

Advancing Patient Outcomes and Economic Value in Total Knee Arthroplasty:

The Evidence of the ATTUNE™ Knee System

David A. Fisher, M.D.

David Parkin, DPhil

Authors:

David A. Fisher, M.D., is a board certified and fellowship trained orthopaedic surgeon who specializes in primary and revision hip and knee replacement. He currently serves as a consultant to the Total Joint Center of Excellence at OrthoIndy Hospital, Indianapolis, Indiana. In addition, he is an Assistant Clinical Professor of Orthopaedic Surgery at the Indiana University School of Medicine. Dr. Fisher is a surgeon innovator of the ATTUNE™ Knee System and he has been compensated for his time to develop this white paper.

Professor David Parkin is a health economist whose previous roles include academic research and teaching as well as Chief Economist in a region of the United Kingdom's National Health Service. He is currently Senior Visiting Fellow at the Office of Health Economics, a London UK based research organization and Honorary Visiting Professor at City, University of London. He has been compensated for his time to develop this white paper.

Executive Summary:

The rise in the global burden of knee osteoarthritis is driven by changing patient demographics and expectations, leading to increased volumes of total knee arthroplasty (TKA). There is, therefore, an urgent need to continue innovation to improve patient outcomes and satisfaction. Limited economic resources require healthcare systems to optimize their processes and effectively do more with less. It remains paramount that innovative technologies demonstrate differentiated value to the healthcare system while maintaining quality of care and ensuring access to patients at affordable prices.

The aim of this evidence brief is to collate and present a plethora of data related to TKA and the value of the ATTUNE Knee from a clinical and economic perspective.

The ATTUNE Knee has shown significant improvement in Patient Reported Outcome Measures (PROMS) including OKS, PKIP, KOOS, WOMAC, EQ-5D-3L compared to other knee systems in several clinical studies. Additionally, across various endpoints, the clinical evidence shows patients recover sooner with demonstrated improvement in functional outcomes.

1. Osteoarthritis & Total Knee Arthroplasty

Osteoarthritis (OA), the most common form of arthritis¹, is a leading cause of disability with an estimated 250 million sufferers globally.² In the United States alone 30 million patients suffer from OA,³ rising concurrently with an aging population and the growing obesity epidemic. The knee is the joint most commonly affected by OA.³

The consequent reduction in quality of life for those with knee OA has been documented in many countries including Brazil,⁵ Morocco,⁶ Netherlands,⁷ New Zealand,⁸ UK⁹ and US.¹⁰ As such, knee OA represents a substantial healthcare and socioeconomic burden to society.

Knee OA has doubled in prevalence since the mid-20th century and now accounts for more than 80 percent of the total global osteoarthritis burden.⁴

1.1 Global Epidemiology of Knee Osteoarthritis

Knee OA is more common in women than in men with 14% and 10% of the respective genders over age 60 reporting symptoms.² The majority of patients who have knee replacement surgery (TKA) are 65 or older, a growing demographic due to the aging population.

However, interestingly, Blue Cross Blue Shield in the US recently reported that knee replacement surgeries grew 18% among members 55-64 years old between 2010 and 2017.¹¹

Additionally, a recent study indicates that the average age of patients in the US undergoing knee replacement surgery has reduced from 68 to just under 66.¹² Price et al. also note the increasing number of younger patients undergoing surgery.¹³

Another factor contributing to the increased demand for total knee replacement is obesity. A study from 2016 showed that nearly 13% of the world's adult population (11% of men and 15% of women) were classified as obese.¹⁴

Leardini et al. concluded that the direct and indirect costs attributable to osteoarthritis of the knee are substantial interventions that alleviate the burden associated with osteoarthritis are, therefore, valued across multiple stakeholders.¹⁵

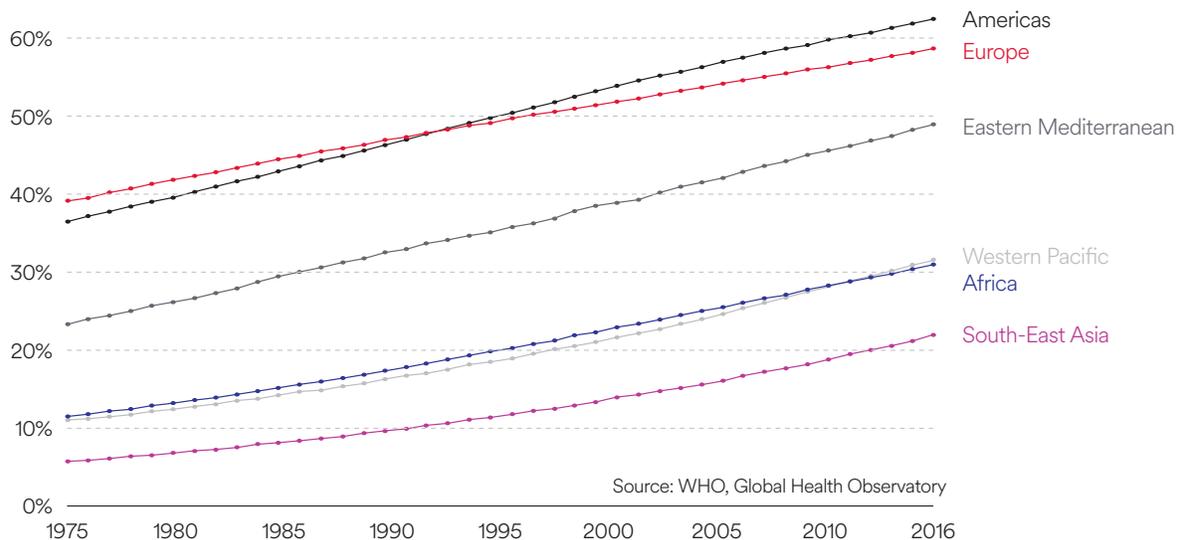


Figure 1: Share of adults aged 18 years and older who have a body-mass index (BMI) greater than or equal to 25.15

1.2 Primary TKA: A Surgical Treatment

When nonsurgical management is unsuccessful, TKA is an accepted surgical treatment option, especially in patients with severe degenerative conditions. Today, TKA is widely recognized as one of the most common and successful surgical procedures with more than 95 percent implant survivorship at 10 years.¹⁶

The exponential growth in the number of TKA procedures is projected to increase as population longevity increases, access to care improves and informed patients seek treatment options for their arthritic knees early on. As of 2018, more than 100,000 knee replacements were performed annually in the UK; in the US, the total number of procedures has reached 700,000 in the same year. The global volume of TKAs performed is expected to grow 2-3 percent annually over a 5-year horizon (2019-2024). The largest projected annual growth increases are expected in Asia Pacific (6 - 7%) and Latin America (5%), with growth rates of 1% and 2% in the US and Europe respectively.¹⁷

In the US, the estimated increase varies substantially depending on the mathematical model used, but a conservative estimate is an increase of 143% in the number of TKAs by 2050.¹⁹

With the growing population of patients needing TKAs, the importance of containing their total cost, while maintaining quality of care, will increase.

