

Placing a Price on Medical Device Innovation: The Example of Total Knee Arthroplasty

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Abstract

Background: Total knee arthroplasty (TKA) is common, effective, and cost-effective. Innovative implants promising reduced long-term failure at increased cost are under continual development. We sought to define the implant cost and performance thresholds under which innovative TKA implants are cost-effective.

Methods: We performed a cost-effectiveness analysis using a validated, published computer simulation model of knee osteoarthritis. Model inputs were derived using published literature, Medicare claims, and National Health and Nutrition Examination Survey data. We compared projected TKA implant survival, quality-adjusted life expectancy (QALE), lifetime costs, and cost-effectiveness (incremental cost-effectiveness ratios or ICERs) of standard versus innovative TKA implants. We assumed innovative implants offered 5–70% decreased long-term TKA failure rates at costs 20–400% increased above standard implants. We examined the impact of patient age, comorbidity, and potential increases in short-term failure on innovative implant cost-effectiveness.

Results: Implants offering $\geq 50\%$ decrease in long-term TKA failure at $\leq 50\%$ increased cost offered ICERs $< \$100,000$ regardless of age or baseline comorbidity. An implant offering a 20% decrease in long-term failure at 50% increased cost provided ICERs $< \$150,000$ per QALY gained only among healthy 50–59-year-olds. Increasing short-term failure, consistent with recent device failures, reduced cost-effectiveness across all groups. Increasing the baseline likelihood of long-term TKA failure among younger, healthier and more active individuals further enhanced innovative implant cost-effectiveness among younger patients.

Conclusions: Innovative implants must decrease actual TKA failure, not just radiographic wear, by 50–55% or more over standard implants to be broadly cost-effective. Comorbidity and remaining life span significantly affect innovative implant cost-effectiveness and should be considered in the development, approval and implementation of novel technologies, particularly in orthopedics. Model-based evaluations such as this offer valuable, unique insights for evaluating technological innovation in medical devices.

Citation: Suter LG, Paltiel AD, Rome BN, Solomon DH, Thornhill TS, et al. (2013) Placing a Price on Medical Device Innovation: The Example of Total Knee Arthroplasty. PLoS ONE 8(5): e62709. doi:10.1371/journal.pone.0062709

Editor: Maarten Postma, Groningen Research Institute of Pharmacy, United States of America

Received: June 29, 2012; **Accepted:** March 26, 2013; **Published:** May 6, 2013

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Funding: This work was supported in part by United States National Institutes of Health (NIH)/NIAMS R01 AR053112. Dr. Suter was supported by an NIH K23 AR054095-01 Mentored Career Development Award and an Arthritis Foundation Arthritis Investigator Award and is currently supported in part by the VA Connecticut Healthcare System and by Contract Number HHSM-500-2008-00251/HHSM-500-T0001, Modification No. 000005, entitled "Measure & Instrument Development and Support (MIDS)-Development and Re-evaluation of the CMS Hospital Outcomes and Efficiency Measures," funded by the Centers for Medicare & Medicaid Services, an agency of the U.S. Department of Health and Human Services. Dr. Losina is supported in part by NIH/NIAMS K24 AR057827 and R01AR064320 and Drs. Losina, Katz and Solomon by NIH/NIAMS P60 AR47782. Dr. Thornhill currently receives support from the Orthopedic and Education Research Foundation (OREF) and the Orthopedic Medical Grants Administration (OMeGA), as well as consulting fees and royalties from DePuy, and he owns stock in Conformis SAB. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have read the journal's policy and have the following conflicts. Among the authors, only Dr. Thornhill has potential conflicts of interest, having received consultancy fees and royalties from DePuy and owning stock in Conformis SAB. However, these financial activities were not in remuneration for his involvement on this paper and were independent of the current work. None of the other authors have any additional disclosures or conflicts. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

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Introduction

Many medical devices are marketed with claims of reduced long-term device failure and/or adverse events. Such claims are often based upon laboratory or *ex vivo* data extrapolated to long-term outcomes in humans and cannot be evaluated with short-term trials. Given the costs and limitations of prospectively collecting long-term efficacy data on innovative devices, simulation modeling is an ideal methodology to evaluate current technologies and anticipate potential health and economic consequences of future technologies.

Total knee arthroplasty (TKA) implant innovation provides an informative case study for examining the impact of medical device innovation on healthcare costs [1]. Over 620,000 TKAs were performed in the US in 2009, predominantly for end-stage osteoarthritis (OA) [2]. TKA inpatient costs exceed \$9 billion per year, the highest aggregate cost among the 10 fastest growing procedures [3]. Over 85% of recipients have functional improvement after TKA [4–7], and TKA is highly cost-effective [8].

Fueled by this success and trends suggesting that TKA recipients are younger, heavier, more active, and surviving longer after TKA than previously [2,9–11], over 35 TKA systems or components have been approved by the Food and Drug Administration (FDA) each year for the last decade through the 510(k) clearance process [12]. This process allows approval of perceived low-risk medical devices based upon claims of similarity to existing approved devices and likely incentivizes incremental improvements. Indeed, most claims of improved device durability are based upon *ex vivo* studies [13–19], rather than clinical trials, and such innovations come at a price, as newer implants are more costly [20–22].

Trade-offs between incremental improvements and their costs are poorly understood. With rising healthcare costs, it is critical to examine the value of technological advancements over existing devices. TKA is an ideal example for studying the cost/benefit trade-offs for medical devices, particularly those that offer quality of life improvement rather than immediate survival benefit. Given the costs and limitations of prospectively collecting long-term efficacy data on innovative medical devices, such as TKA implants, simulation modeling is an ideal methodology to evaluate current technologies and anticipate potential health and economic consequences of future technologies.

We sought to examine cost/benefit trade-offs and present the long-term economic implications associated with the use of innovative TKA implants using a simulation modeling approach. Specifically, we sought to define the conditions, including the patient characteristics, implant performance, and cost assumptions, under which innovative TKA implants might offer clinical benefit and good value for additional dollars spent versus those scenarios under which innovative implants would result in greater costs and/or unfavorable economic value. More broadly, our analysis provides a paradigmatic case study of the impact of medical device innovation on clinical efficacy and cost-effectiveness.

