



University of Kentucky  
UKnowledge

Theses and Dissertations--Rehabilitation  
Sciences

Rehabilitation Sciences

2011

## CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION TO THE KNEE: THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED ASSESSMENT, AND RESPONSE SHIFT

Jennifer Sebert Howard  
University of Kentucky, j.s.howard@uky.edu

[Right click to open a feedback form in a new tab to let us know how this document benefits you.](#)

### Recommended Citation

Howard, Jennifer Sebert, "CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION TO THE KNEE: THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED ASSESSMENT, AND RESPONSE SHIFT" (2011). *Theses and Dissertations--Rehabilitation Sciences*. 1.

[https://uknowledge.uky.edu/rehabsci\\_etds/1](https://uknowledge.uky.edu/rehabsci_etds/1)

This Doctoral Dissertation is brought to you for free and open access by the Rehabilitation Sciences at UKnowledge. It has been accepted for inclusion in Theses and Dissertations--Rehabilitation Sciences by an authorized administrator of UKnowledge. For more information, please contact [UKnowledge@lsv.uky.edu](mailto:UKnowledge@lsv.uky.edu).

## STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained and attached hereto needed written permission statements(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine).

I hereby grant to The University of Kentucky and its agents the non-exclusive license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless a preapproved embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

## REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's dissertation including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Jennifer Sebert Howard, Student

Dr. Carl G. Mattacola, Major Professor

Dr. Patrick Kitzman, Director of Graduate Studies

ABSTRACT OF DISSERTATION

Jennifer Sebert Howard

The Graduate School  
University of Kentucky  
2011

CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS  
CHONDROCYTE IMPLANTATION TO THE KNEE:  
THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED  
ASSESSMENT, AND RESPONSE SHIFT

---

ABSTRACT OF DISSERTATION

---

A dissertation submitted in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy in Rehabilitation Sciences  
in the College of Health Sciences  
at the University of Kentucky

By

Jennifer Sebert Howard  
Lexington, Kentucky

Co-Directors: Dr. Carl G. Mattacola, Associate Professor of Athletic Training and  
Dr. Robert A. English, Associate Professor of Physical Therapy  
Lexington, Kentucky

2011

Copyright © Jennifer Sebert Howard 2011

## ABSTRACT OF DISSERTATION

### CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION TO THE KNEE: THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED ASSESSMENT, AND RESPONSE SHIFT

Autologous chondrocyte implantation (ACI) is a cell based therapy for the treatment of articular cartilage defects. Numerous studies have reported outcomes following ACI using a variety of patient reported outcomes (PROs), but no clear recommendations exist regarding which PRO is the most responsive to changes following ACI. Few studies have documented changes in performance based assessments (PBAs) following ACI. Response shift theory proposes that residual changes in self-report measures occur over time. Failing to account for response shift may result in over or under reporting of outcomes from which clinical decisions are made. The purposes of this dissertation were 1) review the literature concerning ACI outcomes to determine the responsiveness of PROs to changes in self-reported function following ACI, 2) evaluate the reliability of PBAs among ACI patients, 3) develop a descriptive timeline for the return of function 1 year following ACI using both PROs and PBAs, and 4) utilize PROs and PBAs to evaluate patients undergoing ACI for evidence of response shift.

All PRO and PBA measures were collected preoperatively and 3, 6, and 12 months postoperatively. A retrospective then-test PRO evaluation of function prior to surgery was completed at 6 and 12 months. Response shift was calculated by subtracting the original pre-test score from the then-test score.

A systematic review and meta-analyses of existing ACI outcome studies resulted in the recommendation of the International Knee Documentation Committee Subjective Knee Form (IKDC) and Lysholm Knee Scale as highly responsive PROs among ACI patients of varying activity levels. Despite significant increases in PRO scores as early as 6 months following ACI, improvement in PBAs at 12 months following ACI were limited to stride length, walking speed, and step-up force. Finally, no evidence of a group level effect for response shift was observed. These results support the validity of traditional pre-test/post-test research designs with no need to account for response shift when evaluating treatment effects of ACI on the group level. However, the Western Ontario

and McMasters University Osteoarthritis Index (WOMAC) did show evidence of a measurable response shift on a patient by patient basis.

