

Patient Specific Alignment, Anatomy, Recovery and Outcome in Total Knee Arthroplasty

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Authorship Attribution

This work includes a number of published and submitted papers for which I am the corresponding author in addition to papers in which I have significantly contributed to. Chapter 1 further details these contributions, but in brief these are:

Chapter 3 of this thesis was submitted as: Twiggs JG, Wakelin EA, Salazar J, Parker DA, Baré J, Miles BP, *Unexpectedly High Incidence of Anatomical Deformity Across a Population of Prospective TKR Patients*. Article under review: The Journal of arthroplasty

I designed the study, performed all data analysis, interpreted the findings for the discussion and wrote the methods and results sections of the manuscript.

Chapter 4 of this thesis is published as: Twiggs JG, Dickison DM, Kolos EC, Wilcox CE, Roe JP, Fritsch BA, et al. *Patient Variation Limits Use of Fixed References for Femoral Rotation Component Alignment in Total Knee Arthroplasty*. The Journal of arthroplasty. 2018;33:67-7

I designed the study, performed all data analysis, wrote scripts for extraction and compilation of data generated by other contributing authors, directed the review for the introduction and wrote the results and discussion sections of the manuscript.

Chapter 5 of this thesis is published as: Wakelin EA, Tran L, Twiggs JG, Theodore W, Roe JP, Solomon MI, et al. *Accurate determination of post-operative 3D component positioning in total knee arthroplasty: the AURORA protocol*. J Orthop Surg Res. 2018;13:27

I developed the technique reviewed in this paper, designed the study and directed the introduction and discussion sections including all results analysis of the manuscript.

Chapter 6 of this thesis was submitted as: Twiggs JG, Wakelin EA, Salazar J, Roe JP, Solomon M, Parker DA, Fritsch B, Liu D, Miles BP, Ruys A. *Surgical Alteration of the Coronal and Axial Knee Alignment During TKA Correlates with Poor Patient Reported Symptomatic Outcome* Article under review: The Knee

I designed the study, performed all data analysis and wrote the methods, results and discussion from which co-authors separated elements of the discussion and derived the introduction.

Chapter 7 of this thesis is published as: Theodore W, Twiggs J, Kolos E, Roe J, Fritsch B, Dickison D, et al. *Variability in static alignment and kinematics for kinematically aligned TKA*. Knee. 2017;24:733-44.

I co-designed the study with the lead author in addition to performing all data analysis and writing first drafts of the methods, results and directing the discussion and analysis.

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I designed the study and performed all data compilation and statistical and research analysis, as well as drafting and editing all sections of the manuscript.

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I co-designed the study, performed data analysis and developed the tool being studied, as well as drafting and editing all sections of the manuscript.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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22-September-2019

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Andrew Ruys

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Abstract

Total knee arthroplasty (TKA), despite being an otherwise highly successful medical operation, has a recurrent problem of dissatisfaction and recurrent pain rates in the 15-20% range. A variety of factors contribute to this incidence of dissatisfaction which can broadly be considered to fall into one of three groups: factors driven by the surgical outcome, pre-existing factors relating to the patients psychology, appropriateness for surgery or expectation level, and factors driven by the patient's recovery and their management during that recovery process. With consideration to the extensive variation between patients, it is reasonable to posit that addressing patient specific factors in selection for surgery, alignment of components during surgery and post-operative management may reduce the instance of post-operative dissatisfaction.

The first goal of this thesis was to understand the variation of patient anatomy as it relates to standard practice in TKA. Following the finding of extensive variation, a bio-mechanical rigid body dynamics simulation of the knee joint was developed to determine the degree to which this variation was reflected in the kinematic behaviour of the implanted knees. Later studies showed extensive kinematic variation that was responsive to variation in the alignment of the components as well as well as significantly related to patient reported outcome. Later studies further investigated how outcome related to patient selection for surgery and recovery of the patient as measured with simple activity monitoring.

From this work, a pre-operative simulation assessment tool has been developed, the Dynamic Knee Score (DKS), and paired with selection and recovery management tools forms the basis of 360 Knee Systems surgical planning and patient management, which has been used in over 3,000 primary TKA's to date.

Achievements

Publications

1. Twiggs JG, Wakelin EA, Salazar J, Parker DA, Baré J, Miles BP, *Unexpectedly High Incidence of Anatomical Deformity Across a Population of Prospective TKR Patients*. Article under review: The Journal of arthroplasty
2. Twiggs JG, Dickison DM, Kolos EC, Wilcox CE, Roe JP, Fritsch BA, et al. *Patient Variation Limits Use of Fixed References for Femoral Rotation Component Alignment in Total Knee Arthroplasty*. The Journal of arthroplasty. 2018;33:67-7
3. Wakelin EA, Tran L, Twiggs JG, Theodore W, Roe JP, Solomon MI, et al. *Accurate determination of post-operative 3D component positioning in total knee arthroplasty: the AURORA protocol*. J Orthop Surg Res. 2018;13:27
4. Twiggs JG, Wakelin EA, Salazar J, Roe JP, Solomon M, Parker DA, Fritsch B, Liu D, Miles BP, Ruys A. *Surgical Alteration of the Coronal and Axial Knee Alignment During TKA Correlates with Poor Patient Reported Symptomatic Outcome* Article under review: The Knee
5. Theodore W, Twiggs J, Kolos E, Roe J, Fritsch B, Dickison D, et al. *Variability in static alignment and kinematics for kinematically aligned TKA*. Knee. 2017;24:733-44.
6. Twiggs JG, Wakelin EA, Roe JP, Dickison DM, Fritsch BA, Miles BP, et al. *Patient-Specific Simulated Dynamics After Total Knee Arthroplasty Correlate With Patient-Reported Outcomes*. The Journal of arthroplasty. 2018;33:2843-50.
7. Twiggs J, Salmon L, Kolos E, Bogue E, Miles B, Roe J. *Measurement of physical activity in the pre- and early post-operative period after total knee arthroplasty for Osteoarthritis using a Fitbit Flex device*. Med Eng Phys. 2018;51:31-40.
8. Twiggs JG, Wakelin EA, Fritsch BA, Liu DW, Solomon MI, Parker DA, et al. *Clinical and Statistical Validation of a Probabilistic Prediction Tool of Total Knee Arthroplasty Outcome*. The Journal of arthroplasty. 2019.

Conference Presentations

1. Mechanical and Kinematically Aligned TKA Simulation Results of a Series of Patients
Brad Miles, Justin Roe, David Dickison, Willy Theodore, Joshua Twiggs, Jim Pierrepont, Bede O'Connor, David Liu, Brett Fritsch
International Society for Technology in Arthroplasty Annual Congress, Sydney, October 2012
2. Static Measurements of Tibio-Femoral Alignment do not Represent Functional Alignment in TKR Patients
David Dickison, Willy Theodore, Joshua Twiggs, Jim Pierrepont, Bede O'Connor, Brad Miles
Australian Knee Society Annual Science Meeting, Hamilton Island, October 2013
3. Mechanical and Kinematically Aligned TKA Simulation Results of a Series of Patients
Brad Miles, Justin Roe, David Dickison, Willy Theodore, Joshua Twiggs, Jim Pierrepont, Bede O'Connor, David Liu, Brett Fritsch
International Society for Technology in Arthroplasty Annual Congress, Vienna, September 2015
4. Static Measurements Of Tibio-Femoral Alignment Do Not Represent Functional Alignments In TKA Patients
Joshua Twiggs, Brad Miles, Justin Roe, Brett Fritsch
Australian Orthopaedic Association, Brisbane, October 2015
5. Component Alignment Variation In Navigated TKAs And Patient Reported Outcomes
Brett Fritsch, Joshua Twiggs, Justin Roe, Brad Miles
Australian Orthopaedic Association, Brisbane, October 2015
6. Surgeon Expectation Management; A Consultation Solution
Emily Bogue, Joshua Twiggs, Michael Solomon
Australian Orthopaedic Association, Cairns, October 2016
7. Patient Specific Simulated Kinematics following TKA and their Relationship to Patient Reported Outcomes
Joshua Twiggs, Brett Fritsch, Willy Theodore, Brad Miles, David Dickison, Justin Roe
Australian Orthopaedic Association, Cairns, October 2016
8. Femoral Rotational Axes Variation Across Demographic and Radiological Measures, Podium Presentation
Joshua Twiggs, David Dickison, Caitlin Wilcox, Brad Miles, Bede O'Connor
Australian Orthopaedic Association, Cairns, October 2016
9. Prediction of Physical Activity Levels During Recovery for Total Knee Arthroplasty
Justin Roe, Lucy Salmon, Brad Miles, Joshua Twiggs, Ben Gooden
Australian Orthopaedic Association, Cairns, October 2016

10. Biomechanical Simulations of TKA Outcome: A Pathway to Patient Specific Surgical Optimization

Joshua Twiggs, David Dickison, Willy Theodore, Brad Miles, Brett Fritsch, Justin Roe
International Society for Technology in Arthroplasty Annual Congress, Boston, October 2016

11. Non-functional Radiology is Unable to Predict Deformity Correctability in TKA

Willy Theodore, David Dickison, Joshua Twiggs, David Liu, Jonathan Bare, Brad Miles, Emily Bogue
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12. Patient Specific Activity Level Benchmarks During Recovery for TKA

Brad Miles, Joshua Twiggs, Lucy Salmon, Justin Roe
International Society for Technology in Arthroplasty Annual Congress, Boston, October 2016

13. Relationships Between Simulated Kinematics And Patient Reported Outcomes During Activity Following Total Knee Arthroplasty

Joshua Twiggs, Emily Bogue, David Dickison, Brett Fritsch, Justin Roe, Andrew Shimmin and Brad Miles
European Knee Society, London, April 2017

14. Relationships Between Simulated Kinematics And Patient Reported Return To Daily Activities

David Liu, Joshua Twiggs, Emily Bogue, Justin Roe, David Dickison, Brett Fritsch
European Federation of National Associations of Orthopaedics and Traumatology, Vienna, June 2017

15. Patient Specific Simulated Dynamics following TKA Correlate with Patient Reported Outcomes

Joshua Twiggs, Willy Theodore, Andrew Ruys, Justin Roe, David Dickison, Brett Fritsch, Brad Miles
International Society for Computer Assisted Orthopaedic Surgery (CAOS), Germany, July 2017

16. Digital Prehabilitation Reduces Length Of Stay In Patients Prior To TKA

Emily Bogue, Joshua Twiggs, David Lui
International Society for Computer Assisted Orthopaedic Surgery (CAOS), Germany, July 2017

17. Surgical Alteration Of The Tibial Joint Line During TKA Correlates With Poor Patient Reported Symptomatic Outcome

Joshua Twiggs, Emily Bogue, David Dickison, Brett Fritsch, Justin Roe, Andrew Shimmin and Brad Miles
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18. Relationships Between Simulated Kinematics And Patient Reported Outcomes During Activity Following Total Knee Arthroplasty

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International Society for Technology in Arthroplasty, Seoul, Sept 2017

19. Clinical Validation of a Patient Specific Shared Decision Making Tool for Use During the Pre Total Knee Arthroplasty Consultation

Emily Bogue, Michael Solomon, Brad Miles, Joshua Twiggs

International Society for Technology in Arthroplasty, Seoul, Sept 2017

20. Quantification of the Extent of Anatomical Variation in Patients Prior to TKA Surgery

Jonathan Bare, Joshua Twiggs, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

21. Surgical alteration of the Tibial Joint Line during TKA correlates with poor patient reported symptomatic outcome

Richard Boyle, Joshua Twiggs, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

23. Relationships Between Simulated Deep Knee Bend Kinematics Following TKR and Patient Reported Return to Daily Activities

David Liu, Joshua Twiggs, Emily Bogue, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

24. Which osteoarthritic patients will be dissatisfied with their pain and function following total knee replacement surgery? Predicting outcomes at the preoperative consultation

Jonathan Negus, Joshua Twiggs, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

25. Correlations between anatomical complexity and postoperative TKA outcome in a multi-surgeon series of patients

David Parker, Joshua Twiggs, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

26. Mechanically aligned knees exhibit greater medial shift of the patella than kinematic aligned knees: a simulation study

Joshua Twiggs, Jialong Li, Justin Roe, Brett Fritsch, Michael Solomon, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

27. Simulated Patello-Femoral Kinematics Correlate With Patient Reported Outcomes Following Total Knee Arthroplasty

Andrew Shimmin, Joshua Twiggs, Jonathan Bare, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

28. Conventional instrumentation achieves kinematic alignment more accurately than mechanical alignment

Michael Solomon, Edgar Wakelin, Joshua Twiggs, Brad Miles

Australian Orthopaedic Association, Adelaide, October 2017

29. Clinical Validation for a Patient Specific Shared Decision Making Tool

Joshua Twiggs, Emily Bogue, Brad Miles
Australian Knee Society, Noosa Heads, 2017

30. Alteration of the Femorotibial Rotational Profile in Total Knee Arthroplasty Correlates with Poor Patient Reported Outcomes

David Parker, Joshua Twiggs, Brad Miles
Australian Knee Society, Noosa Heads, 2017

31. Biomechanical Simulations of TKA Outcome: A Pathway to Patient Specific Surgical Optimization?

David Dickison, Joshua Twiggs, Willy Theodore, Brad Miles, Brett Fritsch, Justin Roe
Australian Knee Society, Noosa Heads, 2017

32. Effect of Component Geometry and Alignment on Kinematic Outcome of TKA

Jonathan Baré, Willy Theodore, Edgar Wakelin, Joshua Twiggs, Brad Miles
Arthroplasty Society of Australia, Melbourne, May 2018

33. Digital Prehabilitation

David Liu, Justin Roe, Simon Carlton, Micaela Anderson, Joshua Twiggs, Edgar Wakelin, Brad Miles
AOA, Perth, October 2018

34. Clinical Validation of the Patient Expectation Management Tool

David Liu, Michael Solomon, Jonathan Baré, Steve McMahon, David Dickison, Edgar Wakelin, Joshua Twiggs, Brad Miles
AOA, Perth, October 2018

35. Tibial Tray Positioning, Coverage and Relationship to Short Term Outcome following TKR

Michael Solomon, Jonathan Baré, Steve McMahon, Andrew Shimmin, David Dickison, Edgar Wakelin, Joshua Twiggs, Brad Miles
AOA, Perth, October 2018

36. Accuracy of a Patient Specific Patella Reaming Guide

Jonathan Bare, Andrew Shimmin, Leina Suzuki, Justin Roe, Steve McMahon, Michael Solomon, Edgar Wakelin, Joshua Twiggs, Brad Miles
AOA, Perth, October 2018

37. Alignment strategies – Where have we come from and where are we going?

David Parker, Edgar Wakelin, Joshua Twiggs, Brad Miles
AOA, Perth, October 2018

38. Conservative Approaches to Kinematic Alignment and their Impact on Patient Reported Outcomes

Michael Solomon, Jonathan Baré, Steve McMahon, Andrew Shimmin, David Dickison, Edgar Wakelin, Joshua Twiggs, Brad Miles

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AOA, Perth, October 2018

40. Alignment strategies and their effect on outcomes and simulated dynamics
David Parker, Edgar Wakelin, Joshua Twiggs, Brad Miles
AKS, Broome, October 2018

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Brett Fritsch, Ella Moore, Edgar Wakelin, Joshua Twiggs, Brad Miles
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Chapter 1

Introduction

1.1: Research Motivation

Total Knee Arthroplasty (TKA) is an enormously successful surgical operation, bringing pain and functional impairment relief to hundreds of thousands of patients a year. Yet there remains a significant portion of patients who walk away from this surgery dissatisfied, up to 20%. Reasons for this are varied, but ultimately boil down to a pain or functional expectation not being met. This has, for a very long time, been a hidden problem, as practice for a very long time has been to measure surgical outcomes by the alignment of the components to a mechanically neutral goal, and survivorship of the implant. While survivorship is enormously important as the need for a revision or re-operation is an acute cause of patient unhappiness, the focus on these goals as markers for a successful surgery has been somewhat myopic.

Having worked in the field of orthopaedics engineering for some years, I have also seen how this focus affects commercial developments and surgical decision making. It is easy to see how radiographical alignment and implant survivorship have come to dominate as the data to collect both is relatively easy. There is a paradigm that is very tempting to follow - put the knee in straight, as accurately as possible, and the knee will survive for a long time. As a result, commercial development has followed and reinforced this line of thinking, pouring more and more money into implants that last longer and assistive technologies that put the implants in straighter.

Yet there has been a growing body of evidence that straighter knees don't necessarily perform better, and for all the development in this direction, dissatisfaction levels do not appear to be dropping. Research has shown that alternate alignment strategies that match to the patient's specific may perform better; that selection of appropriate patients for surgery may be a greater driver of satisfaction than the specifics of the alignment reached;

that preparation for and management after surgery may be more relevant than the surgery itself.

The goal of this research was twofold: to explore how patient outcomes can be improved by giving due consideration to alignment targets and planning that is not necessarily mechanical alignment, and how tools and services existing outside of the surgery itself might be employed to improve outcomes, either through better selecting patients for or non-surgically managing patients around the surgery.

A major goal in the research presented here has been field implementation. The research has been guided by a need to address problems in the real world in surgeons practice, and so I have endeavored to develop solutions that work in the real world. Furthermore, the chapters that make up this thesis have, where appropriate, been worked on with industry and academic colleagues and been published or submitted for publication as ongoing peer review is a crucial element to development of relevant, clinically successful solutions to problems.

1.2: Thesis Structure

This doctoral thesis seeks to find ways to improve surgical planning with a view to optimisation of patient outcomes, and to improve selection for surgery and non-surgical management of patients in order to achieve a similar goal. Preludes for each chapter that makes up a published paper are presented before the paper in addition to the below. The structure is as follows:

Chapter 1: Introduction - This chapter, presenting the research motivation and structure of the thesis to follow.

Chapter 2: Literature Review - The literature review presented here covers a brief review of Total Knee Arthroplasty and the technological developments that have occurred in the past decades. It then covers sources of dissatisfaction and patient unhappiness with outcomes, breaking them down into patient linked, surgically linked and management linked factors. Activity post surgery, risk prediction models and simulation technology are all looked at closely, as these fields of investigation supply possible solutions to patient dissatisfaction. A summary of the literature review and the direction and aims of this thesis follow.

Chapter 3: Unexpectedly High Incidence of Anatomical Deformity Across a Population of Prospective TKR Patients - This chapter covers a study investigating the range of anatomical variation amongst patients and compares it to what might be anticipated by a standard surgeon user group and literature reported values for healthy (non-osteoarthritic) patient populations. It is found that rates of deformity and patient linked variation are underestimated by surgeons, and hypothesised that the use of 'standard patient' referencing rules of thumb surgically with variable patient anatomy might be a driver for poor outcome. Important to the development of this study was creation of a database of measurements able to be readily updated from the 'working files' of 360 Knee Systems' surgical planning process, a tool which has been used in subsequent academic publications both contained in this thesis and otherwise.

Chapter 4: Patient Variation Limits Use of Fixed References for Femoral Rotation Component Alignment in Total Knee Arthroplasty - The capacity for unexpected patient variation explored in Chapter 3 to lead surgical techniques astray is tested with regards to the Posterior Condylar Angle (or Transepicondylar Axis to Posterior Condylar Axis angle). Rotational alignment in TKA has been shown to (and logically must) alter the balance of the components in flexion, which has been shown in other studies to relate to outcome. It is not captured in 2D radiography and require 3D imaging to view, and there is still confusion and disagreement as to what the best approach is in rotationally aligning the femur, despite the

technology that has been deployed to the operating theatre in the last decades. This study showed that, for a TEA target to be achieved, a patient specific angle from the PCA must be used, and that standard reference rules are insufficient.

Chapter 5: Accurate Determination of Post-operative 3D Component Positioning in Total Knee Arthroplasty: The AURORA Protocol - Following the finding in Chapter 4, it was confirmed that a new technique needed to be developed to further study how component placement might link to outcome beyond coronal mechanical alignment. There was a need to reference native preoperative geometry to the postoperative implanted position of the component. The technique developed involves registering both implant and preoperative bone 3D CT segmented models to a postoperative CT reference frame. Doing so allowed for a more accurate definition of component placement in all 3 planes, going beyond what 2D radiography can provide. Additionally, analysis of the alteration of certain measurements from their preoperative reference, such as the joint line, can be performed. While not the primary author of this paper, my contribution involved, in addition to work on the results, review and statistics, the core development of the technique being validated and interpretation of its capability and applicability in postoperative TKA analysis. The motivation for this technique was to develop further studies as presented in this thesis, and in light of the significant contribution and role of this paper in describing the flow of studies that constitute this thesis it has been included. Permission from the primary author has been obtained.

Chapter 6: Surgical Alteration of the Coronal and Axial Knee Alignment During TKA Correlates with Poor Patient Reported Symptomatic Outcome - This chapter follows the process developed in Chapter 5 to compare the alteration of a number of coronal and rotational measurements following implantation of the components with Patient Reported Outcome Measures. This study is the only study known to the author to investigate pre- to post-operative changes in anatomical measurements with such a large dataset. A number of

statistically significant findings are reached, although their impact is, in many cases, not clinically significant. While the finding of statistical significance is promising, it was determined that alignment of components alone, even assessed in multiple planes and referenced back to preoperative measurements, would not be sufficient to unlock all the surgical technical drivers of poor patient outcome.

Chapter 7: Variability in Static Alignment and Kinematics for Kinematically Aligned TKA

- In order to unpick the relationship between alignment and patient outcomes in surgery suggested in Chapter 6, we decided to investigate multi-body dynamics simulation. Forward dynamic simulation allows for the biomechanical behaviour of the joint to be investigated on a scale not otherwise possible. Comparative approaches to simulation include gait analysis and fluoroscopy (with and without inverse simulation) and cadaveric rig testing, but all present issues with scalability that limit their ability to investigate behaviour and variation across populations. The model presented here is used to investigate variation in kinematics responses between Mechanical and Kinematic Alignment, an alternate alignment strategy with promising results, as a proof of concept, and its initial validation against a cadaveric rig is also described (although further publications on the validation are to follow). While not the primary author of this paper, my contribution involved the Results and Methods section of the paper and the core underlying experimental work and analysis. This study has been included given the significant contributions to this study, role in development of the driving simulation and the crucial role this study played in describing the simulation that formed the core finding in the subsequent study. Permission from the primary author has been obtained.

Chapter 8: Patient Specific Simulated Dynamics following TKA Correlate with Patient

Reported Outcomes - Expanding on the initial work presented in Chapter 7, this work found a relationship between patient outcome and the results of a post-operative simulation. The implications of this are profound. It can be reasonably assumed the mechanism by which

various alignment rules impact patient outcomes is through their impact on the kinematics and kinetics of the patient's knee in motion. Three broad factors contribute to kinematic outcome; the alignment of the components, the implant geometry implanted and the patient specific musculoskeletal system into which the implants have been implanted. With the ability to determine a favourable kinematic target linked to better postoperative outcomes, the alignment or component design to use in a specific patient can be solved for. Multiple further findings relating post-operative outcome to simulation results to the paper presented here have been found and presented to conferences (described in the Achievements section of the preface.) These findings from the basis of the Dynamic Knee Score or DKS, a predictive scoring algorithm that drives selection of preoperative knee alignment plans. This tool has been used in some form in over 2000 Total Knee Arthroplasties to date.

Chapter 9: Measurement of Physical Activity in the Pre- and Early Post-operative Period after Total Knee Arthroplasty for Osteoarthritis using a Fitbit Flex Device - Chapter 8 is the culmination of the work in this paper relating to the technicalities of surgery; this chapter sprung from an investigation into what might be done to improve patient outcomes outside of directly affecting the surgery. One area of significant potential improvement is in the postoperative management of the patient. Patients are frequently unsure and confused as to what should be expected from them during their recovery. While information provision to them is one solution, the reality is that objectively measured patient recovery is highly patient dependent. Pedometers are one mechanism by which an objective, patient specific goal can be communicated to patients on a daily basis. This study conducted a regression analysis on step count and determined an appropriate 6 week recovery target dependent on preoperative step count and demographics. Later research has shown that provision of goals increases post-operative activity level and satisfaction, and the goal setting tool has been used in over 300 managed patient rehabilitation plans.

Chapter 10: Clinical and Statistical Validation for a Probabilistic Prediction Tool of TKA

Outcome - Similar to Chapter 9, this paper dealt with non-surgical avenues for patient outcome optimisation, this one focusing on selection for surgery. An outcome prediction model, developed as a Bayesian Belief Network, is presented and validated. Validation takes two forms. The first is a clinical validation that determines the tool is impactful when implemented into a surgeon's rooms, materially changing the nature of the patients they book for surgery and those they don't. The second is statistical validation of the predictions, which are presented in terms of the predicted change rather than absolute target, and a subset is focused on if patients who weren't predicted to achieve at least a Minimum Clinically Important Difference (MCID). The tool has seen commercial implementation and has been used in the consultation of over 1000 patients prior to consideration for a TKA.

Chapter 11: Conclusions - This chapter presents my conclusions from the work presented and outlines the direction of future work building on this thesis and the clinical tools deployed from it.

Chapter 2

Literature Review

2.1: Developments in TKA Surgery

2.1.1: Osteoarthritis of the Knee

The knee is a complex joint consisting of three bones, the patella, femur and tibia. These bones make up three compartments: the medial and lateral tibio-femoral compartments, in which the femoral condyles interface with the tibial plateau, and the patello-femoral compartment where the posterior face of the patella interfaces with the anterior face of the femur [1], shown in Figure 1. All three compartments handle considerable amounts of force, with the medial and lateral tibio-femoral compartments bearing the bodyweight of the individual and the patello-femoral joint being the primary mechanism by which forces from the quadriceps muscles drive extension of the knee. A number of ligaments and soft tissue structure provide constraint to certain motions at the knee, including the lateral and medial menisci, the anterior and posterior cruciate ligaments, the medial and lateral collateral ligaments medial patello-femoral and retinacular ligaments, the popliteus, the iliotibial band and the combination of structures that define the postero-lateral corner. A thin layer of cartilage covers the articulating bony surfaces in all 3 compartments [2].

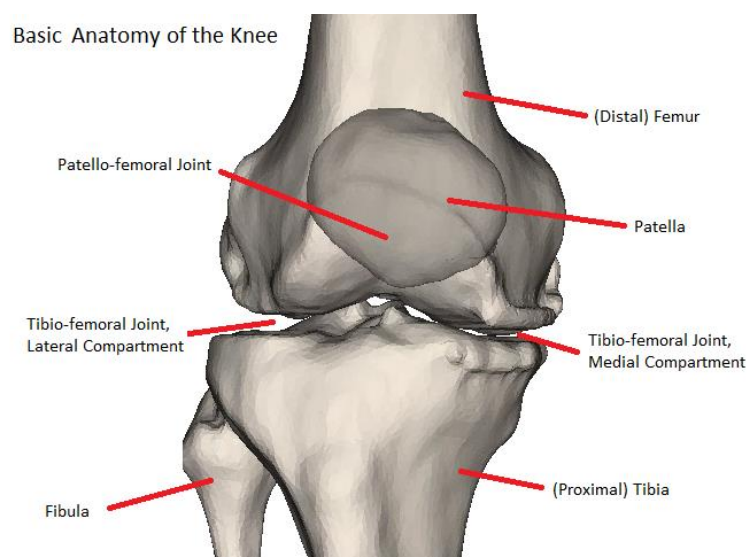


Figure 1: Basic Anatomy of the Knee Joint

Osteoarthritis is the degenerative loss of cartilage tissue in a joint, and is the most common joint disease in the Australian community with approximately 15% of the population adversely affected [3]. Of these, the knee is a common site for osteoarthritic symptoms to emerge, which can cause debilitating pain and loss of functional ability for the sufferer. Incidence increases dramatically with age, with as many as 1/3 of people showing radiographic evidence of knee osteoarthritis in the 60-69 years age group, though a smaller portion suffer symptomatically [4]. As such, the growth in this demographic group in line with the aging population and the consequent increase in work demands placed upon this population group are contributing to an acceleration in the incidence of knee osteoarthritis across the population as a whole [5]. Incidence is also increasing among younger age groups associated with risk factors such as obesity, joint injury and repetitive stress on the joint as a result of physical labour, further contributing to the burgeoning societal burden of knee osteoarthritis [5-11].

Pre-existing anatomical deformity [12], particularly coronal alignment of the knee [13-15], is another well described risk factor development risk factor for osteoarthritis development. Coronally malaligned knees have an angle at the knee joint such that the lower limb segment is either medially angled, a varus misalignment, or laterally angled, a valgus misalignment (see Figure 2). When the knee is neutrally aligned, the longitudinal bone axes and the loading distribution of the knee is approximately 60% in the medial compartment and 40% in the lateral [16]. The result of misalignment is increased loading in either the lateral or medial compartment of the joint relative to the other, which leads to a feedback loop of subchondral bone degradation and meniscal damage as well as osteoarthritic cartilage degeneration driving further malalignment [17]. In a similar way, patellar instabilities and deformities have been linked to development of patello-femoral osteoarthritis, although it is less common for this osteoarthritis to be as uni-

compartmentally localized in the patello-femoral compartments as it is in either of the tibio-femoral compartments [18].

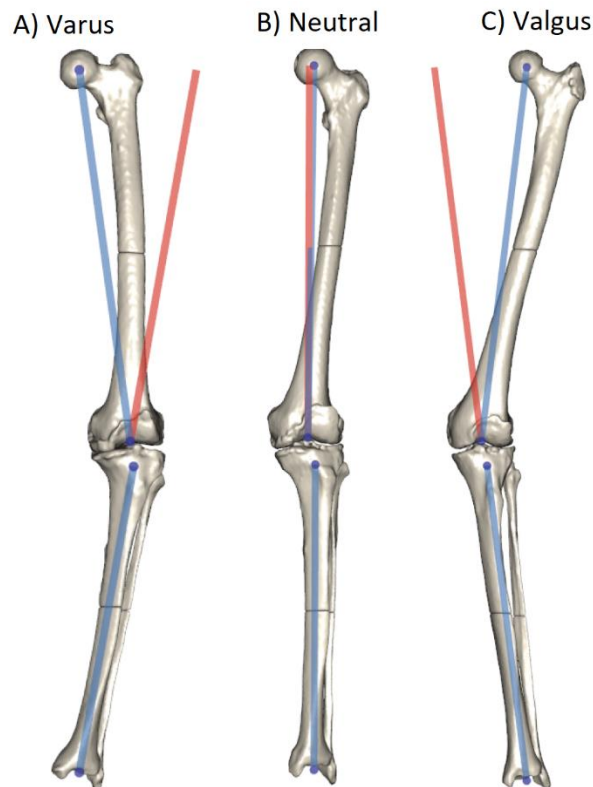


Figure 2: Coronal Alignment & Deformity of the Knee

The usual pattern of disease progression is gradual functional decline mitigated with conservative management strategies. A small subset of patients are reported to suffer from a rapid decline/accelerated knee osteoarthritis, however [19, 20]. Patients who suffer a rapid decline report more pain than patients who don't [21], although explanations for this could include psychological factors such as the existence of a pain 'reference point' that has not adjusted over time [22]. Common drivers of this trajectory are recent injuries [23] as well as higher BMI [24].

2.1.2: Total Knee Arthroplasty

The ultimate treatment for osteoarthritis is Knee Arthroplasty. Its primary goal is to effect pain relief and recover functional ability for the sufferer. As a result of the enormous benefit that can be delivered to patients in terms of lifestyle improvement and work capability, the surgery is considered to be highly successful [25] and its utilisation is rapidly growing.

Indications for Knee Arthroplasty generally are that there is significant functional decline, that the functional decline can be associated with radiologically identifiable osteoarthritis, and that a significant impact on the patient's quality of life has resulted. There is a lot of subjectiveness to these criterion, however, and the timing of Knee Arthroplasty in the osteoarthritic degeneration cycle remains an area of some confusion [26]. Escobar et al. [27] has previously described a set of criterion developed from a group of 12 surgeons evaluating scenarios, reflective of earlier work by Naylor et al. [28]. However, a recent study by Riddle et al. found when using these definitions, almost 1/3 of patients receiving a TKA drawn from a longitudinal database of osteoarthritis sufferers were not appropriate candidates, and these patients did not improve at 2 months post surgery from their baseline state [29]. Even the more objective measurement of radiological grade [30, 31] that makes up part of this indication is inconsistent, with various radiological grades reporting poor inter and intra-grader consistency [32-34].

There are three major types of primary Knee Arthroplasty: Unicompartmental, Total and Patella/Trochlear. The purpose of all Knee Arthroplasty is fundamentally the same: to replace the damaged joint surface and in so doing, relieve the pain caused by the articulation of the arthritic joint. Unicompartmental Knee Arthroplasty involves the implantation of a tray and plastic spacer in either the medial or lateral tibial plateau and a metallic resurfacing of the interfacing femoral condyle. Patella/Trochlear resurfacing, similarly, involves resurfacing of the femoral trochlea and the posterior face of the patella. Both approaches are indicated for when osteoarthritic wear is localised to the resurfaced

compartment, and both approaches will often lead to a long term revision to a Total Knee Arthroplasty (TKA). In the 2017 National Joint Registry Report it was reported that more than 90% of the primary Knee Arthroplasties were TKAs and that this proportion was growing [35].

A Total Knee Arthroplasty generally consists of at least 4 parts. A tibial tray, consisting of a metal backed distal surface with a keel or pegs for fixation is implanted onto a flat surface resected from the tibia and a plastic articulating spacer or insert is fixed to the proximal surface of the tray. This insert articulates with a metallic femoral component which is fixed to the resected distal surface of the femur, typically resected in 5 planes (anterior, posterior, distal cuts and two chamfer cuts that between the anterior and distal and the posterior and distal cuts). Finally, a patella button is often implanted to the posterior face of the patella, which may be an all plastic part or a hybrid plastic articulation with the femur/metal backed component.

2.1.3: Survivorship

The primary objective measure for success in Total Knee Arthroplasty has traditionally been survivorship with regards to revision rate, which sits at 6.5% over a 12 year window [35-37]. Interestingly, this figure is vulnerable to underestimation as the conventional tracking of a patient endpoint when they undergo revision surgery implies that a patient's health deteriorating with age to the point where it is deemed safer not to operate even if a revision surgery is required would be a survival of the implant.

There are a number of reasons for TKA implant revision, including polyethylene wear, aseptic loosening, instability, infection, arthrofibrosis, positioning of components, patello-

femoral pain, periprosthetic fractures and patellar resurfacing, in cases where an initial operation did not involve implantation of a patellar button [35, 38, 39].

Survivorship has been shown to relate to a number of factors, although relationships are not always clear. Judge et al.'s study of NHS data in 2006 was able to show that a higher volume of TKA operations performed at the hospital significantly increased survivorship to five years and 30 day re-operation rates (not necessarily revisions), although the impact was small [40]. Argenson et al. showed decreased survivorship in higher activity patients but no difference in survivorship with implant design and overall knee alignment within the context of a single centre [41], a finding confirmed in further studies [42]. However, registry studies have shown that across the population, implant design does correlate with survivorship as well as gender and age, although there are a number of possible confounders for these findings. Given the design evolution of TKA implants has been partly in response to survivorship and implant failures [43], there is a common sense argument that the design of the implant will influence its survivorship, but the strength of this relationship in modern implant designs is not entirely clear.

2.1.4: Implant Designs, Materials & Fixation Methods

There are a number of design, material and fixation options in TKA. Three broad designs of implant are in common use today - Cruciate Retaining (CR), Posterior Stabilised (or Cruciate Sacrificing, PS) and Medial Pivot (or Medial Stabilised, MP) designs. These broad classifications of implant design have arisen from the result of many successive design iterations during the early development of Total Knee Arthroplasty implants, [43] with Medial Pivot designs being the newest, representing a small but rapidly growing, approaching 10% of primary TKA's in Australia, up from 2-3% in 2013[35]. Other differentiators in implant design include use of a mobile rather than fixed bearing, where

the articulating polyethylene component of the tibia is free to rotate relative to the tibial tray, and the aforementioned use/non use of a patellar resurfacing button.

Materials used in Total Knee Arthroplasty are typically titanium or cobalt-chromium for the metallic components and some form of Ultra High Molecular Weight Polyethylene (UHMWPE) for the plastic components. Highly Cross-linked Polyethylene (XLPE) is the most recent development in this area, with use increasing from 10% of primary TKAs in 2006 to 57% in 2016 [35]. The manufacture involves use of gamma or electron beam radiation to break polyethylene hydrocarbon chains and encourage cross-linking, and has been previously shown to improve clinical wear resistance in Total Hip Arthroplasty. Similar benefits have not yet been shown in TKA, however, and the technology remains unproven in Total Knee Arthroplasty [44].

Fixation comes in one of two forms: cemented or cementless ('press fit'). Cemented TKA involves use of a bone cement mix, typically a polymethyl methacrylate (PMMA) formulation. Cementless TKA involves a press fit component, usually manufactured and tightly toleranced to exactly match the cut surfaces in the case of the femoral component which will often have a porous metallic bone facing surface into which osseointegration can occur. Occasionally, Hydroxyapatite or other coatings are applied to the surface to encourage bioactivity and osseointegration. Use of cementless implants is declining each year, with 2/3 of implants fully cemented, though 'hybrid approaches' where a cementless femur is paired with a cemented tibia remains a little under 30% of all knees [35].

Randomised trials have not shown a population difference in survivorship with cemented or cementless TKAs, although they did observe a gender linked effect for males with cementless fixation to fail at a higher rate [45]. This could be linked to unobserved confounders in the study, whereby weight or gender linked activity difference could be a driver.

2.1.5: Delivery Technology

Traditionally, alignment of implant components to the mechanical axes of the bone has been the benchmark for measuring short term outcomes in Total Knee Replacements. Two factors are at play in determining attainment of this goal. The first is the alignment goal being pursued; recent work has proposed a number of alternate alignment goals with comparable or better outcomes to the traditional align to the bone approach [46, 47]. The second is the accuracy with which the alignment goal has been achieved. Alignment to the mechanical axis has been shown to correlate with survivorship in some studies [48, 49]. Other studies, however, have disputed this finding. Paratte et al's retrospective review of 398 TKA's found no statistical difference in 15 year survivorship when reviewing their database, [42]. Nevertheless, improvement in the metric of alignment to the mechanical axes of the bone has led to development and refinement of a number of different surgical delivery techniques.

Instrumented techniques are this historical standard and make up the majority of all implanted knees today [35]. Instrumentation tools have seen incremental design changes over time, but largely follow a common set of fundamental principles. Femoral distal cuts are aligned using an intra-medullary rod inserted into the distal femur, and a coronal angle is selected from there and a distal cut performed. An antero-posterior sizer is used to set rotation from the posterior condyles in addition to component size and then a 4 cuts in 1 block is placed on the distal cut surface to guide the remaining femoral cuts. The tibial cut axis is defined with either an extra-medullary or intra-medullary rod and then the tibial cut is made, with rotation and translational placement of the tibial component set with the tibial trials [50]. Alternately, gap balancing techniques cut the tibia first and set femoral rotational alignment using spacers or gap balancing tools [51].

Patient Specific Instrumentation (PSI) is one alternative to instrumentation techniques, relying on patient specific guides that are reverse engineered to fit specific patient geometry using CT or MRI scans. The cutting guides, when affixed to the patients bones, supply cutting slots or reference pinholes through which a cutting block can later be inserted and in doing so control the orientation of the cut surface. While this technique showed initial promise, numerous meta-analyses have shown that it does not appear to improve accuracy generally [52-54], though there is some claim of decreased operating times [55] and it is possible that a significant portion of outlier results can be attributed to the surgeon's disconnect from the surgical planning procedure when left in the hands of a technician [56].

Computer navigation is another recent alternative which is currently gaining in popularity. Two broad categories of system exist: image based or imageless. In an imageless system, a virtual model of landmark reference points (and potentially a morphed statistical shape model of a bone itself) is created by the computer navigation system through a tracked pointer and tracked fixed reference points for the bones. Image based systems are similar, with the virtual model of the bone being the result of registration of a pre-existing CT scan to the fixed reference points. Numerous prospective studies [57-59] and meta-analyses [60-62] have demonstrated a gain in accuracy, with the potential cost of surgical time (although the impact appears to be experience and practitioner variable). One potential challenge of imageless systems is the 'garbage in-garbage out' problem where the limiting factor is not the technology but the users ability to identify appropriate reference points. This has been shown to particularly impact rotational alignment accuracy [63, 64] which is not often included in analysis of accuracy as it is not available in conventional 2D postoperative radiography. Recent developments include integration of force sensor technology [65, 66] and robotics [67].

Despite these evolutions in delivery technology, it has not been shown that alignment accuracy necessarily equates to happier or more functionally capable patients [68].

Successive studies have focused on patient satisfaction and Patient Reported Outcomes Measures (PROMS) as a metric for success rather than accuracy to an alignment target. Increasing research into and integration of PROMS into clinical workflows has exposed the enormous variety of other factors, some surgical and some patient linked that drive outcome.

2.1.6: Residual Dissatisfaction & Persistent Pain

It is reported that as many as 20% of patients report dissatisfaction with the pain relief and functional outcomes of their surgery after 1 year [69-71]. There is a relative ease of data collection and hence wider adoption in joint registries of survivorship based data than PROMS data. This, in addition to the relatively greater exposure of the practicing surgeon to a smaller number of highly dissatisfied patients affected by outcomes such as implant loosening than a larger number of less dissatisfied patients may lead to a bias in favour of mechanically 'safer' but not necessarily patient outcome optimal surgical decision making. When considering survivorship with a wider range of endpoints incorporating negative pain or functional outcomes over time, the effective survivorship rate has been shown to fall as low as 48.8% 6 years after the operation [72]. At the core of the issue is a definitional difference between the surgeon and the patients definition of what constitutes a successful surgery, and the failure to fully align patient expectations with the reality of their likely surgical outcome [73].

2.2: Measurement of Outcome

2.2.1: Patient Reported Outcome Measures

Research into PROMS is ongoing, and they are increasingly being used in clinical rather than research contexts to inform decision making [74]. There exists a range of scoring metrics which aim to strike different balances between incorporating objective, directly measurable data such as range of motion (ROM) measurements and subjective, questionnaire based data [75-77]. The advantages of the former are its reproducibility; however, the clinical relevance arguably suffers in comparison to direct patient reported results [72]. Further developments include attempts to resolve the clinical burden through an adaptive questionnaire format in order to get specific information that characterizes a patients expectations and aspirations [78]. While this approach is highly relevant to the aim of providing personalized medical care, it does lead to potential issues around database completeness for data analysis and patient outcome prediction work.

Of these metrics, the most prominent patient focused scores are the Knee Osteoarthritis & Injury Outcome Score (KOOS), [79] the Oxford Knee Score (OKS)[80] and the Western Ontario and McMaster Osteoarthritis index (WOMAC)[81, 82]. Of these three, the KOOS Score is the longest, containing 42 questions subdivided into 5 domains (pain, functionality, activities of daily living, sports and quality of life) [83]. The WOMAC is somewhat shorter at 24 questions and is in fact a subset of the KOOS score. The Oxford Knee Score, at 12 questions, is shorter again [75]. Studies have shown that PROMS measurements give meaningful results by about 6 months post-TKA [84].

More general questionnaires include the SF-36, the SF-12 and the EQ-5D. These questionnaires are often used in conjunction with a specific knee functional questionnaire. Dunbar's 2001 analysis of results from the Swedish Knee Arthroplasty Registry included four

general purpose health questionnaires (NHP, SF-12, SF-36 and SIP) and three disease/site-specific questionnaires (Lequesne, OKS, and WOMAC)[85]. The study found that the SF-12 and OKS provided acceptable levels of fidelity of data from the patients while minimising the response burden and maximising patient completion.

This reflects one of the challenges with using PROMS: the length of the questionnaire and survey fatigue from the patient can corrupt results or lead to non-response. A previous study has confirmed the presence of a significant response bias in PROMs collection, with non-responders significantly more likely to be less happy or dissatisfied patients, particularly in mail-out collections [86]. Rasch analysis [87] has frequently been used to produce shortened versions of questionnaires. The Oxford Knee Score has a slightly reduced version developed using this technique [88] which saw its length reduced from 12 to 10 items. The KOOS score has a Rasch analysis of its activities of daily living and sports sections, reducing them from 22 questions to 7 [89] and a further validated analysis reducing the whole questionnaire to 7 questions [90]. The WOMAC score has had similar work done, reducing it to a 17 [91] and 7 question form [92].

Care should be taken when interpreting results from PROMs studies. The analysis of the results themselves can be non-trivial, [74] and validation exercises for PROMs scores show a wide variety of quality and completeness [93, 94]. One other alternative to PROMS is the use of a Visual Analogue Scale (VAS), in which the patient marks on a scale how much pain they are experiencing anchored at “No Pain” and “Extreme Pain” [95].

2.2.2: Satisfaction, Patient Acceptable Symptom States and Minimum Clinically Important Differences

PROMs measurements will typically return answers on a continuum, and this contributes to the confusion when interpreting the results. A number of alternate approaches exist to give

a binary or categorical outcome rather than a continuous score. The first of these is the Patient Acceptable Symptom State or PASS score. The PASS score attempts to define a binary 'target to hit' in terms of the PROMS score being applied [96]. Patients are asked an anchoring question, usually 'Taking into account your level of pain and also your functional impairment, if you were to remain for the next few months as you are today, would you consider that your current state is satisfactory?'. Patient responses are matched to the PROMS score the PASS is being developed for and the Receiver Operating Characteristic (ROC) maximising cut-off that best matches the PROMS responses to satisfied patients is used [97].

Another alternative is the use of a Minimum Clinically Important Difference or MCID. The MCID is a relative measure assessing the patients state prior to and after the knee replacement. Minimum clinically important differences are developed in a similar way, relating the magnitude of a change in the score to the frequency of the score being reported as perceivable by the patient [97, 98]. MCID's can have their pitfalls, and there are a number of methodological issues that can lead to different estimates being generated[98]. Both MCID's [99, 100] and PASS [101] scores have been calculated for a number of PROMS in use with TKA patients.

The final structure of scoring for TKA outcome looks directly at the satisfaction level of the patient, either by directly asking if they're satisfied with the surgical outcome [71], creating a small set of sub questions [102] or using a visual analog scale [72]. Having the assessment based off satisfaction is philosophically different to a traditional PROMS score, taking the assessment even further from traditional, range of motion driven surgeon assessments of the outcome [103]. Furthermore, there is conflicting evidence as to whether an MCID or PASS ('journey' or 'destination') approach to binarising PROMS outcomes is a better reflection of patient satisfaction. Kwon et al.'s study of 438 knees found that the absolute score (analogous to attainment of the PASS) had a stronger relationship to satisfaction

[104], while Judge et al.'s review of 1784 knees found patients with lower scores preoperatively required lower scores postoperatively in order to be satisfied [84].

The development of some standardization around acceptable outcome levels across disparate scoring mechanisms has improved the ease of interpreting results between studies. However, the range of different questionnaires continues to hinder amalgamation of findings [84].

2.3: Patient Risk Factors

2.3.1: Surgical Timing of TKA

There has been a large amount of work around risk factor analysis for Total Knee Arthroplasty. Typically these studies target one of two primary goals - either a risk factor identification approach (where the focus is on identifying singular key factors that are indicative of a major complication being probable) or outcome prediction (where the consideration is wider with regards to interdependency of input variables, at the cost of presenting a singular focus or isolating an interventions impacts as accurately as possible). This chapter of the literature will deal with the former, while a later chapter will deal with the latter.

One factor that contributes to patient outcome is surgical timing. Osteoarthritis is a degenerative disease, and there is a crucial decision to be made as to when in that process a Total Knee Arthroplasty is called for. The longer a surgery is left to wait, the greater the deformity that develops will become, potentially complicating technical aspects of the surgery [13-15]. It has been shown, however, that patients who are operated on with less severe osteoarthritis when measured radiologically tend to perform worse and have higher dissatisfaction [105, 106].

There is dispute as to the nature of a similar effect for PROMS measures of patients preoperatively. Lingard et al.'s study [107], detailed further below, finds that similar to Judge et al.'s [84] the greatest single determinant of postoperative outcome in WOMAC's function and pain scores is the preoperative result for those same scores. This effect is in the opposite direction to that described for radiology, and presents a question in terms of what the PROMS scores are capturing. Do patients suffering from osteoarthritis to a greater degree prior to their operation have a worse outcome after surgery, or is it simply that

patients who innately *perceive* their state to be worse continue to do so after surgery? This also raises the question of whether the patient improvement (an MCID approach) or their final state (a PASS approach) is more relevant.

An answer to this is perhaps found in the complex relationship between satisfaction and PROMs. Further research from Judge shows that preoperative OKS scores have no meaningful relationship with satisfaction [108], driven by the observation that the PASS score most related to satisfaction differed significantly with patient preoperative score [84]. This reflects earlier findings from Kennedy et al. that lower preoperative scores led to greater gains as a result of surgery but lower scores post-operatively [109]. This suggests a case for earlier intervention in order to maximise PROMs outcomes, at odds with a later intervention potentially maximising satisfaction outcome. Significantly, this study did not control for age, which could be a significant independent factor driving patient satisfaction with a reduced PROMs measured outcome. A potential driver for this is well described in Dunbar's work, wherein Rheumatoid Arthritis (RA) sufferers are identified to be more satisfied despite worse functional outcomes [71] and a causal factor is identified as the existence of a 'healthy reference state' to which the patient's current functional ability is compared in order to drive satisfaction [22].

Most TKA indication algorithms factor in the patient's age in addition to radiological progression [27, 28]. Age plays a significant role in part due to the potential need to revise the knee; revision surgeries are often technically complex and will lead to a deteriorating patient functional state [110]. Therefore, a delay in surgery decreases the likelihood that a further revision will be called for in the life of that patient

Radiology as a tool for assessment also has some challenges. Typically, a radiological grade is specified as a cut off in combination with patient reported pain and symptomology, which correlate but are not identical [111]. There are, however, inconsistencies in scoring of

radiological grades [32-34], which may have contributed to an observed tendency for indicator recommendations for surgery to have not been followed in as many as 1/3 of patients [29].

2.3.2: Social, Demographic and Lifestyle Risk Factors

There are a number of factors that can influence the outcome of surgery related to the patient but not specifically their psychology. Judge et al. in his NHS data fuelled study [112] identifies a number of these. The study considers the EQ5D depression score in addition to the IMD - Index of Multiple Deprivation, an Oxford University score of the socioeconomic deprivation of an area measured across indices of income (22.5%), employment (22.5%), health deprivation and disability (13.5%), education, skills and training (13.5%), barriers to housing and services (9.3%), crime (9.3%) and living environment (9.3%). The study finds the IMD to be a significant predictor, although it does not dive into what the true underlying drivers that the IMD is signaling are. There are a number of possible causative links. One is a poorer quality of healthcare provided to those with a lower means, though the publicly managed nature of the British healthcare system suggests this isn't the key driver in this particular study (not withstanding some potential self selection of higher experience surgeons to more 'prestigious' hospital environments which could receive a patient group from an, on average, less deprived geographic locale). Secondly, a somewhat reduced 'drive' or other mental characteristic relating to patient rehabilitation conformance and outcome perception may exist; patients on disability are known to perform significantly worse [113].

Age as a predictive factor has an interesting relationship, leading to improved satisfaction but lower PROMs outcomes; this may be tied to expectations, explored later in this section [114]. Ghandi et al.'s study also found that age correlated with worse PROMs scores, in addition to coexisting comorbidities, a finding that has been subsequently supported [115,

116]. The relationship is not entirely clear cut, however, with other studies not able to find relationships with general comorbidity scores [117]. One driver of this could be the specific nature of the comorbidity. Concomitant aching joints or osteoarthritis in other regions of the body, particularly back pain, has been shown to have a strong relationship to outcome [113, 118], while other comorbidities have only been shown to affect acute risk of readmittance and mortality, not necessarily long term satisfaction [119].

Other social and lifestyle factors include smoking, which has been shown to affect long term survivorship but not necessarily PROMs [120] and BMI, which appears to affect functional outcome [68, 121] but not necessarily pain or satisfaction [122]. Social support received by the patient, including family availability at home may be another factor, though this is an understudied area [68, 123].

2.3.3: Psychological Risk Factors

Psychological risk factors for a poor outcome have been shown to be significant, perhaps dominant. Systematic reviews, while not being able to do comprehensive meta-analysis given the wide variety of PROMs or satisfaction metrics in use have been able to show consistent relationships between negative psychological factors and reduced patient outcomes postoperatively [124, 125].