Methods

Ethics Statement

The study was approved by the Institutional Review Board of Brigham & Women's Hospital. Our research was conducted entirely in the U.S.A. No participants were involved and so no consent was required.

Analytic Overview

We used a validated, previously published computer simulation model of knee OA natural history and management (the Osteoarthritis Policy or OAPol model) [23,24] to forecast surgical, clinical and economic outcomes associated with “innovative” TKA implants (e.g., highly cross-linked polyethylene or other innovative biomaterials) as compared with “standard” implants (i.e., an ultra-high molecular weight all polyethylene tibial component) [25] in persons with end-stage knee OA. Laboratory data indicate these newer implants experience less wear, implying greater durability [14,19]. Our primary analysis varied implant durability and cost among different patient cohorts. Incremental cost-effectiveness ratios (ICERs), defined as the incremental benefits in additional quality-adjusted life expectancy (QALE) divided by the incremental costs, were estimated for innovative compared with standard implants.

OAPol Model

The OAPol model is a state-transition simulation model that uses a series of annual transitions between health states to describe the natural history and clinical management of knee OA. Pain, comorbidity, treatment, quality of life, and resource use are used to define discreet health states. These characteristics also influence further disease progression, response to treatments, development of additional comorbidities, and mortality. The model is implemented as a Monte Carlo simulation, meaning a random number generator and a set of estimated probabilities are used to determine the state-to-state pathway followed by each simulated patient. Each patient's course is then tracked until death, and large numbers of individual simulations are combined to estimate population outcomes and costs. This model has been used to estimate TKA cost-effectiveness [8], knee OA burden [24], and quality-adjusted life-years (QALYs) lost due to obesity and knee OA [23]. Model specifications, validation, and data sources have been previously published [1,23] and are supplemented in the Technical Appendix S1.

Study Population

We considered a population of individuals with end-stage (Kellgren-Lawrence grade IV) symptomatic knee OA at baseline. We considered four separate age and comorbidity cohorts to explore the impact of these characteristics on implant cost effectiveness. The four cohorts included 50–59 year-olds with and without comorbidity at the time of TKA and 70–79 year-olds with and without comorbidity at the time of TKA (see Population Demographics below for further explanation). We selected these age stratifications because while, historically, most US TKA recipients were in their 70 s, individuals under 65 years old represent the most rapidly growing group among TKA recipients [11].

Input Parameters

Model input parameters are listed in Table 1 and summarized below. Further details are also provided in the Technical Appendix S1.

Population demographics. We derived baseline distributions of sex, race, and ethnicity from 2000 Medicare claims data [26] and validated these parameters against a nationally representative sample of TKR recipients [2]. We dichotomized the baseline presence of medical comorbidities as “healthy” (no comorbidities) versus “with comorbidity” (including baseline obesity, cardiovascular disease, and other, non-OA musculoskeletal disorders). Cohorts “with comorbidity” experienced higher

Table 1. Model Input Parameters*.

Parameter	Estimates				Source
Quality of Life (in QALYs)					
	<65 years old		65+ years old		
	Healthy	With Comorbidity	Healthy	With Comorbidity	
Knee Pain - (No pain relief from TKA)	0.806	0.679	0.884	0.757	NHANES 2005–2008 [33,34], Losina et al, 2011
No Knee Pain - (Pain relief from TKA) [†]	0.952	0.867	0.943	0.858	[23]
Surgical AE [‡]	0.60				Fisman et al, 2001 [32]
Medical AE	Pneumonia	Myocardial Infarction	Pulmonary Embolism		
	0.60	0.65	0.50		Taylor et al, 2009 [29], Melinkow et al, 2008 [30], Weaver et al, 2001 [31]
Costs (in 2010 US\$)					
	Healthy		With Comorbidity		
Underlying Medical Costs	986–1,205		2,388–2,860		Lee et al, 2001 [35], NHANES 2005–2008 [33,34]
Analgesic Treatment [§]	333				Red Book 2008 [36]
TKA Costs	Primary TKA		Revision TKA		
First Year	23,903		28,195		Losina et al, 2009 [8]
Implant	5,414				Mendenhall, 2004 [37]
Annual Follow-Up	103				CMS 2008 [39], Teeny et al, 2003 [40]
Surgical AE	21,213				HCUP 2008 [2]
Medical AE	Pneumonia	Myocardial Infarction	Pulmonary Embolism		
	10,388	18,478	12,090		HCUP 2008 [2]
	~ <i>Standard Implants</i> ~				
TKA Efficacy & Adverse Events					
	Short-Term[†]		Long-Term^{**}		
	Primary TKA	Revision TKA	Primary TKA	Revision TKA	
Technical Failure ^{††} %	1.1	1.1	1.36	1.36	Losina et al, 2009 [8]
Pain Relief Success ^{††} %	86.2	74.3	96.0	94.4	Katz et al, 2007 [7]
Adverse Events ^{§§} %					
Surgical	0.37	0.67	–	–	
Medical					
Pneumonia	1.27	1.27	–	–	
Myocardial Infarction	0.75	0.75	–	–	Katz et al, 2004 [27]
Pulmonary Embolism	0.74	0.74	–	–	
Death from AE	0.63	0.96	–	–	
	~ <i>Innovative Implants</i> ~				
TKA Efficacy					
	Short-Term		Long-Term		
Technical Failure % (Range)	1.1 (1.1–5.5)		0.4–1.1 ^{***}		Losina et al, 2009 [8]
Pain Relief Success % (Range)	86.2 (75.9–100)		96.0		Katz et al, 2007 [7]
Costs (in 2010 US\$)					
TKA Costs					
First Year	24,986–45,559				Losina et al, 2009 [8]

Table 1. Cont.