**KEYWORDS:** Autologous Transplantation, Cartilage, Chondral Defect, Force Plate, Outcomes Assessment

Jennifer Sebert Howard

Student's Signature

April 19, 2011

Date

CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS  
CHONDROCYTE IMPLANTATION TO THE KNEE:  
THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED  
ASSESSMENT, AND RESPONSE SHIFT

By

Jennifer Sebert Howard

Carl G. Mattacola, Ph.D.

Co- Director of Dissertation

Robert A. English, Ph.D.

Co- Director of Dissertation

Patrick Kitzman, Ph.D.

Director of Graduate Studies

April 19, 2011

Date





DISSERTATION

Jennifer Sebert Howard

The Graduate School  
University of Kentucky  
2011

CLINICAL AND FUNCTIONAL ASSESSMENT FOLLOWING AUTOLOGOUS  
CHONDROCYTE IMPLANTATION TO THE KNEE:  
THE ROLE OF PATIENT REPORTED OUTCOMES, PERFORMANCE BASED  
ASSESSMENT, AND RESPONSE SHIFT

---

DISSERTATION

---

A dissertation submitted in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy in Rehabilitation Sciences in the College of Health  
Sciences  
at the University of Kentucky

By

Jennifer S. Howard

Lexington, Kentucky

Co-Directors: Dr. Carl G. Mattacola, Associate Professor of Athletic Training and  
Dr. Robert A. English, Associate Professor of Physical Therapy

Lexington, Kentucky

2011

Copyright © Jennifer Sebert Howard 2011

## DEDICATION

This dissertation is dedicated to my family and its many generations, beginning with Papa, my maternal grandfather and my Grandma Sebert, my paternal grandmother. Both of you left us during the time I was preparing this dissertation, yet the impacts you have had on your families and me are everlasting. One had to leave high school to work in the coal mines and the other received a college degree at a time when few men and even fewer women even considered higher education. Both were left with a tremendous belief in the power and importance of education and hard work. I am forever grateful for all the values they instilled in me. I only hope to be as successful at passing on these values to my own children, beginning with my soon to be born son Brayden who has also joined me on this doctoral journey.

To the rest of my family – both by blood and by friendship – thank you for continual support and love throughout my years of education. In my grandmother, parents, brother, aunts, uncles, cousins, in-laws, friends, and most of all, my husband Alex, I have found strength, courage, motivation, perspective, laughter, and humility. All of it contributed to making me who I am and the success of this journey, and for that I say Thank You.

## ACKNOWLEDGEMENTS

I would like to acknowledge funding support for this dissertation from the University of Kentucky Center for Clinical and Translational Science. Additionally, numerous individuals were instrumental to completion of the presented research. First, I would like to thank my advisor and committee chair Dr. Carl Mattacola. He has been a constant sounding board and motivator throughout my academic career at UK. If not for a phone call from him 5 years ago, telling me to get back to UK and do a PhD, I certainly would not be where I am today, nor would this research be at the level it is. I would also like to thank my other committee members Dr. Tony English, Dr. Thomas Kelly, Dr. David Mullineux, and Dr. Christian Lattermann. All have provided continual feedback and encouragement, while challenging me along the way. Also, Dr. Jen McKeon and Dr. Heather Bush provided consultation along the way, particularly for the meta-analysis portion of this dissertation.

Additionally, I would like to acknowledge Dr. Lattermann for the opportunity to work and conduct research as part of the Center for Cartilage Repair and Restoration. Without his help and the assistance of the UK Department of Orthopaedic Surgery and Sports Medicine staff, this research would not have been possible. I would also like to acknowledge the patients who served as participants in this study for their willingness to share their time and surgical experience.

Thank you to my parents for their constant support and encouragement in every endeavor I have ever undertaken. Finally, I give a huge thank you to my husband Alex. You took a leap with me in coming to Lexington, and I am forever grateful for all you

bring to my life and cannot wait to see what future adventures we will take together with our growing family.