1.3 Continued Challenges for TKA

Global Requirements

While the incidence of OA is increasing globally, the access to surgical treatment is also increasing around the world. Differences in cultures and lifestyles result in different requirements of knee replacement. There is global variation in patient requirements, such as the need for high flexion to participate in traditional activities such as kneeling and sitting cross-legged, for example. For the best results, TKA systems must respond to this patient variation.

Patient Satisfaction

Patient reported outcomes show improved patient satisfaction, function and quality of life after TKA.²⁰

Issues that remain for these patients include ongoing pain or discomfort, stiffness, crepitation (noise or vibration with movement) and difficulty squatting, kneeling or negotiating stairs.^{22,23,24} The recognition that not all patients are satisfied is yet another driver for innovation in TKA.

However, up to 20% of patients are still unable to achieve their expectations of functional outcomes and are dissatisfied after TKA.²¹

2. The ATTUNE™ Knee System

2.1 ATTUNE Knee Design & Benefits

With these unmet needs in mind, the ATTUNE™ Knee System was designed by DePuy Synthes in collaboration with university researchers and a team of 35 surgeon innovators from around the world. To improve the performance of contemporary TKA, the team studied the surgical workflow, implant sizing, kinematics, patellar tracking, ligament balancing and instrumentation needs. The result was the development and testing of new concepts leading to over 30 peer-reviewed publications, close to 215 patents and the development of new methods to address clinical challenges through implant and instrument design and manufacturing.

The ATTUNE Knee is a highly versatile implant system with various options for bearing and patellar design in addition to kinematics and ligament balancing techniques. The instrument system incorporates the use of low weight composite materials designed to allow precise bone preparation, implant balancing, implant insertion and reduction of surgeon fatigue. The primary ATTUNE Knee implant was available in a limited launch in 2011 and has been commercially available globally since 2013.

Proprietary technological innovations with the ATTUNE Knee include the ATTUNE GRADIUS™ Curve, SOFCAM™ Contact, LOGICLOCK™ Tibial Base, GLIDERIGHT™ Articulation and INTUITION™ Instruments.

The ATTUNE Knee comprehensive evidence generation program comprises multiple sources of data including clinical Company-Initiated Studies (CIS), clinical Investigator-Initiated Studies (IIS), Radiostereometric Analysis (RSA), Real-World Evidence data analysis (RWE), retrospective single arm studies and global registry data to evaluate the clinical and economic outcomes of the ATTUNE Knee. Key findings from these studies are discussed in the following sections.

The patented ATTUNE GRADIUS™ Curve is the gradually reducing femoral radius designed to provide a smooth transition from stability to rotational freedom through a patient's range of motion.

SOFCAM™ Contact: The proprietary s-curve design of the SOFCAM™ Contact is designed to provide a smooth engagement for gradual femoral rollback and stability in flexion, while minimizing stresses to the tibial spine.

LOGICLOCK™ Tibial Base: The LOGICLOCK™ Tibial Base has a patented central locking design that provides the architecture for the system that optimizes kinematics. In a study comparing LOGICLOCK Tibial Base with five leading knee brands, it was found to have the lowest level of backside micromotion.²⁵

GLIDERIGHT™ Articulation: The GLIDERIGHT™ Articulation encompasses a trochlear groove designed to accommodate patient variation and soft tissue interaction as well as patella components designed to optimize patella tracking while maintaining bone coverage.

INTUITION™ Instruments: The INTUITION™ Instruments are unique in their ability to combine the surgical process with the implant options to allow the surgeon to balance the soft tissue and precisely control the implant position and fit for each patient.

2.2 Reported Functional Outcomes of the ATTUNE Knee System

Patellofemoral Function

Patellofemoral complications are a common problem encountered in TKA patients. Symptoms usually begin within 12 months of surgery and have been reported in up to 18% of patients after TKA.²⁶ Patellofemoral complications have been a cause of revision surgery in approximately 6% -11.6% of cases.²⁷⁻²⁹ Furthermore, patellofemoral complications, especially crepitus and clunk, are more common in posterior stabilized (PS) implants.³⁰ As crepitation symptoms might appear during flexion, this could be an issue for patients who enjoy active or floor-based activities.²⁶

Four peer-reviewed studies demonstrated improved patellofemoral outcomes in the ATTUNE Knee System, including reduced incidence of symptomatic crepitus compared to the SIGMA PS Knee.³¹⁻³⁴

1. In a prospective study by Toomey et al.,³¹ patellofemoral symptoms were specifically evaluated by patients and investigators. At one and two years, the cumulative incidence of symptomatic crepitus in patients with ATTUNE PS Knee implants was significantly less than that of the SIGMA™ PS Knee design, (0.78% versus 2.95% at one year and 1.21% versus 3.67% at two years). Furthermore, the risk of patellar symptoms increased 5-fold for patients achieving more than 110 degrees of flexion with one the SIGMA PS Knee, while there was no increased risk in the ATTUNE Knee patients.

2. Martin et al.³² reported a single institution study that compared the incidence of crepitus for subjects implanted with the ATTUNE PS Total Knee (N=728) and subjects implanted with the SIGMA PS Total Knee (N=1165). The results showed significantly less symptomatic patellofemoral crepitus at both one and two years post-operatively for the ATTUNE Knee versus the SIGMA Knee design (0.14% versus 2.7%, $p < 0.001$ at one year and 0.33% versus 3.9%, $p < 0.001$ at two years).
3. Ranawat et al.³³ compared 100 ATTUNE PS Knees with 100 SIGMA PS Knees. While not statistically significant, the incidence of symptomatic crepitus at two years was 1.0% for the ATTUNE Knee cohort compared to 4.1% for the SIGMA Knee cohort. Their results also demonstrated a statistically significant reduction in anterior knee pain at two years post-operation (12.5% for the ATTUNE Knee versus 25.8% for the SIGMA Knee cohort, $p = 0.02$).
4. The study by Indelli et al.³⁴ also compared 100 patients with the ATTUNE Fixed Bearing PS Knee and 100 patients with the SIGMA Fixed Bearing PS Knee. The ATTUNE Knee group had significantly less anterior knee pain (2% versus 9%), higher flexion (123 degrees versus 115 degrees, $p = 0.009$) and more patients with over 130 degrees of flexion (37% versus 16%, $p = 0.0008$). Two patients in the SIGMA Knee group required surgery for patellar clunk and there were no reoperations in the ATTUNE Knee cohort. The ATTUNE Knee patients experienced a statistically significant ($p = 0.007$) reduction in the incidence of symptomatic crepitus (1%) compared to the SIGMA Knee patients (5%).

This data suggests that certain design features, including the modified trochlear groove and corresponding patellar articulation, may lead to fewer reoperations for patellar symptoms in ATTUNE Knee patients compared primarily to SIGMA Knee patients.