Depression and anxiety are probably the most significant psychological factors in a poor TKA outcome. Brander et al.'s study in 2003 is one of the first to show depression predisposed patients for a worse outcome postoperatively [126]. Retrospective [112] and prospective [127] studies have confirmed this finding, showing these patients were also at risk for longer stays in hospitals and had a far greater risk in terms of pain outcomes rather than functional outcomes. This has prompted suggestions that preoperative interventions including

psychological management, counseling and pain coping training may be beneficial [128]. However, the interactions of mental factors with other comorbidities or negative predictors of outcome are not always so clear cut.

One study to show this is the study by Inneh et al. covering 5,314 total joint operations (considering TKAs and THAs - Total Hip Arthroplasties) from a single joint center [119]. The endpoints targeted by the study are incidence of reoperation, length of stay greater than four days, readmission within one month and postoperative complications (orthopaedic and non-orthopaedic). This study well defines both the strength and weakness of this type of study in contributing to the body of knowledge around patient outcome prediction. As a major advantage, the study covers a single joint centre with a fairly large database of patient results. This controls for a number of variables that mixed-source datasets suffer from as confounding variables. On the other hand, the scope of the endpoints of the study is somewhat limiting, relying entirely on hospital based-admissions data and not (typically noisier, but more long term clinically relevant) PROMS measures. The statistical procedure of analysis, stepwise multivariate regression (with some filtering of inputs based off logistic univariate regression statistical significance) is a fairly common approach to risk analysis.

The study exposes itself to some noise by considering length of stay as a factor, and the endpoints are generally constructed around managing the cost of care in the short-medium term, likely capturing risk factors relating to infection or patients predisposed to present as dissatisfied regardless of the actual surgical outcomes. It is then not surprising that psychiatric comorbidities present as the greatest single source predictor of negative outcomes for all endpoints considered. This study, although not based off PROMS analysis, is useful in that it underscores even when considering for endpoints best designed to capture the impact of variables directly related to operative issues in surgery, the dominant factor in patient outcome is the presence of a psychiatric comorbidity. This is a factor related dominantly to the patient, rather than the surgery. This reasoning does not consider

the likely causal contribution of a worse case of knee osteoarthritis acting as a contributing factor to a patient's psychiatric comorbidity risk, however, and it is worth noting that the input variables do not contain any radiographic or other preoperative osteoarthritic state variables.

Lingard et al.'s study [107] is an attempt at predicting patient reported outcome measures devised around the WOMAC score as both a preoperative input and a target prediction. The study also uses the Short Form 36 Questionnaire (SF-36), a validated, more general patient response centered health measure as an additional preoperative input to the standard demographic factors and socioeconomic factors. The study suffers somewhat from considering patients recruited from joint centers in Australia, the United Kingdom and the United States, across a patient sample size of just 759 patients. Each of these markets have fundamentally different healthcare regimes that affect a patient's surgical experience and characterize the demographics for the relevant patient groups selected. This implies that the results are impacted by not just the patients experience in receiving a joint replacement but who was able to receive a joint replacement in each country. Although the study goes on to control for this as a factor, several distortions exist such as the US center treating a much higher percentage of high income & education score patients. While the study aims to identify factors that survive these differences in order to characterize robust preoperative predictors, the presence of a limited but disparate sample of patients does not guarantee identified factors will be relevant to the population as a whole. The patients have not been randomly sampled if the population is to be treated as "Western TKA recipients" as a whole but instead have been drawn from a number of 'clusters' within the population.

The study presents some control of this, however, by pursuing a hierarchical model rather than a regression based analysis, limiting the vulnerability of a regression model that may map itself to a non-linear population function that is only presenting some part of its structure with the selective sampling. The study finds that the SF-36's mental health

subscore was a key predictor of poor outcome. Further research from the same author around the impact of psychological distress characterized some of the mental health score as a reversible issue following surgical intervention, though to what extent the causal link is the preoperative patients knee state driving their low mental health score is unclear as the study did not capture radiographic or other osteoarthritis score based variables which might have enabled such an analysis [129].

A number of other studies have sought to characterize mental traits that render a patient more or less susceptible to a poor postoperative outcome. Wylde et al.s 2012 study [130] attempts to find a relationship between the WOMAC pain and functional score outcomes and the psychological attribute self-efficacy, a measure of a “the conviction that one can successfully execute the behavior required to produce the outcomes”, in this case, of a successful TKR operation recovery. This can then be thought of as a derived attribute, in that it captures both the patient’s assessment of their own willpower as balanced against their perception of the relative difficulty of the road to recovery. It likely also captures some hidden correlations not captured in the variables this study includes, as the measure is likely to correlate with the delay the patient has allowed themselves to undergo before seeking treatment and hence the severity of osteoarthritis at surgery. The study seeks to identify self-efficacy as an independent predictor of patient outcome. As such, other mental attributes are incorporated into the regression analysis, many of which have very high correlations and hence lead to some results vulnerable to misinterpretation. One such result is the high level of power given to anxiety to predict poor pain outcomes in the multivariate analysis, which is likely reflecting a combination of its correlation with depression and depression’s own negative correlation with pain severity and the ceiling effect of the score. As such, it is important in regression based models to interpret the true independence of a predictor through the lens of what other factors it has been regressed with. In order to

preoperatively predict postoperative outcome, the patients psyche is relevant only in so far as its impacts on their response to their changing pain state.

Nevertheless, self-efficacy is a useful factor to incorporate in that it captures psychological information explicitly linked to the patients osteoarthritic state and upcoming surgery (it is a measure of how capable they feel of overcoming specific challenges), something which more generic mental health scores do not touch upon. As such, with a relatively small cohort (220 patients), the study was still able to identify self-efficacy as a significant predictor of functional outcome, though not pain. It is worth noting that the study does not find a previously identified link with depression [112, 126, 127] to emerge as an independent factor either, and the author in assessing the landscape of preoperative prediction has previously identified the need for large cohort studies [131]. This could be attributable to insufficient sample size. The author hypothesizes that the causal link might be that greater pain is not in anyway mitigated by self-efficacy, but the pain aversion based component of a patients functional outcomes are - more self efficacious patients are better equipped to overcome pain in restoring their lifestyle. As an observation from this, it is worth keeping in mind the nature of PROMS scores in that their construction and categorization into subscores such as pain and function is not an attempt to isolate specific components of a patients experience post surgery, but to form a number of (sometimes subtly) different clinical perspectives with which to assess their outcomes. It is therefore interesting that the regression did not choose to use preoperative pain as a regressor for postoperative functional outcome or vice versa. It is reasonable to hypothesize that if self-efficacy is capturing the capability of a patient to overcome pain-based disability postoperatively, then a patient with a much higher preoperative functional state than their pain state is one who is highly self-efficacious and the addition of the additional score required to assess this pre-clinically is redundant.

Some further evidence exists that self-efficacy is a major factor. A similar study assessing personality type with a validated instrument as a predictor of TKR showed personality types identified as 'unstable introverts' as being the least likely to express satisfaction post surgery [132]. The paper then goes on to touch on the correlation of this personality typing with self-efficacy and pan catastrophising behaviours, and the personality tests' metrics of neuroticism and extraversion are presented as alternate categorical labels for tendency to catastrophise and self-efficacy. The paper does not seek to find independence of personality subtyping as separate from self-efficacy or other factors but instead profiles another instrument with a more discrete categorisation, acknowledging the problem of an enormous amount of psychological attributes, all of which are imperfectly captured by questionnaire instruments both in terms of design and in terms of response noise and representing factors that are highly correlated. As such, making decisions on instruments for profiling psychological risk factors requires considering multiple dimensions, with a limit caused by survey fatigue and clinical practicality. The amount of correlation or predictive power contributed is not possible to glean from assessing many studies side by side, as sample size, the population sampled from, the other variables regressed against, the different regression or risk analysis techniques used, and the target postoperative outcome all vary. As it is, this particular profiling instrument and others like it[133] suffers from a known issue with binary categorisation of factors that are distributed across a normal curve. Most people would assess themselves as somewhat in the middle of the introversion spectrum, and many of the splits would seem arbitrary (a 49% score is introverted, a 51% extroverted) and suffer from test-retest reliability issues.

Some controversy does exist on this point, with the exact nature of self-efficacy as a construct and its relationship to patient expectations of outcome somewhat unclear [134, 135]. Haanstra et al. show an ability to separate several mental constructs such as optimism, pessimism, hope, treatment credibility and treatment expectancy into individual

psychological factors. However, upon incorporating a general factor into their 5 factor model they find a better fit to the data, despite the presence of some specific variance, suggesting the clinical relevance of separating unique psychological factors may be limited.

Yakabov et al. studied a metric called the Injustice Experiences Questionnaire (IEQ), adapted for TKR recipients [136]. The questionnaire covers three major aspects - do the patients consider their condition irreparable or believe that their life has been permanently negatively impacted, do they interpret it as being in some manner "unfair" and do they consider someone else partly at fault for their condition. The study takes a conservative methodology of stepped introduction of factors into a linear regression model, assuming the factor they wish to correlate has the least significance and is introduced last, aiming to predict WOMAC pain and function scores. As usual, dominant factors are presurgical pain and function scores, and it is worth keeping in mind that these scores likely drown some of the significance of other psychological scores. However, when analysed in univariate regressions, the IEQ had a stronger correlation. It is worth considering the nature of the IEQ and the postoperative scores being considered here. The results for the IEQ questionnaire are dramatically lower (by a factor of 2 to 3) to scores recorded in the questionnaires native domain of injuries and accidents. This certainly makes sense, as the patient group is older and is suffering from a degenerative condition without a source to direct their blame towards. As such, it is possible that the IEQ is acting as a filter for a relatively small amount of doomed-to-dissatisfaction patients, rather than a tool capable of categorizing patients across the breadth of outcomes.

Pain catastrophisation as a potential predictor is further explored by Riddle et al. in their 2010 study of 157 patients [137]. The authors investigate a number of different preoperative indicators linked to psychological status including depression, generalized anxiety or panic disorder measures. This study used the same measure for pain catastrophisation as Sullivan et al's study [138]. This study also sought to binarise the results

of the pain catastrophisation score into a 'high' or 'low' bin but, in the absence of good literature references to the same or a procedure to do so, resorted to segmenting the highest tertile of the patient population into the high pain catastrophisation population group (PCS>16). This study also took the route of characterizing its results in a logistic regression with its improvement scenario based off a percentage gain on the initial state. While this is a very relevant and valid approach to determining the outcome of the procedure, it is different from those explored previously and this makes comparison of the results of this study and synthesis of its odds ratio findings into other models problematic at best.

There is some complexity in how the pain related aspects of psychology relate to outcome. Studies have shown the pain related to pain central sensitization may be a major factor, with patients who reported high pain at rest and low pain thresholds, both signals for pain sensitisation [139, 140], are significantly more likely to be suffering recurrent pain postoperatively [141]. This physiological behaviour is tied closely to pain catastrophising personality types and exists at the border of what can be called psychological in nature [142]. While this represents just one of many possible explanations for post-operative pain following TKA [143], it remains an underexamined and under appreciated area in current surgical practice.

2.3.4: Expectations

Attainment of expectations appears to be a major driver of postoperative satisfaction. Bourne et al.'s [70] study of 1703 patients looked at TKR satisfaction from the perspective of categorizing who is satisfied and who isn't without a focus on prediction by allowing other postoperative variables to feed into the patients prediction of satisfaction. This study found that by far the greatest 'predictor' of dissatisfaction is when the patients expectations have

not been met, more so than any other preoperative or postoperative factor. This finding may seem obvious, but it is interesting as patient expectations being a major predictor of satisfaction represents a very realistic pathway for future interventions towards improving patient outcomes by aligning patient expectations to their surgeons, which have been shown to be radically different (varying between practices and patient groups)[144-147]. Overly optimistic patients who do not achieve their unrealistic expectations have a believable path to poor performance as a result of their mindset; similarly, overly pessimistic patients may be dooming themselves to a negative perception regardless of their actual surgical outcome [148]. On another note, the ability to predict with some confidence a patient outcome, and present it to them as slightly more optimistic than it actually is may push the patient towards better outcomes, ethical considerations notwithstanding. The findings of this study are consistent with many others [149-151], though some controversy remains over the exact definition of satisfaction and expectations [152], the nature of the instruments used to measure the construct expectations seeks to capture, the dependency of those instruments on other psychological constructs and the capacity of those instruments to capture these results in a repeatable way [134].

Sullivan et al's study [153] goes somewhat deeper, looking at presurgical expectations and breaking it down into response expectancies and behavioural outcome expectancies. Response expectancies cover involuntary factors such as pain and ability to sleep. Behavioural outcome expectancies cover factors related to the patient's own decision making such as their capability to overcome specific barriers. The two factors are linked in a similar way to how self-efficacy is linked to preoperative pain scores, but capture both factors in the context of the patients expectations preoperatively about the post-operative state. The results show that the behavioural outcome expectancies better predict pain severity and function at follow up than response expectancies do and outperforms other psychological attributes outside of pain catastrophising, lending further credence to the idea

that incorporating some element of a patient's beliefs about their own capability tempers the noise found in purely psychological attribute based predictions. This builds on earlier work by the author which had isolated the different psychological determinants and their interactions in post-surgical pain and function [138].

It has been shown that expectations are modifiable, and this presents a mechanism to positively influence the satisfaction outcome of a TKA surgery. Mechanisms to drive surgeon-patient expectation alignment begin with first measuring the expectation gap between surgeons and patients on a per patient level using a validated questionnaire instrument, of which there are a number available [147, 154, 155]. Expectations have been shown to be alterable with patient education classes or other information dispersion mechanisms. Some of these studies have used personalized/patient specific reports to achieve this [156-159]. As such, they have necessarily incorporated an understanding of the patient decision making process into their design & development [160] and an understanding of the psychological factors at work. However, approaches such as this, despite their relevance to a preference sensitive clinical pathway such as TKA has seen relatively little clinical incorporation [161, 162].

2.4: Anatomy & Surgical Practice

2.4.1: Surgical Drivers of Outcome

Surgery practice is known to impact patient outcome, although the exact nature of the relationships involved are not easy to discern. There is conflicting evidence of the role component alignment, both in terms of accuracy and the target alignment itself on outcome. Many of the distinctions in alignment approach are subtle, such as gap balancing to a mechanically neutral coronal cut [51], which is an alteration to rotational alignment setting technique on an otherwise mechanically aligned knee. The kinematics achieved surgically and the resulting balance in the joint may resolve some of this confusion, but these are generally harder to study and therefore less frequently studied, as well as difficult to relate back to a specific alignment decision.

Asides from these factors, it is important to note the continued role other surgical factors and surgical incidents have on outcome. Infection rates, ROM achieved on the table while operating [110, 163] and surgeon training and volume of operations [40] are all drivers of patient outcome. As a result, there is by definition a level of 'gap' that no predictive model will ever close by definition. Prolonged operating time as a broad catch all predictor for surgery complications also has predictive power, though the causality is unknown [119].

2.4.2: Patient Specific Anatomy

Patient variation is known to exist and understanding and appreciating this variation is necessary to understand the confusion that exists in the literature regarding knee alignment. Coronal angles of the long leg and of the femur and tibia individually are known to vary extensively. Belleman et al's 2011 study investigates a healthy reference population

of 250 adults aged in their mid 20's to establish a reference for native population coronal angle [164]. Prior to this study, coronal angle was known to vary across the population but broadly assumed to have a mean value 0° , implying that this was a healthy norm and patients, for whatever reason, deviated from it. Bellemans' study showed that a) the mean coronal angle was not mechanically neutral, b) even in healthy populations, the variations was extensive (with 32% and 17% of men and women respectively having a constitutional varus angle greater than 3°) and c) this variation extended to constituent coronal angles such as the Medial Proximal Tibial Angle (MPTA) and Lateral Distal Femoral Angle (LDFA) (see Figure 3).

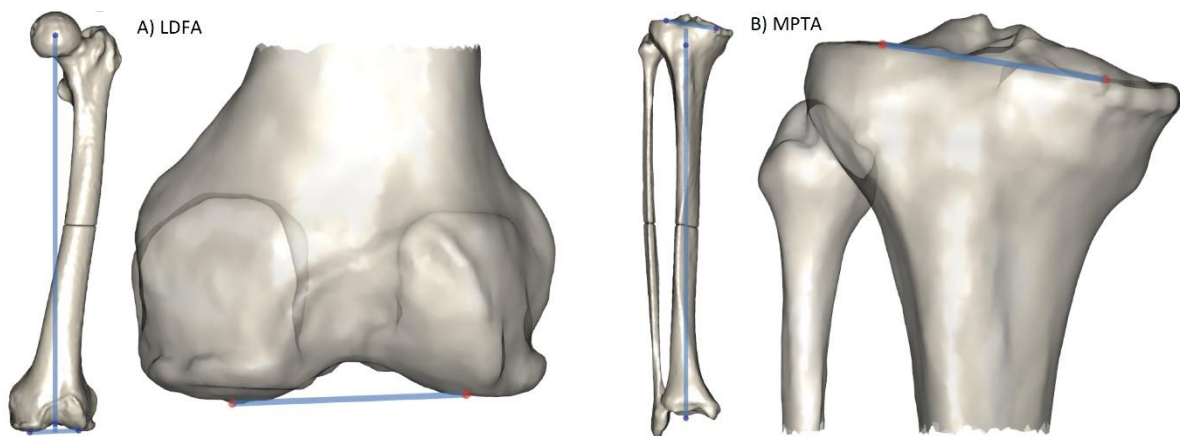


Figure 3: A) Medial Proximal Tibial Angle (MPTA) and B) Lateral Distal Femoral Angle (LDFA)

Similar work from this group has confirmed the impact of these observations on the osteoarthritic knee. A prior study investigated the impact of the presenting coronal alignment of the worn knee on mediolateral ligament stress and found that correctability of the knee (the ability to straighten the knee to neutral without modifying the attachments or structural integrity of the ligaments) to be highly impacted by the coronal alignment of the knee [165]. This implies that 'correction' of the ligaments would be required to straighten the knee; coupled with the previous observation, this implies that in some cases this 'correction' is not a correction to a prior, undeformed state of the knee but a modification to a position it's never been before.

A further study investigates the interaction of constitutional varus and joint line angle to the floor, finding that constitutionally varus knees do not have patterns in joint line angle differing from mechanically neutral knees [166]. The study concludes based off the mean values for each group that both neutral and varus knees are 'parallel to the floor' but neglects to consider the extensive population variation around each mean value implying a level of patient specificity. Besides from impacting the decision that is to be made about alignment in surgery, the shaft angle of the distal femur has also been shown to vary significantly [167], potentially impacting ability to reach a decided upon alignment.

The MPTA and LDFA that make up the joint line angle to the floor are crucial considerations. Ligaments have been previously described as isometric under flexion, though doubtless there is some level of patient specific variation [168]. In order to achieve this in a postoperative knee, changes to the collateral ligament path distance must be maintained in the postoperative position, and so there is a logical argument that changes femorally to the distal condyles must be mirrored in the posterior condyles. Femoral rotation of the Transepicondylar Axis (TEA) relative to the posterior condyles show extensive variation [169, 170]. The TEA is used as an anatomical marker for the centre of collateral ligament attachment and this variation calls into doubt a number of techniques used for setting rotational alignment. While relationships between coronal and axial relationships do exist, ability to rely on them is not known [171, 172].

Beyond these core anatomical variations, a number of other areas of intra- and extra-articular variation do exist with biomechanical implications, pre and post TKA implantation. These include femoral anteversion [173], tibial torsion [174] and trochlear groove morphology [175].

2.4.3: Alignment Philosophy

A number of decisions are made regarding alignment of the knee during TKA. At the highest level, there is a decision of an alignment philosophy that is to be followed. Riviere et al.'s literature review presents the current alignment options to be considered [176]. The most prominent remains Mechanical Alignment (MA), a systematic approach in which all knees are restored to a neutral angle coronally. This approach remains the default and adherence to it historically has been shown to boost implant survivorship [177, 178]. Variations do exist, with tibial first gap balancing techniques driving rotation of the femoral component to equalise flexion gaps [51], whereas bone referencing techniques use identified bony landmarks or fixed references to achieve rotation [179].

Anatomic Alignment is another systematic technique aiming for a coronally neutral long leg with a 2° sloped joint line in all patients, though this technique has seen minimal adoption [176]. Adjusted Mechanical Alignment is a technique used to 'under correct' frontal deformities by implanting the femoral component in residual varus or valgus to reduce soft tissue strain while maintaining a mechanically neutral tibia. In theory this technique could allow for some benefit of following the natural anatomy while limiting exposure to implant wear concerns from uneven tibial load distributions. It is often used with a tibial first gap balancing technique so rotation can be selected to match the distal angle implanted.

Kinematic Alignment (KA) is the most prominent alternate alignment technique to MA. It can be thought of as a 'knee resurfacing technique', with its major goals being to resurface the knee by replacing removed material with implanted material in such a way as to exactly match the healthy norm for that patient [47].

A number of challenges exist to this approach. The first is the difficulty in defining the healthy norm. Studies exist with evidence that this is predictable in the femur, but similar

observations do not exist for the tibia [180]. The second is concerns regarding survivorship. Although research has shown that even in extremes of KA intra operative joint forces remain balanced [181], no such finding exists for external loading directly. There are, however, studies which have shown a tendency for KA knees to maintain a near parallel joint line to the floor [182], reflecting research that this is the healthy norm for most knees [166] and there is not a documented trend of increased early failure for KA TKA [46].

Nevertheless, there exists a string of high quality prospective comparative research suggesting KA implanted patients experience an outcome improvement over MA implanted patients. Published literature reviews weighing all the available evidence have concluded there is a patient outcome advantage to be had for KA [183-185], while studies that have failed to find a difference have not necessarily been structured appropriately. The study by Young et al is one such example, prospectively powering its study to find a difference of 5 points in the OKS, the Minimum Clinically Important Difference. This not a reasonable basis to conclude there is no significant effect as the purpose of the MCID is as a within patient comparator, not an assessment of whether a treatment is useful for a population. Put another way, if 25% of patients KA were to receive an 11 point boost in their OKS score while 75% had no change, then the mean difference would be 2.75 points and not found to be significant in such a study, while also reducing patient dissatisfaction from 20% to 15%, clearly a worthwhile intervention [84].

The last alternate alignment approach is a derivation of KA, called Restricted Kinematic Alignment (rKA). This technique replicates kinematic alignment up to a point, cutting at a 'safe zone limit' of coronal angle when faced with unusual patient anatomy (which occurs in 1/3 to 1/2 of cases) [186, 187]. This technique may be a safer approach to KA than what currently exists, combining the advantages of both techniques, but to date there is no clear evidence one way or another.

Separate to alignment philosophy decisions, there are a number of other, smaller scale decisions to be made in TKA. Rotational alignment of the femoral component is one. There is a relatively fixed philosophy for rotational alignment with KA but a number of competing techniques when considering MA. Broadly these can be considered to be one of either a) a gap balancing technique, b) a sight the TEA and match technique, c) a follow Whiteside's Line technique (WSL) or d) a fixed increment from the Posterior Condylar Axis [179] (PCA). Of the bony references, the TEA is often cited as the best approximation of the native kinematic flexion axis. Previous studies have shown the TEA to more closely match than both WSL and the PCA the projected transverse axis in flexion within a set of cadaveric knee specimens [188]. Other studies have confirmed a closer match to the native kinematic flexion axis [189], the recreation of a more balanced flexion space [190, 191] as well as more stable patello-femoral kinematics [164, 172, 192]. However, the TEA has also been shown to be extremely difficult to target intraoperatively, leading to the propagation of alternate techniques [64].

Setting tibial rotation, likewise, has a number of different techniques in use. There is even more observed difficulty in setting tibial rotation consistently amongst surgeons than femorally [63], and numerous alternate axes have been developed as targets [193, 194]. One thing the literature can agree on is a clear link between aberrant tibial rotations and postoperative pain and functional impairment [195, 196].

2.4.4: Kinematics & Simulations

Kinematics and kinetics of the patients joint are the ultimate result of the interaction between the patient specific anatomy and the component alignment decisions made during

the operation, and it is reasonable to hypothesise that the mechanism by which the surgery affects patient outcomes will be in large part through its impact on kinematic outcomes. In order to study these impacts, it is first necessary to measure TKA kinematic outcomes.

A number of techniques exist to achieve this. Functional techniques such as gait analysis and video fluoroscopy are a means of capturing accurate kinematic information [197].

Mechanical rig testing is an alternate approach but is limited in its capture of patient specific factors. These techniques are used in design validation studies [198], but due to the cost and burden are not especially scalable. Dynamic knee computer simulations are a more scalable alternative [199] and allow the study of both patient and surgical factor's impact on joint dynamics following TKA [200, 201]. Simulations are increasingly used to study the impact of component placement variation [202-204] and are able to incorporate patient specific elements with readily available diagnostic radiology such as Computed Tomography (CT) scans [205, 206].

Development of such a simulation, built in such a way as to allow a patient specific result to be obtained without harm to the patient would allow the kinematics to be related directly to the patient outcomes, potentially solving for the interaction of patient anatomy and alignment decision [207]. Such an approach would enable greater insight into the specific relationship between decisions made in surgery and long term patient outcomes.

2.5: Preparation and Recovery

2.5.1: Postoperative Recovery

Recovery from the surgical operation is a major part of the surgical experience. In the acute context, days 1-3 following surgery, more than half of all patients suffer from severe pain at rest[208]. The proportion of patients being woken by their pain/suffering sleep impairment actually increased from day 1 to 3, suggesting a weakness in the pain management strategies in use, although there is no evidence that this has any impact on longer term outcomes.

There is also evidence that minimising the time spent in hospital improves patient satisfaction [209]. A number of risk assessment tools exist to determine patients most at risk of longer stays in hospital [210], one of the most common of which is the Risk Assessment and Prediction Tool (RAPT)[211, 212]. In addition to the patient characteristics covered in these prediction models, provider characteristics are relevant and in many cases the dominant determinant of length of stay [213]. Early mobilization of the patient has also been shown to reduce length of hospital stay, [214] and early mobilisation is often included as a core element of clinical pathways designed to discharge patients as early as is reasonable [215, 216]. Clinical pathways such as this have been shown to reduce length of stay, though not necessarily outcome [217]. Readmission to hospital following surgery is a major driver of dissatisfaction and the destination to which the patient is discharged as well as BMI and other general health measures significantly impacted readmission rates [218-220].

Physiotherapy provision can be supplied in a number of ways. Traditional approaches have relied on in patient programmes, but they have generally not been able to justify their greater expense [221] with improvement in outcomes relative to telemedicine approaches

and home based programmes [222, 223], despite patient consumer preference [224]. It has been shown independently that telemedicine leads to higher satisfaction than no physiotherapy options [225]. Unfortunately, telemedicine can be hard to study, as every studies version of telemedicine differs somewhat in terms of what exactly is provided, at what frequency and for how long. Quantifying immediate postoperative outcomes with something quicker to evaluate than long term satisfaction might allow for more effective studies into post-operative service provision effectiveness.

2.5.2: Activity Monitoring Technology

One facet of the patient's disease state that functional instruments seek to capture is the degree of impairment and lost mobility brought on by OA. Recovery of this mobility is one of the major goals of surgery and is a crucial component of the assessment of TKA outcome. Historically, patient activity levels have been undertaken using subjective self assessment [226-229] using a number of different developed scales [93] or, occasionally, surgeon 'demand matching' of the patient [230, 231]. These tools have been able to go as far as finding some correlation between subjective self assessed activity levels and wear patterns & extent on postoperatively retrieved specimens [232] and have, in most cases, concluded that patients are more active after receiving a total knee replacement than before.

Subjective self reported measures of activity and mobility level have been shown previously to vary greatly from objective measures in non predictable ways, however, with sub population trends and variable subject level bias both skewing results [233-236]. End stage knee osteoarthritis patients have been previously shown, when objectively measured, to have reduced steps/day counts over healthy comparable age subjects, dropping from about 8800 steps at peak [237, 238] to 6600 [239]. These figures are highly variable within and between patient population groups, however, with delimitations such as public vs. privately

treated patients, age and gender all creating enormous variance [240, 241]. Seemingly at odds with this variation is the observation that only 3 days of active measurement are required to elicit a patient's activity level profile when assessing step count, which would seem to dispute the idea that patients will change behaviour on weekends vs weekdays and other distinguishing factors [242].

The objective measurement of activity level can be done in a number of ways. Step count is the most directly applicable to patient lifestyles, to the point where in rheumatoid arthritis sufferers it can be used as an assessment of treatment outcome [243]. Other studies have looked at activity monitor data as defined by some other metric than step count, including the % of the day the subject spent moving or upright [244]. Such measures can be considered to be measuring somewhat different constructs to step count, however, as it is not difficult to imagine a scenario in which subjects who are active and walking for the same amount of time achieve different step counts based on gait speed. Other studies have used accelerometry based at specific points, such as the study by Roberts et al. which correlated accelerometry data from the tibial tubercle to patient reported knee instability [245]. Gait analysis has also been a historical focus, though it has shown considerably more clinical relevance and effective clinical use in treatments of neurological disorders which more directly target the muscular behaviour that drives gait and movement [246, 247]. Step count has a significant advantage in that the variable it introduces is readily understood and so empowers patient self management of their disease state [248].

Wearable wireless activity monitors such as the Fitbit are an increasingly low cost, clinically relevant off the shelf option for monitoring patient activity levels. These devices have been shown to be valid and reliable assessment tools for ambulation in normal subjects specifically, and the whole field of pedometry generally has been shown to have similar effectiveness [234, 249, 250]. A number of existing small scale studies have looked at the value of wireless activity monitors in chronic disease assessment, but as of yet the author

found no published system wherein activity monitor data is currently being used as a tool for predicting patient outcome results [251]. Studies assessing activity monitoring data of TKA patients post-implantation have found conflicting evidence, but have concluded that patients do not exhibit significant activity level improvement after TKA from their preoperative state [252, 253] or alternately experience some improvement but fail to be restore to the activity level of age matched healthy subjects [254, 255]. However, these figures are averaged results for the full patient cohort, and no doubt hide a degree of variation between patients whose activity level increased and decreased postoperatively. This inter-patient variation in preoperative activity level and postoperative recovery activity level and speed is a potential indicator for medium term outcomes that bears more investigation. The variation between studies is significant as well. One study has, by comparison, shown an improvement of 79% of measured ambulatory activity after the operation [241]. Studies using this data have previously been able to show that higher levels of preoperative activity do lead to higher functional outcome post-operatively [256, 257]. Considering the amount of conflict in the reported results of such studies and their correlations with patient reported outcomes, it is worth deconstructing the exact biases or sample distortions that may be present in each study that has measured ambulation or physical activity in patients.

The first study worth considering is de Groot et al's, [252]. This study recruited a sample of 80 total joint replacement patients, 44 for Total Hip Arthroplasty (THA) and 36 for TKA's from a Dutch population group. This is unfortunate as the individual effects in the TKA population are not clearly reported distinct from the THA population group. As a result, ready comparison of the observations to the other studies assessed here is not possible. The study finds an increase in actual physical activity of 0.7% of the day at 6 months after surgery, a distinct time point from many other studies assessing at 12 months. This is a negligible effect size, as the authors noted. It is worth noting that this is a distinct measure

from many of the other studies in the same field, counting the percentage of time spent above an arbitrary level of activeness as defined by the activity monitor used. Of concern is potential observation bias based on the period over which the devices were worn (48 hours). The study notes efforts to avoid the impact of this observation bias by not explaining the explicit mechanical principles of the device and the measurements being made to patients until after measurements are captured, but it is reasonable to assume that some disclosure of the basic intention of the study (measurement of ambulation) would be required to patients for the ethics application of the study and there is no mention of patients being blinded to this basic intention. As such, it is feasible and reasonable to fear that the short observation period of the study does introduce an observation bias upon the patient, which may lead to patients in the postoperative environment striving to match their preoperative levels. One interesting reported demographic feature of the study is the Kellgren and Lawrence number, an indicator of radiographic osteoarthritis. Ready comparison of this figure to other studies might give some indication of the preoperative severity of disease state in patients, shown to vary between public and private environments or other health system structures, which would be an obvious modulator of preoperative activity level based on the basic principle that OA affected patients have reduced ambulation compared to healthy norms. Unfortunately, these results are not reported in many other studies and so synthesis of results cannot be done effectively.

Hayes et al.[258] study reports on energy expenditure quantification based on an intelligent activity monitoring device, similar in nature to that described by de Groot et al.[252] This study also found no meaningful change in its measure of activity level over 5 different recording periods, covering preoperative, 6 week, 3 month, 6 month and 12 month scenarios. This study criticizes the simplicity of the basic pedometer in its study structure, noting the lack of ability to perform in depth analysis of activity levels while also criticizing the relative complexity of gait lab measured gait patterns. This is an interesting observation,

as it is precisely the simplicity of the variable the pedometer reports (step count) that makes it appealing, allowing for a single value that is patient relevant, understandable and readily intervenable by patients in a self managed way to be reported, an argument that has been noted previously [259]. There is also an interesting dichotomy in terms of what is actually being measured. The device used in this study measures the amount of time spent walking as a percentage of daily activity and reports no meaningful difference on this parameter, but there is an implicit relationship between time spent walking, speed of gait and amount of steps being undertaken. If the parameter worth measuring is in fact functional impairment and its impact on the patient's ability to engage in their daily activities, then this study arguably fails to capture that distinction in its design. As a demonstrative example, a patient who had spent 5% of the day walking pre and postoperatively, whose gait speed was twice as fast postoperatively, would count twice as many steps with a pedometer in the postoperative scenario but the same amount of time spent walking. This criticism is common to de Groot's study and measurement technique. Likewise, so is the relatively short observation time period allowed by these devices (in this case, just 24 hours), although the sample size of 65 TKA only patients is relatively healthy. This study found similar observations to de Groot's in that it reported no meaningful gain in activity level.

Harding et al's study, [253] also of 65 patients (both TKA and THR), assessed patients over a 4 to 7 day period using a relatively small and unobstructive waist mounted device and so represents an attempt to overcome some of the potential observation bias seen in other studies. This study does note sample differences, including a BMI of their patient group larger than that reported in the previous studies. This study failed to find a relationship between activity level and pre and postoperative state, though trends were all in the expected direction (post operative patients being more active.)

Walker et al.'s study [241] as described previously shows an improvement of 79% at 6 months. It is worth dissecting the nature of the study, its measures and its patient group in

order to ascertain why its results differ so dramatically. The reported number of steps taken increases from 10,738 before the operation to 15,641 after, a dramatically higher increase than that reported in other studies (about 45%, as the 79% referenced describes energy expenditure level) which have been reported in the postoperative scenario as 4,988 steps per day [240] and 5,932 after the operation [254]. There does not appear to be any forthcoming explanation for this discrepancy within the paper. The population sample is very small (19 patients) but still finds statistical significance ($P=0.02$). This perhaps underscores the differences exhibited within populations that are not well captured by simple measures such as age and BMI, and the cross cultural and lifestyle factors that can influence outcomes of supposedly generic population sample studies. Alternately, it may be a demonstration of the fallibility of p-values [260].

Brandes et al's study, [254] like Walker's, assesses step count as its nominated outcome measure for activity level. This study found a moderate but statistically significant gain of about 20% in total step count from the preoperative to the postoperative scenario, increasing from a mean of 4,993 steps to 5,932. This study also found that the physical activity parameters it measured did not correlate with its clinical outcome scores, though it is unclear what is intended by 'physical activity parameters' and whether transformations of the underlying parameters to include constructed values such as the percentage gain on a per patient level from the preoperative to the postoperative scenario were performed. The study does make the point that these measures could be used as an assessment target for early recovery interventions designed to drive patient self-efficacy, and so with such a structure a clinical improvement mechanism could be generated.

On the whole, the literature suggests a plethora of objective activity measures in active use, though step count has a particular appeal as it is a readily understandable measure for patients. There is further evidence that information about a patient's own step count compels further activity, supporting this claim [261, 262]. The step count focused studies

available in the literature suggest small to moderate improvements do occur after TKA, but the nature of the relationship with postoperative and preoperative PROMS is unclear. Also unclear is the potential for a patient specific goal to drive appropriate post-operative activity levels during recovery and improve outcomes. Further exploration is warranted.

2.6: Predictive Tools

2.6.1: Predictive Tools in Use

Many of the pre-existing tools for selection for surgery are based on appropriateness criteria or prioritisation needs, and there are relatively few focused on predicting outcome itself [114]. However, a few do exist. One such example is that developed by Lungu et al. in their 2014 study [263]. The study used data from 141 patients to develop a categorization tree model using recursive partitioning, a statistical process for developing a set of hierarchal tree rules to arrive at a categorical prediction for a patient. Significantly, the model sought to predict inclusion in the lowest WOMAC quartile (not satisfaction) and the result that followed is reflective of this, with the final model being dictated primarily by WOMAC preoperative attributes. This is consistent with earlier evidence that preoperative PROMs score state has the strongest influence on post-operative PROMs state than any other predictor [112].

The model is able to achieve an area under the curve of 0.77, having slightly higher sensitivity (82.1) than specificity (71.7). This metric is within the training sample and there is no separate training sample, however, which suggests a risk for overfit (though use of a recursive partitioning approach curtails this somewhat as it is not as unconstrained a machine learning technique as more modern approaches.) Some of the findings are also difficult to comprehend - a patient is designated at risk with use of this model if they have moderate, severe or extreme difficulty taking off socks or stockings, but none or mild difficulty getting off the toilet. While machine learned prediction models cannot necessarily be expected to expose a causative relationship for their predictions, this is likely reflective of the limited sample size and lack of independent training data set (despite a bootstrapped sample being used as a comparator.)

The study by Onsem et al. [264] develops a prediction model to overcome the limitation of Lungu's by focusing on satisfaction. This allows the developed model to overcome the limitation of Lungu's in that postoperative PROMs scores are so dominated by preoperative PROMs scores, despite many other factors contributing to satisfaction. This approach also used a multiple linear regression approach to develop its model, using univariate regression to reduce the inputs from a wide set that included KOOS scores, the OKS, the Pain Catastrophising Scale (PCS), the Euroqol questionnaire (EQ5D) and the Knee Society Score (KSS). From univariate analysis they reduce the inputs to 10 questions which is used in the multiple linear regression. The regression models associations (with the group that was more satisfied) were; gender (males), age (older patients), overall pain (more pain), joint stiffness in the morning (less stiffness), grinding and clicking (less grinding), normal feeling of the knee (more normal), awareness of knee problem (less aware), anxiety and depression (less anxiety), mindfulness of pain (less mindful) and concern over a serious problem happening (less concern).

The regression was performed against a 40 point satisfaction assessment derived from the Knee Society Score and a linear regression model has been employed to predict outcome. The ultimate model has an adjusted R squared of 0.29, suggesting a decent portion but less than 1/3 of the variation in outcome has been explained. The results are then binarised (above 20 points equaling satisfied, below unsatisfied) to derive a sensitivity of 97% but a specificity of 50%, suggesting a model that rarely fails to pick patients that are at risk but can only highlight 'potential' problem patients, not confidently say they're at risk. An opportunity existed for this model to use binary logistic regression to predict probability of falling into the satisfied group, but it has not been applied in this way. This is unfortunate, as prediction of satisfied vs. not satisfied can be assumed to be an easier target than an absolute score on a 40 point scale. This model, again, suffered from a relatively low sample size (113 patients) and did not have sufficient numbers to allow for an internal

training/testing data set approach, so these observations have not been tested with external data sets.

Sanchez-Santos's study [265], working with data from the Knee Arthroplasty Trial in Britain have also developed and externally validated a model for predicting 12 month Oxford Knee Score. This was done in association with Judge's research group, who in addition to aforementioned work identifying risk factors have previously developed a tool for Total Hip Arthroplasty recovery [266]. This study recruited higher patient numbers (1,649) but arrived at a lower R squared value than Onsem's (0.176 under internal validation and 0.211 with external validation, which significantly did not exist with any of the previous described studies). Significantly, surgical factors such as fixed flexion deformity and a damaged PCL were included in this model, not just patient factors, with both measures of knee damage associating with a better outcome. Caution is advised with interpreting these coefficients in this way, however, as interaction effects between variables mean that a positive relationship in the regression is not indicative of a univariate relationship. Again, one explanation for the relatively low performance of this model could be the target, as prediction of an absolute PROMs score is known to be difficult.

Prediction tools for outcome in terms of PROMS are relatively rare, and in many cases flawed in terms of their predictive capability. This is unfortunate, as there is enormous potential for such tools to positively impact pre-surgical selection and management of patients.

2.6.2: Shared Decision Making

Altering a patient's expectations, as described earlier in this review, is one mechanism by which a better satisfaction outcome might be derived. The other is changing the decision to

operate on a patient who may have a modifiable risk factor that can be dealt with prior to the operation, or until their osteoarthritic degeneration has progressed further. A third approach is found in the concept of shared decision making, an area of study focused on the degree to which patients are informed prior to and take ownership of decision making processes. Decision making around knee replacements is highly complex [160]. There is evidence suggesting that patients informed about their decision to operate and the risks and benefits are more likely to be satisfied [267, 268], and the degree to which a surgical consultation has led to a shared decision is measurable, though not without burden [269-271].

One practical application of this concept is in the supply of decision aids. Decision aids involve carefully constructed information packages designed to inform the patient of the risks and consequences of a decision either way. The risks identified and presented to the patient may be standardized but are more powerful when they take into account patient specific risk factors. They have seen success in other fields [272] and there is an appetite for integration into total knee replacement [161, 162].

So far, use in total knee replacements has been largely limited to lifting uptake amongst fringe groups that avoid surgery [156, 157] or studies attempting to correct for distortions in regional surgery uptake as a cost cutting measure [159, 273]. The exception to this is the study by Manusco et al., who showed that expectations can be modified with the deployment of such tools, which when coupled with personalised risk assessments has the potential to positively influence satisfaction likelihood through both the expectation and the shared decision making mechanism [158].

2.6.3: Decision Support Systems

In summary, despite the research that exists into risk factors for poor outcomes, there are five dimensions across which research findings in separate contexts are prevented from being synthesized into effective clinical tools. The first of this is the target population, with significant variations observed across fundamentally different healthcare regimes that affect a patient's surgical experience and characterize the demographics for the relevant patient groups selected (that is, it is not just how the patients experience in receiving a joint replacement but who was able to receive a joint replacement in each country [107]). The second is the nature of the PROMS or satisfaction metric used and protocol biases in how it is applied (self-administered vs guided, for example [75].) The third is whether satisfaction itself or PROMS are actually the target metric at all, as these correlations have been shown to be moderate to weak [104, 152] and the functional and pain states of the patient postoperatively contribute holistically to satisfaction [274]. The fourth is how a successful PROMS result is defined and whether its an absolute outcome score that can be considered to succeed or a relative improvement from a preoperative state [84]. Finally, the use of different instruments in defining the predictor variables and confusion about the constructs they represent, particularly in the psychological area makes comparison of studies with disparate results even more troublesome [134, 135].

These factors influencing postoperative outcomes are all well summarized by Vissers et al. in their review [125]. Despite being a comprehensive, systematic review, a quantitative best evidence synthesis was not possible due to the lack of standardization in outcome measures in the pooled scores. As a result, the combination of observations is somewhat qualitative in nature, despite the best intentions of the author.

A decision support system is one means by which these issues might be overcome [275]. Tools such as this are effectively computational implementations of clinical prediction tools that don't necessarily give a prediction as an output but a recommended course of action, or information to drive selection of a course of action. Bayesian Belief Networks are one

means to develop a decision support system. There has been some application of BBN structures among other expert knowledge systems in the field of rheumatology, though so far real clinical applications have been absent [276, 277]. Other medical fields that have seen implementation of successful BBN models into a clinical context include echocardiography [278], preclampsia [279] and colon cancer prognostics[280]. Particularly appealing in this structure is the relative ease with which expert knowledge modeled observations can be pulled into the model to enhance its predictive capacity and avoid some of the issues associated with the fractured nature of the available data in the literature [281]. These observations can be pulled from either expert individuals, [282] teams [283] or through literature meta analysis [275, 284, 285]. As a further point, Bayesian models have an additional advantage in that the Bayesian Network structure's precision of diagnosis can be quite insensitive to variation of parameters [286].

2.7: Summary

As such, this research's aim will be to investigate and develop mechanisms by which patients' outcomes may be improved post-TKA. Two broad branches of investigation will be pursued in order to achieve this. The first will focus on alignment of the components in surgery and attempt to find a way to step beyond rigid alignment referencing rules in order to drive improved outcomes in patients postoperatively. The second will focus on how patients can be better managed outside of surgery, either through pre-surgical preparation or post-surgical management, or selecting patients for surgery more likely to have a good outcome. In pursuing all this, a database will be created and maintained to provide a research and development resource stretching beyond the life of this doctoral thesis.

Chapter 3

Unexpectedly High Incidence of Anatomical Deformity Across a Population of Prospective TKR Patients

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This chapter covers a study investigating the range of anatomical variation amongst patients and compares it to what might be anticipated by a standard surgeon user group and literature reported values for healthy (non-osteoarthritic) patient populations. It is found that rates of deformity and patient linked variation are underestimated by surgeons, and hypothesised that the use of 'standard patient' referencing rules of thumb surgically with variable patient anatomy might be a driver for poor outcome. Important to the development of this study was creation of a database of measurements able to be readily updated from the 'working files' of 360 Knee Systems' surgical planning process, a tool which has been used in subsequent academic publications both contained in this thesis and otherwise.

3.1: Abstract

Background: Accommodating and correcting anatomical deformities and patient anatomical variation is a major consideration in TKR planning. Rotational alignment is rarely interpreted in the context of the full axial rotational profile of the patient, and the incidence of such deformities is not well understood. This study aims to characterize the incidence of anatomical deformity present in a population of TKR patients compared to the expected.

Methods: A database of patients from 1-Jan-2014 who had a pre-operative CT scan segmented and landmarked as part of a surgical planning process was accessed. From these landmarks, the Femoral Anteversion, Posterior Condylar Angle, Tibial Torsion, Tibial Lateralisation Angle, Medial Proximal Tibial Angle and Lateral Distal Femoral Angle and were all calculated, and incidence of surgeon defined deformities were compared to expected rates.

Results: The population group of 2057 patients contained large anatomic variation. In general, incidence of deformity was significantly underestimated, and significantly more so in the tibia than the femur. Correlation in the anatomical measures captured here were weak, implying deformities were present independently from each other. Results for the coronal angles and the Posterior Condylar Angle differed significantly from the healthy reference population used as a comparator in this study, although this did not appear to drive the underestimation of deformity.

Conclusion: This series of anatomical measurements demonstrates extensive anatomical variation amongst patients, and unexpectedly high incidences of anatomical deformity. Further research is required to study the impact on Patient Reported Outcomes associated with the prevalence and surgical response to deformities in TKA, which may lead to improved surgical planning in these patients.

3.2: Introduction

Despite technological advances such as improvements in accuracy, development of new surgical approaches and changes in implant materials, total knee arthroplasty (TKA) procedures still present considerable rates of patient dissatisfaction with 15% to 20% of individuals reporting long term pain [37, 70, 123, 287]. An integral element of success in knee arthroplasty is achieving an optimal alignment and a balanced outcome with the femoral and the tibial components of the knee, which has both biomechanical consequences [288] and has been shown to relate to patient outcome [65].

There are different surgical approaches aimed at achieving adequate knee alignment, with the dominant practice remaining a Mechanical Alignment (MA) approach. Instrumented surgical TKA for anatomically referenced MA follows specific existing anatomical reference rules, relying on tools such as intramedullary rods to reach a coronal alignment within 3° of a neutral mechanical axis [49] and fixed references for rotation such as setting the femoral component to 3° of external rotation from the Posterior Condylar Line [179]. However, many of these measurements rely on assumptions about the expected patient anatomy which is known to vary throughout the population [164, 167, 289].

At the extremes, this variation is categorized as a deformity, particularly if these variations cause pain and further deterioration at the knee and other joints. These deformities can arise from congenital, environmental or pathological origins, and can be classified as either intra-articular or extra-articular. The presence of these deformities is relevant to the planning and intra-operative adjustments required in the TKA surgery for two major reasons. The first is that they can compromise the surgeon's ability to achieve a desired implant position using standard techniques [290, 291], and the second is that the desired component position and alignment may require accommodation or correction in order to address potential biomechanical consequences of the deformity [292].

Intra-articular deformities can be either corrected or accommodated during surgery. Examples of these deformities include extremes of angles such as the Posterior Condylar Angle (PCA) and highly lateralised tibial tubercles relative to the tibial plateau geometry [293]. Extra articular deformities, by contrast, must be accommodated during TKA surgery if a secondary corrective surgery is to be avoided, and include examples such as tibial torsion and femoral anteversion. Despite not being centred on the knee joint itself, these deformities can have biomechanical and surgical consequences [174, 294]. Coronal alignment deformities can be extra- or intra- articular in nature and can result from trauma, fracture malunion, congenital disorders and nutritional and metabolic causes [292, 295, 296].

The manner in which individual deformities can impact the surgical procedure varies. Rotational alignment of the femur in an MA, anatomically referenced TKA has been shown to have a major impact on post-TKA kinematics and alignment to the surgical TEA seems to give the best results for both tibio-femoral [188] and patella-femoral kinematics [297]. However, these landmarks can be difficult to identify intra-operatively [63, 298] which leads to the adoption of fixed references from the more reproducible Posterior Condylar Line, which may not be adequate when the anatomical variation present is considered [290]. Similarly, accurate tibial rotational alignment using direct landmarks can be challenging to capture [63], which can lead to simple references such as prioritising the anatomical shape of the cut plateau [299] and potentially leading to negative patient outcomes [195]. Accurate CT scan based planning may help, but is not the dominant practice [300].

Extra-articular rotational deformities have a few potential impacts. Tibial torsion has been shown to introduce error in other cut planes when present in patients operated on using an extra-medullary alignment jig [291], while also having a kinematic impact on the joint loading and patellar tracking of the knee [174, 294, 301], potentially as a driver of primarily medial patterns of osteoarthritis development [302]. Hip anteversion, by comparison, has

less of a clear impact but in concert with tibial torsion and rotation at the knee joint plays a role in defining torsional force distribution at the knee and the limits of foot angle a patient is able to reach during gait. [303, 304]

Consequence and handling of coronal deformities varies with the alignment technique to be used. Kinematic Alignment (KA) is one alternate technique that aims to restore coronal alignment rather than reconstruct to MA. The justification for this approach is the observation that greater levels of deformity further alter the native soft tissue balance of the knee, and returning to MA risks creating an uncorrectable imbalance [305]. This approach attracts some controversy when considering the extremes of native coronal alignment, and restricted Kinematic Alignment (rKA) is a proposed compromise [186] to handle the deformity intra-articularly. Extreme deformities that are extra articular can be accommodated or handled with a compensatory distal femoral or proximal tibial wedge resection. Hungerford proposes 4 considerations that must be taken into account when choosing between intra- and extra-articular corrections: the magnitude of the deformity; the relationship of the deformity to the knee, whether it is varus or valgus and whether it is at the femur or the tibia [306]

Previous studies have measured the incidence of anatomical deformities in healthy knees in typically developed populations. For instance, Bellemans et al.[164] found that 32% of men and 17% of women in a normal population of young healthy adults had constitutional varus with a hip knee angle of 3 ° varus or more. Major drivers of this were the Medial Proximal Tibial Angle (MPTA) and the mechanical Lateral Distal Femoral Angle (LDFA). Victor's literature review on femoral rotational alignment, similarly, found that there was large inter-individual variabilities in the Posterior Condylar Angle measurement [179].

To this date, there is limited information on the incidence of pre-surgical deformities in populations of individuals with osteoarthritis (OA), in part owing to a lack of consistent

definition about what would constitute a deformity measurement. Incidence of presurgical deformities may be underappreciated, particularly in rotational deformities, as these cannot be detected by traditional radiographic imaging. Rotational deformities are better identified using CT imaging, [193, 300, 307] and well characterised in 3D reconstruction [305, 308]

The advantage of CT imaging has been corroborated in cadaveric studies such as the one carried out by Chauhan et al. [307] who compared CT scans and a conventional jig-assisted TKA in six cadavers. The CT scan based technique identified multiple parameters quantitatively and showed better individual and relative alignment of the tibial and femoral components. Similarly, Khare et al. used pre and post operative CT scans in 12 cadavers to determine errors between a hand-held robotic partial knee replacement technique and a manual, conventional technique [309]. However, these studies report errors between pre and post-surgery measurements but no absolute rotational values either the preoperatively or postoperatively were reported.