Parameter	Estimates	Source
Implant ^{†††}	6,497–27,070	Mendenhall, 2004 [37]

*Further input parameters are provided in the online Technical Appendix and published literature (Suter 2011, Losina 2011).

[†]In order to capture significant pain, we defined pain as those individuals noting functional limitations. Quality of life estimates were derived from general population data, not specifically from TKA recipients.

[‡]Derived from data for quality of life in persons with prosthetic joint infection.

[§]Annual cost of analgesic treatment was added for individuals who did not achieve pain relief from their TKA.

^{||}CMS = Centers for Medicare and Medicaid Services.

^{*}Short-term refers to the first year following primary or revision TKA.

^{**}Long-term refers to the annual proportion of individuals experiencing a TKA outcome or AE each year following the first year after primary or revision TKA.

^{††}Technical failure is the percentage of individuals who required or qualified for revision surgery due to mechanical failure of the prosthesis, with or without associated symptoms.

^{†††}Pain relief success is the percentage of individuals achieving pain relief without technical failure. In instances of technical failure, pain relief was significantly less than the values reported above.

^{§§}Adverse events (AEs) only occurred in the first year after primary or revision TKA.

^{***}These values represent the range of failure rates used in the Primary Analysis (20–70% reductions in failure for innovative compared to standard implants). Standard implants had long-term failure rates as high as 5.44% in the sensitivity analysis exploring the impact of higher long-term failure in healthy 50–59-year-olds, producing a failure rate of 4.35% for an innovative implant offering a 20% decrease in long-term failure.

^{††††}The implant cost is included in the total first-year cost of TKA.

doi:10.1371/journal.pone.0062709.t001

mortality, reduced quality of life, and increased underlying medical costs, compared to “healthy” cohorts.

Surgical outcomes: TKA Efficacy and Adverse Events for Standard Implants. Surgical outcomes consisted of TKA efficacy and adverse event (AE) rates which were derived from published estimates [7,8,27]. Standard TKA efficacy was comprised of pain relief efficacy (defined as the percentage of individuals achieving pain relief) and the absence of technical failure (defined as the percentage of individuals requiring or qualifying for revision surgery due to mechanical failure). Experiencing recurrent knee pain following surgery resulted in a decrement in quality of life as noted below. Both pain relief and technical failure were further divided into first year (“short-term”) versus subsequent year (“long-term”) rates.

The primary clinical outcome in the model consisted of QALE, a patient-relevant outcome assessment validated for use in a wide range of clinical conditions, including knee osteoarthritis and individuals undergoing TKA. QALE represents an ideal metric for assessing long-term outcomes following TKA as this procedure is focused primarily on improving function and reducing pain, thus directly affecting quality of life. Scores from the SF-36 questionnaire were transformed into quality of life weights using published methods [8,28]. Quality of life estimates for TKA-related AEs were derived from published literature [29–32]. Quality of life valuations over time were influenced by the presence of pain, body mass index (obese or non-obese) and number of comorbidities (0–1, 2–3, or >3).

Economic outcomes: Costs. Underlying annual medical costs, in 2010 US dollars, were stratified by age, presence of knee pain and comorbidity and ranged from \$986 to \$2,860 [33–35]. An additional annual cost of \$333 was added for individuals for whom TKA did not provide pain relief to account for analgesic treatment [36].

The cost of TKA (including hospital, physician, and rehabilitation costs) was estimated at \$23,903 [8], of which the implant cost represented \$5,414, based on survey data from a national sample of hospitals [37]. This estimate of implant cost is consistent with the findings of a recent study utilizing data from sixty-one hospitals in 2008 [38]. Annual follow-up cost for TKA (including a physician visit and imaging) was determined from Medicare reimbursement data and a national survey of orthopedic surgeons [39,40].

Primary Analysis

We measured comparative value in constant (2010) US dollars per QALY gained and reported all economic outcomes from a modified societal perspective, adjusted for time value (with 3% annual discounting), but excluding indirect costs [41]. We estimated the proportion of each cohort surviving with their original implant intact at 5, 10, 15, and 20 years after TKA. We calculated the QALE and costs associated with each combination of innovative TKA implant cost (20–400% over standard cost) [21,37,42] and reduction in long-term implant failure rate (5–70% decreases compared to standard implants) [14,19] in each of the four primary patient cohorts. ICERs compared to standard TKA were calculated for each combination of implant cost, long-term implant failure rate, and patient cohort.

Sensitivity Analyses

Based upon recent data suggesting that younger TKA recipients experience higher revision rates than older individuals [43], presumably due to higher activity levels leading to higher wear, we examined the impact of higher annual TKA failure rates (2.72–5.44%, versus 1.36% baseline risk) among the healthy 50–59-year-old cohort. We also examined the impact of increasing short-term TKA failure consistent with recent orthopedic device failures (100–500% increases in first-year technical failure) [44] while simultaneously decreasing long-term failure (5–70%), as one might anticipate from an innovative technology offering greater long-term benefit at higher short-term risk. We examined the impact of varying the proportion of patients achieving pain relief from innovative TKA implants; we considered values ranging from an 8% decrease to a 20% increase, compared to standard TKA. We also varied TKA cost [8], TKA offer and acceptance rates, and recipient demographics.

