows products to be optimized for function, implying the ease of small modifications to a design to enhance its function
- It allows economical custom products (batch of one).
- The additive nature gives room to reduce waste.
- It has the potential for simpler supply chains with shorter lead times and lower inventories.
- It is perfectly suited for design customization.

3D printing is also prone to a series of disadvantages (20, 21):

- High energy consumption
- Often higher price tag for simple pieces
- Accuracy problems
- Very operator dependent and therefore time consuming

1.2. The process of medical 3D printing

Medical 3D printing is more than the printing process as a standalone. The process of printing an anatomical model can be explained in 3 major steps: image acquisition, image post-processing and 3D printing (22, 23). After the printing process the object needs post-processing to clean out debris or support structures from the printing process. This step can be considered as a 4th and final ‘finishing’ step before the 3D object is tested and used (22). All of the steps are prone to mistakes and therefore inaccuracies compared to the desired physical representation (23-25).

Image acquisition

The very first step in making a physical representation of an anatomy is acquiring an image. For 3D printing, Computed Tomography (CT), Cone-beam CT and Magnetic Resonance Imaging (MRI) are the best suited visualization methods next to more specific imaging techniques like Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) (22). Recently, 3D reconstruction has been made possible for plain X-ray and ultrasonography, allowing printing based on these imaging modalities as well (9). Images are saved in the common ‘Digital Imaging and Communications in Medicine’ (DICOM) format. The quality of the final model will highly depend on the quality of the image (22). Furthermore, the slice thickness and isometric voxel(*) proportions defy the final resolution of the model. The optimal print quality with respect to optimization of digital size and rendering is obtained when the slice reconstruction interval is similar to the printer or acquisition slice resolution (26). High-end medical 3D printers can produce physical models with a precision in the order of micrometers, which make them very reliable to reproduce the actual reality (27).

(*) Voxel: A datapoint in a three-dimentional grid

Image post-processing

The raw images are transformed into 3D data and then processed using 3D post-processing tools, of which the Belgian ‘Mimics’ is the most well-known commercial software package. The post-processing can range from standard segmentation to the complete planning of procedures using Computer-Aided Design (CAD). The later including the development of equipment specifically designed for the procedure (22).

As with all commercial software, freeware is also available for medical image post-processing software, e.g. 3D slicer.

Although the quality of this freeware is increasingly improving, the quality of processing cannot be warranted. Therefore, there is no assurance of having a good representation of the scanned anatomy. Studies have shown that there can be a significant difference in the end result using different software (24, 28). While an anatomically perfect copy is less important for teaching or training, it could definitely be a problem when used to make implants or guides. Surprisingly, the US Food and Drug Administration (FDA) does not require medical doctors to use commercial ‘FDA-approved’ software to make models on which medical decisions are made (29).

While using reliable software is essential for a good representation, the segmentation process is highly operator dependent (28). It is the most important step in terms of the model’s accuracy and requires a good knowledge of anatomy (30).

Printing the physical object

Depending on the specifications, the object is printed using the most appropriate printing technique. The different methods of printing 3D objects are discussed in a separate paragraph.

Post-processing

Often neglected, post-processing is an essential step for most 3D printed parts (20, 23). The post-processing needed for a certain part can vary a lot. Multiple post-processes can be identified:

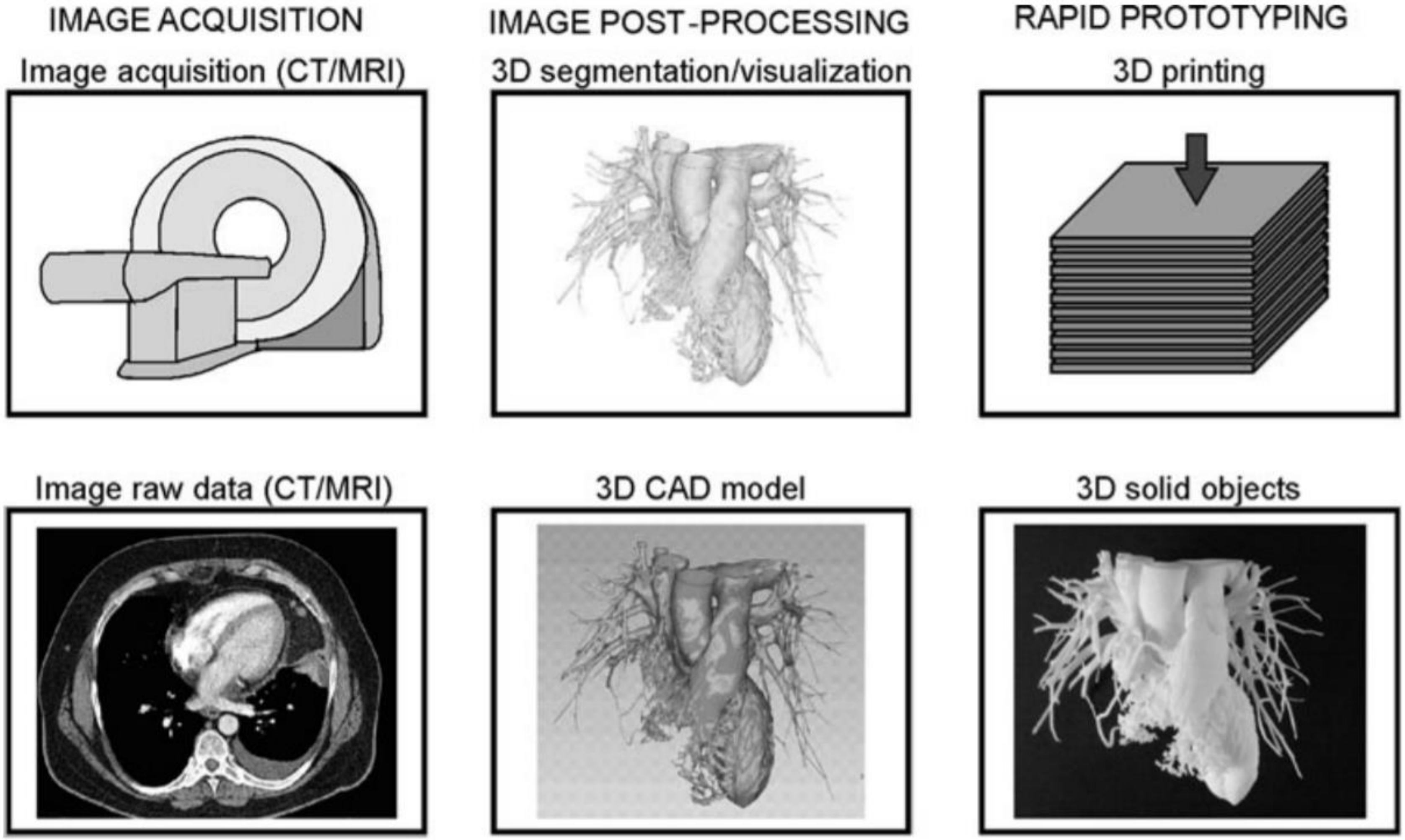
- Removing residual dust or resin
- Removal of supporting structures needed for printing
- Smoothening of the surface
- Painting

Post-processing can be seen as any change needed to result in the final product.

The 3D-model is meant to be a perfect physical representation of the anatomy or a perfect tool to translate the surgical planning into the Operation Room (OR). Therefore, it is of high importance to test and verify the accuracy of the 3D print (25).

An overview of the complete process of medical 3D printing is given in figure 1.3.

Figure 1.3: The process of medical 3D printing. Adapted from Rengier et al. 2010 (22)



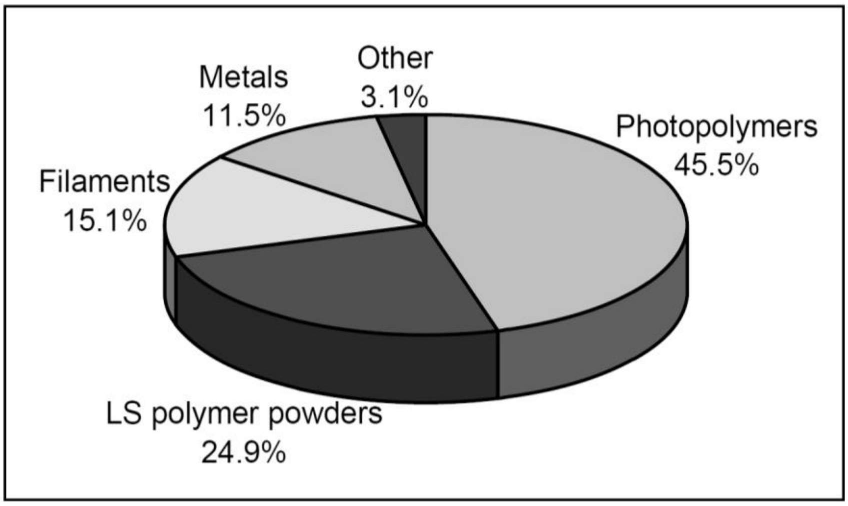
Additional requirements for medical implants and guides

Some medical 3D printing applications require more steps than previously explained for anatomical models. Patient-specific implants, surgical cutting and drilling guides and other surgical templates need an additional modelling step. After image post-processing the surgical steps are simulated to obtain the devices specific to the surgery to be performed. This is done by a close cooperation of both surgeons and engineers. It is known to be very time consuming and often requires multiple addaptations before the final 3D model can be printed For in-surgery uses, the objects undergo sterilization as final step. For all commercial medical 3D prints, in- and outpatient use, material traceability and control are required (31).

1.3. Different types of 3D printing

Three-dimensional printing is a term to summarize all methods of printing three-dimensional objects. While the first prints were made by photopolymers, a very wide variety of materials are now printed including metal and living materials.

Figure 1.4. Types of material printed in 2016. Source: Wohlers Associates 2017 (9).



Printing three-dimensional objects can be done using multiple methods of which stereolithography (SL), fused deposition modelling (FDM), selective laser sintering (SLS) and electron beam melding (EBM) are the most common (32).

For all 3D printing techniques, the thickness of the layer will be the determination factor for the print’s precision and detail. The thinner the layer, the more precise the model will be. Obviously, it is not always necessary to print in the highest quality as it will highly affect the printing speed.

Based on the same principle of Hideo, where UV light hardens the resin, Hull invented the technique called ‘stereolithography’ (SL). These 3D printers use a UV laser to solidify the targeted spot layer by layer with a high precision. The liquid photosensitive polymer solidifies on a tray which is then submerged to allow the laser to solidify the next layer. Although invented in the beginning of the 3D printing revolution, stereolithography is still the most used industrial 3D printing technique (9).

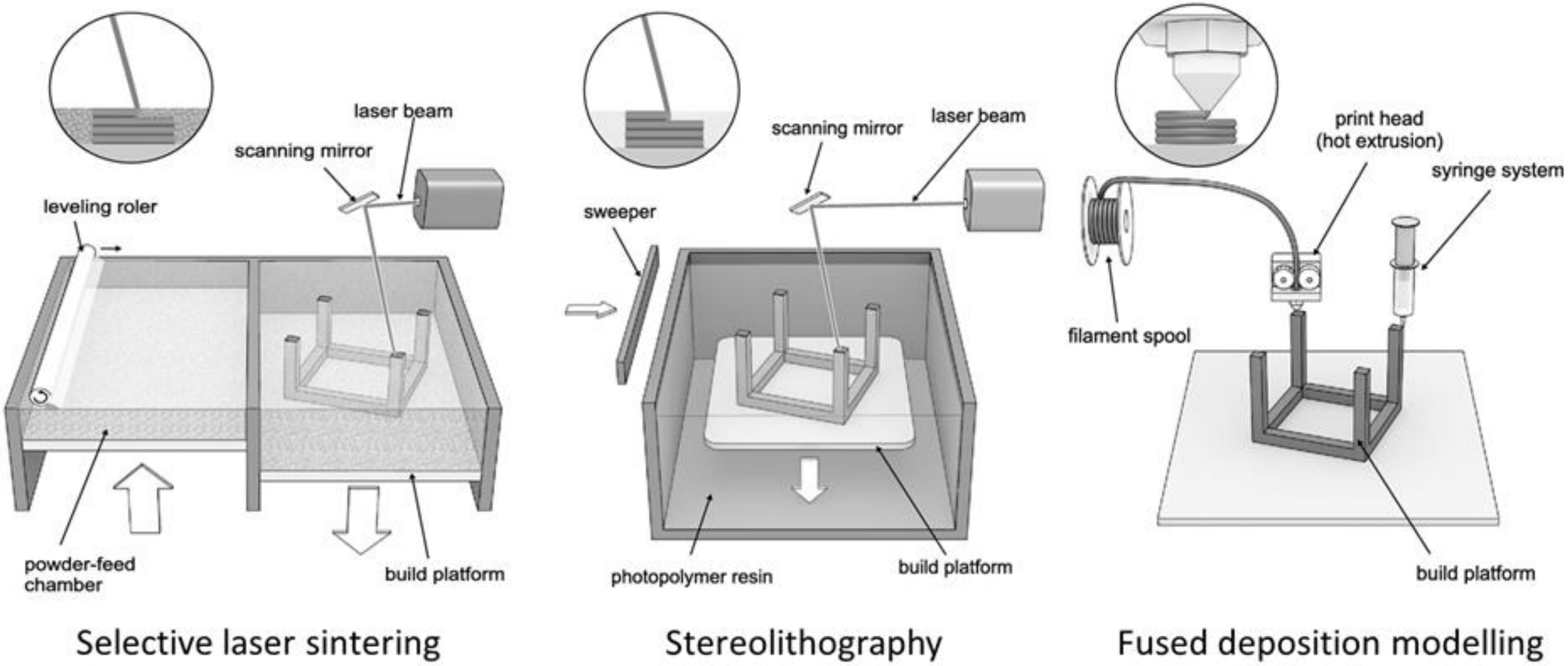
Selective laser sintering (SLS) is the most polyvalent 3D printing technique as the process is applicable to plastics, metals and ceramics. For this process, a powder is heated until just below its melting point. A carbon dioxide laser fuses the powder together on targeted spots. After fusion, a new layer of powder is deposited and the process restarts. When metals are used for SLS the chamber is filled with an inert gas suspension rather than normal air to avoid combustion (32).

Electron beam melding (EBM) is very similar to SLS. In EBM an electron laser beam melts the metal powder in a vacuum chamber (32).

For the general public, the most well-known method will be fused deposition modelling. Fused deposition modelling printers melt plastic filaments and deposit it layer by layer. The liquid plastics solidifies to form a layer-by-layer physical object. This is the type of printers you will find in a desktop setting (33). An visual representation of these techniques can be found in figure 1.5.

A variety of other printing techniques exist. Examples are ‘multi-jet printing’, where printing is possible in multiple colors or types of plastics, or ‘multi-beam printing’, where multiple beams are simultaneously used to print. Depending on the technical requirements and future purpose of the printed part, a suitable 3D printed method can be selected to make the part. Variables that should be considered are the material, strength, resolution and obviously the size of the product.

Figure 1.5: Common printing techniques. Adapted from Jamróz W et al. 2018. (34)



Selective laser sintering

Stereolithography

Fused deposition modelling

2. Health economics – a basic introduction

The following part is meant to give a short and basic introduction into health-economic evaluations to allow readers to understand the methods and reasoning behind chapters 3, 4 and 5.

2.1. Healthcare expenditures

Today, healthcare expenditures account for 10.04% of the Gross Domestic Product (GDP) in Belgium, of which 7.91% are financed by the public sector (35). With increasing age and the associated morbidities, the expenditures have already heavily increased and are expected to follow the same trend in the next decades (36, 37). Similar to normal households, governments have to take into account limited budgets. With that budget governments should try to maximize the health in their country.

Although we'd like to make all health-generating procedures or products available for everyone, healthcare has a cost, which undermines this utopic view. In a public healthcare setting, healthcare budgets are increasingly under pressure, making it a necessity to find ways to compare different interventions with each other, even though they have little in common, to reach an optimal solution. This is where health economics is brought to life (38-40).

Health economics is the science of incorporating financial data into healthcare. By weighing both cost and benefits of healthcare interventions it is intended to support decision-making to cope with increased standards of health and increased therapeutic options while the budgets do not increase likewise (41).

Costs and benefits are not universal but depend on which perspective is taken into account (42). Most studies are based on the perspective of the healthcare system, society, patient or hospital (43).

Value depends on the perspective (38). For the patient, the value will mostly be considered as the personal health gains that can be generated, in short the health value. For a hospital, value could be monetary. This could be a reduction in costs or an increase in turnover and revenues. This can be associated with increases in efficiency of operations, a decreased length of stay considering a fixed budget for a specific pathology or even a premium price due to the usage of the technology. Hence it also has value as a marketing tool or increasing efficiency.

Value depends on what one finds important or in short, the perspective from the person or entity valuating it.

In health economics, one can take different perspectives. The hospital perspective will mostly incorporate the monetary value, but could also incorporate part of the marketing or patient satisfaction. From a patient perspective, value will mostly be defined by health gains, as long as he or she can afford it or the cost is covered by an insurance. For an insurance company, value will mostly be found in reduced costs, which may or may not be present costs, but also in the future.

Similarly, the public healthcare perspective will include both costs and health. In the following chapters, this is the perspective we will be using. Therefore, hospital related costs and benefits will therefore not incorporated.

2.2.A method to estimate health: the QALY

To assess the health value of different interventions, a standardized equity has been introduced: the Quality Adjusted Life Year or simply QALY. QALYs incorporate both the health quantity and quality. It is expressed in utility over a certain time. Utilities express the health at a certain time and usually range from 0 to 1, with 1 being perfect health. They are derived from standardized questionnaires, of which the (EQ-5D) and 36-Item Short Form Survey (SF-36) are the most well-known (44, 45). Using QALYs allows us to compare interventions generating a different health quality and duration, allowing a trade-off between time and health (46) .

The QALY is an imperfect instrument and subject to many debates, but still the cornerstone for health evaluations (47). It assumes evenly distributed effects across all individuals and a stable intrapersonal preference over time (48). Furthermore, it is not well suited for condition-specific evaluations as it is based on general questionnaires like the EQ-5D, which are subject to ceiling effects when approaching perfect health (47, 49). While it does not incorporate personal preferences , it does give a good indication for societal decisions (50).

2.3. Basics in health-economic analysis

In general, two or more alternative strategies are set against each other in terms of cost and benefits. Four types of health-economic evaluations are commonly used (39).

The first being the ‘Cost (minimisation) analysis’, where the 2 strategies are assumed to be equivalent and only costs are guiding the decision-making process.

Second, the ‘cost-benefit analysis’, in which both costs and health benefits are measured in monetary units. It is based on the patient’s willingness to pay for health benefits, or to avoid health consequences (51).

Third, the ‘cost-effectiveness analysis’, in which the examined strategies share a common goal and have an effect which can be measured by a single metric. They are analysed as a ratio of effect/cost. This type of analysis is the most common.

At last, the ‘cost-utility analysis’ evaluates 2 interventions in terms of healthy years, typically expressed in QALYs. Both strategies don’t require the pursuit of similar goals and therefore allow comparison of different interventions against each other. The latter is important when allocating budgets to the interventions that create the most health in total. This type of analysis is considered to be a type of cost-effectiveness analysis, hence why they are often named like that (52). The analyses presented in chapters 3, 4 and 5 are all cost-utility analyses.

2.4. The ICER and QALY threshold

As summary value, the incremental cost-effectiveness ratio (ICER) was introduced. It defines the relative difference in cost per additional QALY between two compared interventions and is calculated by the following formula (53):

$$\text{ICER} = \frac{(\text{Cost of new} - \text{Cost of old/alternative})}{(\text{Effect of new} - \text{Effect of old/alternative})}$$

The ICER thus gives us the cost of 1 QALY for the new intervention.

We can’t put a price tag on health, or can we? The Universal Declaration of Human Rights states that we all have the right to have a an adequate health, implying healthcare as a basic right (54). This has been the subject of many debates, with often very emotional campaigns. As mentioned earlier, resources are limited so only interventions with a good value for money will have a share of these resources (39). This begs the question: What amount can we spend to generate 1 QALY of additional health? The used threshold is country-dependent and has a history of its own.

Historically the maximal acceptable price for 1 QALY was set to the be the cost of dialysis, being approximately $30,000, as the US Medicare is obliged to cover all costs of renal diseases (53). In the UK, the National Institute of Health and Care Excellence (NICE) considers a threshold of £20,000 to £30,000 (55). More and more authors advocated that a ratio of the GDP per capita should be used as a measure to determine the threshold (56). In Belgium, a 1/1 ratio of the GDP/Capita would result in a threshold around €40,000. More simplified, $50,000/QALY is often used, although voices are up that $100,000/QALY or even $200,000/QALY should be the norm in Western countries, especially for rare conditions or when consequences are high (57, 58). Furthermore, while inflation is applied in nearly any domain, the ICER benchmark has remained quietly stable over the past 15 to 20 years (57). The topic of thresholds and how they should be applied remains a topic of debates. Additionally, it has to be noted that value maximization does not only imply looking at the threshold but also looking at the impact on the budget as a whole (53). As a result, NICE calculated the actual threshold used by the National Health Service (NHS) to be around £13,000 rather than the theoretic £30,000 (55).

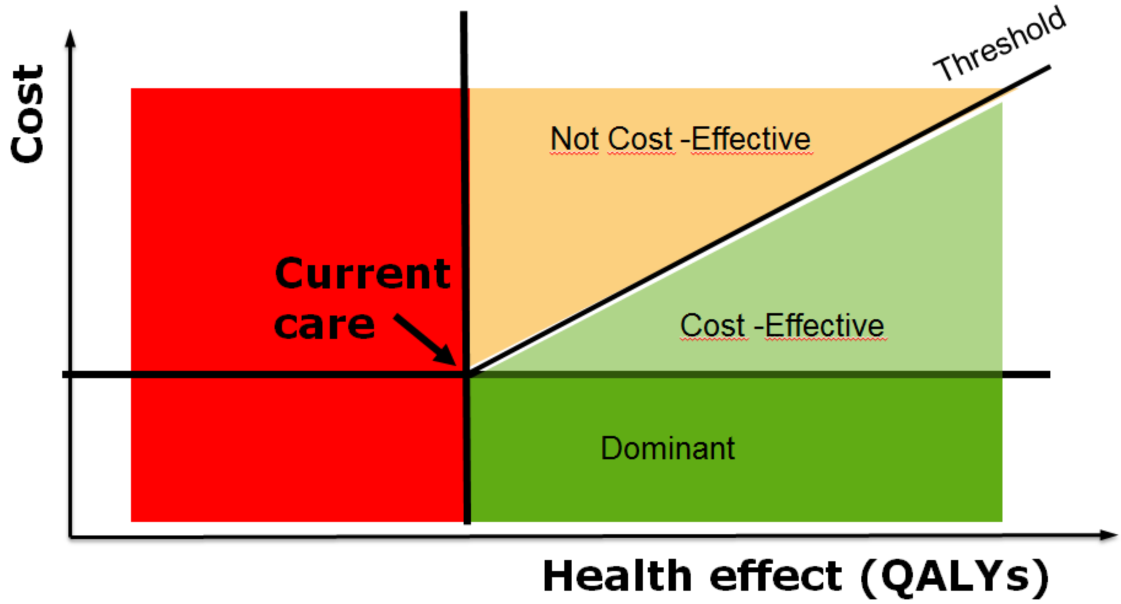
Rather than taking a fixed threshold, a variable threshold based on the severity of the disease has been debated (59). The Netherlands and Norway followed this approach by making a distinction based on the burden of disease (60, 61). The burden of disease is considered to be '*the average disease-related loss in quality and length of life of patients, relative to the situation in which the disease had been absent'* and varies between 0 and 1 (62).

In the Netherlands the threshold varies from €20,000/QALY up to 0.4 to €80,000/QALY above 0.7 with a threshold set at €40,000/QALY in between. This implies that there is a bigger willingness to pay for more severe conditions. The threshold might vary depending on other factors as well. The UK puts forward a higher threshold if the estimated life expectancy is shorter (63). Furthermore, a study based on the Norwegian population, favours the younger patients over the older ones (63).

At last, it is important to note that policy makers are more likely to reimburse technologies with a limited impact on the budget (64).

Figure 1.6 gives a visual representation of the ICER threshold. As mentioned before, new treatments are evaluated against their closest alternatives. The intersection of the graph shows the position of the current care. Interventions on the right create more health than the current standard while on the right, less health is created. From a moral point of view, the interventions on the left will not be considered further. On the right, the lower quadrant means the new intervention creates more heath at a lower cost than the current care. We consider this to be a ‘dominant’ strategy and will adopt the new intervention. The right upper quadrant signifies an increased health at a premium cost. Interventions below the threshold will be considered cost-effective. These interventions provide enough health to accept the additional cost. Interventions above the threshold are too expensive for the limited health benefit that is generated and are considered not cost-effective.

Figure 1.6. Visual representation of the ICER. Based on Annemans L. 2008 (38)



2.5. Discounting health and money

In economics, the practice of discounting future monetary benefits and cost is well-known. It incorporates aspects as inflation and time-preferences. Similarly, health effects are also submitted to a time preference and should be discounted. NICE has been one of the leading authorities in health-economics and originally suggested a discount rate of 3% for both equities and health (39). More recently, a discount rate of 1.5% is deemed to be sufficient for health (55, 65, 66).

3. Aims of this thesis and outline

As many innovations, medical 3D printing is drawing increasing attention in the healthcare sector. The estimated benefits related to the tailor-made approach need to be balanced with the anticipated costs. To date, the literature incorporating the health-economic value of medical 3D printing is scarce and mostly anecdotal or subjective. This thesis intends to give an overview of multiple well-known medical usages of 3D printing and gives early insights into the health-economic value of medical 3D printing. It intends to lead decision makers on how to evaluate these medical innovations and what to be looking for in the data-generation process.

While the first chapter was mend to be explanatory on the process of medical 3D printing and gives an short introduction on how health economic analyses are performed, the upcoming chapters dig further into analysing the usage and value of medical 3D printing.

In the second chapter, we give an overview of the current literature on medical 3D printing applied on living patients, with an eye on the health-economic aspects. This research shows the storyline within the applications of medical 3D printing, and hence, also this thesis.

When looking at the types of applications of medical 3D printing, multiple levels can be deducted. Every level but the last will be discussed in a separate chapter.

3.1. Anatomic models

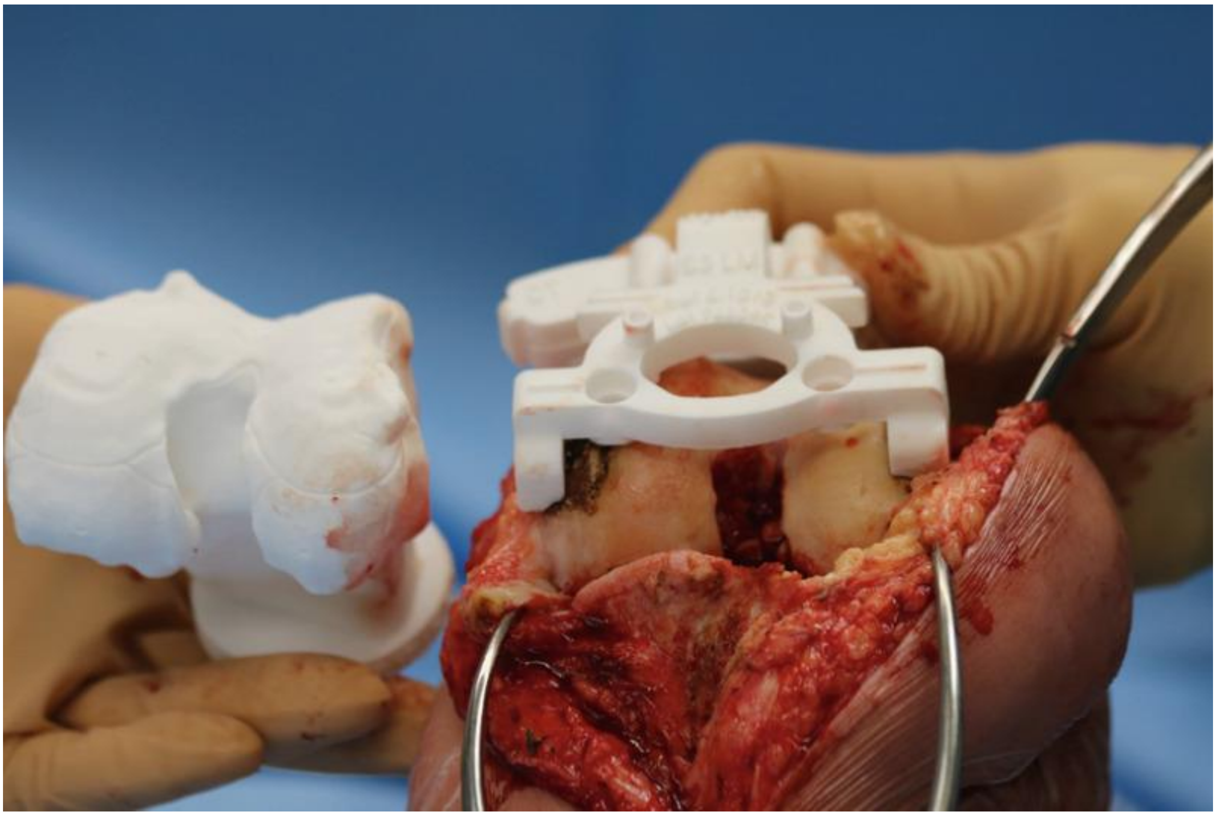
The first layer that can be deducted are the 3D printed anatomic models. They are physical representations based on medical images of a patient. They are used for teaching, preoperative planning, simulation and much more. In chapter 3, we go into more detail on the potential health economic value of these anatomic models used as a tool for surgical planning in congenital heart diseases (CDH). An example of such a model can be found in figure 1.7.

Figure 1.6: Anatomic heart model. Source: Materialise NV (67).

3.2. Surgical guides

Custom surgical guides can be considered as the second layer within medical 3D printing. Where anatomic models only give the physical representation of the pathology, custom guides can translate a pre-planned surgery into a useful tool which could increase precision and ease of positioning and handling. While generally the surgical guides exists in a 'one-for-all solution', with as prime example the cutting guides used in total knee arthroplasty (TKA), the fabrication of patient-specific guides is new. These 3D printed guides are used to translate specific requirement to a precise cut needed to have a perfect positioning of the implant or in cases of osteotomies, to perfectly translate the planned result during the actual surgery. An example of a custom cutting guide for TKA is given in figure 1.8. In chapter 4, we go into more details on the health economic evaluation of CCGs for primary TKA.

Figure 1.8. Custom cutting guide (CCG) (femoral component) for total knee arthroplasty (TKA), from Blakeney 2020 (68).



3.3. Custom implants

As a third level, 3D-printing can also be used produce implants that are specific to the patient’s anatomy. They are often used in cases where standard implants are not suitable or very difficult to use. Thee custom implants can be (parts of) arthroplasty implants, but also surgical plates or other devices. An example of a custom implant can be found in figure 1.9. In chapter 5 we showcase the health economic value of a custom acetabular implant, when used on a specific patient population.

Figure 1.9. Custom 3D printed acetabular implant. Source: Materialise NV (69).

3.4. Bioprinting

At last, bioprinting can be considered the fourth level within medical 3D printing. While this application is still in its early shoes it has the potential to revolutionize the way we practice medicine today. As mass applications close to none existent due to the preliminary state of the technology, we did not engage further into it.

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Chapter 2

3D-printing techniques in a medical setting: a systematic literature review

Based on **Tack P,** Victor J, Gemmel P, Annemans L. 3D-printing techniques in a medical setting: a systematic literature review. Biomed Eng Online. 2016;15(1):115.

1. Abstract

Background

Three-dimensional (3D) printing has numerous applications and has gained much interest in the medical world. The constantly improving quality of 3D-printing applications has contributed to their increased use on patients. This paper summarizes the literature on surgical 3D-printing applications used on patients, with a focus on reported clinical and economic outcomes.

Method

Three major literature databases were screened for case series (more than three cases described in the same study) and trials of surgical applications of 3D printing in humans.

Results

227 surgical papers were analyzed and summarized using an evidence table. The papers described the use of 3D printing for surgical guides, anatomical models, and custom implants. 3D printing is used in multiple surgical domains, such as orthopedics, maxillofacial surgery, cranial surgery, and spinal surgery. In general, the advantages of 3D-printed parts are said to include reduced surgical time, improved medical outcome, and decreased radiation exposure. The costs of printing and additional scans generally increase the overall cost of the procedure.

Conclusion

3D printing is well integrated in surgical practice and research. Applications vary from anatomical models mainly intended for surgical planning to surgical guides and implants. Our research suggests that there are several advantages to 3D-printed applications, but that further research is needed to determine whether the increased intervention costs can be balanced with the observable advantages of this new technology. There is a need for a formal cost–effectiveness analysis.

Keywords

3D printing, Additive manufacturing, Innovation, Surgery, Review, Patient specific, customized, Anatomic model

2. Background

3D printing has become more important in recent decades. 3D printing allows three-dimensional renderings to be realized as physical objects with the use of a printer. It has revolutionized prototyping and found applications in many nonmedical fields. In medicine, the technology has applications in orthopedics, spinal surgery, maxillofacial surgery, neurosurgery, and cardiac surgery, amongst various other disciplines.

Doctors mostly work with two-dimensional x-ray images or two-dimensional images obtained from computed tomography (CT) or magnetic resonance (MR) scans to gain insight into pathologies. This requires excellent visualization skills from the surgeon. The recent emergence of three-dimensional renderings of CT, MR, plain radiography, and echo imagery has improved visualization of complex pathologies but lacks tactile qualities. 3D-printed objects can be used to study complex cases, to practice procedures, and to teach students and patients (1). Furthermore, some current surgical procedures are complex and require guidance to avoid damaging essential parts of the body, or to obtain an acceptable esthetic outcome (2). In some cases, this guidance requires substantial amounts of ionizing radiation and can heavily increase surgical time (3). Additionally, anatomical defects can require custom prosthetics to repair damage as accurately as possible (4).

The need for improved visualization and surgical outcomes has given rise to 3D-printed anatomical models, patient-specific guides, and 3D-printed prosthetics. The growing surgical applications of 3D printing have made it interesting to analyze the current implementation of this new technology.

This article gives an overview of the current usage of 3D-printing techniques in human medicine, more specifically surgery, based on a systematic literature review using three major literature databases.

We attempted to identify domains and usages where the technology is fairly common or has been used several times, and to report its potential advantages and disadvantages. As healthcare budgets are under pressure and both hospitals and doctors desire to improve efficiency, we have included cost and cost effectiveness as variables in the analysis.

This resulted in the following research questions: (1) which surgical 3D-printing applications are commonly reported in human medicine? (2) What advantages, disadvantages, and cost consequences do surgical 3D-printing applications have compared to the standard of care?

3. Method

A systematic literature review was conducted using the Web of Science, PubMed, and Embase.

The search strategy was kept broad to ensure no relevant papers were excluded. The search headings were ‘3D printing’, ‘three dimensional printing’, ‘additive manufacturing’, and ‘rapid prototyping’. After expert consultation, an additional search was performed to include 3D-printing applications referred to as ‘patient specific’ guides and implants. Relevant articles found in references were added as well.

The initial database search was conducted in February 2015. An additional search was conducted in December 2015, to include all papers published in 2015. Only full papers of controlled trials and case series of minimum four cases, written in English, where 3D printing is applied for surgical purposes on living humans, were considered.

Manual screening of the titles and abstracts was performed so as to include only papers consistent with the application of 3D-printing techniques to human medical ends. The inclusion criteria were the use of ‘Computer Aided Manufacturing’ (CAM), ‘Computer Aided Design’ (CAD), ‘Additive Manufacturing’ (AM), ‘printed scaffold’, ’stereolithography’, and ‘reverse engineering’ for human medicine. Additionally, titles containing ‘customized’, ‘patient specific’, ‘templates’ and ‘physical model’ were retained in order not to overlook potential uses.

Examples of virtual 3D modeling or rendering without physical 3D models were excluded. Only clinical uses were considered; cadaveric, in vitro, and animal studies were not retained.

Only case series with more than three cases and clinical trials were selected, because we associate these with higher integration of the technology in the medical field. Publications written in languages other than English, or with no full paper available, were excluded based on the abstract.

Papers retained after the full-text review were analyzed in detail using an evidence table to report relevant study characteristics and outcomes. Based on commonly reported outcomes in the literature, we included the following variables: impact on operation room (OR) time or treatment time, level of accuracy of the printed part, impact on exposure to radiation, clinical outcome, cost, and cost effectiveness.

The impact on OR time/treatment time refers to time savings in the operation room or for the treatment itself, compared to the conventional procedure. This does not include savings in rehabilitation, nor does it take account of any additional work done by the surgeon prior to surgery.

The accuracy of the printed part was used to assess the quality of the printed part. For anatomical models, the resemblance to the original form was taken into account. For guides and implants, the accuracy of the printed part was assessed based on intraoperative adaptations and the need to abort the intended procedure in favor of the conventional procedure. The occurrence of few changes to the guide or few procedures being converted to the conventional procedure was considered to reflect good accuracy.