Accurate identification of anatomical angles preoperatively can determine whether a patient's native anatomy is within normative alignment ranges in the coronal and axial planes or if indeed this is pathological and might require special consideration surgically. This study aims to quantify the incidence of a number of described deformities observed prior to TKA in a population of individuals with OA, as defined by surgeon expectation and compare these results to both literature norms for healthy patients and surgeon expected rates of deformity.

3.3: Methods

Data for this study was acquired from the 360 Knee Systems Database, a Human Research Ethics Committee approved registry kinematics (Bellberry Human Research Ethics Committee, approval number 2012-03-710). Patients contributing to this database undergo a full pass CT scan from the proximal femoral head to the lateral and medial malleoli, which is then used in routine pre-operative TKA planning and creation of patient specific surgical delivery tools.

CT scans were segmented and landmarked by engineers to define patient specific axes from which all anatomic measurements were made. The selection of the landmark points was performed independently by two separate engineers to improve the quality and accuracy of the landmarks chosen. The differences were algorithmically compared, and a mean result found. If a large difference between any two user selected landmark points was found, the landmarking was then triple checked and a new point in relation to the other two points was determined.

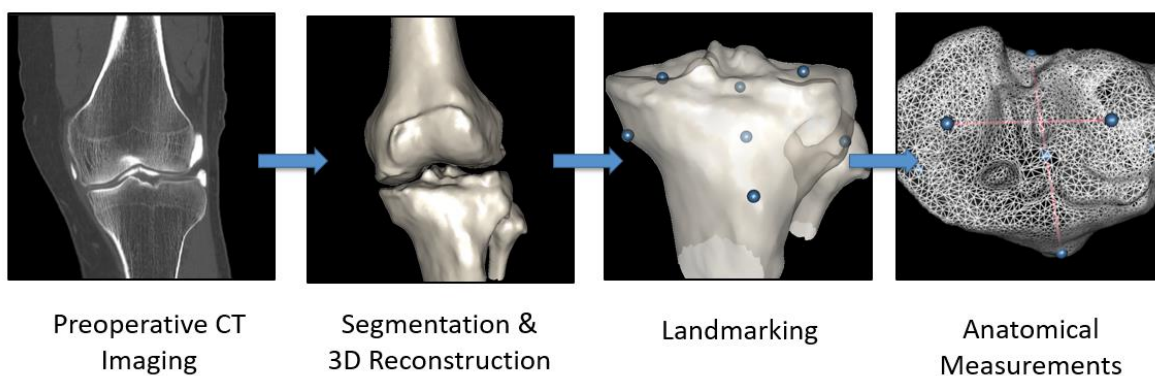


Figure 1: Workflow for deriving anatomical measurements from CT scans

The mechanical supero-inferior (SI), medio-lateral (ML) and antero-posterior (AP) axes of the femur were defined as described Twiggs et al. [290]. The tibia was defined with a mechanical SI axis drawn from the midpoint of the malleoli to the tibial eminence. The direction of the AP axis was defined as the medial third of the medial tubercle to the PCL

attachment oriented and the ML axis was defined perpendicular to these two axes. This process is summarised in Figure 1, and the anatomic measures of interest and their definition to these axes are described in Table 1

Table 1: Definition of anatomic measures and healthy knee range investigated with respect to the patient specific axes defined from CT

Anatomic Measure	Definition	Example	Reference Values
Femur			
Posterior Condylar Angle (PCA)	Angle between the Posterior Condylar Line (PCL) and the surgical Trans-Epicondylar Axis (the TEA, lateral epicondyle to medial sulcus) in the axial plane. Positive values describe an externally rotated TEA.		$3.2 \pm 1.9^\circ$ [179, 310]
Femoral Anteversion	Angle between the line joining the centre of the femoral head tracing the line of the femoral neck to the PCL in the axial plane. Negative values describe retroversion.		$17.6 \pm 10.3^\circ$ [311-313]
Lateral Distal Femoral Angle (LDFA)	Angle between the line joining the distal femoral condyles and a line perpendicular to the femoral mechanical axis in the coronal plane. Positive values describe a valgus femur.		$2.1 \pm 1.7^\circ$ [164]
Tibia			
Tubercle Lateralisation Angle (TLA)	The angle between the tibial AP axis and a line perpendicular to Cobb's definition of the tibial AP axis (a line joining the centre of circles fit to the medial and lateral tibial plateau) in the axial plane. Positive values describe a tibial AP axis that is more externally rotated and hence a tubercle that is lateral to the plateau referencing axis described by Cobb et al.		N/A ($5.0 \pm 10.0^\circ$ reported from Cobb's study, referencing to tibial spine) [193]
Tibial Torsion	Angle between the line joining the lateral and medial malleoli and the ML axis of the tibia in the axial plane. Positive values define an externally rotated distal tibia.		$19.0 \pm 4.8^\circ$ [314]
Medial Proximal Tibial Angle (MPTA)	Angle between the line joining the well points of the medial and lateral tibial plateaus and a line perpendicular to the tibial mechanical axis in the coronal plane. Positive values describe a varus tibia.		$2.9 \pm 2.1^\circ$ [164]

To determine a surgeon expected normal anatomical range and deformity threshold, 7 consultant surgeons with at least 20 years surgical experience were polled. Each surgeon was asked to define an upper and lower limit for each anatomic measure described in Table 1, and to give an estimate of the proportion of patients within a TKA population with anatomy outside each of these limits. From these results, a definition of the expected normal distribution from each surgeon could be defined, and a combined expected distribution calculated by fitting a normal distribution to the sum of the surgeons individual estimated distributions. Additionally, averaged upper and lower limits of the deformity thresholds were defined. Surgeons were also asked for total proportion of knees with at least one deformity and at least two deformities. The poll was conducted using Typeform (Barcelona, Spain). In addition to this, a healthy population reference distribution was found from pre-existing literature for each measurement, shown in Table 1.

The range of measurements in the database was calculated and compared to the literature collected normal distributions for healthy knees and surgeon expected values from the poll. The percentage of patients with any deformity and 2 or more deformities was also calculated and compared to the surgeon expected percentages. T-tests were used to test difference in means, proportionality tests for differences in incidences of deformity and variance used to test difference in distributions. All analyses were performed using R v3.4.2 [315].

3.4: Results

Femoral and tibial anatomic measurements were extracted from a joint replacement registry beginning in January 2014 (360 Knee Systems). A total of 2057 knees, 1215 Female (59%), 983 Left (48%), mean age 70.2 ± 8.1 years were included in this study,

Table 2: Anatomic range outside of which a knee is defined as deformed from literature and surgeon polling

Anatomic Measure	Surgeon Distribution & Undeformed Range	Surgeon Deformity %	Actual Distribution	Actual Deformity %
Posterior Condylar Angle	$2.6 \pm 2.1^\circ$ [-0.1 to 5.4]	14%	$1.8 \pm 1.8^\circ$	17%
Femoral Anteversion	$12.6 \pm 8.9^\circ$ [-0.7 to 26.4]	11%	$15.9 \pm 9.9^\circ$	18%
Lateral Distal Femoral Angle	$3.2 \pm 3.7^\circ$ [-0.1 to 6.4]	17%	$2.9 \pm 2.7^\circ$	22%
Tubercle Lateralisation Angle	$5.5 \pm 6.2^\circ$ [2.8 to 8.2]	21%	$5.0 \pm 3.8^\circ$	46%
Tibial Torsion	$13.6 \pm 9.3^\circ$ [4.0 to 23.0]	14%	$18.8 \pm 8.3^\circ$	33%
Medial Proximal Tibial Angle	$1.8 \pm 3.1^\circ$ [-1.6 to 5.4]	14%	$3.7 \pm 3.1^\circ$	33%
At least 1 Deformity		30%		86%
2 or more Deformities		21%		55%

Table 2 shows the surgeon expected distribution and range for which deformities are defined from the surgeons polled in this study, the expected rate of deformities, the actual distribution of the data and the actual rate of deformities from the surgeon's definitions. In all cases, rates of deformities were higher in the data than expected by surgeons and these differences were statistically significant ($p < 0.001$). Figure 2 shows a histogram of each measurement, with the portion defined as deformities in red and a representative normal curve drawn from the literature defined distributions in Table 1 shaded in black.

Anatomical variation in a TKA Receiving Population, Healthy Anatomical Variation & Surgeon's Expectations

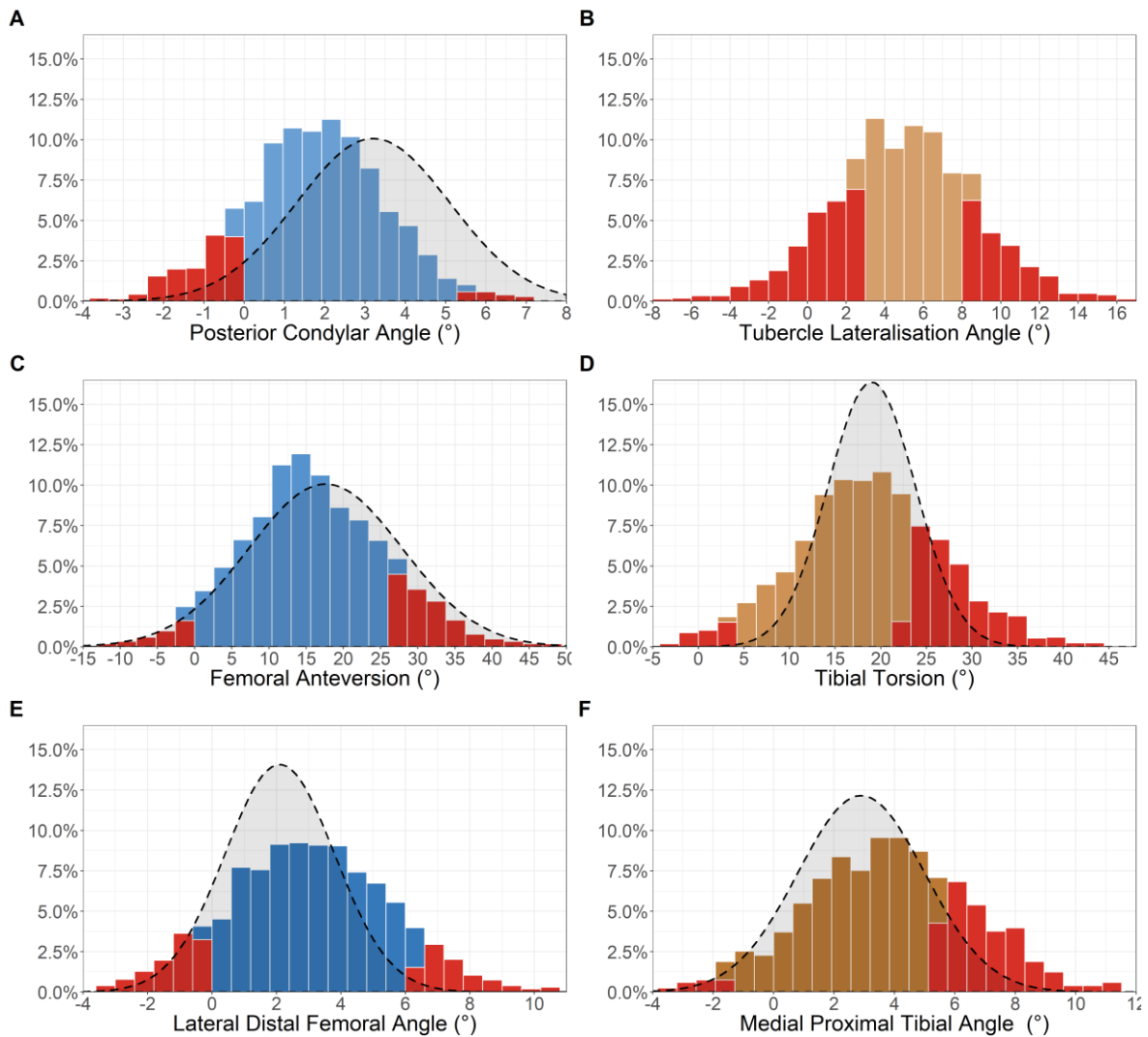


Figure 2: Comparison of the distribution of anatomy from a TKA enrolled population with literature derived healthy values (shaded normal curves) and surgeon expected outlier incidence (red shaded histogram are surgeon defined outliers). Note the omission of a healthy population reference for Tubercle Lateralisation Angle as no existing literature reference for a healthy population could be found.

In all instances excepting tibial torsion, the difference in means between the literature values and the values found in this data were statistically significant ($p < 0.001$), although not necessarily clinically significant. However, for the tibial torsion, medial proximal tibial angle and lateral distal femoral angle, the variance of the distribution was found to be statistically significantly greater than the literature reference distributions, suggesting a greater proportion of extreme measurements in the prospective TKA population. With the exception of medial proximal tibial angle, surgeon expected deformity ranges were not

found to align with the extremes of the literature reference distribution, suggesting that boundaries of deformities was not being driven primarily by knowledge of healthy anatomical measurements.

Table 3: Cross correlation of anatomical measurements analysed in this study

Correlation Table	1	2	3	4	5
1. Posterior Condylar Angle	-				
2. Femoral Anteversion	0.180**	-			
3. Lateral Distal Femoral Angle	0.137**	0.050*	-		
4. Tubercle Lateralisation Angle	0.102**	0.130*	0.084**	-	
5. Tibial Torsion	0.137**	0.093*	0.136**	-0.124**	-
6. Medial Proximal Tibial Angle	0.054*	0.042	-0.156**	-0.003	0.136**

*** Denotes significance to $p < 0.05$, ** Denotes significance to $p < 0.01$**

There were significant differences in the expected and actual rate of deformities based off the surgeon's definition of a deformity, with the rate of one and two or more deformities both being almost 3 times as high as expected by surgeons. On average, surgeons expected only 9% of patients to have exactly 1 deformity, while 21% would have two or more, suggesting an expectation for deformities to occur together or be correlated. Table 3 shows the cross correlation of anatomical measurements included in this study. Owing to the large volume of data, most anatomical measurements had a correlation coefficient that was statistically significant, but in all cases correlations were relatively weak. Figure 3, below, shows the co-incidence of the two strongest correlating measurements, femoral anteversion and posterior condylar angle (suggesting a weak tendency for femoral proximal and distal rotational deformities to occur together) and a negative relationship between medial proximal tibial angle and lateral distal femoral angle (suggesting a tendency for both the coronal measurements to reflect an overall coronal angle.)

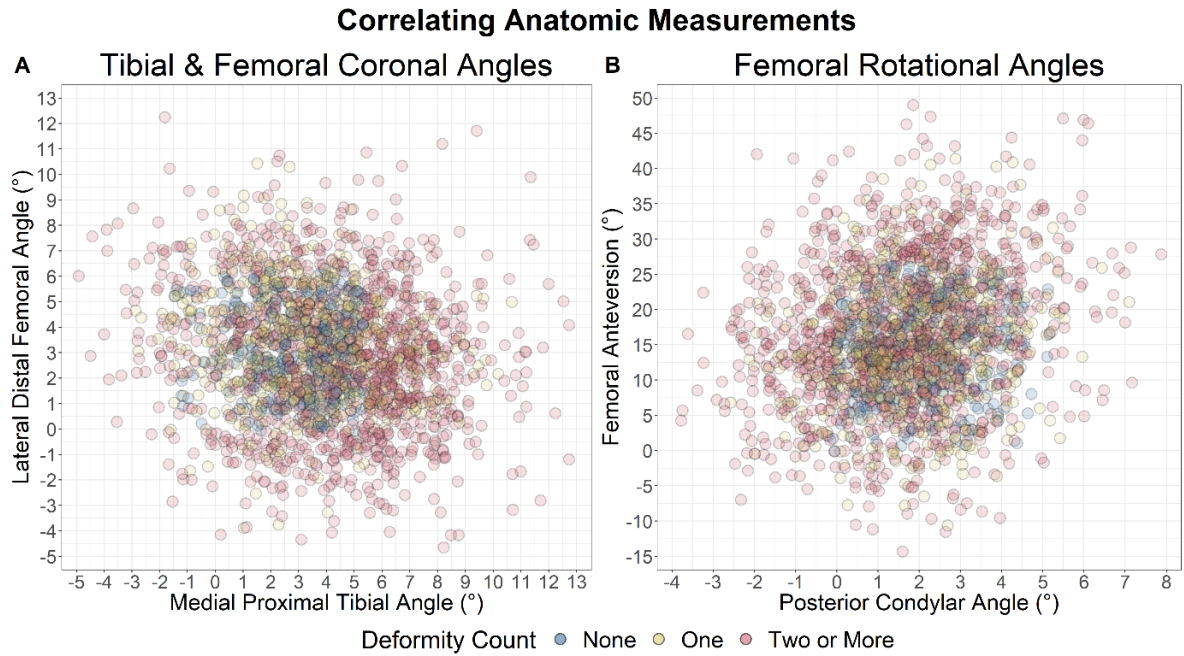


Figure 3: Cross correlations of coronal angles and femoral rotational angles, both of which are statistically significant. Tibial and femoral coronal angles tend to follow a common direction, with highly valgus femurs implying less varus/slightly valgus tibias, a higher posterior condylar angle implies more anteversion, though individual inter-patient variation dominates these relationships.

3.5: Discussion

This work highlights two major issues pertaining knee deformities. Firstly, there is a wide variability in the anatomy of the knee in the general population. Secondly, surgeons' perception and expectations appear to underestimate the degree of the deformity. Deformities may require a modification to a standard plan for a component alignment in order to address potential biomechanical consequences of the deformity [292, 316], and can compromise the surgeon's ability to achieve a desired implant position using standard techniques [290, 291].

In this study, a comparison of expected and achieved deformity rates obtained from polling 7 orthopaedic surgeons were applied to CT scan measurements from a joint replacement registry (360 Knee Systems). It was a general trend for all measurements that surgeon expected deformity rates were lower than those found in the database. Expected deformity rates for one or more and two or more deformities were 21% and 30% respectively, while the actual rates were 86% and 55%. To some degree, this is more reflective of the deceptiveness of summing multiple percentages, as the expected percentage for each individual deformity did not have such a disparity from the actual figures. However, the surgeon expected rate of exactly one deformity (9%) compared to two or more (21%) implies a far greater level of co-occurrence of deformities than was shown to exist in the database, implying some of the discrepancy may be due to an expectation that deformities would 'aggregate' together in individual problem patients.

A healthy literature reference was found for all measurements assessed in this study excepting the Tubercle Lateralisation Angle and were not identical to those found in the data. This is to be expected as degenerative OA is both caused by and can drive [14, 302] anatomical deformity in patients. For the Medial Proximal Tibial Angle and Posterior Condylar Angle, surgeon expected deformity ranges were found to align with the extremes

of the healthy literature reference distribution (and not the data from the OA cohort presented), although this was not true of the other three assessable measurements.

The posterior condylar axis had relatively close rates of expected and actual deformities (14% to 7%). Significantly, greater than 80% of the deformities in the data set were an angle that was negative, implying a TEA internal to the PCA. Previous studies have reported similar rates of this occurring [169]. Deformities leading to outliers in the angle between TEA and PCA can change the collateral ligament balance as the knee flexes, and this has been previously reported to be difficult to perceive in a non-navigated TKA procedure, as well as significantly impacting clinical outcomes [65]. An appreciation of the incidence of this deformity is important, as is the ability to determine its presence on a case by case basis.

Tubercle lateralisation relative to the tibial plateau shape is well understood anatomically, with its presence being the primary justification for anatomic tibial plate designs, which have been previously shown to lead to better alignment to the tubercle while maximising plateau coverage [299]. The high expected and actual rates of this deformity (21% and 44%) reflect previous research describing the difficulty in surgically achieving reproducible anatomical rotational references [63], the volume of proposed anatomical references [193, 194] and the popularity of non-anatomically referenced techniques for setting rotation [317].

This study found relatively high rates of deformity of 33% compared to 14% expected by the surgeon group for MPTA, although figures for LDFA were fairly similar. At the extremes and when the deformity is extra-articular, extra-articular correction may be called for [295].

Otherwise, coronal alignment variation in TKA receiving patients is closely tied to the alignment debate over KA and MA occurring now. The work of Belleman et al. has long made it clear that a native coronal mechanical alignment is not a universal norm for all patients [164]. It is also known that coronal alignment deformity is both caused by and

causes osteoarthritis, especially in the tibia, as imbalanced loading propagates increased wear and bone reformation in response [14]. This mechanism is reflected in the data as the second strongest relationship between anatomical measures was between the MPTA and LDFA and the relationship was negative, indicating that these measurements tend to act together to contribute to the overall knee coronal angle. Having an awareness of the angular deformity present in a specific case allows confirmation of expected cuts regardless of the alignment being pursued, although the need is less pressing in surgical cases where navigation is available.

Extra articular axial deformities such as femoral anteversion and tibial torsion are more complicated to address during TKA without performing derotation osteotomies. These deformities affect the gait cycle by modifying femoral force origin, the line of action of the knee extensor mechanism, and an altered “screw home mechanism” (i.e. decreased excursion in sagittal and axial tibial rotation and posterior tibial translation) [318, 319]. Femoral anteversion and posterior condylar angle were two coexisting deformities with the strongest correlation coefficients, suggesting that proximal and distal axial deformities at the femur tend to occur simultaneously. This relationship was relatively weak, however and there was a lack of meaningful relationships between other rotational measurements. The combination of femoral anteversion [304], tibial tray rotation and tibial torsion will drive postoperative foot progression of the patient but are not immediately discernible from either traditional radiographs or during the operation.

The differences between the rates of deformity expected by surgeons and those found to exist in the data highlight the importance of further research on natural anatomical variability in healthy and OA populations. Surgical approaches that rely on and reference from expected relationships may not be as reliable as assumed. The findings of this study give a basis to the hypothesis that accurate measurement and awareness of normative ranges in healthy populations could improve technical execution of surgery. This can be

achieved through sophisticated navigation techniques intra-operatively or 3D imaging and reconstruction pre-operatively. Patient specific surgical approaches can include both alignment plans that varies in response to patient anatomy [186] and use of anatomical information to guide achievement of an alignment plan [300].

Limitations of this study include the definition of deformities proposed. Broadly speaking, well agreed definitions for what constitutes a deformity do not exist. Surgeons were polled on their experience rather than explicit research of the literature to create a definition most in line with ordinary surgical practice, and these definitions were averaged. The particular surgeon group polled are an Australian group and while there was relatively low variation in the proposed definitions from each surgeon, the result may not be reflective of other population groups, particularly other ethnic groups. In addition, the surgeon group represented here are all experienced surgeons with over 20 years operating experience.

Furthermore, this study is not comprehensive in terms of every anatomical feature that might be called a deformity. Knees are complex joints with the femur, tibia and patella all having highly diverse shapes and anatomical variations across the population. This variation is increased when focusing on an osteoarthritic population. In particular, this study avoided assessment of tibio-femoral deformities such as fixed flexion deformity and extreme long leg coronal alignments as these measurements are known to be affected by functional behaviour such as weight-bearing.

3.6: Conclusion

This study demonstrates that the incidence of deformities in a TKA population is significantly higher than expected, based on deformity definitions from 7 highly experienced surgeons. It also highlights the degree to which anatomical measurements in an end stage OA population deviate from anatomical norms in healthy populations. Given the high incidence of anatomic deformities in TKA patients and the growing debate around alignment strategy, patient specific surgical planning may be called for. Further research is required to study the impact on Patient Reported Outcomes associated with the prevalence and surgical response to deformities in TKA, which may lead to improved surgical planning in these patients.

Chapter 4

Patient Variation Limits Use of Fixed References for Femoral Rotation Component Alignment in Total Knee Arthroplasty

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The capacity for unexpected patient variation explored in Chapter 3 to lead surgical technique astray is tested with regards to the Posterior Condylar Angle (or Transepicondylar Axis to Posterior Condylar Axis angle). Rotational alignment in TKA has been shown to (and logically must) alter the balance of the components in flexion, which has been shown in other studies to relate to outcome. It is not captured in 2D radiography and require 3D imaging to view, and there is still confusion and disagreement as to what the best approach is in rotationally aligning the femur, despite the technology that has been deployed to the operating theatre in the last decades. This study showed that, for a TEA target to be achieved, a patient specific angle from the PCA must be used, and that standard reference rules are insufficient.

4.1: Abstract

Background: Optimal rotational alignment of the femoral component is a common goal during Total Knee Arthroplasty (TKA). The PCA is thought to be the most reproducible reference in surgery, while the TEA seems to better approximate the native kinematic flexion axis. This study sought to determine if rules based on patient gender or coronal alignment could allow reliable reproduction of the TEA from the PCA.

Methods: Three-dimensional (3D) models based on pre-operative CT were made representing a patient's arthritic knee joint. The landmarks were defined and angular relationships determined.

Results: The population group of 726 patients contained large anatomic variation. When applying the standard reference rule of 3° external rotation from the PCA, 36.9% of patients would have a rotational target greater than 2° from their TEA. When applying the mean external rotation of the TEA from the PCA (1.85°) from this population, this proportion dropped to 26.0% of patients. The use of statistically significant gender and coronal alignment relationships to define the femoral rotation did not reduce the proportion of patients in > 2° error.

Conclusion: This study shows that gender and coronal alignment relationships to the TEA to PCA angle are not clinically significant as a quarter of patients would still have a target for rotation greater than 2° from the TEA using these relationships. Superior tools for orienting rotational cuts directly to the TEA in surgery or preoperative identification of relevant patient specific angles might capture the proportion of patients for whom standard reference angles are not appropriate.

4.2: Introduction

Total Knee Arthroplasty (TKA) is an established procedure for relieving pain and restoring a significant degree of function for patients who have osteoarthritis (OA). Surgeons aim to achieve good coronal and rotational alignment of the femoral, tibial and patellar components [320]. Mechanical alignment is determined coronally from a distal femoral cut made perpendicular to the femoral mechanical axis and a tibial cut made perpendicular to the tibia mechanical axis [49, 321].

Traditionally rotational alignment of the femoral component has been achieved by making the anterior and posterior cuts such that the femur is rotationally 3° externally rotated from the posterior condylar axis (PCA). The rationale for this alignment is that the majority of patients have a distal femoral angle in slight valgus and a proximal tibial angle in slight varus [164, 310]. As such, the 3° of external rotation from the PCA changes the alignment of the femur posteriorly so that it approximately matches the change in the distal femur and proximal tibial axes [322, 323]. Other reference axes may be used to define component rotation, such as the surgical Transepicondylar Axis (TEA) as defined by Berger et al. [324] and Whiteside's Line (WSL) [325, 326]. As an alternative to reference axes, gap balancing may be used [51]. Conventional understanding places the surgical TEA at 3° external rotation to the PCA in the average patient and the WSL perpendicular to the TEA [179]. This leads to a typical WSL to PCA angle of 93° in the normal patient [169].

When the knee is in flexion, femoral rotational malalignment can increase both the mechanical and shear stresses placed on the bearing surface prosthesis as well as the bone/prosthesis interfaces [178, 179, 327]. Furthermore, rotational malalignment, either on its own or coupled with tibial rotational malalignment as a combined measure has been linked to occurrence of persistent postoperative anterior knee pain [323, 328-330]. Achieving optimal femoral component rotation relies on both the precision and the accuracy

of the method used. Precision is how close repeated values are to each other and is therefore defined by the reproducibility and repeatability observed when using the approach, whereas accuracy is defined by how close a measured value is to a true, idealised target [331].

Navigation and Patient Specific Instrumentation have both seen introduction as a means of improving accuracy in surgery, but have cost implications. Furthermore, despite improvements in coronal plane accuracy, [61] navigation has not managed to show any significant improvement in axial plane alignment over conventional instrumented TKR, with one recent meta-analysis of 23 studies showing a non-significant increase in the amount of navigated axial outliers of $>3^\circ$ over those achieved with instrumented TKR [60]. PSI, similarly, has seen no significant improvements in accuracy despite the procedure using patient specific imaging and neither approach has come to dominate surgical practice [53].

When using mechanical instruments, AP sizers referencing from the PCA have been shown to be a more precise method than other techniques, with inter and intra-surgeon reproducibility studies resulting in less variation than other instrumented techniques [64, 179]. Poorer reproducibility observed in manually sighting or referencing the TEA and WSL has been demonstrated in many prior studies [51, 64, 332]. Jerosch et al. have demonstrated median variation in inter-surgeon ability to pick the medial and lateral epicondylar points of 9.7mm and 6.4mm respectively, leading to an error range of 23° [333]. Similarly, Jenny et al. demonstrated a mean intra-observer deviation of 5.5° and an inter-observer deviation of 9° , suggesting both inter and intra-observer errors in identification of the TEA [298]. Contrary to conventional understanding, these reference axes have been shown to have wide variation in their angulation to each other across the population [334, 335].

In terms of kinematic outcomes, the TEA is often cited as the best approximation of the native kinematic flexion axis. Previous studies have shown the TEA to more closely match than both WSL and the PCA the projected transverse axis in flexion within a set of cadaveric knee specimens [188]. Other studies have confirmed a closer match to the native kinematic flexion axis [189], the recreation of a more balanced flexion space [190, 191] as well as more stable patello-femoral kinematics [164, 172, 192]. Independent of measurement to the TEA, it has been shown that femoral component rotation 3-5° external to the PCA leads to significantly improved patella tracking and a reduced need for lateral release [297].

The precision in PCA referencing could be used to achieve an accurate outcome of kinematically ideal TEA alignment with CT, MRI or other imaging using a patient specific measurement of the angle between the two axes [300]. Despite having been shown to reduce instances of malalignment, [300] this approach incurs a cost and patient burden if every patient is to be axially imaged prior to TKA. As an alternative, known population trends such as valgus [171] or female [169, 324] knees having a greater external rotation from the PCA could be quantified to produce clinical rules covering observable patient characteristics [336].

This study sought to determine whether a set of reference angles and rules for femoral rotational angle of the TEA to the PCA could be developed across a population of patients undergoing TKA, factoring in gender and coronal alignment. This study sought to achieve this by developing the clinical rules from a large sample of measured TEA to PCA angles and determining the percentage of the sample that fit each rule.

4.3: Methods

This study included patients from 10 different surgeons who were undergoing TKA during the period December 2014 to August 2016. Pre-operative CTs of the hip, knee and ankle were taken for each patient, with the patients instructed to extend their knees as far as possible. Each scan was segmented using ScanIP software (Simpleware, Exeter, UK). Segmentation of the femur, tibia and patella bone were done, filled in and smoothed in order to create a three-dimensional (3D) model representing patient's arthritic knee joint. CT scans were taken at 1.25mm slice thickness, with the coronal and sagittal thicknesses varying but all less than 1.25mm.

The scans were used as part of a preoperative planning process conducted for each patient prior to surgery, while the patients were also enrolled in a registry for retrospective review of the reconstructed CT scans.

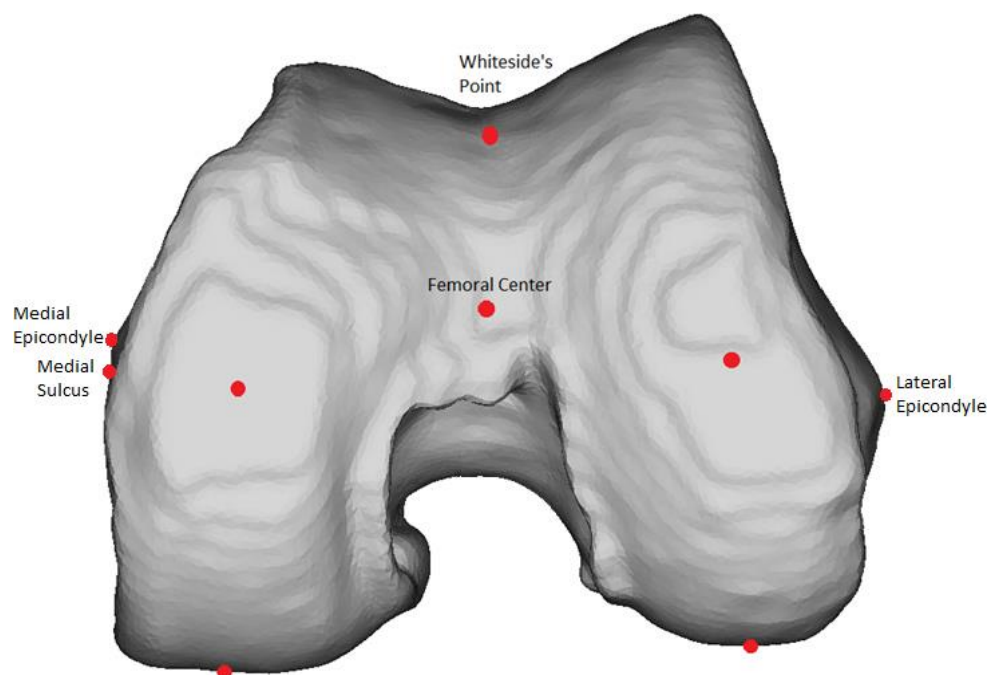


Figure 1: Schematic of landmarks used in defining the inputs to the patient specific model for preoperative surgical planning

Landmarks were defined to assemble a patient specific model that includes all relevant points associated with the reconstructed 3D patient geometry as shown in Figure 1.

The selection of the landmark points was done independently by two separate engineers to improve the quality and accuracy of the landmarks chosen. The differences were algorithmically compared and a mean result found. If a large difference between any two user selected landmark points was found, the landmarking was then triple checked and a new point in relation to the other two points was determined.

The mechanical axis of the femur was defined as the line joining the centre of the intercondylar notch to the centre of the femoral head, from which the axial plane was determined. The surgical TEA was defined by the lateral epicondylar point and the sulcus of the medial epicondyle. The lateral epicondyle was defined by the centre of the prominence on the lateral side of the distal femur, while the medial sulcus was defined in the depression posterior to the medial epicondyle on the medial side of the femur. WSL was defined as medial-laterally at the centre of the trochlear groove, with the superior/inferior position as high as the groove remains.

Lateral posterior and medial posterior condyles were defined by the most posterior point of the condyles, that is, the estimated contact point of the femur with the tibia at 90° flexion. PCA was defined by drawing a line between the two posterior condyles. Definitions of axes are shown in Figure 2. The axial rotational measurements were defined by projecting the 3D landmarks onto the axial plane.

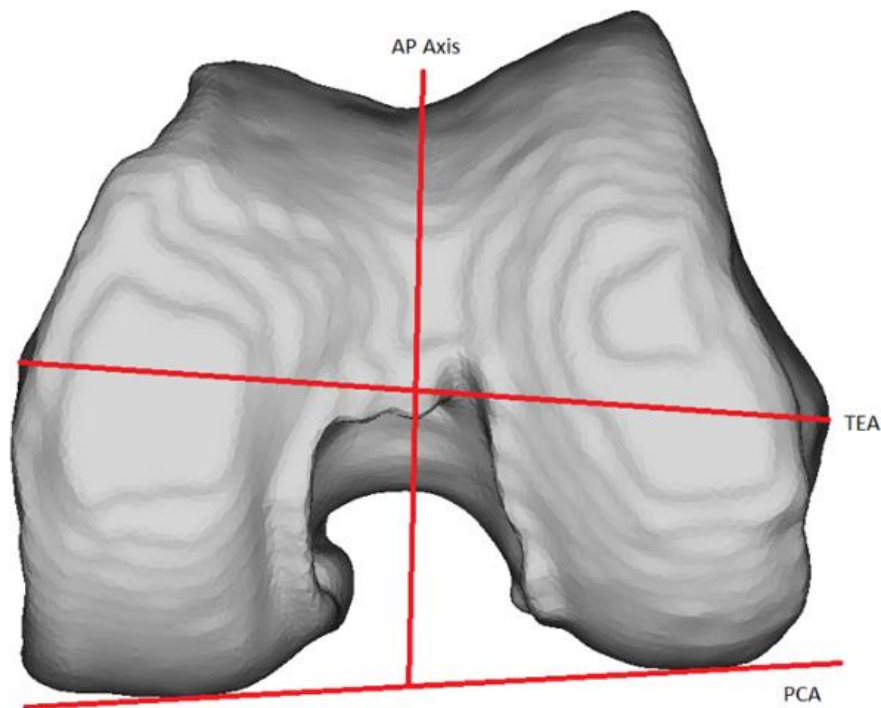


Figure 2: Definition of axes for femoral rotation

A comparison between the femoral axial alignments TEA to PCA and WSL to PCA and WSL to TEA were conducted and compared to the coronal alignment for all patients. Two tailed unpaired t-tests was used to determine significant differences between discrete groups and Spearman's correlations were used between continuous variables. Chi squared tests were used for categorical relationships. A p-value of 0.05 was set for significance.

The TEA to PCA angle was further analysed to determine the proportion of patients whose anatomy would lead to an acceptable or unacceptable error in terms of the TEA angle being targeted from the PCA. Those patients who had a greater than $\pm 2^\circ$ deviation from the accepted standard 3° reference rule were noted as being in error (that is, patients whose TEA to PCA angle was either less than 1° or greater than 5°). This analysis was conducted to replicate the results achieved when using a hypothetical perfectly precise AP sizer in surgery as a reference tool to the PCA to achieve a TEA alignment. The threshold of 2° was selected in line with the work of Michaut et al. [300], whose study demonstrates an ability to achieve rotational alignment of the implanted femur to within 2° of the TEA through use of a preoperative CT assessment of each patient.

This analysis was expanded to include a number of proposed population reference rules making use of correlations found within the data. These are a customised reference rule to this population's mean angle (rather than 3°), individual rules for varus and valgus knees, individual rules for male and female knees and 4 separate rules for valgus female, valgus male, varus female and varus male knees in order to determine an acceptably accurate set of surgical reference rules. Mean error percentage of outliers from each reference rule was determined.

4.4: Results

This study included 726 patients who were undergoing TKA. The group contained 43% (312) male participants with a mean population age of 69.1 ± 8.6 years and 53.5% (388) knees were right. Of the population studied, the average coronal long leg alignment in CT scan was $4.5^\circ \pm 5.5^\circ$ varus. For the varus and valgus groups specifically, the alignments were $6.6^\circ \pm 3.7^\circ$ varus (79%) and $3.9^\circ \pm 3.4^\circ$ valgus (21%). Of the total, 19.8% (149) of the knees were valgus and the remaining were varus (577). Mean fixed flexional deformity in the CT scanner was $5.8^\circ \pm 5.2^\circ$. There was a statistically significant gender difference between genders in terms of coronal long leg alignment (females trending to valgus).

Mean values, Spearman's Correlation Coefficients and their p-value for significant difference from zero for WSL to TEA, WSL to PCA and TEA to PCA across the are shown in Table 1.

Table 1 Table of results for angular relationships between TEA / PCA / WSL

Axes	Mean Angles and Rotation	Spearman's Coefficient	P Value
TEA to PCA	$1.85^\circ \pm 1.834^\circ$ of external rotation	0.16	<.001
WSL to PCA	$92.54^\circ \pm 5.11^\circ$ of external rotation	0.10	.0087
WSL to TEA	$90.69^\circ \pm 5.26^\circ$ of external rotation	0.15	<.001

The relationship between gender and TEA to PCA is shown in Figure 3 (a) for the full population as density curves. There is an observable trend towards females having more externally rotated TEA angles. Figure 3 (b) shows the relationship between coronal alignment and the TEA to PCA angle, with the trend line indicating as the long leg alignment falls into further varus, the external angle of the TEA to PCA decreases. Figure 3: a) Density of the male and female populations across the TEA to PCA angle and b) Coronal plane alignment vs the TEA to PCA angle across the study population.

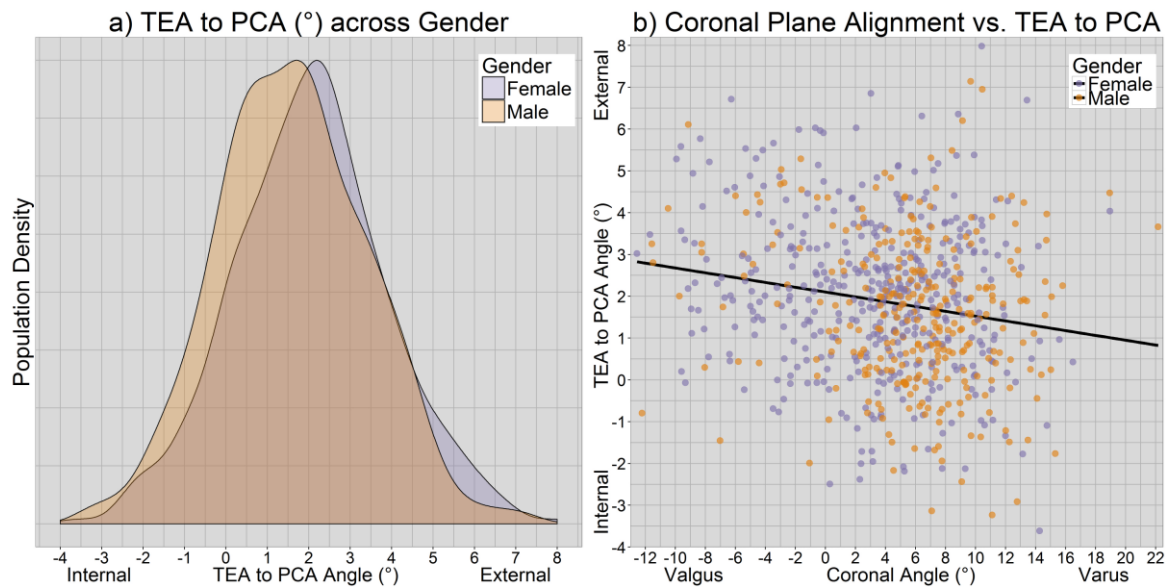


Figure 3: a) Density of the male and female populations across the TEA to PCA angle and b) Coronal plane alignment vs the TEA to PCA angle across the study population

Figure 4 shows two different reference angles for the TEA from the PCA with a 2° margin of error applied to show the proportion of the population captured by each rule. The dashed line in the centre of the green zone in Figure 4 (a) represents a difference of 3° between TEA and PCA as a standard reference. The extent of the green zone covers the 2° margin of error if a fixed 3° AP sizer was used intra-operatively, while the red zone is outside this area. A total of 36.9% (268) of patients would have an error greater than this with this rule. The mean value for the TEA to PCA in this data is 1.85° ($\pm 1.83^\circ$) of external rotation, which is statistically different from 3° (p value < 0.001). When using this as a reference rule, 26.0% (189) of the patients would have an error greater than 2° from the mean, as seen in Figure 4 (b).

Significant differences for TEA to PCA were found between the varus ($1.66^\circ \pm 1.79^\circ$ external rotation) and valgus sub-groups ($2.59^\circ \pm 1.82^\circ$ external rotation). Applying these means as two separate rules depending on coronal alignment leads to 27.3% (198) of the patients having an error greater than 2°, as seen in Figure 5 (a). Likewise, significant differences for TEA to PCA were found between the male ($1.60^\circ \pm 1.10^\circ$ external rotation) and female sub-groups ($2.04^\circ \pm 1.14^\circ$ external rotation) and applying these means as rules leads to 26.9%

(195) of the patients having an error greater than 2°, as seen in Figure 5 (b), where the yellow zones are gender specific (upper yellow zone is female only, lower is male).

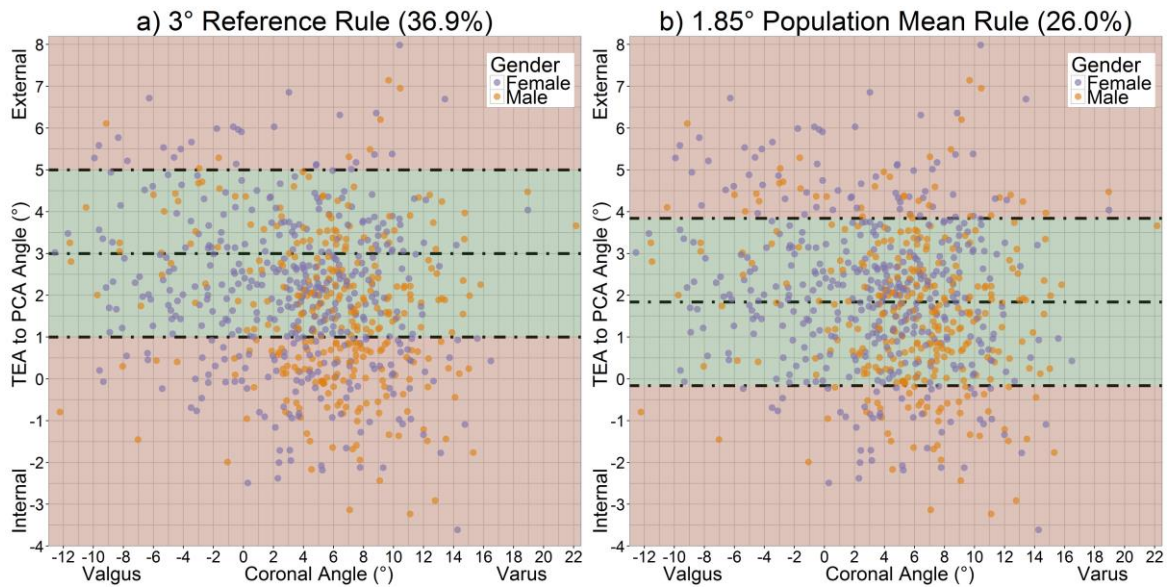


Figure 4: TEA to PCA reference rules with their percentage of patients \square 2° outside the rule: (a) Standard 3°; (b) Study mean 1.85°

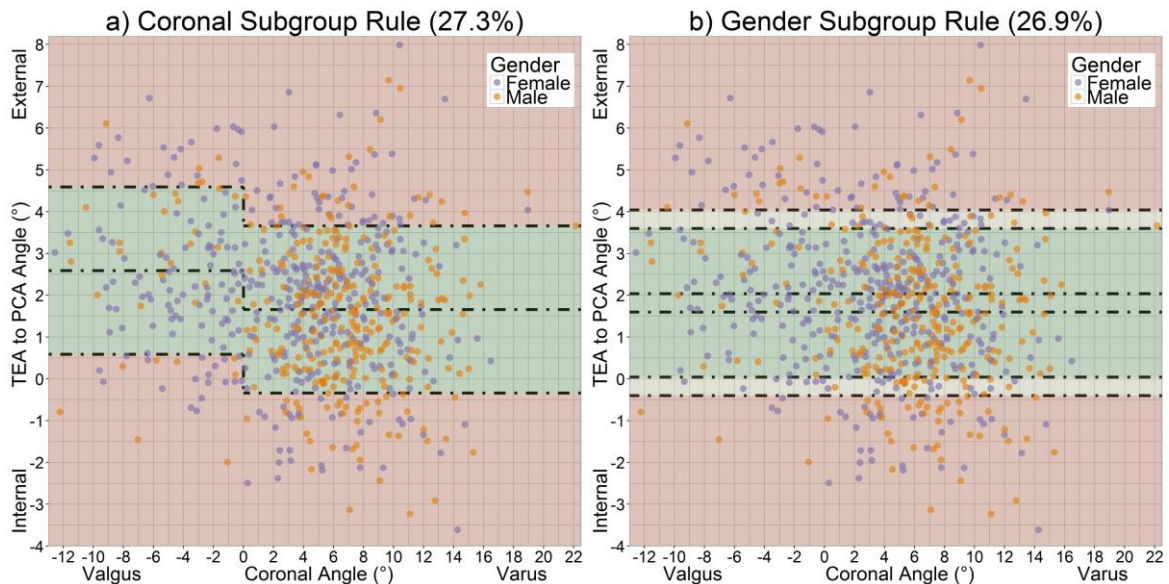


Figure 5: TEA to PCA reference rules with their percentage of patients \square 2° outside the rule: (a) Separate rules for varus & valgus knees; (b) Separate rules for male and female knees

Combining both these factors into four separate subgroups of TEA to PCA angle where valgus males have an angle of 2.67°, valgus females an angle of 2.57°, varus males an angle of 1.60° and varus females an angle of 1.83° and applying these means as rules leads to 26.2% (190) of the patients having an error greater than 2° from their gender mean, as seen

in Figure 6 (a), where the yellow zones are gender specific. Figure 6 (b) shows a boxplot of all anatomical variations of the TEA to PCA angle from each of the 5 rules defined for comparison, showing more than a quarter of patients would still have their rotational target deviate from the TEA if referencing from the PCA using the best fit rule.

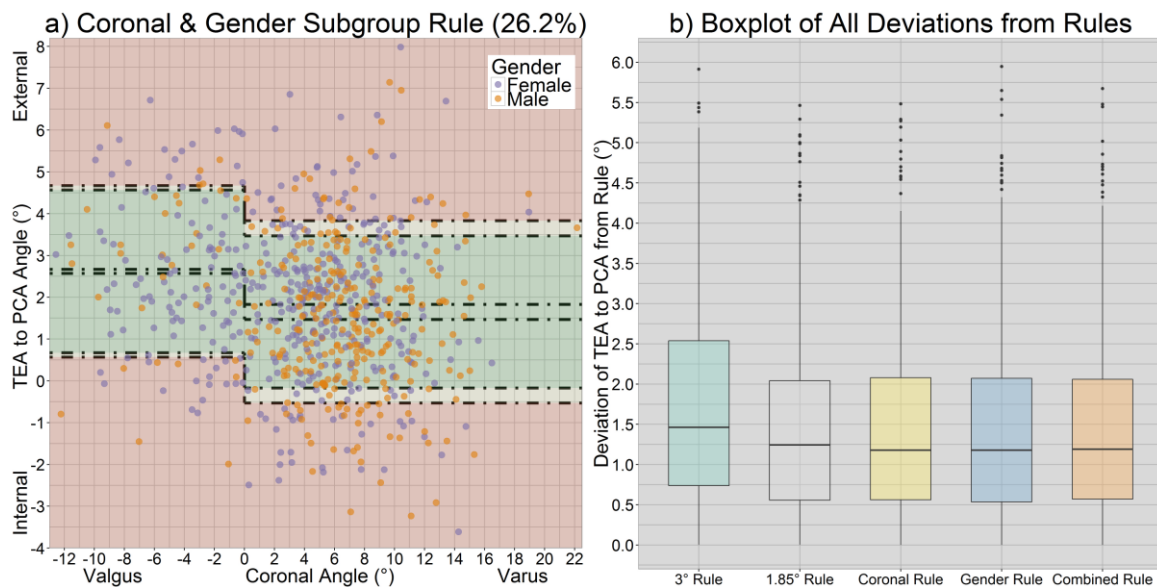


Figure 6: (a) TEA to PCA reference rules with their percentage of patients outside \square 2° the rule; (b) a boxplot of deviations from all rules described

The coronal plane alignment for WSL to TEA is shown in Figure 7 (a). The mean value of the WSL to TEA angle is $92.54^\circ (\pm 5.11^\circ)$. This is significantly different from 93° ($p = 0.016$). The standard deviation in the WSL to PCA angle was more than twice that of the TEA to PCA angle and this difference was significant (t-test, $p < 0.001$). Outliers were mainly females at extreme internal/external rotations. No significant differences were found between the means of the male and female patients and the varus and valgus sub-groups.

The relationship between the WSL to PCA angle and the TEA to PCA angle is shown in Figure 7 (b). The dashed line represents the line where WSL was perpendicular to the TEA, that is, matching one rotational axis will match the other. The mean value for the WS to TEA angle is $90.69^\circ (\pm 5.25^\circ)$ and the difference from 90° is statistically significant ($p < 0.0001$). Significant differences for male (91.14°) and female (90.35°) patients exist ($p < 0.0422$).

Likewise, significant differences for varus (91.14°) and valgus (90.35°) patients exist ($p < 0.0032$). 58.5% (425) of patients had a deviation between these two axes of greater than 2° while 18.3% (133) had a deviation greater than 5° .