Results

Effect of Innovative Implants on Patient and Implant Survival

Patient survival 20 years following TKA ranged from 80.7% among healthy 50–59-year-olds to 13.6% among 70–79-year-olds with baseline comorbidity. Among healthy 50–59-year-olds, 64.9% survived and retained their primary TKA implant at 20

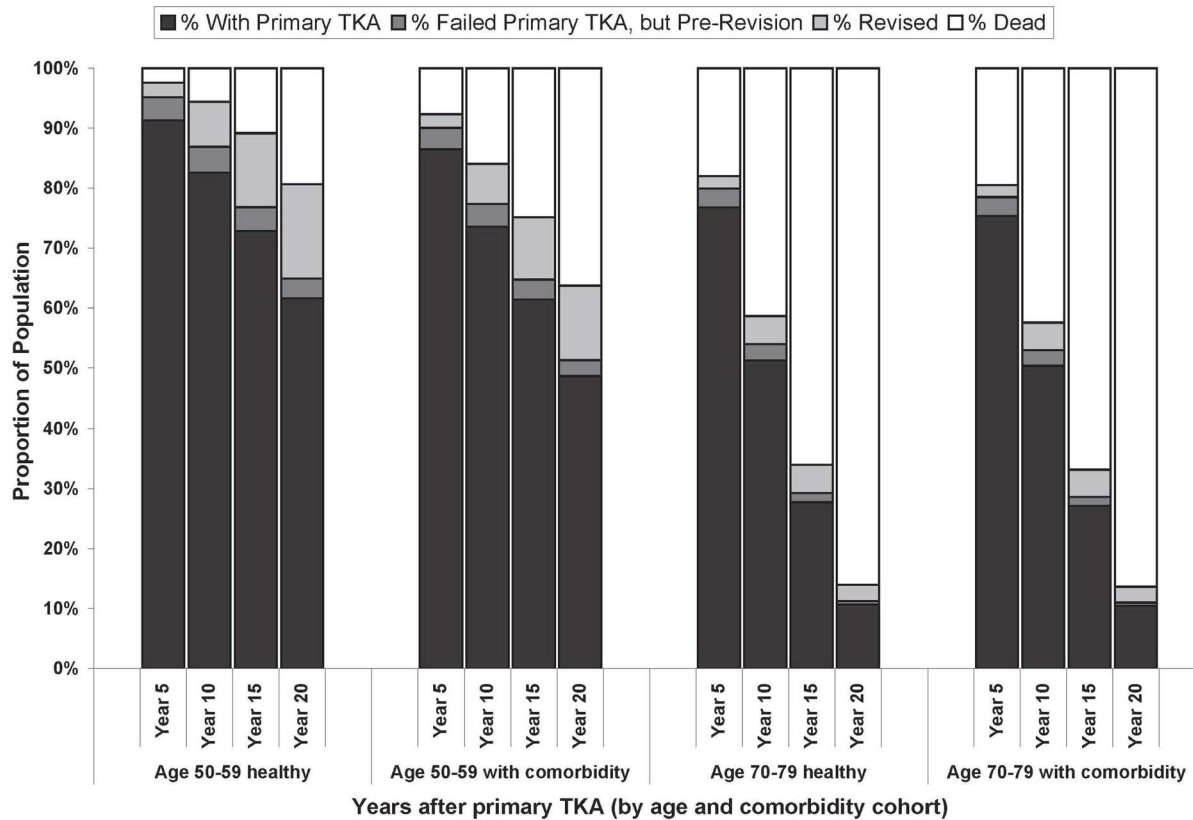


Figure 1. Proportion of population alive with original implant after Standard TKA by age and comorbidity. The estimated proportion of the population surviving with a successful primary TKA implant are noted by black bars among each of the four cohorts at 5, 10, 15, and 20 years after standard TKA. The dark grey bars represent the proportion of the population who have experienced technical TKA failure but have not undergone revision either due to the fact that their failure has not been observed by either the patient or their physician or they have been offered revision but refused. The light grey bars represent the proportion that has undergone revision TKA. As one moves from healthy 50–59-year-olds on the left to those with baseline comorbidity to healthy 70–79-year-olds and finally 70–79-year-olds with comorbidity on the far right, fewer individuals survive to experience TKA failure and therefore TKA revision. TKA = Total knee arthroplasty. doi:10.1371/journal.pone.0062709.g001

years (Figure 1), compared to 11.0% of 70–79-year-olds with baseline comorbidity. In total, 17.8% of healthy 50–59-year-olds and 9.4% of 70–79-year-olds with baseline comorbidity underwent revision surgery within 20 years of their primary TKA.

Innovative implants offering a 5% reduction in long-term TKA failure decreased the proportion of TKA recipients undergoing subsequent revision by only 0.79% and 0.39% (absolute percentage points) over 20 years in healthy 50–59-year-olds and 70–79-year-olds with comorbidity, respectively. Implants offering a 40% decrease in long-term TKA failure decreased the percent of TKA recipients undergoing revision by 6.29% among healthy 50–59-year-olds and 3.28% among 70–79-year-olds with comorbidity. An implant reducing long-term failure by 70% decreased revisions by 11.32% among healthy 50–59-year-olds and 5.83% among 70–79-year-olds with comorbidity.

Effect of Innovative Implants on QALE, Costs, and Cost-Effectiveness

Remaining QALE and costs for standard and innovative implants are reported in Table 2. QALE after standard TKA ranged from 7.57 QALYs among 70–79-year-olds with baseline comorbidity to 16.43 QALYs among healthy 50–59-year-olds. Innovative TKA implants decreasing long-term TKA failure by 5% offered, on average, ≤ 0.01 additional QALYs (<four days) compared to standard TKA among all four populations. Implants

decreasing long-term failure by 40% resulted in ≤ 0.06 additional QALYs among 50–59-year-olds and 0.02 additional QALYs among 70–79-year-olds. A 70% decrease in long-term failure offered an average of 0.10 additional QALYs (<37 quality-adjusted days) across the cohorts.

Remaining lifetime costs ranged from \$42,186 in healthy 70–79-year-olds to \$82,524 among healthy 50–59-year-olds. Innovative implants costing 20% to 400% above standard implants resulted in \$446 to \$20,959 increases in lifetime costs. Greater reductions in long-term failure always resulted in lower costs. Innovative implants offering a 70% reduction in long-term failure at only 20% higher cost resulted in greater QALE but lower lifetime costs than the standard implant in all four cohorts, suggesting such an implant would be cost-saving compared to standard implants if that level of TKA failure reduction could be achieved.