## TABLE OF CONTENTS

ACKNOWLEDGEMENTS .....	iii
LIST OF TABLES .....	viii
LIST OF FIGURES.....	ix
<b>CHAPTER 1: INTRODUCTION AND SYSTEMATIC REVIEW AND META- ANALYSIS OF PATIENT REPORTED OUTCOME INSTRUMENTS FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION .....</b>	<b>1</b>
PURPOSE .....	2
OVERVIEW .....	3
OPERATIONAL DEFINITIONS .....	4
Autologous Chondrocyte Implantation (ACI):.....	4
Patient Reported Outcome (PRO): .....	4
Performance Based Assessment (PBA):.....	4
Response Shift: .....	5
ASSUMPTIONS .....	5
DELIMITATIONS.....	5
LIMITATIONS .....	6
<b>SYSTEMATIC REVIEW AND META-ANALYSIS OF PATIENT REPORTED OUTCOME INSTRUMENTS FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION.....</b>	<b>7</b>
Introduction .....	7
Autologous Chondrocyte Implantation .....	7
Treatment Evaluation .....	8
Methods .....	10
Evidence Acquisition .....	10
Data Extraction.....	13
Data Analysis .....	16
Results .....	18
Study Selection.....	18
Methodology Scoring and Level of Evidence.....	19
Assessment of Publication Bias .....	19
Responsiveness of PROs.....	24
Discussion.....	27
Responsiveness .....	29
Study Quality .....	34
Limitations .....	36
Conclusions .....	37
<b>CHAPTER 2: RELIABILITY OF FORCE PLATE BASED PERFORMANCE MEASURES FOR EVALUATION OF PATIENTS RECEIVING TREATMENT FOR KNEE ARTICULAR CARTILAGE DEFECTS .....</b>	<b>38</b>
INTRODUCTION.....	38
METHODS .....	41
Participants .....	41
Performance Based Assessments (PBAs): .....	41
Statistical Analysis .....	45

RESULTS .....	45
All Patients .....	45
Preoperative vs. Postoperative.....	48
DISCUSSION .....	48
Limitations.....	52
CONCLUSION.....	52
CHAPTER 3: PATIENT ORIENTED AND PERFORMANCE BASED OUTCOMES FOLLOWING KNEE AUTOLOGOUS CHONDROCYTE IMPLANTATION.....	54
INTRODUCTION.....	54
METHODS .....	56
Patients.....	56
Surgical Procedures and Rehabilitation.....	57
Patient Reported Outcomes .....	58
Performance Based Assessments.....	58
Statistical Analysis .....	60
RESULTS .....	61
Patient Reported Outcomes .....	61
Performance Based Assessments.....	62
Relationship Between Patient Reported Outcomes and Performance Based Assessments.....	66
DISCUSSION .....	66
Patient Reported Outcomes .....	69
Performance Based Assessments.....	70
Relationship Between Patient Reported Outcomes and Performance Based Outcomes .....	74
Limitations.....	76
CONCLUSIONS.....	77
CHAPTER 4: INFLUENCE OF RESPONSE SHIFT ON PATIENT REPORTED OUTCOMES FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION .	78
INTRODUCTION.....	78
METHODS .....	81
Patients.....	81
Surgical Procedures and Rehabilitation.....	82
Outcome Measures .....	83
Patient Reported Outcomes.....	83
Performance Based Assessments .....	84
Assessment of Response Shift.....	86
Statistical Analysis .....	88
Main Outcome Measures .....	88
Group Effect.....	88
Individual Effect.....	89
RESULTS .....	90
Group Level Analysis .....	90
Individual Level Analysis.....	92
DISCUSSION .....	92
Group Level Effects.....	92
Individual Level Effect.....	94