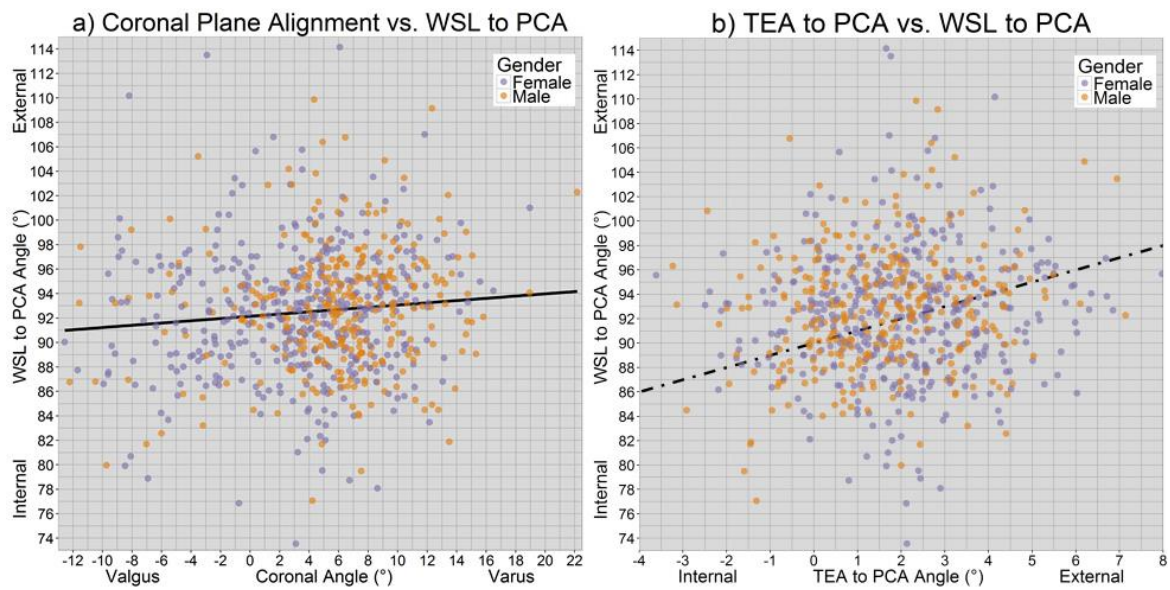


Figure 7 (a) Coronal alignment for WSL to PCA angle by gender. Straight line is the linear trend line, Spearman's Coefficient of 0.10; (b) WSL & TEA angles from the PCA by gender. Dashed line is the line across which the axes are perpendicular

4.5: Discussion

Femoral component rotation in TKA continues to be a source of debate in orthopaedics as no single technique has been shown to be superior to another. This is in part due to the interplay between the precision of a technique and its accuracy to a biomechanically ideal rotation when mechanically aligning the knee. There is a growing consensus that referencing the rotation to the TEA produces biomechanically superior results, despite its relatively poor results in inter and intra-surgeon reproducibility [50, 64, 179, 337]. It is unclear how the degree and predictability of patient anatomical variation in the TEA to PCA angle might be used to develop a set of rules for precisely rotating to the TEA from the PCA.

The reference standard angle used in this study for the TEA to PCA was 3° [169, 179]. The result of 1.85° found in this study was significantly different from this. This study did find statistically significant trends for gender and varus/valgus sub populations. As with our study, several others have reported variation away from 3° TEA to PCA as well as patient-specific variation. Griffin et al. [336, 338] reported a mean of 3.11° and McDougall et al. [171] reported a mean of 1.7° both using only 2D slices from MRI scans and not 3D reconstructions, to which a portion of the discrepancy could be attributed. Theinpont et al. [170] reported a mean angle of 4° using a CT scan database of 2,637 patients which suggests that there may be some population differences or landmarking protocol deviations. This is despite the reported reproducibility of landmarks from CT scan reconstructed models [339].

A statistically significant difference was found between male and female TEA to PCA angles of 0.44° (1.60° for males and 2.04° for females). Other studies have also found a relationship between the TEA to PCA angle and gender. Patel et al. [169] reported a mean angle of 2.38° with a similar difference between genders to that which we observed (2.08° for males and 2.56° for females) using 560 MRI based 3D reconstructions. Berger et al.'s [324] study that

defined the surgical TEA describes an angle of 3.5° for males and 0.3° for females, opposite in trend to the findings of both this study and Patel's. This could be attributed to measurements conducted on non-arthritic femurs or imprecision from instrumentation rather than radiographic imaging driven measurements. Given the larger sample size of both this study and that of Patel et al in addition to the previously noted lack of reproducibility in intraoperative identification of the TEA [298], it is reasonable to conclude that a greater mean TEA to PCA angle is to be found in women.

A statistically significant difference was also found between varus and valgus alignment and TEA to PCA angles of 0.93° (1.66° for valgus knees and 2.59° for varus knees). Luyckx et al. [172] were also able to show a relationship between coronal alignment and rotational TEA to PCA angle in their study of 231 CT scans. This relationship is due to the presence hypoplasia of the lateral condyle in valgus knees, [338] and its existence is frequently accommodated for in valgus total knee arthroplasty by performing the antero-posterior rotational cuts of the femur with additional external rotation from the posterior condyles [340]. Coronal alignment also significantly cross-correlated with gender in our data, with males generally more varus than females [164]. Even so, these relationships between these variables did not explain the majority of the variation in patient TEA to PCA angle.

There was significantly higher variation between the WSL to PCA angle than the TEA to PCA angle. 58.5% (425) of patients had a WSL to TEA angle greater than 2° while 18.3% (133) had a deviation greater than 5° . This is consistent with prior studies which have shown the WSL to PCA angle to have far greater inter patient variability [334]. This evidence indicates that it is not possible to target both axes routinely when rotating the femoral component. Similar to the TEA to PCA angle found in this study, the WSL to PCA angle was significantly different from the literature reference of 93° , but by less than half a degree. Considering the high population variation in this measurement and its previously reported lower reproducibility intra-operatively [64] this is a clinically insignificant difference.

As there is large variability of native TEA to PCA angular relationships for patients undergoing TKA, the use of a single angular reference to target the TEA may result in a significant portion of patients being malrotated relative to the TEA. If the standard TEA to PCA angle was taken to be 3° with a threshold of 2° , 36.9% (268) of patients would have an error greater than this. This is an effect that has been previously observed in surgery and is compounded by deviation during surgical delivery [341]. Using instead the mean value for TEA to PCA angle from this study ($1.85^\circ \pm 1.83^\circ$ of external rotation) leads to 26.0% (189) of the patients having an error greater than 2° .

Statistically significant differences for TEA to PCA angle were found between varus sub-groups ($1.66^\circ \pm 1.79^\circ$) and valgus sub-groups ($2.59^\circ \pm 1.82^\circ$), and if separate rules were developed for varus and valgus patients, 27.4% (199) of the patients would have an error greater than 2° . This is a greater proportion in error than that achieved just using the population mean. Setting new reference angles based on gender and the combination of gender and coronal alignment did not improve this rule either and more than a quarter of patients would remain outside the target rotation. It can be concluded that for developing a consistent TEA targeting reference rule from the PCA, these relationships are not clinically significant.

Aiming for the TEA directly has been shown in numerous studies to have a lower reproducibility than referencing from the PCA. Jerosch et al. conducted a study identifying medial and lateral epicondylar points for rotationally setting the TEA between 8 surgeons and 3 cadaveric specimens. Their results demonstrate median variation in inter-surgeon ability to pick the medial and lateral epicondylar points of 9.7mm and 6.4mm respectively, leading to a potential error range of 23° . A maximal distance between medial and lateral epicondylar points between surgeons of 22.3mm and 13.8mm was observed [333]. Similarly, Jenny et al. demonstrated a mean intra-observer deviation of 5.5° and an inter-observer deviation of 9° , suggesting both inter and intra-observer errors in identification of the TEA.

Their results also found one of the two surgeons to have a good intra class correlation coefficient (0.71), while the other's was poor (0.50), suggesting significant surgeon variability in ability to reference from the TEA [298]. Kinzel et al.'s study across 74 knees had a similar conclusion, with 25% of their surgeon determined TEA's being outside of $\pm 3^\circ$ from the true TEA [342]. The work of Siston et al. [64] and Galaud et al. [332] confirms the persistence of this error in precision when using surgical navigation, despite the improvement in accuracy when directly targeting the TEA.

By comparison, Franceschini et al. [341] has studied TEA targeting delivery and found a mean error of $1.4^\circ \pm 1.9^\circ$, which leads to a mean deviation in angle comparable to precise implementation of the best fit rule developed in this study. This stands in contrast to the poor reproducibility noted in other studies and suggests again that there is a level of inter-surgeon variability in achievement the TEA when directly referencing. In basing its analysis on the TEA to PCA angle in the population, this study did not account for potential additional surgical delivery error when referencing from the PCA. Considering this, these results show that for the surgeon able to reproducibly rotate to the TEA, in the absence of a patient specific TEA to PCA angle, referencing the PCA may perform worse than directly rotating the femoral cuts to a visually referenced TEA.

CT segmentation, double landmarking and defining of axes on the femur was done in this study to improve accuracy and repeatability. Limitations include the fact that the study is CT based, which prevented cartilage being modelled and may produce some of the variation in results between studies. However, it has previously been shown that poor bone contrast in addition to geometric field distortion leads to inaccuracies in MRI relative to CT models.[343] Furthermore, significant posterior cartilage wear prior to TKA is relatively rare in contemporary patients and unworn posterior cartilage thicknesses have been shown to be equivalent between condyles for a given patient [180]. It should also be noted that when performed by users with experience in anatomic literature (as was the case in this study),

femoral landmarks captured from CT scans constructed into 3D models have been shown to be highly reproducible [339]. The study is limited to an Australian population. This may impact generalisability of the findings in terms of specific population measurements presented.

4.6: Conclusion

From a population group of 726 patients who were undergoing TKA this study characterised the ability to achieve the TEA referencing from the PCA in the context of variable patient anatomy. The mean TEA to PCA (1.85°) of external rotation deviated from the standard reference of 3° external rotation. Using the mean value found here as a reference angle from the posterior condyles led to the proportion of patients differing by $\pm 2^\circ$ from the mean reducing from 36.9% to 26.0% of patients. The TEA to PCA angle had a relationship with gender and coronal alignment. It was found that these relationships were not clinically significant and could not be used to meaningfully improve on the population mean reference angle. Superior tools for orienting rotational cuts directly to the TEA in surgery or preoperative identification of relevant patient specific angles might capture the proportion of patients for whom standard reference angles for rotating to the TEA from the PCA do not apply.

Chapter 5

Accurate Determination of Post-operative 3D Component Positioning in Total Knee Arthroplasty: The AURORA Protocol

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Following the finding in Chapter 4, it was confirmed that a new technique needed to be developed to further study how component placement might link to outcome beyond coronal mechanical alignment. There was a need to reference native preoperative geometry to the postoperative implanted position of the component. The technique developed involves registering both implant and preoperative bone 3D CT segmented models to a postoperative CT reference frame. Doing so allowed for a more accurate definition of component placement in all 3 planes, going beyond what 2D radiography can provide. Additionally, analysis of the alteration of certain measurements from their preoperative reference, such as the joint line, can be performed. While not the primary author of this paper, my contribution involved, in addition to work on the results, review and statistics, the core development of the technique being validated and interpretation of its capability and applicability in postoperative TKA analysis. The motivation for this technique was to develop further studies as presented in this thesis, and in light of the significant contribution of this paper in describing the flow of studies that constitute this thesis, it has been included. Permission from the primary author has been obtained.

5.1: Abstract

Background: Successful component alignment is a major metric of success in total knee arthroplasty. Component translational placement however, is less well reported despite being shown to affect patient outcomes. CT scans and planar x-rays are routinely used to report alignment, but do not report measurements as precisely or accurately as modern navigation systems can deliver, or with reference to the pre-operative anatomy.

Methods: A method is presented here that utilises a CT scan obtained for pre-operative planning, and a post-operative CT scan for analysis, to recreate a computational model of the knee with patient specific axes. This model is then used to determine the post-operative component position in 3D space.

Results: Two subjects were investigated for reproducibility producing 12 sets of results. The maximum error using this technique was $0.9^\circ \pm 0.6^\circ$ in rotation and $0.5 \text{ mm} \pm 0.3 \text{ mm}$ in translation. Eleven subjects were investigated for reliability producing 22 sets of results. The intra-class correlation coefficient for each of the 3 axes of rotation and three primary resection planes were > 0.93 indicating excellent reliability.

Conclusions: Routine use of this analysis will allow surgeons and engineers to better understand the effect of component alignment as well as placement on outcome.

5.2: Introduction

Dissatisfaction amongst total knee arthroplasty (TKA) is the result of a complex relationship between the patient anatomy, prosthesis design and position, and other patient specific factors. Prosthesis malalignment has been linked to poor patient outcomes in which coronal and axial malalignment have been most closely studied [49, 344]. To have confidence in the correlation between component alignment and outcome, the method used to determine component placement must be accurate and reliable.

Component alignment refers to the angular difference between the prosthetic components and patient derived antero-posterior (AP), medio-lateral (ML) and superior-inferior (SI) anatomic axes. This measurement has traditionally been the focus of post-operative analysis in TKA due to the ease of measurement. Component placement refers to the translational movement of the prosthetic components along these patient specific axes. Due to difficulty in identifying the origin of these axes and accurately determining translation in space, component placement has been less well investigated. To understand the holistic effect of the TKA components on knee kinematics, both the alignment and placement must be taken in to account. Here we term the combination of component alignment and placement as 'component position'.

The pre-operative state of the patient is a critical source of missing data from most analyses which prevents accurate reporting of component position. Bony resections cannot be accurately determined from a post-op analysis alone and as a result there is very little data available on the outcome of TKA as a result of the modification of the anatomy [345, 346], highlighting the need for improved post-operative analysis techniques. Nevertheless, studies have investigated range of movement and maximum flexion as a function of the posterior condylar offset (PCO) [197, 347]. In these publications a greater PCO resulted in higher maximum flexion due to reduced steric hinderance. Pre- and post- operative

measurements however were limited by the use of ML x-rays, indicating that the relationship must be strong to overcome such errors.

Alteration of the joint line and flexion/extension gaps are associated with a change in joint kinematics [348] and patient outcome [349]. In these studies, patients with less change to the coronal joint line reported improved WOMAC and Knee Society Clinical Rating Scores. Identification of such changes however can be difficult, as the joint line and joint gaps can be modified without affecting the appearance of the component alignment. To better understand the effect of bone resections, joint line and gap modification, accurate pre-operative geometry data is required. Similarly, Bengs et al.[350] found that increasing patella button thickness without increasing the patella resection, decreased maximum passive flexion. Identification of appropriate patella resection for a given button thickness would not be possible with traditional post-operative analysis techniques.

Short leg x-rays have traditionally been used to assess TKA component alignment in the coronal plane, but due to the significant population variation in both the anatomic to mechanical axis of the femur and the tibia, coronal alignment measurements from short leg x-rays alone are inaccurate [351, 352]. Long leg x-rays allow accurate identification of the hip and ankle centre when the patient's leg is correctly positioned perpendicular to the x-ray plane. However, when the leg is positioned with rotation in either the axial or sagittal planes, projection errors alter the apparent coronal plane measurement [353]. To capture the position of the leg space without excessive radiation exposure, 3-dimensional (3D) imaging is required (biplanar x-rays, MRI etc.). Protocols that investigate component alignment with a post-operative CT only are hampered by errors in landmarking patient specific axes due to prosthesis induced CT flare and projection errors when rotations are present in more than 2 planes [307, 354-357].

To improve landmarking and component placement accuracy, a pre-operative CT is required. Fortunately, CT imaging is rapidly becoming a standard of care in pre-operative planning for TKA [339], and is available for a wide range of patients. Pre-operative CT imaging allows a volumetric registration of the pre-operative and post-operative bones and component geometries in 3D space eliminating any projection errors. The correctly placed models can then be used to determine bony resections and component placement. Model transformations can be performed in a number of ways, from manual manipulation of the component in space, to automated techniques such as the Iterative Closest Point method (ICP). A method to compare the pre-operative state of the knee to the post-operative component position and bone resections in which accuracy has not been affected by component flare has not yet been achieved.

Here we introduce a method of 3D reconstruction which utilises both a pre-operative and post-operative CT scan to determine the post-operative component position in TKA. The method may be extended to any joint replacement and is termed here the Australian Universal Resection, Orientation and Rotation Analysis (AURORA) protocol. Landmarks and bone models unaffected by component flare obtained from the pre-operative scan are transformed into the post-operative frame of reference. Component position as defined by the landmarked patient specific axes and bony resections are reported. The reproducibility and reliability of this method are presented and compared to other post-operative analysis techniques.

5.3: Methods

A series of patients received long leg pre-operative CT scans for routine pre-operative planning of TKA surgery [290] and to design patient specific instrumentation. Ethics approval for all data collection and accessing information from a joint registry for this study was approved by Bellberry Ethics (Sydney, Australia) (approval 2012-03-710). The same protocol is followed for post-operative CT imaging. This protocol requires the patient to be in supine at the isocentre of the gantry, with both legs fully extended and parallel to the horizontal plane. The legs are straightened and maintained in a relaxed position. Image acquisition involves a full leg pass CT scan taken through both limbs with all images taken in the same field of view, see Figure 1. This allows detection of any patient movement during the scanning process. Transverse slice thicknesses of 1.25 mm are taken, with less than 1 mm slices taken within the sagittal and coronal axis.

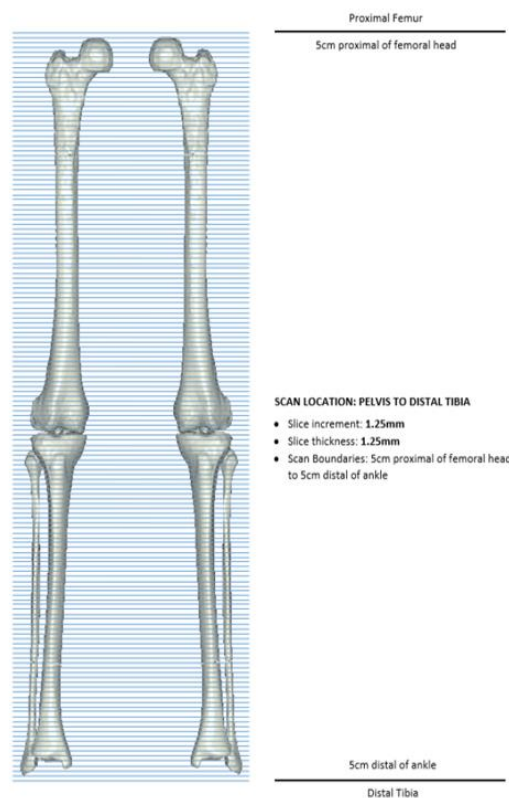


Figure 1: Single pass CT scan through both limbs.

All patients investigated here had a TKA using OMNI APEX implants (Raynham, MA), from 4 different surgeons using 4 different techniques. Patients were randomly selected from a database of over 2000 TKA surgeries.

The CT dose is calculated by multiplying the dose-length-product (mGy.cm) provided as supporting information with the CT scan, by the length of the CT scan in which the patient is imaged. The dose value is then converted to an effective dose based on anatomic conversion coefficients presented by Saltybaeva et al. [358] to allow comparison between different CT protocols. Movement in the scan can affect both individual bone and long leg measurements. Movement is detected by an engineer assessing the scan before processing. All patients were randomly selected from a database of patients scanned over a 3-month period previously confirmed to have not moved.

5.3.1: Image processing and Volumetric Registration

3D reconstructed patient femur and tibia bones are generated within the pre-operative planning process through semi-automated segmentation, used to landmark and identify points of interest by biomedical engineers using the 3D imaging software, ScanIP (Simpleware, Exeter UK). The patient bones are converted to stereolithography (STL) files and landmarked independently by two different engineers. If any landmarks differ by a threshold value (in this case 4 mm), the landmark was reviewed by another trained engineer. Landmark references were used to define patient specific bone axes and soft tissue attachment sites, see Figure 2A. The femoral and hip centres are landmarked to define the mechanical axis of the femur. The tibial mechanical axis is defined from the midpoint of the lateral and medial malleoli to the midpoint of the medial 1/3 of the tubercle and PCL insertion. The tibial AP axis is defined along the medial 1/3 of the tubercle and PCL insertion, while the Transepicondylar Axis (TEA) is defined along the medial sulcus to the

lateral epicondyle on the femur. These axes are used to define a frame of reference from which implant position may be calculated.

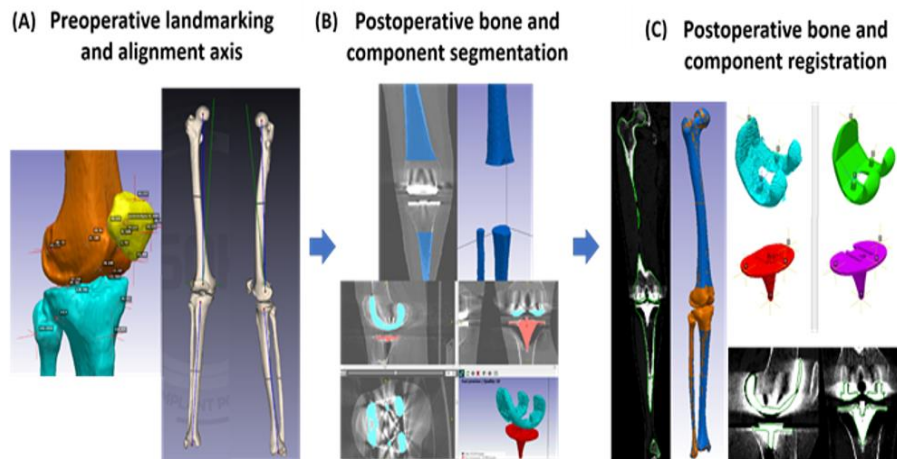


Figure 2: Post-operative process workflow showing a) pre-operative bone segmentation and landmarking, b) segmentation of post-operative bones and components, and c) registration of pre-operative to post-operative bones and components.

Using the post-operative full leg CT scan, 3D post-operative femur and tibia bone sections unaffected by the component flare are segmented, see Figure 2B. 3D registration is then performed, by registering the pre-operative femur and tibia models into the post-operative CT with reference to both the imaging and newly generated post-operative bone models, see Figure 2C. Point-to-point registration is performed on CAD models of the implanted prosthesis and segmented prosthesis models from the CT, see Figure 2C. All registration is refined using model outlines viewed in the full leg CT scan. A second engineer reviews both the registered femur and tibia bones, and the femoral and tibial implant components to further refine both bone and implant positions within the CT scan.

Euler transform matrices are obtained from the resulting registered pre-operative bones and used to transform the pre-operative bone landmarks into the post-operative CT reference frame. Using the transformed landmark references, component alignment and placement are determined within the local reference frames from the defined axes of landmarks identified pre-operatively.

5.3.2: Reproducibility

Two primary TKR patients were processed post-operatively twice by 3 engineers in a 2-week period. Patient CT scans were segmented and registered by an engineer and then reviewed by a second. The same case was processed again by the initial engineer on another day at a different time of day and then reviewed by a third engineer. This process was repeated across the 3 engineers for the 2 cases with alternating reviewers, and a total of 12 registrations was then analysed (see Figure 3).

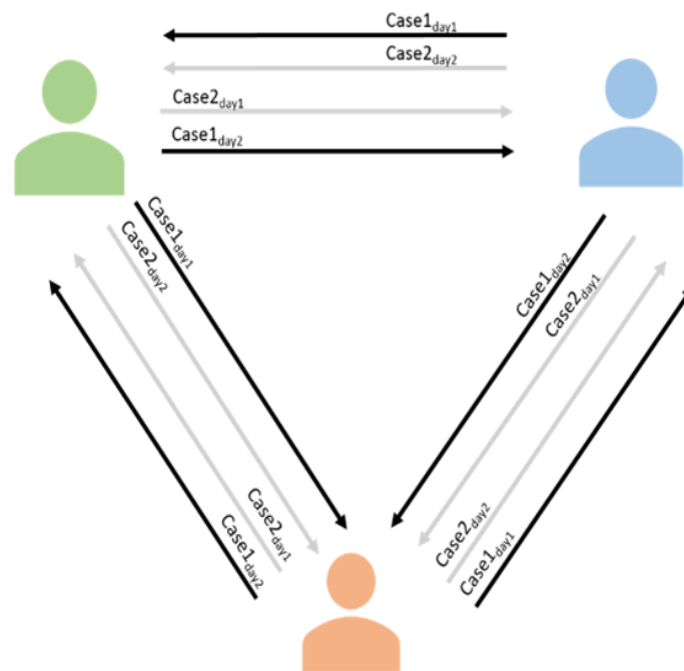


Figure 3 Flow diagram of reproducibility quality control.

Comparison of component alignment angles in flexion/extension (FE), varus/valgus (VV) and internal/external (IE) rotation, and component placement values by measuring the femoral medial and lateral, distal and posterior condyles, and the medial and lateral tibial plateau was recorded. Reproducibility was assessed from these angular and resection measurements by determining the maximum difference and standard deviation from the

mean calculated for each patient, with the 95% confidence interval defined across both cases.

5.3.3: Reliability

To describe the interobserver reliability, 11 TKR patients were processed post-operatively between 2 engineers. Each case was reviewed by a third and fourth engineer, with refinement of the bone and component registration made by the reviewing engineer if necessary. A set of 22 results were produced for comparison of the 3 rotation axes across two components and 6 resection measurements. The intraclass correlation coefficient (ICC) was calculated for each of the measurements. An ICC value of 1 shows perfect reliability, values greater than 0.9 indicates an excellent result, 0.81 to 0.9 is very good, 0.76 to 0.80 is good, 0.5 to 0.75 is moderate and <0.50 is considered to show poor reliability [359].

5.4: Results

5.4.1: Radiation Dose

The average effective radiation dose received per CT scan using this protocol is 1.24 ± 0.96 mSv. This dose is compared to other CT and radiography protocols in Figure 4. The average received dose is lower than all protocols shown in the figure with the exception of the most recent Imperial Protocol [345] and a standard AP radiograph. The spread of values shown for the AURORA CT protocol used here reflect the large range of patient sizes scanned. Smaller patients receive a correspondingly lower dose of radiation and vice versa for larger patients.

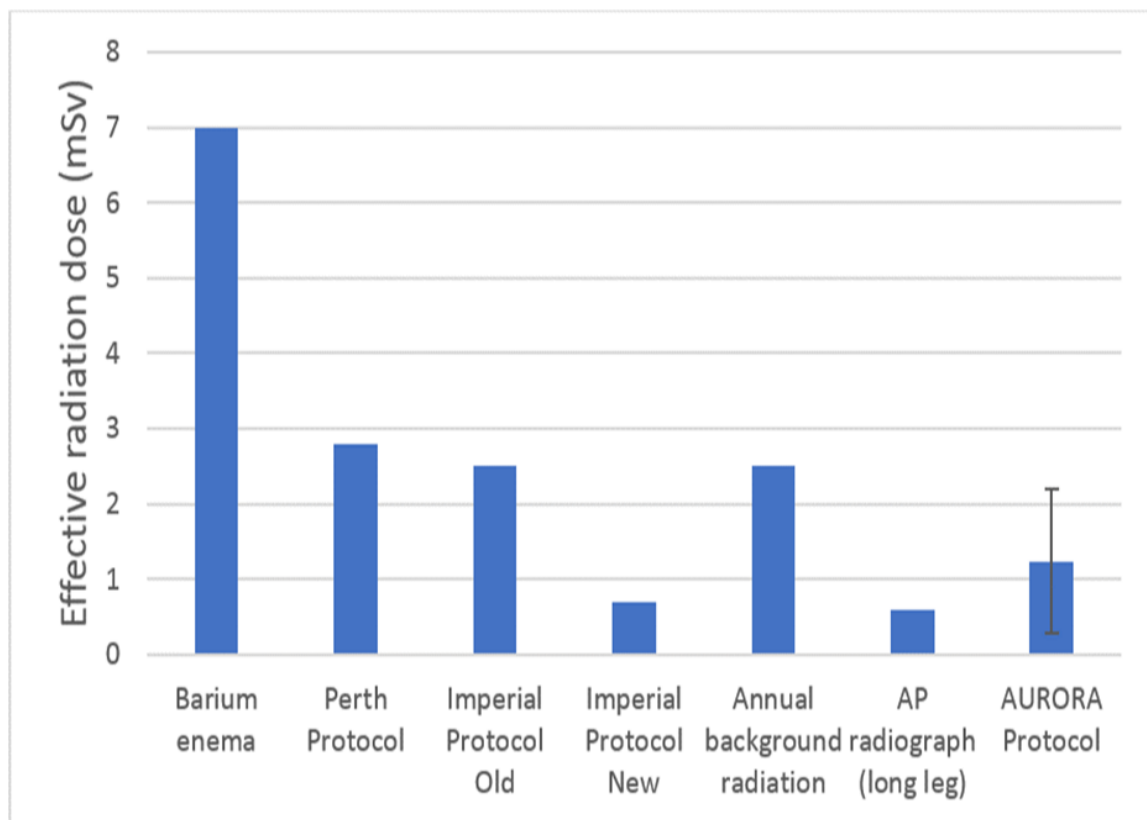


Figure 4: Comparison of the AURORA CT protocol with a barium enema and other relevant protocols for determining prosthesis positioning. AURORA protocol dose is calculated from CT reports, all other data taken from Henckel, et al. [345].

Using the AURORA protocol, patient movement in the CT scan may be detected at any point along the length of the bone. In previous methods, such as the Perth CT and Imperial protocols, movement in the mid femur and mid tibia will not be detected, leaving any measurements to propagate through the protocol as an error. In a database of CT scans obtained for routine pre-operative planning of TKA, the rate of scans identified with movement over a 3-month period is 6.78% (total number of scans: 118). Of this fraction, all movement in the scans were detected in the mid femur and mid tibia regions.

5.4.2: Reproducibility

Table 1 Reproducibility results showing the difference in calculated component angular alignment across two cases performed by three engineers at two different time points. The maximum average difference for each case and a 95% confidence interval is shown for all three axes of rotation for the femoral and tibial components.

Case	Operator	Run	Femoral Component Alignment			Tibial Component Alignment		
			F/E	V/V	IE	F/E	V/V	IE
Case 1	Sim Eng A	Run 1	1.1	-0.6	-0.8	7.1	0.6	5.9
Case 1	Sim Eng A	Run 2	1.0	-0.5	-1.2	7.0	0.4	6.2
Case 1	Sim Eng B	Run 1	1.0	-0.8	-1.5	7.0	0.5	4.5
Case 1	Sim Eng B	Run 2	0.8	-0.7	-0.8	7.4	0.4	4.7
Case 1	Sim Eng C	Run 1	1.1	-0.6	-1.8	6.9	0.8	5.5
Case 1	Sim Eng C	Run 2	1.1	-0.4	-1.0	7.2	0.6	5.9
Maximum Difference from								
Average (°) ± 95% CI			0.2 ± 0.1	0.2 ± 0.1	0.5 ± 0.3	0.3 ± 0.1	0.2 ± 0.1	0.9 ± 0.6
Case 2	Sim Eng A	Run 1	1.9	-0.9	0.1	8.2	1.5	3.0
Case 2	Sim Eng A	Run 2	2.3	-0.8	-0.1	7.7	1.8	2.7
Case 2	Sim Eng B	Run 1	2.3	-0.7	-0.2	7.9	1.7	1.7
Case 2	Sim Eng B	Run 2	2.1	-0.8	0.4	8.4	1.4	2.8
Case 2	Sim Eng C	Run 1	2.0	-0.7	-0.2	7.9	1.0	2.3
Case 2	Sim Eng C	Run 2	1.8	-0.8	0.0	8.4	1.5	2.8
Maximum Difference from								
Average (°) ± 95% CI			0.3 ± 0.2	0.1 ± 0.1	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.2	0.7 ± 0.4

Table 2 Reproducibility results showing the difference in calculated bony resection thicknesses (giving a measure of the accuracy of component placement) for the distal medial and lateral condyles, posterior medial and lateral condyles, and tibial medial and lateral plateaus across two cases performed by three engineers at two different time points. The maximum average difference for each case and a 95% confidence interval is shown for all resections.

Case	Operator	Run	Femoral Resections				Tibial Resections	
			Lat. Condyle	Med. Condyle	Post. Lat. Condyle	Post. Med. Condyle	Lat. Plateau	Med. Plateau
Case 1	Sim Eng A	Run 1	6.5	6.0	10.0	10.3	11.2	10.0
Case 1	Sim Eng A	Run 2	6.2	5.7	10.0	10.7	10.3	9.0
Case 1	Sim Eng B	Run 1	6.1	5.4	10.2	11.1	10.5	9.3
Case 1	Sim Eng B	Run 2	6.8	6.1	10.2	10.6	11.1	9.8
Case 1	Sim Eng C	Run 1	6.2	5.7	9.5	10.7	10.7	9.6
Case 1	Sim Eng C	Run 2	6.4	6.0	9.9	10.3	11.1	9.9
Maximum Difference from Average (mm) ± 95% CI			0.3 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.3
Case 2	Sim Eng A	Run 1	6.0	7.4	10.9	10.3	11.0	6.7
Case 2	Sim Eng A	Run 2	6.2	7.8	10.8	10.3	11.1	7.0
Case 2	Sim Eng B	Run 1	6.1	7.7	10.6	10.2	10.9	6.7
Case 2	Sim Eng B	Run 2	6.1	7.6	10.8	9.9	11.2	6.9
Case 2	Sim Eng C	Run 1	5.9	7.5	11.0	10.6	11.0	6.3
Case 2	Sim Eng C	Run 2	6.0	7.4	10.9	10.4	10.9	6.6
Maximum Difference from Average (mm) ± 95% CI			0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2

The alignment reproducibility results generated from three engineers processing two cases at two different time points which were then QC checked are shown in Table 1. The maximum difference from the mean angle is shown for each case. In both cases the maximum difference is reported for tibial component axial rotation, of 0.9° for case 1 and 0.7° for case 2. In all other angles, the maximum difference in rotation is $\leq 0.5^\circ$. The confidence intervals in all cases are less than 0.3° with the exception of tibial tray IE rotation, which is 0.6° for case 1, and 0.4° for case 2.

The bony resection thicknesses is a proxy measure for the accuracy of measuring component placement and is shown in Table 2 for the distal medial and lateral condyles,

posterior medial and lateral condyles, and tibial medial and lateral plateaus. The maximum difference from the mean resection is shown for each case. In both cases the maximum difference is reported for the medial tibial plateau, of 0.5 mm for case 1 and 0.3 mm for case 2. In all other resections, the maximum difference in resection is ≤ 0.3 mm. The confidence intervals in all cases are less than 0.3 mm.

5.4.3: Reliability

The rotational alignments and bony resections for the femur and tibial components reported for 11 cases performed twice (each time by a team of two different engineers) are shown in Figure 5 and Figure 6. The ICC value is given for each alignment and resection variable. The lowest reported ICC variable is for femoral axial rotation, with an ICC of 0.93. These values are all above 0.9, indicating that across all rotations and resections in both the femur and tibia, the protocol reports excellent reliability.

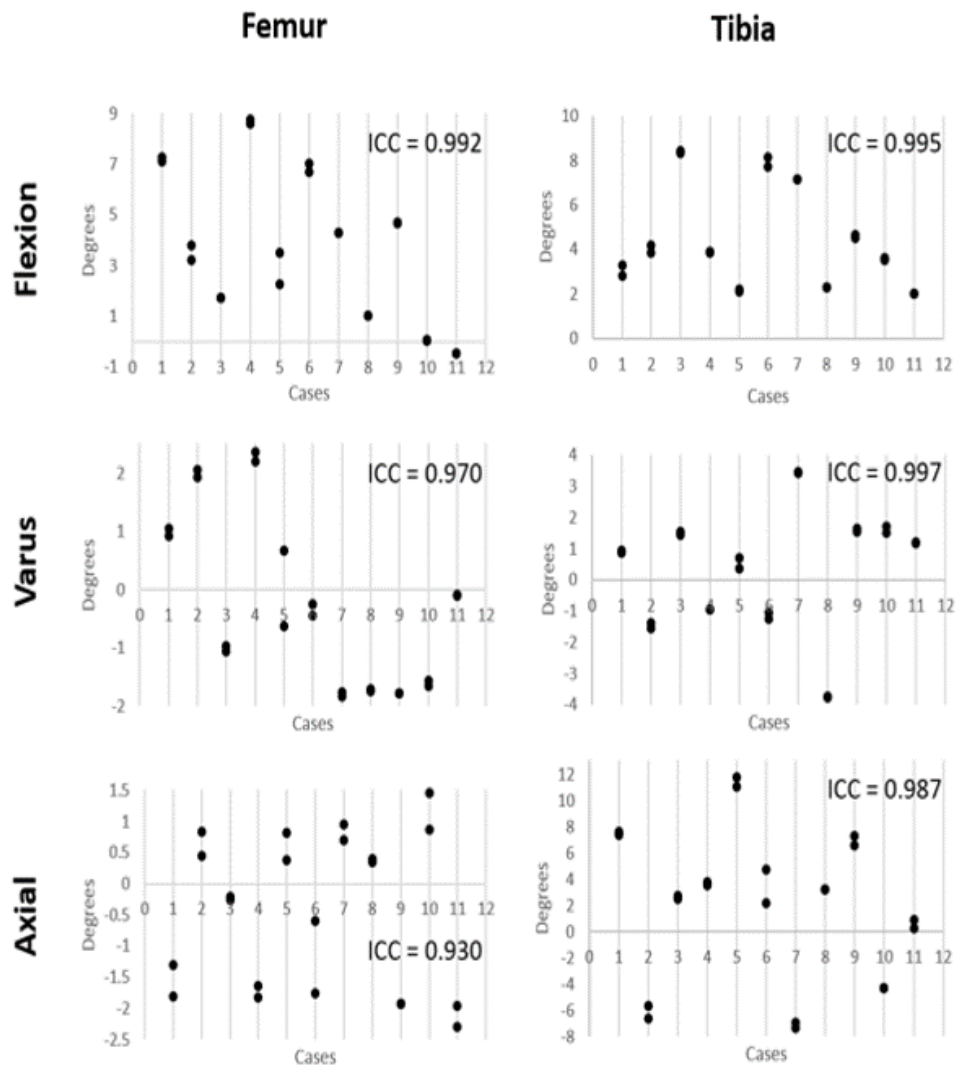


Figure 5: Reliability testing for femur and tibia placement showing the coronal, axial and sagittal rotation reported by the method across 11 cases performed by two engineers, followed by two additional engineers reviewing the placement. The ICC for each rotation in each component is reported. All values are greater than 0.9 indicating excellent reliability.

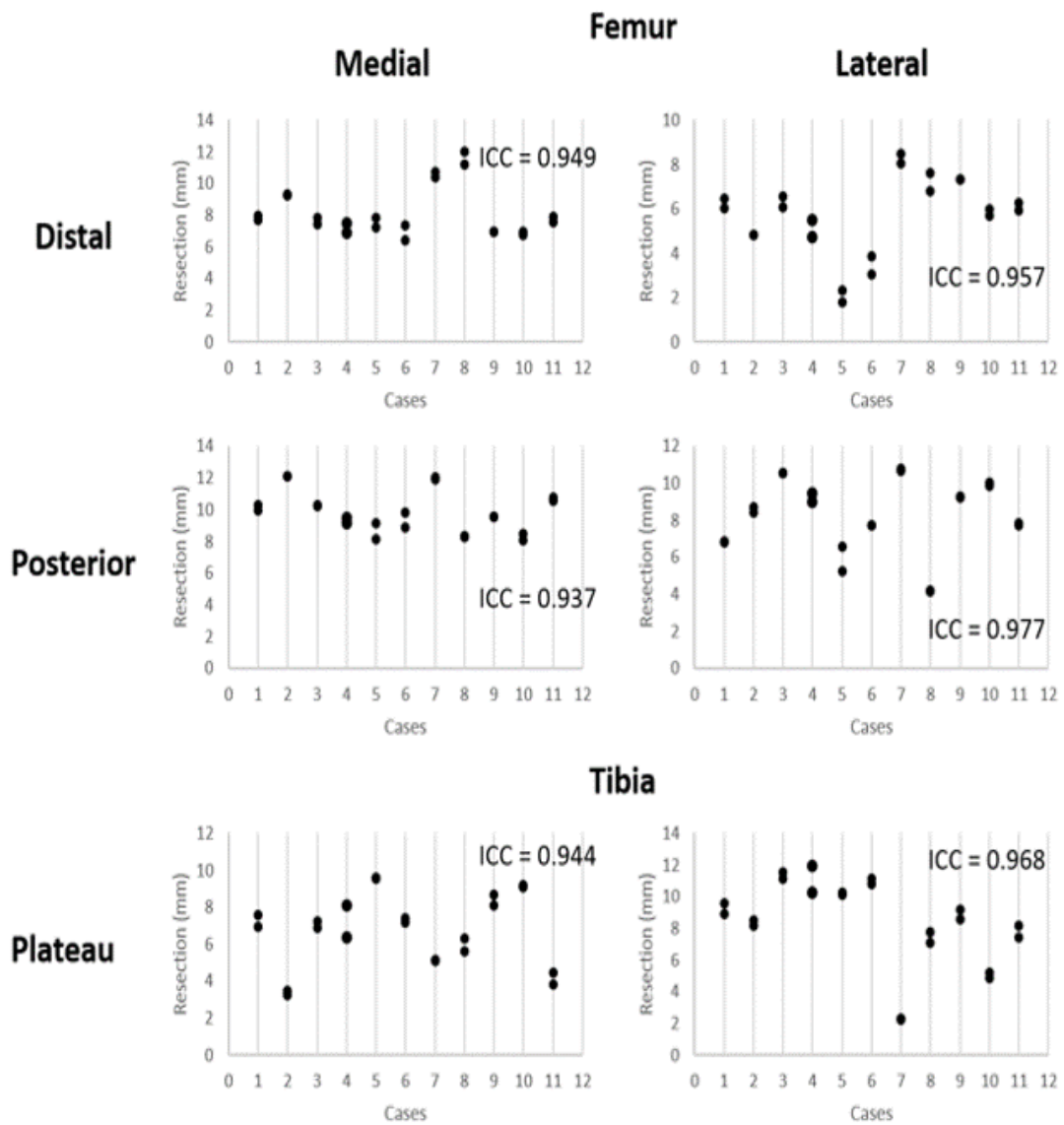


Figure 6: Reliability testing for femur and tibia bony resections reported by the method across 11 cases performed by two engineers, followed by two additional engineers reviewing the placement. The ICC for each rotation in each component is reported. All values are greater than 0.9 indicating excellent reliability.

5.5: Discussion

The maximum component alignment differences from the mean within this study are low compared to previous literature and provide a confidence interval up to 10 fold narrower when compared to protocols in which individual CT slices were investigated [307, 354, 357, 360], or only post-operative CT scans were available [361]. The maximum error of $< 1^\circ$ is similar to protocols using more advanced techniques, such as a computational edge detection, however these studies did not include ICC coefficients, so an assessment of the repeatability was not possible [362]. The highest deviation from the mean was the tibial IE rotation at 0.9° and 0.7° for the two cases, with a confidence interval of 0.6° and 0.4° respectively. These values represent an 8 fold improvement in accuracy compared to previous attempts to measure tibial rotation [363]. Previous attempts have reported difficulty in measuring tibial IE rotation due to the variability in the landmarks required to define a useful axis [63]. By combining the pre-op and post-op CT, the landmarks that define the AP axis can be identified more easily than using post-op CTs alone. Although there may still be some debate over which landmarks are the most appropriate, this method allows points to be defined that accurately reproduce an anatomic axis across multiple subjects. The origin of all axes may be redefined based on future literature if needed.

The resulting resection level measures of the femur and tibia also show high reproducibility, with the highest deviation seen for the medial tibial plateau resection at 0.5 mm and 0.3 mm between the two cases and confidence intervals of 0.6° and 0.4° , respectively. The magnitude of the error here however, is only slightly above the other resections, indicating that there may not be a systematic reason for reduced accuracy when placing this component. Previous attempts have been made to investigate the effect on TKA outcome arising from resection levels. These studies have mainly focussed on the femur, particularly the posterior condylar offset [197, 364, 365]. These techniques however have primarily

relied upon fluoroscopic images, and planar x-rays which were discussed previously to be inaccurate, limiting the reliability of such studies.

Across both femoral and tibial component alignments and bony resections, this 3D pre-operative registration process shows excelled reliability, in which all ICC values report greater than 0.93. The lowest reported ICC value of 0.93, resulting from the femoral axial IE rotation measure, is primarily due to the difficulty of post-operative registration of the femur component. The posterior condyles, which dominate the axial rotation positioning, of the APEX implant used in this study are thicker than the distal condyles (11 mm vs 9 mm) and tibial tray (~3 mm). As such, the CT flare is greater in these regions, reducing the accuracy of the registration. The ICC values reported here are consistently higher than other post-operative analysis techniques [346, 357] indicating this method is not only accurate, but suitable for routine post-processing by multiple users.

The high reproducibility and reliability of calculating both component alignment and bony resections performed by surgeons, can lead to a better understanding of the influences of component alignment and component placement. Current literature has thoroughly reviewed the influence of component malalignment on poor patient outcomes [366-368]. Missing from all of these analyses however, is an understanding of the patient's preoperative anatomy, leading Hadi et al. [366] to conclude that there is a dubious link between component malalignment and patient outcomes. From this post-operative analysis, we can begin to determine how the bony resections and the combination of component placement and alignment influence outcome on a patient specific level in greater detail. For example, the use of reliable bone resection measures from pre-operative bones may provide insight into the change of a patient's soft tissue profile post-surgery. From the pre-operative CT scans, comparative ligament lengths and change in length resulting from component alignment and placement can be investigated from landmarked attachment sites. CT scans in this analysis however, are performed in a non-functional

supine position, such that the distance between ligament attachment sites may not be representative of the functional length of the ligament. Functional imaging (such as weightbearing or joint distraction imaging) may be introduced to this workflow in future without requiring development of new processing techniques.

The proposed 3D registration process for post-operative analysis involves additional pre-operative CT imaging compared to other processes [307, 345]. Though this increases x-ray exposure to the patient, pre-operative planning, generally requiring a CT scan, is becoming the standard of care for TKA [339], such that the pre-operative scans are not for post-operative analysis alone. The protocol used here is a low dose CT, with radiation exposure less than the typical yearly background radiation and similar to protocols currently in use [345]. All patient movement identified in pre-operative scans occurred in the mid femur and mid tibia regions, indicating that protocols which did not include the mid femur and tibia sections would report inaccurate component placement. The resulting error in component position if these scans were used is the subject of further study.

Manual translation and rotation of the pre-operative bones and component geometries into the post-operative CT scan is reasonably labour intensive, requiring on average 60 minutes to complete, before the registration is quality control checked by a second engineer with additional experience. Further refinement of the proposed post-operative analysis process would include the use of automated registration methods such as ICP. A preliminary automated registration process using the ICP method was performed on these cases. The registration time was observed to reduce to approximately 2 minutes, from which the results were then fine-tuned by one engineer and quality control checked by a second engineer, representing a 30-fold decrease in time. Further development of the ICP method to optimise parameters around fitting regions of interest, reliability, and time for analysis may allow accurate post-operative analysis to be part of routine care, and is the subject of future studies.

Joint infection and component loosening are a cause of dissatisfaction and revision surgery. Joint infection can be identified by swelling of the joint and pathology reports, however these are not always conclusive. Combining component position as determined using the AURORA protocol with SPECT imaging could identify bone metabolism associated with infection or component movement [369]. Although current methods integrating SPECT imaging with CT do not improve the accuracy of determining component placement, such methods may be used to augment a pre-operative and post-operative CT 3D reconstruction to add metabolic activity.

The proposed post-operative 3D registration method described here has some limitations. The current time taken for this analysis as mentioned is approximately 60 minutes, this represents a high engineering burden, and must be reduced to improve use in routine analysis. Commercially, TKA component geometry varies between medical device manufacturers, forming a significant part of their IP portfolio, as such, the component geometries must be obtained from the implant companies, which may be difficult – limiting the generalisability of this technique to engineering firms with a close relationship with implant companies. The reproducibility analysis performed here utilises 2 cases processed at multiple time points by multiple engineers of equal training. To better understand the reproducibility, particularly when processing outlier or severely pathological anatomy, a greater number of cases should be analysed.

Other methods to assess component position such as bi-planar x-rays followed by 2D to 3D registration offer a number of advantages over a CT, such as providing long leg assessments in a functional state. Such techniques however, may require fluoroscopic agents [370], may only capture the region around the knee, and are performed on apparatus less widely available than traditional x-ray or CT machines, limiting its use [362].

5.6: Conclusion

Component alignment has been of great interest in total knee arthroplasty, however the focus has previously been on achieved component alignment and identification of malalignment without regard for the component placement or pre-operative anatomy. The method presented here uses a low dose CT scan to analyse the position and rotation of all components in 3D space, with comparison to the pre-operative anatomy, allowing surgical changes to the joint to be determined. The method shows excellent reliability and reproducibility by removing sources of error that are typically associated with post-operative total knee arthroplasty analysis. Routine use of this analysis in TKA as well as other joint replacement procedures will allow surgeons and engineers to better understand the effect of component alignment as well as placement on outcome.

Chapter 6

Surgical Alteration of the Coronal and Axial Knee Alignment During TKA Correlates with Poor Patient Reported Symptomatic Outcome

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This chapter follows the process developed in Chapter 5 to compare the alteration of a number of coronal and rotational measurements following implantation of the components with Patient Reported Outcome Measures. This study is the only study known to the author to investigate pre- to post-operative changes in anatomical measurements with such a large dataset. A number of statistically significant findings are reached, although their impact is, in many cases, not clinically significant. While the finding of statistical significance is promising, it was determined that alignment of components alone, even assessed in multiple planes and referenced back to preoperative measurements, would not be sufficient to unlock all the surgical technical drivers of poor patient outcome.

6.1: Abstract

Background: Alternate alignment strategies in total knee arthroplasty (TKA) are of increasing interest to reduce the persistently high rate of post-operative patient dissatisfaction. Due to the lack of routine 3D imaging, the effect of modifying joint geometry on outcome is not well understood. This study aimed to examine axial and coronal joint-line modification on patient outcome as measured by the knee injury and osteoarthritis outcome score (KOOS).

Methods: This study retrospectively investigated TKA patients from a joint registry. All patients had pre- and post-operative CT scans, and post-operative KOOS scores obtained at least 6-months after surgery. The change in axial and coronal joint-line because of surgery and its effect of KOOS pain and symptoms was analysed.

Results: 372 patients satisfied all requirements. 62% were female, with an average age of 69.8 ± 8.1 years. The mean 6-month KOOS pain and symptoms score were 85 ± 17 and 79 ± 17 respectively. Significant weak correlations were found for the absolute change in femoral coronal alignment, coronal joint-line angle, and femoro-tibial mismatch (transepicondylar axis-to-Insall's) with KOOS symptoms. Patients with a change in coronal femoral or joint-line angle of $<3^\circ$ reported significantly higher KOOS symptoms scores (diff 4.2 and 3.6 points respectively, $p < 0.05$), those with a change in axial femoral and femoro-tibial mismatch angle $<6^\circ$, also reported significantly higher KOOS symptoms scores (diff 6.7 and 3.8 points respectively, $p < 0.05$).

Conclusion: Greater modification of the native anatomy correlated with worse TKA symptomatic outcomes. Alignment strategies that aim to match the prosthesis geometry to native anatomy may result in improved outcomes.

6.2: Introduction

Despite total knee arthroplasty (TKA) revision rates decreasing, patient dissatisfaction following TKA in recent years has remained at 10 - 25% [37, 70, 287]. Patients who are likely to be dissatisfied following surgery tend to be older, with preoperative pain, low functional scores, presence of postoperative complications, and unmet expectations [70]. An integral element of successful TKA, both for function and longevity, is achieving ideal alignment between the femoral and the tibial components of the knee [288, 371], both in the coronal and axial planes. However, the interpretation of what “ideal alignment” means can vary between surgeons, clinicians and researchers alike. Different types of alignment approach in these planes are currently the subject of debate, which among others, primarily includes mechanical alignment (MA) and kinematic alignment (KA).

MA is classically achieved by two main surgical strategies, gap balancing and angular resections based on population values [51, 178]. MA takes a one size fits all approach and attempts to reconstruct the knee, achieving alignment within 3° of the neutral mechanical axis [372]. While this approach has good long-term survivorship, patient dissatisfaction remains [176]. Some surgeons have relied on computer navigation [187, 372] and patient specific instrumentation to achieve a neutral postoperative mechanical axis following TKA [373]. Although these techniques have resulted in reduced outlier component placement [356], debate still exists around whether a justifiable improvement in pain, function or gait parameters has been achieved compared to conventional instrumentation [374-376]. Furthermore, meta-analysis has found no improvement in radiographic alignment or clinical outcomes in TKA when using patient specific instrumentation [377]. Conversely, KA attempts to restore the native geometry of the knee. KA considers the fact that the native tibio femoral coronal, axial and joint line alignment are not neutral, and that there is a normal alignment variability within the population [186, 378-380]. By modifying the

component placement to match the patient anatomy, this technique aims to restore the joint to the pre-arthritis state to achieve improved functional outcomes [381] and reduce hard and soft tissue trauma compared to MA TKA. Computer navigation has also been used for KA, allowing for partial correction of more extreme anatomy, that would otherwise be unsuitable using classic TKA methods [187].