Radiation exposure was captured when mentioned explicitly by authors. Clinical outcome was assessed as improved surgical precision or improved final outcome. Note that there is an overlap between accuracy of the printed part and clinical outcome, as accurate guides result in better postsurgical alignment and therefore a positive outcome score. Cost was captured when mentioned by the authors. As some authors have begun to debate cost effectiveness, we considered this variable when it was mentioned.

4. Results

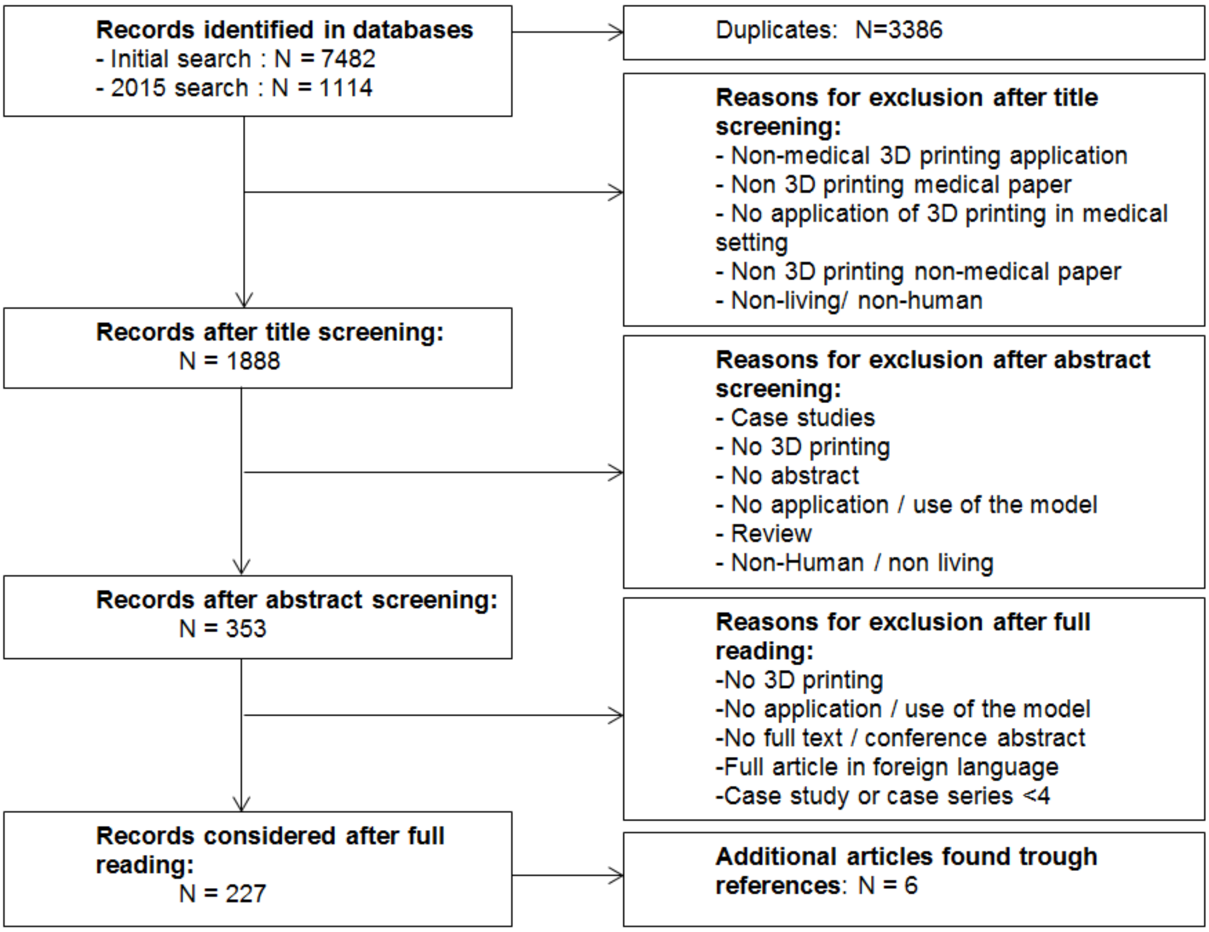
After the initial database search in February 2015, 7482 papers were selected. The additional search in December 2015, including all 2015 publications, resulted in 1114 papers. 3386 duplicates were removed. Screening of titles resulted in 1873 retained articles, with 2223 articles being excluded.

353 papers were selected for full reading; 1520 articles were excluded, most of which were case studies.

After reading the full papers, 224 papers were retained for further analysis. With the exception of three papers, all were surgical. Nonsurgical papers were excluded. Six relevant papers found in references of the accepted papers were added to the final analysis table, bringing the total number of papers to 227.

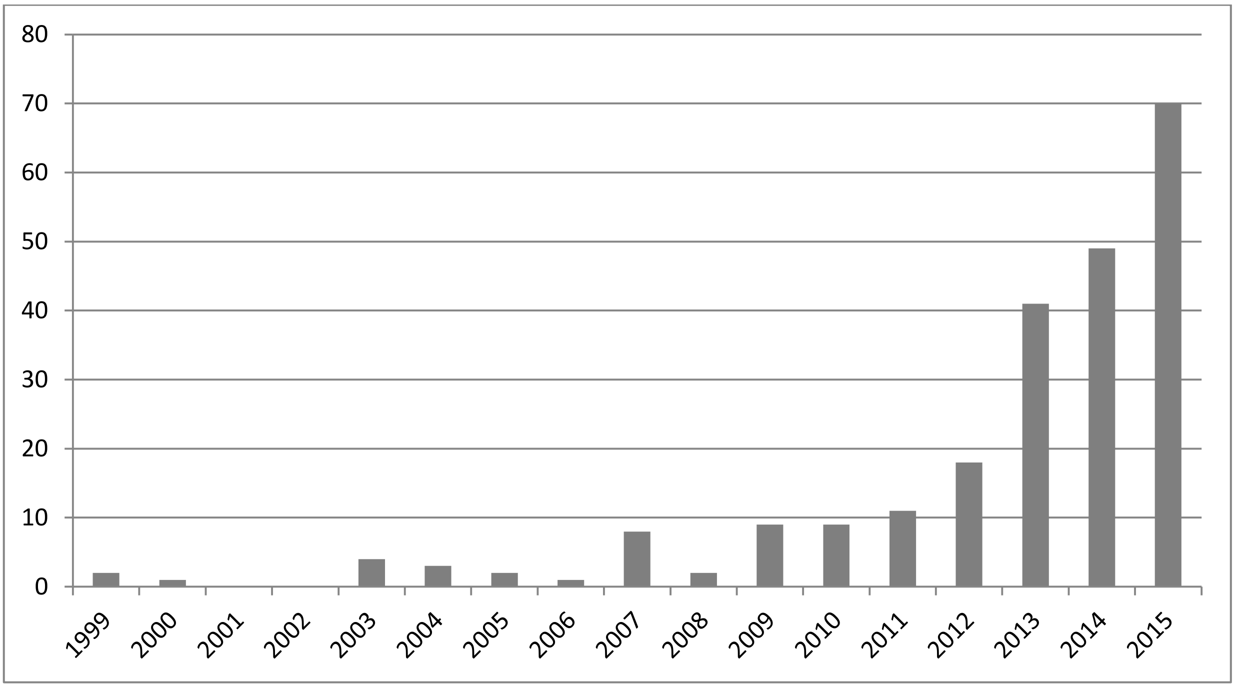
One paper was split in three, as three different studies were published together. Another paper was split in two since two different studies were discussed in it. This resulted in 230 observations in the 227 included papers. The search strategy and reasons for exclusion are given in Figure 1.

Figure 1. Search strategy and reasons for exclusion



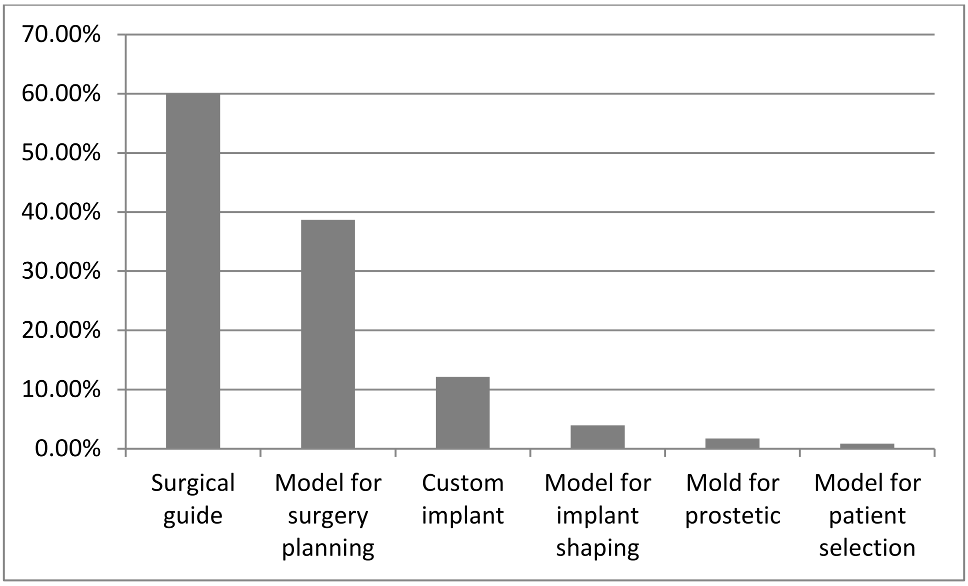
Only two papers were dated before 2000. Eight papers were dated between 2000 and 2005, 30 between 2006 and 2010, and 189 between January 2011 and 25 February 2015. Figure 2 gives an overview of the number of selected papers per year.

Figure 2. Overview of selected papers based on publication year



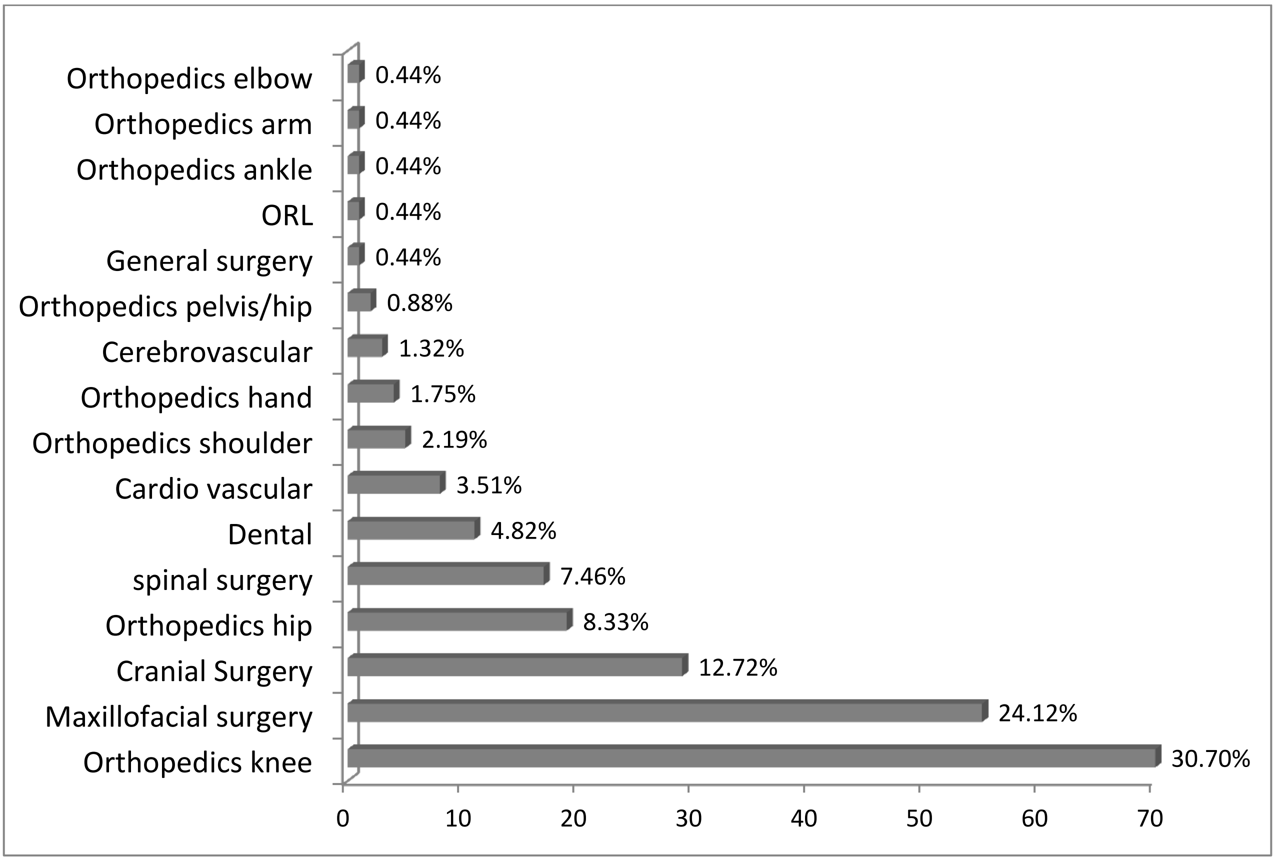
The published results on 3D printing most often concern surgical guides (60%) and models for surgical planning (38.70%) (Figure 3). Additionally, there are reports on the outcomes of using 3D printing to make custom implants (12.17%), molds for prosthetics (3.91%), models of implant shaping (1.74%), and models for patient selection (0.87%). Note that some papers used 3D-printing techniques for multiple purposes, resulting in a total greater than 100%.

Figure 3. Overview of the usage of 3D-printing techniques as percentage of total number of papers



The reports on 3D printing outcomes concern multiple surgical domains. Orthopedics has the largest share, with 45.18% (Figure 4): this is made up of knee (30.70%), hip (8.33%), shoulder (2.19%), and hand (1.75%) orthopedics. Maxillofacial surgery also accounts for a large share (24.12%). This is followed by cranial surgery and spinal surgery, representing 12.72% and 7.46% respectively.

Figure 4. Overview of papers per specific field



More in-depth results are collected in an overview table (Table 1). The data is organized by usage of the technology and discipline. An overview of the number of papers is given in each category. The total of 270 exceeds the total number of papers, as one paper can address multiple usages of 3D printing. The first variable in the table is impact on operation room (OR) time/treatment time. Reductions in operating time are assessed as beneficial. Secondly, the accuracy of the printed part is evaluated. As explained above, radiation exposure is only taken into account when the change in radiation exposure is explicitly mentioned in the paper. Medical outcome and cost are the final regular variables. The last of these, cost effectiveness, is only reported when the authors explicitly mention cost effectiveness. Appendix 2.1 gives an overview of the applications of the 3D printing technology per discipline with some addition details on the advantages and potential costs.

Table 1. Evidence table

	-	Custom implant	Model for implant shaping	Model for patient selection	Model for surgery planning	Mold for prosthetic	Surgical guides	Total
	Number of studies	**30**	**9**	**2**	**89**	**4**	**136**	**270**
OR / treatment time	Not mentioned	11	4	2	37	3	68	125
	Time reduction	17 (4)	5 (1)	0	48 (13)	1	53 (28)	123 (46)
	No time difference	1 (1)	0	0	3 (2)	0	8 (1)	12 (4)
	Time increase	1	0	0	2 (1)	0	7 (5)	10 (6)
Accuracy of printed part	Not mentioned	3	1	1	4	0	16	28
	Good/better accuracy	26	8	1	80 (4)	4	87 (13)	205 (17)
	Average accuracy	1	0	0	6 (1)	0	23 (3)	30 (4)
	Bad accuracy	0	0	0	0	0	10 (6)	10 (6)
Radiation exposure	Not mentioned	30	7	2	77	4	121	241
	Less radiation	0	0	0	8 (1)	0	9	17 (1)
	equal radiation	0	0	0	1	0	2	3
	Increased radiation	0	2	0	3	0	4	9
Clinical outcome	Not mentioned	1	0	2	10	0	15	28
	Improved	25 (2)	9 (2)	0	73 (8)	4	85 (15)	195 (27)
	Equal	4	0	0	7 (1)	0	30 (7)	41 (8)
	Negative impact	0	0	0	0	0	7 (2)	7 (2)
Cost	Not mentioned	16	7	1	52	3	94	173
	Cheaper	0	0	0	4	1	2 (1)	7 (1)
	Equally expensive	0	0	0	1	0	1	2
	More expensive	14 (4)	2 (2)	1	32 (21)	0	39 (19)	88 (46)
Cost effectiveness	Cost-effective	1	0	0	8	1	10	19
	Neutral	0	0	0	2	0	1	3
	Not cost-effective	0	0	0	1	0	6	7

(x) = Number of studies quantifying the data with numbers/statistics

4.1. Custom implants

Custom implants are used in cranial surgery, dentistry, and maxillofacial surgery (4–32). According to 17 out of 28 papers, custom implants reduce OR/treatment time. 25 papers mentioned good accuracy of the custom implants and improved medical outcomes. Radiation exposure was not mentioned in these papers. 14 papers mentioned increased costs, but one described an increase in cost effectiveness (4).

The custom implants were mostly made of titanium (10 of 28), polyether ether ketone (PEEK) (10 of 28), epoxide acrylate hydroxyapatite (2 of 28), hydroxyapatite (2 of 28), polymethyl methacrylate (1 of 28), polypropylene–polyester (1 of 28), and nonspecified acrylic-based resin (4 of 28).

4.2. Anatomical models

Anatomical models can be used for implant shaping in maxillofacial surgery, a topic that was discussed in nine studies (33–41). Five papers mentioned time reduction as advantage (33, 36, 38–40). Eight studies concluded that printed models provide good anatomical representations and nine studies mentioned improved surgical outcomes. Two studies mentioned exposure to ionizing radiation (36, 41) and two mentioned increased costs (39, 41).

Anatomical models are also used in selecting patients for cardiovascular surgery; this was discussed in two studies (42, 43). None of the papers mentioned time reductions, exposure to ionizing radiation, or medical outcome. One paper found the model to be a good representation of the actual pathology but did not mention the associated costs (42). Another publication mentioned that costs increased as a result of using an anatomical model (43).

Multiple domains use anatomical models for surgical planning. Our research showed anatomical models being used in cardiovascular surgery, vascular neurosurgery, dental surgery, general surgery, maxillofacial surgery, neurosurgery, cranial/orbital surgery, orthopedics, and spinal surgery (1–3, 9, 14, 15, 35, 37, 43–122). Among the 89 studies, 48 (53.93%) mentioned reduced operation room time. Two (2.24%) studies mentioned increased operation room time and 37 (41.57%) did not mention any impact on operation room time. Only 13 of the 48 studies mentioning reduced operation room time and supported this statement with actual numbers or statistics (3, 44, 72, 74, 78, 81, 84, 99, 107, 109, 118, 120, 121). In 80 (89.89%) of the publications, the printed part showed good accuracy, although this was only supported numerically in four studies (3, 81, 97, 106). Exposure to ionizing radiation was not mentioned in 77 (86.51%) of the publications, and eight mentioned decreased exposures (3, 59–61, 74, 79, 101, 107). Three publications mentioned increased exposure to ionizing radiation (92, 112, 115). No publication mentioned decreased medical outcomes with the use of anatomical models, while 73 publications mentioned improved medical outcomes. On the cost side, 52 publications did not mention costs, four mentioned decreased costs, and 32 mentioned increased costs. Two thirds of the studies reporting increased costs supported this claim with numbers or statistics. Eight studies, of which four used the models for maxillofacial surgery, estimated the anatomical models to be cost-effective (44, 58, 67, 74, 79–81, 97).

4.3. Molds for prosthetics

3D-printing techniques can be used to produce molds for making prosthetics, as discussed in three studies (45, 123, 124). We encountered this approach in cranial surgery, maxillofacial surgery, and ear surgery. In all the studies, the printed parts were accurate and improved the medical outcome. Both cranial studies were discussed in a single paper. One of these studies mentioned reduced OR time as an advantage (45). The study using 3D-printed molds for ear prosthetics stated that their use reduced costs and was cost-effective (124). None of these studies mentioned exposure to ionizing radiation.

4.4. Surgical guides

Surgical guides are the most popular medical application of 3D printing, with mentions in 137 of the 270 papers (50.74%) (10, 15, 30, 31, 39, 48, 59, 60, 62, 70, 71, 73, 74, 76, 77, 79–81, 83, 84, 86, 88, 89, 92, 93, 96–98, 106, 108, 109, 112–114, 119, 125–227). Apart from orthopedics (guides for knee arthroplasties), 3D-printed surgical guides were also used in neurosurgery, dental surgery, spinal surgery, and maxillofacial surgery. 28 of the 53 studies that mentioned reduced operation room time also supported this claim with numbers or statistics (39, 74, 81, 84, 109, 119, 132, 133, 136, 137, 141, 142, 146, 152, 153, 163, 176, 178, 182, 191, 195, 197, 201, 208, 211–213, 220). Increased procedural time was seen in seven papers, of which five supported this with numbers or statistics (62, 73, 126, 144, 154, 162, 226). 88 studies reported that the guides had good accuracy, while 23 reported average accuracy, and ten mentioned insufficient accuracy. Interestingly, six out of the ten papers reporting insufficient accuracy backed this up with numbers or statistics (149, 166, 183, 186, 192, 212). Radiation exposure was not mentioned in 123 (89.13%) studies. Less radiation was mentioned in nine studies, including by six of the 11 spinal surgery studies. Surgical guides improved clinical outcomes in 86 (62.31%) cases, gave similar results in 31 cases, and had a negative impact on clinical outcome in seven studies, all of which were knee orthopedics. The cost associated with the guides was only mentioned in 42 studies, of which 39 stated it to be more expensive and two stated it to be equally expensive. 19 of the 39 studies which indicated that the new technology was more expensive supported this finding with numbers or statistics. Ten studies stated that the guides were cost-effective, while six stated that they were not cost effective. None of these studies backed these claims with numbers.

Considering all applications, the new 3D-printing technology reduced operation room time in 46% of the studies. 76% of the studies mentioned that the printed part had good accuracy, and 72% mentioned improved medical outcomes. On the other hand, 33% of authors stated that the technology was more expensive.

4.5. Reductions in operation room time

Operation room time has always been one of the major arguments for medical 3D printing. Of the 227 articles, 42 described the precise impact of using 3D printing technology on OR time. For the majority of applications, 3D printing resulted in time savings. The results are given in Table 2. 3D applications such as surgical guides for maxillofacial surgery, models for spinal and maxillofacial surgical planning, and models for shaping implants used in maxillofacial surgery seem to benefit the most from the technology.

Table 2. Reported impact of medical 3D printing on operation room time

		Count	Average (in minutes)	Standard deviation
Cranial Surgery	Custom implant	4	-69.16	92.62
Cranial Surgery	*Custom implant*	*3*	*-15.81*	*7.74*
Maxillofacial surgery	Model for implant shaping	1	-42	
Cerebrovascular	Model for surgery planning	1	-30	
Maxillofacial surgery	Model for surgery planning	5	-5.8	78.52
Maxillofacial surgery	*Model for surgery planning*	*4*	*-43.5*	*24.52*
Orthopedics hip	Model for surgery planning	2	0.75	6.75
Spinal surgery	Model for surgery planning	2	-45.5	17.5
Maxillofacial surgery	Surgical guide	6	-60.33	61.85
Orthopedics ankle	Surgical guide	1	-12	
Orthopedics hip	Surgical guide	4	-0.025	5.72
Orthopedics knee	Surgical guide	20	-6.73	13.68

Italic text = outlier correction (outlier defined as study with a highly different outcome compared to the average of the remaining studies within the group)

5. Discussion

At the time this review was begun, no other analysis of the integration of medical 3D-printing techniques, domain, and use existed. Around mid-2015, Hammad et al. reviewed 93 articles concerning current surgical applications (228). Both their review and the present one come to similar conclusions. This review is more elaborate, including as it does 227 surgical papers and using a standardized form to evaluate these papers.

One of the main inclusion criteria was the use of 3D-printed materials for in vivo medical purposes. Papers describing 3D models used for medical teaching and testing purposes were therefore not included. Case series of four or more trials were considered, as we believe these reflect the maturity of the technological application for the specific domain. The number of publications meeting our selection criteria is increasing: only two studies were selected from 1999, while there were 70 qualifying studies in 2015, showing the growing interest of the medical sector in 3D-printing technologies. 3D-printed parts have several purposes in the medical setting. While anatomical models made up the biggest share in the early years of medical 3D printing, the growing importance of 3D-printed guides is noticeable. Surgical guides are now the most commonly reported type of 3D-printed application, with 60% of studies mentioning the use of printed surgical guides.

5.1. Anatomical models

3D-printed anatomical models see broad use in the surgical field. Our review suggests that, in orthopedics, their use has been shown to be beneficial, especially in complex hip replacements, where improved medical outcomes were reported unanimously. Also, studies of cranial (mostly orbital) fractures have reported improved results which have been credited to the use of anatomical models as guides prior to and during surgery, in order to understand the pathology better and to avoid pitfalls. These cranial anatomical models are often also used to shape the implant prior to surgery, resulting in an improved fit of the implant, improved medical outcome, and reduced surgical time. As with the anatomical models used for orthopedic and cranial purposes, our research suggests that spinal and maxillofacial models improve operation planning and clinical outcome, while reducing operation time. Furthermore, anatomical models can reduce the need for fluoroscopy during spinal surgery, reducing exposure to ionizing radiation.

Our research found anatomical models useful for planning vascular procedures such as percutaneous valve implantation, repair of aorta and cranial aneurisms, and surgical planning of complex congenital heart malformations. Furthermore, two cardiovascular studies suggested that the models improve patient selection for endovascular procedures, as compared with standard medical imaging.

Anatomical models can have direct usage during surgical procedures. During tooth transplant surgery, 3D models of teeth are used to prepare the donor site, improving the procedure’s success rates. Furthermore, anatomical models of the mouth are used to make drilling guides for dental implants and to make custom obturators for patients following maxillectomy. The latter reduced the amount of labor-intensive work on the part of both dentists and technicians. Furthermore, maxillofacial models are frequently used to shape implants prior to surgery, further enhancing surgical speed while improving clinical and esthetic outcomes.

Although anatomical models can be used on their own, our study perceived a tendency toward using anatomical models in combination with printed surgical guides. Apart from the previously mentioned benefits, anatomical models can be used for teaching medical students and can improve patient communication and knowledge of the pathology.

5.2. Surgical guides

Our research suggests that surgical guides are well incorporated in orthopedic surgery, spinal surgery, maxillofacial surgery, and dental surgery with more than half of the selected studies of our review mentioning the use of guides. Knee surgeons seem to be most interested in using guides. The uniquely positive results of knee orthopedic papers from 2012 gave way to more neutral results the years after, suggesting the initial excitement was tempered when the technology became more common. More recent studies mention no substantial difference in clinical outcome between patient-specific guides and standard instrumentation for total knee arthroplasty. Increased procedural complexity and less-experienced low-volume surgeons favor the use of surgical guides. Apart from clinical results, patient-specific guides reduce the number of surgical trays needed and slightly reduce OR time. Greater reductions in OR time were when surgeons have become more used to the guided procedure, according to one of the selected papers. Cost-effectiveness remains to be proven, but recent studies mentioning the cost-effectiveness of knee-guides suggest that the technology does not offer enough advantages to cover the additional costs associated with the guides.

Based on our findings, surgical guides seem to reduce operation room time and improve medical outcomes for spinal and cranial surgery. This is due to the simulation on models and the accurate translation of the preliminary surgery by means of guides. More than half of the selected studies reported reduced exposure to ionizing radiation due to the decreased need for fluoroscopy. In maxillofacial surgery, 3D-printed models and surgical guides are increasingly used for mandibular reconstructions and orthognathic surgery. The guides are used for the resection of both the mandibular part and the graft, as well as to reconstruct the missing part during oncological mandibular resections and reconstructions. According to the results of our research, spinal surgical guides translate the surgical planning accurately and make the outcomes less dependent on the surgeon’s experience. Similar results are seen with the use of guides during dental surgeries. Some authors question the systematic use of dental guides because of the associated higher costs, and suggest that guides be used only in complex cases. Finally, 3D-printed stereotactile fixtures can be used to guide implantation of deep brain stimulation implants with a substantial reduction of surgical time.

The accuracy of the guide or model and the accurate placement of the guide play important roles in the final clinical outcome or advantage provided by the model. The overlap between accuracy and clinical outcome is therefore unavoidable. The accuracy of guides can vary depending on the manufacturer providing the 3D-printed element and the time between the scan used for the production of the guide and the moment of surgery. Furthermore, surgical experience is needed to detect defective guides. Finally, the use of MRI or CT has an impact on the accuracy of the guide.

5.3. Custom implants

Anatomical models can be used as molds to manufacture prosthetics, as seen in selected cranial and ear surgery studies. Furthermore, patient-specific 3D-printed prosthetic molds have been used in chin augmentation surgery, resulting in both decreased surgical time and an improved esthetic outcome on account of the personal profile match. Finally, our research suggests that 3D-printing techniques can successfully be used to directly print the final implant, most commonly in cranial surgery. Cranial custom implants seem to be accurate and to decrease OR time, while being associated with improved clinical outcomes in nearly all the studies considered.

Likewise, 3D-printed trays and fixation plates improve medical outcomes and reducing operation room time for maxillofacial surgery. Moreover, one selected study presented the additional advantage of improved bone formation and angiogenesis with the use of custom implants.

Finally, complete dentures can also be made by rapid prototyping. The results vary, with one study mentioning lower esthetics for 3D-printed dentures and another study mentioning esthetics similar to standard dentures, while highlighting the advantages of face simulation before printing the final prosthetic.

5.4. General

3D-printing techniques are widely used for medical purposes. In the majority of the studies selected here, the medical outcome is improved by the use of 3D-printing. However, we believe that the enthusiasm should be tempered somewhat, as only 14% of the investigated studies supported this statement with numbers, making this major advantage rather subjective.

Operation time reduction is mentioned in nearly half of the selected studies and backed with numbers in only two thirds of these cases. In general, most 3D-printing applications seem to reduce the OR time, but wide variances can be seen between the different usages. Some OR time reductions are too small to result in relevant benefits. Although OR time reduction is a major advantage that could contribute to significant financial reduction, the increased time needed for surgical planning is rarely considered. Few studies explicitly mentioned the increased preparation time or discussed whether outsourcing surgical planning is an option. According to two selected studies using surgical guides for knee arthroplasties, surgeons and patients spend more time preparing for surgery than can be reduced during the surgery. Furthermore, these studies suggest that the planning might be more accurate when performed by the surgeon himself than when outsourced.

Although the large majority of the selected studies do not mention exposure to ionizing radiation, two thirds of the studies that do mention radiation report a decrease in this ionizing radiation. This can be explained by the high proportion of spinal surgery applications that mentioned decreased exposure to ionizing radiation, as fluoroscopic guidance is a well-known practice in that specific domain. It would be questionable to extrapolate this finding to other domains, as medical 3D printing requires CT scans or MRI. The first of these exposes the patient to a significant amount of ionizing radiation; fluoroscopic guidance, on the other hand, is not that frequently used.

Patients can additionally benefit from technology as anatomical models improve patient understanding of the pathology and procedure. This results in improved patient–doctor communication and greater patient satisfaction. Tactile anatomical models can also assist medical and surgical students to improve their knowledge.

Cost-effectiveness of the new technology is suggested in 7% of the selected publications, but is nowhere supported by numbers. Other publications question the cost-effectiveness and conclude that the use of 3D printing is not cost effective. Several authors mention that the complexity of cases can justify the additional cost of surgical guides. The growing economic pressure on healthcare makes it increasingly important for researchers to consider the economic sides of new technologies and techniques. Even small analyses made by noneconomists can be an indication of whether a new technique tends to be cost-effective or not. Fuller cost-effectiveness studies would be needed to evaluate the acceptability of the technology, both for complex cases and for routine cases using 3D printing. Although this was one of the key points of this review, few data on it could be found in the literature.

The cost of 3D-printed parts depends heavily on the manufacturing facility. Cheap desktop 3D-printers allow cheap 3D models and guides, but have less quality approvals and controls than commercial manufacturers, who are required to meet high quality standards. Furthermore, the reported costs of self-printed parts differ from author to author, with few mentioning direct preparation costs (CT, MRI, multiple prints, software, and computer) or the time cost involved in designing the model. The heterogeneity of these printed parts prevents more in-depth analysis.

Therefore, we would encourage future research to present the data in a much more transparent and objective way, and to make the first steps into cost-effectiveness calculations.

Although we considered additional articles found in the references of the selected publication, we are aware that some relevant articles might have been missed. We included case series and trials with four or more observations with the assumption that the most integrated practices will have publications stating their specific use. This means that subjects only reported in case reports could have been missed, even if they are well integrated. Surgical publications were considered and analyzed using an evidence table. Not all aspects that might be advantageous for a specific usage can be considered, especially when these advantages are not the direct result of the 3D-printed part. Medical 3D-printing applications used for testing, demonstrations, and training only were not incorporated in this review.

6. Conclusion

3D printing is already well integrated in medical practice and the literature. Applications vary from anatomical models (mainly for surgical planning) to surgical guides and implants. The main advantages stated by the authors of the selected papers are reduced surgical time, improved medical outcome, and decreased radiation exposure. Unfortunately, the subjective character and lack of evidence supporting majority of these advantages does not allow for conclusive statements. The increased cost of this new technology, and the often limited or unproven advantages, make it questionable whether 3D printing is cost effective for all patients and applications. Several authors have indicated that medical 3D printing has greater advantages when used to handle complex cases and with less experienced surgeons.

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Chapter 3

An early health technology assessment of 3D anatomic models in pediatric congenital heart surgery: potential cost-effectiveness and decision uncertainty

Based on Philip Tack, Ruben Willems & Lieven Annemans (2021) An early health technology assessment of 3D anatomic models in pediatric congenital heart surgery: potential cost-effectiveness and decision uncertainty, Expert Review of Pharmacoeconomics & Outcomes Research

1. Abstract

Background

During the last decade, three-dimensional anatomic models have been used for surgical planning and simulation in pediatric congenital heart surgery. With healthcare budgets under pressure, economic considerations are now increasingly important when considering new healthcare technologies. This research is the first to evaluate the potential cost-effectiveness of 3D anatomic models with the intend to guide surgeons and decision makers on its use.

Method

A decision tree and subsequent Markov model with a 15-year time horizon was constructed and analyzed for nine cardiovascular surgeries. Epidemiological, clinical and economic data were derived from databases. Literature and experts were consulted to close data gaps. Scenario, one-way, threshold and probabilistic sensitivity analysis captured methodological and parameter uncertainty.

Results

Incremental costs of using anatomical models ranged from -366€ (95% credibility interval: -2,595€; 1,049€) in the Norwood operation to 1,485€ (95% CI: 1,206€; 1,792€) in atrial septal defect repair. Incremental health benefits ranged from negligible in atrial septal defect repair to 0.54 Quality Adjusted Life Years (95% CI: 0.06; 1.43) in truncus arteriosus repair. Variability in the results was mainly caused by a temporary postoperative Quality Adjusted Life Years gain.

Conclusion

For complex operations the implementation of anatomic models is likely to be cost-effective on a 15 year time horizon. For the right indication, these models thus provide a clinical advantage at an acceptable cost.

Keywords:

Cost-effectiveness, 3D anatomic model, congenital heart disease, surgery

2. Introduction

Medical three-dimensional printing has significantly grown in interest during the last decade. Anatomic models were the first applications of three-dimensional printing for medical purposes. They have been used to represent patient-specific pathologies in a physical model allowing manipulation and surgical simulation. Different specialties have adopted these models to a great extent for surgical planning, patient selection, implant shaping, simulation, patient communication and device development (1-4).

Surgeons operating on congenital heart diseases (CHD) are often confronted with challenging cases where an extensive understanding of the patient's pathology is required. The understanding of the spatial relationship and the complexity of the anatomy was shown to be improved by using 3D anatomic models compared to conventional imaging (5-8). Three-dimensional anatomic models are mainly based on Computed Tomography or Magnetic Resonance Imaging (9) and have been used in line with the broad application of anatomic models for surgical planning, simulation and patient communication (1, 2, 4, 9).

A previously conducted review of the literature on medical three-dimensional printing (2) showed the potential advantages of anatomic models in surgical planning of CHD surgery. Three-dimensional anatomic models may improve diagnostic accuracy and patient selection (10). They may enhance the surgeon's strategic operative plan and improve patient safety by extended patient-specific anatomical knowledge (6, 8, 11). If appropriate, surgeons have the possibility to perform simulative procedures on the model (10, 12-15). Simultaneously, three-dimensional models may improve the surgical instrument selection process (16). The majority of the suggested advantages could be aggregated to a decreased incidence of complications and mortality (11). Several studies reported a perceived complication rate reduction (10, 16-19). Moreover, surgical and functional outcome may improve using three-dimensional anatomic models (20). Finally, intraoperative use of the models possibly decreases the need for ionizing radiation (17) and tends to decrease operation room time (10, 20-22). However, to the authors' knowledge, no quantitative evidence has been published yet to objectify or at least obtain a better insight into the stated advantages. The aim of this research is to conduct an early health technology assessment to assess the potential cost-effectiveness of the implementation of three-dimensional anatomic models as standard practice in nine cardiac procedures of different complexity.