ICERs for innovative compared to standard implants varied with changes in both long-term implant failure and implant cost. Innovative implants costing at least three times more than a standard implant yielded ICERs above \$150,000 per QALY gained in all populations except for healthy 50–59-year-olds, for which the ICER was \$81,493. Implants offering a 20% reduction in long-term failure at 50% increased implant cost yielded ICERs of \$71,007 per QALY gained (compared to standard TKA) among healthy 50–59-year-olds, \$158,622 among 50–59-year-olds with baseline comorbidity, \$189,494 among healthy 70–79-year-

Table 2. Lifetime QALE, cost, and cost-effectiveness estimates associated with Standard and Innovative TKA.

% Decrease in Long-Term Failure	% Increase in Implant Cost	Ages 50–59						Ages 70–79					
		Healthy*			With comorbidity†			Healthy*			With comorbidity†		
		Cost	QALE	ICER‡	Cost	QALE	ICER‡	Cost	QALE	ICER‡	Cost	QALE	ICER‡
Standard TKA		\$61,589	16.43	–	\$82,523	12.88	–	\$42,186	8.57	–	\$55,606	7.57	–
	20%	\$62,508	16.44	\$98,576	\$83,443	12.88	\$256,918	\$43,152	8.57	\$285,846	\$56,568	7.58	\$253,792
	50%	\$64,135	16.44	\$272,947	\$85,042	12.88	\$703,083	\$44,734	8.57	\$754,131	\$58,136	7.58	\$667,360
5%	100%	\$66,834	16.44	\$562,378	\$87,734	12.88	\$1,454,320	\$47,358	8.57	\$1,530,912	\$60,723	7.58	\$1,349,707
	200%	\$72,220	16.44	\$1,139,780	\$93,034	12.88	\$2,933,511	\$52,632	8.57	\$3,091,912	\$65,951	7.58	\$2,728,599
	400%	\$83,034	16.44	\$2,299,170	\$103,648	12.88	\$5,895,966	\$63,148	8.57	\$6,204,194	\$76,378	7.58	\$5,478,685
	20%	\$62,035	16.46	\$15,392	\$83,031	12.89	\$38,457	\$42,856	8.58	\$56,394	\$56,275	7.58	\$82,829
	50%	\$63,648	16.46	\$71,007	\$84,618	12.89	\$158,622	\$44,437	8.58	\$189,494	\$57,852	7.58	\$278,098
20%	100%	\$66,352	16.46	\$164,242	\$87,283	12.89	\$360,432	\$47,069	8.58	\$411,024	\$60,453	7.58	\$600,244
	200%	\$71,754	16.46	\$350,514	\$92,614	12.89	\$763,998	\$52,333	8.58	\$854,102	\$65,675	7.58	\$1,246,999
	400%	\$82,548	16.46	\$722,735	\$103,245	12.89	\$1,568,953	\$62,861	8.58	\$1,740,275	\$76,103	7.58	\$2,538,459
	20%	\$60,290	16.53	Cost saving	\$81,486	12.93	Cost saving	\$41,846	8.61	Cost saving	\$55,308	7.60	Cost saving
	50%	\$61,911	16.53	\$3,114	\$83,088	12.93	\$12,082	\$43,420	8.61	\$28,197	\$56,850	7.60	\$47,443
70%	100%	\$64,615	16.53	\$29,254	\$85,757	12.93	\$69,145	\$46,058	8.61	\$88,485	\$59,463	7.60	\$147,106
	200%	\$70,019	16.53	\$81,493	\$91,079	12.93	\$182,905	\$51,328	8.61	\$208,939	\$64,694	7.60	\$346,593
	400%	\$80,814	16.53	\$185,840	\$101,741	12.93	\$410,828	\$61,858	8.61	\$449,577	\$75,108	7.60	\$743,764

*No obesity or comorbidity at baseline.

†Baseline obesity, cardiovascular disease, and non-OA musculoskeletal disease.

‡ICER = incremental cost-effectiveness ratio in 2010 US\$ per quality-adjusted life-year (QALY) gained, compared with standard TKA. “Cost saving” indicates greater QALYs achieved at a lower cost compared to standard TKA.

doi:10.1371/journal.pone.0062709.t002

olds, and \$278,098 among 70–79-year-olds with baseline comorbidity. More favorable ICERs were obtained when we considered a healthier, younger target population and when we assumed cheaper, more effective innovative implants (Figure 2). This trend persisted in the 60–69-year-old and 80–89-year-old cohorts (Figure 1 in the Technical Appendix).

Sensitivity Analyses

Increasing the standard implant failure rate among healthy 50–59-year-olds produced lower ICERs for innovative implants. Tripling the standard failure rate among healthy 50–59-year-olds from 1.36% to 4.08% reduced the ICER for an implant that decreased failure by 20% at 50% greater cost from \$71,007 to \$22,475 per QALY gained.

Increasing short-term implant failure while simultaneously reducing long-term failure decreased cost-effectiveness across all cohorts (i.e., fewer innovative implants produced ICERs <\$100,000 compared to standard TKA; Figure 3). Doubling short-term failure from 1.1% (the value for a standard implant) to 2.2% for an innovative implant offering a 20% reduction in long-term failure at 50% increased cost raised the ICER from \$71,007 to \$141,022 per QALY gained among healthy 50–59-year-olds and from \$278,098 to \$807,358 per QALY gained among 70–79-year-olds with comorbidity. When the short-term failure rate was doubled and reductions in long-term failure rates from innovative implants were small, innovative implants offered similar or worse QALE compared to standard implants, but at greater cost (“dominated” scenarios in Figure 3).

The impact of increasing age and comorbidity on innovative implant cost-effectiveness could be offset by either greater reductions in long-term TKA failure or improved pain relief after TKA, as might be expected with an implant that offers both technical (decreased long-term failure) and clinical (increased likelihood of pain relief) benefits (Figure 2 in the Technical Appendix). A 4% increase in the percentage of individuals experiencing pain relief after TKA reduced the ICER for an innovative implant offering a 70% reduction in long-term TKA failure at twice the cost of a standard implant, from \$147,106 to \$76,270 per QALY gained among 70–79-year-olds with baseline comorbidity.