There is evidence, that KA leads to improved patient outcomes [184]. For instance, in a retrospective study Salzman and colleagues found an improvement in the High Flexion Knee Score in a group of patients whose pre-operative varus alignment was preserved postoperatively than those in which the varus alignment was reduced [382]. While this was a retrospective study and the post-operative preservation of varus was unintentional, the results support the hypothesis that preserving the original anatomical alignment may provide better results than the mechanical alignment. Similarly, Vanlommel and colleagues observed better outcomes in patients with slight varus under correction postoperatively [383]. Dosset also found that anatomically aligned implants were associated with improved flexion and clinical outcomes compared to MA components [184]. Other studies however have shown no difference in functional outcomes between patients with post-operative residual varus and those with neutrally aligned TKA [384, 385]. A recent meta-analysis however has found improved functional outcomes in kinematically aligned patients [183], indicating that although debate remains on the optimal TKA alignment strategy, a one size fits all MA approach may not be ideal for every patient.

The patient specific pre-osteoarthritic alignment however, is often difficult to determine without historical imaging, and has led to the development of restricted kinematic alignment (rKA), which enforces limits on target alignments [176, 186]. Cases in which the pre-arthritis alignment is outside such limits, rKA will not achieve anatomical restoration and a compromise between reconstruction and restoration is performed. Such a situation

poses the question, how does one approach individualised alignment, based on patient anatomy and functionality to maximise postoperative outcomes?

There is evidence that component alignment in TKA has some impact on post-operative range of movement (ROM) [177]. ROM can be limited by two major factors, mechanical constraints arising from the geometry of the articulating surfaces of the prosthesis [386], and soft tissue constraints [387] in which a translational or rotational movement in the joint is restricted by ligament forces. In this era of new alignment strategies, the preoperative state can impact the postoperative state and any analysis investigating the postoperative coronal alignment alone will not be able to consider the impact of the variability amongst individuals in the preoperative state [164]. Similarly, without sufficient pre-operative information, post-operative computational mechanical models cannot determine whether the intended target was met.

In the debate between reconstruction vs. restoration, the fact remains that some osteoarthritic knees have wear and a level of deformity and pathology that makes a reconstruction impossible [186]. Similarly, if reconstructed using MA, this scenario would alter significantly the native anatomy and functionality, which may also result in poor outcomes. Thus, the degree to which the coronal and axial alignment is modified using various techniques and its impact on patient outcome is currently not well understood. Therefore, this study aims to determine any relationships between Knee Injury and Osteoarthritic Outcome Score (KOOS) at 6 months postoperatively and changes in the joint line, coronal and axial alignment of the knee resulting from TKA.

6.3: Method

Patients who received a TKA with pre- and post- operative CT scans, and 6-month post-operative KOOS scores from January 1 2014 were selected from the 360 Knee Systems Joint Registry. Surgery was performed by multiple surgeons, using mechanical instruments, navigation and patient specific instrumentation. Surgeons targeted a mixture of mechanical and kinematic alignment but may have made intra-operative adjustments in line with their standard technique. All patients received either a CR or PS OMNI APEX prosthesis (OMNIs, Raynham). Inclusion criteria were patients receiving a primary TKA for end stage osteoarthritis. Exclusion criteria were patients receiving any other type of knee arthroplasty, or a diagnosis of rheumatoid-arthritis. Ethics approval for this registry was provided by Bellberry ethics: 2012-03-710.

A CT scan was obtained for pre-operative planning. A post-operative CT scan was obtained to determine the final component positioning and change in joint geometry. The CT scans were a full leg pass from hip to ankle obtained at most 6 months before and after surgery. All scans were taken at 1.25 mm slice thickness, with the coronal and sagittal thicknesses varying but all less than 1.0 mm. Segmentation of the femur, tibia and patella bone were performed using ScanIP software (Simpleware, Exeter, UK) to generate a 3-dimensional model of the knee, which was then landmarked independently by 2 engineers.

Patient specific axes of the femur and tibia were then defined from the obtained landmarks according to the method previously described in Chapter 4 [290]. The coronal knee joint line was defined as previously described by Vendittoli et al. [182]. The combined femoro-tibial angle (FTA) is defined as the average of the angle between: the PCA and transepicondylar axis (TEA), in which internal PCA rotation is positive; and the angle between Cobb's definition of tibial rotation and the line perpendicular to the TEA, in which internal rotation of Cobb's tibial axis is positive [193]. This angle defines the direction the knee faces in

extension and is an estimate of the change to the active soft tissue during flexion and extension.

The pre-operative bone models were then registered to the post-operative CT and corresponding landmarks transformed. Implant geometries were registered to the post-operative CT scan using the +CAD module within ScanIP. The implant positions were then combined with the bone geometry and landmarks to generate the final joint geometry, and compared to the pre-operative state. The workflow is shown in Figure 1.

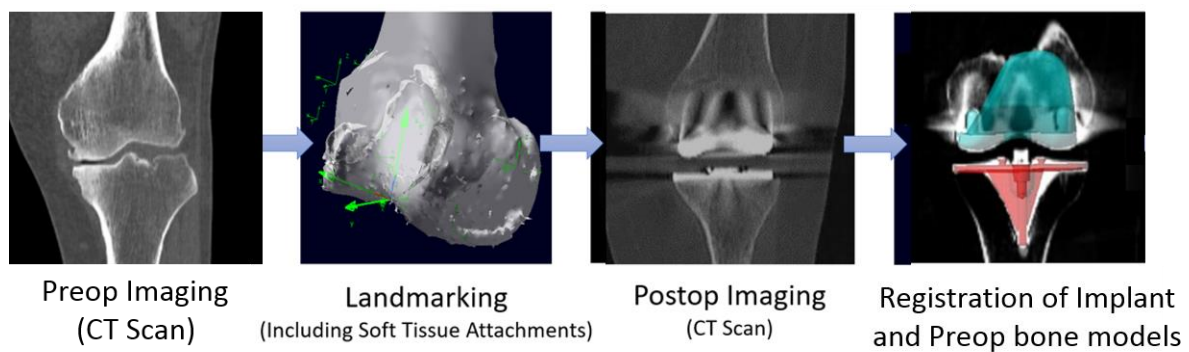


Figure 1 To generate accurate patient specific axes from which to calculate component placement and change in knee alignment a pre-op CT is used to landmark the femur tibia and patella. Segmented pre-op bones and implant models are then registered to the post-op CT giving joint angle data.

Post-operative KOOS scores were obtained at least 6 months following surgery. Patients were interviewed individually and were asked to consider the previous seven days as a time frame. The resultant KOOS scores scale from 0 to 100, with more positive values being a better outcome (or less symptomatic impact and pain). Linear Spearman's correlations between the KOOS Symptoms subscores and change in joint line, coronal and axial knee alignment were determined. The change in femoral coronal angle was subdivided into patients with a change less than 3° from native, and those with a greater change. Likewise, the change in axial alignment was subdivided into patients with a change less than 6° from native and those with a greater change. The resultant groups created were then t-tested for difference. Significance was set to $p = 0.05$, all statistics were performed with R version 3.4.2 [388].

6.4: Results

A total of 372 patients (229 female, 69.8 ± 8.1 years old) who had a preoperative and postoperative CT scan in addition to 6-month postoperative KOOS score were included in this study. The mean 6-month KOOS Pain Score was 85 ± 17 and KOOS Symptoms Score was 79 ± 17 . Histograms of the scores for the population are shown in Figure 2. Both scores are right shifted, however the lower mean score for KOOS Symptoms indicates a smaller fraction of patients are scoring 100.

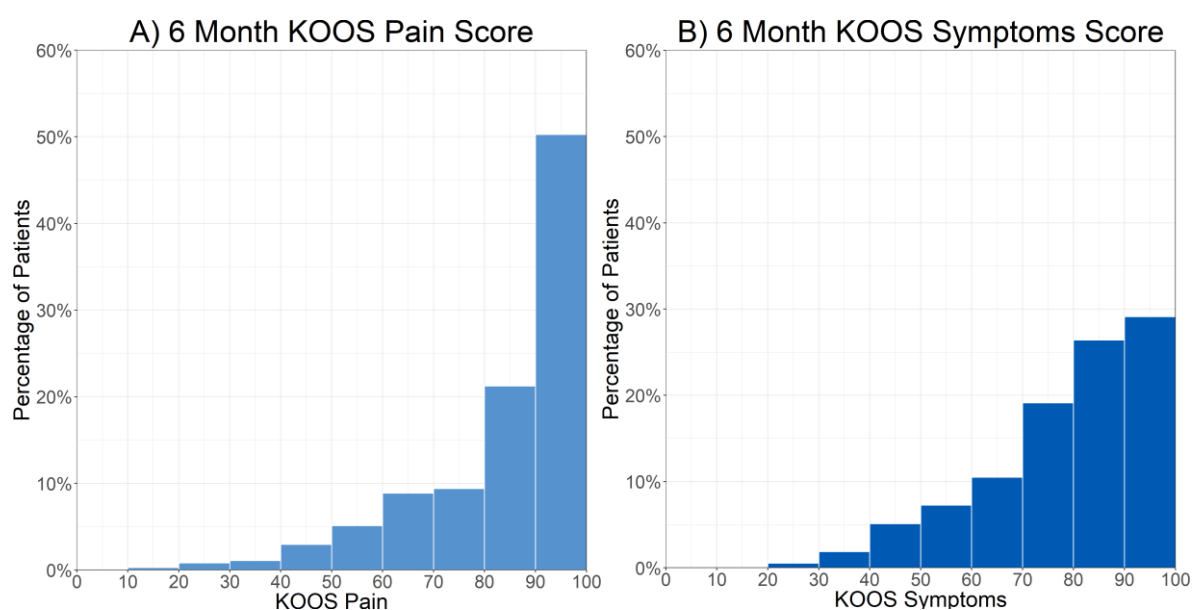


Figure 2. Six months postoperative KOOS Score distributions for the KOOS Pain subscore (a) and KOOS Symptoms subscore (b). Both distributions are significantly right shifted (low pain/symptomatic issue), with pain having generally higher scores than symptoms.

Table 1 shows the mean, standard deviation and range of each of these measurements as well as the pre- to post-operative change. In all measurements the trend is for implanted angles to have a lower magnitude than pre-operatively.

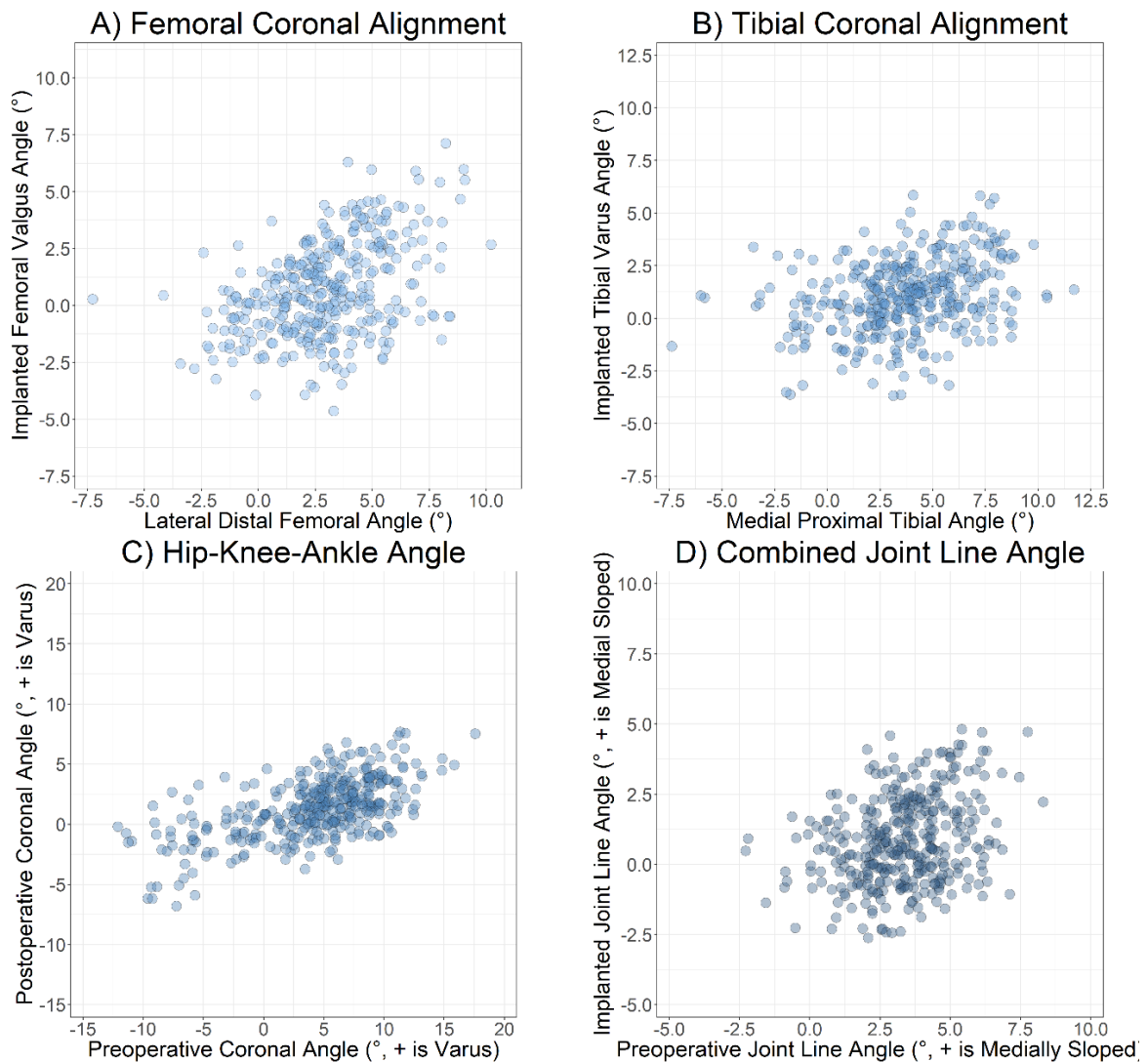


Figure 3. Comparison of the pre- and post-operative coronal plane measurements for femoral alignment (a), tibial alignment (b), overall long leg alignment (c) and joint line (d) angles.

Table 1 Statistical details of Femoral and Tibial coronal angles pre-operatively, post-operatively, and change.

	Preop	Postop	Change
Femoral Joint Angle	2.93 ± 2.52° (-7.28 to 10.22)	0.68 ± 2.07° (-4.64 to 7.13)	2.62 ± 2.09° (0 to 9.55)
Tibial Joint Angle	3.75 ± 2.98° (-7.38 to 12.73)	1.04 ± 1.75° (-3.67 to 5.85)	3.33 ± 2.22° (0.02 to 10.4)
Hip-Knee-Ankle Angle	4.13 ± 5.48° (-12.11 to 17.58)	1.30 ± 2.47° (-6.8 to 7.68)	4.46 ± 2.8° (0.01 to 11.92)
Combined Joint Line Angle	3.34 ± 1.73° (-2.28 to 8.31)	0.86 ± 1.56° (-2.62 to 4.81)	2.67 ± 1.69° (0.02 to 8.18)

There was a weak but significant correlation ($r = -0.14$, $p = 0.002$) between the absolute change in the femoral component coronal alignment and KOOS's symptoms scores at 6 months, in which the greater the change in femoral coronal alignment, the worse the KOOS

scores. There was also a weak but significant correlation ($r = -0.14$, $p = 0.007$) between the change in the joint line angle and KOOS symptoms scores at 6 months (The greater the joint line change the worse the KOOS symptoms scores).

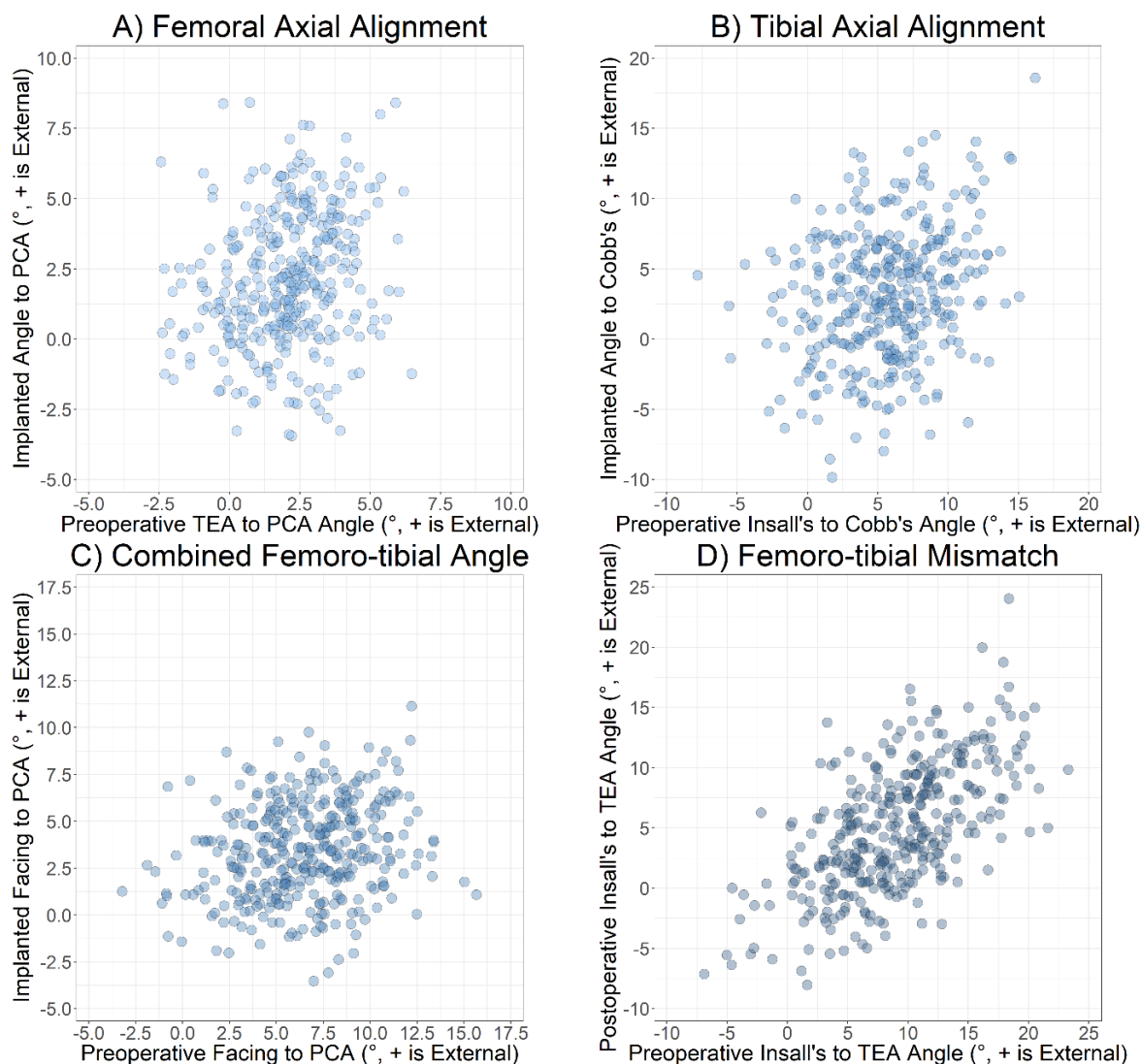


Figure 4. Comparison of the pre- and post- operative axial plane measurements for femoral alignment (a), tibial alignment (b), combined femoro-tibial (c) and femoro-tibial mismatch (d) angles.

Figure 4 shows the pre-operative and post-operative measurements in the axial plane for the tibial, femoral, HKA and joint line angles. Table 2 shows the mean, standard deviation and range of each of these measurements as well as the pre- to post-operative change. The tibial, femoral and FTA all display post-operative variation independent of the pre-operative state. The post-operative femoro-tibial mismatch show a trend towards retaining the native alignment post-operatively.

Table 2 Statistical details of Femoral and Tibial axial angles pre-operatively, post-operatively, and change.

	Preop	Postop	Change
Femoral Axial Angle	2.04 ± 1.72° (-2.44 to 6.48)	2.14 ± 2.36° (-3.45 to 8.42)	2.57 ± 1.89° (0.01 to 8.42)
Tibial Axial Angle	5.56 ± 3.88° (-7.83 to 16.19)	3.16 ± 4.73° (-10.92 to 18.59)	4.7 ± 3.34° (0 to 17.36)
Combined Femoro-tibial Angle	8.91 ± 5.33° (-6.91 to 23.28)	4.98 ± 5.2° (-8.05 to 24.03)	4.94 ± 3.49° (0 to 16.58)
Femoro-tibial Mismatch	6.50 ± 3.17° (-3.22 to 15.67)	3.44 ± 2.55° (-3.53 to 11.14)	3.83 ± 2.79° (0.03 to 14.58)

There was a weak but significant correlation ($r = -0.13$, $p = 0.011$) between the change in femoro-tibial mismatch (TEA to Insall's) and KOOS symptoms at 6 months. There was also a weak but significant correlation ($r = -0.14$, $p = 0.008$) between the change in the FTA and KOOS pain.

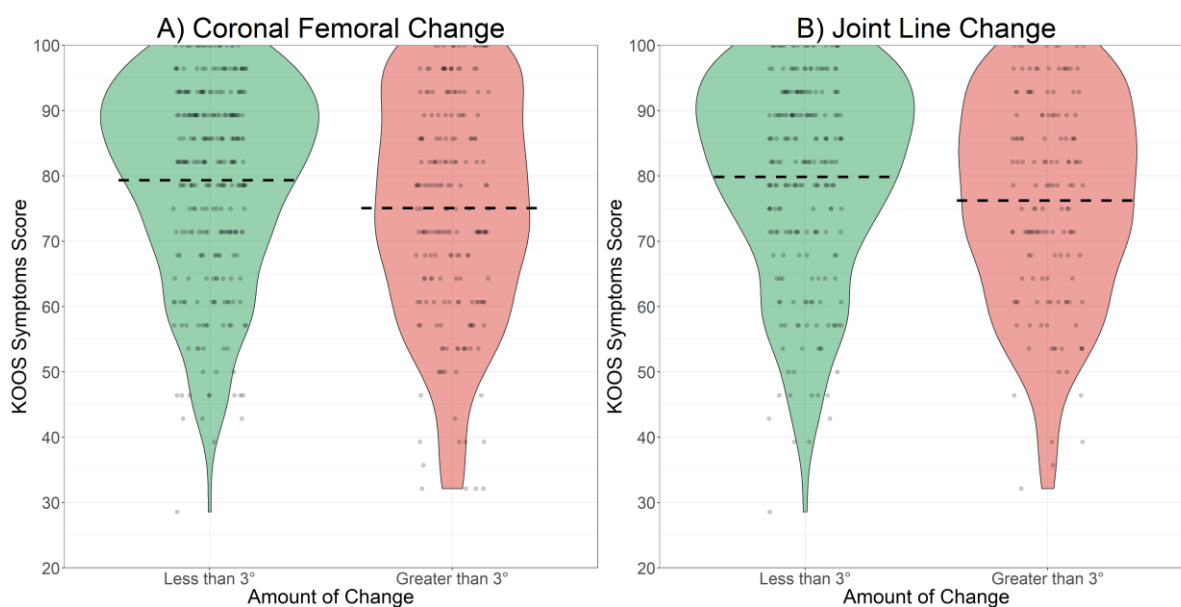


Figure 5 Violin plot of the change in coronal femoral angle (a) and joint line (b) subdivided into groups in which the change is less than or greater than 3° against KOOS symptoms. The dotted lines are population means. In both cases, patients with less than 3° change report improved outcomes.

The change in femoral coronal angle and change in joint line were subdivided into groups in which the change was less than or greater than 3° and plotted against the KOOS Symptoms scores in Figure 5. The patients in which the change in femoral and joint line change was less than 3° reported significantly higher KOOS symptoms scores (difference = 4.2, $p = 0.006$ and difference = 3.6, $p = 0.035$ respectively). Similarly, in Figure 6, patients in which the change in

the femoral axial alignment and femoro-tibial mismatch was less than 6° reported significantly higher KOOS symptoms scores post-operatively (diff = 6.7, $p=0.019$ and difference = 3.8, $p=0.032$ respectively).

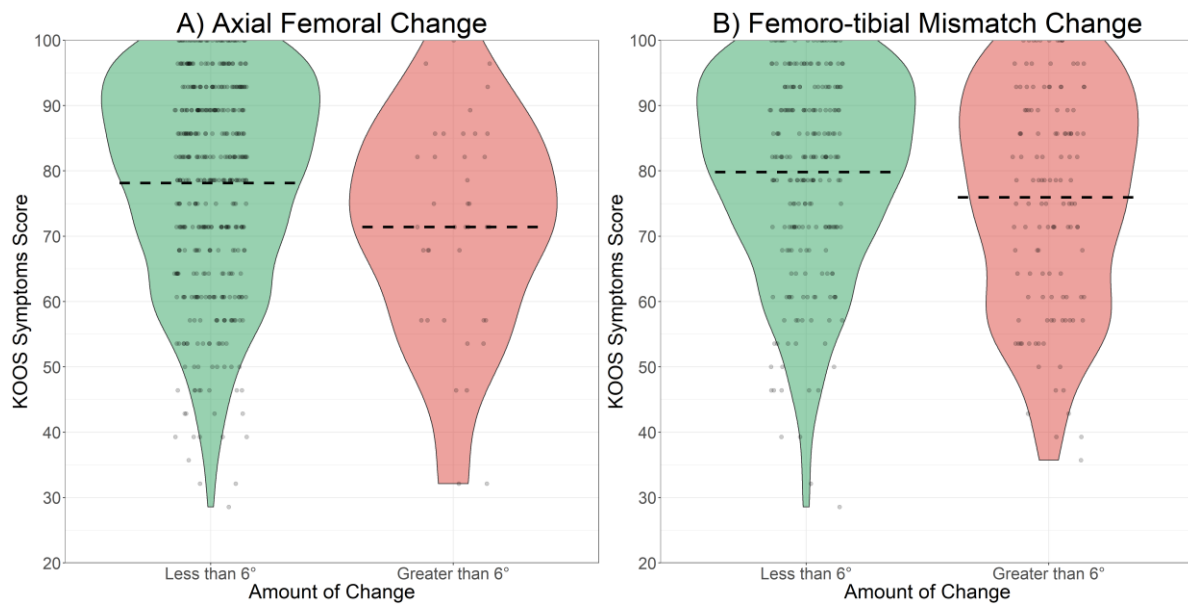


Figure 6 Violin plot of the change in axial femoral angle (a) and tibio-femoral angle (b) subdivided into groups in which the change is less than or greater than 6° against KOOS symptoms. The dotted lines are population means. In both cases, patients with less than 6° change report improved outcomes.

6.5: Discussion

Results from this study indicate that changes in the coronal plane of more than 3 ° and in the axial plane of more than 6° from pre-operative measurements show a significant decrease in the post-operative KOOS symptoms scores. This supports the hypothesis that modifying the native alignment of the knee has a negative impact in clinical outcomes, potentially leading to a higher rate of patient dissatisfaction. These results support the findings by Dosset, Salzmänn and Vanlommel, who observed improved functional scores in patients whose long leg alignment and native anatomy were least changed post-operatively [184, 382, 383], these studies however only focussed on the change to long leg alignment. The strength of the present study in comparison to the outcomes found in the existing literature is that all measurements are referenced to reconstructed pre-operative anatomy, allowing identification of postoperative changes in the anatomical angles of the femur and tibia individually as well as their relationships to each other.

The mean patient age in this study of 69.8 years is somewhat higher than other joint registries throughout the world, such as the Australian, New Zealand and Swedish Joint Registries [35, 36, 71]. This difference is reflective of the selective nature in which patients have been referred to the 360 Knee Systems Registry for pre-operative surgical planning and post-operative analysis. The increased age in this cohort is the likely reason for the increased pre-operative varus alignment of 4.1° compared to previous population studies [164]. Debate over KA or MA carries greater weight in patients with large deformities due to the difference in target alignment. The patients investigated here represent a subsection of the TKA population in which decision about technique is more meaningful due to the wider distribution of pre-operative alignments.

Improper positioning of components in TKA at the extremes can result in poor patient-reported outcomes (PROMS) [177, 389] and reduced ROM [390], but the exact mechanism by which this occurs is not well understood. One possible explanation for restriction in ROM after TKA is an inability of soft tissue to achieve flexion/extension balance in the new dynamic environment, leading to excessive stiffness or instability. The finding here, that changes in femoral articulation angle and associated femoro-tibial angular relationships (joint line and FTA angle) correlated with outcome but tibial measurements and combined femoro-tibial measurements (Hip-Knee-Ankle and femoro-tibial mismatch angle) did not, supports this idea. For instance, a valgoid placement of the femoral component may lead to looser lateral structures, such as the LCL, when the knee is in extension but no change when in flexion. Conversely, when the femoral component is placed in external rotation from the posterior condylar axis (PCA) – typical in MA when targeting the TEA - the result is tighter lateral structures when the knee is in flexion but no difference when the knee is in extension, coronal alignment being held constant. Such changes result in a dynamic joint gap, in which soft tissue may be incapable of adapting to the new environment, affecting patient recovery. Conversely, a tibial angular change postoperatively will loosen or tighten structures in both flexion and extension, soft tissue adaptation may occur more readily in this environment due to the balanced nature of the modification.

An important factor to consider however, is that the final alignment measured using this technique is a combination of the planned alignment, the surgeon's decision based on intraoperative observations and random variability in component placement. For this reason, the threshold values were chosen to reflect the level of accuracy that can be expected for a target alignment parameter. Intraoperative observation is a crucial element in decision making at the time of surgery. For instance, the patient cohort in this study were OA subjects in which the joint line may have been affected by the disease progression and may therefore be pathological. In this population, a change in joint line may be required in

significantly deformed patients to target any alignment philosophy. Within this study however, the difference between intentional philosophy driven component placement and random variability cannot be distinguished.

While MA is still the preferred approach among most surgeons, when the native alignment is outside an established threshold, greater ligament release is likely needed during surgery to achieve balance. However, this approach appears to negatively impact symptomatic outcomes and may introduce undesirable knee kinematics such as post-operative instability [187, 391, 392]. Literature indicating improved functional outcomes with kinematically aligned TKA components [381, 393], combined with the present findings, indicate patients tend to prefer more native knee alignments, rather than mechanically stable neutrally aligned components. This may be due to more balanced ligament forces throughout the flexion cycle without the need for ligament release.

When surgeons have a preference for KA and severe deformities in the native alignment are not biomechanically viable, surgeons may intentionally change the joint line, effectively targeting rKA over KA [186]. For patients in which the native alignment requires component alignment that is far from neutral, further analysis of the optimal surgical compromise is required. While the biomechanical restoration of severely deformed native alignment may not be viable, targeting mechanical alignment may also result in poor outcomes. Based on the results from this study, reducing the deviation from native anatomy as far as practicable, results in better functional outcomes, lending strength to opting for KA over MA.

Limitations of this study include the relatively small sample size confined to an Australian population. Pre-operative anatomy was measured using CT scans, and as such, the analysis does not include information on cartilage, whose wear is included in the definition of OA. Thus, the joint line was not exactly identified, but rather a calculation of the approximate joint line from the bony joint angles. Additionally, this study combines data from different

techniques from 12 different surgeons and as such is not a controlled analysis of the performance of a single operating technique. However, this very limitation also provides realistic information on variability across the industry, adding confidence to the population results. Patients investigated here who had a greater change in anatomy may have presented with native outlier anatomy, such that targeting KA may have compromised the survival of the implant. Further work is required to isolate the effect of modified anatomy post-operatively to patients with similar pre-operative anatomy.

6.6: Conclusion

Total knee arthroplasty outcomes are multifactorial and dependent on the femoral and tibial component alignment in the sagittal, coronal and axial planes. Alternative alignment strategies have become popular in recent years in an attempt to reduce the persistently high dissatisfaction rate in TKA. This study utilises pre- and post-operative analysis of patient anatomy to determine the change in knee axial and coronal alignment. Greater differences between pre- and post-operative anatomy were negatively correlated with KOOS pain and symptoms, indicating that matching the prosthesis to the native anatomy may result in improved outcomes. This study and the evidence found in the literature suggest kinematic alignment may have advantages over mechanical alignment.

Chapter 7

Variability in Static Alignment and Kinematics for Kinematically Aligned TKA

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In order to unpick the relationship between alignment and patient outcomes in surgery suggested in Chapter 6, we decided to investigate multi-body dynamics simulation. Forward dynamic simulation allows for the biomechanical behaviour of the joint to be investigated on a scale not otherwise possible. Comparative approaches to simulation include gait analysis and fluoroscopy (with and without inverse simulation) and cadaveric rig testing, but all present issues with scalability that limit their ability to investigate behaviour and variation across populations. The model presented here is used to investigate variation in kinematics responses between Mechanical and Kinematic Alignment, an alternate alignment strategy with promising results, as a proof of concept, and its initial validation against a cadaveric rig is also described (although further publications on the validation are to follow). While not the primary author of this paper, my contribution involved the Results and Methods section of the paper and the core underlying experimental work and analysis, including contributions to development of the model and all data analysis and interpretation. This study has been included given the significant contributions to this study, role in development of the driving simulation and the crucial role this study played in describing the simulation that formed the core finding in the subsequent study. Permission from the primary author has been obtained.

7.1: Abstract

Background: Total knee arthroplasty (TKA) significantly improves pain and restores a considerable degree of function. However, improvements are needed to increase patient satisfaction and restore kinematics to allow more physically demanding activities that active patients consider important. The aim of our study was to compare the alignment and motion of kinematically and mechanically aligned TKAs.

Methods: A patient specific musculoskeletal computer simulation was used to compare the tibio-femoral and patello-femoral kinematics between mechanically aligned and kinematically aligned TKA in 20 patients.

Results: When kinematically aligned, femoral components on average resulted in more valgus alignment to the mechanical axis and internally rotated to surgical transepicondylar axis whereas tibia component on average resulted in more varus alignment to the mechanical axis and internally rotated to tibial AP rotational axis. With kinematic alignment, tibio-femoral motion displayed greater tibial external rotation and lateral femoral flexion facet centre (FFC) translation with knee flexion than mechanical aligned TKA. At the patellofemoral joint, patella lateral shift of kinematically aligned TKA plateaued after 20-30° flexion whilst in mechanically aligned TKA it decreased continuously through the whole range of motion.

Conclusions: Kinematic alignment resulted in greater variation than mechanical alignment for all tibio-femoral and patello-femoral motion. Kinematic alignment places TKA components patient specific alignment which depends on the preoperative state of the knee resulting in greater variation in kinematics. The use of computational models has the potential to predict which alignment based on native alignment, kinematic or mechanical, could improve knee function for patient's undergoing TKA.

7.2: Introduction

Total knee arthroplasty (TKA) is an established procedure for improving pain and restoring a significant degree of function, especially for low-demand activities of daily living. However, an understanding of optimal alignment and patient specific kinematics are needed to restore knee motion closer to normal, allowing performance of physically demanding activities that more active patients consider important. [394-396]

The philosophy of mechanical alignment of the implant after TKA has traditionally been done to preserve longevity of the implant and enhance post-operative knee function [321, 389, 397]. However, studies have shown that although a mechanically aligned TKA improves the patient's function, 20% to 25% of patients remain dissatisfied [70, 287]. In addition, recent data has challenged the importance of post-operative mechanical alignment in TKA. Paratte et al [42], in a study reviewing 398 TKAs, demonstrated no improvement in the fifteen year implant survival rate in patients within and outside of a post-operative mechanical alignment $0^\circ \pm 3^\circ$.

Recently, kinematic alignment has been proposed by Howell et al [47, 395, 398] as an alternative to restore normal knee motion and function. Kinematic alignment references the femoral transcondylar axis, believed to be the flexion extension axis of the knee. The aim is to align the angle and level of the distal joint line of the femoral component, posterior joint line of the femoral component, and joint line of the tibial component to those of the normal knee [47].

Kinematically aligned TKA has been performed since 2006 however unanswered issues continue regarding patient outcomes, survivorship, surgical technique and use of specialised surgical guides [46, 184, 399, 400]. A randomized controlled study demonstrated kinematically aligned TKA resulted in better pain relief, post-operative function and range of

motion than mechanically aligned TKA in 88 patients (88 knees) [184]. Other studies emphasized higher function as assessed using the Oxford Knee Score and WOMACTM score on 198 patients (214 knees) [46]; on 101 patients (101 knees) with kinematic alignment [399]. However, one small series emphasized the potential for malalignment using the OtisKnee system, which places implants at higher risk of early failure [400]. The optimal targets for alignment in TKA remain unclear, and indeed a single philosophy may not be applicable to an optimal outcome in all patients. Computer simulations are powerful tools that can provide insight into how different alignments influence post-operative outcomes for TKA patients. It allows control of component alignment for the same subject in ways not possible with in-vivo [401-404] studies. With imaging data, computer simulations are also able to include patient variations into the analysis [405-408]. Previous studies with computational models have shown comparable kinematic and forces to those measured experimentally or with in-vivo fluoroscopy [401-404].

Ishikawa et al [200] were able to analyse kinematic alignment for TKA using a computational knee simulation. Their study suggests kinematically aligned TKA produces near-normal knee kinematics and may provide better clinical results than mechanically aligned TKA. However, only a single model was used in the study and the kinematic alignment for that single model was defined with the clinical average and therefore its conclusions were limited.

The aim of our study was to compare the alignment and motion of kinematically and mechanically aligned TKAs with a computational knee simulation using pre-operative CT scans from a series of 20 patients undergoing TKA. Computer simulation of both kinematic and mechanical alignment was performed for each subject. Measures of tibio-femoral translation, tibio-femoral rotation, patellar tilt and patellar shift were taken and compared between kinematic and mechanically aligned knees.

7.3: Methods

7.3.1: Simulation Set-up

A validated musculoskeletal computational simulation was used to evaluate the kinematic behaviour of kinematically and mechanically aligned TKA in a series of 20 subjects selected from 'The Joint Dynamics Registry' which includes pre-operative CT scans of TKA patients (Bellberry Human Research Ethics Committee, approval number 2012-03-710). The simulation was developed using ADAMS MSC, California, a dynamic, quadriceps-driven, closed-kinetic-chain knee simulator based on the Oxford Knee Rig (OKR) [409]. Experimental validation results of the simulation model are provided in Supplementary Material.

Each model was assembled from CT scan segmentations of patient geometry using ScanIP segmentation software (Simpleware, Exeter, UK). CT scans were taken from degenerative joint diseased knees at a maximum of 6 weeks before scheduled TKA surgery. The population group had a mean age of 69.8 ± 7.3 years. Five of the patients were male and 15 were female. Of the simulated knees, 8 were left knees and 12 were right. CT scans were taken at 1.25mm slice thickness, with the other axial thicknesses varying but all less than 1.25mm.

Landmarks were defined in order to assemble a patient specific model of relevant axes, ligament and tendon attachment sites associated with the reconstructed 3D patient geometry as shown in Figure 1.

The model includes the lateral collateral ligament (LCL), medial collateral ligament (MCL), posterior cruciate ligament (PCL), patella tendon, quadriceps tendon and posterior knee capsule. The LCL was considered to be a single fibre bundle and the MCL was considered to consist of anterior and posterior bundles. Likewise the PCL was modelled as an anterior and

posterior bundle and was differentiated into anterior and posterior bundles by translation determined from experimental validation.

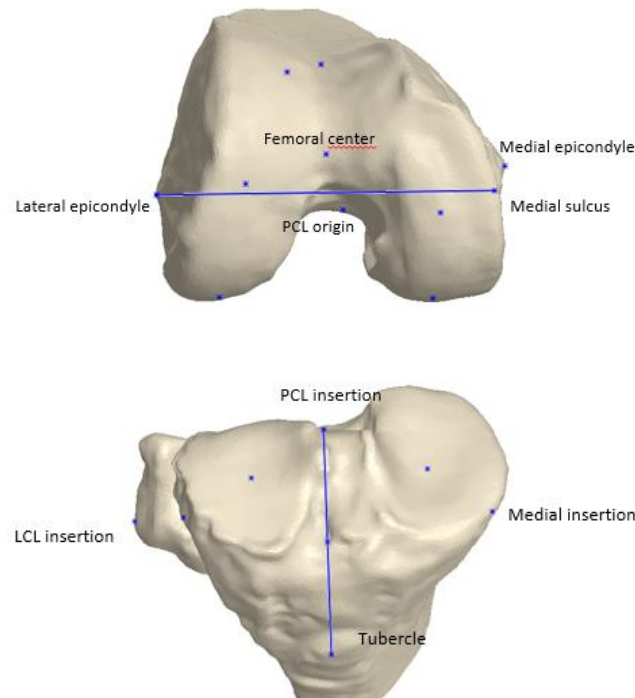


Figure 1 Schematic of landmarks and attachment points. Line connecting lateral epicondyle and medial sulcus define the surgical transepicondylar (TEA) axis of the femur. Line connecting PCL insertion and tubercle define the tibia anterior-posterior (AP) axis which then projected onto a plane perpendicular to the mechanical axis to be used as AP rotational axis as defined by Insall [410]

The femoral attachment points for the LCL and MCL were defined as the epicondylar prominences. The fibular LCL attachment was defined as attaching to the lateral-proximal centre of the fibular head. The tibial attachment points of the MCL bundles were modelled as attaching at the superior-inferior level of the peak medial prominence of the medial edge of the tibia distal to the plateau, with anterior-posterior position at the peak medial projection. The PCL's attachment on the femur was modelled as residing midway distally down the posterior intercondylar fossa when viewed from a posterior perspective, with the centre of attachment of the band placed one third of the width of the intercondylar fossa from the lateral edge of the medial condyle. Its tibial attachment was defined as the centre of the posterior intercondylar fossa.

The mechanical axis of the femur was defined as the line between the centre of the intercondylar notch to the centre of the femoral head, while the tibial mechanical axis was defined as the midpoint of the medial and lateral malleoli at the ankle to the midpoint of a line joining PCL insertion point and medial third of the tibial tubercle. The PCL insertion point and medial third of the tibial tubercle were then projected onto a plane perpendicular to the mechanical axis in order to define the tibial anterior-posterior (AP) rotational axis, as defined by Insall. [410] The surgical transepicondylar axis (the neutral femoral rotational axis) was defined by the lateral epicondylar point and the sulcus of the medial epicondyle.

Ligaments were modelled as point to point non-linear springs, shown in Equation 1 [407].

$$\begin{aligned}
 f &= \frac{1}{4}k \frac{\varepsilon^2}{\varepsilon_l}, & 0 \leq \varepsilon \leq 2\varepsilon_l \\
 f &= k(\varepsilon - \varepsilon_l), & \varepsilon > 2\varepsilon_l \\
 f &= 0, & \varepsilon < 0
 \end{aligned}$$

Equation 1 Axial force sustain by ligament

Where f is the axial force sustained by the ligament, k is a stiffness parameter, ε is the strain and $2\varepsilon_l$ is the threshold strain which indicates the change from the toe to the linear regions. The threshold strain used is adapted from literature [411]. The stiffness coefficients of the PCL, LCL and MCL were initially adapted from previous studies [407, 411-413]. Ligament stiffness's were then adjusted based on experimental validation performed with a cadaver study. Initial pre-strain in each ligament in extension was assumed to match values reported previously in literature [411]. The patella tendon and quadriceps tendon were modelled as wrap-able segmented links with femoral component contact to allow for wrapping about the anterior femoral component in flexion.

7.3.2: The Simulation

The simulation model simulated a closed-kinetic-chain knee extension based on the OKR. All components were modelled as rigid bodies with kinematic and compliant constraints, using a penalty-based contact between components. The model initialised in extension and then the ankle joint was held rigid, which had three degrees of rotational freedom but was constrained in translation. The hip joint was positioned above the ankle joint and was allowed freedom in flexion-extension and varus-valgus, with the vertical motion guided by the axis drawn from the ankle-joint to the hip joint.

In the flexion cycle of the simulation, a negligible force was applied through the extensor mechanism to model soft tissue tension. Following the flexion cycle, the extensor mechanism was activated, using a force applied through the quadriceps tendon to drive the knee back into extension. A PID (proportional-integral-derivative) controller was used to generate the reactive quadriceps force required to achieve extension, [402, 414, 415] as seen in Figure 2. The simulation runs through the flexion and extension cycle over a 10 second period, simulated using a dynamic multibody solver.

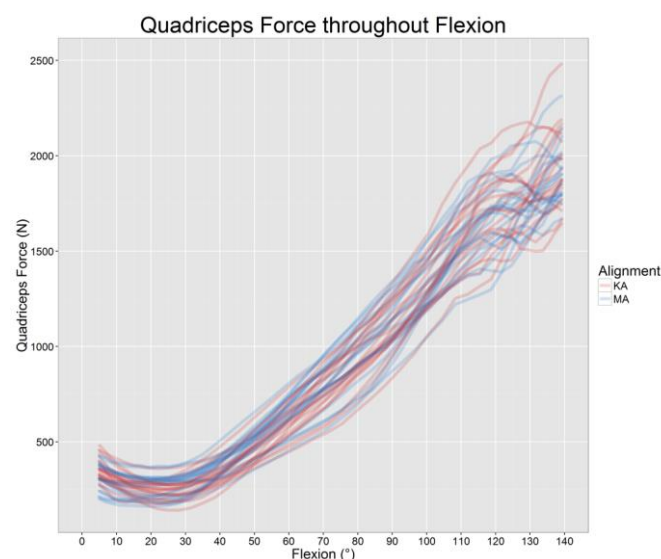


Figure 2 *Quadriceps force throughout flexion for mechanical and kinematic alignment*

7.3.3: Mechanical and Kinematic Component Placement

A fixed bearing, cruciate-retaining, symmetrical femoral and tibial condyle multi-radius implant design (Apex CR; OMNIlife science, East Taunton, MA, USA) was used to model both kinematic and mechanical TKAs for each of the 20 patients.

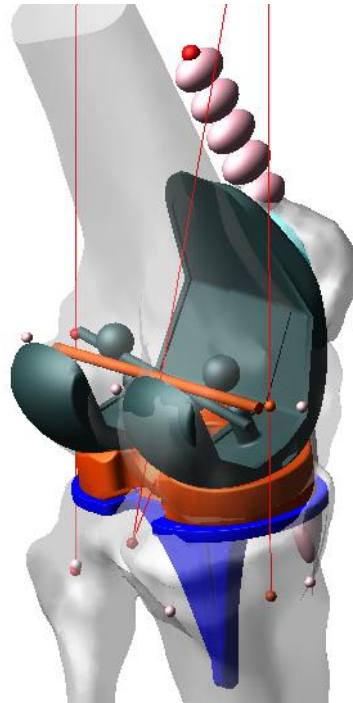


Figure 3 Simulation showing boundary conditions and ligaments present in the computational model (LCL, anterior MCL, posterior MCL, anterior PCL, posterior PCL). Ligaments were modelled as non-linear springs. Ligament forces were illustrated with the red lines.

The mechanically aligned femoral components were aligned in the coronal plane perpendicular to the mechanical axis of the femur and rotated to be parallel with the projection of the surgical transepicondylar axis. Translationally, the femoral components were placed such that the most distal condyle of the native femur was level with the most distal point on the condyle of the implant, and likewise for posterior placement [180].

Femoral component flexion and size were then set by incrementally flexing the component until the anterior flange was flush to the anterior surface of the femur. A maximum of 5° flexion was used as an upper limit before an upsized component was selected. Medial-

lateral positioning was performed to result in equal amount of exposed bone on the medial and lateral sides.

The tibial component was placed perpendicular to the mechanical axis for all 20 mechanically aligned simulations and rotated to match tibial AP rotational axis defined above. The component was placed proximally to match the resection level of the thinnest tibia insert and had its medial-lateral and antero-posterior position chosen to maximize coverage subject to those orientations. Posterior slope for all tibial components was set at 3° from a line perpendicular to tibia mechanical axis.

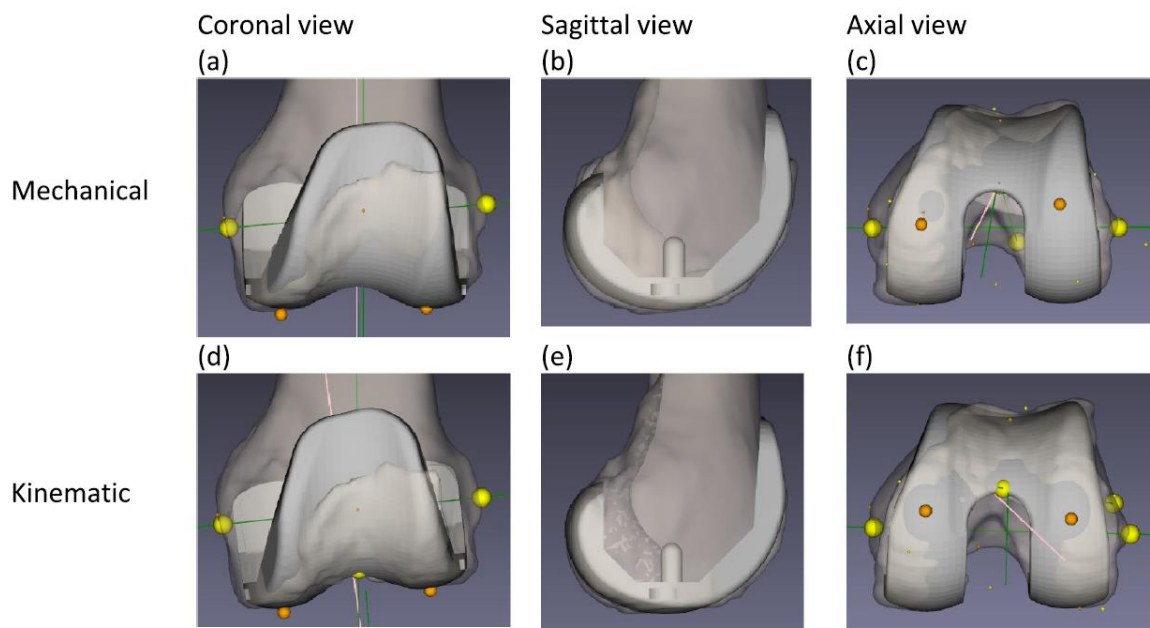


Figure 4 Mechanically aligned femoral component (a), (b) and (c); kinematically aligned femoral component (d), (e) and (f) in coronal, sagittal and axial views.

For the kinematically aligned knees, the femoral component was positioned such that the distal and posterior condyles of the femoral component match the joint line of the native femur. The component was then flexed and upsized as needed to avoid femoral component notching. For the tibial component, rotation was defined by a best fit ellipse drawn on the lateral plateau of the tibia in order to replicate the intra-operative technique described by Howell et al [47]. Posterior slope of the tibial component was set at 3° less than the

posterior slope of the native medial condyle. Coronal plane alignment was set level to tibia joint line and proximalised to match the resection level of the thinnest tibia insert. Medial lateral and antero-posterior placement of the component was performed to optimize coverage. No medial tibial bone wear was encountered for patients included in this study.

For both the kinematic and mechanically aligned knees, patella implantation was modelled as an onlay patella matching the resected surface at its posterior apex with an 8mm thickness patella button. The largest patella button that could fit on the resected surface without overhang was implanted and centred on the resected plane. The resection plane was drawn parallel to the patella tendon-quadriceps tendon attachment point axis and the femoral transepicondylar axis projected from the CT scan.