In-vivo Kinematics

The ATTUNE Knee offers 10 standard and 4 narrow femoral implant sizes, allowing closer replication of femoral anatomy seen in real-world populations. Coupled with the ATTUNE GRADIUS Curve, favorable kinematics are recreated when combined with the ligament balancing and tibial bearing options available with the ATTUNE Knee. This helps to fit different anatomies and meet unmet needs for knee function globally.

A German study reporting early (6-month) clinical results from 55 prospectively analysed ATTUNE Knee patients showed significant post-operative improvement in range of motion (112 degrees pre-operation to 123 degrees post-op; $p < 0.001$) and coronal stability throughout the range of motion.³⁵

The stability tests were carried out in a standardized fashion at 0, 30 and 90 degrees of flexion. The study's authors believed that the improved kinematics observed in these patients were a result of the femoral component design and the ability to fine-tune the knee balance with 1 mm increments in polyethylene thickness. An in-vivo fluoroscopic analysis (video x-rays which allow researchers to study the relative motion of the components during activities) of the ATTUNE Knee gradually changing radius (ATTUNE GRADIUS Curve), compared to the SIGMA Knee multi-radius design, showed improved kinematic function and femoral rollback with the ATTUNE Knee.³⁶ A navigation-based kinematic study from Japan showed smooth rollback of the ATTUNE Knees compared with an abrupt change at mid-flexion with the SIGMA Knees.³⁷

Another fluoroscopic analysis of 32 patients with ATTUNE PS Knees showed consistent lateral condylar rollback with minimal anterior medial slide and no lift off during deep knee bend, gait or down ramp walking.³⁸

These 4 studies, which focus on stability, are consistent with experimental data performed by finite element analysis and previous experimental laboratory research.³⁹

These in-vivo kinematic studies demonstrate the ATTUNE Knee provides a smooth transition from extension to full flexion with maintained stability to rotational kinematics with lateral rollback in deeper flexion when compared to the SIGMA Knee.³⁵⁻³⁸

2.3 Radiosteriometric Analysis (RSA) & Survivorship

RSA Studies

This technology uses tantalum beads implanted around the knee at the time of surgery. The distance of the beads from the knee implants can be very accurately assessed using standard radiographs and changes of the implant position in any direction can be identified and followed over time. This information can indicate the stability or lack of stability in implant fixation and can be used as a tool to predict the risk of future implant loosening.

Radiosteriometric Analysis (RSA) is an established measure to help predict long-term survivorship by assessing early fixation. One RSA study performed at the Leiden University Medical Center in the Netherlands was a randomized trial of 74 ATTUNE Knees and P.F.C.™ SIGMA™ Knees.⁴⁰ Study data at one year showed no difference in RSA migration between the two knees, with both judged to be well fixed and functioning implants.

Another study from the Canadian RSA Network in Halifax evaluated 30 patients with the ATTUNE PS Fixed Bearing Tibial Base.⁴¹ This study found significant improvement in the PROMs scores and minimal micromotion of the tibial bases over the first 12 months with the average maximum total point motion (MTPM) of 0.2 mm (SD 0.10).

Additionally, the mean MTPM between 12-24 months was 0.08 mm which is well below the published threshold of 0.2 mm ($p < 0.001$)⁴² suggesting the risk of medium-to-long-term failure due to aseptic loosening is low.

Survivorship in Global Registries

The ATTUNE Knee is performing in line with its class of TKA as demonstrated by current results from a number of joint registries.^{16,27,43-46}

Per the 2022 published report from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR), the 5-year ATTUNE Fixed Bearing Knee Implant cumulative revision rate is 2.06% (1.88-2.27), while the ATTUNE Rotating Platform cumulative revision rate is 1.37% (1.03-1.83).¹⁶ Based on point estimates and confidence intervals, the ATTUNE FB Knee is performing in line with the overall class of total knee replacement for which the revision rate is 2.10% (2.07, 2.13).

ATTUNE Knee survivorship data is also available in the 2022 Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) Annual Report, in which 20,427 ATTUNE CR Knees show the estimated cumulative percent revision rate is 3.1% (2.8,3.4) at 5 years and 10,431

ATTUNE PS Knees with an estimated cumulative percent revision rate of 2.6% (2.3,3.0),²⁷ both performing favorably with their respective cemented class.

The Kaiser Permanente Total Joint Registry, a closed total joint registry in the US maintained by the Kaiser Permanente Healthcare System, began collecting data in 2001. A 2-year implant survivorship study by Kelly et. al. compared the ATTUNE FB Knee (N=1,707) and SIGMA FB Knee (N=2,984), finding no statistical difference with both having greater than 98% implant survivorship at 2 years ($p=0.638$).⁴³ None of the 1,707 ATTUNE FB Knees were revised for pain or aseptic loosening in this study.⁴⁴

2.4 Patient Reported Outcome Measures (PROMs)

PROMs Background

A primary aim of any healthcare intervention is improving patients' health or preventing its deterioration, with an important feature of modern health service provision being the ability to measure such improvements using validated tools.

While objective physiological and functional measures can report on the effectiveness of healthcare interventions, a further important indicator is patients' perceptions of their own health condition and subsequent changes to that perception post-intervention.⁴⁶ This has led to the establishment of PROMs as a key factor in evaluating the effectiveness and cost-effectiveness of healthcare technologies.

In 2006, Robert Temple from the US Food & Drug Administration (FDA) stated, "The use of PRO instruments [PROMs] is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels."⁴⁷ Additionally, a new survey by Modern Healthcare's CEO Power Panel shows that PROMs are commonly used by US hospitals and health systems.

PROMs aim to measure patients' perceptions of their health, whereas healthcare delivery surveys measure patients' experience of or satisfaction with, the care that they receive. They include such factors as whether they are treated with respect and compassion, have a comfortable care environment and are provided with enough information about their care. These are important quality measures and, while health outcomes may be influenced by patients' experience of healthcare delivery, the two are separate and measured in different ways.

PROMs are standardized, validated questionnaires that ask patients to assess their own health, often in terms of the impact of ill-health on their quality of life. They are usually

used to capture changes over time at specified time points, especially pre- and post-intervention. The responses to different questions are processed to generate either a “profile” of health – a combined summary of the responses giving a picture of health in different dimensions – or a number that gives an overall score.

73.9% of US health system Chief Executive Officers say that patient reported outcome measures are used by their organizations, reflecting the overall shift towards patient-centered care.⁴⁸

There are thousands of such PROMs available in multiple languages. Some, known as condition-specific or disease-specific measures, focus on the key dimensions related to a particular condition, treatment or symptom. Others, called generic measures, aim to capture a wide range of dimensions of ill-health and be applicable, in principle, to any condition.

PROMs used in Orthopaedic Surgery

The orthopaedic specialty is leading the way in terms of development and adoption of PROMs. Common generic measures used to assess a person’s state of health are the EQ-5D and the SF-36.^{49,50} As well as generating a “profile” in 5 and 8 dimensions respectively, these enable a score to be calculated that can be interpreted as the value of a patient’s relative health state.