Varying standard TKA implant cost (compared to the base assumption of \$5,414) from \$2,390 to \$11,952 produced ICERs among healthy 50–59-year-olds that ranged from \$82 (for lowest standard implant cost) to \$92,272 (for highest standard implant cost) per QALY gained for an innovative implant that costs twice a standard implant and offers a 70% decrease in long-term failure. Performing the same analysis among 70–79-year-olds with baseline comorbidity produced ICERs ranging from \$36,585 to \$386,828 per QALY gained when the cost of the standard implant was similarly ranged (Figure 3 in the Technical Appendix).

Discussion

We used TKA to demonstrate how simulation modeling can measure the value of new healthcare technologies. We quantified the impact of implant cost and longevity, and recipient age and comorbidity on innovative TKA implant cost-effectiveness. The

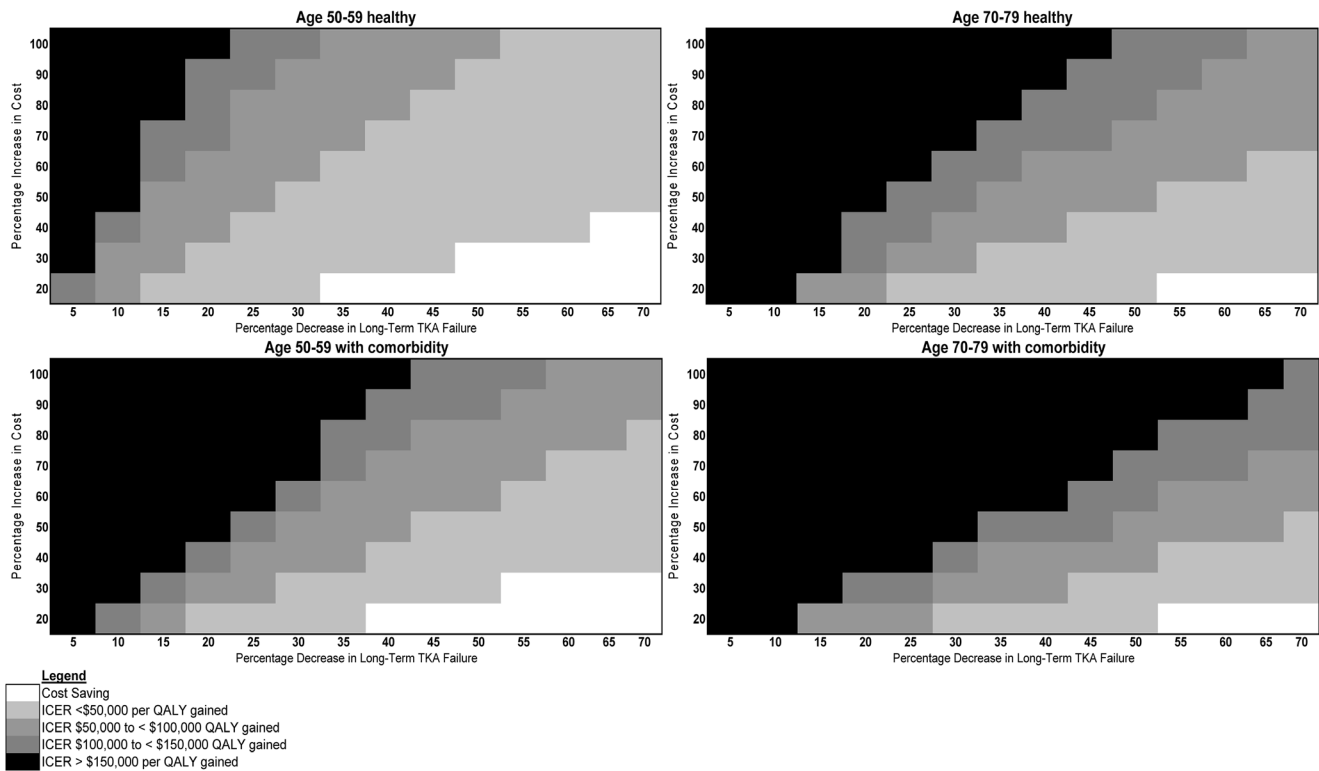


Figure 2. Implant cost and long-term TKA failure rate thresholds. Each shaded area represents implant cost increases (vertical axis) and failure rate reductions (horizontal axis) required to achieve a given ICER range (see Legend contained in Figure) among the four primary cohorts. ICER = incremental cost-effectiveness ratio in 2010 US\$ per quality-adjusted life-year (QALY) gained, compared with standard TKA. doi:10.1371/journal.pone.0062709.g002

hypothetical ability of innovative TKA implants to delay the need for revision resulted in quality of life gains as high as 0.10 QALY, consistent with other medical device innovations, such as dual-chamber pacemakers, which offer incremental QALE benefits of 0.14 QALY compared to standard pacemakers [45]. It is important to note, however, that because the revision rates of TKA with standard implants are already low, much of the population may not experience any benefit from innovative implants, while a small group of people may experience large benefits by avoiding otherwise complex revision procedures. Taken as an average across the whole population, innovative TKA implants therefore offered smaller increases in QALE than other novel therapeutics, such as dabigatran for stroke prevention in atrial fibrillation, which provided 0.42 more QALYs than warfarin, a four times greater QALE benefit than even the most optimistic innovative TKA implant in our study [46]. Further, these gains are attenuated in older populations or those with greater comorbidity that may not survive long enough to benefit from decrements in long-term TKA failure.

While there is no single accepted threshold below which a novel therapy might be considered “cost-effective”, the WHO Commission on Macroeconomics and Health offers the following guidance: interventions should be labeled “cost-effective” in a given country if their ICER is less than three times that nation’s per capita gross domestic product; interventions whose ICER is less than the per capita GDP may be labeled “highly cost-effective” [47,48]. The GDP in the US is roughly \$50,000 [49], suggesting that that innovative TKA implants offering at most a 15% reduction in long-term failure are unlikely to offer cost-effective value to a broad range of patient populations. Such implants would need to provide at least a 50% relative decrease in

actual TKA failure compared with standard implants to be considered broadly cost-effective according to WHO standards.