3. Methods

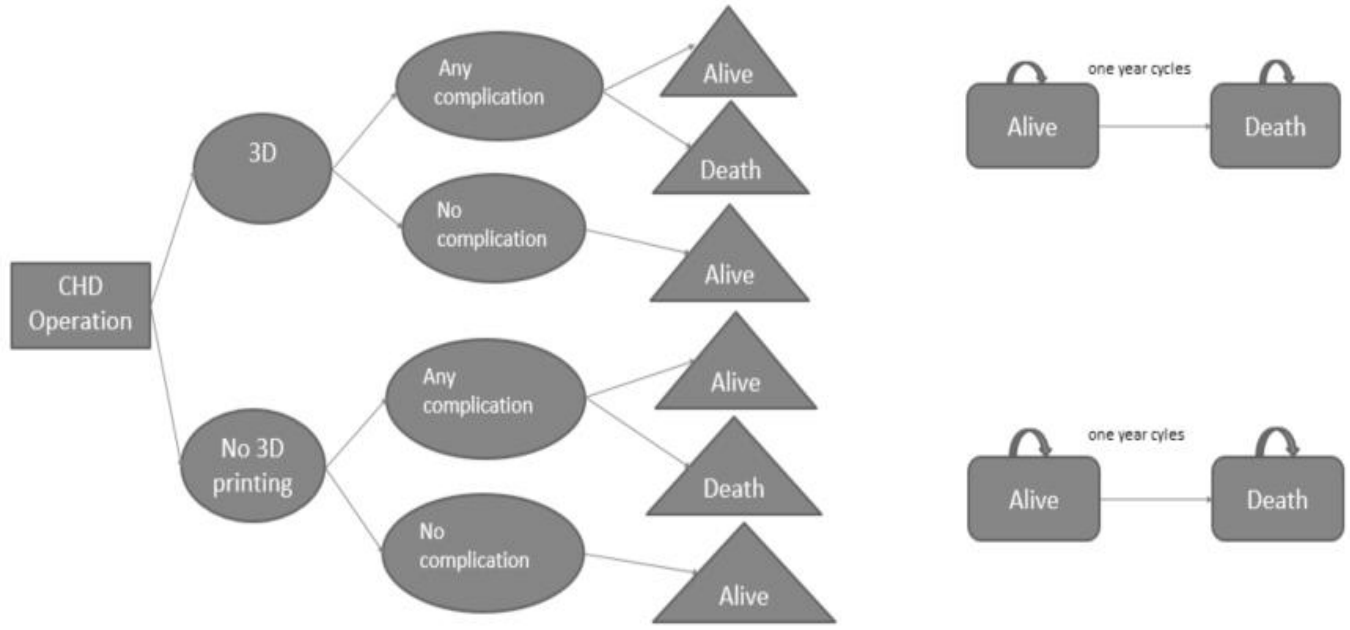
3.1. Overview study design

Based on Pasquali et al.'s inquiry (23), nine CHD surgeries were selected: Atrial Septal Defect repair, Ventricular Septal Defect repair, Tetralogy of Fallot repair, Complete Atrioventricular Canal Defect repair, Bidirectional cavopulmonary (Glenn) anastomosis, Total Cavopulmonary Connection, Arterial Switch Operation, Truncus Arteriosus repair and Norwood operation.

3.2. Model

A decision tree representing the index hospitalization was constructed with a simplified Markov model (figure 1) to incorporate the long-term health changes and costs. The model was developed in Microsoft® Excel 2016 (Microsoft Corporation, Redmond, WA, USA). The cost-effectiveness analysis was conducted in a Belgian setting using the health care payer perspective (i.e. public health payer and patient's perspective) and a 15-year time horizon divided into one-year cycles. Costs are displayed in 2017 euros. To assess health changes, Quality Adjusted Life Years are used. According to Belgian guidelines, costs are discounted at a 3% rate and Quality Adjusted Life Years at a 1.5% rate (24). The model's final outcome is the incremental cost per Quality Adjusted Life Year gained.

Figure 1: illustration of the model. Starting at the CHD operation. One year cycles with the patient being alive or being dead.



3.3. Clinical data input

Clinical input data was retrieved from an earlier study researching the pediatric cardiac procedures that occurred at Ghent University Hospital between 2007 and 2016. The study describes the hospital invoice data and clinical data of 537 index hospitalizations (25). An overview of the clinical data can be found in table 1a.

Complications were grouped in major and minor complications as described by Jacobs et al. (26). Renal failure, neurologic deficits, pacemaker after Atrioventricular block, necessary mechanical circulatory support, phrenic nerve injury/paralyzed diaphragm and unplanned reoperations were considered to be major complications. All other complications were considered to be minor complications (26). The early mortality was calculated from the clinical data of the previous study and defined as death within 30 days after the operation or death before index hospitalization discharge. Late mortality could not be calculated based on our data and was obtained from several international publications (27-36). The mortality should be seen as the total mortality up to the year at which it is stated. Yearly mortality rates are calculated using the following

$$1 - (1 - \text{Mortality rate from year X to year Y})^{\frac{1}{\text{years between } X \text{ and } Y}}$$

We counseled expert opinion to estimate the implications of using 3D anatomic models in CHD surgery, as literature is non-existent. Inclusion criteria for experts were (a) having hands-on experience with printed three-dimensional anatomic models and (b) being a cardiac surgeon, cardiologist or pediatric cardiologist. In total, 10 out of 42 medical doctors contacted, fitted the inclusion criteria and participated in the expert panel. The expert opinions were gathered by semi-structured interviews. Whenever an interview was not possible, the experts could respond through a questionnaire handling the same questions.

Experts estimated the rate of minor complications, major complications and mortality for all types of surgeries while assuming three-dimensional heart printing was used. This enabled us to estimate relative risk reductions accountable to the use of three-dimensional printing. The complication and mortality rates of the standard procedure without the use of three-dimensional printing were given as a guideline (23, 26, 37). Complications and mortality were estimated independently for each other. Additionally, the experts estimated the expected Health-Related Quality-of-Life of these patients at age <15 years and 15-24 years. Health-Related Quality-of-Life scores are subjective and generally based on a person's mobility, self-care, pain level, feelings of anxiety and depression and the possibility to perform daily activities (38). Health-Related Quality-of-Life scores of the general Belgian population were given as a guideline to the experts for the purpose of the exercise (39).

Table 1a. Clinical input data

	ASDr	VSDr	TOFr	TCPC	BCPA	CAVCr	ASO	TAr	NO	Distribution	Source
Complication rate standard procedure											
Minor complication Rate	3.0%	14.6%	27.9%	56.30%	24.30%	23.3%	27.9%	0.0%	20.0%	Beta	25
Major complication rate	1.5%	10.4%	13.2%	15.60%	29.70%	25.6%	16.2%	66.7%	80.0%	Beta	25
Estimated % reduction with 3D anatomic models											
Major complication	2.08%	20.75%	15.56%	11.02%	5.73%	12.66%	16.61%	12.69%	10.20%	Beta	expert opinion
Minor complication	1.67%	5.50%	7.05%	4.33%	3.76%	3.38%	3.93%	5.23%	5.18%	Beta	expert opinion
Mortality	0.00%	6.12%	2.86%	6.12%	8.16%	7.14%	6.88%	10.94%	8.33%	Beta	expert opinion
Mean age operation (years)	5.11	1.08	0.67	3.86	0.65	0.35	0.08	2.98	0.02	-	25
Early mortality	0.10%	1.00%	1.50%	3.10%	10.80%	7.00%	0.10%	50.00%	25.00%	-	25
Quality of Life											
<15 year	0.83	0.82	0.77	0.68	0.69	0.78	0.81	0.75	0.63	-	expert opinion
15-24 year	0.89	0.89	0.78	0.66	0.65	0.8	0.86	0.73	0.63	-	expert opinion
Late mortality (per cycle)											
1			2.80%		12.00%		3.60%			-	27-36
5	0.60%		8.04%		17.00%			18.64%	21.90%	-	
8			10.84%		26.00%					-	
10		1.69%	12.24%	6.00%		8.04%		21.35%		-	
15			15.38%					24.97%		-	
20		4.67%				10.94%	4.00%			-	
30	2.00%									-	

Table 1b. Cost input data.

	ASDr	VSDr	TOFr	TCPC	BCPA	CAVCr	ASO	TAr	NO	Distribution	References
Index hospitalization cost standard procedure											
No complication	€ 10,903	€ 14,514	€15,223	€ 14,097	€ 14,784	€ 13,880	€ 18,399	€ 21,097	€ 21,934	Gamma	25
Minor complication	€ 15,448	€ 16,766	€ 15,412	€ 14,808	€ 17,102	€ 15,407	€ 20,605	€ 21,097	€ 27,826	Gamma	25
Major complication	€ 22,298	€ 22,047	€ 42,661	€ 30,681	€ 25,607	€ 27,275	€ 28,866	€ 28,201	€ 35,345	Gamma	25
Annual hospitalization cost	<1 year	1-10 year	11-20 year								
Moderate CHD	€ 14,834	€ 9,409	€ 10,118							Gamma	25, 34, 40
Complex CHD	€ 16,467	€ 9,837	€ 7,869							Gamma	25, 34, 40
Annual hospitalization rate	<18 year	>= 18 year									
	8.30%	4.70%								Beta	30

3.4. Cost data input

The unit cost of the models was estimated to be €1,500, based on prices provided by one of the main three-dimensional model manufacturers. Index hospitalization costs were taken from the study on hospitalization costs of CHD in the United States of America and the study on the hospitalization costs of CHD in Belgium [23, 24]. The average long-term hospitalization charges were based on US data and estimated for three age categories (<1 year, 1-10 years and 11-20 years) and stratified for complex and simple procedures, based on the following equation:

$$\frac{\text{US long} - \text{term hospitalization costs } (40)}{\text{US index hospitalization costs } (23)} = \frac{\text{Belgian long} - \text{term hospitalization charges}}{\text{Belgian index hospitalization charges } (24)}$$

Of all included procedures, only Atrial Septal Defect repair and Ventricular Septal Defect repair are categorized as ‘simple’ CHD procedures. All amounts were converted to 2017 Euros. An overview of the included cost data can be found in table 1b.

3.5. Outcome measures and sensitivity analysis

The incremental cost-effectiveness ratio was the main outcome measure and was calculated as follows:

$$\text{Incremental Cost} - \text{Effectiveness Ratio} = \frac{\text{COSTof 3D} - \text{COST of standard}}{\text{QALYs of 3D} - \text{QALYs of standard}}$$

The Quality Adjusted Life Years (QALYs) are calculated by the multiplying the number of years an individual lives with a disease and the utility score for that condition. We defined the post-operative utility score as the experts’ estimated Quality of Life score because literature is scarce regarding patients’ utility scores after specific CHD surgery. We appraised the health economic results at a €40,000 per Quality Adjusted Life Year threshold. All Incremental Cost-Effectiveness Ratios below the threshold were considered to be cost-effective. The result was considered dominant when the three-dimensional printing based approach generated fewer costs and more health benefits compared to the standard procedure.

Two base case scenarios were conducted. One scenario did not have a a post-operative Quality Adjusted Life Years gain while the other scenario assumed there was a a post-operative temporary Quality Adjusted Life Years gain. The avoidance of a complication is reflected in a better Quality of Life during the post-operative period compared to the normal scenario with the complication. This scenario assumed a temporary Quality Adjusted Life Years gain of 0.1 for a 3-month period per avoided major complication.

One-way sensitivity analysis and threshold analysis, on the scenario without a postoperative temporary Quality Adjusted Life Years gain, captured uncertainty surrounding expert opinion. Parameters were varied one by one while all other parameters were kept at baseline values, providing us with information about the impact of the parameters' uncertainty. Included parameters were (a) the cost of three-dimensional heart printing, (b) the estimated mortality reduction, (c) the estimated major complication reduction, (d) the estimated minor complication reduction, and (e) the estimated Health-Related Quality-of-Life of patients. The low and high end of each parameter were assumed to be 70% and 130% of the deterministic value respectively. The threshold analysis shows the impact of the experts' estimated effect on mortality and major complications at levels varying between 0% and 300% of the experts' estimate.

Parameters were varied all together in the probabilistic sensitivity analysis. Costs and probabilities were modeled using a gamma distribution and a beta distribution respectively (41). For the temporary Quality Adjusted Life Years gain a random number following a uniform distribution between 0 and 0.1 was used. Some variables were not varied in the probabilistic analysis: (a) discount rates, (b) average age upon the operation and (c) standard procedure's early and late mortality rates. The Monte Carlo analysis consisted of 10,000 iterations.

We conducted a Population Expected Value of Perfect Information analysis. The value of additional information, if future quantitative research validates expert opinion, was calculated as the difference between the maximum expected net monetary benefit with perfect information and with current information (41), and multiplied with the population size. Therefore, the yearly total number of operations per procedure in Belgium was estimated based on the number of operations performed in one teaching hospital during a 10-year time period (25), knowing that only four hospitals are legally allowed to perform CHD surgery in Belgium (42). The value of additional information is presented over a 10-year time horizon and was discounted at a rate of 3%.

3.6. Assumptions

Several assumptions were made. First, we considered two base cases. The first scenario did not incorporate a post-operative gain in Quality of Life associated with avoiding complications. The second scenario assumed a temporary Quality Adjusted Life Years gain in case a major complication was avoided. In the probabilistic scenario analysis, a random Quality Adjusted Life Years gain between those two opposite scenarios is taken. Second, we conservatively assumed that three-dimensional anatomic modelling had a one-time benefit and only affected morbidity and mortality during the index hospitalization. Long-term morbidity and mortality incidence rates were considered to be similar to the standard procedure. Third, we assumed that the average annual hospitalization rate and costs of operated CHD patients equals the average annual hospitalization rate and costs of the whole CHD population, as longitudinal literature regarding operated CHD patients only is scarce. During index hospitalization, we assumed that death could only be the result of a peri- or postoperative complication. At last, we assumed three-dimensional printing could be used for all surgical procedures presented by Pasquali et al (23). We reckon current resolution might be insufficient for some parts of the anatomy but wish to include them to analyze the potential of these procedures in the future.

4. Results

4.1. Two base case scenario analyses

Different ICER estimates were found in each of the two base cases (see Table 2). 3D models were estimated to be cost-effective in Complete Atrioventricular Canal Defect repair, Bidirectional cavopulmonary (Glenn) anastomosis, Truncus Arteriosus repair and Norwood operation in both scenarios, while the 3D model appeared to be cost-effective in Ventricular Septal Defect repair, Tetralogy of Fallot repair, Total Cavopulmonary Connection and Arterial Switch Operation as well, if a temporary QALY gain was assumed. The results were cost-ineffective in both scenarios in Atrial Septal Defect repair.

4.2. One-way sensitivity analysis and threshold analysis

The results of the one-way sensitivity analysis were synthesized by using tornado diagrams (supplementary material). In general, the patients' quality of life, the 3D model's cost and mortality reduction had the greatest impact on the Incremental Cost-effectiveness Ratios. In addition, major complication reduction had a big impact on the Incremental Cost-effectiveness Ratios in Norwood operation. However, single variable manipulation did not impact the cost-effectiveness decision at a €40,000 threshold. Threshold analysis showed that in Tetralogy of Fallot repair and Total Cavopulmonary Connection, the true effect should be respectively 60% and 108% higher than the experts' estimates to be cost-effective at a €40,000 threshold. The true effect should be over three times higher than the experts' estimates in Ventricular Septal Defect repair, Arterial Switch Operation and Atrial Septal Defect repair (see figure 2). Tornado diagrams can be found in appendix 3.1.

4.3. Probabilistic sensitivity analysis

Incremental costs ranged from -€366 (95% credibility interval: -€2,595; 1,049) in Norwood operation to €1,485 (95% CI: €1,206; €1,792) in Atrial Septal Defect repair. Incremental health benefits ranged from negligible in Atrial Septal Defect repair to 0.54 Quality Adjusted Life Years (95% CI: 0.06; 1.43) in Truncus Arteriosus repair (see table 3). Atrial Septal Defect repair was cost-ineffective in 100% of the scenarios. Nearly 100% of trials in Truncus Arteriosus repairs and Norwood operations resulted in a cost-effective Incremental Cost-Effectiveness Ratio (figure 3). For these more complex operations, the implementation of three-dimensional anatomic models is most likely to be cost-effective on a 15-year time horizon. Complete Atrioventricular Canal Defect repair, Bidirectional cavopulmonary (Glenn) anastomosis and Total Cavopulmonary Connection proved to give a good value for money in the majority of the observations with an ICER under the threshold in 77%, 65% and 73% of the iterations respectively (see figure 3).

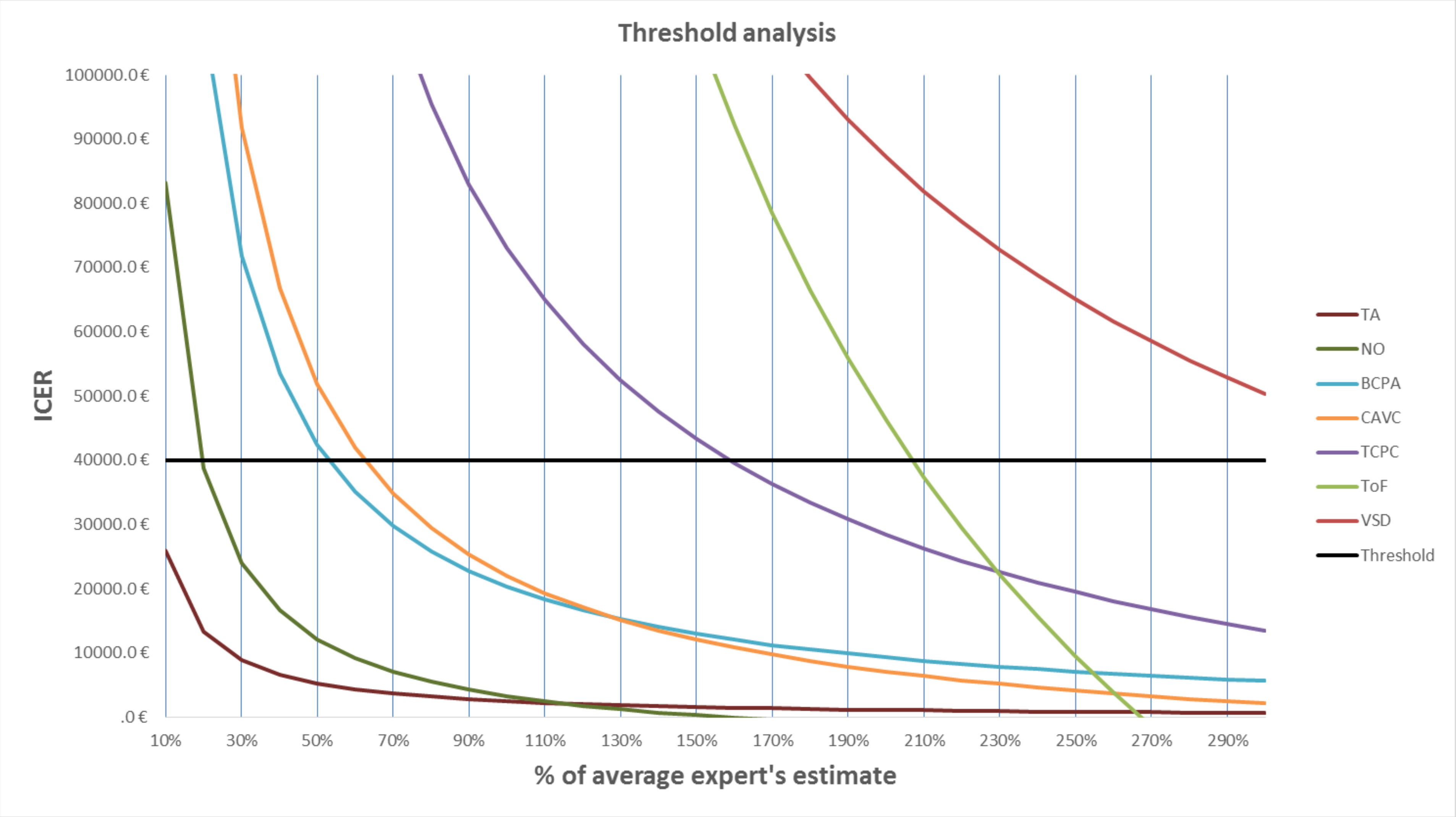
Table 2. Scenario results and (population) expected value of perfect information.

	No QALY gain			Temporary QALY gain		EVPI	PEVPI
	Delta Cost	Delta QALY	ICER	Delta QALY	ICER		
ASDr	€ 1,494	0	> € 1,000,000,000	0.01	€ 291,118	€ 0	€ 0
VSDr	€ 1,325	0.01	€ 197,895	0.06	€ 22,925	€ 20	€ 7,443
TOFr	€ 936	0	€ 229,698	0.04	€ 22,083	€ 165	€ 29,518
TCPC	€ 1,214	0.02	€ 73,093	0.04	€ 27,743	€ 30	€ 15,491
BCPA	€ 1,365	0.07	€ 20,383	0.08	€ 16,836	€ 59	€ 24,979
CAVCr	€ 1,100	0.05	€ 22,083	0.08	€ 13,581	€ 23	€ 14,985
ASO	€ 1,195	0	€ 1,677,685	0.04	€ 28,703	€ 126	€ 32,951
TAr	€ 1,374	0.54	€ 2,556	0.57	€ 2,416	€ 0	€ 15
NO	€ 534	0.16	€ 3,300	0.19	€ 2,857	€ 1	€ 56

Table 3. Probabilistic sensitivity analysis.

	Delta Cost	95% lower bound	95% upper bound	Delta QALY	95% lower bound	95% upper bound
ASDr	€ 1,484	€ 1,195	€ 1,800	0.000	0.000	0.001
VSDr	€ 874	€ 269	€ 1,366	0.009	0.002	0.022
TOFr	€ 448	€-499	€ 1,118	0.006	0.001	0.017
TCPC	€ 400	€-679	€ 1,164	0.018	0.003	0.045
BCPA	€ 1,044	€ 416	€ 1,545	0.067	0.003	0.223
CAVCr	€ 852	€ 202	€ 1,364	0.050	0.005	0.142
ASO	€ 355	€-991	€ 1,237	0.001	0.000	0.002
TAr	€ 563	€-1,211	€ 1,975	0.542	0.062	1.459
NO	€-348	€-2,550	€ 1,059	0.162	0.019	0.431

Figure 2. Threshold analysis.



X-axis: The base case is 100%, which fully incorporated the experts' estimations of major complication reduction and mortality reduction. At higher levels, eg. 140%, the values given by the expert are incorporated at a factort of 1.4. The threshold at a threefold of the experts' estimations is above 100,000 in ASO and ASDr and are therefore not shown. Y-axis: ICER threshold

Figure 3. Cost-effectiveness Acceptability Curves

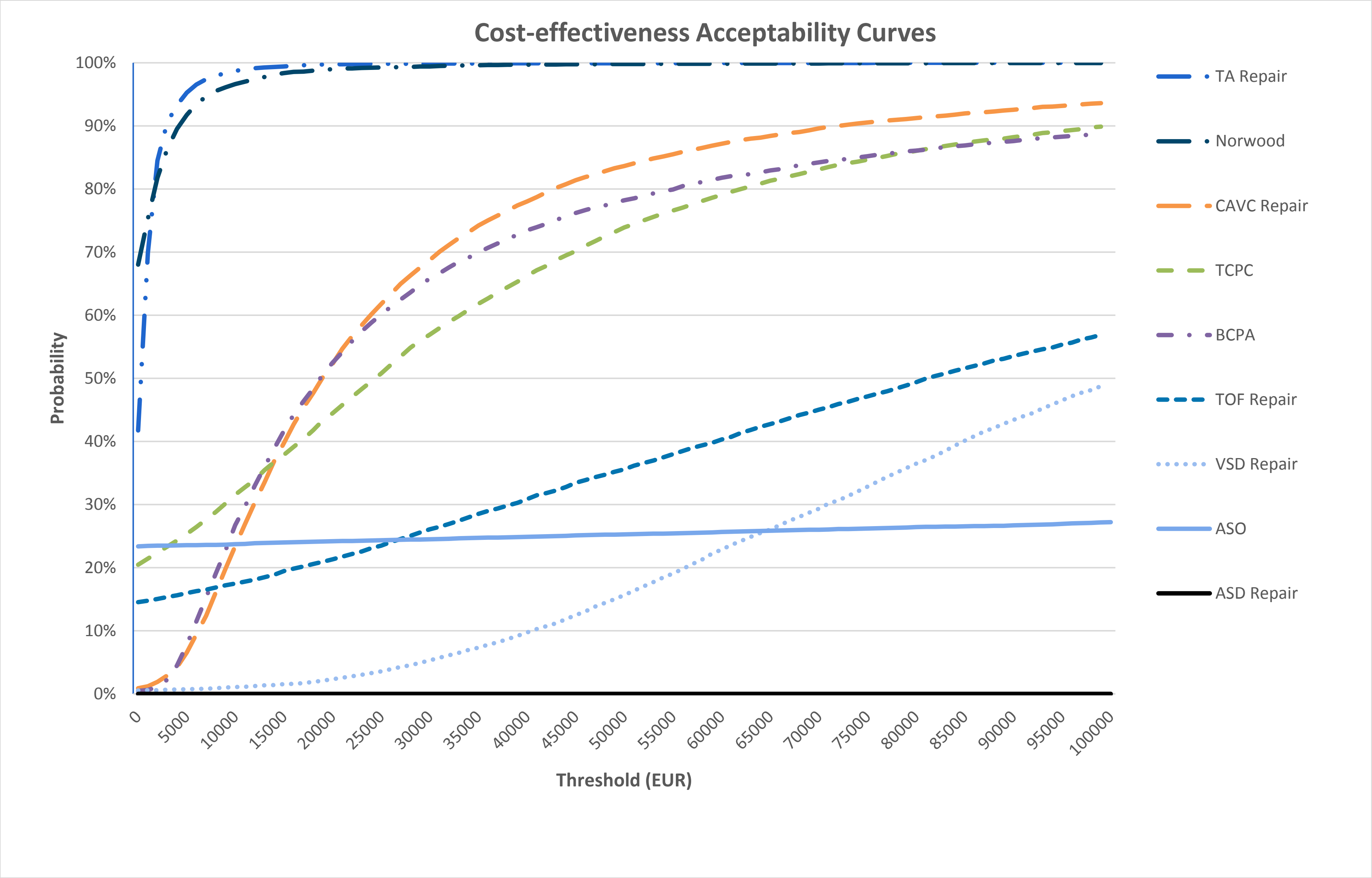
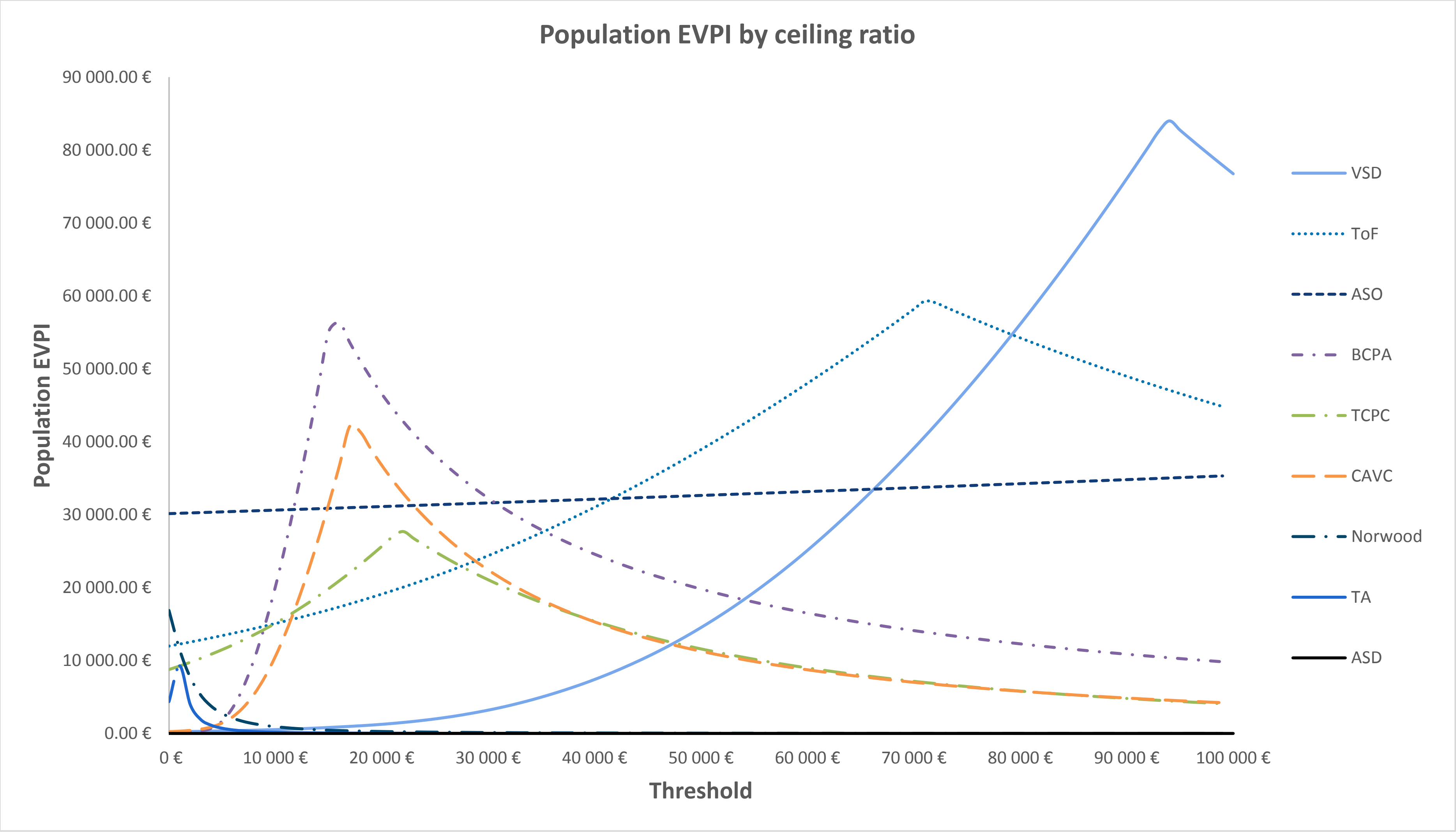


Figure 4. Population EVPI by ceiling ratio



4.4. Expected value of perfect information

The average number of operations per procedure per year in Belgium was estimated between 4 (Trunctus Arteriosus repair) and 42.8 (Ventricular Septal Defect repair). Figure 4 summarizes the Population Expected Value of Perfect Information results. Our analyses suggested a negligible value (close to €0 per person) for additional information in Atrial Septal Defect repair, Truncus Arteriosus repair and Norwood operation. Individual Expected Value of Perfect Information ranged in the other procedures from €20 in Ventricular Septal Defect repair to €149 in Tetralogy of Fallot repair. The value for additional information for all complications together in Belgium was €125,878 at a €40,000 threshold. This is the price the public healthcare provider would be willing to pay to remove the uncertainty from the model. Stratified over the procedures, Atrial Septal Defect repair, Ventricular Septal Defect repair and Bidirectional cavopulmonary (Glenn) anastomosis accounted for €32,119, €31,018 and €24,577 respectively. All values can be found in table 2.

5. Discussion

The aim of this study was to conduct the first early health technology assessment of three-dimensional anatomic heart models as part of standard practice (2). We therefore incorporated both simple and complex procedures to analyze their impact. Monte Carlo analysis favored three-dimensional heart printing in Complete Atrioventricular Canal Defect repair, Bidirectional cavopulmonary (Glenn) anastomosis, Total Cavopulmonary Connection, Truncus Arteriosus repair and Norwood operation at a €40,000 threshold, with up to 100% probability of being cost-effective in the latter two interventions. Patients' quality of life, the model's unit cost and mortality reduction were the parameters characterized with the highest uncertainty. However, single variable variation did not impact the Incremental Cost-Effectiveness Ratio in a way that it surpassed the threshold. A reduction in minor complications had little effect on the results, consistent with expert opinion. Importantly, little incremental health benefits were found in less complex procedures in the scenario without a temporary Quality Adjusted Life Years gain. This caused a high sensitivity to temporary Quality Adjusted Life Years gains in these particular procedures.

As Belgium does not have a country-specific willingness to pay threshold for health gains, the per capita gross domestic product was used resulting in a threshold of €40,000 per Quality Adjusted Life Years. The World Health Organization project 'Choosing Interventions that are Cost-Effective' suggested using a threshold up to three times the per capita gross domestic product (43). Only Arterial Switch Operation and Atrial Septal Defect repair remained cost-ineffective in that case. However, one might argue that conservative thresholds must prevail if the input data is characterized by expert opinion. Our experts estimates were similar to the results of Ryan, reporting an observed decrease in readmissions of 11.6% (19).

The Population Expected Value of Perfect Information was estimated at a surprisingly low €125,878, accumulated over all procedures. We should emphasize that the valuation only applies to the Belgian patient population. Some procedures are rarely performed because Belgium is a small country with approximately 11 million inhabitants and the CHD prevalence is only 8 in 1,000 newborns (44). In small patient populations, a higher level of decision uncertainty is accepted to support a policy decision because budget impact remains limited (41). Note however that we used expert opinion to estimate the effect on mortality and morbidity, thus the reported Population Expected Value of Perfect Information is applicable only if these estimates are validated in future research.

Above finding imply that, 3D-printed anatomic models can provide additional insights at a societally acceptable cost when used for complex pathologies. In these specific cases, public healthcare providers should reimburse the use of these models if the surgeon requires it. As quantitative data is required to build stronger models, the reimbursement could be coupled to a mandatory registration; generating the needed data to validate these findings.

To the authors' knowledge, there is little quantitative evidence available supporting the assumed advantages of three-dimensional anatomic models. Recently, some articles tried to evaluate the benefits of using three-dimensionally printed models for CDH surgery. For Double Outlet Right Ventricle operations, the printed models significantly reduced the mechanical ventilation time and ICU stay (45). Furthermore, a retrospective study on 928 cases of Double Outlet Right Ventricles, of which 79 patients had printed three-dimensional models for surgical planning, showed a non-significant reduction in OR-time (19). The lack of research validating the anatomic models or supporting the stated potential advantages is one of the main disadvantages of three-dimensional heart printing, according to our experts. Comparative studies are difficult and only tech-savvy surgeons tried the printed anatomic models and described their findings in case studies. The experts reason that small sample sizes trouble research, next to the rare usage of anatomic models and the not reimbursed cost of the model. Questions regarding the accuracy of prints still persist. Although 33.5% of the studies included in the review of Martelli et al. (46) point to the accuracy as a main advantage, 20.9% of the included studies report unsatisfying results. On the other hand, it has to be stressed that models in the early days of three-dimensional printing are not comparable to the new prints made nowadays (18). In addition, the questioned experts highlighted the delivery time of the anatomic models as one of the contra-indications for its practical use, consistent with Martelli et al. (46).

The focus of this study was to evaluate the cost-effectiveness of three-dimensional heart printing as an aid for pediatric cardiovascular surgeons. In addition to the use of printed anatomic models as a tool for surgical planning, experts highlighted the teaching potential for both patients and inexperienced professionals. Patient-specific models have been shown to be useful tools for patient education in other domains as they enhance patients' physiological, anatomical and surgical procedure knowledge (47). On the contrary, Biglino et al. (1) found no significant improvement in parental knowledge about CHD even though both parents and cardiologists found the anatomic model helpful. In addition, consultation time increased with 5 minutes on average. Other publications have shown that students' knowledge improved significantly (5), particularly in students with low spatial abilities (48).