The most widely used condition-specific PROMs for knee OA are the Oxford Knee Score (OKS) and the Knee injury and Osteoarthritis Outcome Score (KOOS).^{51,52} The OKS has 12 questions, each of which generates a score between 0 and 4. These are added together to give an overall score between 0 (indicating severe knee arthritis) and 48 (indicating no knee problems). KOOS, by contrast, does not calculate an overall score but generates scores from 0 (extreme symptoms) to 100 (no symptoms) in 5 subscales: Pain, Other Symptoms, Daily Living, Sports and Recreation and Knee Related Quality of Life. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) is applicable to both hip and knee conditions and can be calculated from answers given in the KOOS questionnaire.⁵³

The Patient’s Knee Implant Performance (PKIP) is a relatively new condition-specific PROM that has been specifically developed to assess the functional status of a patient’s knee from their own perspective, before and after TKA.⁵⁴ It was developed to address gaps in other common PROMs by assessing a patient’s satisfaction with their implant, which represents an innovative approach to better understand the nuances involved in outcomes for TKA patients.

PKIP has 4 subscales (Confidence, Stability, Modify Activities and Satisfaction), each of which generate a score from 0 to

10, where higher scores indicate better knee function and an overall score which ranges from 0 to 100. This measure has been shown in initial studies to perform well in terms of key psychometric criteria such as reliability, validity and responsiveness, which may help discriminate between the impact of different implant designs and surgical techniques.⁵⁵ It is important to note that “satisfaction,” here, refers to the implant, which enables a proper assessment of the procedure itself, rather than more general patient satisfaction with the care that they receive, which will be influenced by the environment in which care is provided.

The Use of PROMs

PROMs have many uses but assessing the results of a healthcare intervention usually requires changes in health over time to assess outcome measures. Typically, this requires patients to complete PROMs questionnaires both before and after the intervention.

Although PROMs are widely used in clinical trials and observational studies, they are also increasingly collected routinely for many different purposes including in clinical practice, in joint registries (for example in England, Wales, Northern Ireland and Isle of Man and New Zealand) and as part of quality monitoring and improvement programs.⁵²

For TKA, this may be referred to as “pre-operative” and “post-operative” health states or “baseline” and “follow-up”. It is important to ensure that these assessments are carried out at times that will properly reflect the period over which improvements will be realized and that there are further assessments for possible longer-term effects. For example, a common post-operative PROMs assessment for TKA is six months, but, in some cases, the follow-up will also be at one year or longer, enabling a profile of changes over time to be assessed.

ATTUNE Knee PROMs - Clinical Use of PROMs

DePuy Synthes has sponsored 2 prospective clinical trials assessing the PROMs of patients undergoing TKA. PROMs data collection was identical in both studies including assessments and follow-up windows (Table 1).⁵⁶

From this data, a direct comparison of 752 SIGMA Knees and 1,129 ATTUNE Knees was completed. Subject demographics were similar between the groups and surgeries were performed by the same surgeons. In addition

to the previously mentioned PROMs, an OMERACT-OARSI responder analysis was performed to compare the rates of high responders or the number of patients with the best scores in each group. Radiographic interpretations and implant survivorship curves were recorded at the same time intervals.

	Study #1 Current Product	Study #2 ATTUNE Knee
Population (Geography)	USA, UK, Aus, NZ 19	USA, UK, Aus, NZ 23 (18 from Study #1)
Sites		
Number of Cases	752 Knees	1,129 Knees
Intervention	SIGMA® Knee 89%, Triathlon 7%, NexGen 3%, Other 1%	ATTUNE
Study Design	Single arm	Single arm
Data Collection	Pre-surgery, <1 year post-op, 1 year, 2 years	Pre-surgery, <1 year post-op, 1 year, 2 years
PROMs Measured	OKS, PKIP, KOOS, WOMAC, EQ-5D-3L	OKS, PKIP, KOOS, WOMAC, EQ-5D-3L

Table 1: Identical data collection in two DePuy Synthes-sponsored prospective clinical trials.⁵⁶

The OMERACT-OARSI responder analysis is a method to record the individuals with the highest response rate to a given intervention, represented by the percentage of all responders.^{57,58}

2-year results from these two global studies showed improved patient reported outcomes with the ATTUNE Knee compared to other leading knee systems including confidence in knee performance, increased activities of daily living and quality of life.^{58,59}

Study results showed that, at 2 years, the ATTUNE Knee had significantly better scores in the KOOS subscales of Activities of Daily Living, Sport & Recreation, and Quality of Life compared to the SIGMA Knee outcomes (Table 2). While the OKS scores were higher for the ATTUNE Knee, it was not statistically significant. For the PKIP subscales, the Overall, Confidence and Stability scores were significantly better for the ATTUNE Knee, and the 2-year OMERACT-OARSI responder analysis showed significantly more High and Moderate Responders for ATTUNE Knee patients in both the OKS and WOMAC scores.⁵⁶

The ATTUNE Knee has shown significant improvement in PROMs including OKS, PKIP, KOOS, WOMAC and EQ-5D-3L compared to other knee systems in several clinical studies. A study by van Loon et al. followed 200 ATTUNE Knee patients through their recovery, recording PROMs of KOOS-PS, PKIP and EQ-5D scores through 2 years post-operatively. They found the greatest rate of improvement in the first 6 weeks following surgery, with 80% of the improvement in scores occurring in the first 6 months.⁶⁰ Similarly, a single surgeon series of 500 ATTUNE Knees and

		1yr CFB Mean (SD)			2yr CFB Mean (SD)		
		SIGMA	ATTUNE	p-value	SIGMA	ATTUNE	p-value
Activities of Daily Living	0-100	34.9 (19.87)	38.1 (19.32)	0.0012	36.8 (20.49)	39.3 (19.56)	0.0169
Pain	0-100	38.2 (20.36)	42.3 (19.79)	<0.0001	40.6 (20.59)	44.4 (19.70)	0.0002
Symptoms	0-100	30.2 (22.24)	33.4 (21.76)	0.0035	33.6 (21.95)	37.3 (21.34)	0.0011
Sports & Recreation	0-100	35.1 (31.22)	41.6 (29.96)	<0.0001	40.8 (31.79)	46.2 (29.75)	0.0008
Quality of Life	0-100	44.6 (25.83)	48.8 (25.80)	0.0014	48.7 (26.64)	52.4 (25.19)	0.0045

Table 2: Changes in KOOS subscales for ATTUNE Knee and SIGMA Knee patients at one year and two years post-surgery. Bold indicates statistical significance (p < 0.01).^{56,59} CFB = Change from Baseline

500 SIGMA Knees showed better 2-year OKS scores in the ATTUNE Knee group, as well as better implant survivorship for the ATTUNE Knee at 4 years of clinical follow up.⁶¹

Analysing ATTUNE Knee and SIGMA Knee patients’ health states using the EQ-5D-3L

Clinical studies often report index numbers that combine different aspects of patients’ health, as measured by their responses to a PROMs questionnaire, into a summary measure. The responses, themselves, are usually not analysed and reported; however, they contain useful information at a level of detail hidden using index numbers.