Healthy 50–59-year-olds, those with the greatest anticipated life expectancy among our four cohorts, received the most meaningful clinical and economic benefit from decreasing the TKA failure rate. In fact, if innovative implants could be proven to reduce true long term TKA failure by at least 35% among this cohort, and if such implants cost only 20% more than existing implants, they might even offer a cost saving alternative to standard implants. This finding was accentuated when we assumed that younger, healthier TKA recipients had a higher baseline risk of revision than older less healthy individuals, as recent data suggest [43]. However, the true efficacy of innovative implants is poorly understood and, based upon recent experience with metal-on-metal implants [22], might actually lead to increased, rather than decreased TKA failure rates.

While implant cost and efficacy affected innovative TKA implant cost-effectiveness, recipient comorbidity and remaining life span also had a substantial impact. Our results suggest these factors may be even more important if innovative implants lead to increased short-term TKA failure, as one might expect with a novel technology that requires the development of specific skills and/or surgical experience to produce optimal results. When the short-term failure risk is doubled for healthy 50–59 year olds, an innovative implant with only a 10% reduction in late-term failure led to worse QALE than standard implants. The results were even less favorable in older and sicker cohorts (Figure 3). Despite yielding acceptable ICERs under some scenarios, increases in innovative implant survival offered at most a 11.32% absolute reduction in the cumulative risk of revision among healthy

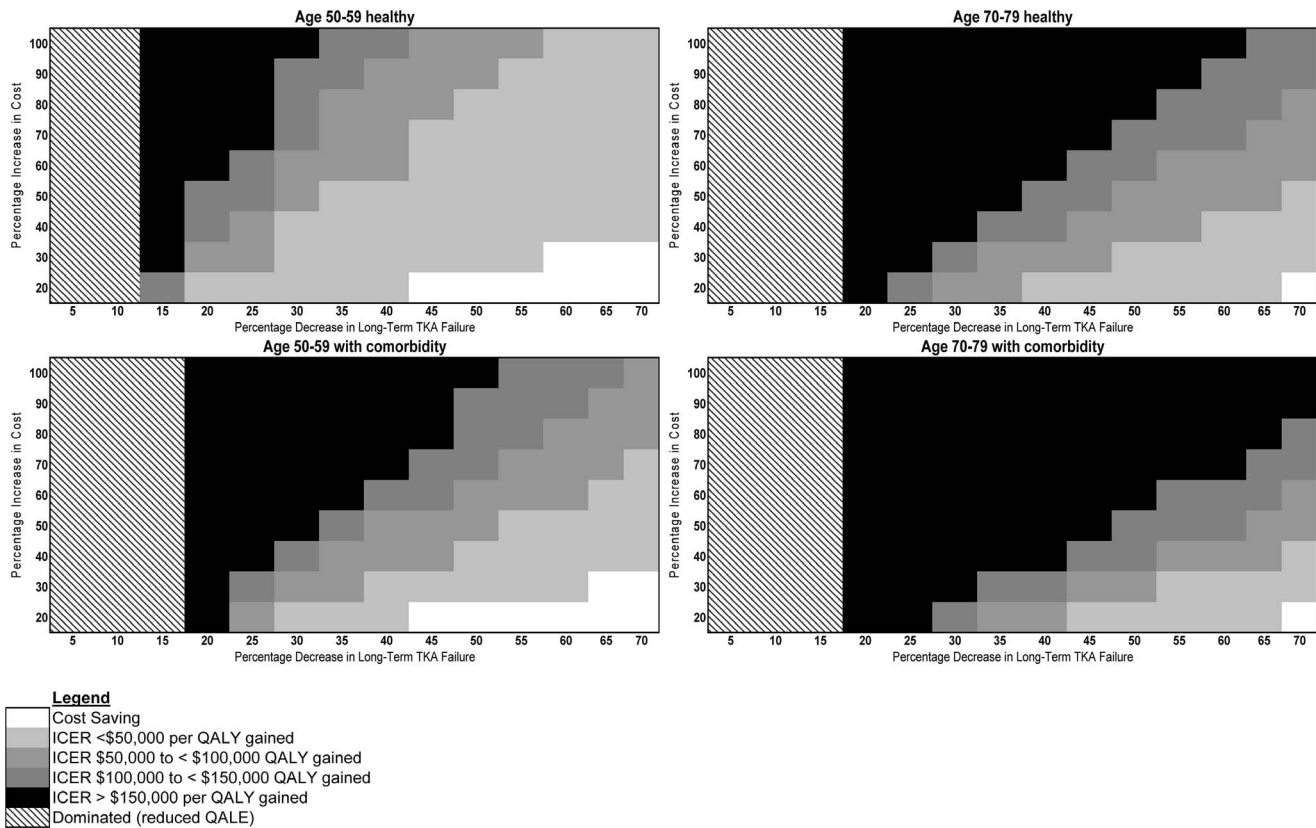


Figure 3. Implant cost and long-term TKA failure thresholds in a scenario where the base short-term failure rate doubles. Each shaded area represents implant cost increases (vertical axis) and failure rate reductions (horizontal axis) required to achieve a given ICER range (see Legend contained in Figure) among the four primary cohorts in 2010 US\$ per quality-adjusted life year (QALY) gained, compared with standard TKA. Areas with black and white diagonal lines indicate assumptions under which innovative implants offer lower QALE for greater cost compared to standard implants (i.e., such an innovative implant is “dominated” by the standard implant). doi:10.1371/journal.pone.0062709.g003

50–59-year-olds and 5.83% absolute reduction among individuals aged 70–79 with baseline comorbidity.