Limitations.....	100
CONCLUSIONS.....	101
CHAPTER 5: FUNCTIONAL OUTCOMES FOLLOWING ARTICULAR CARTILAGE IMPLANTATION: BALANCING PATIENT ORIENTED AND PERFORMANCE BASED MEASURES.....	102
PURPOSE AND AIMS.....	102
SUMMARY .....	103
Responsiveness of Patient Reported Outcomes (PROs).....	103
Reliability of Performance Based Assessments (PBAs) .....	105
Application of PROs and PBAs to Evaluate Changes in Patient Function Following ACI.....	106
The Influence of Response Shift on Patient Reported Outcomes following ACI .....	108
SYNTHESIS OF RESULTS AND CONCLUSIONS .....	109
FUTURE RESEARCH .....	110
APPENDICES.....	112
APENDIX A – PATIENT REPORTED OUTCOME INSTRUMENTS .....	112
International Knee Documentation Committee Subjective Knee Form (IKDC).....	112
Lysholm Knee Scale .....	114
Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) .....	115
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).....	118
APPENDIX B: PROPOSED METHOD FOR VERIFYING RESPONSE SHIFT WITH PERFORMANCE BASED ASSESSMENTS .....	119
REFERENCES.....	121
VITA .....	133



## LIST OF TABLES

Table 1.1 Descriptive Variables for Autologous Chondrocyte Implantation Studies Included in Systematic Review and Meta-Analyses.....	20
Table 1.2. Orwin's Fail Safe N Analysis to Evaluate Publication Bias .....	23
Table 2.1 Functional tasks evaluated on the NeuroCom Balance Master ® Long Force Plate.....	43
Table 2.2 Descriptive Data and Reliability Statistics for Performance Based Assessments Among Autologous Chondrocyte Implantation Patients Pre and 12 Months Post Operatively .....	46
Table 3.1. Patient Reported and Performance Based Assessments Over 12 Months Following Autologous Chondrocyte Implantation.....	63
Table 3.2. Correlations Between Performance Based Assessments and Patient Reported Outcomes By Follow-up Time Point.....	67
Table 4.1. Linear Regressions Proposed to Verify Occurrence of a Response Shift.....	89
Table 4.2. Main Outcome Variables for Response Shift among Autologous Chondrocyte Implantation Patients.....	91

## LIST OF FIGURES

Figure 1.1 Search Process and Study Selection Results for Patient Reported Outcomes Following Autologous Chondrocyte Implantation.....	11
Figure 1.2. Funnel Plot to Evaluate Publication Bias .....	23
Figure 1.3. Forrest Plot of Effect Sizes by Patient Reported Outcome Among Autologous Chondrocyte Implantation Patients .....	25
Figure 1.4. Forrest Plot of Effect Sizes by Time Point Among Autologous Chondrocyte Implantation Patients .....	26
Figure 1.5. Forrest Plot of Summary Mean Effects Sizes Across all Time Points for Each Patient Reported Outcome .....	28
Figure 3.1. Patient Reported Outcome Scores .....	62
Figure 3.2. Timeline of Functional Recovery Following Autologous Chondrocyte Implantation .....	69
Figure 4.1. Then-Test Method for Assessing Response Shift.....	87

***CHAPTER 1: INTRODUCTION AND SYSTEMATIC REVIEW AND META-ANALYSIS OF PATIENT REPORTED OUTCOME INSTRUMENTS FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION***

Articular cartilage defects of the knee are a complex and challenging pathology with limited options for treatment and clinical management. The poor healing of these defects has been documented for over 200 years,<sup>75</sup> and when left untreated can progress to osteoarthritis.<sup>99</sup> Defects have been observed to occur in 63% of all knee arthroscopies,<sup>39</sup> and may be associated with trauma or be idiopathic in nature. One report observed defects present in 16 to 46% of ACL reconstructions.<sup>30</sup> If not treated appropriately defects to the articular cartilage can become increasingly painful and disabling. This is particularly true for lesions of the knee where biomechanical stresses result in both shear and compressive forces during normal activities of daily living.

Treatment of articular cartilage injuries represents a complex and challenging problem for both orthopedic surgeons and rehabilitation specialists. Treatment options for articular cartilage defects can range from simple debridement to marrow stimulating techniques or more complex auto- and allograft treatments. One emerging form of treatment is cell based therapies. These treatments are based on the implantation of chondrocytes into the symptomatic defect. The use of autologous chondrocyte implantation/transplantation (ACI or ACT) in a human population was first reported in 1994.<sup>28</sup> The ACI procedure involves a two step surgical process. During the first surgery a biopsy of healthy chondrocytes is obtained from a low weight bearing portion of the knee such as the intracondylar notch. These cells are then cultured and expanded in a laboratory and then transplanted into the defect in a second surgery. The original

procedure called for cells to be transplanted under a periosteum flap harvested from the patient during the second surgery.<sup>28</sup> The procedure has since been modified to commonly use a porcine type I/III collagen membrane to cover the defect in place of the periosteal flap (ACI-C).<sup>21, 59, 92</sup> In some regions the seeding of chondrocytes on a porcine type I/III collagen bilayer matrix (MACI) prior to implantation has also been introduced into practice as the third generation of the ACI procedure.<sup>13, 35</sup>