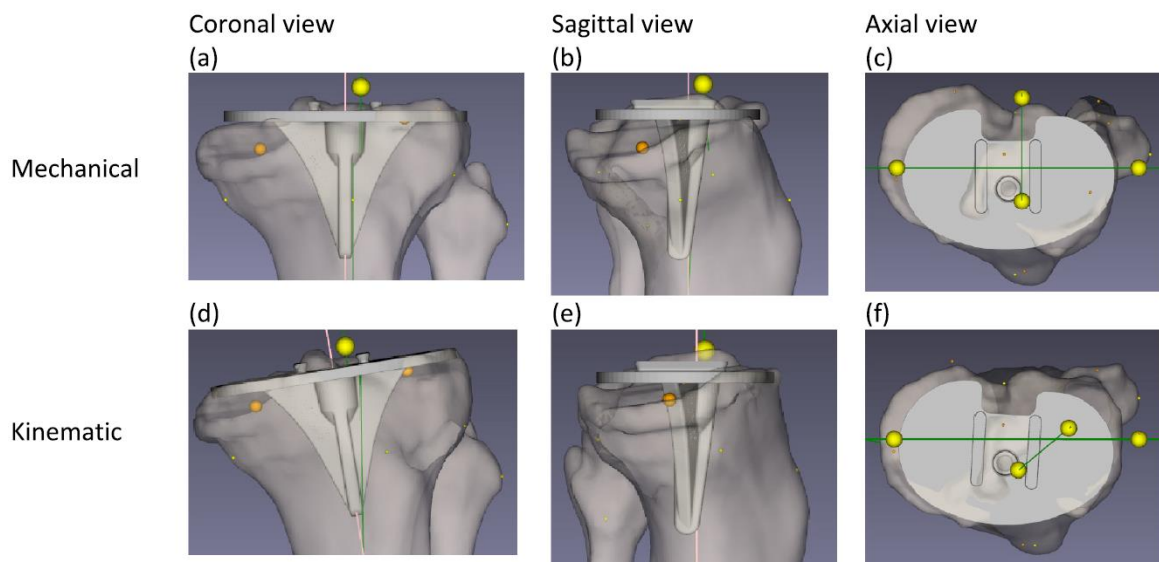


Figure 5 Mechanically aligned tibia component (a), (b) and (c); kinematically aligned tibia component (d), (e) and (f) in coronal, sagittal and axial views.

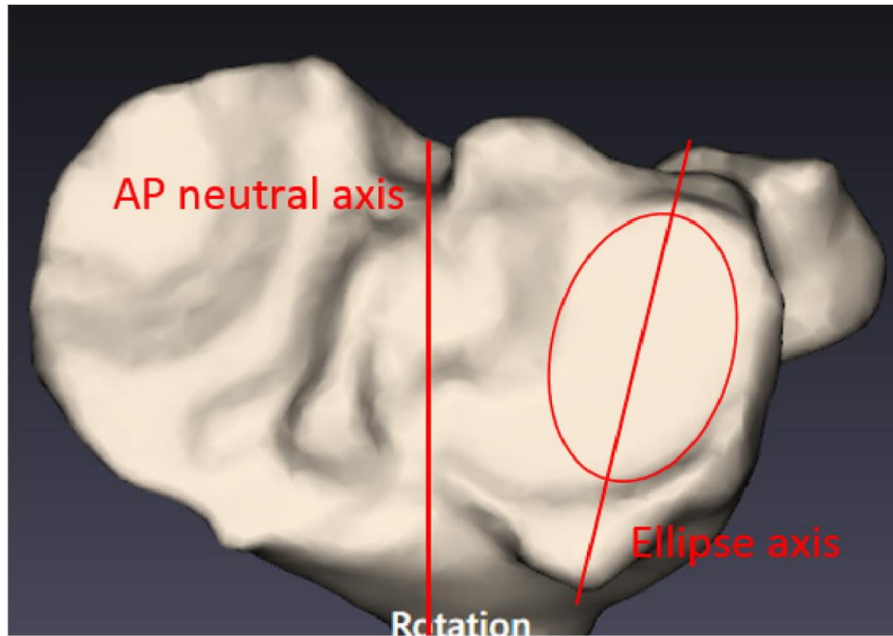


Figure 6 Ellipse used to define kinematic rotation angle and its angle relative to tibial AP rotational axis

7.3.4: Data Analysis

Kinematics was assessed using an implant to implant reference frame for both mechanical and kinematic alignment simulations and were based on the Grood-Suntay measurement system [416]. Reporting kinematics to bone based reference frames was trialled however the native mechanical axes results were dominated primarily by the static effects of component placement relative to the bone. Static placement of the implants in kinematic alignment was done independently.

Component placement for the kinematically aligned knees relative to the mechanical axes was then assessed. The simulated closed-kinetic-chain knee extension was performed and measurements of position were extracted. The medial and lateral flexion facet centre (FFC) condyles were identified as the point equidistant from the most distal and posterior planes of the implant, as the multi radius implant design did not have a single flexion centre. These points were used as the reference points for measuring the movement of the femoral component relative to the tibia throughout the motion. The medial and lateral FFC measurements were taken from these reference points to the lowest dwell point on the

tibial insert. Measurements were rescaled about the femoral AP measurement to account for implant size geometry.

Rollback was measured from the centre of these two FFC points to the tibial dwell point posterior translation of the transepicondylar line, hence is the average of the medial and lateral FFC translation measurements. The internal-external rotation measurement was the angle between the femoral and tibial components projected onto the tibial component plane. Patella lateral shift was defined as the translation from the centre of the patella button relative to the centre of the tibial insert, with positive in the lateral direction and negative in the medial direction. Patella external tilt was defined as external rotation of the patella relative to the transepicondylar axis of the femur projected onto the tibial plane.

7.4: Results

7.4.1: Simulation Component Alignment for Kinematically Aligned Knees

Native coronal alignment (hip-knee-ankle angle) for all knees as measured from CT scan had a mean of $3.1^\circ \pm 5.7^\circ$ varus (range 8.7° valgus to 11.8° varus).

For mechanically aligned knees the femoral and tibial components were 0° to the mechanical axis. For kinematically aligned knees the mean tibial component coronal and axial alignment was $3.0^\circ \pm 2.4^\circ$ (range -1.8° to 7.2°) varus to the mechanical axis and $7.2^\circ \pm 6.6^\circ$ (range -9.4° to 15.4°) internal to tibial AP rotational axis respectively for kinematically aligned knees. Both component alignment parameter means were significantly different from mechanically aligned knees (0° varus and 0° rotation) ($p < 0.05$). Tibial slope in the kinematically aligned knees had a mean value of $4.6^\circ \pm 2.8^\circ$ (range 0° to 11.2°). Kinematically aligned tibial slope mean was also statistically different to the mechanically aligned tibia slope (3° slope) ($p < 0.05$).

The mean femoral component coronal and axial alignment for kinematically aligned knees was $3.0^\circ \pm 2.3^\circ$ (range -0.8° to 7.2°) valgus to the mechanical axis and $2.5^\circ \pm 1.6^\circ$ (range -0.2° to 5.4°) internal to the surgical transepicondylar axis respectively. As with the tibial component placement, both component alignment parameter means were significantly different from mechanically aligned knees ($p < 0.05$). Femoral flexion in the kinematically aligned knees had a mean value of $2.4^\circ \pm 1.7^\circ$ (range 0° to 5° , as per the planning process). Femoral flexion mean in the mechanically aligned dataset had a mean value of $3.3 \pm 1.7^\circ$ (range 0° to 5°) and was not statistically different to that of the kinematically aligned cases.

Figure 7 shows tibial and femoral component alignments for kinematically aligned knees. The horizontal and vertical lines represent 0° coronal and 0° axial alignment respectively. The cross section between the two lines is the mechanical alignment.

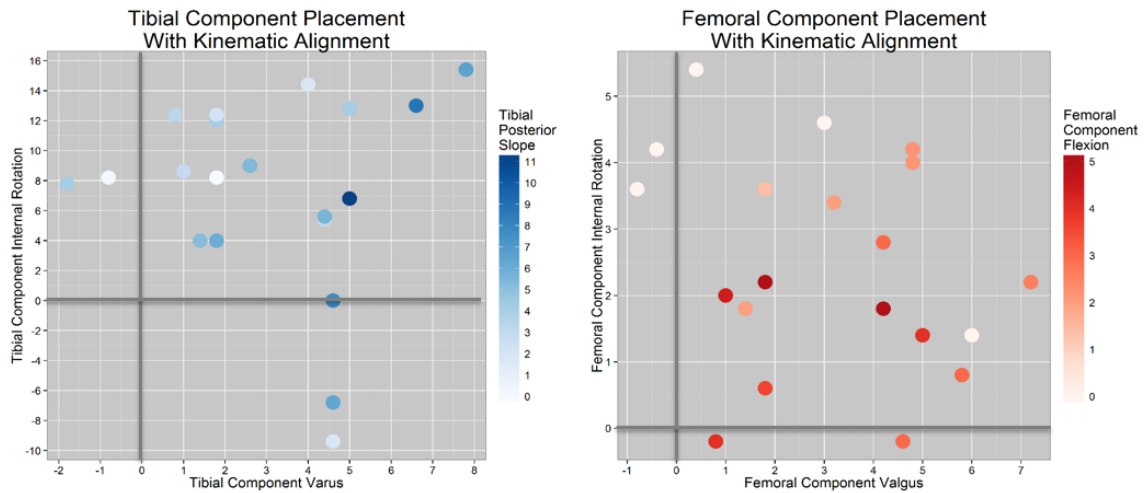


Figure 7 Coronal and axial component alignment for kinematically aligned knees. The cross section of the 0° horizontal and vertical axis represents mechanical alignment.

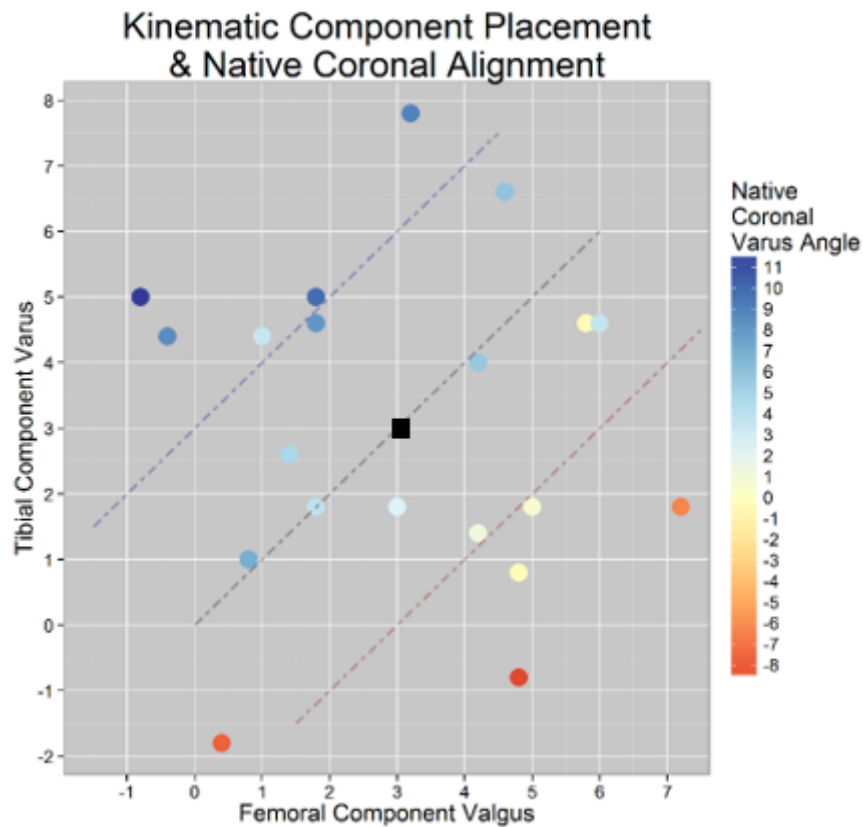


Figure 8 Kinematic alignment for femoral and tibial component valgus and varus angle shaded by the native coronal varus angle. The reference lines represent a 3° varus (blue), neutral (black) and 3° valgus (red) as the final coronal alignment. Mechanical alignment for femoral and tibial component is at zero (black square).

Figure 8 shows kinematic femoral and tibial component coronal alignment shaded by the native coronal alignment angle. The reference lines represent a 3° varus (blue), neutral (black) and 3° valgus (red) as the final coronal alignment. There was variation in the level of joint line obliquity with a given tibio-femoral coronal alignment. However, a trend between the native and kinematic tibio-femoral final alignment is present. Linear regression of final alignment as a function of native alignment yields an R^2 of 0.75.

7.4.2: Simulation Tibio-Femoral Kinematics

Tibio-femoral kinematic results are shown in Figure 9. Statistically significant differences for paired t-tests at every time parameter were found ($p < 0.05$), with the exception of femoral AP translation from 30° of flexion and lower. The difference between the mean results for medial FFC AP translation for the kinematic and mechanical simulations starts at 0.4 ± 0.9 mm at 5° flexion, increasing steadily to 1.7 ± 1.4 mm in deep flexion, kinematically aligned being anterior to mechanical. The lateral femoral FFC mean AP translation difference is 0.4 ± 0.6 mm at 5°, increasing to 2.9 ± 1.9 mm in deep flexion with mechanically aligned anterior. The change in medial and lateral femoral FFC throughout flexion also implicitly describes the tibio-femoral internal-external rotation; Kinematically aligned knees' lateral femoral FFC translates more posteriorly and medial femoral FFC translates more anteriorly than that of mechanically aligned knees', as flexion increases. Thus there is more external rotation of kinematically aligned knees. Also, there is relatively little difference in rollback behaviour, starting with no difference peaking at 0.8 ± 0.9 mm at 96°, kinematically aligned posterior to mechanical.

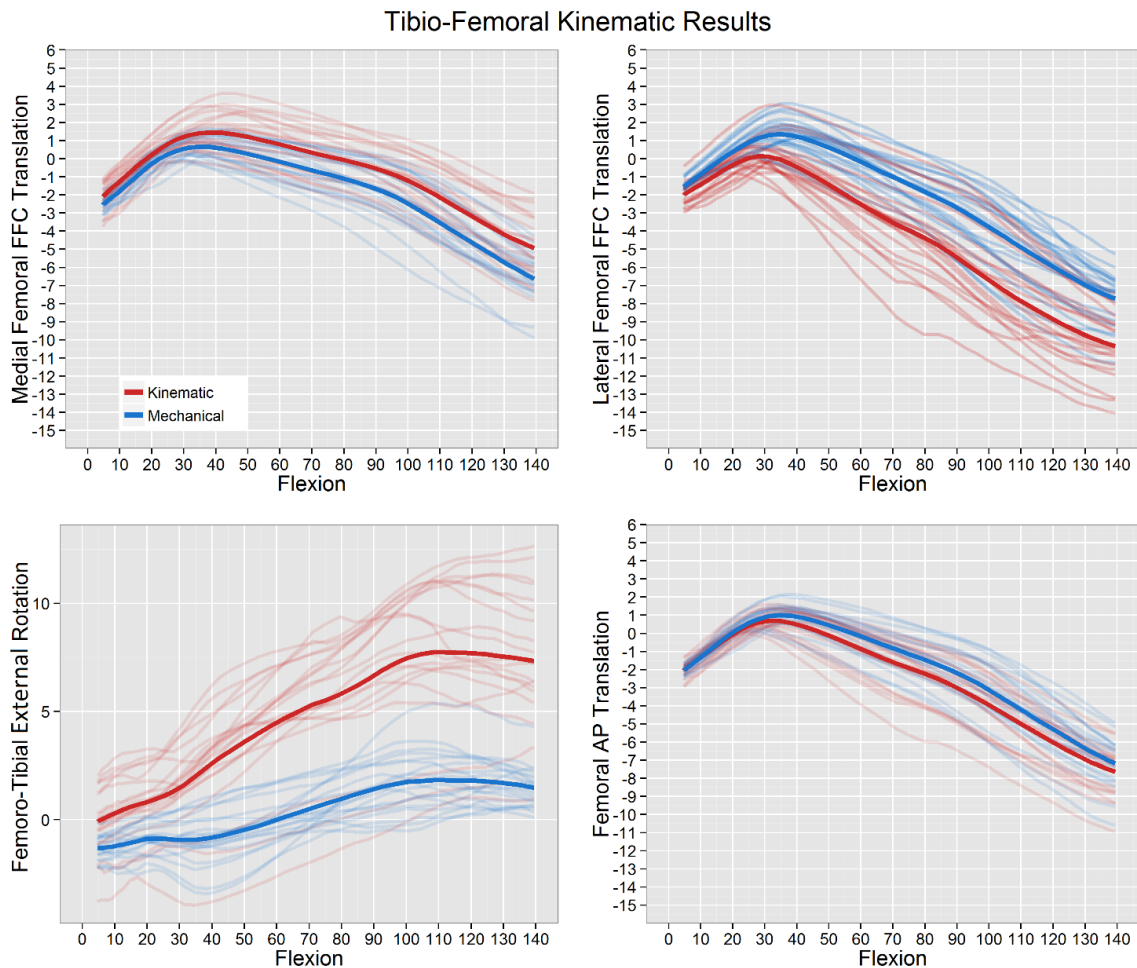


Figure 9 Tibio-femoral kinematic results for knee flexion. Red lines are kinematic alignment and blue lines are mechanical alignment. Solid lines are averages of each alignment. (a) and (b) medial and lateral flexion facet centre (FFC) antero-posterior drift from the lowest point of the tibial insert. Positive values indicate anterior translation. (c) Femoro-Tibial internal external rotation. Positive values indicate external rotation. (d) Femoral AP translation relative to the lowest point of the tibia insert.

7.4.3: Simulation Patello-Femoral Kinematics

The patello-femoral kinematic results are shown in Figure 10. Patella lateral shift exhibited statistically different parameter values for measurements of flexion between 10 and 40° and at angles greater than 80°. Patella lateral shift for both alignment paradigms displayed a tendency towards medialising throughout the flexion cycle, though trend lines are different.

After starting in a common position, the kinematically aligned patellae tended towards shifting medially, peaking at 15° flexion where they were placed 1.8 ± 1.2 mm more medial. The kinematically aligned patellae then tracked without further medial lateral shift while the

mechanically aligned continue to drift medially, finishing in deep flexion $2.2 \pm 1.6\text{mm}$ medial. Mean differences in patella lateral tilt under kinematic and mechanical alignment are significant up to 30° of flexion ($p=0.05$). Kinematic alignment begins the simulation at $2.7^\circ \pm 2.1^\circ$ more internal tilt relative to the mechanically aligned at 5° flexion, with the kinematically aligned knees tilting internally by a mean 3.5° while the mechanically aligned knees are 0.8° . The means converge until about 60° , where they effectively show identical movement into 5° external tilt at 140° flexion.

Intra-patient differences for patella tracking are high, however, with the difference in tilt for a given patient with either alignment approach ranging from 6° more externally tilted to 6.5° more internally tilted.

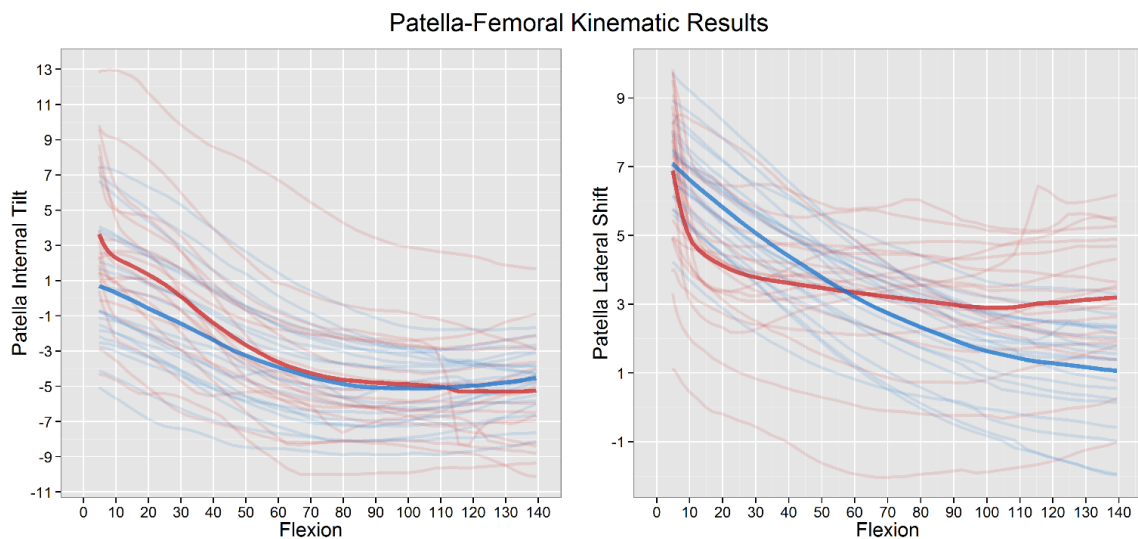


Figure 10 Patello-femoral kinematic results for patella external tilt (left) and patella lateral shift (right) for knee flexion. Red fine lines are kinematic alignment and blue fine lines are mechanical alignment. Solid lines are averages of each alignment.

7.5: Discussion

Recent data has challenged the importance of traditional mechanical alignment philosophy [42]. Recently, Bellemans et al [164] have introduced the concept of “constitutional varus”, which hypothesizes that correction to a neutral mechanical alignment may not be “normal” for a significant proportion of the population. Their study showed 32% of asymptomatic men and 17% of asymptomatic women possess a natural mechanical alignment of 3° varus or more [164].

In conjunction with this principle, several surgeons have supported the restoration of kinematic, rather than mechanical, alignment in TKA [46, 184, 399] and Ji et al [417] reported that native and ‘healthy’ joint line were one and the same for kinematically aligned knees. However, kinematically aligned knees shows lack of consistency regarding patient outcomes, survivorship, and surgical technique [46, 184, 380, 393, 399, 400]. Therefore, it remains unclear what are the optimal alignment targets for TKA despite of the emphasis on alignment philosophies for TKA.

Recently, Ishikawa et al [200] used computational model to analyse the kinematics of kinematically aligned knees. Their study suggests kinematically aligned knees produces near-normal knee kinematics. However, only a single model was used in the analysis and therefore the kinematics outcomes reported were limited.

In this study, pre-operative non-weight bearing CT scans of diseased joints in 20 patients were used to compare kinematic and mechanical alignment in a validated computational simulation. From patient CT scans, native coronal alignment was determined and kinematic and mechanical alignment were planned (Figure 8). Ishikawa et al [200] used a clinically derived average kinematic alignment at 3° tibial component varus and 3° femoral component valgus which is equivalent to coordinates (3,3) on Figure 8. Our average

alignment values were similar to reported alignment in clinical kinematic alignment studies [200]. However instead of using an average kinematic alignment, our study accounts for significant variation of patient pre-operative anatomy.

Results for kinematic alignment (Figure 8) showed there was variation in the level of joint line obliquity with a set tibio-femoral coronal alignment. However, a trend between the native and kinematic tibio-femoral final alignment was observed. Any variation observed most likely occurred due to a condition of the pre-operative diseased joint and the wide range of adjustments necessary to attain kinematic alignment. When kinematically aligned, femoral components on average resulted in more valgus alignment to the mechanical axis and internally rotated to surgical transepicondylar axis whereas tibia component on average resulted in more varus alignment to the mechanical axis and internally rotated to the tibial AP rotational axis. This is consistent with other reports [184, 399].

In regards to tibio-femoral kinematics, both kinematic and mechanical alignment resulted in a broad trend towards anterior translation of the femoral component up to 30° flexion, followed by posterior translation as flexion increases (Figure 9). The kinematically aligned knees experience external rotation of the femoral component on the tibial component during flexion, with the angle increasing steadily from $1.2^\circ \pm 1.5^\circ$ at 5° flexion to $5.9^\circ \pm 3.3^\circ$ at 140° flexion. This internal rotation of the femur relative to the tibia as the knee reaches full extension is comparable to screw home mechanism observed in native knee motion [418]. This effect is less so for mechanically aligned knees.

In regards to patello-femoral kinematics, for both kinematic and mechanical alignment there was high intra-patient differences for patella tracking (Figure 10). However, the difference in tilt for a given patient with either mechanical or kinematic alignment ranged from 6 degrees more externally titled to 6.5 degrees more internally tilted. There was less medial movement of the patella in deep flexion in kinematic aligned than mechanically

aligned knees, though it arrived as its medial-lateral position earlier in the flexion.

Differences in component alignment and potential impact on Q angle could explain some of the variation seen in patella-femoral kinematics for kinematically aligned knees.

Results for tibio-femoral kinematics for flexion and rotation as well as patello-femoral kinematics for tilt and shift were similar to that of previous computational biomechanical studies [200, 402-404]. Variations existed primarily due to patient CT input, on which knee joint testing rig was simulated, e.g. Oxford Knee Rig or Kansas Knee Simulator, or if the implant was cruciate retaining (CR) or substituting (PS), or the alignment strategy simulated.

Our results for tibio-femoral kinematics for flexion and rotation using both mechanical and kinematic alignment closely match results reported by Ishikawa et al [200]. All models exhibited anterior translation of the femoral component relative to the tibia during the early flexion phase and then posterior translation as flexion increased. The anterior translation from 0° to 30° of flexion was similar bilaterally in all models.

Patella lateral shift kinematics also replicated a similar pattern of mechanical alignment to that reported by Ishikawa et al [200]. However, patella lateral shift kinematics for kinematic alignment as well as patellar external tilt for both alignments varied markedly between our results and those reported by Ishikawa [200]. In the study reported by Ishikawa et al [200], in the kinematic alignment models the patella tilted more externally relative to the femoral component at 0° and 30° and after 60° increased in all models. It was similar in our study until 60-70° and then tilting plateaued. Plateauing after 60° flexion was also reported by Kobayashi et al [419] using healthy subjects in an in vivo study. Other explanations for this difference could be patient anatomy (1 subject versus 20), model assumptions, patellar button size or design of the intercondylar notch and anterior patella groove of the femoral component.

There were several limitations in this study. The study involved 20 subjects only and this may be insufficient given how variable knee alignment is across the population. The implants used in this study were multi-radius femoral component with a single design fixed bearing cruciate retaining TKA. Therefore the results may not be applicable to other knee designs nor to mobile bearing or posterior stabilised knees. Also, the kinematics analysed were for closed-kinetic-chain knee extension and therefore functions such as walking or stair climbing may not be comparative.

The simulation model was subject to assumptions and variables common to many computational models: boundary conditions and muscle forces were assumed, only the lower extremity was modelled, there was limited soft tissue representation and cartilage was not accounted for. Such assumptions and variability are consistent with other computational modelling as well as in vitro modelling studies. However, computational modelling does offer the ability to simulate kinematics of different alignments on the same subject and thereby be potentially used as a predictive tool for pre-operative scenarios. Moreover, there are a number of studies that have shown that computational models could predict forces and kinematics that compared favourably to those found experimentally or in vivo fluoroscopy [402-404].

7.6: Conclusion

In conclusion, kinematic alignment had more variation than mechanical alignment for all tibio-femoral and patella-femoral kinematics. This was particularly true for tilt and shift of the patella-femoral joint for kinematically aligned knees. Kinematic alignment corrects long leg alignment to a patient specific alignment which depends on the preoperative state of the knee. Also, when kinematically aligned, femoral components on average resulted in more valgus alignment to the mechanical axis and internally rotated to surgical transepicondylar axis whereas tibia component on average resulted in more varus alignment to the mechanical axis and internally rotated to the tibial AP rotational axis. The use of computational models has the potential to predict which alignment, kinematic or mechanical, could improve knee function patient specifically.

Chapter 8

Patient Specific Simulated Dynamics following TKA Correlate with Patient Reported Outcomes

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Expanding on the initial work presented in Chapter 7, this work found a relationship between patient outcome and the results of a post-operative simulation. The implications of this are profound. It can be reasonably assumed the mechanism by which various alignment rules impact patient outcomes is through their impact on the kinematics and kinetics of the patient's knee in motion. Three broad factors contribute to kinematic outcome; the alignment of the components, the implant geometry implanted and the patient specific musculoskeletal system into which the implants have been implanted. With the ability to determine a favourable kinematic target linked to better postoperative outcomes, the alignment or component design to use in a specific patient can be solved for. Multiple further findings relating post-operative outcome to simulation results to the paper presented here have been found and presented to conferences (described in the Achievements section of the preface.) These findings form the basis of the Dynamic Knee Score or DKS, a predictive scoring algorithm that drives selection of preoperative knee alignment plans. This tool has been used in some form in over 2000 Total Knee Arthroplasties to date.

8.1: Abstract

Background: Component alignment variation following TKA does not fully explain instance of long term post-operative pain. Joint dynamics following TKA vary with component alignment and patient specific musculoskeletal anatomy. Computational simulations allow joint dynamics outcomes to be studied across populations. This study aims to determine if simulated post-operative TKA joint dynamics correlate with Patient Reported Outcomes.

Methods: Landmarking and 3D registration of implants was performed on 96 segmented post-operative CT scans of TKAs. A cadaver rig validated platform for generating patient specific simulation of deep knee bend kinematics was run for each patient. Resultant dynamic outcomes were correlated with a 12 month post-operative Knee injury and Osteoarthritis Outcome Score (KOOS). A Categorisation and Regression Tree (CART) was used for determining non-linear relationships.

Results: Non-linear relationships between the KOOS pain score, rollback and dynamic coronal alignment were found to be significant. Combining a dynamic coronal angular change from extension to full flexion between 0° and 4° varus (long leg axis) and measured rollback of no more than 6mm without roll forward formed a 'kinematic safe zone' of outcomes in which the post-operative KOOS score is 10.5 points higher (p=0.013).

Conclusion: The study showed statistically significant correlations between kinematic factors in a simulation of post-operative TKR and post-operative KOOS scores. The presence of a dynamic safe zone in the data suggests a potential optimal target for any given individual patient's joint dynamics, and the opportunity to pre-operatively determine a patient specific alignment target to achieve those joint dynamics.

8.2: Introduction

Total Knee Arthroplasty (TKA) is an established procedure for improving pain and restoring function to patients who have osteoarthritis (OA). However, approximately 20% of recipients remain dissatisfied post-operatively [70]. Major contributing factors for post-operative dissatisfaction include recurrent pain and functional impairment [69, 287] as measured by Patient Reported Outcome Measures (PROMs) [72].

Component alignment has been shown to impact post-operative PROMs including coronal alignment [48, 58, 389] and rotation of the femoral and tibial components [195, 196, 328] when deviating from mechanical references, but the relationship is not well understood. There is evidence that non-mechanically aligned strategies can have at least equivalent PROMs results [184, 420]. Studies of TKA's that targeted mechanical alignment have also failed to show a reduced outcome in the medium term when varus post-operative alignment reflects a pre-operative varus deformity [385]. This would suggest that a neutral mechanical axis target is not necessarily ideal in all cases.

Variations in component alignment alter the knee kinematics, with individual alignment parameters combining in a complex manner to define the dynamic behaviour of the joint. This complexity might explain the inconclusiveness in the literature regarding alignment approach and outcomes. Previous studies have shown post-operative joint dynamics to significantly differ from pre-operative dynamics following TKA [421-423]. Joint dynamics also vary with component alignment and geometry, with relationships between rotational placement of the components and axial rotation in motion [424], coronal alignment and load distribution [425, 426].

Other alignment parameters have not been shown to have clearly identifiable reproducible relationships with joint dynamics outcomes, indicating that patient specific characteristics

are a significant factor [197, 427]. These factors may include variations in patient anatomy [164, 169] and ligamentous constraints [428]. Previous cadaveric studies have shown a relationship between native knee dynamics and lower limb alignment [429] as well as gender [430]. The dynamic result of component placement and patient specific factors may be more relevant to outcome than component placement alone.

TKR dynamic outcomes can be measured in a number of different ways. Functional techniques such as gait analysis and video fluoroscopy are a means of capturing accurate kinematic information [197]. Mechanical rig testing is an alternate approach but is limited in its capture of patient specific factors. These techniques are used in design validation studies [198], but due to the cost and burden are not especially scalable. Dynamic knee computer simulations are a more scalable alternative [199] and allow the study of both patient and surgical factor's impact on joint dynamics following TKA [200, 201]. Simulations are increasingly used to study the impact of component placement variation [202-204] and are able to incorporate patient specific elements with readily available diagnostic radiology such as Computed Tomography (CT) scans [205, 206].

Simulations incorporating patient specific elements may be a mechanism for uncovering an underlying relationship between post-operative TKA joint dynamics and PROMs. This study aims to determine if the post-operative joint dynamics derived from a computational model incorporating component alignment and patient geometry correlates with post-operative PROMs.

8.3: Methods

A musculoskeletal computational simulation of an Oxford Knee Rig (OKR) was developed. The simulation uses post-TKA CT scan inputs of all relevant landmarks, bones and registered component positions. This model has been previously validated in Chapter 7, against a series of 8 cadaveric knees [378]. A series of 116 patients gave informed consent to a Human Research Ethics Committee approved registry of simulated kinematics (Bellberry Human Research Ethics Committee, approval number 2012-03-710). Patients enrolled into the registry were required to answer a Knee injury and Osteoarthritis Outcome Score (KOOS) at least 12 months after their operation in addition to a post-operative CT scan, which was used to build a simulation.

The simulation replicated a deep knee bend performed in an OKR. The OKR allows 6 degrees of freedom in which the ankle is modelled possessing all 3 rotational degrees of freedom but constrained in translation, while the hip does not allow internal-external rotation but does allow for flexion-extension and varus-valgus rotation in addition to vertical translation [431]. The simulation was modelled using ADAMS software (MSC Software, Newport Beach, California) in which the femoral, tibial and patella components were considered as rigid bodies in contact.

Each model was assembled from CT scan segmentations of patient geometry using ScanIP (Simpleware, Exeter, UK). CT scans were taken at 2 mm slice thickness. Attachment and insertion sites for the lateral collateral ligament (LCL), medial collateral ligament (MCL), posterior cruciate ligament (PCL), quadriceps tendon and patella tendon were identified, in addition to the distal femoral and hip centres and the lateral and medial malleoli of the distal tibia. The LCL was modelled as a single bundle while the MCL and PCL were modelled with both anterior and posterior bundles. All ligaments were modelled as non-linear springs as described by Abdul-Rahman et al. [411] with fixed parameters further adapted using a

process previously described in Chapter 7 [378]. An example of the simulation with strained ligaments during the extension cycle is shown in Figure 1.

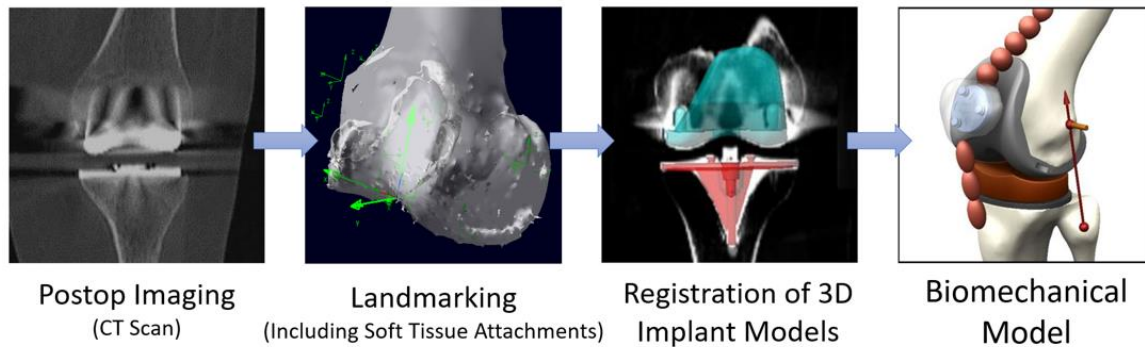


Figure 1: The simulation in extension cycle, with both PCL bundles, the LCL and MCL posterior bundle all actively strained.

From the hip centre, femoral centre and tibial malleoli, the mechanical axes of the femur and tibia were defined. Rotationally, the tibial anterior-posterior axis was defined along these two points, while the Transepicondylar Axis (TEA) from the medial sulcus to the lateral epicondyle was used for the femur. A patella superior-inferior axis was constructed from superior and inferior points of the patella bone and a rotational anterior-posterior axis created by these two points and the medial edge of the patella bone. The 3D Implant geometries were registered to the CT scan using the +CAD module within ScanIP. The implant positions were then combined with the bone axes to generate the biomechanical model. This procedure is summarised in Figure 2.

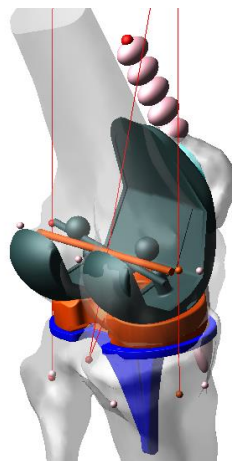


Figure 2: Creation of a patient specific biomechanical model from a post-operative CT scan

Coronal alignment and Internal/External (IE) rotation throughout the full flexion cycle were extracted for each simulation as per Grood & Suntay's joint coordinate system, with the measurements recorded in the tibial reference frame [416]. Rollback was recorded as the antero-posterior position of the midpoint of the TEA relative to the tibial insert. Patella tilt and medio-lateral shift were also extracted measured relative to the mechanical axis and TEA midpoint respectively. Values of each of these parameters at 10°, 45° and 90° degrees of flexion were tabulated.

From this registry of patients' simulation results, a retrospective analysis was performed. All enrolled patients in the registry were investigated. Patients were excluded if their CT scan was not of an acceptable standard or a post-operative KOOS conducted at least 1 year following surgery was not captured or incomplete. All patients received a cruciate retaining TKA using a common implant system (Triathlon, Stryker, Michigan, U.S.A). Surgeries were performed by one of two surgeons and all surgeries aimed to achieve mechanical alignment.

Linear Spearman's correlations between the KOOS Pain and Symptoms subscores (scores out of 100, with positive values being a better outcome), and each of the kinematic parameters were determined. Non-linear relationships were investigated using Classification and Regression Trees (CART) constrained to whole unit increments and individual kinematic variables. The resultant groups created were then t-tested for difference and a combined CART model ran where effects were significant. Significance was set to $p = 0.05$ and all statistics were performed with R statistical software (version 3.4.2) [315].

8.4: Results

Of the 116 patients data extracted from the registry, 11 failed to have a CT scan or the CT scan was not captured to an acceptable standard, 6 failed to return their KOOS scores and 3 were missing both acceptable CT scan and KOOS score, leaving a total of 96 patients with post-operative KOOS scores and dynamic simulations. The patient population was 57% female with a mean age of 69 +/- 12 years. Mean 12 month KOOS Pain score was 86 +/- 18 and KOOS Symptoms score was 76 +/- 21. Histograms of the scores for the population are shown in Figure 3.

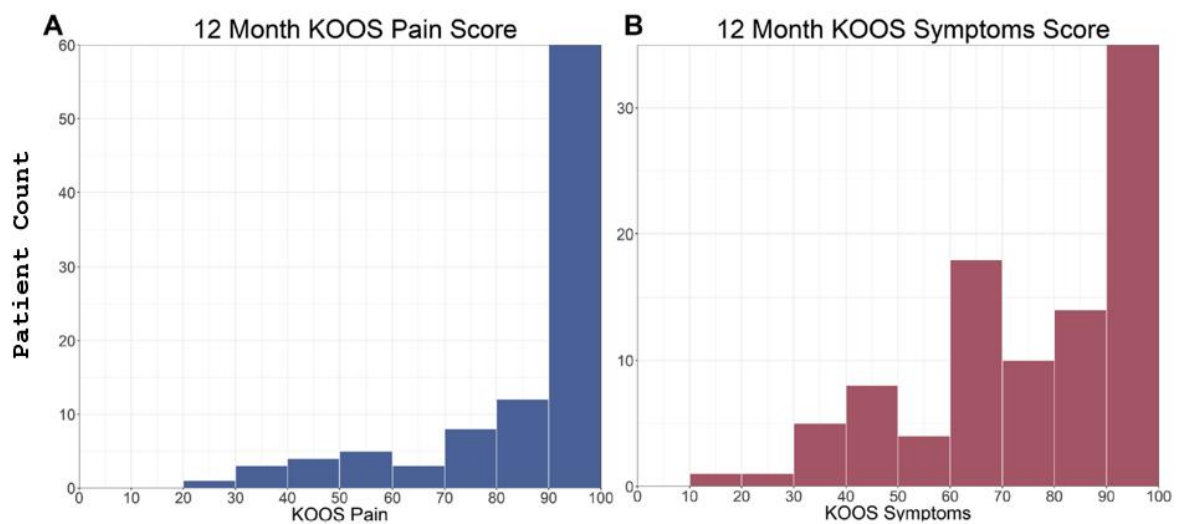


Figure 3. 12 months post-operative KOOS Score distributions for the KOOS Pain subscore (blue) and KOOS Symptoms subscore (red).

There was considerable inter- and intra-patient variation in the kinematics measured from the simulation. Figure 4 shows the variation between patients at each of the three flexion increments in the simulation cycle. Coronal angle trended from 0.72 +/- 1.99° at 10° of flexion to 4.00 +/- 2.93° at 90° of flexion. Mean rollback was from an anteroposterior position of 0.55 +/- 2.16 mm anterior to the starting reference to 1.41 +/- 2.46 mm posterior, with more occurring on the lateral side than the medial as the knees rotate from 7.00 +/- 5.46° external rotation of the tibia (Insall's line to the TEA) to 4.06 +/- 5.41° external rotation. The patella tended to drift from a lateral to a more centralised position with

flexion (8.29 ± 2.92 mm to 2.69 ± 2.08 mm) while tilt drifted from lateral facing relative to the TEA, to more parallel ($7.93 \pm 5.36^\circ$ to $4.86 \pm 4.41^\circ$).

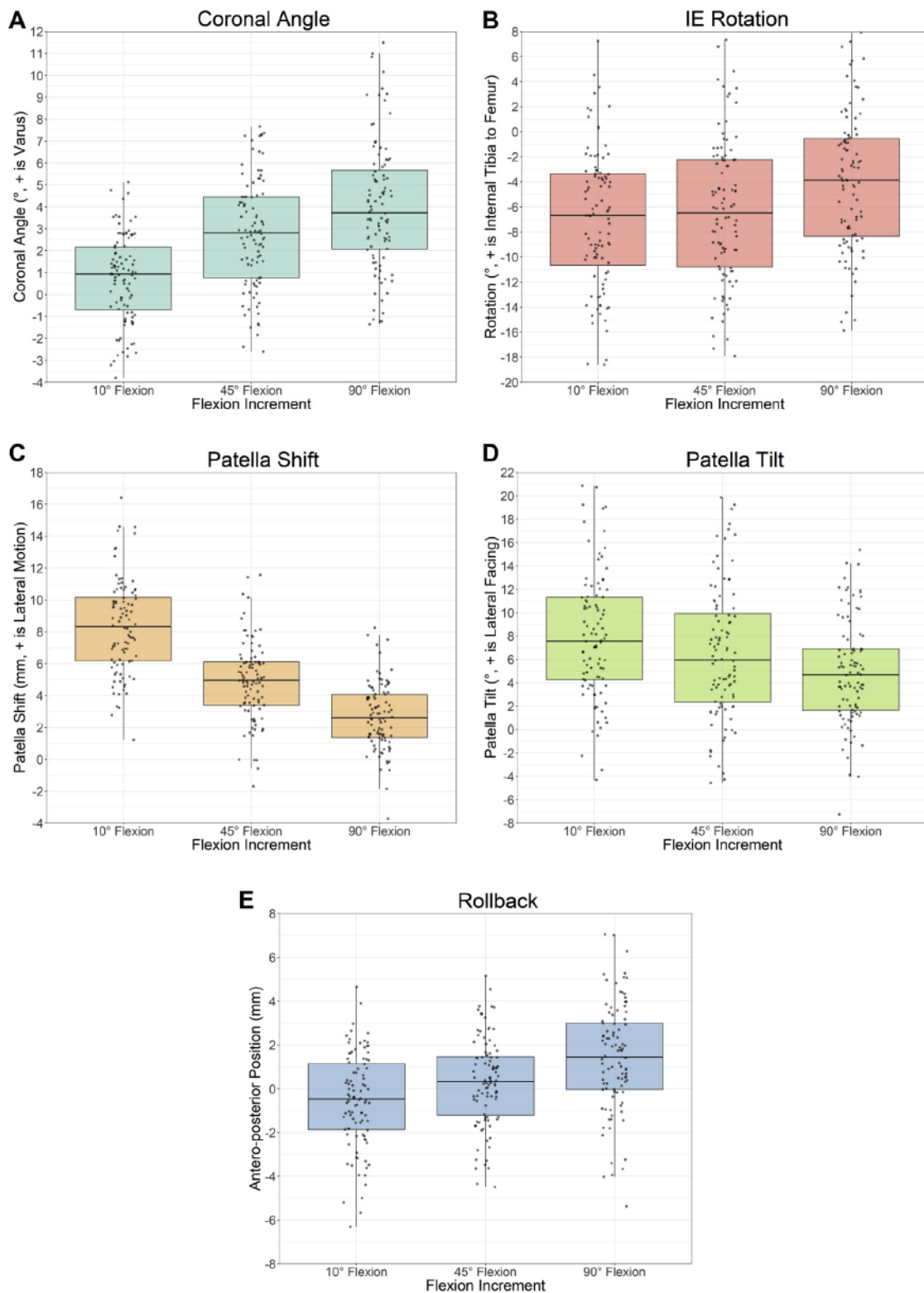


Figure 4. Box plots with scatter points of the kinematic results across the full sample of 96 patients for a) coronal angle, b) IE rotation, c) patella shift, d) patella tilt and e) rollback

Table 1: Spearman's Rho cross correlation table for kinematic parameters across all simulated patients at 10°, 45° and 90° of flexion. (*) denotes significant difference from 0 to $p < 0.05$

10° Flexion - Variables	1	2	3	4	5
1. Coronal Angle	-				
2. IE Rotation	0.103	-			
3. Patella Shift	0.264*	-0.364*	-		
4. Patella Tilt	0.346*	-0.453*	0.592*	-	
5. Rollback	0.296*	0.098	-0.004	0.172	-
45° Flexion - Variables	1	2	3	4	5
1. Coronal Angle	-				
2. IE Rotation	-0.315*	-			
3. Patella Shift	0.288*	-0.275*	-		
4. Patella Tilt	0.478*	-0.155	0.543*	-	
5. Rollback	0.078	0.120	-0.046	0.091	-
90° Flexion - Variables	1	2	3	4	5
1. Coronal Angle	-				
2. IE Rotation	-0.331*	-			
3. Patella Shift	0.120	-0.434*	-		
4. Patella Tilt	0.506*	0.139	0.086	-	
5. Rollback	-0.026	0.005	-0.008	-0.086	-

Table 1 is the cross-correlation table for all dynamic parameters at 10°, 45° and 90° flexion. Correlations between different kinematic factors are moderate to weak, suggesting these parameters are relatively independent from each other. A statistically significant negative correlation (-0.34 , $p < 0.001$) was found between the post-operative KOOS Symptoms score and the rollback occurring from 10° to 45° flexion. Likewise, a significant negative correlation was found between the quadriceps force at 45° of flexion and the post-operative KOOS Symptoms score (-0.23 , $p = 0.025$). Patella lateral tilt negatively correlated at all three flexion points with the symptoms score (-0.26 , $p = 0.009$ at 10° flexion, -0.28 , $p = 0.005$ at 45° flexion and -0.26 , $p = 0.010$ at 90° flexion). Patella lateral shift at 90° flexion had a significant positive relationship (0.25 , $p = 0.012$).

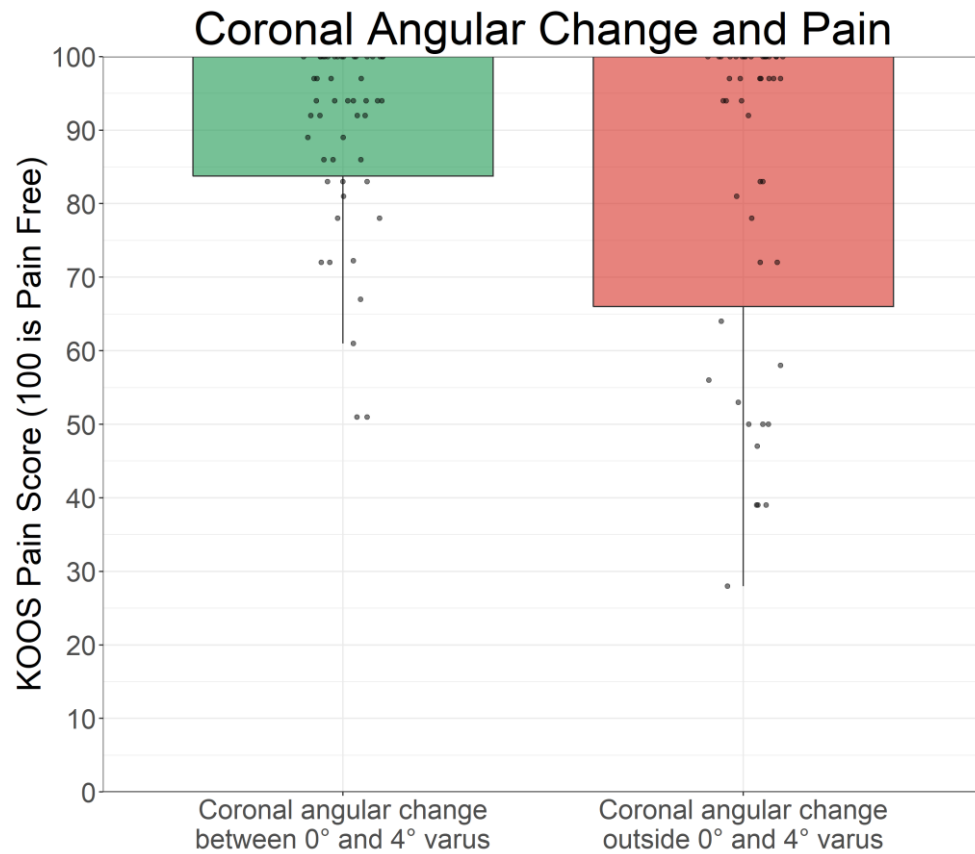


Figure 5. Patient reported post-operative KOOS Pain score and grouping by coronal angular change from flexion to extension within 0° to 4° varus (green) or greater than 4°/less than 0° (red)

The CART analysis found those with a varus angular change from 10° to 90° flexion of between 0 and 4° (long leg axis) had a significantly improvement in KOOS Pain score of 7.1 points (82.5 & 89.6, $p=0.049$) than those with either a greater varus change or a valgus change. This relationship is shown in Figure 5. Similarly, for anterior-posterior positions of the femur on the tibia between 10° and 90° of flexion, measured rollback of no more than 6mm without roll forward scored 10.1 points higher (79.0 & 89.1, $p=0.015$) in the post-operative KOOS Pain score than the counterpart of roll forward or rollback greater than 6 mm. This relationship is shown in Figure 6

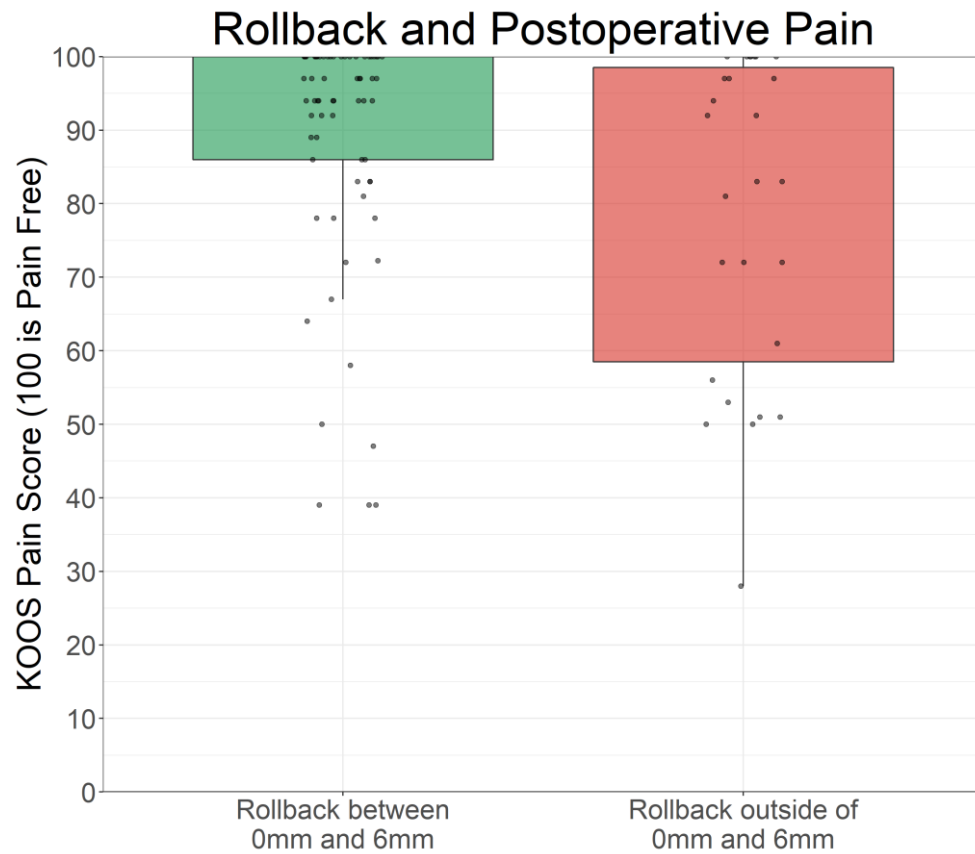


Figure 6. Patient reported post-operative KOOS Pain score and grouping by rollback within 6 mm (green) or greater than 6 mm/less than 0 mm (red).