This study was characterized by several limitations. First, to enable a health economic comparison, we analyzed CHD based on procedures and used the paper of Pasquali et al. as a basis. We hereby categorized on procedures rather than pathologies. Therefore not all procedures suitable for double outlet right ventricle were incorporated. It has been argued that three-dimensional anatomic models might be most beneficial in the surgical treatment of the heterogeneous and complex double outlet right ventricle pathology (7, 45, 49, 50). Second, we compared three-dimensional printing to the conventional method. As three-dimensional renderings are very often present in hospitals, we did not distinct whether surgeons are already using three-dimensional visualizations or not. Third, we used a public health payer perspective and did not calculate the hospital perspective. Other variables should be included to assess the potential positive impact of these models from the hospital perspective. A reduction in used surgical trays due to better planning could lead to savings for the hospital (2). Additionally, the potential time reduction in the operation theater could positively affect hospital's finances (2), taking into account the ongoing argument about monetization of freed operation room time (51). Surgical time is valuable as 10 minutes of saved time in the operation theater equals one hour of work on the model's design or its production (46, 52). On the other hand, employees' time investment during the long lasting digitalization process could surpass the time benefits during the surgery, which may negatively affect hospital's finances. Fourth, we only included hospitalization costs. Societal costs and routine follow-up costs associated with CHD patients were not accounted for, underestimating the real-life cost. Fifth, the structure of our model is limited due to literature gaps. The Markov model only consists of two states, alive and dead. Adding additional states associated with reoperations and the severity of the complications might have given us additional information. Sixth, the model assumes a three-dimensional model is built in all cases. It is unlikely that surgeons require such detailed patient-specific information in all cases. We calculated the cost-effectiveness of the implementation of anatomic models in all cases. In real life, surgeons have the choice to build a model if there is an uncertainty they would like to tackle. Furthermore, the model may also lead the decision to restrain from operating the patient. Our expert panel highlighted that three-dimensional anatomic models could not only be beneficial in complex aberrations but may also be opportune in less complex procedures when there are anatomic indications. The value of three-dimensional anatomic models is likely to be significantly higher in targeted cases, based on the surgeon's appraisal. Finally, there are some specific health economic methodological issues. Researchers often seek expert opinion when empirical information is lacking, which occurs often in new health technology assessment. Selection bias is not unthinkable, as cardiologists needed to have some hands-on experience with three-dimensional printing to be part of our expert panel. Ideally, a multi-center randomized controlled trial on the impact of three-dimensional anatomic models should be organized to eliminate expert bias and to obtain fully objective results. Data to build health economic models are often scarce. A more systematic approach on medical and financial data collection across medical centers, ideally in a centralized database, would enhance future decision making for medical innovations.

6. Conclusions

In conclusion, this study suggests that the implementation of three-dimensional heart printing is potentially cost-effective in Total Cavopulmonary Connection, Complete Atrioventricular Canal Defect repair, Truncus Arteriosus repair and Norwood operation on a 15-year time horizon. These results may guide governmental policy decision makers in allocation resources toward cost-effective innovations. Even though the effectiveness is not proven yet, we argue for early reimbursement for several reasons. The budget impact is limited, a three-dimensional print is most likely not harmful and we talk about a very young patient population with a lethal condition. Furthermore, more certainty on the effectiveness of the technology can be given with a relatively limited investment.

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Chapter 4

The value of custom cutting guides for primary total knee arthroplasty. A health-economic approach using registry data.

Based on Philip Tack, Tine Willems, Paul Gemmel, Lieven Annemans, Jan Victor (2021) The value of custom cutting guides for primary total knee arthroplasty. A health-economic approach using registry data. In review in the The Journal of Bone & Joint Surgery.

1. Abstract

Background

Custom cutting guides (CCG) for primary Total Knee Arthroplasty have been adopted by many orthopedic surgeons. Unfortunately, multiple meta-analyses did not show convincing evidence to routinely support its use. We approached the matter differently, using registry data, to analyze the use of CCG in Belgium, its effect on revision surgery and its health-economic implications.

Method

Data of the Belgian Arthroplasty Register were collected and analyzed. A survival analysis with revision surgery as outcome was run to analyze the impact of using the CCGs. To assess the health-economic impact, a Markov model with a duration of 5 years was built. A deterministic and probabilistic sensitivity analysis estimated the robustness of the model.

Results

112,070 procedures were selected, of which 5,735 (5.13%) with CCGs. No relevant differences were found in the characteristics concerning the prosthesis, diagnosis, patients and surgical method, with the exception of the fixation of the prosthesis between procedures with and without CCGs.

There was no significant difference in infection rate, malalignment or liner wear in revision surgeries. Survival analysis with corrections for fixation and surgical experience showed an odds ratio of 0.696 [CI: 0.558, 0.868] for revision within 5 years in favor of CCGs. CT-based guides resulted in an Incremental Cost-Effectiveness Ratio (ICER) of €28,839 while MRI-based guides had an ICER of €52,735. On average, guides can be a cost-effective strategy at a cutoff of €40,000 if the total price, including all costs, does not exceed €587.

Deterministic sensitivity analysis showed the revision rate, cost of the guide and cost of revision to be the most important factors influencing the ICER. Probabilistic sensitivity analysis showed 51.74% of the CT-based and 45% of the MRI-based CCGs to be cost-effective.

Conclusion

The use of CCG results in a significant reduction of the chance of undergoing revision surgery at 5-year follow-up. CCGs are a cost-effective strategy for guides based on CT.

2. Introduction

Total knee arthroplasties (TKA) are common procedures to improve the quality of life in patients with advanced osteoarthritis (1). Custom cutting guides (CCG) have been adopted by many orthopedic surgeons with over 80,000 procedures performed with CCG in 2012 worldwide (2). The custom guides were thought to improve the accuracy and therefore outcomes of TKAs but the multiple meta-analyses performed to evaluate its potential benefits did not show convincing evidence to support its routine use (3-10). In 2020, the hype seems to be over and the number of publications slows down, but up to now, we could not find conclusive evidence to support or reject the use of custom cutting guides, especially from a health-economic perspective when considering its premium price. The Belgian national registry for knee and hip arthroplasties "Orthopride" has been collecting data of all knee and hip arthroplasties in Belgium since 2009. On July 1st 2014, the registration of hip and knee arthroplasties became mandatory for reimbursement (11). At the time of evaluation in May 2020 the database contained over 110,000 registered total knee arthroplasties. We used the database to analyze the impact of using custom cutting guides, allowing correction for potential influencing factors.

This resulted in three main research questions. First, how are cutting guides used in Belgium; with respect to the surgeons, patients and prosthetics? Second, what is the effect of using custom cutting guides on implant survival? Third, what is the health-economic implication of using these custom guides for primary TKA?

3. Method

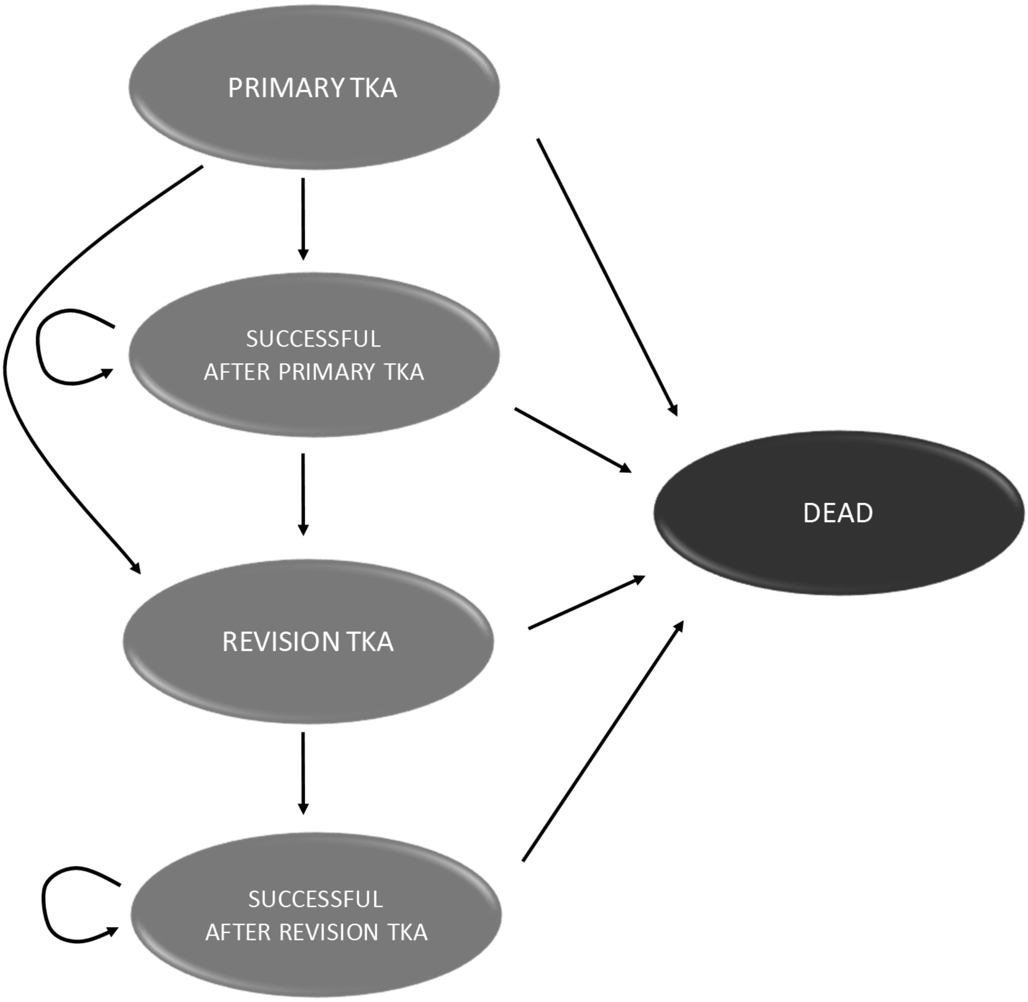
We obtained the raw dataset of Orthopride up to May 2020. This dataset includes encrypted patient demographics, procedures, implant types and potentially, reasons for revision. The database was linked to mortality registers. Data analysis was performed using SPSS 27 (IBM co.). A significance level of 5% was used throughout the analyses. Chi² and Fisher's Exact Test, in case the cell count is less than 5 observed values were used to analyze differences concerning the patient and procedure characteristics of the primary surgery and differences in the revision profile of primary TKAs with or without guides. A Cox-regression survival analysis with revision surgery as outcome was run and life tables were built to analyze the impact of using the custom cutting guides (12). Fixation type and surgical experience were incorporated as covariates in the model. To provide a binary variable for surgical experience the median number of surgeries in our data was used to determine high- and low-volume surgeons. To assess the health-economic impact of using these guides in primary TKA a Markov model with a duration of 5 years was built with Excel 2010 (Microsoft co.). The model layout can be found in figure 1. The model assumes a primary TKA with guides, while revisions are assumed to be without guides. Input data concerning quality of life and pricing was retrieved through literature search and requested from manufacturers. Transition probabilities were derived from Orthopride data. The price of guides varies between €375 and €400. This information was obtained from direct communication with the manufacturers in June 2020. Only direct costs were incorporated in the model. Costs are set in 2020 euro (13, 14). A deterministic sensitivity analysis was performed by changing a single variable at a time by their confidence interval or 30% if none is to be found. The cost of revision surgery could not be lower than the primary procedure while the utility of a revision surgery could not be higher than that of a primary procedure. For the probabilistic data analysis, mean and standard error were used per variable. Where none could be found an arbitrary 10% was used as standard error. Costs were modelled with a gamma distribution while utilities and transition probabilities were modelled with a beta distribution. The technology was assumed cost-effective with an ICER below €40,000, being the gross domestic product per capita in Belgium.

4. Results

4.1. Descriptive analysis

Descriptive statistics of patients and procedures for all registered primary procedures are presented in Table 1. A total of 112,070 primary procedures were registered, of which 5,735 (5.13%) with custom cutting guides. Although some significant differences were found in the characteristics concerning the patients, prosthesis, diagnosis and surgical method, all were practically irrelevant, with the exception of the fixation of the prosthesis. The femoral component was cemented in 98.4% of the cases with custom guides compared to 90.4% without. The implants were slightly different with a preference to prosthetics with fixed inserts (93,4%) when using custom guides compared to the procedure without custom cutting guides (75.3%). Furthermore, more ultra-congruent and posterior-stabilized prosthetics and less posterior cruciate ligament retaining prosthetics were used in combination with the custom guides.

Figure 1: Overview of the model.



To provide a binary variable for surgical experience, we distinguished between low and high volume surgeons by taking the median of the performed surgeries between 2015 and 2020. This resulted in a cutoff value of 248 registered surgeries or approximately 50 procedures per year; which is consistent with cutoff values suggested in the literature (15-17).

Table 1: Descriptive statistics of the primary procedure

	Registered primary procedures with guides (n, %) (N=5,753)		Registered primary procedures without Guides (n, %) (N=106,317)		P- Value
Gender					0.442
Female	3,610	62.7%	67,040	63.1%	
Male	2,143	37.3%	39,274	36.9%	
Unknown	0	0.0%	3	0.0%	
Side					0.013
Left	2,655	46.1%	50,433	47.4%	
Right	3,098	53.9%	55,884	52.6%	
ASA classification					<0.001
ASA-Class I	467	17.6%	6,088	16.1%	
ASA-Class II	1,622	61.0%	25,372	67.3%	
ASA-Class III	527	19.8%	5,780	15,3%	
ASA-Class IV	14	0.5%	404	1.1%	
ASA-Class V	27	1.0%	70	0.2%	
ASA-Class VI	3	0.1%	5	0.0%	
Missing (as % of all surgeries)	3093	53.7%	68,598	64.5%	
Primary diagnosis					<0.001
Osteoarthritis	5,568	96.8%	100,839	94.8%	
Avascular necrosis	25	0.4%	1,273	1.2%	
Fracture	9	0.2%	369	0.3%	
Inflammatory arthropathy	37	0.6%	723	0.7%	
Trauma	83	1.4%	2,178	2.0%	
Previous infection	2	0.0%	93	0.1%	
Indication other	29	0.5%	842	0.8%	
Pre-operative status (more than 1 option possible)					
Pre-op Osteosynthesis – tibia	59	1.0%	1,200	1.1%	0.469
Pre-op Osteosynthesis – femur	40	0.7%	914	0.9%	0.186
Pre-op Osteotomy	59	1.0%	1,559	1.5%	0.006
Pre-op Synovectomy	24	0.4%	500	0.5%	0.565
Pre-op Meniscectomy	1,456	25.3%	21,340	20.1%	<0.001
Pre-op ACL reconstruction	77	1.3%	1,869	1.8%	0.018
Pre-op Other	248	4.3%	4,582	4.3%	0.997
Pre-op None	3,947	68.6%	77,092	72.5%	<0.001
Implant subtype					<0.001
Posterior cruciate retaining	365	6.3%	21,114	19.9%	
Posterior-stabilized	4,078	70.9%	62,957	59.2%	
Constrained Condylar	10	0.2%	1,368	1.3%	
Ultra-congruent	1,144	19.9%	16,049	15.1%	

Hinge	11	0.2%	980	0.9%	
Bicruciate retaining	1	0.0%	343	0.3%	
Other	144	2.5%	3,506	3.3%	
Insert type					<0.001
Fixed	5,375	93.4%	80,059	75.3%	
Mobile	364	6.3%	25,969	24.4%	
None	14	0.2%	289	0.3%	
Femoral fixation					<0.001
Antibiotic-loaded bone cement	5,654	98.3%	95,387	89.7%	
Bone cement without antibiotics	9	0.2%	682	0.7%	
None	90	1.6%	10,164	9.6%	
Tibial fixation					<0.001
Antibiotic-loaded bone cement	5,668	98.5%	99,999	94.1%	
Bone cement without antibiotics	8	0.1%	682	0.6%	
None	77	1.3%	5,636	5.3%	
Patellar fixation					<0.001
Antibiotic-loaded bone cement	5,005	99.2%	79,554	98.3%	
Bone cement without antibiotics	8	0.2%	480	0.6%	
None	31	0.6%	911	1.1%	

4.2. Analysis of the revisions

2352 revisions were reported after a primary procedure using standard instrumentation and 83 revisions were reported using custom cutting guides.

When looking at the primary revision surgeries, there was no significant difference in reason for revision surgery between the procedures performed with or without custom cutting guides. Similarly, revision of components was not significantly different with or without custom guides. Numerical data on the reported reasons for revision and revised component can be found in table 2.

Out of the 540 surgeons performing TKAs in Belgium, 116 used CCG once or more. Only 14 surgeons are using CCG in more than 50% of their TKAs, accounting for 78.5% of all procedures with CCG, and only 10 in more than 80% of their TKAs, accounting for 63.5% of the procedures with CCG. When considering the 14 surgeons using CCG in more than 50% of their surgeries, 50% was found to be high-volume surgeons. There was no difference in observed revisions between the high-volume (1.33%) and low-volume surgeons (1.57%) using CCG in more than 50% of their surgeries (P = 0.690). Similarly, we could not find a significant difference in revision rate between the surgeons performing more than 50% of their surgeries with CCG (1.35%) and surgeons using less than 50% guides (1.73%) when the surgery is performed with CCG (P= 0.321). A graphical representation of the number of TKAs performed with our without CCG per surgeon can be found in figure 2. For graphical reasons, only surgeons with more than 20 registered surgeries were incorporated in the graph.

Table 2: Profile of the revision surgeries.

Reported reasons for revision		Guides (N= 83)	No Guides (N=2352)	P-Value
Infection	No	64 (77.1%)	1,858 (79.0%)	0.678
	Yes	19 (22.9%)	494 (21.0%)	
Aseptic loosening	No	67 (80.7%)	1,892 (80.4%)	0.949
	Yes	16 (19.3%)	460 (19.6%)	
Instability	No	66 (79.5%)	1,805 (76.7%)	0.556
	Yes	17 (20.5%)	547 (23.2%)	
Pain	No	67 (80.7%)	1,834 (78.0%)	0.552
	Yes	16 (19.3%)	518 (22.0%)	
Liner wear	No	80 (96.4%)	2,327 (98.9%)	0.068*
	Yes	3 (3.6%)	25 (1.1%)	
Mall alignment	No	77 (92.8%)	2,200 (93.5%)	0.781
	Yes	6 (7.2%)	152 (6.5%)	
Stiffness of the knee	No	74 (89.2%)	2,178 (92.6%)	0.242
	Yes	9 (10.8%)	174 (7.4%)	
Revision of components		Guides	No Guides	P-Value
Patellar component	No	46 (57.5%)	1,395 (64.2%)	0.223
	Yes	34 (42.5%)	779 (35.8%)	
Femoral component	No	39 (48.8%)	1,259 (57.9%)	0.103
	Yes	41 (51.2%)	915 (42.1%)	
Tibial component	No	38 (47.5%)	1,138 (52.3%)	0.394
	Yes	42 (52.5%)	1,036 (47.7%)	
Insert	No	12 (15.0%)	405 (18.6%)	0.412
	Yes	68 (85.0%)	1,769 (81.4 %)	

* Fisher's Exact Test

Figure 2: The use of custom guides for TKAs between 2015 and 2020 (bar) compared to the total number of registered TKAs per surgeon performing more than 20 registered TKAs in Belgium (line).

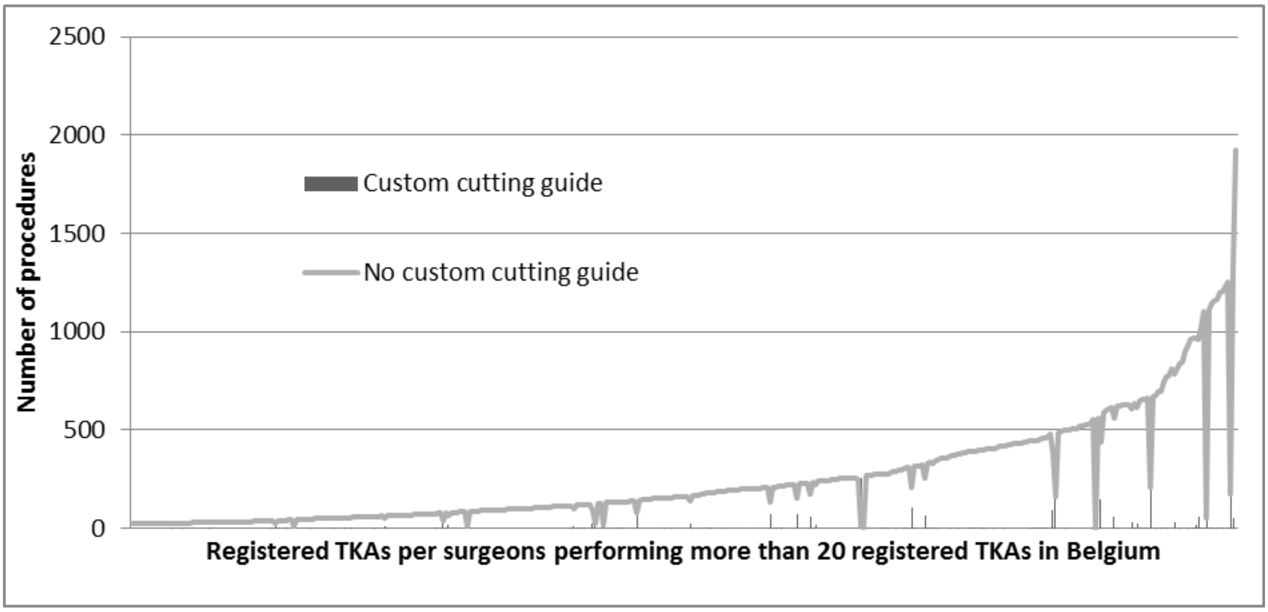
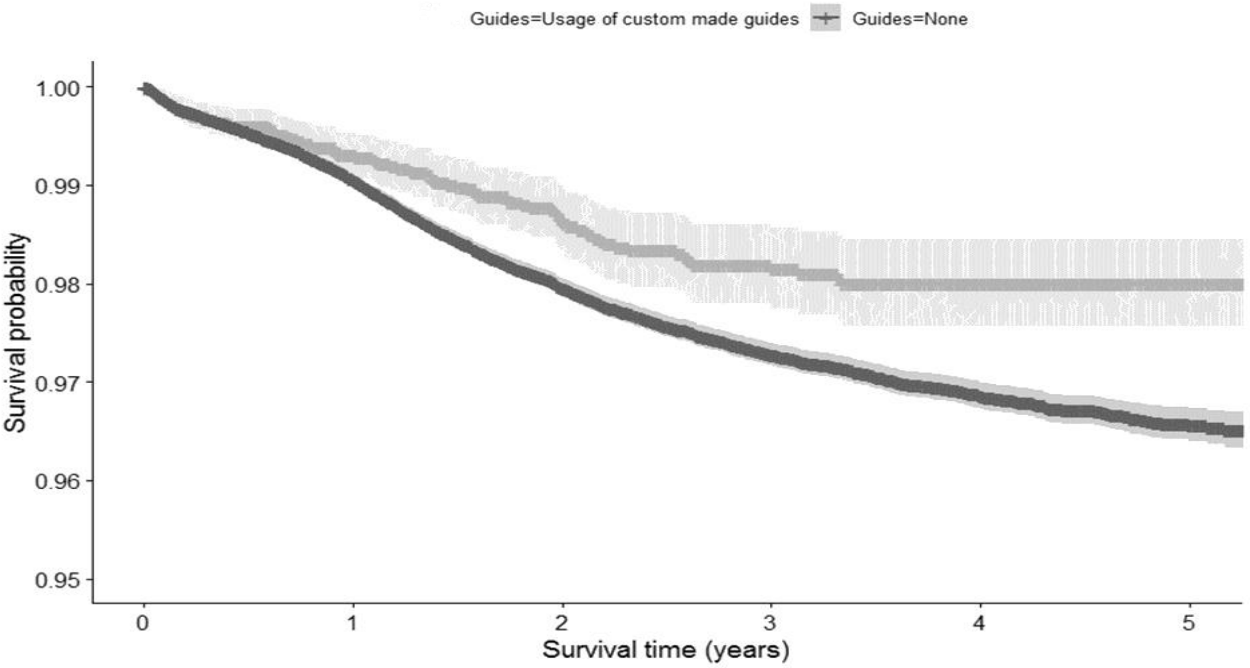


Figure 3: Kaplan-Meier curve of implant survival with and without custom cutting guides including confidence intervals. Grey line: CCG, Black line no CCG



Cox regression analysis showed a significantly decreased hazard ratio of 0.696 [95% CI: 0.558,0.868] for revision in the advantage of custom guides when correcting for fixation and surgical experience as both are known to have a high impact on implant survival (11). Figure 3 gives the survival function for using guides. Table 3 gives an overview of the model's parameters.

Table 3: Cox regression model parameters.

		- B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
Fixation	Fixation			10,582	2	**0.005**			
	Hybrid	0.201	0.09	4,930	1	**0.026**	1.222	1.024	1.459
	Uncemented	0.212	0.084	6,410	1	**0.011**	1.236	1.049	1.457
Surgical volume	Low-volume surgeon	0.426	0.047	82,965	1	**0.000**	1.532	1.397	1.679
Guides	Usage of custom guides	-0.362	0.113	10,337	1	**0.001**	0.696	0.558	0.868

Model with references (0=) Cemented, High surgical volume, Regular guides

Analysis of the life tables with the use of guides and the surgeons experience showed a higher positive impact on the use of guides for unexperienced surgeons.

Table 4: Yearly revision risk based on the surgical experience and use of guides.

	Low volume		High volume	
	Guides	No guides	Guides	No guides
Year 0	0.006 [0.003-0.009]	0.014 [0.013-0.015]	0.007 [0.006-0.008]	0.008 [0.007-0.009]
Year 1	0.008 [0.003 - 0.013]	0.015 [0.014-0.016]	0.006 [0.005-0.007]	0.010 [0.009-0.011]
Year 2	0.004 [0.000-0.008]	0.009 [0.008-0.010]	0.005 [0.004-0.006]	0.006 [0.005-0.007]
Year 3	0.006 [0.000-0.0012]	0.005 [0.004-0.006]	0.002 [0.001-0.002]	0.004 [0.003-0.005]
Year 4	0.000 [0-0]	0.004 [0.003-0.005]	0.000 [0-0]	0.003 [0.002-0.004]

4.3.Health-economic modelling

An overview of the data used in the model can be found in table 5.

When the additional cost of imaging to make the guide was not included, the use of custom cutting guides resulted in a cost-effective strategy for the average 68-year-old person with an incremental cost-effectiveness ratio (ICER) of €4,541. When CT images are used to build the guide, the ICER including the cost of the CT, is found to be cost-effective with an ICER of €28,839. When incorporating the price of an additional MRI to make the guides, the result is less favorable with an ICER of €52,735. On average, guides can be a cost-effective strategy at a total price of €546 (including all costs), considering a cutoff at €40,000 per QALY.

Deterministic sensitivity analysis showed the cost of the guide, cost of revision and the revision rate to be the most important factors influencing the ICER. An overview is given in figure 4.

Figure 4: Deterministic sensitivity analysis.

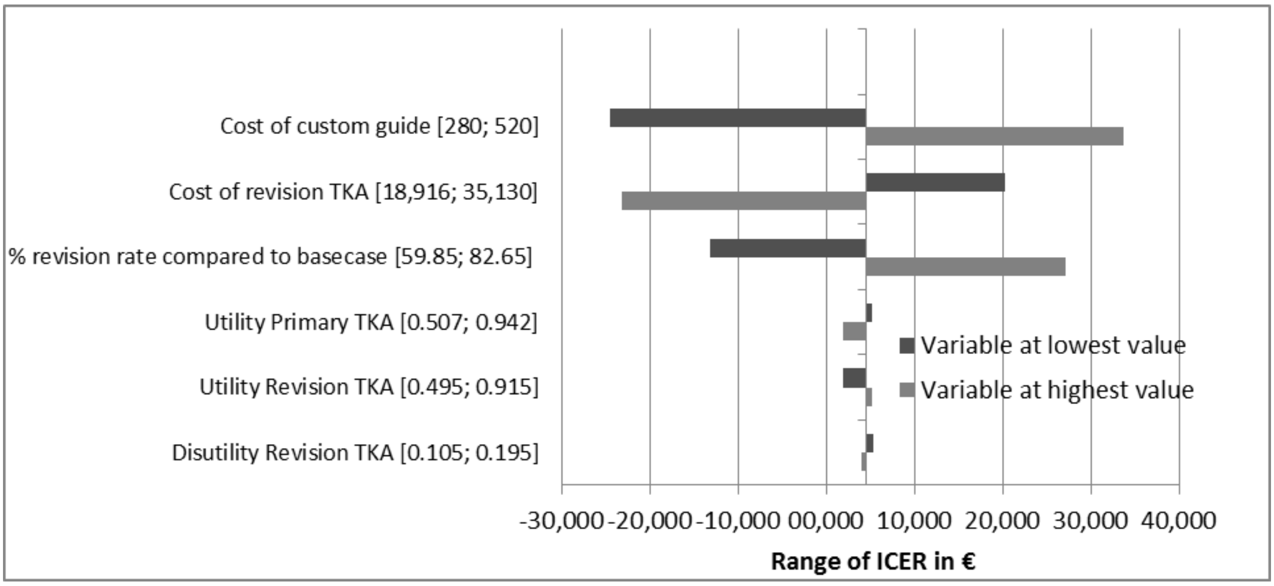


Table 5. Data used in the model.

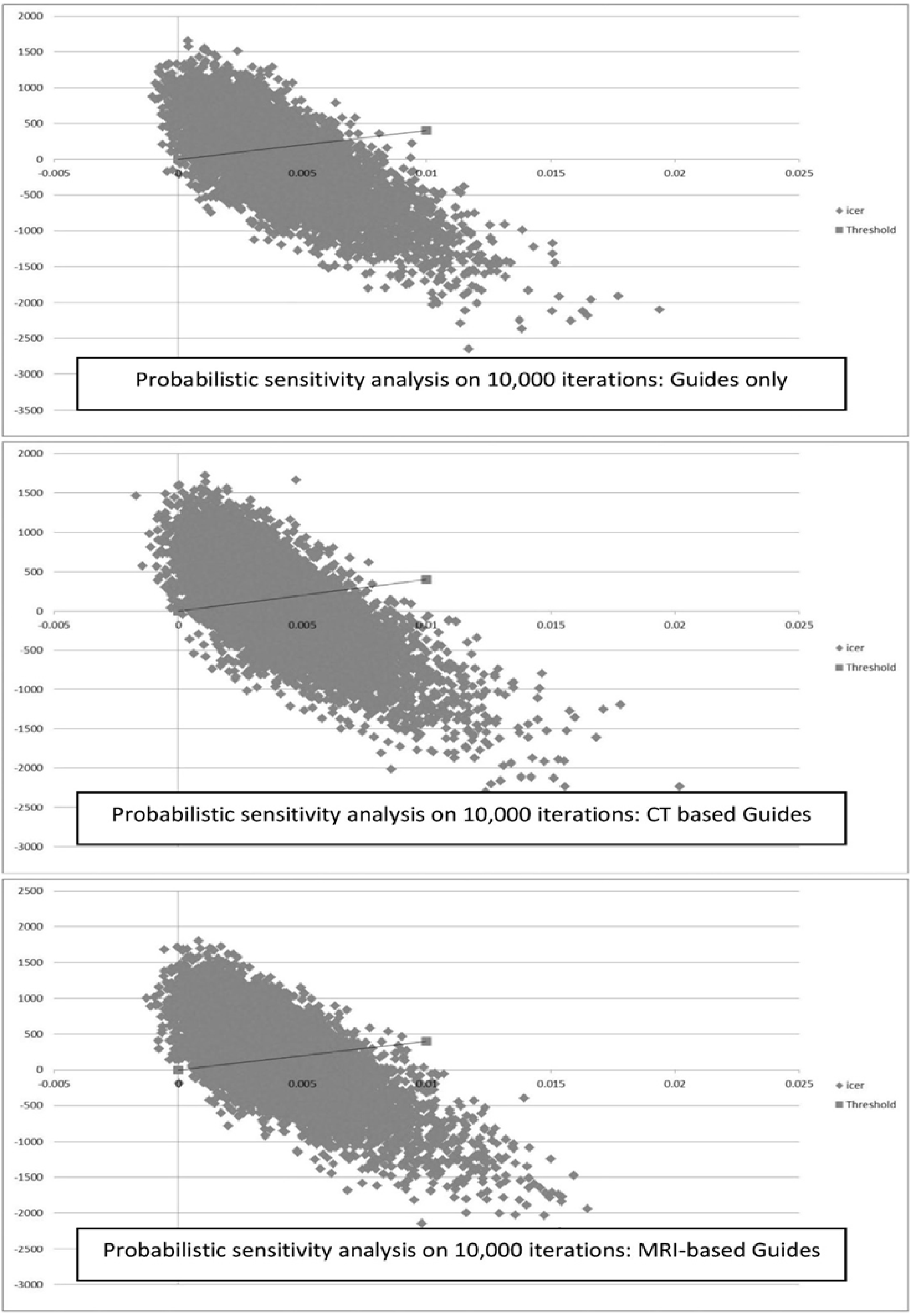
	Custom Guides	Standard procedure	Reference
Transition probabilities			
Primary TKA - Successful after primary TKA	97.759%	97.470%	Derived value
Primary TKA - Death	Peri-operative mortality + 11/12 age specific mortality		StatBel (18); Calculated from Orthopride
Primary TKA - revision (Y1)	0.712%	0.954%	Calculated from Orthopride
Successful after primary TKA - Revision Y2	0.636%	1.110%	Calculated from Orthopride
Successful after primary TKA - Revision Y3	0.514%	0.700%	Calculated from Orthopride
Successful after primary TKA - Revision Y4	0.219%	0.725%	Calculated from Orthopride
Successful after primary TKA - Revision Y5	0.000%	0.300%	Calculated from Orthopride
Successful after primary TKA - Death	Age specific mortality		StatBel (18)
Successful after primary TKA - Successful after primary TKA	1 - Revision risk - Mortality risk		Derived value
Revision TKA - Successful after revision TKA	1 - Age specific Death Risk		Derived value
Revision TKA - Death	Peri-operative mortality + 11/12 age specific mortality		StatBel (18); Boddapati et al, 2018 (19)
Costs			
Primary TKA	22450		Adapted from Ferket et al, 2017 (20)
Revision TKA	27024		Adapted from Ferket et al, 2017 (20)
Custom Guide	400		Personal communication with manufacturer
MRI	198.51		Tienpont et al, 2015 (21)
CT-scan	115.2		Van den Wyngaert et al, 2018 (22)
Utilities / Disutilities			
Utility of a Primary TKA	0.725		Slover et al, 2006 (23)
Utility of a Revision TKA	0.707		Slover et al, 2006 (23)
Disutility during the Primary TKA	-0.1		Slover et al, 2006 (23)
Disutility during the Revision TKA	-0.150064625		Slover et al, 2006 (23)

Probabilistic sensitivity analysis was run without and with cost of CT and MRI. Results can be found in table 6. A visual representation can be found in figure 5.

Table 6: Results of the probabilistic sensitivity analysis on 10,000 iterations.

% after 10,000 iterations	Guide alone	CT-based guide	MRI-based guide
Dominant	45.57%	38.35%	31.64%
Cost-effective at €40,000	56.44%	49.46%	42.70%
> €40,000	43.56%	50.54%	57.30%

Figure 5: Plot of the deterministic sensitivity analysis run on 10.000 iterations.


Probabilistic sensitivity analysis on 10,000 iterations: Guides only

Probabilistic sensitivity analysis on 10,000 iterations: CT based Guides

Probabilistic sensitivity analysis on 10,000 iterations: MRI-based Guides

5. Discussion

The goal of this study was to 1) evaluate how cutting guides for TKA are used in Belgium, 2) evaluate the effect of using custom cutting guides on implant survival and 3) evaluate its health-economic implications.

3-D printed patient-specific cutting guides are used in approximately 5% of the primary TKAs performed in Belgium. Opposite to most analyses on the value of these guides, we did not perform a clinical trial but used the national arthroplasty database as input. Patient demographics were found to be very similar in the primary procedure with and without custom guides. The often very low P-value for the Chi²-test were rather a result of the big sample size than the clinically significant differences between the two groups (24). Custom guides were less likely to be used by lower-volume surgeons, although previous research suggested they might be the ones benefiting the most from it (20). Additionally, there was a higher use of cemented implants in combination with the custom guides. Both surgical experience and implant fixation were considered to be confounding variables and analyzed in more detail during the modelling part. There was no significant difference in reasons for revision surgery nor the revised components between the group with or without custom guides.

In general, custom guides show a clear advantage compared to standard instrumentation because of the lower revision rate. Survival analysis showed an odds ratio of 0.696 for revision in the advantage of custom guides. Two confounding variables were incorporated in the analysis: implant fixation and the surgeon's experience. Corrections for fixation type and the surgeon's volume still resulted in a significant reduction of the chance of having a revision surgery when using custom cutting guides.

Literature suggests a lower implant survival rate with uncemented implants, especially on the tibial side (25). This is congruent with the findings in the Belgian Arthroplasty register. On the other hand, more recent literature suggests the fixation of the implant might not be of such influence for future revisions (11, 27).

As both our data and the literature suggest, surgical volume and surgical success are positively correlated (28). Several theories are suggested for this finding: 1) surgeons with better results will attract more patients through referrals, 2) the experience with the procedure results in a higher efficacy by both surgeon and hospital staff, 3) small-volume surgeons are often located at more rural sites which attracts a higher proportion of patients with a low social economic status, which is positively linked to higher failure rates (28, 29). While the surgeon's experience showed to have the biggest impact on implant survival, custom guides significantly improved the outcomes compared to the standard technique. This benefit, however, was found to be bigger in the case of less experienced surgeons. Furthermore, we have to reckon that the majority (63.5%) of the CCG are being used by 10 surgeons, all performing 80% or more of their TKAs with CCG.