## **PURPOSE**

For each generation of ACI introduced, numerous reports of treatment outcomes have been presented. However these outcomes have focused primarily on patient reported outcomes (PROs) and disease oriented outcomes such as magnetic resonance imaging (MRI) or tissue biopsy. Very few investigators have documented ACI outcomes using performance based assessments (PBAs). PBAs provide a direct, objective measure of patient function that can be combined with PROs to form a full picture of clinical outcomes following treatment without regard for the biologic outcome that is assessed by MRI or tissue biopsy. This study was an investigation of clinical and functional outcomes following ACI to the knee and the methodology for documenting those outcomes. The primary purposes of this dissertation were the following:

1. To systematically review and evaluate via meta-analysis the responsiveness of common instruments used to measure PROs following ACI at varying time points.  
*Hypothesis: All instruments will demonstrate improved self-reported function and health related quality of life following ACI with the simplest instruments showing the greatest treatment effect.*

2. To determine among articular cartilage patients the reliability of the following NeuroCom Balance Master<sup>®</sup> long force plate assessments: Walk Across, Weight Bearing Squat, Unilateral Stance, Sit-to-Stand, Step Up/Over, and Forward Lunge tests. *Hypotheses: The reliability of all measures of time, distance, and force will demonstrate acceptable ICC values >0.75. There will be poor reliability of measures of sway and balance with ICC values <0.75.*
3. To document the clinical outcomes of ACI patients over one year following surgery utilizing both patient reported outcomes (PROs) and performance based assessments (PBAs), and to examine the relationship between PROs and PBAs. *Hypotheses: All PROs and PBAs will demonstrate an initial decrease in function at the three month time point. There will be improved function at 6 months and improvements from baseline at the 12 month time point based on PRO and PBA evaluations.*
4. To determine if patients undergoing ACI experience a response shift between preoperative assessment and evaluation at 6 and 12 months postoperative. *Hypotheses: There will be evidence of a response shift as assessed via PROs. Further evidence of this response shift will be supported by changes in the relationship between PROs and PBAs over time.*

## **OVERVIEW**

This dissertation is organized according to the following: Chapter 1 consists of a systematic review of the use of PROs to document patient outcomes following ACI. This chapter will provide a historical context of the use of PROs and treatment outcomes following ACI. Chapter 2 presents the reliability of a series of PBAs utilizing the NeuroCom Balance Master<sup>®</sup> long force plate in an ACI patient population. Reliability was evaluated both preoperatively and 12 months following ACI to determine the

reliability of the chosen measures across time points. Chapter 3 reports PRO and PBA outcomes prior to ACI and at 3 months, 6 months and 12 months following ACI. This information will provide a time line for recovery and return of function following ACI. Chapter 4 investigates the evidence of a response shift phenomenon influencing PROs following ACI. The relationship between PROs and PBAs across time will be examined in an attempt to validate the occurrence of a response shift. Chapter 5 will summarize the results of all portions of this dissertation and interpret these findings for future research and clinical application.

## **OPERATIONAL DEFINITIONS**

### **Autologous Chondrocyte Implantation (ACI):**

Two stage, cell based surgical therapy for the treatment of articular cartilage defects. Stage one involves the biopsying of healthy articular cartilage from a non-or low-weight bearing portion of the knee. This cartilage is then cultured and expanded, and these chondrocytes are transplanted into the defect during a second surgery.

### **Patient Reported Outcome (PRO):**

Self report questionnaires or instruments intended to document the patients' perspective of their level of function and/or health related quality of life.