For most PROMs, their complexity means that it is difficult to analyse this more detailed information; however the EQ-5D-3L is sufficiently uncomplicated to allow for this type of analysis.

For example, the OKS implicitly defines over 244 million different health states. However, one of them, the EQ-5D-3L, is sufficiently uncomplicated to permit this to be done, defining just 243 different health states.

In order to provide insights into patients’ Health Related Quality of Life (HRQOL) and the impact of TKA treatment that may be obscured by using an overall index number, a novel analysis of individual dimensions, levels and combinations thereof over time was recently undertaken. Data from the two clinical trials mentioned above was used for the analysis.⁵⁶

The EQ-5D-3L questionnaire collects data from patients on 5 aspects of their HRQOL, called dimensions: Mobility; Self-

Care; Usual Activities; Pain & Discomfort; and Anxiety & Depression. Patients select one of 3 levels to describe problems they have in each dimension, essentially: No Problems, Some Problems or Extreme Problems. This allows for analysis within dimensions, profiles and categories of change to assess pre- and post-surgery differences. These changes can be compared over time and across different knee replacement systems.

EQ-5D Profiles

Patients’ overall HRQOL can be described by a unique combination of each dimension’s level, called an ‘EQ-5D profile.’ Each has a label consisting of 5 numbers, one for each dimension, giving the level from 1-3 for a total of 243 possible profiles.

For example, a patient who recorded some problems in walking about (Mobility level 2), No problems with self-care (Self-Care Level 1), unable to perform their usual activities (Usual Activities Level 3), moderate pain or discomfort (Pain & Discomfort Level 2) and moderate anxiety or depression (Anxiety and Depression Level 2) would be labelled 21322. Figure 4 stratifies the percentage of ATTUNE Knee patients by each of the three levels reported per dimension at 3 time points: pre-surgery; up to 10 months post-surgery (< 1 year); and 10-22 months post-surgery (> 1 year).

For ATTUNE Knee patients pre-surgery, Pain & Discomfort was the most frequently reported problem, Usual Activities and Mobility problems were also frequent; a minority had problems with Self-Care and Anxiety & Depression.

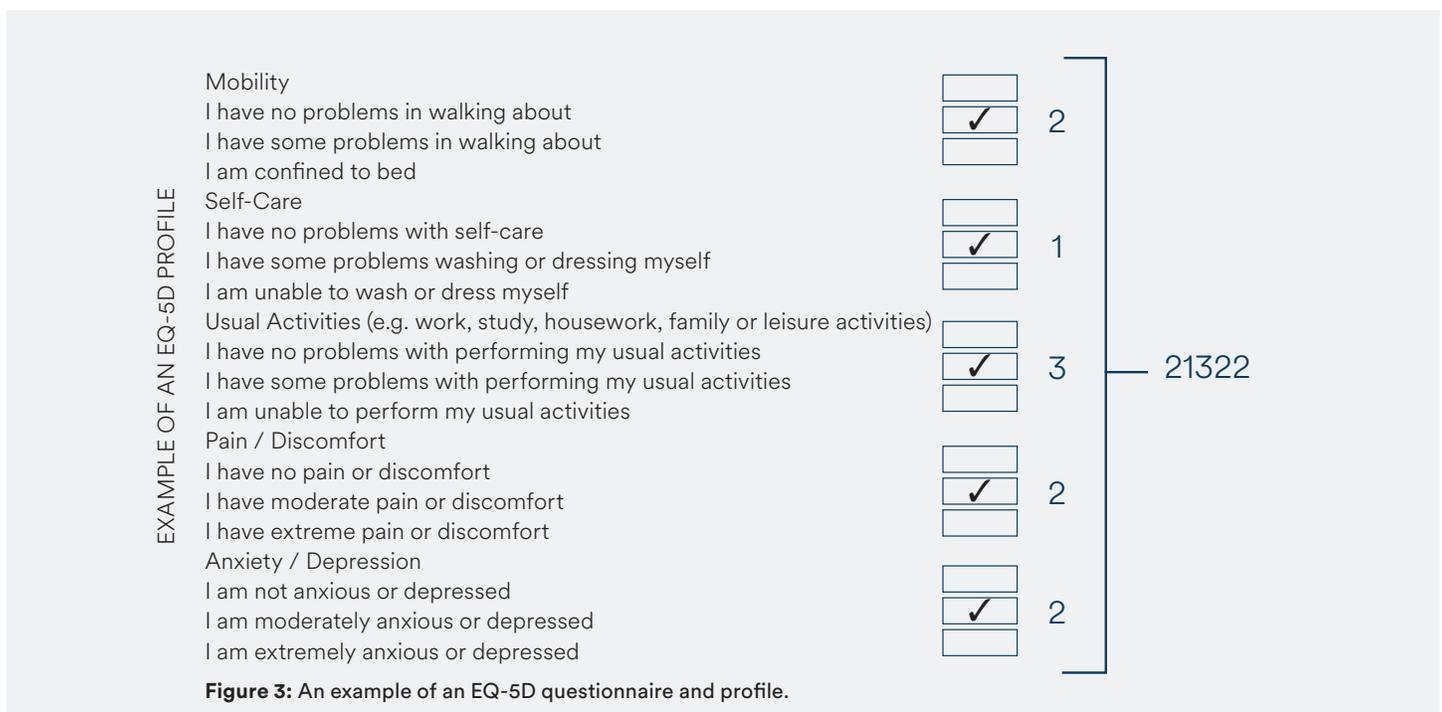


Figure 3: An example of an EQ-5D questionnaire and profile.

Post-surgery, there were large improvements in every dimension for ATTUNE Knee patients; however, the time over which they were observed differed. Mobility, Self-Care and Anxiety & Depression mainly improved in the first year while Usual Activities and Pain & Discomfort had continued improvements over 2 years.

Key findings suggest that, although pre-surgery ATTUNE Knee patients had worse mobility, including extreme problems; Post-surgery, a greater proportional reduction in mobility problems was reported compared to SIGMA Knee patients.⁵⁹ For example, pre-surgery 85.8% of ATTUNE Knee patients reported problems with Usual Activities, compared with 86.8% of SIGMA Knee patients; post-surgery the figures were 28.5% and 31.8%, giving a reduction of 57.3 and

54.9 percentage points (pp) respectively. The reductions in percentage points were similar for Pain & Discomfort (56.6, 51.1 pp), but even greater for Mobility (64, 60 pp). Anxiety & Depression and Self-Care were lesser problems pre-surgery, but they also demonstrated improvements post-surgery that were greater for ATTUNE Knee patients (24.9, 19.2 pp; 16.8,12.6 pp).