The clinical advantages of guides have been analyzed by multiple researchers; often resulting in the final conclusion that guides do not provide clinical benefits (30-34). These studies are mostly based on the accuracy and alignment, and not on long-term implications to draw conclusions. Our research did not focus on alignment but on revisions to estimate the clinical benefit. Furthermore, these clinical studies are often single-center, hence incorporating a bias. As with any surgical technique, using CCG also has a learning curve (35). By using registry data, we eliminate potential biases and rely on statistics, allowing a different approach to the question. Finally, some surgeons had to abort procedures with CCG due to an unsatisfactory peroperative alignment, information that could not be retrieved from registry data (30, 32, 36). These studies are dating from the beginning days of CCG while our analysis only used observations from 2015 and later. Potentially, early inaccuracies and mistakes in the early days of CCG explain the differences in results.

As cost aspects have an increasing importance on medical decision-making, we ran a health-economic analysis to gain insights into this matter. The current price of guides was set to be €375 to €400 according to one of the main manufacturers. During this analysis we took the upper bound of €400, this still being 20% lower than the estimate used in the analysis by Thienpont (22).

Guides proved to be cost-effective when not considering the price of image acquisitions for these guides. MRI-based guides do not tend to be cost effective, while CT-based guides are cost-effective at €40,000 per QALY

Multiple studies have been published on accuracy of MRI versus CT-based custom guides but recent literature review has shown that CT-based guides are not inferior to MRI-based guides while MRI-based guides add a disproportional cost to still be cost-effective (37). Therefore, we advocate the use of CT-based guides, as they prove to be cost-effective.

During this analysis, the main driver was the reduced revision rate. We did not intend to engage in the discussion on alignment or outliers and solely used the hard data. While the healthcare perspective used in this health-economic analysis is perhaps the most important, we can also recall the advantage of custom guides from a hospital perspective. Guides tend to give a slight reduction of OR-time and reduce the number of trays used during the surgery, implying a reduced sterilization cost (31, 22, 38-42). Additionally, hospitals might be tempted to use this technology as a tool to position themselves as an innovation center. Therefore, both the financial and non-financial benefits for the hospital can be drivers to use the technology, even in absence of full reimbursement.

While the magnitude of data generated by using registry data is a big benefit for estimating implant survival, it also has a substantial drawback: only data incorporated in the registry could be used. While the use of the registry is mandatory in Belgium, it is not mandatory to complete all information concerning ASA classification, BMI and other demographics. Furthermore, we only know about revision surgeries and have no information on the rehabilitation process nor problems that don’t require a revision surgery. Incorporating patient reported-outcomes and complications that don’t require a revision surgery would highly improve the model.

6. Conclusion

3D-printed custom cutting guides are used in 5.13% of the primary TKAs in Belgium. While surgical experience tends to have the biggest impact on implant survival, guides significantly reduce the chance of having a revision surgery within a 5 year follow-up. Health-economic analysis suggests that the use of custom guides is a cost-effective strategy for guides based on CT-images. For MRI-based guides the total cost, including the cost of the additional MRI to make the guides, is slightly too high to justify its routine use for primary TKA.

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Chapter 5

Health economic analysis of aMace Integrated for revision hip arthroplasty of Paprosky type 3B acetabular defects: a decision modelling approach.

Based on **Philip Tack,** Jan Victor, Paul Gemmel, Lieven Annemans (2020). Do custom 3D-printed revision acetabular implants provide enough value to justify the additional costs? The health-economic comparison of a new porous 3D-printed hip implant for revision arthroplasty of Paprosky type 3B acetabular defects and its closest alternative. Orthopaedics & Traumatology, Surgery & Research : OTSR. 2020 May:102600. DOI: 10.1016/j.otsr.2020.03.012.

1. Abstract

Introduction

Total hip arthroplasty (THA) is a common operation for patients suffering from coxarthrosis. It has been proven effective in improving quality of life while being cost-effective. Medical 3D-printing has grown over the years and the use of 3D-printed implants has become more frequent. To date, the cost-effectiveness of 3D-printed implants for THA has not been evaluated. Therefore we performed a health economic analysis to: 1) analyse the cost-effectiveness of the aMace implant compared to its closest alternative on the market. 2) Have a better insight into Belgian costs of revision hip arthroplasties and 3) estimate the budget impact in Belgium.

Method

Custom Three-flanged Acetabular Components (CTAC) were compared to a 3D-printed implant (aMace) by means of a Markov model with four states (successful, re-revision, resection and dead). The cycle length was set at 6 months with a 10-year time horizon. Data was obtained through systematic literature search and provided by a large social security agency. The analysis was performed from a societal perspective. All amounts are displayed in 2019 euros. Discount rates were applied for future cost (3%) and QALY (1.5%) estimates.

Results

Revision hip arthroplasty has an average societal cost of €9950 without implant. Based on the outcomes of our model, aMace provides an excellent value for money compared to CTAC. The Incremental Cost-Effectiveness Ratio (ICER) was negative for all age groups. The base case of a 65 year old person, showed a QALY gain of 0.05 with a cost reduction of €1265 compared to CTAC. The advantage of using aMace was found to be greater if a patient is younger. The re-revision rates of both CTAC and aMace and the utility of successful revision have the highest impact on costs and effects. A Monte Carlo simulation showed aMace to be a cost-effective strategy in 90% of simulations for younger patients and in 88% of simulations for patients above 85 years old. In Belgium it would imply a cost reduction of €20500 on an annual basis.

Conclusion

Based on the findings of this model, the new 3D-printed aMace implant has the potential to bring an excellent value for money when used in revision arthroplasty of Paprosky type 3B acetabular defects. For all patients, aMace resulted in a dominant, cost-saving strategy in Belgium compared to CTAC.

Keywords:

3D-printing, hip arthroplasty, revision, acetabular implant, health economic evaluation, hip

2. Introduction

Total hip arthroplasty (THA) is a common operation for patients suffering from coxarthrosis. It has been shown effective in improving quality of life while being cost-effective, especially in patients younger than 65 years (1-4). An analysis by Belgium's biggest health insurer revealed that 17347 primary and 2372 revision THAs were performed in Belgium in 2009 with a general implant-survival rate of 93%. The cost of a primary THA was estimated to be €9496 in 2009 (5). Paprosky et al. (6) introduced a now widely used classification system for acetabular defects in which Paprosky type IIIA and type IIIB are severe acetabular defects, which are particulary challenging to repair. The size of the defect is correlated with a higher failure rate and positively correlated to the potential future need for a revision arthroplasty (7-9).

Recently, Materialise NV (Belgium) has launched a new type of implant targeting revisions of Paprosky type IIIB acetabular defects. aMace is a 3D-printed cementless custom titanium triflanged plate with a porous structure filling the acetabular defect. Implant design is based on the patient's CT-scan and a virtual 3D anatomic reconstruction. Screw trajectory and size are determined based on bone density and geometry prior to surgery and co-determine the implant's shape to assure optimal stability of the implant. Screws are incorporated both in the flanges and the cup. While other Custom Triflanged Acetabular Components use 3D printing to produce an anatomic model and prototype of the implant, the aMace implant itself is printed in one piece, while other CTAC are milled and coating has to be applied afterwards.

The custom production of aMace significantly increases the cost of the implant compared to Custom Triflangd Acetabular Components (CTAC) to manage severe acetabular bone loss in THA revision. However, to our best knowledge there is no health-economic analysis investigating the use of this new type of implant.

We hypothesized that the use of this new implant can be a cost-effective strategy in a Belgian setting. Therefore we performed a health-economic analysis using a Markov model to: 1) analyse the cost-effectiveness of the aMace implant compared to CTAC, which is its closest alternative on the market targeting these serious acetabular defects, using the perspective of the public healthcare provider. 2) Have better insights in cost of revision hip arthroplasties in Belgium. 3) Estimate potential additional costs of using the new implant in Belgium. Results are given in quality adjusted lifeyears (QALY) and costs in euro.

3. Material and Methods

3.1. Method

To evaluate the health economic impact of aMace Integrated a Markov-model was used. The model has a total duration of 10 years, a cycle length of 6 months and uses CTAC as comparator. The model consists of 5 states, each associated with a specific cost and quality of life (Figure 1a and 1b). A detailed description of the states is given in table 1.

Figure 1a: Visualization of the Markov model in cycle 1 (0-6 months)

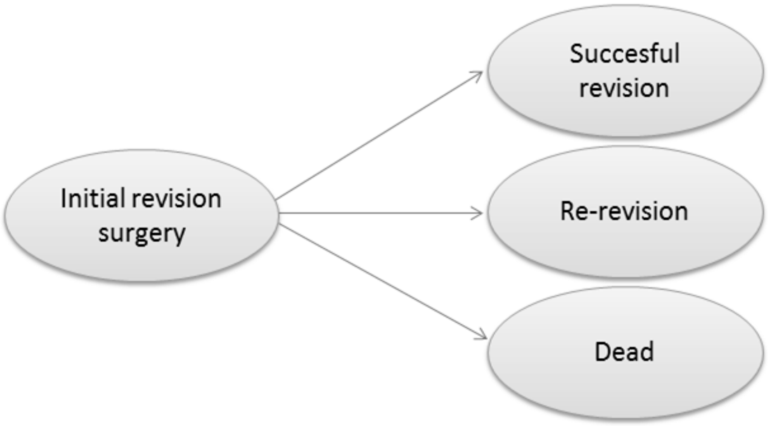


Figure 1b: Visualization of the Markov model in cycle 2 and further (6 months – 10 years)

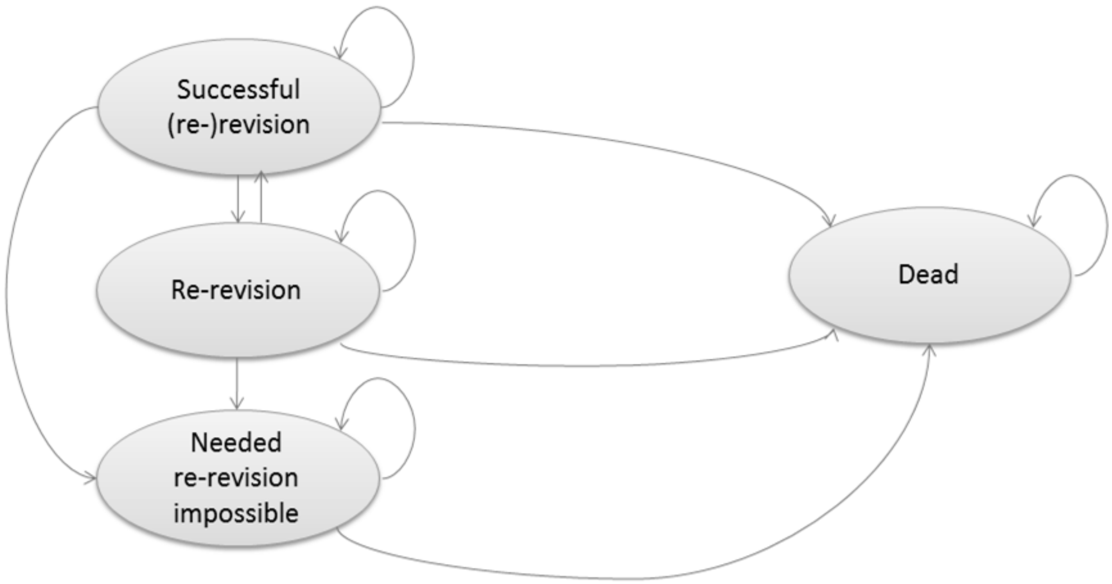


Table 1: Description of the states.

State	Description
Initial revision	This state is the starting state in the model. All patients enter the model here. The patients in this state have just had a revision with either of the considered comparators. This state incorporates possible complications associated with (re-)revisions (eg: infection, sciatic nerve palsy, dislocation, etc..) according to the adverse event rates found in the literature for that specific implant.
Re-revision	The patient undergoes an additional revision for any reason. All complications related to this re-revision are incorporated in this state, even if they occur beyond 6 months.
Successful revision	The patient had a successful revision and does not require an additional revision. As complications are accounted for in the revision and re-revision states they are not incorporated in the 'successful revision' state.
Needed re-revision impossible	The patient requires an additional revision surgery but revision surgery is not possible anymore. This is often due to the growing acetabular defect or the presence of recurrent infections. Patients most often undergo a 'resection arthroplasty' or 'Girdlestone procedure' as final treatment.
Dead	The patient died. This is an absorbing state.

The model starts at the initial revision surgery. After the first cycle the patient will be in one of the following states: ‘successful revision’, ‘re-revision’ or ‘dead’. ‘Needed re-revision impossible’ is not allowed after the initial revision and therefore can only occur after re-revision.

3.2. Transition probabilities

Transition probabilities between states have been estimated based on literature data and additional information received by the implant manufacturers. Articles from 2012 to 2018 were considered and analyzed to estimate the occurrence of events, and with this the transition probabilities between states. Older papers were not considered as technologies change and these older findings might be associated with previous versions of the implant.

For the alternative treatment options, 5 papers of CTAC were found relevant (11-15). From these papers, the events were synthesized and analyzed to estimate transition probabilities. Transitions from a successful revision to re-revisions were based on the average number of patients receiving a revision during the follow-up. The 6 month transition probability was calculated as =1-(1-X)^(6/N) with X being the % of revision and N being the follow-up expressed in months. The final transition probability was calculated by taking the weighted average. The transition from re-revision to impossible re-revision was calculated as the percentage of patients with resections or failed revision. The specific transition probabilities can be found in appendix 5.1.

3.3. Quality of life measurements

To measure the impact on quality of life (QoL), Quality Adjusted Life Years (QALYs) were used. One QALY is the value of one year in perfect health. A QALY reflects both quality and duration of life and is calculated by multiplying the utility of a health state, being the value attributed to one’s health at a given time, with the duration of that state. The quality of life (QoL) estimates associated with each state are specific for the Belgian population, and the specific condition of the patient. The impact of the states on Quality of Life (QoL) was assessed by using data from the literature (16-18) . These utility estimates apply for both procedures. The utility estimates without corrections for age or gender can be found in table 2. The utilities reported in table 3 were then adjusted for age and gender specific variances, based on the age and gender utilities of the Belgian population using 2013 Belgian EQ-5D data (table 4) (19) .

Table 2: QoL Estimates per state (Not adjusted)

Yearly QoL estimates	Average	St. Err.	Distribution	Source
Successful revision	0.913	0.15	Beta	Gu et al. [12]
(Re-)revision surgery	0.5624	0.34	Beta	Pulikottil-Jacob et al. [7]
Needed re-revision impossible	0.533	0.202	Beta	Gu et al. [12]
Dead	0			

Table 3: QoL scores per age group and gender specific for the Belgian population

BELGIAN EQ-5D DATA 2013	Average between Men & Women	Men	Women
<65	0.83	0.85	0.82
65-74	0.79	0.82	0.77
75+	0.68	0.74	0.65

The utilities for the revision state not only incorporated the disutilities resulting from the revision itself but also the possible association with complications. The complication profile of aMace was based on published literature on the aMace implant (20-25). The complication profile of the standard procedure (CTAC) was calculated by using the weighted average of five studies (11-15). The complications were then grouped into 5 classes: Infection: long-term antibiotic use; resection arthroplasty; non-operative medical complication; operative mechanical complications; and short-term major medical complication, based on Klouche et al. (26). An overview of these grouped complications is given in table 4. Complications that are not related to the hip were not considered due to the lack of information, most present in the aMace group. The disutilities for the complications were incorporated into final utilities. These final QoL estimates with corrections for complications specific to the profile of the chosen implant can be found in table 5. We incorporated the QoL estimates without complications as well, to allow a clear comparison of the impact of the complications on both types of implants.

Table 4: Overview of the grouped complications per implant type

Average complication per implant	**CTAC**	**aMace**
Reinfection: long term AB use	2.63 %	2.63%
Resection arthroplasty	6.38%	0.00%
Medical complication non operative	6.31%	9.09%
Mechanical complication operative	27.36 %	15.15%
Short term major medical complication	0.00%	15.15%

Table 5: Final QoL scores

Final QoL estimates used in the model					
Group	Successful Revision	Re-revision without complications	Re-revision with aMace	Re-revision with CTAC	Needed re-revision impossible
Avg <65	0.7596	0.4679	0.4174	0.4206	0.4434
Avg 65-74	0.7213	0.4443	0.1982	0.3693	0.4211
Avg 75-85	0.6208	0.3824	0.3178	0.3179	0.3624
Avg 85+	0.6208	0.3824	0.3178	0.3179	0.3624
Men <65	0.7731	0.4762	0.3958	0.3958	0.4513
Men 65-74	0.7487	0.4612	0.3833	0.3833	0.4371
Men 75-85	0.6756	0.4162	0.3459	0.3459	0.3944
Men 85+	0.6756	0.4162	0.3459	0.3459	0.3944
Women <65	0.7493	0.4616	0.3836	0.3836	0.4374
Women 65-74	0.7030	0.4330	0.3599	0.3599	0.4104
Women 75-85	0.5935	0.3656	0.3038	0.3038	0.3465
Women 85+	0.5935	0.3656	0.3038	0.3038	0.3465

3.4. Cost measurements

Costs are calculated from the public health care provider’s perspective and based on data from the largest health insurance fund (CM) in Belgium, the literature and the implant manufacturers. All costs have been translated into 2019 euros based on the Belgian Health index (27). The data from the health care insurer can be found in appendix 5.2. The (re-)revision state incorporates all costs associated with the revision, including rehabilitation and possible implant specific complications.

The implant cost was set at €6002.7 for the CTAC and €8419.25 for the aMace implant. The cost of surgery was based on data from the largest public insurance company in Belgium. The provided data does not discriminate based on size of defect. Therefore the P75 result (€17030) was used as the average cost of revision surgery using the standard triflanged implant based on the assumption of higher costs due to the bigger defect. The cost of a revision surgery with the CTAC without complications was calculated by subtracting the weighted average cost of complications occurring with the CTAC. The cost of a revision with aMace without complications was calculated as follows:

(P75 cost for revision) – (price of triflanged implant) + (price of aMace implant)

Rehabilitation for both the standard triflanged implant and aMace was taken as the P75 cost of revisions from the health insurer data. We do this to take into account the longer rehabilitation associated with multiple revisions and the more severe defects (28). For cost estimations, complications were attributed an individual price for each complication as opposed to disability estimations where the complications were grouped.

Dislocations of the hip were estimated to add an additional cost of 19%, i.e. €3069.49, based on a paper of Sanchez-Soleto et al. (29). Sciatic nerve palsy is mostly treated conservatively; additional costs are mainly due to additional (neurological) consultations, MRI imaging and longer revalidation (30). An additional cost of €1732.35 was deemed to be reasonable (cost of MRI, neurological consult and 50% longer rehabilitation). Infections were split in two groups; minor infections needing only antibiotics and major infections needing longer hospitalization and surgery. Based on Klouche at al. (26), the cost of minor infections is €399.95. For major infections, the total cost of revisions was assumed to be approximately the delta P90-P75 cost from the health insurer data, setting the additional cost for the major infection at €11756.76. The cost of loosening of the implant was assumed to be the same (€11756.76). Hematomas were not attributed any costs as they do not have to be treated. The cost of a needed debridement was arbitrarily set to be 50% of the additional cost of loosening of an implant (€5878.38). The cost of bursitis was estimated as the cost of NSAIDs during 1 month (€10) added with a longer revalidation accounting for an additional 5% of the revalidation cost totaling to be €158.09. The cost of pelvic instability was estimated as 10% longer rehabilitation and the cost of a hip brace (approximately €200) totaling €496.19.

The follow up cost associated with a successful re-revision was set to €0 as rehabilitation costs have already been attributed to the re-revision state. The cost associated with patients being unable to get another revision was calculated based on their estimated mobility status after a resection arthroplasty (‘Girdlestone procedure’). Based on a Belgian study by Sharma and Kakar (31) 33.3% of the patients are wheelchair bound and 66.6% need assistance for their mobility. Costs associated with these conditions were estimated based on the requirement for a nurse every two days.

3.5. Assumptions used in the model

4 additional assumptions were used in the model:

Re-revisions and death are separate states and will therefore not be considered as a ‘complication’.

Complications occur within 6 months after revision and are therefore incorporated into the initial ‘(re)revision’ state according to the rates found in the literature for that specific implant.

Impossible re-revision can only occur after being in the ‘re-revision’ state (excluding the first revision with the studied implant). This simplification can be justified since a resection arthroplasty is also an operation. The impossible re-revision state only incorporates the cost and QALY after the resection.

An annual discount rate of 3% was attributed to future costs and an annual discount rate of 1.5% is attributed to future QALYs (32)**.**

3.6. Statistics

Statistical analysis and modelling were performed using Excel 2010 (Microsoft co.) As common practice, one-way sensitivity analysis was performed using an arbitrary 30% up or down variation on all variables, except the impossible revision rate of aMace that varies between 0 and the rate of the comparator as no impossible revisions have been observed yet with aMace (33). The cost-effectiveness cut-off is set at €50000 per QALY, as standard in Europe (34). Standard deviations were often not present. If no standard deviation could be found in the literature it was assumed to be 10% of the mean. The probabilistic sensitivity uses a gamma distribution for costs and a beta distribution for utilities and transition probabilities.

4. Results

4.1. Basic results

The average cost of revision hip arthroplasty in Belgium is €15300, as can be found in appendix 1. AMace shows to be cost-effective in all base-cases compared to CTAC at a €50000 per QALY cut-off (32). The new implant gives a cost reduction of €1266 and health benefit of 0.05 QALY for a 65 year old person. Only for elderly above 85 years old, the new implant does not result in a dominant strategy. The new 3D-printed implant thus provides additional health at an increased but acceptable cost. An overview of the results for all age and gender groups is given in table 6.

4.2.One-way sensitivity analysis

A sensitivity analysis was performed to analyze the impact of the different assumptions. Table 8 shows the outcomes for the average 75 to 84 years old person, for each input value being raised with 30% or lowered with 30%. Tornado diagrams of the cost impact and QALY impact are given in Figures 2 and 3 for the same case. With a 30% variance on one single value at a time aMace still remains a cost-effective strategy at a threshold of €50000/QALY.

The tornado diagram of the QALY estimates shows that the re-revision rate of both aMace and CTAC and the utility of a successful revision have the highest impact on the QALY estimate. The tornado diagram of the costs shows that the cost of surgery and the price of the aMace implant have the highest impact on the cost estimates. The sensitivity analysis of the ICER was not performed since all results were dominant. Other variables have a minor impact on the ICER.

Table 6: Overview of all base case results

	aMace Integrated				CTAC				Delta (aMace vs. CTAC)				ICER	
	NOT DISCOUNTED		DISCOUNTED		NOT DISCOUNTED		DISCOUNTED		NOT DISCOUNTED		DISCOUNTED		NOT DISCOUNTED	DISCOUNTED
	QALY	COST	QALY	COST	QALY	COST	QALY	COST	QALY	COST	QALY	COST		
Male <65y	7.70	€ 27,080	7.10	€ 26,547	7.65	28871	7.05	27801	0.05	-1791	0.05	-1254	Dominant	Dominant
Male 65-74y	6.11	€ 26,432	5.67	€ 26,024	6.08	27572	5.63	26757	0.04	-1140	0.03	-733	Dominant	Dominant
Male 75-84y	5.26	€ 26,294	4.88	€ 25,911	5.22	27294	4.85	26530	0.03	-1000	0.03	-619	Dominant	Dominant
Male 85+	3.26	€ 25,230	3.07	€ 25,035	3.24	25172	3.05	24792	0.02	57	0.02	243	2611.57	11981.52
Female <65y	7.53	€ 27,110	6.94	€ 26,571	7.48	28930	6.89	27848	0.05	-1821	0.05	-1278	Dominant	Dominant
Female 65-74y	7.19	€ 26,948	6.64	€ 26,440	7.14	28603	6.59	27585	0.05	-1655	0.05	-1145	Dominant	Dominant
Female 75-84y	6.36	€ 26,548	5.89	€ 26,117	6.32	27798	5.85	26937	0.05	-1250	0.04	-820	Dominant	Dominant
Female 85+	3.96	€ 25,393	3.71	€ 25,170	3.92	25487	3.68	25050	0.04	-94	0.03	120	Dominant	3703.99
Average <65y	7.60	€ 27,095	7.01	€ 26,559	7.55	28900	6.96	27824	0.05	-1806	0.05	-1266	Dominant	Dominant
Average 65-74y	6.28	€ 26,469	5.82	€ 26,054	6.24	27646	5.78	26816	0.04	-1176	0.04	-762	Dominant	Dominant
Average 75-84y	6.22	€ 26,438	5.76	€ 26,028	6.17	27578	5.72	26760	0.04	-1140	0.04	-732	Dominant	Dominant
Average 85+	3.90	€ 25,340	3.66	€ 25,126	3.86	25382	3.63	24964	0.03	-42	0.03	162	Dominant	5136.72

Figure 2: Impact analysis on discounted QALYs on an average 75 – 84 year old patient

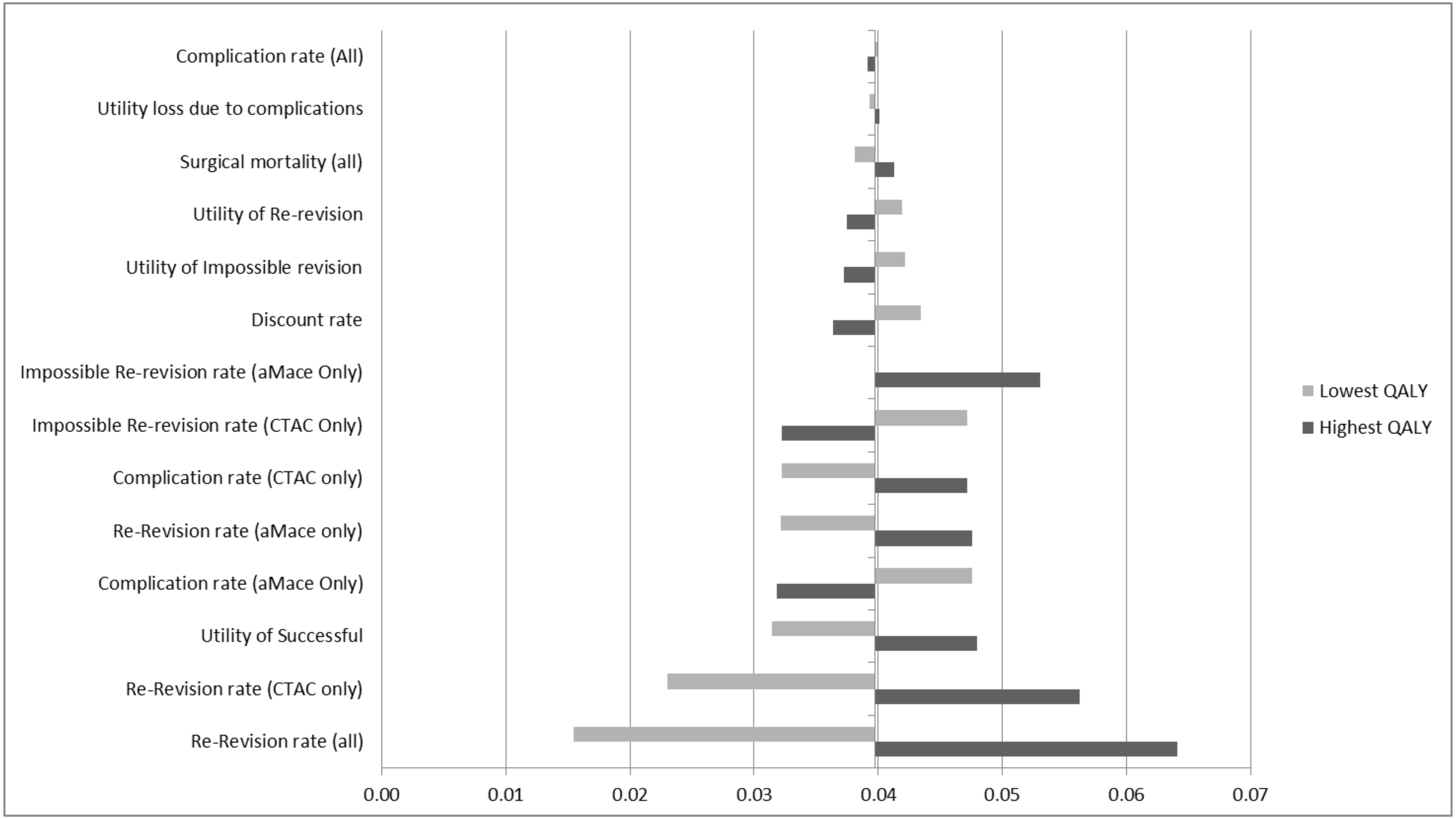
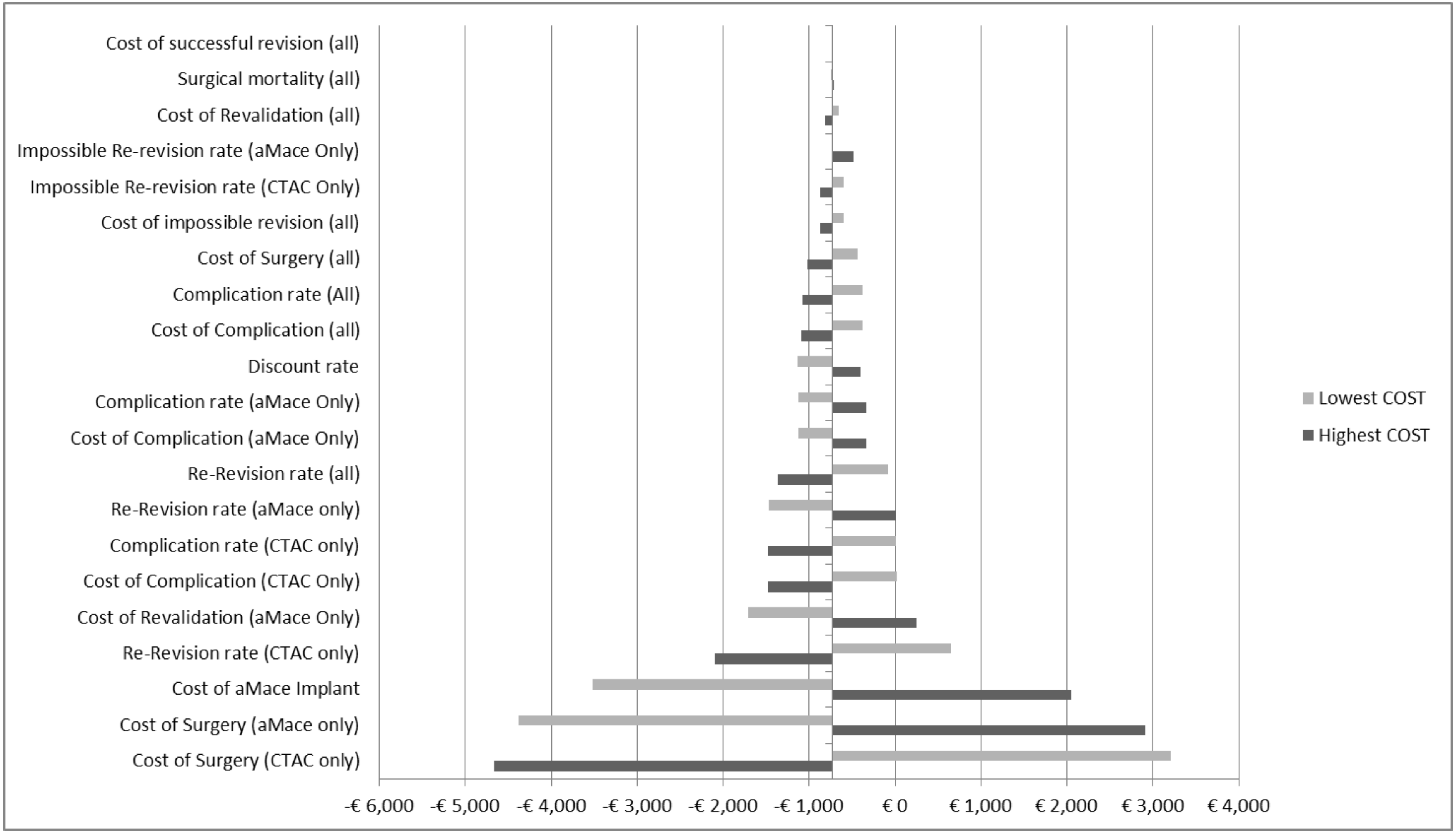


Figure 3: Impact analysis on discounted COSTS on an average 75 – 84 year old patient



4.3.Probabilistic analysis

To assess the impact of multiple variables, both for aMace and CTAC, changing at the same time, a 'Monte Carlo' simulation was run on 10000 iterations.

Overall, aMace largely remains cost-effective and in some cases dominant. In the case of a male subject less than 65 years old 86.83% of the scenarios were found to be dominant and 90.04% of the scenarios indicated aMace Integrated to be a cost-effective strategy.

For a subject of 85 years old or older the majority of the observations are cost-effective on a €50000 threshold. However, 12.61% of the observations are above the threshold and should be considered not cost-effective. 76.84% of observations are dominant. On average, aMace also provides an excellent value for money for these older patients. Figures 4 and 5 show the plot of the scenarios and the boundary for cost-effectiveness, set at 50000€/QALY for subjects younger than 65 years old and above 85 years old respectively.

In Belgium, 835 hip revision surgeries involving the acetabular component are performed on a yearly basis (35). No data is available on the classification of the defects. If assumed that the proportion of patients having revision surgery for a Paproski type 3B defect is similar to the Norwegian data (1.94%) this would imply 16 patients annually in Belgium with an estimated cost reduction of €20500.71 and QALY gain of 0.81 on an annual basis assuming patients up to 65 years old (36).

Figure 4: Monte Carlo simulation on 10000 iterations for a male subject up to 65 years old using discounted values

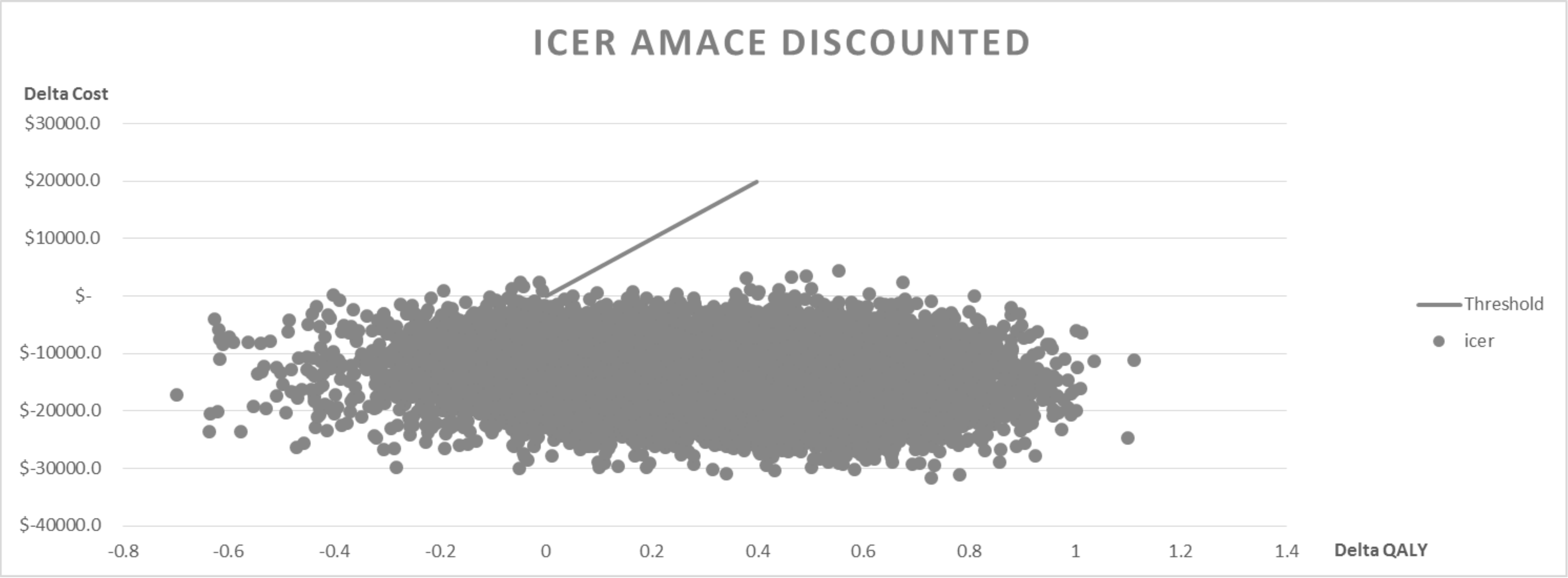
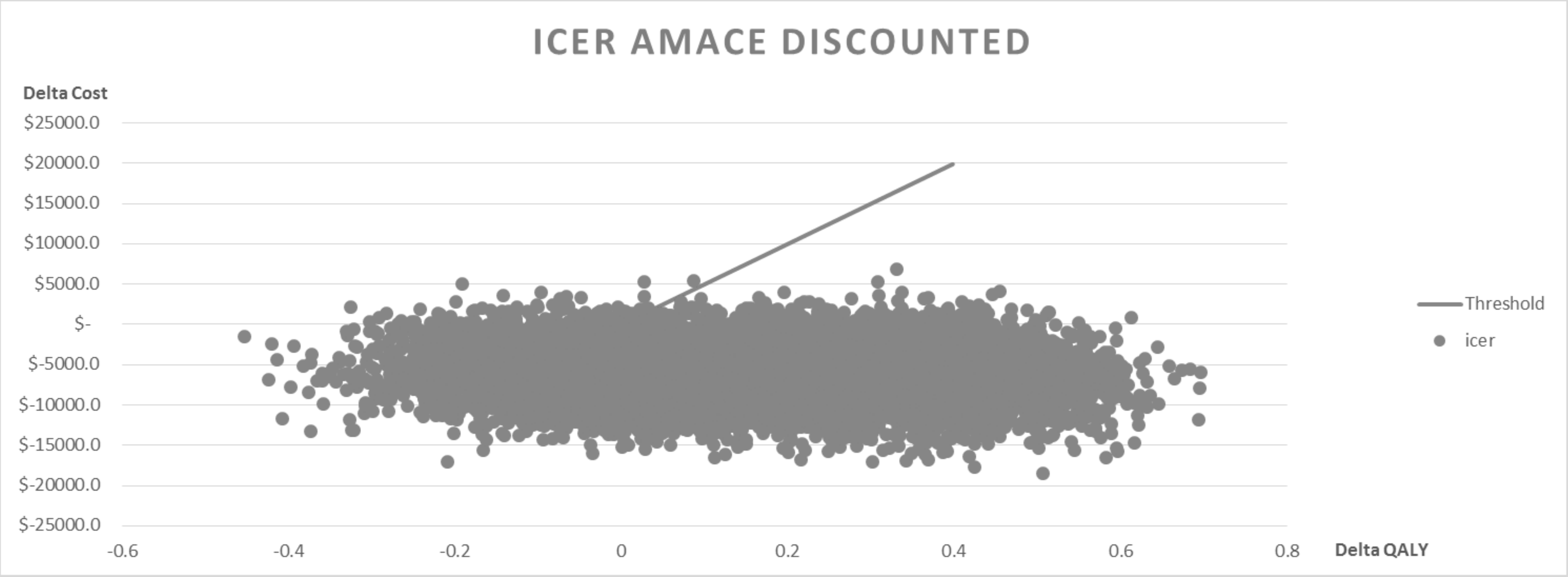


Figure 5: Monte Carlo simulation on 10000 iterations for a male subject over 85 years old using discounted values



5. Discussion

Acetabular discontinuities remain challenging; with arthroplasty re-revision rates as high as 70%, current alternatives for hip arthroplasty revisions with acetabular discontinuities are insufficient (7,9,10). A new 3D-printed implant for revision arthroplasty of Paproski type IIIB acetabular defects aims to provide better results than current alternatives. As health budgets are increasingly under pressure, this paper provides the first early health-economic analysis of this new implant.