### **Performance Based Assessment (PBA):**

Form of an objective evaluation requiring physical or mental function, ability, or competence of a task that is typically measured in a quantifiable variable such as time, speed, force, distance, or errors.

**Response Shift:**

A residual change in perception that occurs over time and can affect PROs based on the patient's internal frame of reference pre- or post-intervention. These changes are due to recalibration, reconceptualization, and reprioritization of internal standards and references utilized for self-appraisal.

**ASSUMPTIONS**

The primary assumptions of this dissertation were the following;

1. Subjects provide honest answers and best effort when completing PROs and PBAs.
2. Subjects clearly understood and followed instructions for both PROs and PBAs.
3. Changes in PBAs were related to changes in knee health and not other, unknown, unreported, underlying conditions.
4. All patients were compliant with activity restrictions and rehabilitation protocols.

**DELIMITATIONS**

1. For the meta-analysis portion of this dissertation, only those studies presenting statistics from which effect sizes could be calculated were included.
2. For the meta-analysis portion of this dissertation only those studies reporting PROs using the Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale (SF-36 PCS), the International Knee Documentation Committee Subjective Knee Form (IKDC), the Lysholm Knee Scale (Lysholm), the modified Cincinnati Knee Rating System (MCKRS), the

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), or the Knee Injury and Osteoarthritis Outcome Score (KOOS) were included
3. All surgeries were performed by a single surgeon and all patients were recruited from a single practice.
  4. All physical therapy was completed in individual outpatient clinical settings and was not directly supervised or controlled.
  5. No direct measures of cartilage healing such as MRI or tissue biopsy were utilized in this study.
  6. All patients undergoing ACI regardless of defect locations or the occurrence of realignment procedures have been included
  7. Previous injury or surgery was not controlled for.
  8. The “then-test” method was used to test for response shift among ACI patients, and this method may be susceptible to recall bias.

## **LIMITATIONS**

1. A number of patients (n=5) were lost to follow-up during the course of this study. Despite multiple attempts to contact these patients complete data for these patients could not be obtained and is therefore missing from the presented results.
2. A number of patients (n=6) were declared clinical failures during the course of this study and either underwent surgical revision prior to study completion or performance testing was contraindicated by the treating physician. When possible data from these patients were included in the results of this study.



# SYSTEMATIC REVIEW AND META-ANALYSIS OF PATIENT REPORTED OUTCOME INSTRUMENTS FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION

## Introduction

The limited ability of articular cartilage to heal on its own has been a topic of discussion for over 200 years.<sup>75</sup> The treatment and management of articular cartilage damage can be particularly challenging in the knee joint where such defects have been frequently observed during arthroscopic surgery.<sup>30, 39, 68, 182</sup> Restorative and reparative treatment of these defects, whether they penetrate to the subchondral bone (osteochondral lesions) or remain limited to the cartilage surface (chondral lesions), is highly desirable to prevent the progression of osteoarthritis.<sup>99</sup>

### *Autologous Chondrocyte Implantation*

Over the last three decades, approaches to treating chondral defects have shifted towards cell based therapies. These therapies have focused predominantly on the implantation of autologous chondrocytes directly into pathologic defects. The first published reports of human outcomes following autologous chondrocyte implantation were presented in 1994.<sup>28</sup> As originally described, autologous chondrocyte implantation/transplantation (ACI or ACT) is a two stage treatment where a cartilage biopsy is taken in one surgery and during a later surgery cultured chondrocytes are implanted into the defect.<sup>28</sup> Due to complications with graft hypertrophy considered to be linked to the use of the periosteal flap used to cover the defect and to reduce concomitant trauma, the procedure has since been modified to commonly use a porcine type I/III collagen membrane to cover the defect in place of the periosteal flap (ACI-C).<sup>21, 59, 92</sup> In efforts to further advance the procedure, a third generation of ACI involves the seeding of

chondrocytes on a porcine type I/III collagen bilayer matrix (MACI) prior to implantation.<sup>13, 35</sup> Finally, the 4<sup>th</sup> generation of ACI to become commercially available is characterized chondrocyte implantation (CCI).<sup>152</sup> This method involves the use of a gene marker profile to determine the cartilage forming potential of cells to selectively choose cells for expansion and implantation.