Identifying changes in patients' overall health state

Using the EQ-5D, it is possible to classify changes in patients' HRQOL into 4 groups:

- Improve - an improvement in at least one dimension and no deterioration in any other dimension
- Worsen - a deterioration in at least one dimension and no improvement in any other dimension

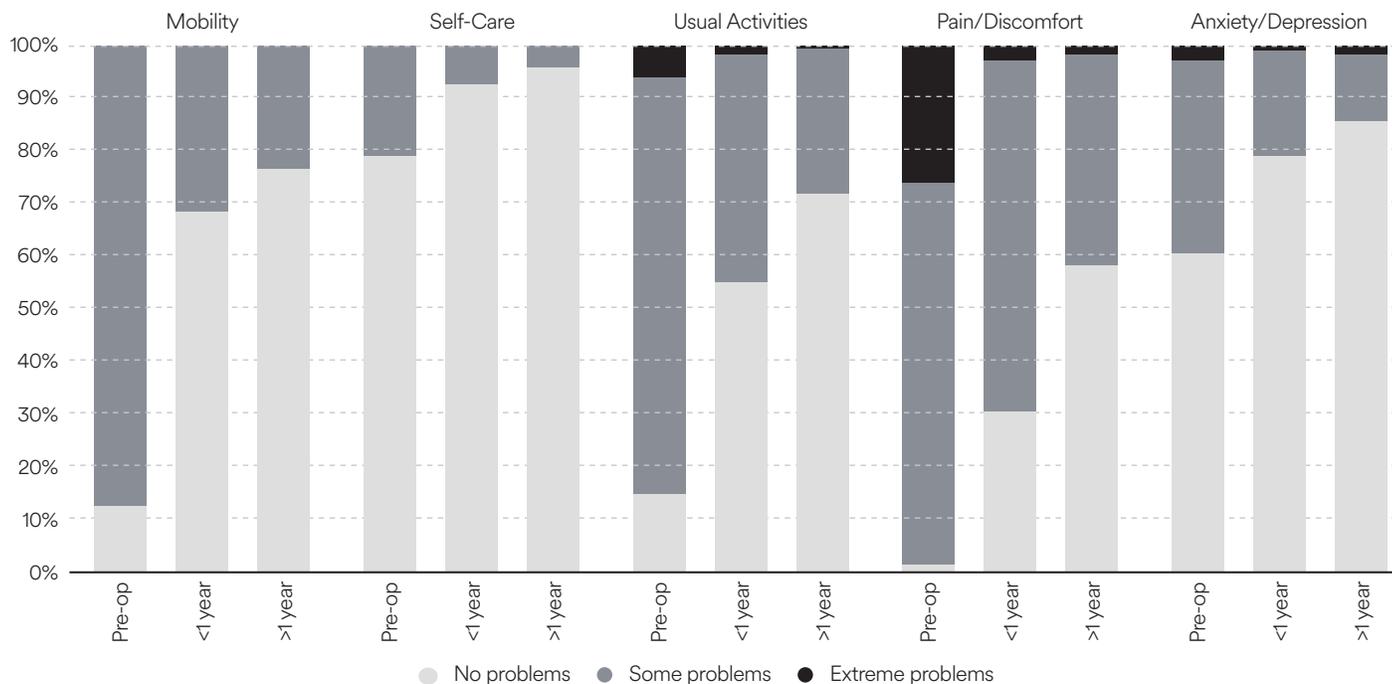


Figure 4: Percentage of ATTUNE Knee patients by level within EQ-5D-3L dimensions at different observation points.⁵⁹

- No change - no change in any dimension
- Mixed - an improvement in at least one dimension and a deterioration in at least one dimension

Table 3 compares these change categories for ATTUNE Knee and SIGMA Knee patients up to and after one year. 77% of ATTUNE Knee patients improved in the first year post-surgery, rising to 86% in the following year. Whereas only 8% worsened in the first year, falling to 3% in the following year. Compared to SIGMA Knee patients, at both the first and second years post-surgery, a greater percentage of ATTUNE Knee patients improved, fewer worsened or had no change and fewer had a mixed change.⁶²

Of those patients who worsened overall, they very rarely worsened in Mobility and Pain, the dimensions that surgery affects directly; those who worsened overall did so in the other dimensions.

There was no evidence that a patient’s pre-surgery quality of life can predict whether they will improve or worsen.

2.5 The Economics of TKA

Converting PROMs to QALYs

PROMs that, like the EQ-5D and the SF-36, generate a single score representing the value of a health state can be used to calculate Quality Adjusted Life Years (QALYs). QALYs are a measure that combine length of time and health-related quality of life into a single score.

For example, a person who enjoys a year without any health problems would generate one QALY; someone who had a quality of life value of 80% would have 0.8 QALYs for that year. If there were an intervention that would cure the second person’s health problem, they would gain 0.2 QALYs each year. If that improvement lasted for 10 years, they would gain 2 QALYs, the equivalent of 2 additional life years with no health problems.

QALYs are a particularly useful measure of benefit that ensure procedures like TKA, which do more to improve patient’s quality of life than reduce mortality, are judged fairly in comparison with procedures that extend life expectancy. TKA is a well-established, cost-effective procedure, which generates improvements in patients’ quality of life.²⁰

Multiple scientific studies in countries including the US, UK, Finland and Spain have concluded that TKA is the most cost-effective means of managing osteoarthritis, according to standards that are widely accepted in developed countries.⁶³⁻⁶⁶

Economic decision-makers assess the value of a given technology by weighing the incremental cost against the incremental benefit of a new intervention versus the current standard of care.

In the UK, a study analyzed data from a large, randomized trial of different knee prostheses measuring both costs and quality of life.⁹

They estimated an average cost-effectiveness ratio of £5,623 per QALY gained, using conservative assumptions about the extent of changes in costs and quality of life due to TKA. This ratio is well below £20,000 per QALY gained, which is a threshold defined by National Institute for Health and Care Excellence (NICE) at which pharmaceutical and other interventions are, without further qualification, accepted for funding. Moreover, although patients’ age, gender and baseline severity, as measured by ASA (American Society of Anesthesiologists) grade and OKS score, impacted on cost-effectiveness, there are very few eligible patients for whom the cost per QALY gained exceeds the NICE threshold. Although TKA costs more for patients who had worse pre-operative health states, the greater QALY gains they achieved meant it was more cost-effective than for patients with only moderate symptoms.⁹

	ATTUNE Knee				SIGMA Knee			
	< 1 year		> 1 year		< 1 year		> 1 year	
	N	%	N	%	N	%	N	%
Improve	816	76.5	833	86.1	534	73.9	552	83.8
Worsen	83	7.8	30	3.1	51	7.1	27	4.1
No change	90	8.4	60	6.2	75	10.4	36	5.5
Mixed	77	7.2	45	4.6	63	8.7	44	6.7
Total	1066		968		723		659	

Table 3: Changes in overall Health Related Quality of Life for ATTUNE Knee and SIGMA Knee patients at up to and after one year post-surgery.⁶²

This study also examined the impact of different assumptions about factors that affect cost-effectiveness. This included the length of stay in hospital following the procedure, confirming that shorter hospital stays would improve cost-effectiveness.