Coronal angular change and rollback are relatively independent at 90° of flexion. Figure 7 a) shows the coronal angular change and femoral rollback plotted on the x and y axes respectively. Each point represents a single patient's combination of these two kinematic parameters. The colour of each point is its post-operative KOOS Pain score. There is a clear trend towards a central dynamic safe zone and plotting both of the prior relationships defines a region wherein the post-operative KOOS score is 10.4 points higher (82.4 & 91.8, $p=0.013$), as shown in Figure 7

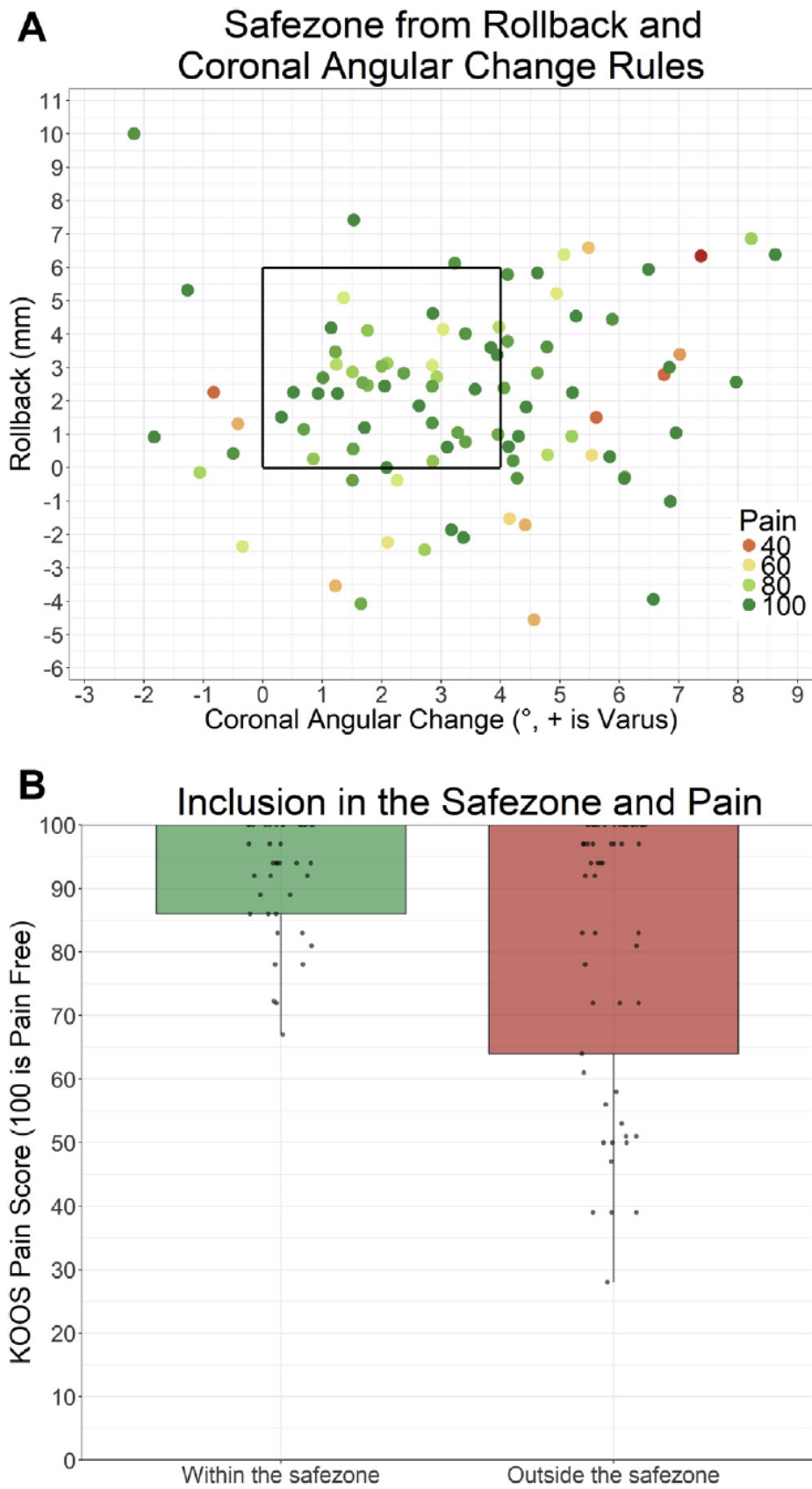


Figure 7. a) Patient reported post-operative KOOS Pain score and the safe zone box formed by applying both rules and b) boxplot of KOOS Pain scores for those within and those without the group

8.5: Discussion

This study showed statistically significant relationships between post-operative KOOS scores and kinematic factors in a simulated environment of post-operative TKA. Relationships between component alignment and joint dynamics outcomes have been previously shown to exist [421, 424-426]. This has historically been done with reference to kinematic objectives expected to correlate with patient outcome and has been used to validate surgical references [192] or inform implant design characteristics [426, 432]. This study is the first relationship shown between a patient reported outcome score and a validated, computationally measured dynamic outcome.

The kinematic factors outputted by the simulation are the result of both the variation in implant position and the patient specific musculoskeletal anatomy in which the components were implanted. The presence of a dynamic safe zone in the data suggests a potential optimal target for post-TKA joint dynamics. One potential future application of this is the simulation of a number of possible implant positions and alignments prior to a TKA for a given patient. The results from these simulations could drive selection of an alignment plan that best matches the dynamic safe zone.

Figure 5 shows that patients who had a coronal alignment change between 0 to 4° of varus from 10 to 90° of flexion had an increased post-operative KOOS Pain score relative to those outside of that range. The change in coronal alignment through flexion is a combination of the femoral and tibial coronal alignments and the rotation of the femoral component in addition to any implant lift off the components might be undergoing. Internal rotation of the femoral component will drive a measured valgus change in flexion, which is a component alignment measurement that has been previously observed to relate to worse outcomes [195, 328].

Figure 6 shows the relationship between post-operative KOOS Pain and rollback inside of 0mm and 6mm or outside of that range. The mid-range rollback group is related to a lower instance of pain post-operatively. It is not clear what the mechanism driving this observation is. One possibility is that found by Churchill et al., who noted increasing rollback produced a decrease in patellar loads [433]. Failure to manage the compromise between maintaining patellar loads that are sufficient to resist undesirable patella mobility while not overstuffing or overloading the patella-femoral joint might lead to extreme rollback measurements driving patient reported pain. Another possibility is that found by Belleman's et al. who identified component impingement in the tibio-femoral joint as a mechanism for range of motion limitation [197]. Subsequent studies have confirmed that insufficient rollback is flexion limiting in the post-operative TKA knee [434]. Although ROM limitation is not synonymous with post-operative TKA pain, it is possible that the impingement behaviour produces some level of patient discomfort.

There are a number of limitations to this study. The simulation platform used in this study is a multibody model, without the capacity to perform contact stress and deformation calculations seen in finite element models [200, 206]. Rollback here has been measured in terms of the anteroposterior motion of the trans-epicondylar axis to define a measurement that combines the simulated motion of the components relative to each other with their relationship to the axes of the anatomical knee. This alters the interpretability of the results in the context of other studies. This can be observed in the results presented in the box plots for Figure 4 b), IE Rotation. The median rotations of the tibia relative to the femur are 6.69°, 6.48° and 3.86° at 10°, 45° and 90° of tibia rotation external to the femur. This doesn't necessarily imply medial condylar rollback or lateral condylar rollforward of the implants, as the measurements are of Insall's axis of the tibia relative to the TEA. Another plausible explanation is that there has been a tendency to externally rotate the femoral components

relative to the TEA in surgery, coupled with known variation in tibial rotational placement [63].

Other limitations of this study relate to the nature of the study design. The study is retrospective and further research to confirm the findings prospectively is required. Two surgeons performed the TKAs simulated in this study aiming for a mechanically aligned knee but with variations in technique, and this number is not sufficient to assume generalisability across all variations in surgical technique. Moreover, kinematic and other alternate alignment philosophies have not been incorporated into this study at all. It is possible that the kinematics of the knee post-TKA are a driver of outcome independent of alignment, but the findings here only directly support these kinematics being ideal in mechanically aligned TKAs. Similarly, the use of CR implants of a single design hampers generalisability across implant designs.

Rullkoetter et al. [207] describes two broad computational model categories for assessing TKA. Models that measure component mechanical constraint in isolation from anatomic features can investigate component movement defined within the component specific frame of reference. Such models provide useful information on prosthesis wear under ideal conditions, but do not allow any representation of the patient specific musculoskeletal environment. More complex models that include soft tissue and musculature may investigate patient specific joint dynamics, but require highly invasive and resource intensive data capture.

The model utilised here is in many ways a hybrid between these two approaches as a generic ligament model with patient specific insertions is used to define the ligaments. This approach has been taken so that the process used here can be replicated in a pre-operative simulation with a planned instead of registered implant position as profiling the ligament properties of individual patients prior to surgery is not feasible. While the model presented

here has been validated [378], there is potential for the model to not fully capture highly unusual soft tissue profiles. This may also cause the model to not fully capture the kinematic impact of an extensive soft tissue release. Similarly, the simulation only being a deep knee bend limits its applicability as the motion does not reflect the functional range of activities patients perform.

Table 1 shows the independence of many of the measured dynamic parameters from each other as the knee flexes. The relationships linking each dynamic parameter with component alignment and patient factors are not trivial. Simulations are uniquely placed to model the impacts of complex alignment and anatomic interactions on a patient by patient basis. Clinical findings relating outcome to simulation measured kinematic parameters have the potential to be used in a routine pre-surgical planning workflow, by virtually modelling multiple alignment options. From this, the most kinematically ideal alignment option can be selected on a per case basis for surgical implantation. Future developments will need to see models find an acceptable compromise between the precision of sophisticated patient specific models and the scalability of more basic implant contact models.

8.6: Conclusion

Kinematic measurements derived from a computational model of a deep knee bend are shown here to correlate with patient reported outcomes post-TKR. Two kinematic measurements that significantly correlated with patient outcome were found to have a low cross-correlation, producing a synergistic relationship in which a dynamic 'Safe Zone' of higher outcome score achieving patients could be defined. Such an approach to TKR analysis raises the prospect of pre-operative simulations and planning to achieve desired joint dynamics on a patient specific basis that may improve patient outcomes.

Chapter 9

Measurement of Physical Activity in the Pre- and Early Post-operative Period after Total Knee Arthroplasty for Osteoarthritis using a Fitbit Flex Device

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Chapter 8 is the culmination of the work in this paper relating to the technicalities of surgery; this chapter sprung from an investigation into what might be done to improve patient outcomes outside of directly affecting the surgery. One area of significant potential improvement is in the postoperative management of the patient. Patients are frequently unsure and confused as to what should be expected from them during their recovery. While information provision to them is one solution, the reality is that objectively measured patient recovery is highly patient dependent. Pedometers are one mechanism by which an objective, patient specific goal can be communicated to patients on a daily basis. This study conducted a regression analysis on step count and determined an appropriate 6 week recovery target dependant on preoperative step count and demographics. Later research has shown that provision of goals increases post-operative activity level and satisfaction, and the goal setting tool has been used in over 300 managed patient rehabilitation plans.

9.1: Abstract

Total knee arthroplasty (TKA) is a standard treatment for patients with end stage knee osteoarthritis (OA) to reduce pain and restore function. The aim of this study was to assess pre- and early post-operative physical activity (PA) with Fitbit Flex devices for patients with OA undergoing TKA and determine any benchmarks for expected post-operative activity. Significant correlations of pre-operative step count, post-operative step count, Body Mass Index (BMI) and Short Form 12 Physical Component Summaries (SF-12 PCS) were found. Mean step counts varied by 3,203 steps per day between obese and healthy weight patients, and 3,786 steps per day between those with higher and lower SF-12 PCS scores, suggesting the need for benchmarks for recovery that vary by patient pre-operative factors. A backwards stepwise regression model developed to provide patient specific step count predictions at 6 weeks had an R^2 of 0.754, providing a robust patient specific benchmark for post-operative recovery, while population means from BMI and SF-12 subgroups provide a clinically practical alternative.

9.2: Introduction

The aim of total knee arthroplasty (TKA) as a treatment for Osteoarthritis (OA) is the restoration of function, a reduction in pain, satisfaction with surgical outcome and restoration of a healthy lifestyle [394].

The need for Physical Activity (PA) as part of a healthy lifestyle is undisputed for all of us including for patients with OA. Although it has been found that pain and discomfort experienced during PA limits patients with OA from reaching recommended levels of PA, it is expected that PA levels after TKA would improve [253, 435, 436].

PA can be directly measured or patient reported in Patient Reported Outcome Measures.

Direct measures of PA can include, accelerometry, pedometry, heart rate monitoring, global positioning systems and direct observation. There are also a number of techniques such as doubly-labelled water and calorimetry that measure energy expenditure, a related concept often substituted for PA in studies [437]. Historically, many of these techniques have been impractical for use outside of research studies due to their cost or technical requirement. PROMs assessments of PA have lower costs and technical barrier, but have relatively poor validity and correlation to objective measures [233].

Wearable wireless activity monitors such as the Fitbit Flex are an increasingly low cost and clinically accessible option for monitoring step counts. Pedometers and step count as a measurement holistically has been validated as a means of capturing relative PA between subjects, showing robust construct and convergent validity [234, 250]. In particular, convergent validity was well demonstrated between directly observed and accelerometric measurements of PA and step count as measured by the activity trackers [234]. Fitbit Flex devices have been shown to be valid and reliable assessment tools for ambulation in normal

subjects, reporting both high inter- and intra-device reliability [438, 439] and consistency with other objective measures of activity level [249, 440].

PROMs measure health-related quality-of-life. In addition to those used in assessments of physical activity, some are specific to the knee and one popular one is the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The Knee Injury and Osteoarthritis Outcome Score (KOOS) is self-administrated and was adapted from the WOMAC [79].

Scores can be calculated for pain, symptoms, activities of daily life function (ADL), sport and recreation function and knee-related quality of life (QOL). The Medical Outcomes Short Form-12 (SF-12) is a shorter version of the Medical Outcomes Study Short Form-36 (SF-36) [25] consisting of 12 questions regarding holistic health that produces summary scores of physical and mental functioning: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [441, 442]. Scores for both the KOOS and SF-12 are transformed into a 0-100 scale where zero represents extreme health or knee problems and 100 represent no problems.

Generally accepted pre-operative indicators for outcome after TKA include age, gender, BMI, diagnosis leading to surgery and function/pain as measured by PROMs, socioeconomic circumstances and anxiety/depression. Clinically important indicators of poor TKA outcomes such as pain were diagnosis of rheumatoid arthritis (RA) versus OA and area deprivation (living in a poorer area) whereas age and gender were specifically associated with function outcomes [112].

Like age and gender, a patient's pre-operative physical functioning and PA levels could be a predictor of restoration of function after TKA. Brandes et al [254] found moderate correlations between pre-operative and post-operative PA as measured by step count suggesting that a higher pre-operative PA level could serve as a moderate predictor for higher PA levels post-operatively. However, pre-operative baseline PA levels influencing PA

for OA patients after TKA are not known [253]. PA levels in the early recovery period is also not known although early mobilization after TKA surgery can result in reduced length of stay (LOS) in hospital without an increase in negative outcomes [443]. Across populations, even when experiences of pain and stiffness, functional capacity and self-reported physical functioning were improved by TKA, it has been shown that actual directly measured PA increased only slightly six months after surgery [252].

The aim of this study was to assess pre- and early post-operative physical activity (PA) with Fitbit Flex devices for patients with OA undergoing TKA and determine any benchmarks for expected post-operative activity. Meaningful correlations could be used to determine simple, clinically applicable benchmarking rules for expected recovery. More sophisticated modelling was also employed to predict baseline step counts at post-operative time points based on pre-operative step count, PROMs, demographic data and hospital Length of Stay (LOS). This produces a less clinically applicable but more personalised and relevant post-operative benchmark.

9.3: Methods

A total of 94 patients undergoing TKA were recruited to the study over a 21 month period, from December 2013 to September 2015. Ethics was approved by St Vincent's Human Research Ethics Committee (SVH 13/034).

Exclusion criteria for this study were rheumatoid arthritis and a fixed flexion deformity of >15 degrees, or patients who were wheelchair bound or otherwise completely immobilized in a pre-operative state. The Fitbit Flex, a small, lightweight commercially available wristband containing a triaxial accelerometer was used. Fitbit Flex device uses a set of algorithms in order to detect steps by using an accelerometer sensor, and the summed daily step counts were available to the authors in this study. Of the 94 patients recruited, 3 did not return any devices or contribute any data to the study and were not carried forward in any analysis, leaving a total of 91 patients.

Each device was linked to an account controlled by the investigators and denoted by an ID number engraved on the physical tracker. The devices were pre-set to unattainable goals of daily activity in order to limit the feedback provided by the device, effectively blinding the patients. In this way patients were informed of the basic intent of the study but were denied specific feedback of their step count to limit observation bias and ensure the captured data was representative of the patient's regular daily routine.

Devices were mailed to patients fully charged with instructions for securing the Fitbit Flex to their non-dominant wrist. The instruction set included diagrams of how to secure the device using the devices clip, where on the wrist to attach it, that it was waterproof and once affixed, should not be removed for the next 7 days. A pre-paid envelope was supplied for return of the device upon completion as well as a piece of paper to record the dates the patient had started and finished wearing the device. Although manufacturers of Fitbit claim

that the device charge would last approximately 5 days between charges, the authors found that battery life was extended if the wireless data transfer dongle or synchronized phone was removed thus stopping the wireless data transfer cycles. Patients were asked to wear the device at 3 time points; 2 weeks pre-operatively, the day following the operation and at 6 weeks after the operation. During each time period, patients were instructed to wear the device for 7 days and to not remove the device for the entirety of each 7 day recording period.

Pre-operative KOOS and SF-12 for each patient as well as age, sex, height and weight were recorded. The Sports subdomain of KOOS was not included in this analysis as it was not readily answered by the population undertaking the study. Body Mass Index (BMI) was further derived as the weight of the patient divided by the height squared.

All surgical procedures were performed by a single surgeon in a single centre and all participants received Omni Apex (Omni Life Sciences) prosthesis for their TKA. Post-operative patient protocol management was consistent and all patients underwent a post-operative physiotherapy regimen that was consistently applied between patients in order to control for its potential impact on patient recovery in PA.

When returned, step count data was uploaded using the wireless synchronisation USB devices distributed with each Fitbit Flex and linked to patient's device ID. Using start and finish dates (exclusive of the start and finish date) a step count per day for each patient was determined. Data was included if at least 3 full days of use could be attained. This is in accordance with previously published research suggesting that three or four days was the appropriate minimum period and that variation between days of the week was minor [238, 242, 444]. There was some data loss due to either patient non-compliance, protocol failure with regards to fully charged devices, technical failures of the devices or delays in mail out service causing less than 3 days of wear to be available and occurred at a rate of 26%. For

the immediate post-operative period, days 2 through 4 only were extracted and averaged as there was improvement observed in each consecutive day. If there was no data at one of the three time points for a given patient, the rest of the patient's data has been retained for use in paired analysis. All such subgroups created as a result had no statistically significant differences in demographic profiles with regards to BMI, gender and age.

Statistical analysis was performed using R a programming language software environment supported by the R Foundations for Statistical Computing [388]. Descriptive data of clinical outcome and step count parameters were given in mean +/- SD values. Shapiro-Wilks test showed the days 2-4 post-operative step count data to not be normally distributed, and so Mann-Whitney tests between groups and Spearman's Rho for correlation were conducted. Outliers were investigated for potential measurement or recording failures but otherwise retained. All tests for significance had a p-value of 0.05 set as the level of significance.

Strongly correlating results have been investigated as indicators of clinically relevant benchmarks of patient recovery and post-operative step count for use in clinics. In developing clinical benchmarks, reference has been made to existing literature classifications or population norms. For the SF-12, these have been based on placement above or below mean population score for patients prior to and six months following Total Knee Arthroplasty who would go on to be satisfied with the surgery. For the Physical Component Summary (PCS) of the SF-12, these values are 29.6 and 40.5 [274]. BMI has been categorised as per the National Heart, Lung, and Blood Institute (NHLBI) guidelines [445].

For investigating the predictive effect of pre-operative step count, PROMs (four KOOS subdomains and the two SF-12 component summaries) and demographic data (gender, BMI and age) in generating 6 week and days 2-4 post-operative step count prediction models, a stepwise-backward multiple linear regression model with significance of the predictors as the criterion was developed. Hospital length of stay was also used for the 6 week step count

prediction. Intercepts were retained regardless of reported significance as there was no reason to assume a path through the origin for the regression.

9.4: Results

A total of 94 subjects were recruited to the study over a 21 month period, from December 2013 to September 2015. Of the 94 patients recruited, 3 did not return any devices or contribute any data to the study and were not carried forward in any analysis, leaving a total of 91 patients. Step count data was complete for 69 of 94 patients in the pre-operative period, 68 in the day 2-4 post-operative period and 68 at 6 weeks post-operatively. Patient demographics and summary results are shown in Table 1.

Table 1. Demographics and score results for the full cohort of patients and stratified by gender. Means +/- Standard Deviations for the population are given. Mean results and standard deviations for step count are also included for each of the 3 time periods (pre-operative, days 2-4 post-operative and 6 weeks post-operative) in addition to hospital length of stay in days. ADL and QOL are the Activities of Daily Living and Quality of Life subscores of the Knee Injury and Osteoarthritis Outcome Score (KOOS) score. PCS and MCS are the Physical and Mental Component Summaries of the Medical Outcomes Study Short Form 12 (SF-12) questionnaire.

	Total (n = 91)	Women (n = 46)	Men (n = 45)
Age (Years)	67.5 +/- 13.1	66.1 +/- 16.8	69.1 +/- 6.6
Height (cm)	167.5 +/- 12.4	159.5 +/- 11.2	175.7 +/- 6.9
Weight (kg)	84.1 +/- 16.3	79.7 +/- 16.4	89.1 +/- 14.8
BMI (kg/m ²)	30.1 +/- 6.3	31.3 +/- 7.7	28.9 +/- 4.1
KOOS pain	45.6 +/- 18.7	42.7 +/- 17.8	48.7 +/- 19.4
KOOS symptoms	43.4 +/- 18.8	40.4 +/- 17.9	46.6 +/- 19.4
KOOS ADL	50.3 +/- 19.5	48.0 +/- 17.2	52.8 +/- 21.6
KOOS QOL	23.8 +/- 18.5	22.1 +/- 16.6	25.7 +/- 20.4
SF-12 PCS	31.6 +/- 9.0	29.2 +/- 6.9	34.3 +/- 10.4
SF-12 MCS	54.9 +/- 9.7	55.1 +/- 9.9	54.7 +/- 9.6
Preop step count (steps/day)	6409 +/- 3228	5601 +/- 2950	7263 +/- 3332
Day 2-4 step count (steps/day)	1170 +/- 857	1102 +/- 785	1228 +/- 922
6 Week step count (steps/day)	6231 +/- 2924	5759 +/- 2916	6717 +/- 2893
Hospital length of stay (days)	5.95 +/- 1.33	5.81 +/- 1.05	6.125 +/- 1.62

Figure 1 shows the differences in pre-operative, day 2-4 and 6 week results with error bars representing the standard error of the mean in order to quantify the spread of population means that may exist. Statistically significant differences were not found between the 6 week step count and pre-operative step count, though statistically significant differences were found between the day 2 to 4 post-operative step count and both the pre-operative and 6 week step count as expected ($p < 0.001$).

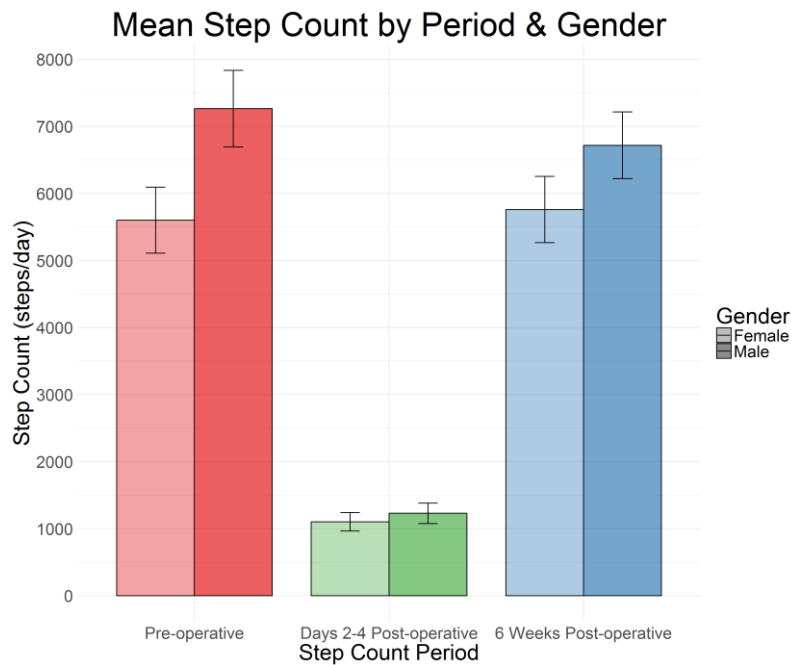


Figure 1. Average step counts pre-operative, immediately (2-4 days) and 6 weeks post-operatively with the standard error of the mean.

Statistically significant differences in step counts were observed between genders ($p=0.041$) for the preop period but not for the other two time periods. A Shapiro-Wilks normality test returned a p-value of 0.0002 for normality of the day 2-4 post-operative period, indicating this data was not normally distributed. As such, the probability distribution (Gaussian density estimation) is shown in Figure 2.

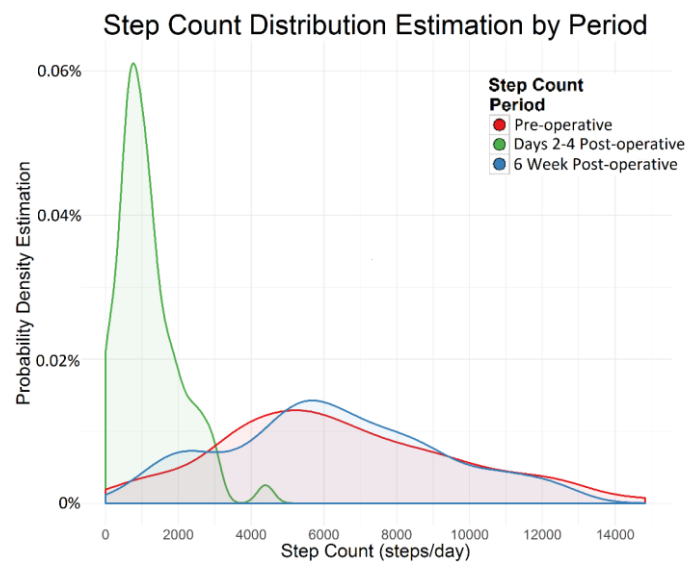


Figure 2. Step count probability distribution estimations for pre-operative (red); day 2-4 post-operative (green); and 6 weeks post-operative (blue). The Probability Density Estimation is probability per individual step count level (discrete number of steps/day).

Table 2 shows the full set of Spearman's rho correlation coefficients between the step count data and continuous potential predictors on which data has been collected. BMI, the SF-12 PCS and the KOOS ADL subscores have significant correlations with all three time points. There was a slight but not statistically significant trend towards higher step counts indicating lower lengths of stay. KOOS QOL was significantly associated with post-operative 6 week step count, while KOOS Pain was significantly associated with post-operative day 2-4 step count and pre-operative step count.

Table 2. Spearman's Rho correlation coefficients for continuous potential predictors for pre-operative, days 2-4 post-operative and 6 weeks post-operative step count. ADL and QOL are the Activities of Daily Living and Quality of Life subscores of the Knee Injury and Osteoarthritis Outcome Score (KOOS) score. PCS and MCS are the Physical and Mental Component Summaries of the Medical Outcomes Study Short Form 12 (SF-12) questionnaire. Bold and italics indicates significant difference of the correlation coefficient from 0 to $p < 0.05$.

	Pre-operative step count	Post-operative days 2-4 step count	Post-operative 6 week step count
Age (Years)	-0.004	-0.076	-0.107
BMI (kg/m ²)	-0.526	-0.346	-0.553
KOOS pain	0.280	0.259	0.122
KOOS symptoms	0.022	-0.021	0.101
KOOS ADL	0.282	0.259	0.309
KOOS QOL	0.233	0.207	0.338
SF-12 PCS	<i>0.403</i>	<i>0.416</i>	0.521
SF-12 MCS	0.230	0.136	0.095
Hospital length of stay (days)	-0.114	-0.134	-0.131
Preop step count (steps/day)	-	0.389	0.709
Day 2-4 step count (steps/day)	-	-	0.536

The correlation between pre-operative and 6 week post-operative step count was statistically significant and the strongest single correlation investigated. This correlation is shown in Figure 3 (a). Although there was no statistically significant difference in the means of these two groups, the mean difference for a given individual's step count between the pre-operative period and the 6 week post-operative period was 1,781 steps per day. The maximum difference was 7,017 steps per day (a patient whose step count had declined from 12,496 steps per day to 5,446). 44% of patients had a higher step count at 6 weeks, while 56% had a lower step count. There is a weaker positive correlation between the pre-operative step count and days 2-4 post-operative step count seen in Figure 3 (b). Spearman's rho correlations between the pre-operative period and the immediate post-

operative period were 0.389 ($p < 0.01$). Spearman's rho correlations between the pre-operative scenario and the 6 week post-operative scenario were 0.709 ($p < 0.001$).

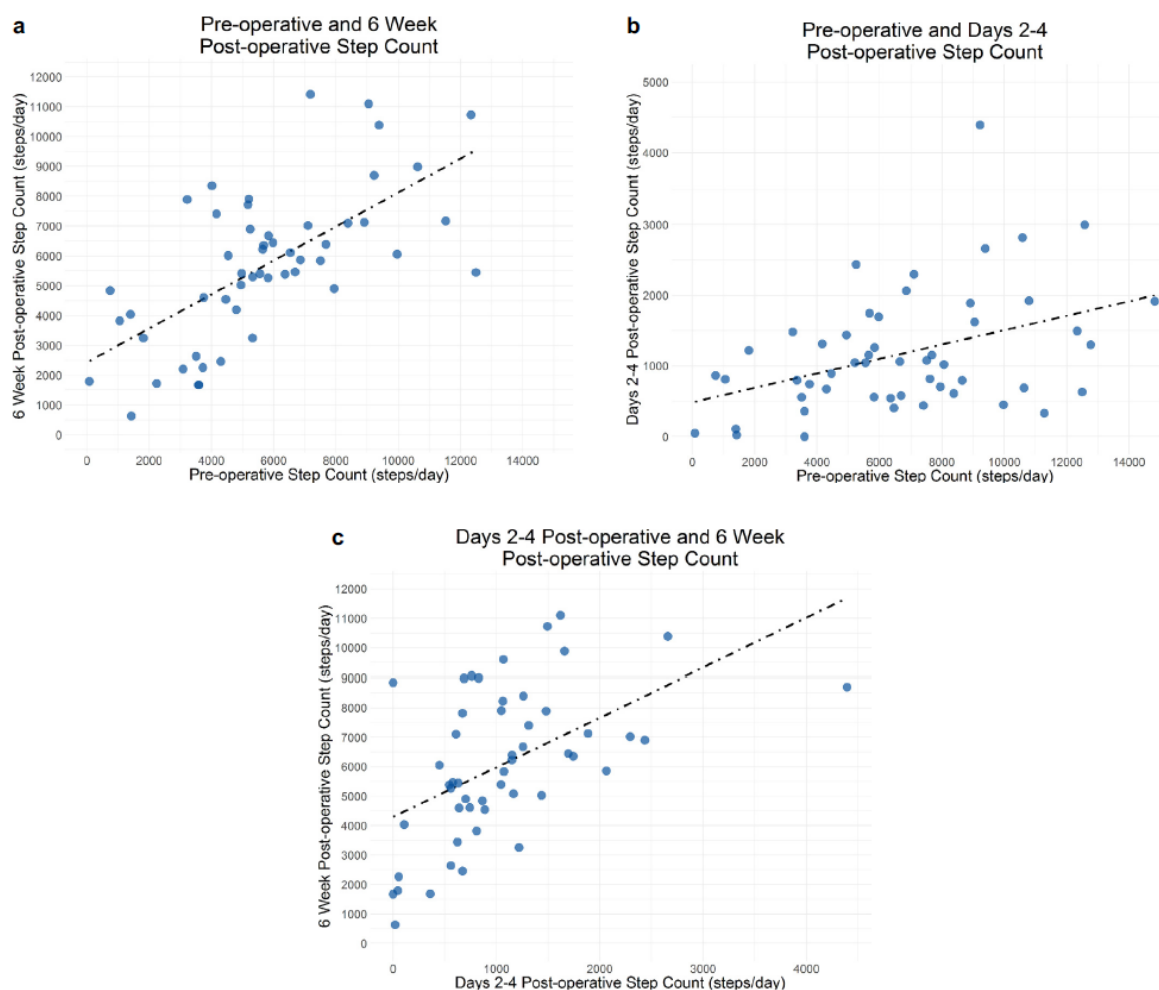


Figure 3. (a) days 2-4 post-operative steps compared with pre-operative step count; (b) 6 week post-operative step count compared with pre-operative step count; and (c) 6 week post-operative step count compared with days 2-4 post-operative step count

Days 2-4 post-operative steps and 6 weeks post-operative steps also had a significant correlation as seen in (c). It can be seen that individuals who completed more steps immediately post-operatively achieved a higher step count 6 weeks post-operatively. Between these two time periods, Spearman's rho was 0.536 ($p < 0.001$).

Of the pre-operatively collected PROMs, the correlations with SF-12 PCS were higher than all other scores for each period. The correlations were 0.403 in the pre-operative period

($p < 0.001$), 0.416 in the immediate post-operative period ($p < 0.001$) and 0.521 in the 6 week post-operative period ($p < 0.001$). These results are shown in Figure 4.

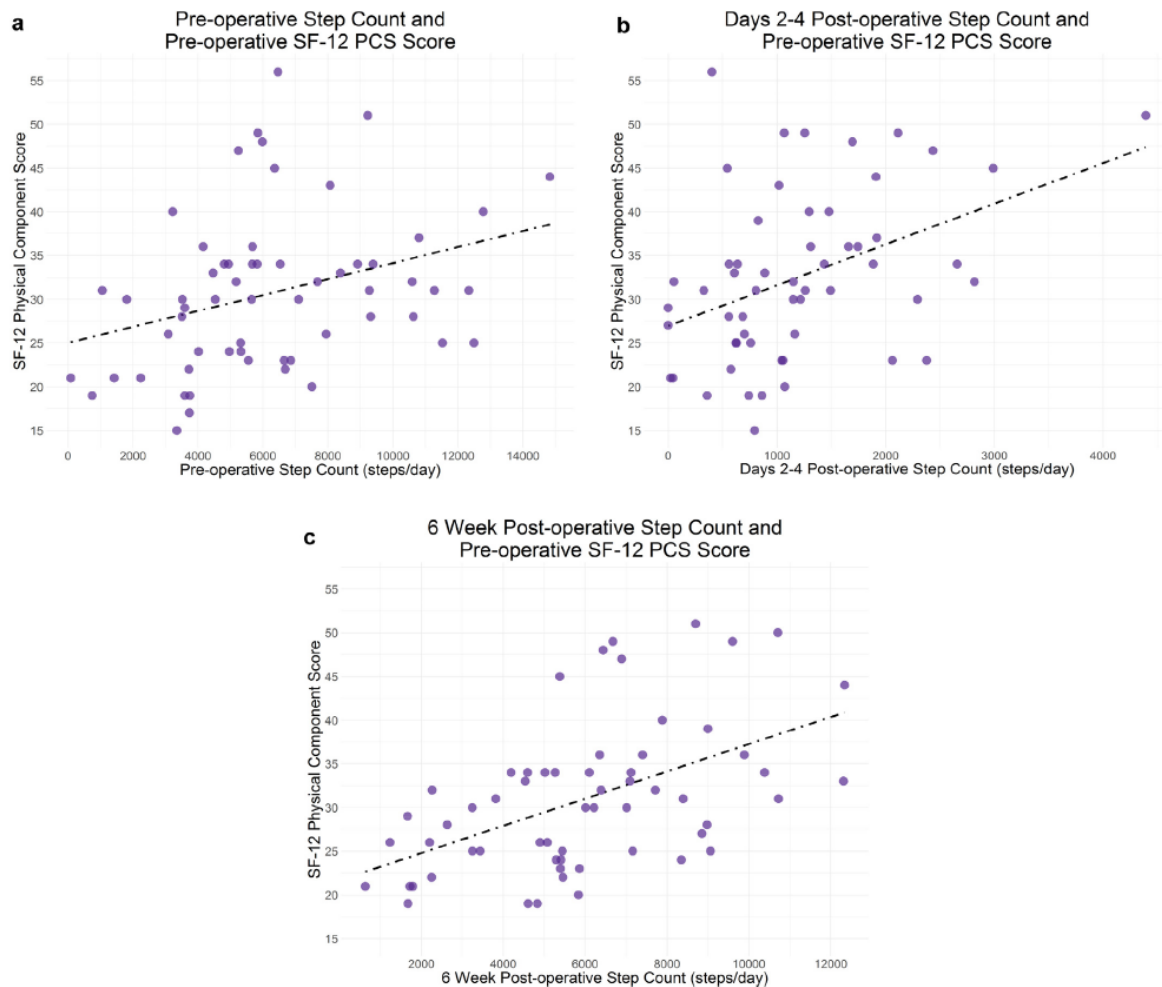


Figure 4. (a) Pre-operative step count, (b) days 2-4 post-operative and (c) 6 week post-operative compared to preoperative SF-12 Physical Component Summaries (PCS).

Based off a previously identified pre-operative mean SF-12 PCS of 29.6 for patients satisfied with TKA surgery, those who scored less than 29.6 were considered low range SF-12 scores (as this was the mean pre-operative score for satisfied patients). Those who scored between 29.6 and 40.5, the mean value at 6 months post-operative of the satisfied patients were considered high, while those scoring greater than 40.5 were very high range. Table 3, below, shows the mean step counts for each SF-12 sub group. For the low SF-12 PCS subgroup this difference is significant, indicating that patients who score below 29.6 cannot, on average,

expect to have returned to pre-operative levels of daily step count by 6 weeks post-operatively.

Table 3. Mean step counts by SF-12 Physical Component Summaries (PCS) subgroup for each of the pre-operative, days 2-4 post-operative and 6 weeks post-operative daily step counts. The fifth column, p-value, is the p-value of a paired 2-tailed Wilcoxon sign-rank test of difference in step count between the pre-operative (second column) and 6 week post-operative (forth column) periods.

SF-12 PCS subgroup	Pre-operative step count	Post-operative days 2-4 step count	Post-operative 6 week step count
Low	5294 +/- 3176	769 +/- 602	4556 +/- 2504
High	6753 +/- 3169	1312 +/- 689	6758 +/- 2451
Very high	7750 +/- 3139	1802 +/- 1167	8342 +/- 2406

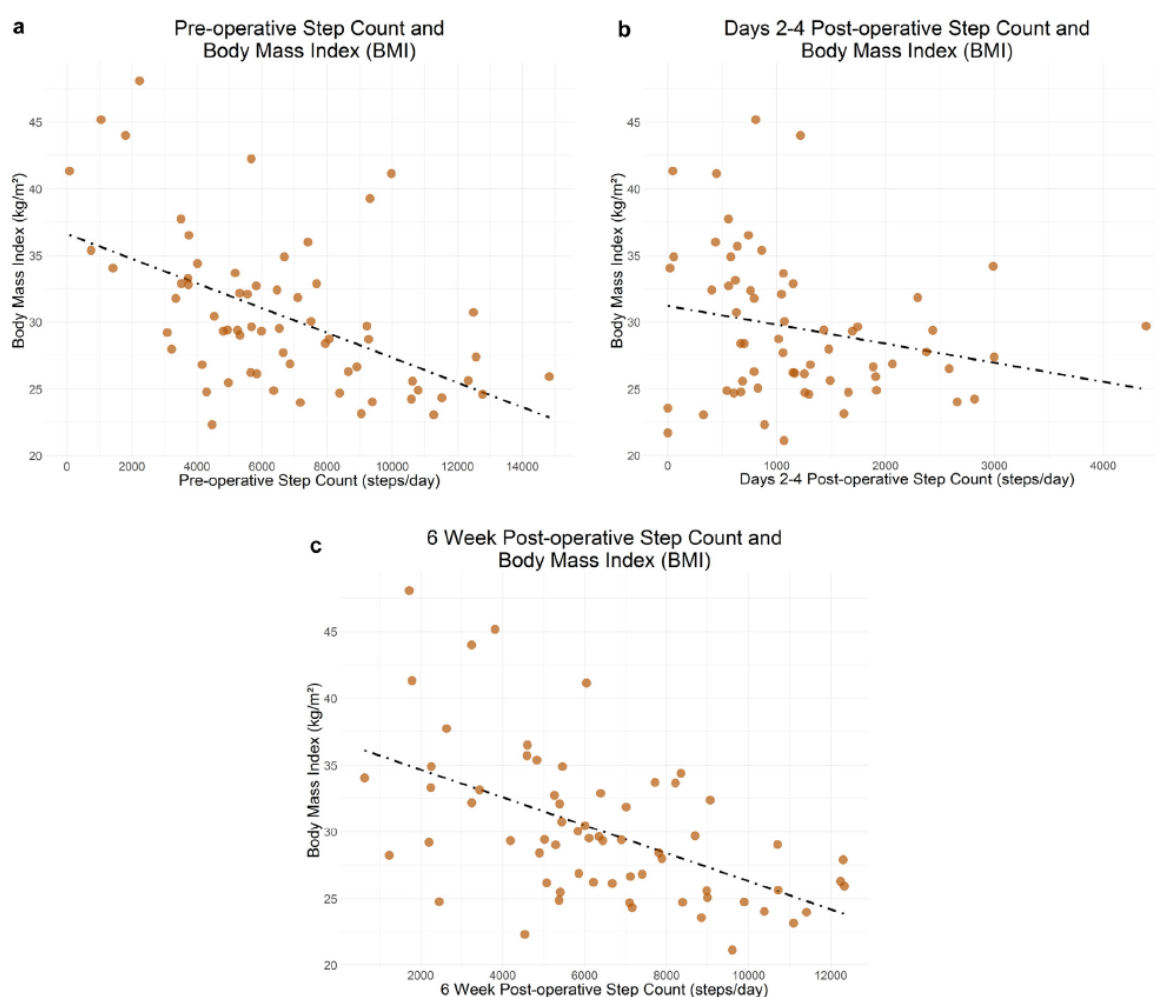


Figure 5. (a) Pre-operative step count, (b) days 2-4 post-operative and (c) 6 week post-operative compared to preoperative Body Mass Index (BMI).

Body Mass Index (BMI) also had significant correlations with all step count periods. The correlations were -0.526, in the pre-operative period ($p < 0.001$), -0.346 in the immediate

post-operative period ($p < 0.001$) and -0.553 in the 6 week post-operative period ($p < 0.001$). These results are shown in Figure 5.

Segmenting patients by NHLBI weight status, patients with a BMI of less than 25kg/m^2 are considered normal weight, those between 25kg/m^2 and 30kg/m^2 are overweight and those greater than 30kg/m^2 are obese. Table 4, below, shows the mean step counts for each BMI sub group.

Table 4. Mean step counts by Body Masss Index (BMI) subgroup for each of the pre-operative, days 2-4 post-operative and 6 weeks post-operative daily step counts.

BMI subgroup	Pre-operative step count	Post-operative days 2–4 step count	Post-operative 6 week step count
Normal weight	8840 +/- 2776	1156 +/- 863	8022 +/- 2781
Overweight	7257 +/- 2985	1631 +/- 870	7151 +/- 2833
Obese	4989 +/- 2926	825 +/- 657	4819 +/- 2238

Backwards stepwise multivariate regression was performed to develop a model predictive of patient step count. The regression coefficients acquired through stepwise regression are presented in Table 5 and Table 6. In addition to the two backwards stepwise models, a second day 2-4 post-operative model was developed including all variables found to be significant in the 6 week post-operative model despite statistical insignificance of the predictors in the backwards stepwise day 2-4 model. This was done as their relevance was indicated by presence in the 6 week model and the R^2 value so obtained was increased after adjusting for more factors.

Table 5. 6 week post-operative step count regression results. All available data points collected prior to 6 weeks post-operative were included in the backwards stepwise regression. The adjusted R^2 , raw regression coefficients per regressors and p-values for significant difference of the regressors coefficient from 0 are presented.

Model	Adjusted R^2	Parameter	Unstandardised coefficients (std err)	T	p-Value
Stepwise regressed model	0.7544	(Intercept)	839.62 (819.80)	1.024	0.3145
		Pre-operative SF12 PCS	60.023 (29.258)	2.052	0.0497
		Pre-operative daily step count	0.469 (0.066)	7.043	<0.0001
		Gender (coefficient is male)	-1008.00 (445.99)	-2.26	0.0318
		Days 2–4 post-operative step count	0.743 (0.312)	2.377	0.0245

For the day 2-4 post-operative period, only the SF-12 PCS remained as a significant predictor of day 2-4 post-operative step count after stepwise elimination. For the 6 week step count

period, gender (with males doing less steps), day 2-4 post-operative step count, pre-operative step count and the SF-12 PCS all remained as significant predictors after stepwise elimination. 75% of the variation at 6 weeks post-operatively was explained in the model, while 14% was explained in the stepwise day 2-4 model and 18% in the model inclusive of the 6 week post-operative parameters.

Table 6. Days 2-4 post-operative step count regression results. Two models are presented, the first of which was developed through backwards stepwise regression and the second which contains all parameters present in the 6 week post-operative step count model. The adjusted R^2 , raw regression coefficients per regressors and p -values for significant difference of the regressors coefficient from 0 are presented.

Model	Adjusted R^2	Parameter	Unstandardised coefficients (std err)	T	p-value
Stepwise regressed model	0.1432	(Intercept)	121.18 (427.69)	0.283	0.77841
		Pre-operative SF12 physical component summary	34.94 (12.60)	2.772	0.00849
6 week matched predictor model	0.1795	(Intercept)	167.21 (499.96)	0.334	0.7399
		Preop SF12 PCS	32.286 (13.383)	2.412	0.0209
		Preop step count	0.063 (0.036)	1.746	0.0891
		Gender (coefficient is male)	-246.65	-0.98	0.3336

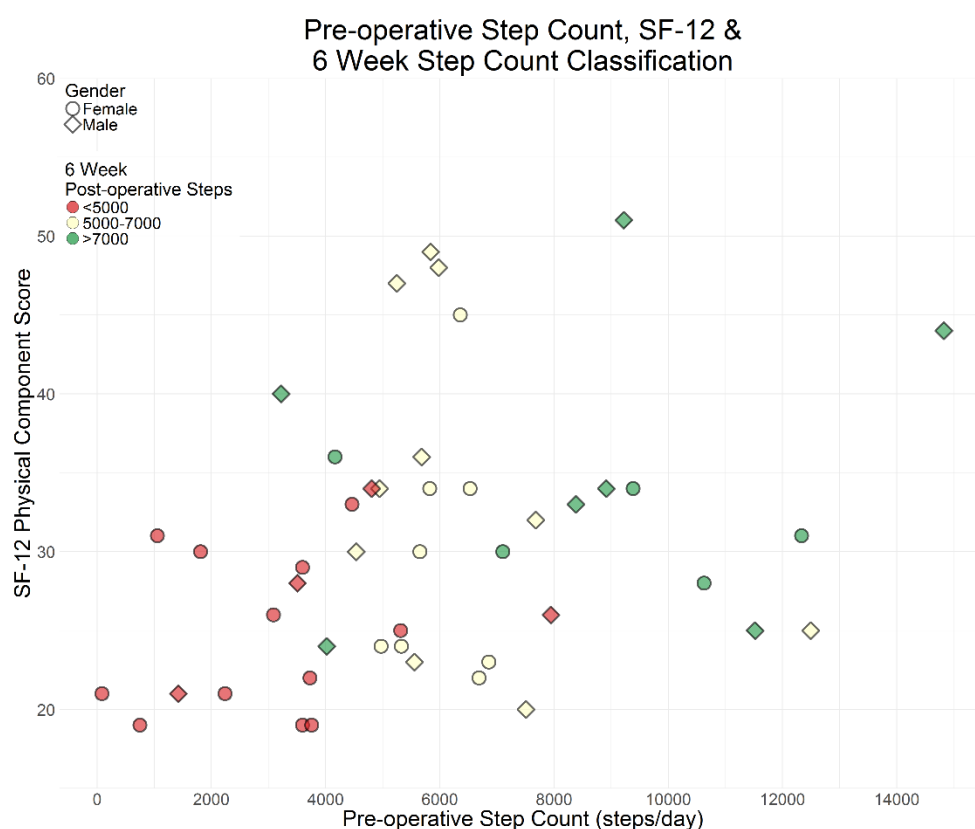


Figure 6. Pre-operative self reported SF-12 Physical Component Summaries and pre-operative step count separated by gender as classifiers for 6 week post-operative post-operative step count.

Figure 6 is a cross plot of the SF-12 PCS score (y axis) and pre-operative step count (x axis), selected as they are continuous, pre-operatively available variables that survived the stepwise backwards elimination of 6 week step count. Patients are grouped by gender and

are also grouped into three groups of High, Medium and Low post-operative step count attainment. These groups were selected to be roughly equivalent but also set thresholds with round units of 1000 steps. Classification ranges were: low (red) <5,000; medium (yellow) 5,000-7,000 and high (green) > 7,000 steps per day.

Figure 7 a) and b) are charts of the regression presented in Table 5, with the expected classification ranges for each zone of pre-operative as described for Figure 6. Mean days 2-4 post-operative steps are assumed.

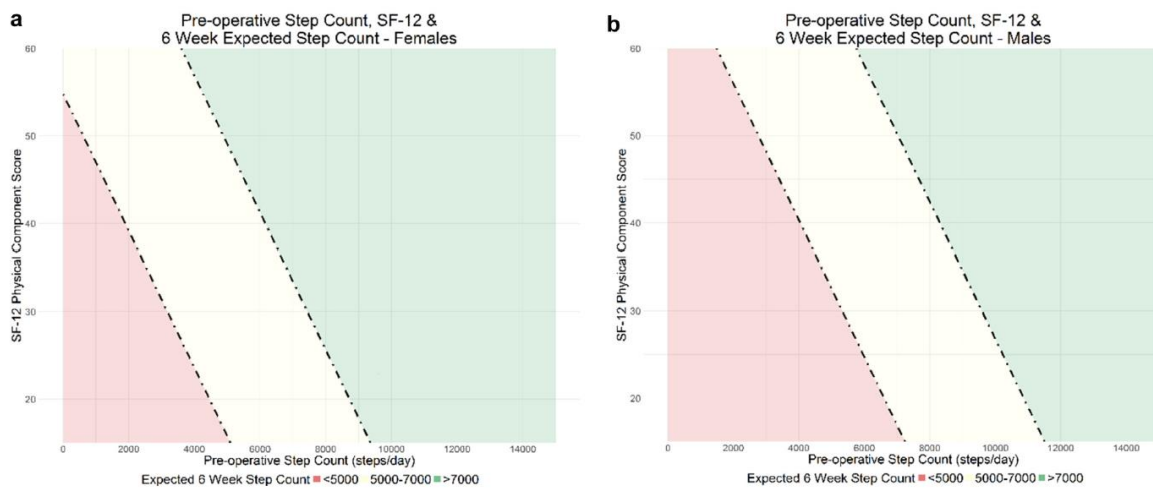


Figure 7. Expected post-operative step count range by SF-12 Physical Component Summaries, (a) days 2-4 post-operative and (b) 6 week post-operative compared to Body Mass Index (BMI).

9.5: Discussion

From a series of 91 subjects undergoing total knee arthroplasty we assessed the mean daily step count as 6,409 +/- 3,228 pre-operatively, 1,170 +/- 857 2-4 days post-operatively and 6,231 +/- 2,924 at 6 weeks post-operatively. Step count at all time points (pre-operatively, days 2-4 post-operatively and 6 weeks post-operatively) correlated positively with higher scores on the Short Form-12 Physical Component Score (SF-12 PCS) score and the Knee Osteoarthritis and Outcome Score Activities of Daily Living (KOOS ADL) subscore. Step counts also correlated negatively with BMI, and each step count period significantly correlated with each other period.