### *Treatment Evaluation*

As new methods for treating cartilage are developed it is necessary to evaluate these treatments to determine their effectiveness. While second look arthroscopies with cartilage biopsies provide the most diagnostic method of evaluating cartilage repair, they are not always feasible or ethical to perform. In addition, biopsies allow for the assessment of the histological tissue repair, but they cannot be used to evaluate patient oriented outcomes such as pain and function. To evaluate patient oriented outcomes researchers and clinicians have relied on patient reported outcome instruments (PROs). Numerous PROs have been developed to address outcomes associated with a specific body part or region, a specific disease, or health related quality of life as a whole. Numerous PROs have been utilized to document patient response to cartilage repair. While the widespread use of PROs is beneficial for documenting treatment outcomes, the wide variety in the PROs makes comparison across studies and instruments difficult. Ideally, a standard instrument or battery of instruments would be more advantageous for reliably and validly assessing patient response to treatment.

Some of the most commonly used PROs to evaluate articular cartilage repair outcomes include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),<sup>105, 106, 179</sup> the International Knee Documentation Committee Subjective Knee Form (IKDC),<sup>77</sup> the Lysholm Knee Scale (Lysholm),<sup>96, 168</sup> the modified Cincinnati Knee Rating

System (MCKRS),<sup>31</sup> the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),<sup>18, 19</sup> and the Knee Injury and Osteoarthritis Outcome Score (KOOS)<sup>148</sup>.

While all of these instruments have been widely used to evaluate ACI treatment efficacy, there is no clear standard regarding which outcome instrument is ideal for evaluating treatment progress or overall treatment effect following ACI. PRO responsiveness is the evaluation of change in the instrument score over time in response to treatment.<sup>85</sup> The reported responsiveness in self-reported function following ACI has not been compared among instruments. Identification of the most responsive instrument for an ACI population will provide clinicians and researchers with a disease specific tool to compare treatment effects between therapies.

The purpose of this study is to systematically review and summarize the scientific literature in regards to changes in PRO scores after ACI treatment. For analysis, we have selected the commonly utilized outcome instruments in cartilage repair studies including the IKDC, Lysholm, MCKRS, KOOS, WOMAC, SF-36. The outcome of interest for this systematic review is PRO responsiveness following ACI treatment. Meta-analyses of PRO score changes will be compared among instruments to determine the responsiveness of each instrument at specified postoperative time points. Secondly, a within-instrument comparison was performed to evaluate the responsiveness of individual PROs at specified time points to determine if the instrument is more responsive to changes in self-reported knee function at different time points during recovery. A better understanding of the responsiveness of each instrument will allow for improved selection of outcome instruments in future cartilage research.