In 2016, a study using NJR data compared the relative cost-effectiveness of different implants.⁶⁵ In identifying the most cost-effective option, they found that the main determinant was differences between the implants in the post-operative quality of life they generate for patients. For the range of implants covered, factors such as their cost and revision rates were less important. Improving patients' quality of life was found to be the key difference that determined their relative cost-effectiveness. Moreover, the differences in measured post-operative quality of life between implants were relatively small, but they had a large impact on cost-effectiveness. This further emphasizes the importance of this factor because what may appear to be small changes in quality of life at a single point of time can translate into large changes in QALYs if the improvement is sustained over a long period of time. This study covered TKAs implanted between August 2008 and July 2012. Since then, new implants have been introduced which may affect the conclusions. The evidence suggesting that TKA is highly cost-effective in terms of improvements to patients' quality of life applies to all relevant age groups.

Additional benefits may be applicable to TKA patients whose ability to work is affected by knee problems. TKA could enable such individuals to continue working, which is beneficial on both personal and societal levels. These are known as indirect costs, by contrast to the direct costs of healthcare that arise from either TKA or its alternatives. Ruiz et al. estimated the total additional direct costs of TKA over the lifetime of a patient in the US to be on average \$20,635 (in 2009 dollars), offset by a reduction in lifetime indirect costs of \$39,565.⁶⁷ TKA, therefore, generates an average societal savings of \$18,930 per patient. Most of these savings directly benefit patients by increasing their employment potential and earnings, but there is a wider benefit to society of increased production and reduced disability payments.

The full cost of a TKA includes resources that are used within the hospital, including overheads and costs directly associated with the surgical procedure such as operating room staff, physicians, implants and disposables.

There are also costs of providing nursing care and therapy after surgery. Upon discharge, patients usually continue rehabilitation with the attendant costs of ongoing treatments. Some of them require placement in skilled nursing facilities or rehabilitation units. Bozic et al. found that up to 35% of the costs of an episode was related to care after discharge.⁶⁸

Unpredictable events such as complications and readmissions can also add considerably to costs.

In many countries, a global evaluation of the episode of care is a major focus. The mandatory bundled payment initiatives in the US are one example. These involve a 90-day window of time where all associated costs are included within the bundle. This process creates incentives for hospital systems to improve patient care management following TKA procedures. Hospitals must manage the total costs for a given procedure, including post-acute care. Any complications or readmissions will greatly increase the chances of the hospital exceeding this fixed price and, therefore, owing a penalty payment back to Medicare (CMS). This puts additional risk on the providing hospital but allows the payer, for example Medicare, better forecasting of the cost of care to a given population. With the growing population of patients needing TKAs, it is critically important to reduce the total cost of this procedure, subject to maintaining quality of care.

In England, healthcare providers are reimbursed by healthcare commissioners under the "Payment by Results" system. Each patient treated is assigned to a Healthcare Resource Group (HRG), similar to the Diagnosis Related Group (DRG) classification found in the US and other countries' healthcare systems, for which there is a "tariff" payment covering all inpatient services. Knee replacements are one of a few procedures that are reimbursed using a "Best Practice Tariff," which offers a much larger payment to providers who provide a high standard of performance, such as minimum average improvements in PROMs scores and good data provision, including rates of registration with the National Joint Registry (NJR). They also attract a special additional tariff for post discharge rehabilitation care that follows a defined clinical pathway, including specified numbers of nurse, physiotherapist and occupational therapy appointments and consultant-led clinic visits.

Globally, each element of cost for the episode of care is under review for potential cost savings by hospital systems. Length of hospital stay and post-discharge disposition are two areas under review by payers and providers. Decreasing length of stay clearly reduces the cost of inpatient care. With established protocols and procedures, it can be done safely with many patients now being discharged directly home within 48 hours.⁶⁹ The use of skilled nursing and rehabilitation units has also been identified as high-cost items associated with between 35% and 50% of the episode of care cost and efforts to rationalize the use of these facilities are underway.^{68,70}

The ATTUNE Knee & Resource Utilization Reduction

Recovery from TKA is a process that takes time. Most patients will experience an acute, rapid recovery phase occurring in the first 6 weeks. Efforts to enhance early recovery from TKA have included pre-operative exercises, less invasive surgical approaches, aggressive physical therapy pathways, pain management protocols and educational efforts to help prepare patients for the recovery phase of their treatment. While some of these have been shown to reduce length of hospital stay and made the recovery more tolerable for many patients, surgical pathways and implant design may also contribute to the speed of recovery.

This recovery is mainly the result of soft tissue healing and the remodeling process that occurs following surgery. Recovery rates vary between patients; but, in general, TKA patients will continue to have difficulties over the following 6 to 12 weeks with start-up stiffness, discomfort, difficulty sleeping through the night and weakness going up and down stairs.

While length of stay, rehabilitation time and return of function are multifactorial, implant design and surgical technique may be contributing factors. The ATTUNE Knee was designed to allow surgeons to provide stability and anatomical reconstruction of the arthritic knee. With 14 primary femoral sizes, 10 tibial sizes and 1 mm increments in polyethylene thickness, the options to size and balance

the knee. Improving construct stability was one way the design team felt they could impact function with activities such as climbing and descending stairs.

Another effect of this construct stability may be enhanced post-operative recovery. While patient reported outcomes up to two years have favored the ATTUNE Knee versus other leading knee systems, some early recovery data also lends support.

Length of stay

Retrospective data analysis studies in different countries have reported lower lengths of stay (LoS) for ATTUNE Knee patients compared with patients who received other knee systems.

A study by Etter et al. using US claims data of hospitals and surgeons from 2013-2014 found ATTUNE Knee patients had a statistically significantly lower length of stay than those who received the Triathlon® Knee System, by an average of 0.19 days (2.94 versus 3.13; $p < 0.010$) adjusted for case-mix.⁷¹ Sensitivity analyses in this study indicated that these effects could not be explained by patient factors including age, insurance or marital status. A review of medical records in a UK public hospital found that ATTUNE Knee patients stayed

on average 1 day less than similar patients who received the Columbus system and 0.8 days less than SIGMA Knee patients.⁷² Similar studies, involving one surgeon, reported a 4-day shorter LoS for ATTUNE Knee patients compared with SIGMA Knee patients in Italy and a 0.8 day shorter LoS in the Netherlands.^{73,74} The latter finding was despite an established enhanced recovery program. A study in a private clinic in Germany reported a 2.1 day shorter LoS for ATTUNE Knee patients compared with those who received the LCS™ Total Knee System.⁷¹

These results are important for healthcare systems that are interested in reducing length of stay. The variation in the estimated size of impact of the ATTUNE Knee emphasizes this will depend on factors like the individual hospital and healthcare system. Even where the reduction seems small expressed in per patient terms, this may be important where there is a large volume of patients.