There are limitations to our analysis. We estimated proportional decreases in TKA implant failure based upon laboratory studies of tibial and acetabular bearing surfaces [14,19], which are unlikely to correlate precisely with clinical TKA outcomes and likely overestimate the true clinical benefit of innovative implants. However, in addition to exploring a wide range of possible effects of innovative implants on reducing TKA failure, we chose conservative estimates and assumed laboratory wear underestimates true failure our conservative estimates demonstrated that innovative biomaterials require a minimum of 50–55% reduction in true long-term failure to be considered broadly cost-effective. Published studies suggest innovative hip implants may reduce short-term *in vivo* wear rates between 40–72%, [50–53] but these radiographic findings may not accurately reflect clinical outcomes such as implant failure or the need for revision. Robust, long-term clinical data on TKA implants are unavailable, which is one of the advantages of simulation modeling in this area. As true TKA failure rates are unlikely to be reduced as much as short-term *ex vivo* knee or *in vivo* hip studies indicate, it is improbable that existing innovative implants offer marked economic value across all populations.

Increased activity levels among younger, healthier TKA recipients, who may therefore be at greater risk of TKA failure, may further enhance innovative implant cost-effectiveness. However, we did not model dynamic decreases in TKA failure as an

individual ages, so our model likely overestimates the cost-effectiveness of innovative implants under such assumptions. In contrast, our base implant cost estimate may exceed the average cost experienced by some hospitals [54], thereby underestimating cost-effectiveness. Since TKA cost-effectiveness is sensitive to implant cost, TKA innovations may be more or less cost-effective depending upon the implant cost each hospital pays, producing variability in value according to the negotiated cost [21]. While we did not assess the impact of surgical technique on cost-effectiveness, we did examine the possibility that innovative technology might offer greater short-term failure due to the potential for increased technical complexity associated with novel devices. We also did not consider that the decision, from a patient’s or society’s perspective, to adopt an innovative implant today is to forgo the option of an even better implant tomorrow. However, similar limitations are likely to affect the evaluation of any innovative medical device and can be addressed by sensitivity analyses to assess the impact of data uncertainty.

The FDA 510(k) clearance process has been criticized for insufficient safety oversight and suppressing innovation through incentivizing incremental gains [44,55]. Limited oversight of medical device approval combined with economic and other incentives serve to speed technology adoption [56]. However, recent data demonstrate expedited approval is associated with increased rates of high-risk product recalls [57]. Our analyses suggest that small, incremental improvements in device longevity may have little to no effect on QALE and cost-effectiveness,

further supporting the Institute of Medicine's recent call for redesigning the 510(k) approval process [58]. Furthermore, extensive recent data demonstrate that not all innovative implant technologies will lead to actual improvements in longevity, and some, such as metal-on-metal hip implants, may even lead to worse long-term outcomes [22,59–62]. Innovative implants providing no clinical benefit at an added cost would not be cost-effective. Decisions as to the marketing, use and reimbursement of medical devices are currently being made without robust outcomes data to guide decision making. Our approach serves as a model for evaluating a wide range of innovative technologies.

Because innovative implant technologies are released at about a rate of 30 per year [11], surgeons and hospitals are often faced with choices of whether to use specific innovative devices. These devices may utilize one or more innovative technologies, such as cementless fixation, rotating or sliding bearing inserts, novel biomaterials, or gender-specific designs. For several of these technologies, it is not clear whether they offer a significant improvement in clinical outcomes over existing prostheses [63–65]. However, as data from joint registries and head-to-head trials uncover which specific implants can offer improved clinical outcomes and/or reduced rates of revision, our model allows decision makers to combine these outcomes data with the implant's marketed cost to determine whether such a device would be cost-effective in particular patient populations.

While it is difficult to predict the benefit of an innovative TKA implant to any one individual, the incremental benefit to society appears modest, and the excess cost of using innovative implants indiscriminately across populations could be substantial. Compared to per capita healthcare expenditures among industrialized nations, TKA alone is responsible for \$3 billion in increased US spending [66]. Targeting implants to specific populations based on their expected clinical benefit may offer significant savings. Moreover, TKA is representative of many medical devices, ranging from hip and spinal implants, plates, screws and other orthopedic hardware, to cataract and ophthalmologic implants, which offer improvements in quality of life rather than survival benefits. This work has implications for the development and adoption of any medical device offering long-term clinical benefit at a greater initial cost. Our analysis demonstrates that small decreases in long-term device failure can provide clinical and economic value under certain circumstances, but these innovations

may not offer equal benefit in all populations. In addition, many innovative technologies offer improved long-term outcomes at the expense of increased short-term complications due to increased complexity of the procedure and/or the technical skill required to optimally implement such advances. Our data suggest that even if innovative implants lead to some increases in short-term complications, the impact on overall cost-effectiveness will be small in situations where innovative devices offer substantial benefit over standard devices in reducing long term failure. In situations where innovative implants are associated with lowering rather than increasing short-term complications, cost-effectiveness will likely be more favorable.

These results also provide important insights regarding the costs and benefits associated with the diffusion of technology into clinical practice. The modeling approach presented here can and should focus and improve device development, identify optimal populations for testing novel technologies, and provide physicians, insurers and patients detailed information on the clinical benefits expected for a given investment. The complex trade-offs between short- and long-term health and economic consequences of technological innovation cannot easily be captured by even the most sophisticated randomized trials. Model-based evaluations such as those presented here may provide important insights for evaluating medical device innovation and merit consideration as a standard component of the evaluation process.

Supporting Information

Technical Appendix S1 Additional information to supplement the methods and results sections of this manuscript. It further explains input parameters utilized to model total knee Arthroplasty as a treatment for knee osteoarthritis and provides supplemental results including a number of sensitivity analyses not present in the manuscript. (DOC)

Author Contributions

Conceived and designed the experiments: LGS ADP DHS TST JNK EL. Performed the experiments: LGS BNR SA EL. Analyzed the data: LGS BNR SA EL. Contributed reagents/materials/analysis tools: LGS JNK EL. Wrote the paper: LGS ADP BNR SA DHS TST JNK EL.

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