Step count 2-4 days post-operatively was significantly lower than both pre- and 6 week post-operative time periods. Population mean step count pre- and 6 weeks post-operatively was similar. The fact that 6 weeks post-operative step count had not increased above pre-operative step count is consistent with other research which reports significant declines in functional performance between 1 month to 6 weeks with improvement only observed by 3 months after surgery [446, 447]. Harding et al's accelerometry study [253] has previously found that by 6 months there was no change measured for PA levels compared to pre-operatively. However, Issa et al, [448] found that PA levels as measured by self reported scores had exceeded their pre-operative level by 3 months post-operatively and continued to rise to a peak at two years post-operatively which was maintained at the 5 year follow up. Paxton et al.'s [449] literature review of activity level changes pre- and post-operatively finds that studies using objective measurements such as accelerometry tend to show little change or a decrease inactivity level following the operation. This is in comparison to studies using subjective measurements or self-reported assessments which typically find an increase, suggesting that patient's perceptions of their activity levels increase following surgery even though their actual activity level generally does not. [449]

Average daily step count for pre-operative and 6 week post-operative time points compares to healthy subjects who complete approximately 6500 to 8900 steps per day: 8576 [239]; 6943 [450]; 8813 [238]; and 6495 [236]. A range found between 2000-9000 steps per day for healthy subjects has been reported and this type of variation for any patient population group would be expected, accounting for patient demographics [237].

The correlation coefficient of pre-operative and 6 week post-operative step count of 0.707 was the strongest correlation in this study. Brandes et al's [254] study investigated step counts at 2 months post-operatively, a similar time point to our 6 weeks post-operative. Their study reports a high step count overall of 9,460 (+/- 3,118), compared to our mean of 6,231 (+/- 2,924). Both studies found a slight but not statistically significant decrease in 6 week/2 month step count compared to pre-operative step count. Prior studies investigating activity level longer term after TKA (6 to 12 months) show differences between PA levels when objectively measured before and after TKA were insignificant [241, 252-254, 451], with the exception of self-reported activity level studies [449]. As such, our results and others suggest that pre-operative PA levels are one of the biggest indicators of post-operative PA levels. Brandes et al [254] hypothesised that self-reported PA levels seemed to be more accurate if it was painful, that is, while walking with a degenerated knee, compared to after surgery when pain was reduced.

Although mobilization of a patient within 24 hours is associated with a reduced length of stay (LOS) [443]; actual reports of PA levels or inter-patient variance in the days 2-4 post-operative period are limited. This study is the first to report daily step counts less than 1 month after TKA surgery using commercially available wristband pedometers. At 2 months post-operative Brandes et al [254] measured step count and Hayes et al [258] measured energy expenditure. At 3 months post-operative Walker et al [241] measured step count, Hayes et al [258] measured energy expenditure and deGroot et al [252] measured percentage of time active. Krenk et al. [452] have reported on activity levels using Actigraph

accelerometry devices during hospitalisation following TKA and Total Hip Arthroplasty, although this was in a fast track setting and hypothesis generating in nature. Although this early recovery period presents challenges of patient capability, the use of commercially available wristband pedometers are an easily accessible way to measure and potentially encourage PA levels.

This day 2-4 post-operative step count period was also noted to not be normally distributed. On visual inspection of Figure 2, a probability density plot of step count in each time period, the lack of normality is noted to be a tail effect associated with greater step counts which cannot be symmetrical due to the floor effect of less than 0 steps not being possible. With larger sample sizes, it is possible that a model of probability of patients to recover quickly and reach high step counts making up this tail early could be developed.

Our results provide means for different populations that might be used as baselines or expected 6 week step counts. Given the strong correlation (0.707) and lack of statistically significant difference between pre-operative and 6 week post-operative step count, a patient's own mean pre-operative step count seems an appropriate benchmark to aim to reach by 6 weeks post-operatively. While clinical implementation of such a reference rule requires the additional burden of measuring step count prior to the TKA operation, it offers a highly patient specific goal for patients to work towards recovering to.

Other clinical benchmarks that avoid the need for pre-operative measurement of step count are also presented here. We find that use of the SF-12 PCS score and division into 3 population groups by score gives a mean step count of 4,556 for the low scoring subgroup, 6,758 for the high scoring subgroup and 8,342 for the very high scoring subgroup. These divisions offer some utility as clinical benchmarks, as the inclusion of the SF-12 into a routine pre-operative score capture is common place and, while each subgroup's daily step counts vary significantly about the subgroup mean, the allocation of a goal to the healthiest

patient group that is 80% higher than the least healthy suggests significant personalisation of the patient goal is occurring.

Similarly, population means for normal weight, overweight and obese patients are found to be 8,022, 7,151 and 4,819 steps per day respectively. BMI is, again, routinely collected and these figures could be used as expected, patient specific benchmarks. Daily goal setting has been previously shown to reduce hospital LOS following TKA [453]. Future studies could investigate the impact of patient relevant step count goals to strive for at 6 weeks of recovery in increasing speed of recovery and potentially reducing the need for manipulations.

For the aim of building the model to predict baseline step counts at post-operative time points based on pre-operative data, the regression coefficients acquired through stepwise regression showed interesting results. Gender, the pre-operative step count and the SF-12 PCS were the significant predictors of step count 6 weeks post-operatively, together explaining 75% of the variation in step count. For the days 2-4 post-operative period, the result was less clear as only 18% of the variation in step count could be accounted for when using the same predictors of step count as for the 6 weeks post-operatively. This suggests there are other factors impacting on a patient's step count in the days 2-4 post-operative period. These may be factors such as intra-operative events, ligament released and anaesthetic response of the patient. It is also feasible that variable pain management practice received in the days 2-4 post-operative period and the patient's self-efficacy and determination for recovery may also influence step count in this period.

BMI was not incorporated into the regression models despite significant correlations consistent with existing literature [454]. This suggests that one of its significant cross correlators such as the SF-12 PCS captures the impact a high patient BMI has on the patient's step count achieved [441]. Figure 7 (a) and (b) provide the findings of the

regression in a reference chart format whereby, as an alternative to calculating an expected 6 week step count for a patient, their expected attainment of one of 3 zones (groups corresponding to a high step count of greater than 7,000 steps, a medium step count of 5,000-7,000 steps and a low step count of less than 5,000 steps, each approximately 1/3 of the population). This could be used clinically to apply the multivariate model without the need for impractical calculations by visual reference of the pre-operative step count and SF-12 score against the appropriate gender chart to determine which band of patient performance is expected.

PA levels and hospital LOS were not significantly correlated in this study. Previous studies have found that self-reported questionnaire items of mobility are predictive of discharge destination and extended inpatient rehabilitation [258]. A more recent report determined an absence of fully generalizable effective clinical tools for predicting LOS and that two of the top three predictive characteristics were provider rather than patient based [210, 213]. Further studies in a fast track arthroplasty setting with discrete check list based discharge criteria, such as that conducted by Krenk et al. [452] could investigate this relationship.

Limitations of this study include missing data so, where possible, pairwise retention of data records in individual analyses were used rather than case wise deletion. Missing data may cause bias in the results obtained, but case wise deletion may amplify the biases generated if the data is missing not-at-random. As all subgroups created from pairwise matching of step counts between periods had no statistically significant differences in demographic profiles with regards to BMI, gender and age or step count level, we conclude that the reported findings are representative of the entire study sample. Imputation was a potential solution to this problem, but with the percentage of variance explained in the regression model as a key observation the potential for imputation to bias the regression model was a concern. The Fitbit Flex devices were validated for step counting in normal populations but this may not extend to the immediate post-operative period where patients move at a lower

level [249]. Additionally, step count is but one of several potential measures of physical activity, different measures of which have been shown to respond in different ways following TKA [449]. Step count, however, offers the advantages of being strongly related with other objective measures of activity, [234, 250] while also being a patient interpretable metric and hence providing an opportunity for clinically relevant patient goal setting [238].

9.6: Conclusion

Significant correlations exist between all pre-operative, days 2-4 post-operative and 6 week post-operative step count, BMI and SF-12 PCS score for patients undergoing TKA. Obese patients reach a mean of 4,819 steps compared to 7,151 for overweight patients and 8,022 steps for normal weight patients. Similarly, segmentation by SF-12 PCS score produced expected step counts of 4,556, 6,758 and 8,342. Pre-operative step count of the individual patient or the mean of the BMI or SF-12 group they fall into could be used as expected benchmarks for monitoring of patient recovery. A backwards stepwise regression is also presented for more sophisticated personalisation of patient benchmarks, with an R^2 of 0.754 for predicting 6 week step count. The days 2-4 post-operative period, by comparison, had a lower R^2 of 0.179 with the same regressors, indicating that intra-operative, immediate post-operative or pre-operative factors other than those we measured are the primary driver of variation in activity level in early recovery following TKA.

Chapter 10

Clinical and Statistical Validation for a Probabilistic Prediction Tool of TKA Outcome

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Similar to Chapter 9, this paper dealt with non-surgical avenues for patient outcome optimisation, this one focusing on selection for surgery. An outcome prediction model, developed as a Bayesian Belief Network, is presented and validated. Validation takes two forms. The first is a clinical validation that determines the tool is impactful when implemented into a surgeon's rooms, materially changing the nature of the patients they book for surgery and those they don't. The second is statistical validation of the predictions, including a particular focus on those not predicted to achieve at least a Minimum Clinically Important Difference (MCID) improvement in their KOOS score. The tool has seen commercial implementation and has been used in the consultation of over 1000 patients prior to consideration for a TKA.

10.1: Abstract

Background: Despite generally excellent patient outcomes for Total Knee Arthroplasty (TKA), there remains a contingent of patients, up to 20%, who are not satisfied with the outcome of their procedure. Models to predict outcome do exist but have not seen implementation into a functional tool. This study aims to evaluate and validate a model developed for use in a clinical tool for its predictive accuracy and clinical utility.

Methods: A Bayesian Belief Network (BBN) is developed using data from the Osteoarthritis Initiative, a National Institute of Health funded observational study. The model, following internal validation, is implemented into a clinical tool to be used by surgeons when consulting patients. A consecutive case series cohort is used to evaluate the clinical impact of the tool and a retrospective review evaluates the accuracy of its outcome predictions.

Results: Prior to the introduction of the tool, the population of patients booked for TKA surgery did not have a statistically significantly different pain score ($p=0.18$); afterwards they did ($p<0.001$), indicating the tool had changed the surgeons habits in booking patients for surgery. Of 164 operated knees retrospectively reviewed, 22 were predicted to be at risk of not having an improvement greater than the Minimum Clinically Important Difference (13%) and 8 did not in reality (5%). In total, there was a 27.2% chance of not improving if predicted not to and a 1.5% chance if predicted to improve. This resulted in a risk ratio of patients 18.8 times ($p < 0.001$) as likely to not improve if predicted not to improve by the tool.

Conclusions: In order to be useful clinically, a prediction tool has to provide outputs and be usable in a way that fits with clinical consultation workflows. The model presented here has validation comparable to its contemporaries and when implemented into a clinical tool, can be shown to meaningfully change surgical practice. Further research should focus on models built to enable clinical implementation if they are to have any impact on the dissatisfaction rates of total knee arthroplasty.

10.2: Introduction

Total knee replacement (TKR) is still the mainstay therapy for advanced osteoarthritis of the knee [7]. In spite of the advances in materials and delivery techniques over the past 20 years [44, 53, 62], patient dissatisfaction and poor outcomes remain up to 20% [69, 70].

Previous studies have shown a variety of factors are linked to poor postoperative outcome. These factors are a part of a few major groups. The first group, lifestyle and comorbidities, includes factors such as back pain and other aching joints [113, 118, 274], pre-existing pain and functional state of the knee [287], ASA grade [110], whether the patient lives alone [70] and their socioeconomic status [112]. The second group covers psychology of the patient and includes depression and anxiety [112, 126, 208], the pain catastrophising personality type [138] and self-efficacy of the patient [130]. Of these factors, it has been reported that the impact of non-surgical factors tends to dominate the surgically linked factors [110].

Currently, patient selection for surgery relies on a number of factors. First and foremost are the diagnostic criteria being met, but these diagnostic criteria are often ill defined and have cross dependent. For example, the work of Escobar et al. [27] has previously described a set of criterion developed from a modified Delphi panel judgement with a group of 12 surgeons and included age, previous surgery, pain localization within the knee, mobility, symptom occurrence and radiological criteria. The tool 26.8% of the scenarios evaluated appropriate and was reflective of earlier work by Naylor et al. [28]. The decision tree that develops is complex. For example, in the case of an Ahlback radiological score [31] between 1 and 3 with slight to moderate pain or symptomology, surgery is deemed not appropriate. However, if the pain and symptomology is severe, age is greater than 55 and mobility is limited, then radiological grades 2 and 3 are deemed appropriate for surgery, while if age is greater than 65 then grade 1 is appropriate. Such algorithms are hard to follow and it is therefore no surprise that a recent study by Riddle et al. found when using these definitions, almost 1/3

of patients receiving a TKA drawn from a longitudinal database of osteoarthritis sufferers were not appropriate candidates[29]. Alternative methods of selecting patients for surgery such as use of fixed Patient Reported Outcome Measure (PROMs) score cutoffs[455] have also been shown to be flawed[108].

One promising improvement on previous attempts to select patients for surgery is the use of predictive models. With a prediction of outcome as a driver in decision making, more informed choices can be made. An example of such a model is that developed by Lungu et al. in their 2014 study [263]. The study used data from 141 patients to develop a categorization tree model using recursive partitioning, a statistical process for developing a set of hierarchical tree rules to arrive at a categorical prediction for a patient. Significantly, the model sought to predict inclusion in the lowest WOMAC quartile (not satisfaction) and the result that followed is reflective of this, with the final model being dictated primarily by WOMAC preoperative attributes. This is consistent with earlier evidence that preoperative PROMs score state has the strongest influence on post-operative PROMs state than any other predictor [112].

Sanchez-Santos et al.'s study [265] goes further by externally validating a model for predicting 12 month Oxford Knee Score. This study recruited higher patient numbers (1,649) but achieved an R squared value of 0.176 under internal validation and 0.211 with external validation. One explanation for the relatively low performance of this model could be the target, as prediction of an absolute PROMs score is known to be difficult. An alternate design is to focus on satisfaction which may be better as the binary target (probability yes/no) is potentially less challenging to interpret than predicted PROMs scores [74]. The study by Onsem et al. [264] develops such a prediction model. The model developed has an adjusted R squared of 0.290, suggesting a decent portion but less than 1/3 of the variation in outcome has been explained. The results are then binarised to derive a sensitivity of 97% and a specificity of 50%, suggesting a model that rarely fails to pick patients that are at risk

but can only highlight 'potential' problem patients. This may be an ideal approach as aggressively highlighting potential problem patients at the cost of false warnings allows scope for clinical judgement to act. However, the nature of regression means the coefficients of predictors themselves are not interpretable, limiting the information that can be supplied for that clinical judgement.

A decision support system is one a tool that could combine a prediction of outcome with further useful information in making the decision [275]. Bayesian Belief Networks are one means to develop a decision support system. There has been some application of BBN structures in the field of rheumatology, though so far real clinical applications have been absent [276, 277]. Other medical fields that have seen implementation of successful BBN models into a clinical context include echocardiography [278], preclampsia [279] and colon cancer prognostics [280]. An additional potential benefit is the ability to perform expectation management. It has been shown that expectations are modifiable, and this presents a mechanism to positively influence the satisfaction outcome of a TKA surgery. Expectations have been previously shown to be alterable with patient education classes or other information dispersion mechanisms. Some of these studies have used personalized/patient specific reports to achieve this [156-159]. Use of clearly linked and interpretable risk factors to drive a prediction of outcome could enable a tool for shared decision making [267, 268], and this may be a mechanism for improving patient satisfaction with the surgical process.

There is a clear need for prediction models and tools that inform both the surgeon and patient of the risks and benefits of TKA, when considering that patient's own risk factors. There is still a lack of a predictive model that can perform an assessment with non-expert input, is relatively fast to complete, delivers fast and scalable results and is clinically implementable. It should take into account all of the parameters that can influence the

outcome after TKR be straightforward and interpretable in the information it delivers, both for the patient and the surgeon.

The purpose of this study is to develop and validate a Bayesian Belief Network implemented in just such a clinical tool. Validation must cover two aspects: the statistical accuracy of the developed tool as a predictor of outcome, and its impact on the surgeon's practice on implementation. We hypothesized that the surgeon will not change his practice immediately after implementation of the tool and that the tool can predict the outcome of surgery.

10.3: Methods

A Bayesian Belief Network was developed for this study. The data used to develop this model is a publicly accessible database created and maintained by the National Institute of Health Osteoarthritis Initiative (OAI). The OAI dataset consists of clinical evaluation data (medical history, physical exam, joint-specific observations), imaging (x-ray; magnetic resonance, MR), and a biospecimen repository (biochemical and genetic) from 4,796 volunteers aged 45-79 over the course of 108 months. A subset of 330 patients who underwent a TKR replacement were extracted.

A total of 110 potential preoperative variables were identified from the following categories: preoperative knee pain, preoperative functional impairment (both with the Knee Osteoarthritis & Injury Outcome Score (KOOS)), use of pain medication, historical surgeries, recent falls, other musculoskeletal pain, smoking and drinking habits, weight, blood pressure and pulse measurements, patellar grind & crepitus, knee alignment, marital status, demographics, employment status and support network for the patient. Continuous data was treated with decision tree driven discretization with a k-means algorithm. The patient's knee pain score at least 6 months after the operation was included as the target variable.

Variable selection and model generation was performed with the use of a Tree Augmented Naive Bayes Network in BayesiaLab (Bayesia S.A.S, France) attempting to predict the postoperative pain. Variables were then removed if a statistically significant relationship could not be shown with postoperative pain. The variables that survived this elimination process are KOOS Activities of Daily Living score, KOOS Pain score, KOOS Symptoms score, pain when pivoting on their knee, pain when standing, pain when bending the knee, difficulty standing, difficulty bending the knee fully, frequency of back pain, severity of back pain, occurrence of hip pain and occurrence of falls in the preceding year, in addition to age

and gender. From these, a model was defined that had an R squared of 0.23, comparable to previous efforts [265] and with statistically similar results under 10-fold cross validation.

Figure 1 shows an example of the probabilistic dependencies that underpin the model. A cut off KOOS pain score of 70 separates the postoperative outcomes into two groups, the lower portion of which represents 19% of the population, analogous to the reported dissatisfaction in the literature. However, when separating by back pain, it is found that only 7% of the no back pain group fall into the postoperative pain group, while 43% of the extreme back pain group do, and this difference is statistically significant ($p < 0.001$).

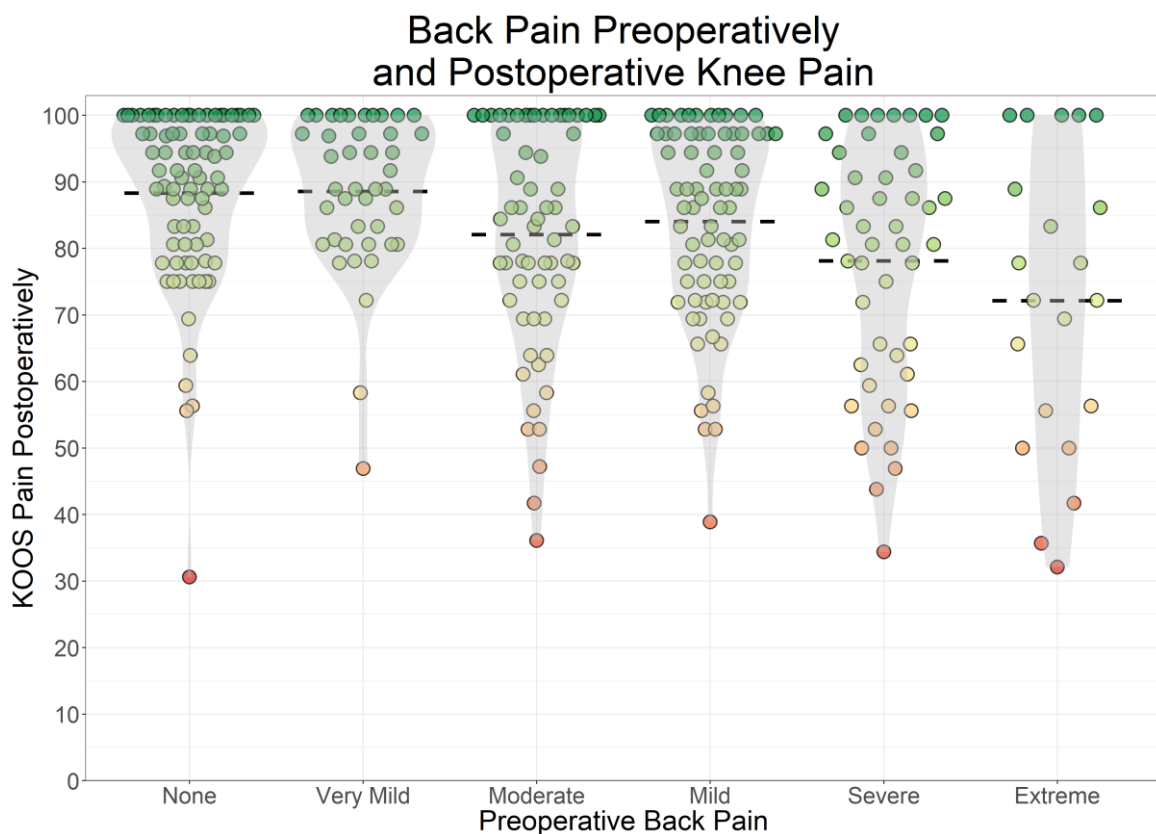


Figure 1: Dependence of postoperative knee outcomes on preoperative back pain (dotted line indicating group means). The spread of data for all 330 patients is shown with both the datapoints and the violin plot, separated by their preoperative back pain. There is a strong trend towards more severe back pain leading to worse preoperative outcomes, and this dependency is captured in the predictive model.

Clinical implementation of the tool was through a workflow as described in Figure 2. A questionnaire was developed capturing all of the relevant information, based on the KOOS score with 6 additional questions. Patients fill in the questionnaire using a web application,

and the data is electronically transferred to a server. A calculation of the predicted post-operative score is performed and the results are available in a web portal interface for the surgeon to use during the consultation, an example of which is shown in Figure 3. The prediction is converted to a representative percentile scale of results describing the range of pain of a population of patients seeing an orthopaedic surgeon for osteoarthritis. The preoperative KOOS Pain score is also displayed on the same scale, allowing the change from preoperative to postoperative to be reviewed.

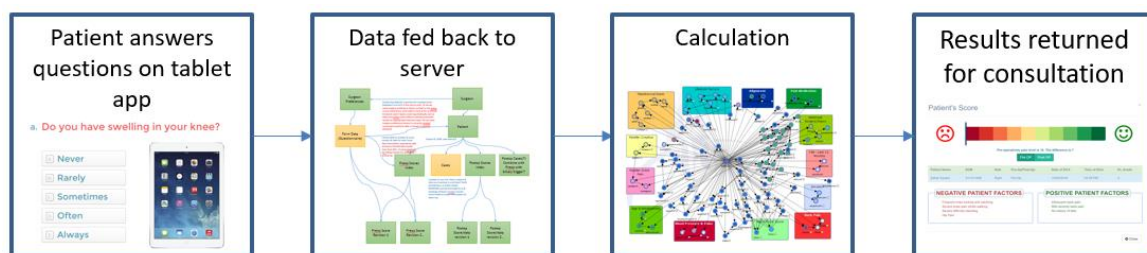


Figure 2: Flow chart of the tools use. A questionnaire is taken by the patient in a digital application, either at the consultation or prior to via email. Calculation of the predicted score and risk factors is performed server side, and the score can be accessed by the surgeon through their own web portal for assessment before or during the consultation with the patient.

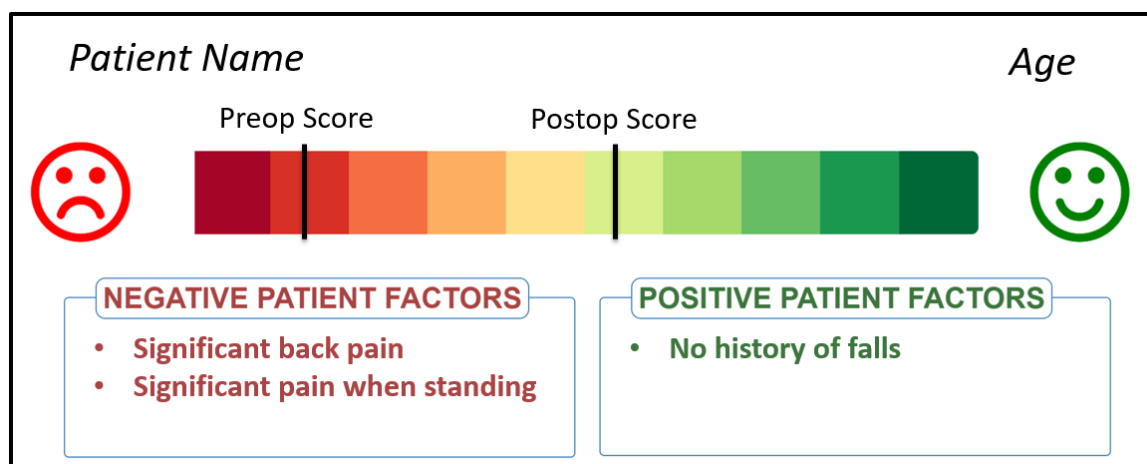


Figure 3: Interface created for use in the patient consultation. 3 elements on the interface are defined, a preoperative reference state, a postoperative prediction and a set of boxes calling out positive and negative prediction points. The live version incorporates a toggle switch to jump between preoperative position and postoperative prediction.

Two external validations were performed the first was a prospective consecutive case series of 150 presenting to one surgeon in one centre at his consultation rooms. Inclusion criteria were patients over 55 years of age with knee pain and without history of meniscal or

ligamentous injury. The data was collected over a three month period between November 2015 and January 2016. All of the data was collected digitally [456]. The first cohort of 75 patients were blinded to the tool and were booked for TKA as per normal practice. The second cohort of 75 patients were exposed to the tool and then consulted and booked for TKA surgery. A research assistant collected the data on bookings for surgery in both cohorts. End point for this experiment was the difference in preoperative pain of patients booked for surgery and those not booked before and after introduction of the tool. A two week period in which the tool was used but no data recorded separated the two series to allow the surgeon to acclimatise to use of the tool.

The second validation performed was a validation of the predictions supplied by the model. All available patients in the 360 Knee Systems database who had been consulted with the prediction tool since February 2016, gone on to have surgery and answered a postoperative KOOS questionnaire were included. Two predictions were of interest: the absolute change in pain score expected and achieved following surgery (analysed as a correlation), and the binary prediction of a change in the Minimum Clinically Important Difference (MCID), assumed to be 10 points for the KOOS score[8, 83]. This was matched to a predicted change of less than one 'colour box' in the visual display, representing 10 points on the 100 point percentile scale. This binary target was chosen as the validation target because it describes attainment of significant improvement rather than a minimum score being reached, as initial scores are known to affect the final score that would lead to patient satisfaction[108].

Statistical significance was set to $p = 0.05$ and Chi squared tests were used for categorical variables, T-Tests used for continuous variables. All analyses were performed using R v3.4.2 [315].

10.4: Results

For the first investigation, the consecutive case series of the clinical application of the tool, a number of findings were made. The demographics and the difference in pain scores preoperatively between the two groups was investigated and are shown in Table 1, indicating substantial equivalency between the two groups.

Table 1: Demographics and characteristics of both groups included in the consecutive case series. No significant differences were found.

	Standard Surgeon's Practice (n=75)	Use of Tool (n=75)	P-value
Mean Age	65.7 (± 13.4)	65.0 (± 11.9)	0.75
Gender = Male	35 (47%)	40 (53%)	0.37
Preoperative Pain Score	52.7 (± 20.1)	50.3 (± 18.3)	0.45

The use of the tool did not appear to change the numbers of patients booked. Without the use of the tool, 20 patients (26.7%) were booked for surgery. With the use of the tool, 24 patients (32%) were booked for surgery. Statistical significance under Chi square testing was not observed ($p = 0.44$). However, a change in pain threshold for booking for surgery after starting the use of the tool was observed. Prior to use of the tool, there was a difference of 6.5 points in the KOOS pain scores of those patients booked for surgery vs. those patients not booked and this difference could not be shown to be statistically significant ($p=0.18$). This indicates a decision making process not dominated by the patients presenting pain state. After introduction of the tool the difference was 15.2 points and this difference was statistically significant Figure 4 shows these results graphically and Table 2 summarizes the findings.

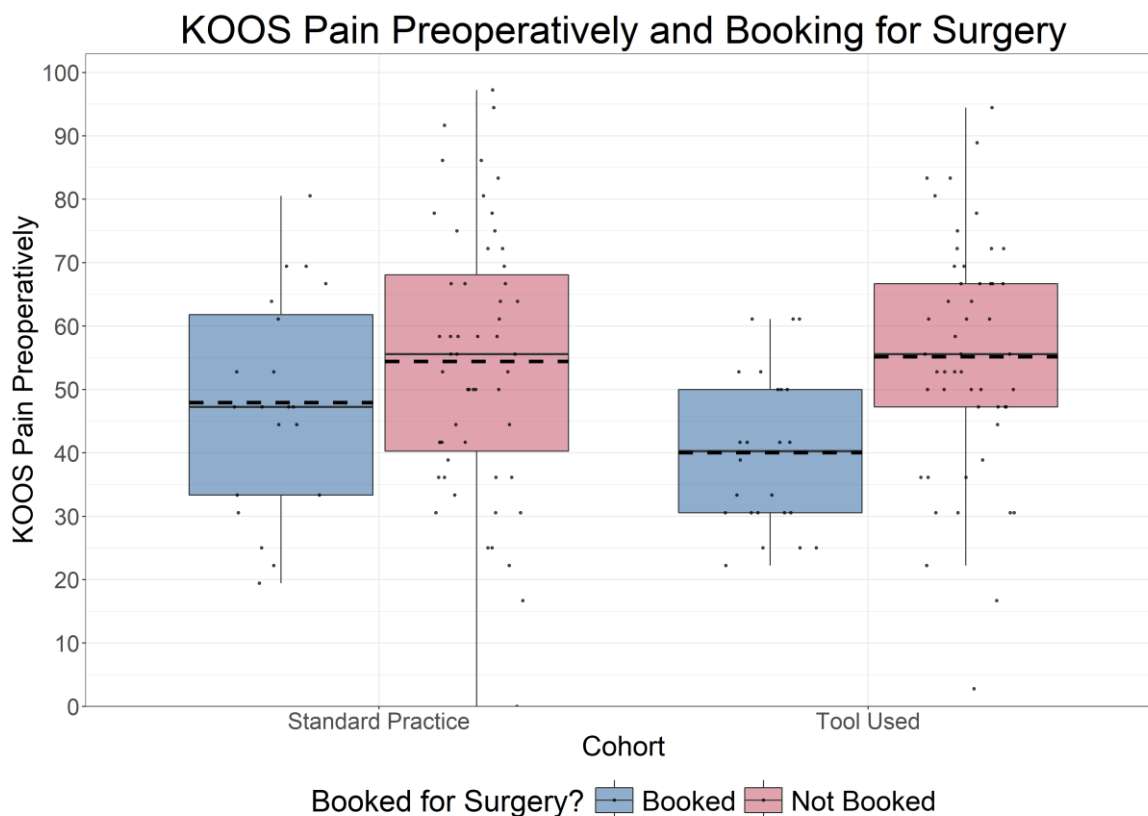


Figure 4: Boxplot of patients preoperative KOOS scores, with dashed lines representing mean scores. The distribution is undifferentiated prior to use of the tool, but introduction of the tool drives a clear separation of the pain scores

	Booked for Surgery KOOS Pain	Not Booked KOOS Pain	P-value
Standard Surgeon's Practice (n=75)	47.9 (+/- 17.1)	54.4 (+/- 21)	0.18
Use of Tool (n=75)	40.0 (+/- 12.3)	55.2 (+/- 18.8)	<0.0001

Table 2: Table of patients preoperative KOOS scores. The difference following introduction of the tool are significant; prior to the tool, the booked cohort is statistically indistinguishable from the not booked cohort

The second investigation looked at the predictive accuracy of the model rather than the clinical impact of the tool with which it was used. A total of 164 patients were included in this validation, with 101 females (61%) and a mean age of 68.5 +/- 7.5 years. The first arm of this was the correlation of the predicted changes with the actual changes. The correlation was found to be 0.53 giving an R squared of 0.29. The dot plot of all 164 patients and the

correlation line is shown in Figure 5.

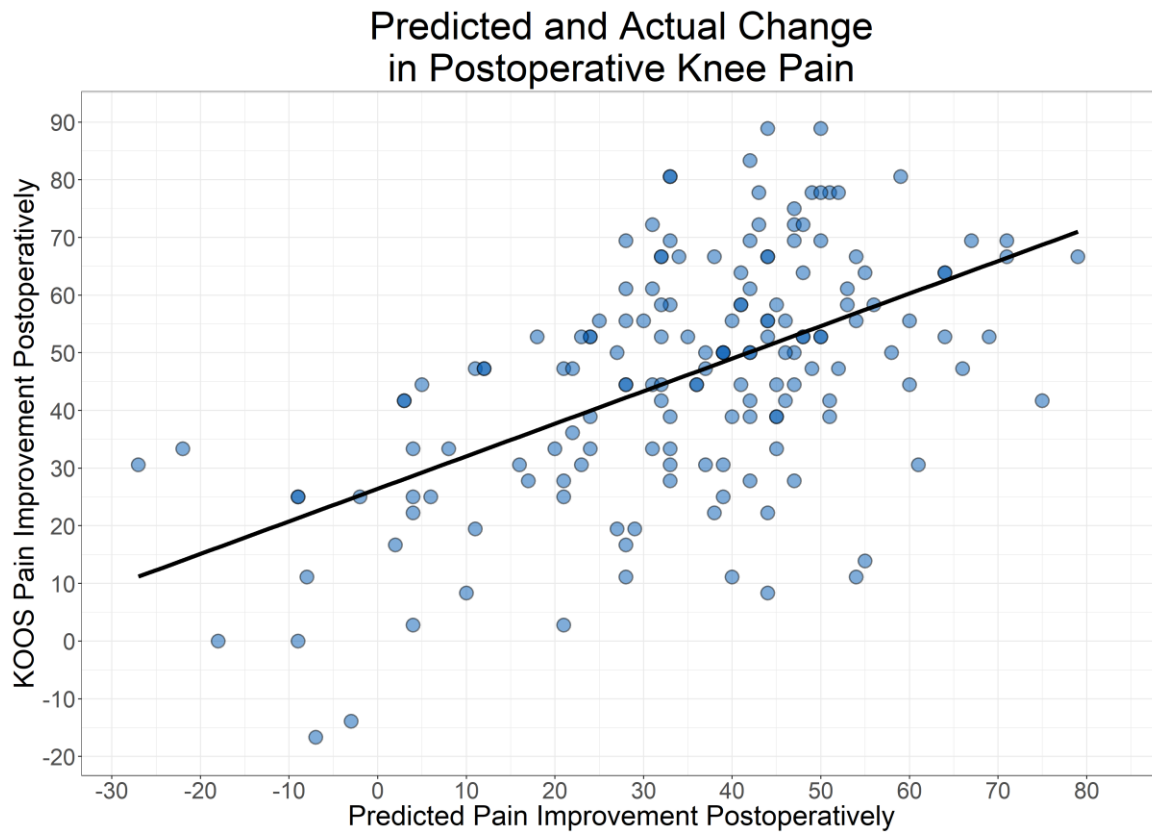


Figure 5: Correlation between the predicted improvement in the patient's pain state and the actual improvement was moderately strong

The second objective of this arm of the study was to investigate the efficacy of the model as a binary predictor of a risk factor for a negative outcome. Within the study, 22 (13%) of patients were not predicted to improve over the MCID preoperatively and these patients not predicted to improve had a significantly lower actual improvement of 21 points compared to 50 points for the rest of the group ($p < 0.001$). When predicted to be at risk, patients were 27% likely to not improve vs. 1.5%, creating a risk ratio of 18 ($p < 0.001$). Figure 6 shows the distribution of improvements for those patients not predicted to improve over the MCID against those who were.

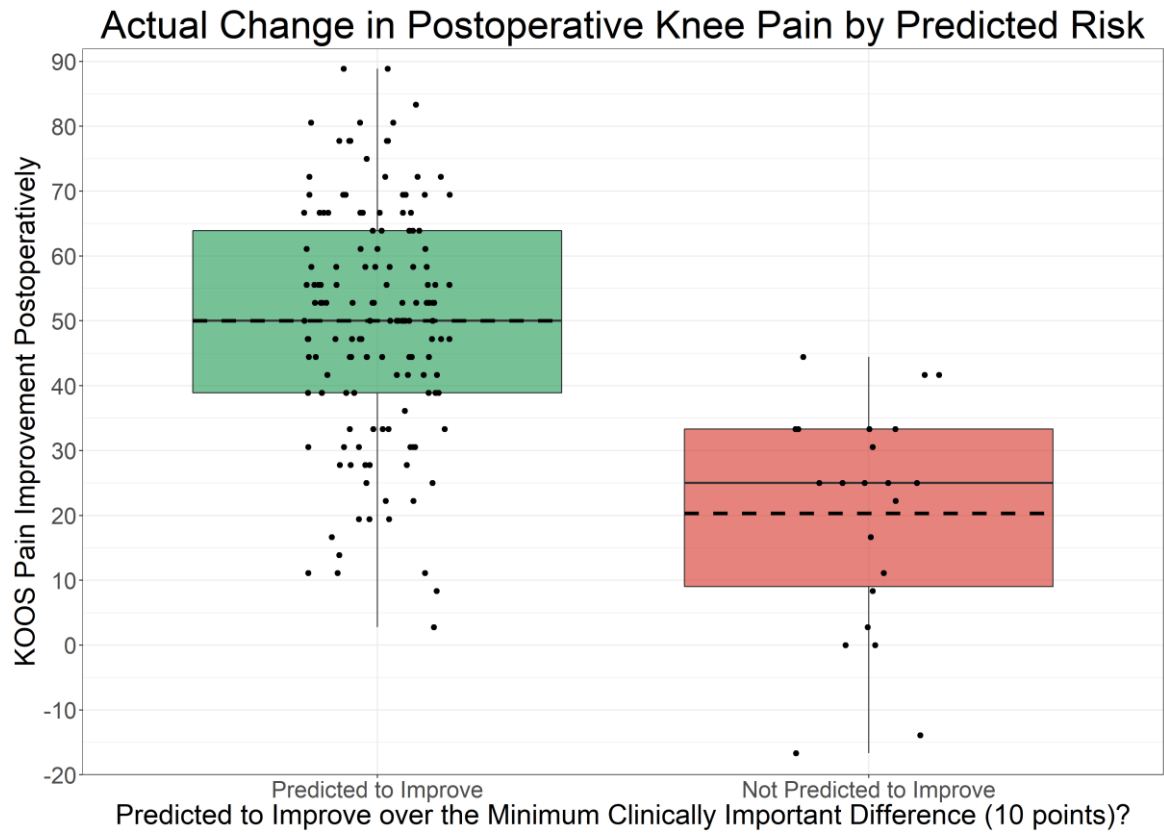


Figure 6: Boxplot of actual improvement in KOOS pain score by prediction to improve or not. The group not predicted to improve had substantially lower actual improvement and an 18x risk of not meeting the minimum clinically important difference for improvement.

10.5: Discussion

There is clearly a pressing need for clinical tools to aid in selection of patients for surgery. Historical focus on surgical accuracy and decision making as the primary driver of outcomes has not solved the dissatisfaction of patients. Use of fixed cutoffs for in selecting for surgery such as PROMs scores [455] and radiology [105] are incomplete solutions, highlighting risk factors but not effectively guiding surgical decision making, whereas more complicated algorithmic approaches developed to represent standard surgeon intuitive practice [457] do not actually appear to do so [29].

While there has been some work on development of prediction tools for outcome following TKA, clinical implementation has been lacking. This study demonstrates both validation of the predictions being made by the developed model in addition to validation of the clinical utility of the tool the model has been embedded in. This study does this by demonstrating change in the characteristic preoperative KOOS pain scores of patients booked for surgery prior to and after introduction of the tool. This study also demonstrates a moderately strong correlation between predicted and actual improvements in KOOS score.

A number of prior models have been described. Of these, the only previous one to validate its predictive capability is that presented by Sanchez-Santos et al. [265]. This model achieved an R-squared of 0.21 under external validation, somewhat lower than that achieved with this model. The models themselves, however, have been deployed to predict different things, with this one focusing on a relative change from pre to postop and not the absolute PROMs score. There are also significant differences in the predictors used in each model, as this model has its strongest relationship in back pain, a factor not present in the dataset used by Sanchez-Santos et al., while having anatomical measurements such as fixed flexion deformity and the preoperative state of the ACL. Both models heavily used the

baseline PROMs scores (KOOS and the Oxford Knee Score (OKS) respectively) in their predictions.

Two other studies have developed and internally validated prediction models. Onsem et al.'s [264] model has an R squared of 0.290, a similar portion to that achieved with this model's external validation. It shares other attributes, in that its high sensitivity but low specificity suggest a model that rarely misses potentially problematic patients but does not pick them with certainty. There remains a significant portion of the result unexplained, likely driven by factors such as the surgery itself or data not captured in the predictive models developed. It is perhaps unreasonable to think that preoperative profiling can explain a higher proportion of the variation as it is well known that postoperative dissatisfaction has a number of drivers [70].

Perhaps the model that goes furthest towards a clinically implementable process is that produced by Lungu et al. [263]. Here a categorization tree is developed, creating a relatively simple flow chart for the surgeon/reviewer of the patient's answers to follow. This model achieves a strong internal validation result with an Area Under the Curve of 0.77, but unfortunately this validation is only internal to the model. The previous two models have used forms of linear regression, a relatively constrained model fitting technique. The recursive partitioning used to develop categorization trees is, by comparison, a relatively sophisticated machine learning technique, and here it has been applied to a relatively small amount of data (141 patients total). While the paper does attempt to address this with bootstrapped resamples, the volume of data appears to be insufficient to allow for either testing/training or any k-fold independent to model training validation techniques. The paper recognizes the need for this and calls for external validation of the model to follow, in addition to impact analysis of its cost-benefit.

There are a number of different mechanisms to assess a patient centric outcome, including satisfaction, PROMs score, attainment of a specific PROMs score such as a Patient Acceptable Symptom State or PASS score [96] and attainment of a certain level of improvement such as a Minimum Clinically Important Difference or MCID [97]. This study assessed its ability to predict MCID as a metric for success.

There are a couple of reasons for this. The first decision is whether to target satisfaction or a PROMs score. Satisfaction is complex and there is increasing understanding of the pivotal role of unmet expectations in determining patient satisfaction [148] and the “expectation gap” [146]. One major advantage of the clinical implementation of this tool is its potential utility as a modulator of expectations and, as a result, driver of overall satisfaction. This objective of the study means a proper validation with satisfaction would not be possible as the tool could be heavily influencing the very factor it seeks to predict. Future work will investigate if use of the tool can be shown to improve satisfaction rates with surgery.

The second decision was to target a continuous level of improvement rather than an absolute PASS score. Prediction of an absolute PROMS score is not trivial, and previous evidence has suggested that the ‘journey’ rather than the ‘destination’ may be more relevant to patient satisfaction [84]. In this context, the model signalling a failure to meet the MCID drove a statistically significant 18x risk ratio for actually failing to do so.

One major advantage of Bayesian Belief Networks is the interpretable nature of their coefficients (primarily simple probabilistic relationships), which stands in contrast to the hidden interactions amongst the regressors in a linear regression approach. An example of this is shown in the probabilistic relationship with back pain in Figure 1, a well known relationship in the literature [10, 118, 458]. The relationship depicted visually is implemented directly in the tool as a probabilistic relationship. This allows for the impact of

modification of a risk factor (through an alternative treatment) on the risk profile to be inspected and understood, enabling a clinical tool that goes beyond simple predictions.

There are, however, some limitations to the model presented. There are potential interaction effects of predictors which are not well captured. The dataset used for the model generation was longitudinal and not centered on the knee replacement, so timing of data collection pre and postoperatively to fuel the model was not consistent. In addition, the nature of the models predictive outputs are probabilistic; in order to present these on a scale that references preoperative position to postoperative, these have had to be converted to an expected result, losing some fidelity of the prediction.

The validation presented here does have limitations too. The R squared value reached of 0.29 is comparable and quite strong relative to what exists in the literature but fails to explain the majority of the variation in outcome. Furthermore, the model was created using American data from the Osteoarthritis Initiative and applied on Australian population. This suggests some generalisability to western populations, but there are potential inconsistencies as a study by Lingard et al. has shown different patient expectations and satisfaction rates between these two countries [107].

Data availability is inherently limited; the data used in this model and all the described models have significant areas where they do not overlap and potential predictors are missing from every data set. In addition to testing the ability of the experimental tool to positively influence satisfaction, future work should focus on clinical integration and a means of harnessing existing expert knowledge and literature into an evolving predictive tool of patient outcomes.

10.6: Conclusion

In order to be useful clinically, a prediction tool has to provide outputs and be usable in a way that fits with clinical consultation workflows. Indications for TKA are complex, and restricting access to surgery based on prediction of outcome alone is not reasonable given the limitations of prediction tools and the real, pressing need for pain relief patients have. Instead, clinical tools should aim to communicate their information to both patients and surgeons, highlight potentially modifiable risk factors and enable a shared decision making process. The model presented here has validation comparable to its contemporaries and when implemented into a clinical tool, can be shown to meaningfully change surgical practice. Further research should focus on models built to enable clinical implementation if they are to have any impact on the dissatisfaction rates of total knee arthroplasty.

Chapter 11

Conclusions

Total Knee Arthroplasty has been an enormously successful operation and has over the course of some decades refined itself. For the first generation of arthroplasty surgeons, the field was in many ways an art, with each surgeon drawing on their experience and observations to improve their surgical practice. For the generation that followed, practice became more structured; rules and references were created to dictate surgical practice, and accuracy to these standardised rules was the benchmark for good practice. In parallel, implant design was refined and converged on the designs we see in use today, with materials science creating better and tougher implants that lasted longer and longer. In this way, survivorship was bolstered, and the practice improved, and the thresholds at which TKA was a reasonable solution crept lower and lower.

These days, younger and more active patients are receiving knee replacements than ever before, and this has exposed another challenge for TKA to overcome; the 20% of patients who walk away from a very expensive operation dissatisfied with their outcome. It is tempting from a commercial perspective to say that by continuing as we have so far, developing ways to put knees in tighter and more accurately to our existing rules, we will be able to overcome this challenge. The truth is that this is part of the solution, though not covered in detail in this thesis. The secret to a satisfied patient, at the highest level, appears to be putting the right implant in the right way in the right patient, and managing the patient through that process as best as possible. Neglecting any of these factors will only ever lead to a partial solution.

The first aim of this thesis was to investigate if a more nuanced, patient specific approach to surgical planning than the current parading of rigidly applied alignment philosophies. This was achieved through a sequence of steps. Chapter 3 investigated the spread of patient alignment throughout the population, partially a confirmation that there was an opportunity for refinement here due to the wide spread in patient anatomical measures, and partially a test of my ability to develop a database using the outputs from a

conventional surgical planning process. Both of these were a success. Over 2000 patients measurements were assessed and the spread of data referenced to surgeons expectations. It was very quickly found that the variation within the population dwarfed surgeon's expectations, and there was a real risk of surgical planning being misguided. Chapter 4 investigated this further, with the finding that a commonly used rule and more sophisticated derivatives of it simply could not be trusted to achieve an acceptable result in over 1/4 of patients. Given this, there was real scope to adapt planning to take into account the patient specific anatomy being worked with. Prior to doing this, work needed to be done to allow outcomes to be directly studied in relation to this more sophisticated planning paradigm. Chapter 5 presents such a method, developed to allow superposition of the preoperative bone on the postoperative result and investigate how implantation has changed the nature of the patient's anatomy. With this technique in hand, the study presented in Chapter 6 could be undertaken, relating anatomical changes directly to the patient outcome. The results were promising, reaching statistical significance but not real clinical relevance, and it became clear that no silver bullet would overcome the 20% dissatisfaction rate.

Chapter 7 was the first exploration of a technique that came about as a result of a technology transfer. Rigid body dynamics simulations of the sort employed have been commonly used in automobile, aeronautical and heavy machinery simulation where deflection of components was of less importance and the complexity of a Finite Element Analysis approach unnecessary and impractical. The practicality enabled by rapidly solving rigid body dynamics models translates well to the clinical setting, allowing for preoperative per patient simulation to be performed. It was shown in chapter 7 that this approach well distinguished between different alignment philosophies but also incorporated a patient specific element. Chapter 8 combined the technique of recreating a postoperative implantation described in chapter 5 with the simulation tool defined in chapter 7 to show that measurable kinematics from the simulation related to outcomes, and did so more

strongly than the relationships with alignment found in chapter 6. This work and a number of similar studies have fuelled the development of the Dynamic Knee Score, an algorithm that characterises the risk factors for the output kinematics of a given alignment in a given patient with a given implant. This has been deployed with a surgical planning process that plans multiple alignments per patient; these are then comparatively scored and the best result recommended to the surgeon. This tool has been used in some form in over 2000 TKAs planned with 360 Knee Systems to date.

The second aim of this thesis was to investigate how patients can be better managed outside of surgery, either through pre-surgical preparation or post-surgical management, or selecting patients for surgery more likely to have a good outcome. Two major studies have been performed in this area. The first, presented in chapter 9, looks at the postoperative step count of patients as predicted from their preoperative step count and lifestyle factors. Patient mobility is highly patient specific and giving patients a generic goal to achieve in the postoperative period is insensible. Even so, having a specific goal to return a patient to allows for two benefits. The first is that individualised goals supplied to patients on a daily basis give a constant stream of communication which, even in an automated fashion, leaves the patient more connected to the healthcare system dealing with them. The second is that aberrations from the expected goal for that patient can be detected, and issues like falls or early swelling/possible infection can be detected in a semi 'automated' way. Subsequent studies have indicated that the provision of daily goals increased activity levels shown an increase in the proportion of patients satisfied by the surgery (though not significant, the study was not powered to find this and arrived at a p value of 0.08 [459]). This prediction has gone on to be implemented in 360 Knee Systems patient management platform and been used with over 300 managed patient rehabilitation plans.

Chapter 10 addressed this aim in a different way, by reporting on the development of and implementation of a tool designed to predict patient improvements in pain state as a result

of surgery. The tool itself is a Bayesian Belief Network implemented in a web portal that takes patient answers from an Ipad application in the surgeon's waiting rooms and uses them to render a prediction in the portal for the surgeon to use. Two forms of validation are presented, showing that the tool is impactful when implemented into a surgeon's rooms, statistical valid in its predictions and sensitive to the portion of patients who weren't predicted to achieve at least a Minimum Clinically Important Difference (MCID). This tool has a number of applications in the clinical setting. The first and most obvious use is selection for surgery, but this is not where most of the utility comes from as generally speaking, when a patient meets the diagnostic criteria for surgery, surgeons will not in good conscience turn the patient away. More utility is found in its use for expectation management - a patient who needs surgery but is predicted to have a reduced outcome will be counselled in that regard, removing unrealistic expectations associated with long term postoperative dissatisfaction.

There is still more work to be done, of course. Future work will need to look to how these different factors related to each other. Validation work for the Dynamic Knee Score is in progress, as is improvements to the underlying simulation and penalty score model. As data collection grows, opportunities for more sophisticated machine learning techniques to produce better models exist and will need to be worked on. On the flip side, there is also room for clinical and orthopaedic knowledge to be used in these tools. The orthopaedic community is one dedicated to improving its practice, and it would be foolish to assume solutions to every problem exist in the data I am able to collect. The unifying theme for all this work will remain finding patient specific solutions; standardised universal practice has already met 80/20 rule, and we are now dealing with the remaining 20% of dissatisfied patients.

In conclusion, several different tools have been developed over the course of this thesis, all working in concert to improve the outcomes of patients selected for surgery and all seeing

clinical deployment in order to do so. The 20% dissatisfaction in TKA is a multifactorial problem, all factors of which are interrelated, and the solution must therefore be multifactorial. My hope is that this thesis has gone some way towards resolving that problem.

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