First, we aimed at having a better view on cost of revision arthroplasties in Belgium. While a lot of studies cover the cost of primary THA, few cover the costs of revisions, and these are nonspecific for Belgium. Therefore, a specific search on the costs of revision hip arthroplasty was conducted by a major health insurer in Belgium. Average treatment costs in Belgium seem to be similar with the average prices in France averaging between €8105 for patients with comorbidities and €7529 for patients without comorbidities (37).

Second, we hypothesized that the use of this new 3D-printed implant could be a cost-effective strategy in a Belgian setting. AMace is a cost-effective and even dominant strategy for revision arthroplasty of Paproski type 3B acetabular defects. Based on our analysis, the use of aMace would imply a cost reduction while adding extra health in a Belgian setting. The new implant should therefore become the new standard for revision arthroplasties of major acetabular discontinuities.

Major complications and revisions can highly affect these results, and therefore it is of importance to minimize these. It has been shown that the new implant can be implanted through a direct anterior approach, potentially further reducing dislocation risks (38). Cost of surgery and implant pricing have the biggest effect on the cost-effectiveness.

The cost-effectiveness analysis was based on a comparison with its closed alternative being CTAC. As mentioned earlier, Paproski Type IIIB acetabular defects are often treated with trabecular metal cups in constructs. We reckon the value of analyzing the cost-effectiveness of ‘one-piece’-implants against TM-constructs. The analysis was performed from a public healthcare provider perspective, hence variables as freed-OR-time or other productivity gains with monetary value for the hospitals were not taken into account (39). An analysis from a hospital perspective could give us more insights into the value of this 3D printed implant for the hospital itself. Furthermore, both the 3D printed implant and the milled CTAC are patient-specific pieces. Standard cage-cup constucts and instrumentation need to be present in the OR in case the implant does not fit well enough to be implanted. To date, no data is available on the percentage of cases where the original plan had to be abandoned. This element should definitely be incorporated if a comparison between (3D printed) CTACs and TM augments is made.

Cost-effectiveness was calculated with a €50000 threshold, although voices are up to move this threshold to 100000 as the wealth of countries goes up (24). Increasing the threshold to €100000 would make the aMace implant cost-effective in almost 95% of the cases; also for older people.

Several weaknesses can be noted. The cost data obtained from Belgium’s biggest health insurer could not be linked to the clinical condition of the patients nor surgical information due to privacy reasons. Linkage of specific conditions and the associated cost could provide valuable information and significantly reduce the variance in cost estimates, improving the quality of the model.

We did not include the societal cost due to loss of productivity. Adding societal cost would signify a significant increase of uncertainty, as all variables would have to be estimated without numerical evidence. As aMace has shorter rehabilitation times and a better success rate, aMace is most likely more cost-efficient than the results of the model indicate, as the high societal cost of patients not being able to move by themselves are not considered in the model. By using a rather low estimate for the cost of people not being able to receive an operation to solve their hip problem we underestimate the advantages of the new 3D printed alternative as it is able to tackle these difficult cases.

The preliminary nature of the analysis was only possible using a first-order Markov model. This widely known weakness obviously implies a simplification of the reality, where transition probabilities vary over time (40,41). The utilities for aMace and CTAC implant were very similar. This raises the question if the difference in utilities is really relevant. Using the same utility estimates would not have changed the outcomes in a major way and would have made the model more simple.

Only hip-related complications were considered in the ‘re-revision’ state. Non hip-related complications, e.g. pulmonary embolisms, could not be included due to the lack of available data, especially for aMace. If one could assume the ratio of these complications is similar for both aMace and CTAC implants, this would be in favor of the new aMace implant due to the lower re-revision rate.

The data input used in this model reflects the initial results with the new implant but is subjected to a multitude of uncertainties. With the increasing availability of data on the utilization of aMace more reliable results will be obtained. While it is important to perform preliminary analyses, as it can give valuable information about its potential, it is also advisable to remodel the value of aMace when bigger controlled studies are available (42).

6. Conclusion

Based on current literature aMace offers an excellent solution for patients with acetabular discontuinity at a slightly superior price than the most important comparator. The procedural results of aMace show a significant reduction in reoperations. The modelling aproach suggests that the aMace implant is cost-effective and even a dominant strategy for revision of hip arthroplasty in patients with a Paprosky type 3b defect compared to the non-porous CTAC and implies cost savings in Belgian healthcare budgets.

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Chapter 6

General discussion

1. Introduction

It is widely known that the medical sector is accepting innovation with open arms, whether it's operating with robots, manipulating forms of life or customizing medicine to a personal level. A key innovation like printing three-dimensional objects therefore easily found applications in medicine. With Belgium as one of the key drivers behind the technology, we found ourselves in a good position to witness how the technology is developing.

The aim of the PhD project was to analyze the spread of the technology, its application, strengths and pitfalls; and to make the bridge to the economic implications of its use. The technology was found to be at its very beginning in some medical domains, while other domains, like orthopedics and maxillofacial surgery, had been using it on a wider scale (1). Unfortunately, the lack of strong data was one of the main lines connecting all of its applications. As with every new discovery, most literature was case-based.

Case reports are the best way to get novelties to the public and they are therefore very useful as a preliminary tool to reveal the potential uses, generate hypotheses and start the discussion of how the novelty can be optimally used in the future (2). For innovations, they are the best way to get the word out and spark adoption by multiple tech-savvy researchers, increasing the rate at which the awareness is generated (3). Furthermore, costs of setting up a large-scale trial are often too high to handle for innovative start-ups (4). Unfortunately, as valuable as they are, these case-based reports are of lesser value when needing epidemiological quantities, establishing cause-effect relations or even simply wanting to make a generalization (3). These limitations are, unfortunately, essential for health-economic evaluations.

The main objective of this PhD thesis is to assess the health-economic value of applications of medical 3D-printing. Despite the technology getting more mature, large clinical trials are often inexistent. Therefore the available scientific data was sometimes too limited and had to be extended with expert opinion to reach a preliminary result. When taking in mind the limitations, an important step was taken toward determining the potential health-economic value of the technology. In the end, a balance has to be made between the scientific robustness of only using data from large scale clinical trials and bringing preliminary health-economic results to the public, which can guide decision makers to further invest in the new technology.

This general conclusion will give an overview of the previous chapters, with a critical view on shortcomings and pitfalls. In the following section, a brief overview of the implementation is given, with a reflection on additional findings from after the publication of the systematic review. Second, the findings of the health-economic evaluation of anatomical models used for surgical planning of CDH are highlighted, with an elaboration on the role of anatomical models and their use and valuations in other domains. Third, we highlight the results of the analysis on custom-made cutting guides used for primary TKAs. Fourth, the health-economic evaluation of custom 3D printed implants for revision hip arthroplasty with an acetabular discontinuity is discussed while exposing the value of custom implants in other disciplines. In the end, a general conclusion is given on medical 3D printing applications, its medical and non-medical value, the valuation of medical innovations in general and finally, practical recommendations for decision makers and future research in this domain.

2. General discussion on medical 3D printing

2.1. Levels within medical 3D -printing.

3D-printing can provide a substantial value in medicine. As can be deducted from these evaluations, 3D-printing will have its biggest benefits when used on complex pathologies. The results of the multiple evaluations follow the general consensus found in the literature (5). For complex cases the benefits are directly linked with the new way of operational planning. The medical 3D–printing technology can provide multiple levels of support. The previous chapters were sequenced in a very specific way as described below.

Anatomic models can be seen as the first level of usage of medical 3D-printing. The tactile advantage of having a physical model gives the surgeon hands-on insights on the defect, its size and, possibly, the position of surrounding tissues that are of importance, making it a great tool to visualize the procedure and its pitfalls (6, 7). Having planned the procedure in advance often results in a shorter OR time, a higher accuracy of the procedure, and as a result, better health outcomes with a decreased number of complications and a decreased mortality (1, 8). Although anatomical models being classified as the first level of use, they are very valuable and the only 3D printed tool necessary for a lot of complex procedures. Anatomic models are very accessible as they could be printed in house by a trained staff member (9). Additionally, the models have can be used to teach the patients, who mostly have insufficient medical knowledge to be able to visualize the defect and the planned treatment (10, 11). Finally, these models can be used to test new medical equipment (12).

Custom surgical guides can be seen as the second level of use of the 3D printing technology. The guides further incorporate the preparatory work and bridge the conceptual planning on models with the real-life scenario. Guides can have great health advantages when used on complex cases. In maxillofacial surgery, especially reconstructions of mandibular defect, the use of guides has a significant impact on both graft survival and esthetical and performance outcomes (13).

Custom implants can be seen as the third level of use for the 3D printing technology. Again, these implants have their value in complex pathologies where the general alternatives do not provide a similar, satisfying result. The custom implants are most often accompanied by an anatomical model, a surgical guide and a test implant. The availability of these additional pieces allows the surgeon to perform a simulation surgery, including the resection of bone fragments needed to fit the implant. After sterilization, the test implant can be used to assess the fit of the implant instead of using the actual implant, thus reducing the risks of contamination.

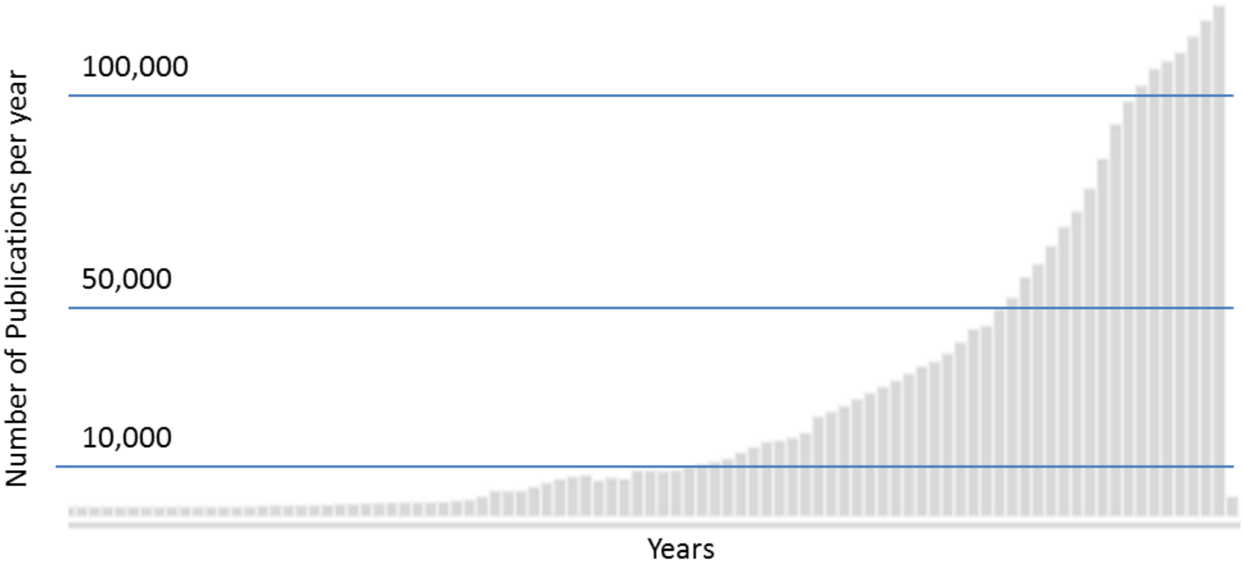
Finally, the emerging industry aiming at making scaffolds and bioprinting will become the fourth level of medical 3D printing. Although this technology is not available yet and the first livable cubic cm of tissue has to be printed, it is already a well-known use within the public opinion. Apart from the time of availability, it remains the question whether the likely much higher cost due to the complexity of printing living tissue will bring a benefit that can legitimize its cost. Therefore, even with a future envisioning almost limitless possibilities of 3D printing living tissues, the other levels of medical 3D printing will still hold a significant value.

2.2. Paper 1: Implementation of medical 3D printing: a systematic review and beyond

The first article discussed in this PhD dissertation evaluated the integration and applications of the technology (1). A systematic research was conducted on Pubmed, Embase and Web of Science incorporating articles up to December 2015. Although we value case reports, we did not incorporate them, and used case series with a minimum of 4 participants as lower value for acceptance. Since we estimated to be at the beginning of the general integration, we wanted to focus on finding the already existing quantitative data. At that time, we identified 227 papers that matched all criteria. 3D printing seemed to be adopted by a magnitude of medical specialties. Approximately half of the publications were orthopedics-related, followed by maxillofacial and cranial surgery. A lot had to do with the use of surgical cutting guides for TKAs, the most widespread application of 3D printing at that time. A full overview of the data can be found online on DOI: 10.1186/s12938-016-0236-4.

The search in 2015 exposed an exponential growth in publication citing 3D printing in starting from 1999 to 2015. Although a useful project, the search had not been redone to incorporate data up to 2020. A simple search in Pubmed shows that the exponential rate at which the evidence is growing has not stopped. Figure 6.1 shows the growth in publications on Pubmed. This view is similar to the trends in publications for 3D printing outside the medical industry (14).

Figure 6.1 Number of publications by year on Pubmed (syntax: '3D printing OR patient-specific OR custom-made') Ran on January 2th 2021



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Since the time of publication, multiple systemic reviews of medical 3D printing applications within specific domains have been published (15-22). Again, they noted a lack of good quality data and the need for randomized controlled trials (RTCs) (15, 20, 23, 24). A clear example of initial enthusiasm toward the technology was found in our review. Unfavorable results are more often supported by numbers and statistics than favorable results (see table 2.1). For example OR time reduction is supported by numbers in 46/123 (37%) compared to 6/10 (60%) for increased OR time. The same holds for "good/better accuracy" 17/205 (8%) compared to "bad accuracy" 6/10 (60%) and improved outcome 27/195 (14%) compared to negative impact 2/7 (29%). This indicates that the studies published might suffer from initial enthusiasm by early adopters, promoting the technology without hard data in many cases. On the other hand, detractors present more hard data to make their point.

As the knowledge and potential applications of the technology are growing we can assume that nearly every specialty is or will be using the technology to some extent (23).

While RCTs are the gold standard in evidence collection, they are not always feasible nor ethically justifiable. An example would be oncologic surgery. In these cases, case studies or small case series are the only literature source available. It is therefore of importance that authors give sufficient structured information that could allow pooling for further analysis. Furthermore, guidelines on what data should be reported could enhance data pooling and ease future comparative analyses.

2.3. Paper 2: The value of 3D printed models, elaboration on models used for surgical planning of CHD and beyond

The second article described the value of using 3D printed anatomical models to plan surgery on patients with a congenital heart pathology. In line with common sense, the cost-effectiveness highly depended on the risk profile of the procedures, which was also linked to its complexity.

For CDH in particular, the models have been well used in determining the surgical plan for double outlet right ventricles (DORV). We did not focus on pathologies but rather on procedures to evaluate its costs and complications more easily. DORV are a heterogeneous group of defects with different procedural approaches, all varying in difficulty. The models therefore provide a significant benefit in understanding the pathology and deciding what surgical technique is the most suitable for the patient. Our model does not allow to objectify these benefits.

We only explored one aspect of 3D printed anatomical models in one specific domain. Their value has also been assessed by other researchers; often in a qualitative way. As part of our research, the questioned experts were also asked to analyze pediatric cardiac models in a quantitative way.

To put our obtained quantitative results in perspective, we chose to enrich our research with a qualitative analysis based on a semi structured questionnaire. The questionnaire can be found in appendix 6.1

We allocated data into two main themes: (a) advantages of 3D anatomic models and (b) contraindications for 3D anatomic models. The most important subthemes are explored below.

2.3.1. Advantages of 3D anatomic models for CDH

Anatomical and surgical complexity have to be considered as two different types of complexity. A severe pathology such as a univentricular heart leads to a complex surgical procedure. Expert opinion indicates that 3D heart printing is likely to have more benefits in complex surgical procedures than in less complex procedures. Although less complex procedures, like a VSD repair, tend to have limited benefit from using 3D anatomic models, case-specific anatomic aberrations can substantially increase the surgical complexity and therefore the value of using anatomic models. More specifically, several experts suggest that mainly intra-cardiac operations and double outlet right ventricle (DORV) repair could benefit from 3D anatomic models.

Experts point out the strategic planning of an operation as one of the main advantages. 3D anatomic models may give surgeons more case-specific knowledge, leading to an improved surgical strategy. For example, improved knowledge of which equipment to use for the operation and whether it is opportune to repair an aberration or, better, to conduct a palliative surgery. Several experts note that operation time could be shortened by using 3D anatomic models. Two experts argue that radiation in the Cath Lab may be reduced and one expert suggest that the consultation time might be reduced.

Experts note that mainly students and starting cardiologists may have problems with the mental conversion of 2D to 3D. 3D anatomical modelling has the potential to improve this ability. It may enhance anatomical knowledge. Parents of patients may better understand the pathology of their child. Visualization makes the cardiologist’s explanation less abstract.

2.3.2. Contraindications for using 3D anatomic models for CDH

Hospitals are reluctant to implement 3D anatomic models as standard practice because it is relatively expensive and not reimbursed. The cost price has a bigger impact in Europe compared to the USA, where surgical procedures are usually more expensive. Higher costs will also be a consequence of the time-consuming off-table digitalization process. The waiting time to receive the prints might also be an issue in some cases. Anesthesia could be necessary because children have to lie still during the imaging process, yet this may have negative effects on children.

Experts argue that until today there is no scientific evidence confirming the hypothesized positive effects such as complication reduction. 3D anatomic models have been applied on small sample sizes, making it hard to apply statistical analysis. Moreover, some surgeries are rather rare, impeding scientific research. There has been no conclusive validation research, thus it is unclear if the prints reflect reality. The 3D printing technology is still evolving, testing new materials.

Several experts question the beneficial effects of 3D printing. They are positive about virtual 3D but doubt that 3D heart printing would add value. Furthermore, some experts question if cardiac surgeons are awaiting 3D anatomic models.

Several experts argue that 3D anatomic models are unlikely to have a major or even any effect on the rate of small complications. One expert thinks that 3D printing will have no effect on all listed surgeries in this paper. Another expert argues that 3D printing will have no effect on extra-cardiac surgeries.

2.3.3. 3D printed anatomical models for CDH and other applications.

A recent systematic review by Batteux et al. elaborated on all aspects of anatomical models of CHD (15). They estimated that the 3D models are reliable to assess pathologies and serve as a planning tool for CHD interventions. Although value is seen in the use of these models, the additional cost and time involved in the model make its practical use questionable (25). Ryan et al. performed the first comparative study involving measurements on OR-time, Length of Stay, readmission rates and 30-day mortality with or without anatomical models for CDH (26). While they show clinically convincing evidence that the models reduce the OR-time and reduce readmissions and 30-day mortality, they could not show statistical significance. As the high Cohen’s D in their study suggests, the sample (N=79 with anatomical models) might have been too small. The results of their qualitative analysis were similar to ours, with surgeons stating the models improved their surgical plan in complex cases.

By analyzing different procedures, our data suggested a trend in which more difficult pathologies benefit more from the technology, similarly to what experts intuitively assumed. This clearly shows the need to select the right cases, if not to lose valuable resources that could have been better spent. During the analysis, we assumed all patients required a preoperative model. Again, this should not be the case. Surgeons can feel confident on straightforward cases and request an additional model when the pathology has some challenges. This could again increase the added value to be created by anatomical models, also in other medical domains than that of CHD.

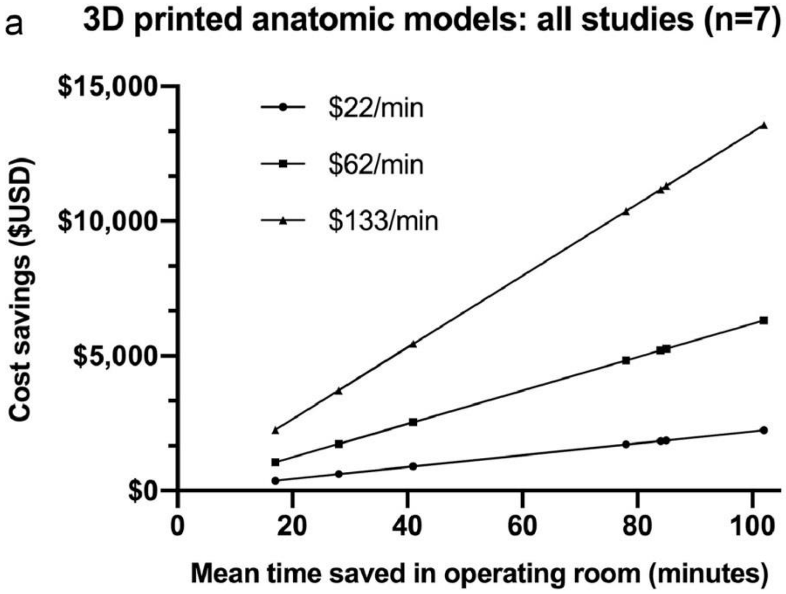
As stated in chapter 2, anatomical models already have a wide range of applications within different medical domains. They have shown to be of significant advantage for preoperative planning and simulation (24). As an example, in general surgery the possibility to access e.g. a kidney cancer with instrumentation from a certain angle can be evaluated upfront with the patient-specific anatomical model. In orthopedics, difficult fractures and osteotomies can be performed in advance to test screw and plate positioning (27, 28). Furthermore, the use of models to make surgical templates for vascularized bone transplants shows to reduce the avascular time of the bone graft, increasing chances of success (29). Similarly, in reconstructive surgery, anatomical models prove to reduce flap harvesting time of complex microvascular flaps significantly (30). While very valuable, it is very difficult, if not impossible, to quantify the advantages of these applications in terms of value for money.

Unfortunately, while stating many health advantages, health-economic evaluations are lacking. To date, no other economic analysis concerning 3D printed anatomic models has been published. The cost of the model is often used as reason to discourage the use of the technology (16). Furthermore, authors often only consider case-specific OR-time reduction to claim cost-effectiveness of the models for a specific application (31).

A great example of such a cost-benefit study can be found in an analysis of using anatomical models to pre-contour hardware for midfacial distraction (32). Authors retrospectively compared 9 procedures with anatomic models and 20 procedures without models. OR-time was non-significantly reduced by 31 minutes. None of the patients (N=9) with anatomic model encountered complications compared to 7 (30%) without model. In cases with complications LoS was increased by an average of 4.6 days (7.8%). Authors state that the technology is cost-effective since the reduced operating room cost (estimated at $33.09 per minute) barely offset the costs of the model ($1036 on average) and this without incorporating the (non-quantified) advantages of the reduced complication rate.

Similarly, Ballard et al. analyzed the cost savings due to OR-time reduction for anatomical models used for surgical planning in orthopedics and maxillofacial surgery, using the studies we identified in our systematic review (chapter 2) (31). Their conclusions are based on US data and are summarized in figure 6.2.

Figure 6.2 Mean saved monetary value of OR-time in $ 2019 by using anatomic models for surgical planning in orthopedics and maxillofacial surgery. A dot simulates the result of one study. From Ballard et al. 2020 (31)



While both being a great start, complete health-economic evaluations are necessary to guide decision makers in a more robust way.

Apart from patient-specific advantages, 3D printed anatomic models also have a great future for educational purposes (33, 34). While the models have proven to enhance understanding of the pathology in both patients and students, the models can also be used to perform simulative surgeries. These could increase the learning curve of young surgeons (35). 3D printed models of specific pathologies can be made more easily at an acceptable cost, especially considering the high cost of making conventional 3D anatomic models (36).

2.4. Paper 3: Custom surgical guides, notes on the use of PSA for primary TKA, madness or acceptable and valuable?

The third article analyzed the use of custom cutting guides (CCG) for primary total knee arthroplasties (TKA). The technology has been greatly received by the orthopedic community leading to a magnitude of publications a small decade ago. With contradictory results varying among the studies, no clear conclusion could be drawn before the hype slowed down. Multiple researchers engaged in systematic reviews to assess its clinical value, often from the perspective of ‘perfect positioning’ of the implant, again leading to inconclusive results toward its benefit.

The optimal alignment of TKAs is still a subject of discussion (37). The most commonly accepted alignment method is the neutral mechanical alignment, in which one tends to remain within a 3° range of coronal alignment since a higher angle results in higher revision rates due to mechanical wear (38). Currently, there is a trend to give more importance to the kinematic alignment, which is technically more challenging to attain and for which CCG might be of great help (39). Table 6.1 gives an overview of the reviews and their main findings. Studies incorporated in the different reviews can be found in appendix 6.1.

The growing importance of the financial perspective was often incorporated in the analysis, again with sometimes very diverging conclusions. Table 6.2 gives an overview of the studies tackling the economic implications of these guides.

As can be seen in table 6.2, most of the (pseudo-)economic analyses were based on reduced OR time, reduced sterilization cost and incorporated the cost of the guide and sometimes the cost of the scan to make the guide. While some authors state the guides are cost-effective, other stated guides were too expensive, despite a reduction in OR time and reduced sterilization cost, the latter due to the reduced number of trays used during surgery (40, 41). Others did not find a reduction in OR time and only saw the advantage of the reduced number of surgical trays (42). Furthermore, one author stated the cost-effectiveness of the guides will solely depend on a reduced revision rate and/or increased patient satisfaction on the patient reported outcomes (43)

Table 6.1: Overview of systematic reviews analyzing CCG vs. conventional TKA.

Year	Author	# Studies	# Patients	PSI mechanical axis	PSI Malalignment	Other
2013	Thienpont, E. et al.	13	589	No difference	Reduction (P=0,02)	OR time decrease ranging between 7 and 12 minutes
						Cost-effectiveness is questioned.
2014	Conteduca, F. et al.	9	957	decreased accuracy (P=0.02)	No difference (P>0.05)	non-significant OR time decrease of 11 minutes on average
						Increased overall costs
2014	Thienpont, E. et al.	16	1755	No difference (P=0.84)	No difference (P>0.05)	
2014	Mannan, A. et al.	26	1972	No improvement (P>0.05)	No reduction (P>0.9)	
2014	Cavaignac, E. et al.	15	916	No difference (P>0.05)	No reduction (P>0.3)	In 30 cases the PSI procedure had to be stopped because of poor match.
						Experienced surgeons do not utilize full potential op PSI
2014	Sassoom, A. et al.	16	2023	No improvement (P>0.05)	/	No significant benefit in OR time reduction.
						The use of PSI decreases the number of surgical trays needed for TKA
2014	Shen, C. et al.	14	1906	/	No difference (P=0.94)	No significant difference in OR time.
2015	Zhang, Q. et al.	24	2739	/	No difference (P=0.81)	
2015	Jiang, J. et al.	18	2417	/	No difference (P=0.84)	
2015	Fu, H. et al.	10	837	No difference (P=0.44)	No difference (P=0.29)	Alignment of the tibial component was less accurate (Sagittal and coronal plain) in the PSI group. An irrelevant surgical time reduction was found in the PSI group (3.54 minutes, P<0.001).

Table 6.2 Overview of the studies tackling the economic implications of CCGs.

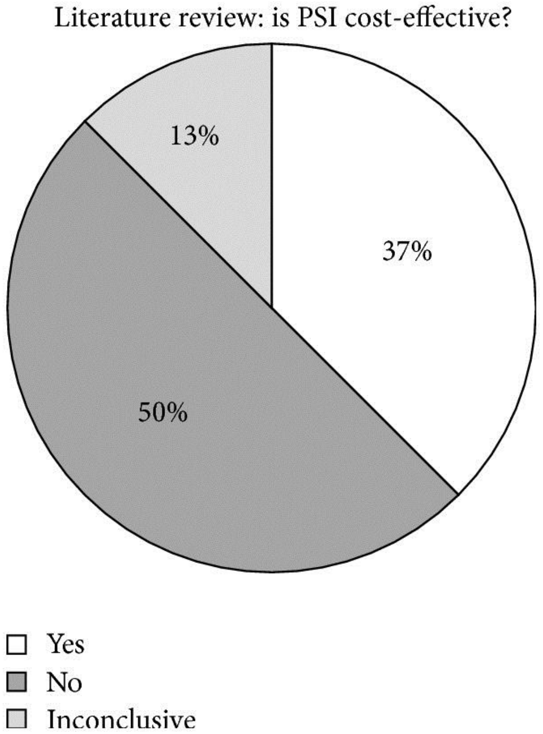
Year	Author	Price of Guide	Price of MRI	# Trays	Price/Tray	OR Time difference	Price of OR difference	Other	Price difference PSI	Conflicts of interest
2010	Watters, T. et al.	925$	NA	5	58,18$	-13'	-101,01$	OR turnover time reduction estimated 15'	533,09$ cost	Researchers received grants from manufacturer
2011	Fautsch, M.	NA	NA	3.2	60$	-6,7'	-167,5$	LOS with PSI: -0,3 days, 4396,18$/day	1679$ saving	Consultant for S&N
2012	Slover, D. et al.	1500$	1000$	Na	NA	NA	NA	Not all costs given.	3980$ cost	NA
2012	Barrack, R. et al.	950$	1250$	4	30,96$	-11'	-201,37$	Not all costs given.	1775$ cost	NA
2013	Tibesku, C. et al.	700 €	92.50 €	4	40 €	-30'	-553€	OR setup reduction of 20' with PSI included	59€ cost	Consultant for S&N
2014	DeHaan, A. et al.	500$	430-1360	4	60$	-24,4'	-1326$	6,4' OR turnover time, not quantified	766$ cost to 294$ saving	NA
2015	Thienpont, E. et al.	500 €	183 €	5	30 €	-3'	-20€	Pre-operative planning of surgeon: 20', sterilization cost of guide: 4€	1142€ cost	NA

While the surgeons were well-acquainted with the conventional TKA guides, the CCG might be new for them. It is important to note that there is a learning curve for guides (44). Surgeons must gain some expertise before enrolling into a trial as the lack of expertise with the new technology might bias the results (45). Additionally, as the technology matured, it is very likely that the quality of the guides (and the associated preoperative planning) improved, leading to better outcomes than the original studies suggest. This could explain while studies in the beginning of the CCGs reported multiple procedures using CCG being aborted and switched to the conventional guides (46, 47).

In the literature to date, the most complete analysis on the cost of CCG was made by Tienpont (48). Tienpont analyzed the cost of CCG, including the additional societal, indirect costs associated with the process of manufacturing custom guides. By including the indirect costs (e.g. loss in GDP for not working due to additional MRI, additional time spent by the surgeon to prepare the surgery,…) the actual cost of PSI is estimated more accurately and completely from a societal point of view. The indirect costs make up approximately 40% of the total costs of PSI (indirect cost: €459, direct cost: €683, total cost: €1142).

In a recent meta-analysis, Leone et al. reviewed articles stating cost-effectiveness of custom cutting guides for TKAs (49). 50% of the studies concluded that CCG are not cost effective.

Figure 6.3 Literature review on ‘cost-effectiveness’ of CCG from Leone et al. (2015) (49)



Our analysis was made from a payer perspective. Hospital related costs and benefits were therefore not incorporated. As can be seen from the economic approaches in the overview, these hospital-related benefits were often used to justify its use.

Furthermore, our analysis took a different approach and used data from the Belgian Arthroplasty registry as main input rather than study-based data. By doing so, we eliminated potential selection biases. Our results show that guides have a positive impact on implant survival on a 5-year time horizon, and additionally, could be a cost-effective strategy when CT-based guides are used. The premium price of an MRI inflated the total direct cost of the guides too much to remain below the ICER-threshold of €40.000.

The Belgian registry did not allow us to give hard numbers on the use of MRI or CT to build the guides. On the other hand, it did allow us to make the educated guess that most of the guides used in Belgium were MRI based. In Belgium, the ‘Visionaire’ system from Smith & Nephew holds a market share of 39.5% and is purely MRI-based. We can therefore consider this as the lower bounder of the utilization of MRI based guides in Belgium. According to personal communication with Zimmer-Biomed, which is holding 21.9% of the Belgian market in terms of custom cutting guides for TKA, the majority of their guides is also MRI-based. We can therefore conclude that the majority of the guides used for TKA in Belgium are not cost-effective. More recent literature suggests that using CT-based guides does not lead to inferior results compared to MRI-based guides for TKA (50, 51). While one meta-analysis reported a preference for MRI-based guides over CT-based guides, the most recent meta-analysis comparing CT-based guides and MRI-based guides for TKA reported a significantly decreased risk of femoral rotational outliers (RR= 0.48), indicating a higher accuracy for CT-based guides (52, 53). It could therefore be advisable to highlight these facts and advise the users and producers to switch to the most cost-effective alternative. While advocating for CT-based guides for TKAs we do not extend our pledge for other applications. The imaging should be adapted towards the pathology that should be exposed. E.g. for bone tumors MRI will yield a superior visualization of the lesion (54).

While our analysis only targeted the use of 3D printing for TKAs, 3D printed guides already know a wide range of applications beyond TKAs.

As a guidance to improve precision in shoulder arthroplasty, 3D printed guides have been used. Implant positioning is often used as metric as it is an important factor for implant survival. Similarly to the guides for TKA, the different meta-analyses are not aligned on whether or not the 3D printed guides show superiority in terms of prosthetic positioning (55, 56). In line with our finding on CCGs for TKAs, where meta-analysis does not support the evidence that custom cutting guides improve implant positioning but registry data did show superior results in term of implant survival for TKAs using them, it seems interesting to see what the future of ‘shoulder guides’ have to offer, especially in terms of survival rates.

Similarly, CCGs have also been used for total ankle replacement and give similar results compared to the conventional technique, but decrease OR time. Authors state that the guides can be cost-effective if the price remains below $863 based on an economic evaluation incorporating reduced OR times (38 minutes saved × $23.20 per minute) (57).