For example, in the UK lower LoS has been found to reduce cost enough to improve the cost-effectiveness ratio.⁹

Compared with other leading systems, ATTUNE Knee patients in different countries had a shorter LoS (US, UK, Germany, Italy, the Netherlands) and reduced incidence of referral to rehabilitation settings (US, the Netherlands).

Discharge Disposition

The US claims data study also found the adjusted odds of ATTUNE Knee patients in the dataset being discharged to a skilled nursing facility were 39% lower than for the Triathlon® patients.⁷¹ The Netherlands study showed discharge to a rehabilitation centre was significantly lower for the ATTUNE Knee patients (4.4%) compared with SIGMA Knee patients (11.4%).⁷⁴ Because such specialist post-acute care facilities are comparatively very expensive, reduced use of them is also likely to improve cost-effectiveness.

3. Conclusions

Knee osteoarthritis has doubled in prevalence since the mid-20th century representing a significant healthcare and socioeconomic burden. With the growing population of patients needing TKAs, it is critically important to reduce the total cost, subject to maintaining quality of care.

Survivorship of modern knee replacements sits at 95% at 10 years. Despite this, up to 20% of patients remain dissatisfied with their outcome. The ATTUNE Knee addresses challenges in knee replacement, including patient dissatisfaction, crepitus, survivorship and fixation.

The ATTUNE Knee has shown significant improvement in PROMs including OKS, PKIP, KOOS, WOMAC, EQ-5D-3L compared to other knee systems in several clinical studies. Additionally, across various endpoints, the clinical evidence shows patients recover sooner with demonstrated improvement in functional outcomes compared to the SIGMA Knee.

Despite heterogeneity in both aspects of care delivery (e.g. healthcare systems, pathways of care and clinical practice) and patient factors (e.g. patient demographics and expectations) related to TKA procedures, the ATTUNE Knee has demonstrated favorable results in clinical and real-world data across multiple geographic settings.



4. Continued Innovation of the ATTUNE™ Knee Portfolio

The ATTUNE Knee technologies have been incorporated across the entire ATTUNE Knee System portfolio. The tibial base with ATTUNE S+™ Technology was developed to help address the industry-wide challenge of aseptic tibial loosening. The ATTUNE Revision Knee System offers comprehensive solutions that are designed to simplify complex revision TKA procedures through enhanced fixation, improved stability and increased operating room efficiency. Furthermore, the ATTUNE Cementless Knee provides the opportunity for biologic fixation for younger, more active patients.

The ATTUNE S+™ Technology was designed to enhance tibial fixation with its innovative combination of macrolock features and a microblast surface finish on the tibial base. These features are designed to provide greater residual pull off strength under a range of simulated intra-operative conditions and the presence of lipid infiltration.

The ATTUNE™ Revision Knee System takes the proprietary technology and benefits of the design to address unique revision surgery challenges through improved kinematics, fixation, patient fit and OR efficiencies through streamlined workflows. With both fixed-bearing and rotating platform options, it is one of the most comprehensive revision knee systems available on the market today.

The ATTUNE™ Cementless Knee combines the performance of the ATTUNE Knee with the opportunity for biologic fixation with POROCOAT™ Porous Coating and improved OR efficiency, designed with younger, more active patients in mind.

The ATTUNE Knee System is a knee portfolio with kinematics that work in harmony with the patient's anatomy to deliver improved functional outcomes and patient performance in a dynamic world that demands STABILITY IN MOTION™.

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Table KT9 Cumulative Percent Revision of Cemented Primary Total Knee Replacement by Prosthesis Combination

Femoral Component	Tibial Component	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	10 Yrs	15 Yrs	20 Yrs
ACS	ACS Fixed	23	735	1.5 (0.9, 2.8)	2.8 (1.8, 4.3)	3.6 (2.4, 5.4)			
	ACS Mobile	30	1310	0.8 (0.4, 1.5)	1.9 (1.2, 2.9)	3.1 (2.1, 4.6)			
Active Knee	Active Knee	121	3280	0.9 (0.6, 1.3)	2.7 (2.2, 3.4)	3.7 (3.0, 4.5)	5.4 (4.5, 6.6)	7.9 (5.3, 11.6)	
Advance	Advance II	63	850	1.5 (0.9, 2.6)	4.3 (3.1, 5.9)	5.1 (3.8, 6.8)	7.1 (5.5, 9.1)	8.0 (6.2, 10.4)	
Anatomic	Anatomic	29	1263	1.2 (0.7, 1.9)	2.8 (1.9, 4.0)	2.8 (1.9, 4.0)			
Apex Knee CR	Apex Knee	56	4926	0.5 (0.4, 0.8)	1.2 (0.9, 1.6)	1.8 (1.3, 2.4)			
Apex Knee PS	Apex Knee	133	5548	0.8 (0.6, 1.0)	2.3 (1.9, 2.8)	3.1 (2.6, 3.8)			
Attune CR	Attune	473	20427	0.9 (0.8, 1.0)	2.3 (2.1, 2.5)	3.1 (2.8, 3.4)			
Attune PS	Attune	206	10431	0.9 (0.7, 1.1)	2.1 (1.8, 2.4)	2.6 (2.3, 3.0)			

Table KT12 Cumulative Percent Revision of Primary Total Knee Replacement (Primary Diagnosis OA)

Knee Class	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	10 Yrs	15 Yrs	20 Yrs
Total Knee	25251	711978	1.0 (1.0, 1.0)	2.5 (2.4, 2.5)	3.2 (3.2, 3.3)	4.7 (4.7, 4.8)	6.4 (6.3, 6.5)	8.0 (7.8, 8.3)
TOTAL	25251	711978						

Note: Restricted to modern prostheses

Table KT13 Primary Total Knee Replacement by Reason for Revision (Primary Diagnosis OA)

Reason for Revision	Number	Percent
Infection	6724	26.6
Loosening	5667	22.4
Instability	2427	9.6
Pain	2020	8.0
Patellofemoral Pain	1994	7.9
Patella Erosion	1655	6.6
Arthrofibrosis	989	3.9
Fracture	893	3.5
Malalignment	584	2.3
Wear Tibial Insert	351	1.4
Lysis	340	1.3
Incorrect Sizing	253	1.0
Metal Related Pathology	113	0.4
Other	1241	4.9
TOTAL	25251	100.0

Note: Restricted to modern prostheses

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‡Bench testing may not be indicative of clinical performance.

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DePuy Orthopaedics, Inc.
700 Orthopaedic Drive
Warsaw, IN 46582
USA
Tel: +1 (800) 366-8143
Fax: +1 (800) 669-2530

DePuy International, Ltd.
St Anthony's Road
Leeds LS11 8DT
England
Tel: +44 (0) 113 270 0461

DePuy Ireland UC
Loughbeg, Ringaskiddy
Co. Cork, Ireland
Tel: +353 21 4914 000
Fax: +353 21 4914 199