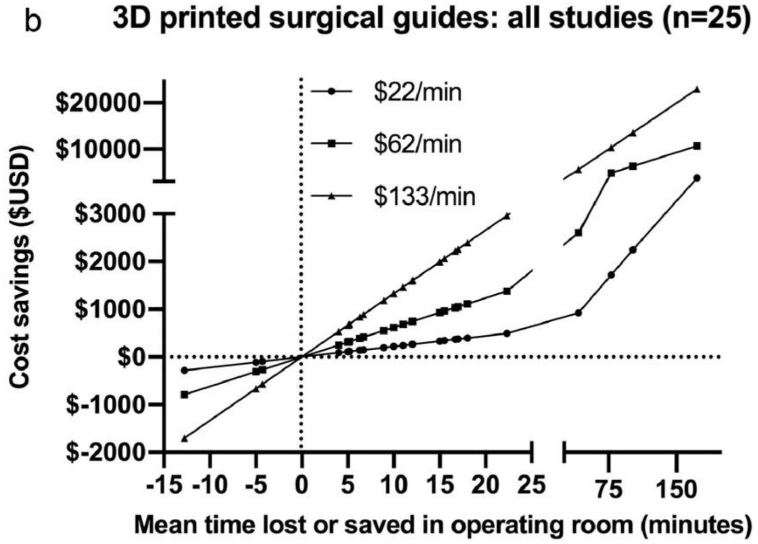
Custom-made guides have proven to be of great use in biplane osteotomies and precise reconstructive procedures. In both applications, the use of the guides provides an efficient way to perform complex tasks in a more precise way, leading to better patient outcomes (28). Additionally, they tend to reduce the OR time and, equally important, heavily reduce the need for intraoperative fluoroscopy (up to almost a factor of 7x) (58).

Furthermore, guides can be very useful for pathologies which are difficult to see intraoperatively but can be distinguished easily on CT or MRI. As an example, the resection of a talocalcaneal coalition can be made significantly easier and more reliable by using 3D printed guides based on the patient's CT (59, 60).

Additionally, 3D printed guides can be of great value in oncologic surgery. In bone tumor resection surgical guides have showed a tendency towards a more precise resection of the tumorous bone, shorter OR time and a better positioning of the implantation of the bone implant (61, 62). Considering the high consequences in case of a failed resection, and the more limited number of yearly procedures, the use of surgical guides for oncologic resections will likely be cost-effective. Further analysis should objectify this. Custom cutting guides have its second biggest application in maxillofacial surgery. Surgical guides are frequently used for mandibular resections and orthognathic surgery (62-65). Meta-analyses showed no statistical difference in graft survival, infection rates or other complications with custom cutting guides for jaw reconstruction. Additionally, while some studies declare a reduced length of stay, none of these results were significantly different compared to the procedure without 3D printed guides (66). On the other hand, increased precision is very often stated as a benefit (64). With the increased accuracy, better functional and aesthetic outcomes might be the biggest advantages of the custom guides in maxillofacial surgery (1, 64). While very difficult to quantify in monetary value, it is of great importance for the patients. Cost-effectiveness studies are still lagging behind for maxillofacial applications. Two studies were found stating technology is 'cost-effective', unfortunately, authors wanted to say that their in-house printing method was less expensive than commercial prints (65, 67).

In the same way as for anatomical models, Ballard et al. analyzed the potential cost savings due to OR time reduction by using custom guides in orthopedics and maxillofacial surgery (31). Their conclusions are summarized in figure 6.4.

Figure 6.4 Mean saved monetary value of OR time in $ 2019 by using custom guides in orthopedics and maxillofacial surgery. A dot simulates the result of one study. From Ballard et al. 2020 (31).



2.5. Paper 4: Custom implants, a health-economic evaluation of a 3D printed acetabular implant used in revision hip arthroplasty with acetabular discontinuity.

The last article contributing to this PhD thesis is the health-economic evaluation of a 3D printed acetabular implant. This custom implant fully endorsed the potential value to be brought by 3D printing by filling the gap where standard implants fail. Despite the premium price it showed to be a cost-effective and mostly dominant strategy for these specific patients. The model had several limitations, two of which will be further discussed.

First, the comparator we used in our analysis was a non-3D printed three-flanged implant (CTAC). Three-flanged implants are mostly considered to be the last step in acetabular reconstructions and therefore often subjected to the comparison with more well-known treatment options such as non-custom cup-cage constructs or trabecular metal jumbo cups with or without augments (68, 69). While these constructs have their value, the goal of our study was to make a comparison with is closed alternative, used when the acetabular defect is beyond the scope of cups, augments, and cages. From this rationale, considering pricing of trabecular cup-cage constructs are similar to those of CTAC, the conclusions of a comparative study with aMace will remain the same, if not more pronounced (68). aMace, the implant we subjected to our analysis, could be considered a step-up from other CTACs as it was made by 3D printing the implant itself, while other CTACs are manufactured in a more classical way, by milling the implant, using a 3D replica of the patient's pelvis. Hence, the added value to visualize and optimize screw trajectories is not present.

Second, we used financial data from Belgium's biggest healthcare insurance company. Unfortunately, while they can link costs to a procedure, they cannot link it to a pathology. For our study this implies that all hip revision surgeries are pooled together, without knowing the defect size, its complication profile or even the patient's demographics. Theoretically, it should be possible to link the raw database of the insurer to the Belgian Arthroplasty register through the patient's date of birth or (encrypted) personal identifier combined with the date of the surgery. Unfortunately, we did not obtain this raw database from the insurance company. Furthermore, data on perioperative complications not necessitating a revision surgery still won't be incorporated in the model as they are not part of the Belgian Arthroplasty Registry. To allow health-economic research based on a bigger portion of ‘hard data’, an easier access to databases and a legal framework to do so would be necessary.

The above analysis was important to showcase how 3D printed implants can heavily influence healthcare in a cost-effective manner, when the right patient population is selected. Apart from the price tag, these custom implants also have disadvantages, discouraging their routine use.

First, standard implants are subjected to a magnitude of tests before being used on actual patients. Many of these tests imply destruction of the implant. With custom implants, this is not an option as only one is made. Making multiple copies would drastically increase its already premium price. Second, the procedure should be planned well in advance since the implant needs to be made specifically for the patient (16).

Custom implants are finding their way into the medical practice. In orthopedics, custom implants have been made for spinal fracture reconstructions and calcaneum fractures (27). Similarly to the CCG, the custom implants have been well accepted by maxillofacial surgeons to make 3D printed plates (64). These custom plates allow surgeons to plan the screw trajectories, which can be particularly important in e.g. upper maxilla repositioning to avoid interference with dental roots (64).

While 3D printed implants can be of great use, especially in very complex cases, one has to note that in most cases, standard implants can be adapted upfront using a 3D printed anatomic model with similar clinical result but at a significantly lower cost. A great example can be found in pre-bending of plates for facial trauma reconstructions (70). Similarly, instead of directly printing the implant, the technology can also be used to print a mold, which is then used to manufacture the implant. The high cost difference to print metal compared to plastic makes this method a good alternative to directly produce the implants if technically feasible (71).

It is important to note that by using custom implants one is dedicated to the preoperative plan. Standard implants, and perhaps the standard cutting guides, still need to be present at the site of surgery in case the planned procedure is modified.

2.6. Limitations and Further Research

Above studies were subject to several limitations. First, as the technology is still in its early days, we do not have long term quantitative data. The results are therefore dependent on the different assumptions made in the models. Without underestimating the value of these preliminary analyses, it is important to perform these analyses again once stronger quantitative data is available with a longer follow-up. Additionally, data was dependent on clinical trials, often conducted in a slightly different way. It would be of great interest to have a more standardized way of collecting data, especially in the case of technical innovations. The arthroplasty registry, which was used in the chapter on CCG, is a nice example on how it can be done.

Furthermore, all models were conceived from the healthcare payer perspective meaning we only incorporated the direct cost. While already having a great source of uncertainty due to the preliminary nature of the analyses, we did not want to add a surplus of additional assumption.

Taking a societal perspective means that all costs and health effects should be incorporated, regardless of who bears those costs or experiences the health effects. This could impact our analysis in both ways. In the case of hip revision surgery, for instance, it would imply that the surplus cost of potential informal caregivers is taken into account and it would also incorporate the advantage of a faster return to work in case of a successful surgery. This would benefit the case of the 3D printed implant. For TKA, Tienpont calculated the societal cost to be approximately 40% of the total cost when using CCG, leading to an increased price for the guides. On the other hand, our research suggested a decrease in revision rates, which was not clear at the time of that specific article. This finding would be in favor of the CCG due to a reduction in sick leave, decreased need for additional help and transport to medical appointments, to name a few.

Although not the standard in Belgium and subject to debate, some countries (e.g. The Netherlands and Sweden) require cost of added life years, or ‘survivor costs’ to be incorporated in health economic analyses (72, 73). By adding these costs, future medical costs from the increased lifespan are also taken into account, which is of importance when considering the total healthcare budget and ideology to maximize its use (72). In our analysis, it would most likely benefit the case of the CCG for TKAs and 3D printed implants for hip revision arthroplasty as they reduce revision rates and, therefore, additional medical consults and the medical disadvantages of a more sedentary lifestyle. In the case of CDH, the expanded life will entail additional related and unrelated medical expenses. From a societal perspective, the question is whether their contribution to society can cover these additional medical expenses, in surplus to the additional non-medical expenses due to the prolonged life (72).

Furthermore, we did not perform the analysis from a hospital perspective. Multiple studies analyzed during this thesis mentioned hospital-related advantages such as the use of a significantly lower amount of surgical trays, potentially implying a decrease in surgical equipment stock, decrease in sterilization costs, simplified supply, etc. Up to now, this has only been quantified in a theoretical way and not proven by means of experimental data.

It could therefore be interesting to redo the analyses from a different perspective to have a wider view on the technology.

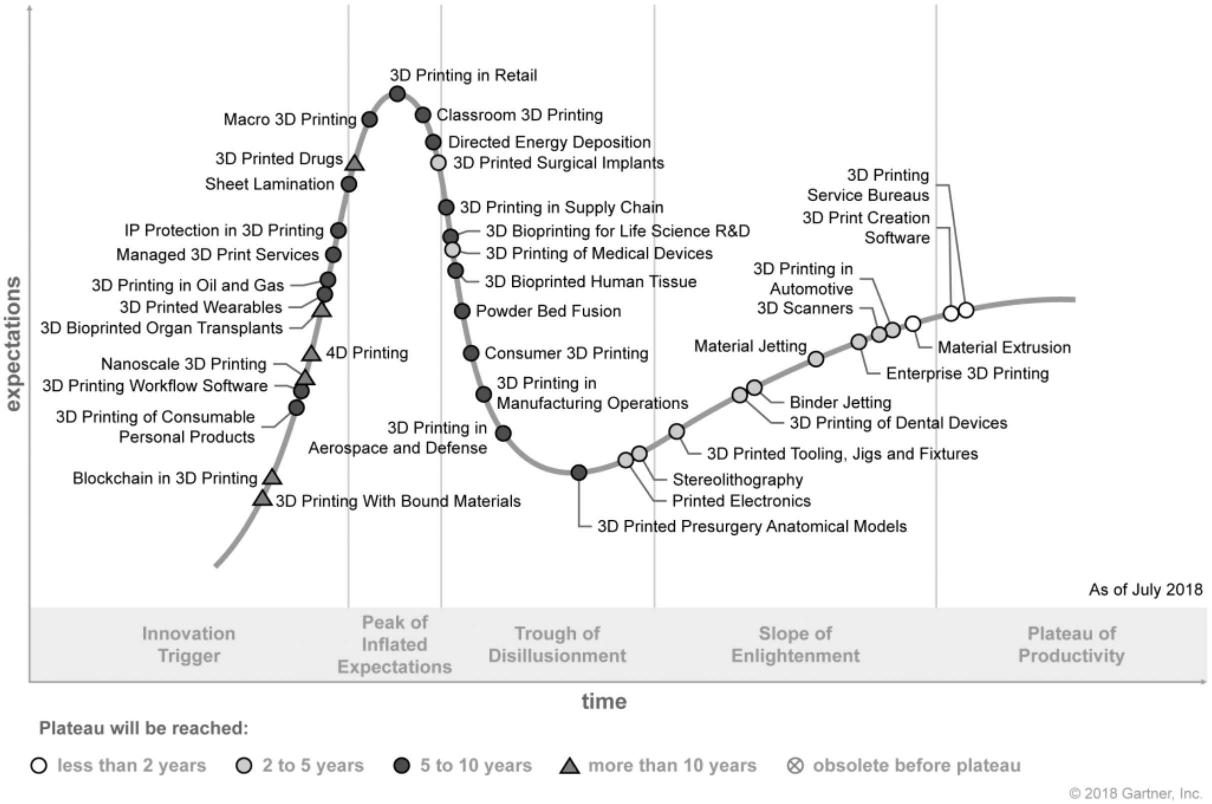
At last, while the ICER is an important variable in reimbursement politics, the budget impact should not be forgotten (74). Policy makers are more likely to reimburse technologies with a limited impact on the budget (75). While giving a glance at the budget impact with the EPVI in the analysis on anatomic models of CDH, we did not evaluate this aspect to a greater extent.

3. The Value of medical 3D printing, innovations and its hype.

3.1.The Hype of 3D printing

Innovations trigger a hype, and nearly all hypes follow a specific pattern (76). It starts with an interesting idea, convincing people to use the technology, often looking very positive towards their potential (77). This initiates an inflated flow of success stories, followed by the disillusionment when results are tried to be replicated or new evidence becomes clear. At that point a lot of the early adopters leave the seemingly sinking ship. Some do persist, gaining knowledge on the technology and locating its actual value; leading to the maturation of the technology. While 3D printing used for prototyping can be considered to be a mature technology, the other applications are not (78).

Figure 6.5 The hype cycle of 3D printing. From Gartner report 2019 on 3d printing (78)



As can be deducted from the graphical representation above, the previously described levels are ordered in the same way. While 3D printed pre-surgical models are reaching maturity, medical devices like guides are nearing the shifting point towards reacceptance.

3.2. Value of medical 3D printing

A multitude of stakeholders are involved when bringing an innovation to the market. It is highly important to note that none are independent and all should work together to create value. Figure 6.6 gives an overview of these interactions (79).

Figure 6.6 relationships between stakeholder when bringing innovations to the patient. From Price, C. and John A. 2014 (79).

Value depends on the perspective; the different stakeholders might have different opinions about what is value (74). This depends on the payer, the patient, surgeons, etc. For our analyses we have mostly adopted the perspective of the public healthcare provider. From that perspective, 3D printing provides its biggest value in complex, often one-of-a-kind procedures that do not occur that frequently. By allowing the surgeon to plan the procedure in a more intuitive way than before, the procedure is more often a success, giving a health advantage, expressed in QALYs. Varying on the potential additional cost of the new technology, the technology can bring value at an acceptable cost, i.e. be cost-effective (74). Cost-effectiveness was seen as a cost per QALY lower than €40,000 or €50,000, as this is considered a good benchmark in developed countries (80). Recently, it has been suggested to raise this particular benchmark to €100,000 or more which would make the technology cost-effective in more cases.

3D printing has proven to add direct costs with the printed parts and specific imaging but often reduces the overall cost in complex cases, as was shown in the case of complex revision hip surgery (81). It provides a great health-economic value, especially with high morbidity associated to failure and a young age of the patient. It is often the high cost associated with failure, that could be reduced by using the 3D printing technology. Additionally, younger people have a longer time to benefit from the increased QoL, pushing the ICER down (82).

The given benefits of 3D printing mostly don't come for free and benefits are not always noticeable in the beginning moments. A nice example can be found in custom cutting guides for TKA. While the initial publications could not support its routine use from a societal perspective, our research based on registry data did provide sufficient evidence to support its use in the daily practice. It shows the importance of reevaluating the technology, even when the hype is slowing down.

Donabedian denoted three types of efficiencies in his book (83). First, clinical efficiency, which consists of only using useful and not harmful treatments and highly dependent on the physicians' knowledge and skills. Second, the managerial/production efficiency consists of changes in procedures that increase productivity and reduce errors compared to the standard procedure. Third, distributional efficiency consists of selecting subgroups or individuals who best fit the need resolved with the new technology and are more likely to benefit from it. By having access to innovations, the caregiver has a wider pallet to operate on to improve the health quality of his/her patients. In an ideal world, he/she is free of choice and therefore it is his/her responsibility to take into account all layers of efficacies and find the most effective solution within the preferences of the patient.

Unfortunately, practitioners are dependent on the local access of the technology and financial considerations for the patient, reflecting the need for a fourth variable to consider: its feasibility.

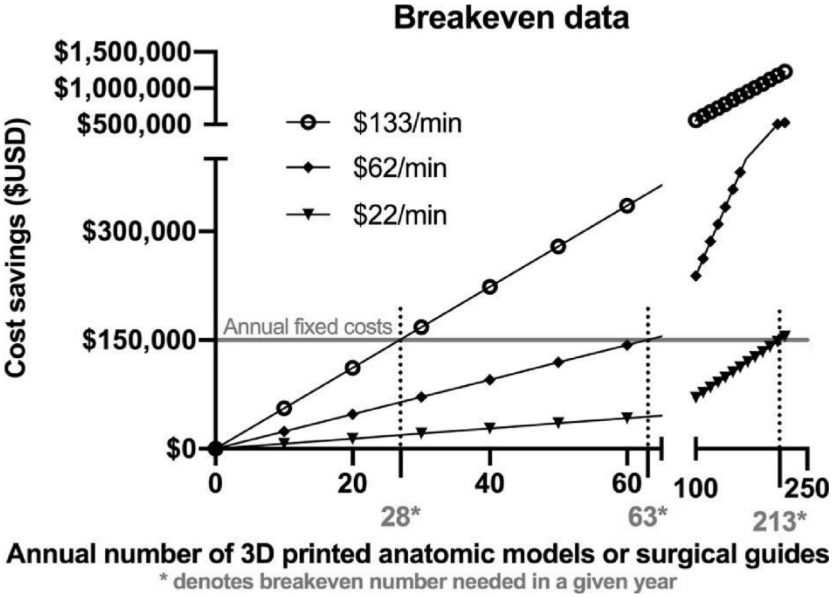
A nice example of this fourth variable to consider can be found in the example of resection guides for the resection of a talocalcaneal coalition. The procedure is less time consuming, which is a benefit for the hospital. It is easier to perform and at an increased precision, which benefits the surgeon and patient. Unfortunately, the guides are not reimbursed. Therefore there is a need to evaluate the financing of this guide. Can the patient or his insurance cover it or will the hospital pay for the cost of the guide?

3.3. Non-medical advantages; whose benefit?

Although the benefit for complex cases can be easily seen from the medical side, the operational side of 3D printing should not be forgotten; especially for routine operations. 3D printed models, custom cutting guides and soon available 3D printed disposable instruments can reduce costs made in the OR room and in the organizational path that precedes the surgery (31, 48, 84-87). Examples given are the use of a significantly lower amount of surgical trays, implying a decrease in surgical equipment stock, decrease in sterilization costs, simplified supply, etc. Up to now, this has only been quantified in a theoretical way and not been proven by means of experimental data. Other benefits like a reduced OR time cannot be quantified as easily, since only the time that can be used to plan additional surgeries, on top of the regularly planned surgeries without using the 3D printing application, can be counted as a benefit. Unused freed OR time does not have any monetary value.

As the benefits of using the new 3D printing technology do not only have an impact on the public health but also on the hospital itself, public healthcare providers might have an opportunity to share the cost associated to the use of the technology. As the benefits can be distributed amongst multiple parties, e.g. hospital savings due to reduction in used trays, the additional cost of the 3D printing technology should also be distributed amongst them. As costs vary per region and even per hospital, a conservative approach should be taken when making the users co-payers. An excellent example is the cost of OR time, which is very high in the USA, making custom surgical guides for TKA cost-effective in the USA, as compared to not being cost-effective in Belgium, this from a hospital perspective. Ballard et al. 2020 estimated the potential break-even point on having an in-house 3D printing facility, only using the OR time reduction generated by using custom guides and anatomical models (31). A summary can be found in figure 6.7.

Figure 6.7 Breakeven point of in house printed 3D printed anatomic models and surgical guides. The breakeven point was calculated by the following formula = fixed costs/(cost-savings from 3D printed constructs per case − variable costs of the models or guides. From Ballard et all. 2020 (31)



They came to the conclusion that an in-house 3D printing facility can be cost-effective in the USA at a minimal volume of approximately 63 printed constructs annually when considering an OR price of $62 per minute, an annual fixed cost of $150,000 and a mean variable cost of $220 per print. In Belgium, reimbursement is not always case-based (88). If the cost of printers are reimbursed as ‘lump sum’, as is the case with radiological equipment such as an MRI or CT, the number of prints needed will have less of an impact on its cost-effectiveness.

Apart from the economic evaluations incorporating the direct costs and benefits policy makers should take into account the indirect effects of some slightly less quantifiable benefits, like aesthetics. The stereotype example is the use of custom 3D printed surgical guides for maxillofacial surgeries like mandibular reconstructions. While the increased surgical success rate and improved QoL for the patients, partly due to the better mental health of these patients due to the improved aesthetics compared to the non-3D method should be taken into account as criteria for reimbursement by decision makers, the fact that the indirect effects of a better aesthetic result e.g. improved chances on the job market and therefore improved productivity should also be taken into consideration.

3.4. In-house printing

The price of 3D printing is often considered the problem to use the technology on a more frequent basis. 3D printing could potentially be done in a less expensive manner by printing ‘in-house’. Although the unit price will be lower if sufficient volumes are reached, the quality of the work, and therefore its benefit, could also potentially be lower. The quality of prints depends on multiple variables: the quality of the original image or scan, the renderings and segmentation and the precision of the printer.

A first step to reduce costs can be to use freeware rather than commercial packages for segmentation. The danger of using freeware software or having less controlled protocols while printing could lead to mistakes in the final products, which again could lead to very big problems with high impact on the persons being operated on. The decreased printing cost in-house does not necessarily mean a decreased total cost for using the 3D technology if the quality of that print is not similar to the commercial, more expensive prints and may not provide benefits but is instead, a disadvantage due to its incongruence with reality. The print itself is then worthless and often results in additional OR time, exposing the patient to un unnecessary risk. Therefore serious quality control programs should be put in place to allow in-house medical printing when the model is used for more than just teaching purposes. (9)

It has to be noted that not all prints need to have the same quality. Different print quality for different purposes can be defended. This is particularly true when models are not used for surgical planning but rather for teaching purposes, both to students and patients. The in-house prints can heavily reduce the high cost of making conventional 3D anatomical models (36). In that case, cheaper in-house prints are not a real issue.

For surgical planning, in-house printing can be highly attractive if its accuracy is comparable or outperforms that of industrial prints. To date, only one, rather small (N=15) study compared in-house printed models to industrially printed skull models in terms of efficiency (70). The results of this study tend to be very positive, with comparable clinical results at a reduced price and significantly shorter production time. Multiple studies analyzed the accuracy of in-house printed models and guides and concluded the in-house prints were of a similar quality (65, 67, 89). While these latter studies were not directly comparing the clinical results with both production methods, one can assume they will be similar as well. As mentioned above, the major factor one should be aware of is that the accuracy of the guides and its coupled clinical potential is highly depending on the in-house technician making the prints and the used equipment. A bad rendering or segmentation, or a printer of insufficient quality can ruin all efforts.

Furthermore, the lead-time is also considered to be a problem when considering 3D printing as a tool for urgent operations. By printing in-house, the production time can be reduced from days or weeks to hours (70, 90).

In Belgium, the need of higher volumes to become cost-effective can be solved with the already existing hospital associations. Therefore, the ‘in-house’ printing facility should not be present in every hospital, but only on one campus. The increased number of cases will also allow the technicians to gain more experience.

3.5. Risks and considerations when using 3D printed models, guides and implants.

While a lot of attention has already been given towards the benefits of medical 3D printing, some drawbacks have to be highlighted is more detail as well.

Possible OR time reduction and its potential benefits were often very present. On the other hand the additional time needed to prepare the model was often not mentioned while being very relevant. From a surgeon’s perspective, the additional time spent to make the models is very significant, and in Belgium, no nomenclature can be found to get a remuneration for it. Additionally, even in the procedural nomenclature, no difference is made between e.g. a very challenging hip revision with significant acetabular bone loss requiring a custom implant and a straight forward revision. A specific nomenclature number in more complex cases could allow to finance the surplus cost of additional tools to help perform the surgery and increased time spend by the surgeon before and during the surgery.

The logistics of using custom guides, and even more, custom implants are more demanding. Standard guides and implants are often available at the hospital. The custom implants on the other hand, have to arrive on time, and sometimes require sterilization prior to be being used in the OR room (91, 92).

The producers of the guides and implants often handle this logistic step but it still requires the OR responsible to perform an additional check. Furthermore, while the use of custom implants is often said to reduce inventories, this will only be partly true. It is sometimes necessary to fall back to the standard guides or implants due to a bad fit with the custom implant (47). This thus requires the alternative arsenal to be present in the OR, in a sterile state, just in case.

To date, not a single study describes the differences in logistic flows, as wel as its advantages and disadvantages, both in time and finances, in a quantitative way.

Patient safety is always a priority. Guides and implants can be printed using a magnitude of materials and material qualities. Using the right material for its purpose is crucial for multiple reasons. First, when considering guides, we need to take into account the possibility of material shredding when getting used. The particles could cause adverse tissue reactions, but to date little is known about it (93). Second, not all materials can be sterilized as efficiently (94). The equipment has to be designed for that specific purpose and the sterilization process has to be tailored towards it (95, 96). Some porous structure of the print can cause sterilization problems and hence increase infection rates. Especially in-house printing facilities should be very careful for this. Further research into this topic would be very helpful to create guidelines, perhaps per specific application, to further ensure and improve patient safety.

3.6. The future of 3D printing

Medical 3D printing is still in its infancy. As an already usable application, 3D printing scaffolds shows promising results in maxillofacial surgery based on preliminary trials (97). To date, the dream of printing functional organs is not yet a reality. Bioprinting is starting to provide a proof of concept with studies mentioning the printing of cartilage and heart valves among others (98). Currently, vascularization of tissues is the major bottleneck (17).

3D printing has also caught the attention of the pharmaceutical industry. The technology could be very useful to print patient-specific drugs and enhances the precision of targeted release drugs (99).

A new part of 3D printing is 4D printing, in which the 3D printed material has the properties to change its shape with an external stimulus (100). It will be interesting to see its role in medical applications.

3.7. Data is the problem.

Innovative products have to be validated, the process of which are an important part of the innovation itself. Data generation and collection are partly the responsibility of the producers and utilizers (101).

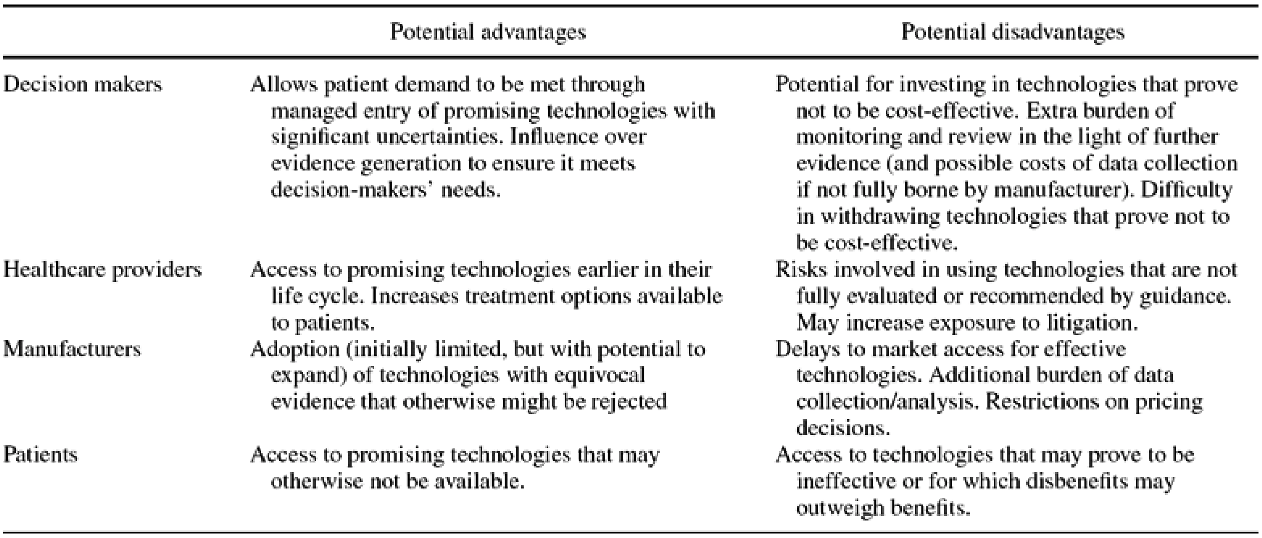
At this moment, one can see that they are in fact collecting data, but each individually, having their own methodology and quality, resulting in a heterogeneous and dispersed data pool. To date, orthopedics and maxillofacial surgery have published the most evaluations on the clinical efficacy and effectiveness of 3D printed devices, while most other fields did not assess their clinical relevance in sufficient detail (23). Several authors have expressed the need for guidelines on how to report experiences with medical innovations (16, 23). It is the role of the government to make the harvest of data more solid and structured, to allow comparative evaluations (101). Standardized data generation will allow data aggregation with databases from other domains. With the growth of digital medicine, patient stratification and selection can be further improved to highlight individuals needing tailored solutions. An example could be the need for a custom three-flanged acetabular implant to ensure its solid fixation in dense bone parts rather than using a standard revision cup, even without the defect to be indicative to do so, based on aggregated data on the patient's physical activity, his bone quality etc… just to avoid an additional revision in the future.

While incorporating innovation, organizations should keep in mind that not all innovations will enhance their financial results (102). The cost of data has fallen over the years. Currently, standard databases are being made. An example is the Belgian surgeon-based arthroplasty registry 'Orthropride', which has grown to be a necessity for reimbursement. Additionally, innovative companies could be asked to generate standardized data to get any form of reimbursement.

The danger exists that incomplete data is generated at the beginning of the innovation's implementation. Although it can be seen as a learning and maturation curve for that innovation, it is of high importance to minimize the missing data. An expert review of potential valuable data could therefore be of great use. Coupling a mandatory standardized and expert-based database with its reimbursement should be the way to go. Furthermore, the long-term feedback is of essence, considering the importance of future events as one of the main contributors to the innovation's value (103). Therefore, short but standardized feedback forms should be made and used on follow-up consults. This could enable large scale long-term follow-up while practically eliminating the problem of ‘lost in follow-up’.

The concept of managed entry agreements, more specifically ‘coverage with evidence’, is not new (104-106). It has been used by many countries, including the Netherlands to introduce expensive drugs (often for oncologic purposes) and orphan drugs (107). While very attractive, this approach also has risks (104). An overview can be found in table 6.3.

Table 6.3. Advantages and disadvantages of coverage with evidence. From Hutton et al 2007 (104).



	Potential advantages	Potential disadvantages
Decision makers	Allows patient demand to be met through managed entry of promising technologies with significant uncertainties. Influence over evidence generation to ensure it meets decision-makers’ needs.	Potential for investing in technologies that prove not to be cost-effective. Extra burden of monitoring and review in the light of further evidence (and possible costs of data collection if not fully borne by manufacturer). Difficulty in withdrawing technologies that prove not to be cost-effective.
Healthcare providers	Access to promising technologies earlier in their life cycle. Increases treatment options available to patients.	Risks involved in using technologies that are not fully evaluated or recommended by guidance. May increase exposure to litigation.
Manufacturers	Adoption (initially limited, but with potential to expand) of technologies with equivocal evidence that otherwise might be rejected	Delays to market access for effective technologies. Additional burden of data collection/analysis. Restrictions on pricing decisions.
Patients	Access to promising technologies that may otherwise not be available.	Access to technologies that may prove to be ineffective or for which disbenefits may outweigh benefits.

To minimize these risks, it is advisable to ensure the technology will provide sufficient clinical benefits before engaging in this type of agreements (105, 108).

Coverage with evidence agreements is often limited to a specific application, e.g. a cutting guide for a biplane osteotomy of the tibia. As the applications of 3D printing are rather heterogeneous it could be subject to difficulties (e.g. cutting guides for biplane osteotomies in general), since we do not want valuable applications to be left out. It will therefore be important to incorporate all applications in the agreements and ensure sufficient data is generated to evaluate both the general application (e.g. cutting guides as a group) and the more specific application (e.g. a cutting guide for tibia ostreotomies).

Big data, or using databases to make decisions has proven to be increasingly important in the pharmaceutical industry, leading more and more towards personalized medicine by finding trends between individuals and better selecting those that benefit from certain drugs (109). The same could be done for medical devices and small scale innovations, leading to an enhanced, faster incorporation of innovations in the daily practice; or help to see more clearly when clinical studies give contradicting results. Furthermore, as reimbursement systems are evolving to a pathology-based payment systems (e.g. a flat rate for a primary total knee arthroplasty), the use of machine learning and big data could enhance the knowledge on what to expect from a specific patient and to lead to a fairer reimbursement, reducing the chances of surgeons and hospitals cherry-picking patients with fewer chances of complications (110).

3.8. Innovations in medicine, medical 3D printing and its future.

Another aspect of medical 3D printing lies in the willingness to innovate. Being innovative, or using newer technologies might influence patients to choose a specific doctor or hospital that is offering this technology over another hospital, leading to a competitive advantage. Innovation is more than inventing, it also reflects the need to implement it in a value-generating way (111).

3D printing is seen by the general population as the way of going for the future. The new technology is perceived better for all its applications, as custom-made for one person gives the impression that it will undoubtedly be better, without questioning the necessity of e.g. a new custom implant for a routine hip arthroplasty and the additional cost for the society.

Innovations are often classified as ‘incremental’ or ‘disruptive’ (112, 113). In general 3D printing would be considered to be disrupting; it is new and different from other types of production techniques, and has been well adopted while changing the market forever (114). In medicine, its applications are both. A model can be seen as disruptive, since we can finally hold a physical representation of a patient’s anatomy and even carry tests on it or perform a simulative surgery. On the other hand, personalized guides or prosthetics are only an incremental step. They were present for a long time, but now we have a patient-specific modification of it (113).

Anyhow, both can have a tremendous value in healthcare. Since the beginning of the 20th century, innovations have added approximately 25 out of the 30 years of increased lifespan in humans (115). Surprisingly, innovations account for approximately 2.2% of annual growth in the healthcare budget per capita, which means half of the growth in healthcare spending is only attributed to new technologies (4). The term ‘innovation’ captures ‘value’, making the distinction for a regular invention, which does not need to be useful nor economically sustainable.

Innovations are often more expensive than the current standard of care and studies mostly focus on the short term, not incorporating the frequent decrease in price associated with the maturation of the technology (116). Furthermore, its current or projected value could differ from one application to another. In this thesis, specific applications have been evaluated. Conclusions drawn from one study cannot be transferred to other applications of the same technology.

While innovations can come from the need of the practitioners, it will often be pushed by the industry. Even in medicine, companies are driven by potential profits and will therefore put more resources towards the most profitable applications. The latter is often driven by the volumes, as is the case with the CCG for TKA. Companies will therefore put more effort in research to prove its added value. Some rare conditions, however, could have great benefits by the innovation, but they are currently not being pushed towards the market as actively. Resection guides for oncologic surgery are one of the prime examples of these. Similar to the drug industry, governments should install stimulatory measures to encourage investments into these ‘orphan applications’ as well (117). On the other hand, these projects could be viewed as cutting edge, honorable projects, in which case they could attract financing out of marketing or ‘social acceptance’ purposes.

3.9. Early health economic evaluations

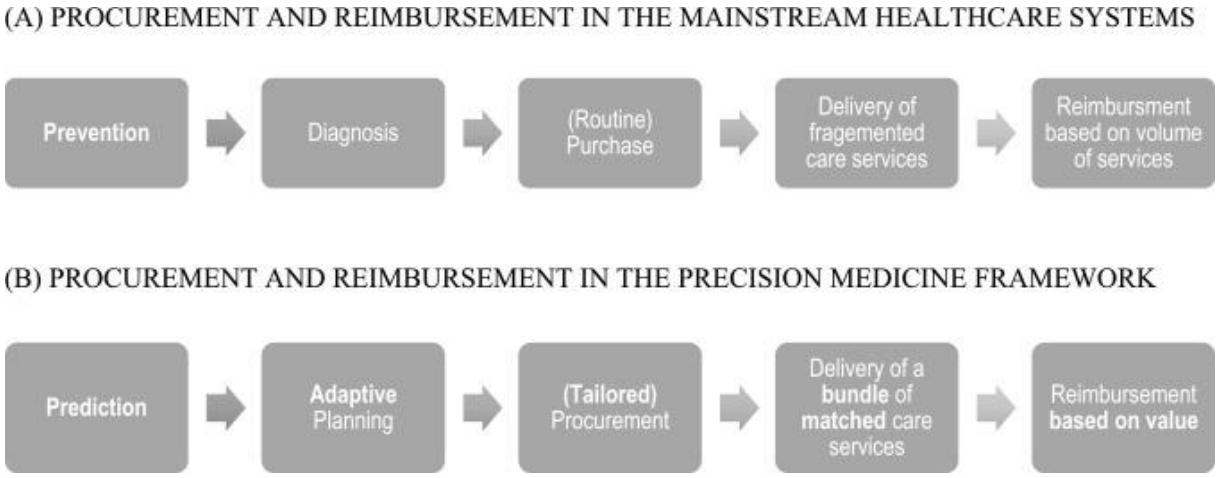
While being challenging due to the lag of data and high uncertainty, early health economic evaluations are being used increasingly (118). They are important to guide further development of innovations and provide insights into its potential cost-effectiveness (119). Furthermore, they can identify applications that have a higher value for money early on and can highlight key factors that should be further examined and incorporated in future analyses. They thus benefit both society and companies developing the technology (118, 119). While uncertainty is high, these models should still aim to have the same quality standards as later stage models (120).

Our analyses were performed on products that already exist at a ‘market access stage’. Even earlier analyses can already hint at whether or not to continue investments; this is particularly important if the investments that have to be made are high (120). In practice, the discontinuation of the technology is less frequent and a relocation towards more valuable uses is advocated (119). Furthermore, integrating these early models from the very beginning of the development progress with stepwise integration of new data into the models could help companies and decision makers to have a clear understanding of its value as the technology grows (121). The latter could be very valuable when countries engage in risk sharing agreements like coverage with evidence (122). Despite the growing interest in early health technology assessments the literature from both academic and policy perspective on this specific type of evaluation is scarce (123).

3.10. Medical innovations and Pay-For-Quality/Pay-For-Performance

As noted before, the financial impact of medical decisions is increasingly important, but so is the quality, or patient satisfaction. Since the late 1990s, a new model emerged where financing not only depends on the procedures, but also on outcomes (124).

Figure 6.8 Changing the reimbursement based on value for personalized medicine. (Denicolai, S. 2020) (125).



The Belgian government is trying to shift healthcare financing from a pay for services to a P4Performance-model (126). In a P4P-model, the outcome is the decisive factor, where hospitals get rewarded based on their performances. To date a first step was taken by setting indicators on which hospitals are scored. To allow a further shift nationwide databases will be required to further measure the performances of the hospitals and doctors.

Being innovative and embracing innovations might therefore be a lucrative strategy, given the innovation results in better health results at an acceptable cost. In this model, financing innovations could therefore be a multi stakeholder responsibility. The additional cost of using the right innovations could be pushed towards the hospitals, in full or partially, as they will be financially rewarded for their improved patient outcomes, on top of previously stated other potential advantages like deduced OR time and others.

A nice example of this would be the custom cutting guides used for TKA. The lower revision rate leads to higher patient satisfaction and quality of life while being a cost saving for the public health care. In addition, hospitals also benefit from the reduction in surgical trays requiring sterilization and potential OR time reduction. Implementing the technology thus benefits all involved parties.

Additionally, as stated earlier, a value-based approach can help innovations find the needed funding if they tackle a fundamental problem, potentially with high costs of failure.

The added value of innovations is not always noticeable on a short term. Again, the use of CCG for TKAs, of which the benefit is a reduced revision rate, can be used as an example. Its biggest value is therefore not present at the moment of use, but only noticeable at a later time. It is not surprising that innovations with a preventive nature often have difficulties to get the correct remunerations (127).

3D printing is a part of the new movement of personalized medicine. Personalized or precision medicine makes the solution of the medical problem dependent on the patient and its surroundings. They also increase the importance of future happenings on the long term; in a way incorporating prevention strategies, like decreasing the need of future revision by using a specific implant instead of a normal implant with risk of failure after some years. These preventive factors should be taken into account while changing the reimbursement from fixed to value based (125). Reimbursements of these kinds of innovations are not only political decisions but also highly depend on the end user and the country’s willingness to adopt innovations (128).

End notes and recommendations

In this thesis, multiple health-economic evaluations were performed on 3D printing applications. Health-economic evaluations are important to objectify the value of new technologies in terms of health for a certain price compared to its closed alternative. However, it has to be noted that the evaluations do not lead to a product price, as the added value has to be divided between the society and the company creating the product, whose innovation should be rewarded (129).

The section on the value of 3D printing was solely targeting the surgical usage while other usage exists. A lot of scientific papers have been published on medical 3D printing, but few good evidence has been generated. The majority of the publications found during the literature search was rejected due to being a case report. (1) The lack of structured data makes in-depth analyses difficult and less reliable, so expert opinion was more often required to fill in the gaps. It opens the opportunity to link structured registration to (preliminary) reimbursements to create more structured evidence. Governments should aim to reimburse (part of) the innovation in exchange. By having a financial incentive, companies have more interest in making the full data available for analysis and publication rather than removing the failures and only publishing the success stories. It is of the most importance that governments are open to accept these innovations in a more structured way, so their widespread implementation is facilitated. ‘Access with evidence development’ has been used in several countries. Germany, France and the United Kingdom have been using these systems to allow medical innovations to prove their potential (130). Belgium could easily improve the data gap and stimulate medical innovations by implementing similar systems. It would allow easier access to the market and motivate innovators to find better solutions to medical problems or improve the way we currently work. Innovation is mostly seen as a cost and long-term benefits are often neglected. Furthermore, it is unrealistic to assume new technologies to immediately provide cost cuts (131). Governments should look at new technologies beyond costs and assess their total value in healthcare (116) . By creating data and allowing innovations and current technologies to be evaluated on a larger scale, the best innovations can be retained and ineffective strategies can be cut off. Governments should strive toward an active support of innovations, providing sufficient evidence of their effectiveness and those showing potential while providing preliminary evidence.

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ABOUT THE AUTHOR

Philip Tack (°1988, Ostend) obtained his Master of Science in Business Engineering at Ghent University in 2012 and degree of Medical Doctor in 2019. He joined the Department of Health Economics and the department of service management at Ghent University as a PhD student in 2015. Since 2019, Philip is also active as an orthopedic resident. Philip presented at multiple congresses such as ISPOR (Vienna) and the ‘Evidence Congress’ at RAPID (Orlando). Chapter 2, 3 and 4 of this PhD thesis were published in A1 journals at the time of publication of this thesis.

Appendix 2.1: Overview of the applications of the 3D printing technology per disciple (appendix 2)

Use of 3D printing	**Discipline**	**Number of studies**	**Not mentionned**	**Time reduction**	**No time difference**	**Time increase**	**Not mentionned**	**Good/better accuracy**	**average accuracy**	**Bad accuracy**	**Not mentionned**	**Less radiation**	**equal radiation**	**Increased radiation**	**Not mentionned**
Custom implant	Cranial Surgery	16	5	10 (4)	0	1	1	15			16				1
Custom Implant	Dental	2	1	1			1	1			2				
Custom implant	Maxillofacial surgery	9	3	6				8	1	0	9				
Custom implant	Orthopedics hip	1	1					1			1				
Subtotal Custom implant		28	10	17 (4)	0	1	2	25	1	0	28	0	0	0	1
Model for implant shaping	Maxillofacial surgery	9	4	5 (1)	0	0	1	8	0	0	7	0	0	2	0
Model for patient selection	Cardio vascular	2	2	0	0	0	1	1	0	0	2	0	0	0	2
Model for surgery planning	Cardio vascular	8	6	2			2	6			7	1			5
Model for surgery planning	Cerebrovascular	3	2	1 (1)				3			3				2
Model for surgery planning	Cranial Surgery	13	4	8	1			13			13				
Model for surgery planning	Dental	5	3	2				4	1		5				
Model for surgery planning	General surgery	1	1					1			1				
Model for surgery planning	Maxillofacial surgery	27	9	16 (8)	2 (2)		1	22 (3)	4 (1)		26			1	

Model for surgery planning	Neuro surgery (Cranial)	1		1				1			1				
Model for surgery planning	Orthopedic pelvis/hip	2	1	1				2			2				1
Model for surgery planning	Orthopedics hand	2	2					2			1			1	
Model for surgery planning	Orthopedics elbow	1				1		1			1				
Model for surgery planning	Orthopedics hip	10	4	5 (1)		1 (1)		9	1		8	1	1		
Model for surgery planning	Orthopedics knee	1	1					1			1				
Model for surgery planning	Orthopedics shoulder	2	1	1				2			1			1	
Model for surgery planning	Spinal surgery	13	3	10 (3)			1	12 (1)			7	6 (1)			2
Subtotal model for surgery planning		89	37	48 (13)	3 (2)	2 (1)	4	80 (4)	6 (1)	0	77	8 (1)	1	3	10
Mold for prostetic	Cranial Surgery	2	1	1				2			2				
Mold for prostetic	Maxillofacial surgery	1	1					1			1				
Mold for prostetic	ORL	1	1					1			1				
Subtotal mold for prostetic		4	3	1	0	0	0	4	0	0	4	0	0	0	0
Surgical guide	Cranial Surgery	4		3	1			4			4				
Surgical guide	Dental	5	4	1				5 (1)			4	1			
Surgical guide	Neuro surgery (Cranial)	2		2				2			2				
Surgical guide	Orthopedics ankle	1		1 (1)					1		1				
Surgical guide	Orthopedics arm	1	1					1			1				
Surgical guide	Orthopedics elbow	1				1		1			1				
Surgical guide	Orthopedics hand	3	1	1	1			2	1		2			1	1
Surgical guide	Orthopedics hip	10	5	3 (2)		2 (2)		7 (1)	2	1	7	1	1	1	1
Surgical guide	Orthopedics shoulder	4	3	1				4			4				
Surgical guide	Spinal surgery	11	5	6			1	10			5	6			2

Surgical guides	Maxillofacial surgery	26	10	14 (6)	1	1 (1)	1	21 (2)	4		25			1	1
Surgical guides	Orthopedics knee	70	1	21 (19)	6(2)	3 (2)	15	31 (9)	15 (3)	9 (6)	67	1	1	1	10
Subtotal surgical guides		138	69	53 (28)	9 (2)	7 (5)	17	88 (13)	23 (3)	10 (6)	123	9	2	4	15
Total		270	125	123 (46)	13 (5)	10 (6)	28	205 (17)	30 (4)	10 (6)	241	17 (1)	3	9	28

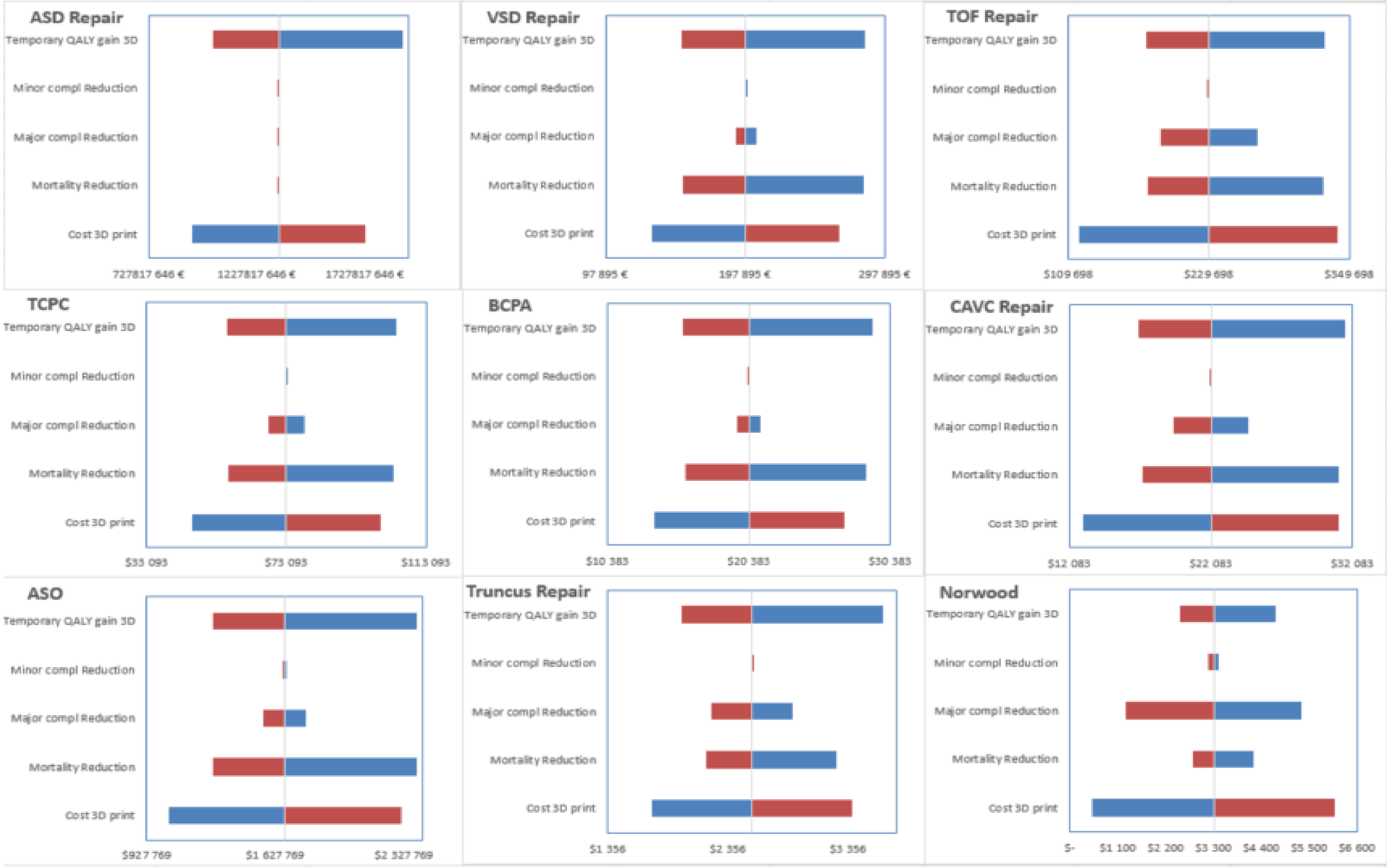
(x) = Number of studies quantifying the data with numbers/statistics

			Clinical outcome				Cost				Cost effectiveness		
Use of 3D printing	**Discipline**	**Number of studies**	**Not mentionned**	**Improved**	**Equaly**	**negative impact**	**Not mentionned**	**Cheaper**	**Equaly expensive**	**More expensive**	**Cost-effective**	**Neutral**	**Not cost-effective**
Custom implant	Cranial Surgery	16	1	13 (1)	2		8			8 (4)			
Custom Implant	Dental	2		1	1		2						
Custom implant	Maxillofacial surgery	9		9			4			5(1)	1		
Custom implant	Orthopedics hip	1		1						1			
Subtotal Custom implant		28	1	24 (1)	3	0	14	0	0	14 (4)	1	0	0

Model for implant shaping	Maxillofacial surgery	9	0	9 (2)	0	0	7	0	0	2 (2)	0	0	0
Model for patient selection	Cardio vascular	2	2	0	0	0	1	0	0	1	0	0	0
Model for surgery planning	Cardio vascular	8	5	2	1		6			2 (1)			
Model for surgery planning	Cerebrovascular	3	2		1		2			1 (1)			
Model for surgery planning	Cranial Surgery	13		13 (1)			8	1		4 (1)	2		
Model for surgery planning	Dental	5		4	1		5						
Model for surgery planning	General surgery	1		1			1						
Model for surgery planning	Maxillofacial surgery	27		24 (3)	3		12	1	1	13 (8)	4	1	1
Model for surgery planning	Neuro surgery (Cranial)	1		1			1						
Model for surgery planning	Orthopedic pelvis/hip	2	1	1			2						
Model for surgery planning	Orthopedics hand	2		2 (1)			1	1					
Model for surgery planning	Orthopedics elbow	1		1 (1)			1						
Model for surgery planning	Orthopedics hip	10		10 (2)			5			5 (4)	1	1	
Model for surgery planning	Orthopedics knee	1		1			1						
Model for surgery planning	Orthopedics shoulder	2		2			1			1			
Model for surgery planning	Spinal surgery	13	2	10	1 (1)		6	1		6 (6)	1		
Subtotal model for surgery planning		89	10	73 (8)	7 (1)	0	52	4	1	32 (21)	8	2	1

Mold for prostetic	Cranial Surgery	2		2			2						
Mold for prostetic	Maxillofacial surgery	1		1			1						
Mold for prostetic	ORL	1		1				1			1		
Subtotal mold for prostetic		4	0	4	0	0	3	1	0	0	1	0	0
Surgical guide	Cranial Surgery	4		4 (1)			3			1			
Surgical guide	Dental	5		5			4			1			
Surgical guide	Neuro surgery (Cranial)	2		2			2						
Surgical guide	Orthopedics ankle	1		1			1						
Surgical guide	Orthopedics arm	1		1			1						
Surgical guide	Orthopedics elbow	1		1 (1)			1						
Surgical guide	Orthopedics hand	3	1	2 (1)						3 (2)			
Surgical guide	Orthopedics hip	10	1	8 (2)	1		7			3 (2)	1		1
Surgical guide	Orthopedics shoulder	4		4			4						
Surgical guide	Spinal surgery	11	2	8	1		5	1		5 (5)	5		
Surgical guides	Maxillofacial surgery	26	1	21 (2)	4 (1)		14	1 (1)	1	10 (7)	4		
Surgical guides	Orthopedics knee	70	10	29 (9)	25 (6)	7 (2)	54			16 (3)		1	5
Subtotal surgical guides		138	15	86 (16)	31 (7)	7 (2)	96	2 (1)	1	39 (19)	10	1	6
Total		270	28	195 (27)	41 (8)	7 (2)	173	7 (1)	2	88 (46)	19	3	7

Appendix 3.1: Tornado diagrams for the different procedures



Appendix 5.1: Transition probabilities per 6 months.

		AMACE				CTAC			
	MEN <65	**Successful revision**	**Re-revision**	**Needed re-revision impossible**	**Dead**	**Successful revision**	**Re-revision**	**Needed re-revision impossible**	**Dead**
MEN <65	**Revision (0-6m)**	0.9850	0.0082	0.0000	0.0068	0.9591	0.0341	0.0000	0.0068
	Successful revision (6m)	0.9896	0.0082	0.0000	0.0022	0.9635	0.0342	0.0000	0.0022
	(Re-)revision (6m)	0.9850	0.0082	0.0000	0.0068	0.9425	0.0095	0.0412	0.0068
	Needed re-revision impossible (6m)			0.9978	0.0022			0.9978	0.0022
	Dead				1.0000				1.0000
MEN 65-74	**Revision (0-6m)**	0.9707	0.0081	0.0000	0.0213	0.9451	0.0336	0.0000	0.0213
	Successful revision (6m)	0.9689	0.0080	0.0000	0.0230	0.9434	0.0335	0.0000	0.0230
	(Re-)revision (6m)	0.9707	0.0081	0.0000	0.0213	0.9288	0.0093	0.0406	0.0213
	Needed re-revision impossible (6m)	0.0000	0.0000	0.9770	0.0230			0.9770	0.0230
	Dead	0.0000	0.0000	0.0000	1.0000				1.0000
MEN 75-84	**Revision (0-6m)**	0.9621	0.0080	0.0000	0.0299	0.9368	0.0333	0.0000	0.0299
	Successful revision (6m)	0.9644	0.0080	0.0000	0.0276	0.9390	0.0334	0.0000	0.0276
	(Re-)revision (6m)	0.9621	0.0080	0.0000	0.0299	0.9206	0.0093	0.0402	0.0299
	Needed re-revision impossible (6m)			0.9724	0.0276			0.9724	0.0276
	Dead				1.0000				1.0000
MEN 85+	**Revision (0-6m)**	0.8896	0.0074	0.0000	0.1030	0.8662	0.0308	0.0000	0.1030
	Successful revision (6m)	0.9131	0.0076	0.0000	0.0793	0.8891	0.0316	0.0000	0.0793
	(Re-)revision (6m)	0.8896	0.0074	0.0000	0.1030	0.8513	0.0086	0.0372	0.1030
	Needed re-revision impossible (6m)			0.9207	0.0793			0.9207	0.0793
	Dead				1.0000				1.0000
WOMEN	**Revision (0-6m)**	0.9854	0.0082	0.0000	0.0064	0.9595	0.0341	0.0000	0.0064

<65									
	Successful revision (6m)	0.9904	0.0082	0.0000	0.0014	0.9644	0.0343	0.0000	0.0014
	(Re-)revision (6m)	0.9854	0.0082	0.0000	0.0064	0.9430	0.0095	0.0412	0.0064
	Needed re-revision impossible (6m)			0.9986	0.0014			0.9986	0.0014
	Dead				1.0000				1.0000
WOMEN 65-74	**Revision (0-6m)**	0.9793	0.0081	0.0000	0.0126	0.9536	0.0339	0.0000	0.0126
	Successful revision (6m)	0.9861	0.0082	0.0000	0.0057	0.9602	0.0341	0.0000	0.0057
	(Re-)revision (6m)	0.9793	0.0081	0.0000	0.0126	0.9371	0.0094	0.0409	0.0126
	Needed re-revision impossible (6m)			0.9943	0.0057			0.9943	0.0057
	Dead				1.0000				1.0000
WOMEN 75-84	**Revision (0-6m)**	0.9669	0.0080	0.0000	0.0251	0.9414	0.0335	0.0000	0.0251
	Successful revision (6m)	0.9738	0.0081	0.0000	0.0181	0.9482	0.0337	0.0000	0.0181
	(Re-)revision (6m)	0.9669	0.0080	0.0000	0.0251	0.9252	0.0093	0.0404	0.0251
	Needed re-revision impossible (6m)			0.9819	0.0181			0.9819	0.0181
	Dead				1.0000				1.0000
WOMEN 85+	**Revision (0-6m)**	0.8955	0.0074	0.0000	0.0970	0.8720	0.0310	0.0000	0.0970
	Successful revision (6m)	0.9245	0.0077	0.0000	0.0679	0.9001	0.0320	0.0000	0.0679
	(Re-)revision (6m)	0.8955	0.0074	0.0000	0.0970	0.8569	0.0086	0.0374	0.0970
	Needed re-revision impossible (6m)			0.9321	0.0679			0.9321	0.0679
	Dead				1.0000				1.0000
AVERAGE <65	**Revision (0-6m)**	0.9852	0.0082	0.0000	0.0066	0.9593	0.0341	0.0000	0.0066
	Successful revision (6m)	0.9900	0.0082	0.0000	0.0018	0.9639	0.0343	0.0000	0.0018
	(Re-)revision (6m)	0.9852	0.0082	0.0000	0.0066	0.9427	0.0095	0.0412	0.0066
	Needed re-revision impossible (6m)			0.9982	0.0018			0.9982	0.0018
	Dead				1.0000				1.0000

AVERAGE 65-74	**Revision (0-6m)**	0.9713	0.0081	0.0000	0.0206	0.9458	0.0336	0.0000	0.0206
	Successful revision (6m)	0.9703	0.0081	0.0000	0.0217	0.9448	0.0336	0.0000	0.0217
	(Re-)revision (6m)	0.9713	0.0081	0.0000	0.0206	0.9295	0.0093	0.0406	0.0206
	Needed re-revision impossible (6m)			0.9783	0.0217	0.0000	0.0000	0.9783	0.0217
	Dead				1.0000	0.0000	0.0000	0.0000	1.0000
AVERAGE 75-84	**Revision (0-6m)**	0.9649	0.0080	0.0000	0.0271	0.9395	0.0334	0.0000	0.0271
	Successful revision (6m)	0.9698	0.0080	0.0000	0.0221	0.9443	0.0336	0.0000	0.0221
	(Re-)revision (6m)	0.9649	0.0080	0.0000	0.0271	0.9233	0.0093	0.0403	0.0271
	Needed re-revision impossible (6m)			0.9779	0.0221			0.9779	0.0221
	Dead				1.0000				1.0000
AVERAGE 85+	**Revision (0-6m)**	0.8937	0.0074	0.0000	0.0989	0.8701	0.0309	0.0000	0.0989
	Successful revision (6m)	0.9208	0.0076	0.0000	0.0715	0.8966	0.0319	0.0000	0.0715
	(Re-)revision (6m)	0.8937	0.0074	0.0000	0.0989	0.8551	0.0086	0.0373	0.0989
	Needed re-revision impossible (6m)			0.9285	0.0715			0.9285	0.0715
	Dead				1.0000				1.0000

Transition probabilities per 6 months

Appendix 5.2: Data from the public health insurer

CM 2014-2015 data for revisions	Total hip arthroplasty revision	Actualization 2019
Average community supported cost	€ 11,770	€ 12,769
p10 community supported cost	€ 5,927	€ 6,430
p25 community supported cost	€ 6,868	€ 7,451
median community supported cost	€ 8,706	€ 9,445
p75 community supported cost	€ 12,562	€ 13,628
p90 community supported cost	€ 21,105	€ 22,896
		€ 0
Average cost for the patient	€ 2,333	€ 2,531
p10 cost for the patient	€ 616	€ 668
p25 cost for the patient	€ 833	€ 904
median cost for the patient	€ 1,242	€ 1,348
p75 cost for the patient	€ 3,136	€ 3,402
p90 cost for the patient	€ 5,437	€ 5,899
		€ 0
Average total cost	€ 14,103	€ 15,300
p10 total cost	€ 6,543	€ 7,098
p25 total cost	€ 7,702	€ 8,355
median total cost	€ 9,949	€ 10,793
p75 total cost	**€ 15,698**	**€ 17,030**
p90 total cost	€ 26,542	€ 28,795
Physiotherapy		€ 0
Average reimbursed cost	€ 2,013	€ 2,184
Average standard cost for patient	€ 340	€ 369
Average supplements	€ 19	€ 21
Average patient cost	€ 360	€ 390
Total	**€ 2,732**	**€ 2,964**

Appendix 6.1: Questionnaire on 3D printed anatomic models for surgical planning of congenital heart diseases.

Dear doctor, dear professor

We want to express our gratefulness for your collaboration on our investigation on the potential positive health economic effects of the use of 3D anatomic models in the treatment of pediatric congenital heart defects. We incorporated 9 cardiovascular operations as being a subject of our health economic evaluation.
We would like to emphasize that all data will be analyzed anonymously and confidentially.
The questionnaire consists out of three parts.
In part 1, you will find general questions. The first question about your experience with 3D anatomic models is of high importance. We kindly ask you not to continue with this questionnaire if you have no (in)direct experience with 3D anatomic models.
In part 2, we will ask to give estimates of complication rates, mortality rates, quality of life etc. As a guidance, you will find indicative estimates from the literature regarding the conventional method (without the use of 3D anatomic models). We acknowledge the difficulty to respond on some of the questions. Still, we would kindly ask to give an answer/estimate on all questions. If you which, there is an opportunity to give additional comments after each question.
In the 3rd part, you will find two open-ended questions concerning the advantages and disadvantages of working with 3D anatomic models.
Questions or criticism can be addressed to Ruben Willems via e-mail (Ruben.Willems@UGent.be).
Our gratitude in advance.

Yours Sincerely

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Prof. Dr. Lieven Annemans, Professor Health Economics, Ghent University
E-mail: Lieven.Annemans@UGent.be

1. General questions

A. Job function / specialism:

……

…………………………..

B. In what hospital are you currently employed?

……

……………………………

C. Do you have experience working with 3D anatomic models?

Yes / No

If you answered yes, how frequently do you work with 3D anatomic models?

……

…………………………….

If no, we thank you for responding to our questionnaire.

D. In general, what is your attitude towards 3D anatomic models used during the treatment of congenital heart diseases?

Negative / Rather negative / Neutral / Rather Positive / Positive

Remarks:…………………………………………………………………………………………………

……

……

……………………………………………………………………………………………………….

2. 3D anatomic models may affect the complication rates when used in treatment congenital heart diseases. Next you will find a list of major complications that could possibly occur during surgery. Please read this list thorough.

   Major complications:
   (1) postoperative acute renal failure requiring temporary or permanent dialysis
   (2) postoperative neurological deficit persisting at discharge
   (3) postoperative requirement of a permanent pacemaker
   (4) postoperative mechanical circulatory support (ventricular assist device, intra-aortic balloon pump, cardiopulmonary support, extracorporeal membrane oxygenation)
   (5) phrenic nerve injury/paralyzed diaphragm
   (6) unplanned reoperation or re-intervention

   In the table below, an overview is given of the frequency of major complications per surgery without usage of 3D anatomic models. Please estimate the frequency of major complications with the systematic use of 3D anatomic models.

Procedure	% major complications without 3D models	Estimation % major complications with 3D models
Atrial Septum Defect Repair	0.6 %	
Ventricular Septum Defect Repair	2.5 %	
Tetralogy of Fallot Repair	5.6 %	
Fontan Operation	9.3 %	
Bidirectional Glenn Operation / Hemi-Fontan Operation	7.2 %	
Complete Atrio-ventricular Canal Repair	7.7 %	
Arterial Swith Operation	12.9 %	
Truncus Arteriosus Repair	23.5 %	
Norwood Operation	32.2 %	

Remarks:………………………………………………………………………………………………………

………

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3. 3D anatomic models may affect the complication rate when treating congenital heart diseases. Above we asked you to give estimates of major complications when using 3D anatomic models. Not listed complications could be categorized as ‘minor complications’. For example: bleeding or atrial fibrillation without necessary reoperation, perioperative hypothermia, wound problems, thrombocytopenia, mild gastrointestinal problems, short-term neurological problem…

In the table below, an overview is given of the frequency of minor complications per surgery without usage of 3D anatomic models. Please estimate the frequency of minor complications with the systematic use of 3D anatomic models.

Procedure	% minor complications without 3D models	Estimation % minor complications with 3D models
Atrial Septum Defect Repair	12.7 %	
Ventricular Septum Defect Repair	25.9 %	
Tetralogy of Fallot Repair	36.7 %	
Fontan Operation	47.1 %	
Bidirectional Glenn Operation / Hemi-Fontan Operation	32.6 %	
Complete Atrio-ventricular Canal Repair	44.7 %	
Arterial Swith Operation	40.0 %	
Truncus Arteriosus Repair	42.9 %	
Norwood Operation	43.6 %	

Remarks:………

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4. Several procedures related to CHD are given below. Please estimate (in minutes) the average duration (read: operation room time) of the given procedures, with and without 3D anatomic models.

Procedure	Without 3D anatomic model (conventional method)	With 3D anatomic model
Atrial Septum Defect Repair		
Ventricular Septum Defect Repair		
Tetralogy of Fallot Repair		
Fontan Operation		
Bidirectional Glenn Operation / Hemi-Fontan Operation		
Complete Atrio-ventricular Canal Repair		
Arterial Swith Operation		
Truncus Arteriosus Repair		
Norwood Operation		

Remarks:……

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5. Please estimate in minutes the average surgical preparation time for a cardiologist with and without 3D anatomic models for the given procedures (patient contact, communication and discussion with colleagues…).

Procedure	Without 3D anatomic model (conventional method)	With 3D anatomic model
Atrial Septum Defect Repair		
Ventricular Septum Defect Repair		
Tetralogy of Fallot Repair		
Fontan Operation		
Bidirectional Glenn Operation / Hemi-Fontan Operation		
Complete Atrio-ventricular Canal Repair		
Arterial Swith Operation		
Truncus Arteriosus Repair		
Norwood Operation		

Remarks:……………………………………………………………………………………………………

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6. 3D anatomic models may affect the occurrence of early mortality (death within 30 days after surgery or before discharge). Please estimate the early mortality when using 3D anatomic heart models for the given procedures.

Procedure	% early mortality without 3D anatomic model	Estimation % early mortality with 3D anatomic model
Atrial Septum Defect Repair	0.0 %	
Ventricular Septum Defect Repair	0.7 %	
Tetralogy of Fallot Repair	1.0 %	
Fontan Operation	1.4 %	
Bidirectional Glenn Operation / Hemi-Fontan Operation	2.1 %	
Complete Atrio-ventricular Canal Repair	3.2 %	
Arterial Swith Operation	2.7 %	
Truncus Arteriosus Repair	9.6 %	
Norwood Operation	15.6 %	

Remarks:……

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7. ‘Quality of life’ can be displayed on an scale of 0 to 100 with 0 being dead and 100 being perfect health. The score is calculated regarding a person’s mobility, self-care, pain level, feelings of anxiety and depression and execution level of daily activities.

   Belgian research suggest that a person younger than 15 years old has an average quality of life of 81/100. A 15 to 24 year old person has an average quality of life score of 89/100

   Please estimate, per surgery, (1) the average ‘quality of life’ after surgery for a person under 15 years old and (2) the average ‘quality of life’ after surgery for a 15 to 24 year old person. Consider the average surviving patient after one of the surgeries listed below.

Surgery	< 15 year	15-24 year
Score general population	***81***	***89***
Atrial Septum Defect Repair		
Ventricular Septum Defect Repair		
Tetralogy of Fallot Repair		
Fontan Operation		
Bidirectional Glenn Operation / Hemi-Fontan Operation		
Complete Atrio-Ventricular Canal Repair		
Arterial Switch Operation		
Truncus Arteriosus Repair		
Norwood Operation		

Remarks:………

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8. In general, what are the main advantages of 3D anatomic models? (e.g. reduction in operation room time, complication rate reduction, decrease of radiation….)

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9. In general, what are the main disadvantages of 3D anatomic models? (e.g. time limitations, costs…)

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Thank you for your collaboration!

Appendix 6.2: Overview of studies incorporated in the reviews analyzing conventional TKA vs. CCG.

	Thienpont, E. et al. (2013)	**Conteduca, F. et al. (2014)**	**Thienpont, E. et al. (2014)**	**Mannan, A. et al.(2014)**	**Cavaignac, E. et al. (2014)**	**Sassoom, A. et al. (2014)**	**Shen, C. et al. (2014)**	**Zhang, Q. et al. (2015)**	**Jiang, J. et al. (2015)**	**Kizaki, K. et al. (2019)**	**Rodrigues A. et al. (2017)**	**Huijbregts, H. J. et al. (2016)**	**Fu, H. et al. (2015)**	**Gong, S. et al. (2019)**
Abane (2015)										X		X		X
Abdel (2014)										X	X	X		
Anderl (2016)										X				
Bali (2012)	X	X	X	X										
Barke (2013)						X					X			
Barrack (2012)	X		X	X	X	X	X	X			X			
Barrett (2013)			X	X	X	X	X		X					
Barrett (2014)									X		X			
Boonen (2012)	X	X	X	X	X	X	X	X	X					
Boonen (2013)		X	X	X				X	X	X	X	X	X	X
Boonen (2016)										X				X
Chareancholvanich (2013)			X	X	X	X	X	X	X	X	X	X	X	X
Chen (2013)		X	X	X	X	X	X		X					
Chen (2014) (check 2013)											X			
Chen (2015)										X				
Chotanaphuti (2013)			X					X	X	2014		X	X	
Conteduca (2012)	X	X		X										
Culler (2017)										X				
Daniilidis & Tibesky (2013)		X		X		X	X		X					
Daniilidis (2013)		X	X	X	X			X			X			
De Vloo (2017)														X
Dossett (2012)								X						
Dossett (2014)										X				
Ferrara (2015)										X		X		
Gang (2015)														X
Hamilton (2013)			X		X	X	X	X	X	X	X	X	X	X
Heyse (2014)			X	X		X	X	X	X		X			
Howell (2008)	X			X										
Huijbregts (2016)										X		X		X

Ivie (2014)											X			
Khuangsirikul (2014)														X
Klatt (2008)	X													
Koch (2013)		X		X										
Kosse (2018)										X				X
Kotela (2014)								X			X	X		X
Kotela (2015) / 2014?										X				
Kwon (2017)										X				
Leeuwen (2018)										X				
Lombardi (2008)				X										
Lustig (2013)	X	X		X										
Macdessi (2013)				X	X				X					
Marimuthu (2014)					X		X	X	X		X			
Maus (2018)										X				
Molicnik (2015)										X		X		
Moubarak (2014)								X						
Nabavi (2015)										X				
Nam (2013)		X		X										
NCT02539992 NA										X				
Ng (2012)	X	X	X	X		X	X	X	X		X			
Ng (2013)								X					X	
Ng (2014) /2013?										X		X		
Noble (2012)	X	X		X		X		X	X	X	X	X	X	
Nunley (2012)	X	X		X	X			X	X		X (2x)			
Paratte (2013)		X	X	X	X	X	X	X				X	X	X
Pfitzner (2014)										X				
Pietsch (2013)										X		X	X	X
Pourgiezis (2016)										X				
Rathod (2015)										X				
Renson (2014)										X	X			
Roh (2013)			X	X	X		X	X	X	X	X	X	X	X
Scholes (2013)		X												
Silva (2014)			X			X		X			X	X		X
Spenser (2009)	X			X										
Steimle (2018)										X				
Stolazczyk (2018)										X				
Stronach (2013)											X			
Stronach (2014)								X			X			
Tammachote (2018)										X				X
Thienbont (2015)										X				
Tibesku (2013)														
Van Leeuwen (2018)														X
Victor (2013)	X		X	X	X		X		X		X	X	X	X

Vide (2017)										X				X
Vundelinckx (2013)	X	X				X		X		X		X		X
White (2016)										X				
Woolson (2014)					X			X		X		X		X
Yaffe (2013)				X	X	X								
Yan (2015)										X		X		X
Zhu (2017)										X				