## Methods

### *Evidence Acquisition*

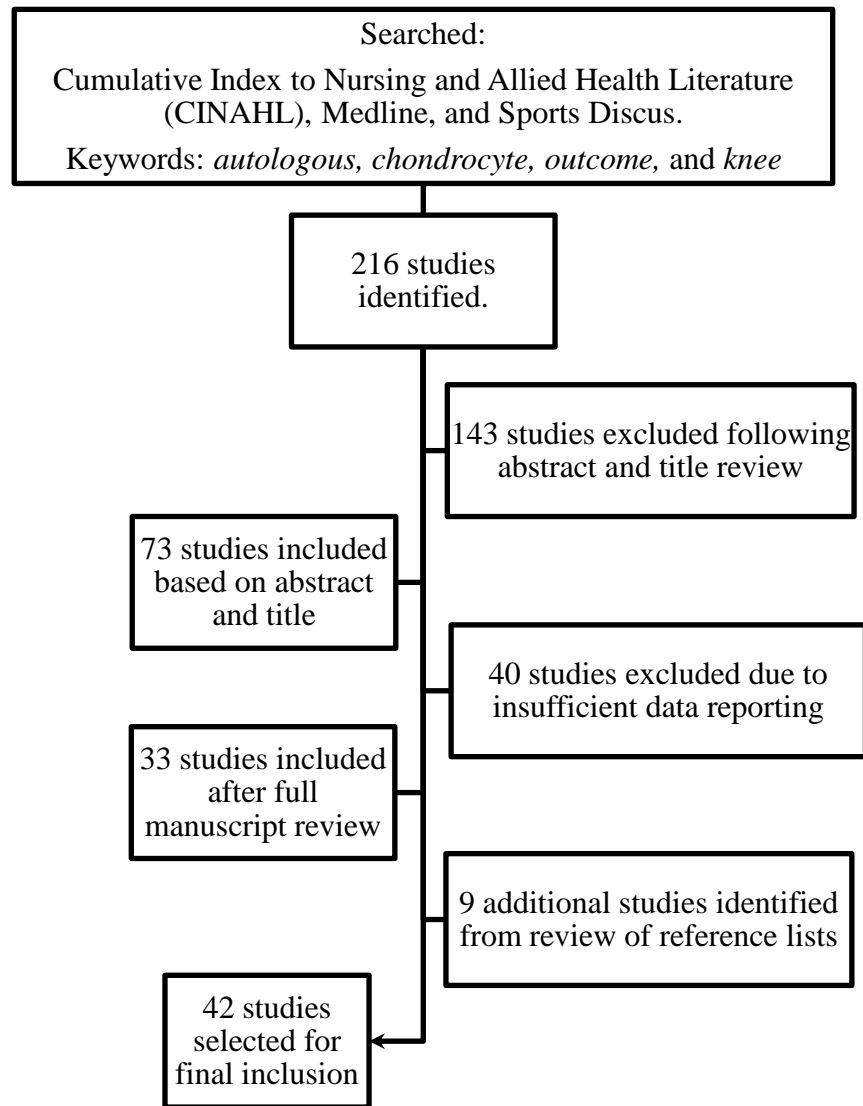
#### Search Strategy

In February 2010 investigators conducted a systematic search of the literature using CINAHL (from 1981), Medline (from 1966), and SPORTDiscus (from 1800) to identify reports of PROs following autologous chondrocyte implantation/ transplantation. Search terms used were *autologous*, *chondrocyte*, *outcome*, and *knee*. All abstracts were then reviewed for study inclusion/exclusion. In the event the abstract did not provide sufficient information to determine study eligibility the full manuscript was reviewed. Additionally the reference lists of all included studies were reviewed to identify other potentially eligible studies (Figure 1.1.).

#### Selection Criteria

All studies were required to meet the following inclusion criteria; 1) publication in the English language, 2) investigations with human participants, 3) prospective evaluation of patient outcomes following cell based treatment of articular cartilage defects with some form of cultured autologous chondrocytes, 4) utilization of at least one of the following PRO instruments: IKDC, Lysholm Knee Scale, MCKRS as described by Browne et al.<sup>31</sup>, KOOS, WOMAC, or SF-36 Physical Component Scale (SF-36 PCS) preoperatively and at a minimum of 1 postoperative time point, and 5) reporting of statistics from which effect sizes and 95% confidence intervals could be calculated. These included sample sizes and any of the following: preoperative and postoperative means and standard deviations, exact p-values for identified parametric statistical tests, preoperative and postoperative means and standard errors, or mean change scores and standard deviations.

**Figure 1.1 Search Process and Study Selection Results for Patient Reported Outcomes Following Autologous Chondrocyte Implantation**



#### Assessment of Methodological Quality and Level of Evidence

The quality of all included studies was assessed using the Coleman Methodology Score modified by Kon-Verdonk.<sup>37, 87</sup> This assessment tool was specifically adapted to evaluate the quality of cartilage repair studies and includes 11 parameters on a 100 point scale (100 = highest quality): study sample size (10 points possible for >60 defects evaluated), average follow-up period (10 points possible for a mean follow-up >60

months), number of concomitant surgical procedures performed (10 points possible if only a single isolated surgical procedure was reported on), study design (15 points possible for a randomized controlled trial), description of the surgical procedure (up to 5 points for adequate, detailed description), description of postoperative rehabilitation (up to 5 points if well described), the inclusion of MRI outcome (10 points possible if results reported for >80% of patients), the inclusion of histological outcome (10 points possible if reported for >50% of patients), outcome criteria (5 points if clearly defined with reported good reliability and sensitivity), procedure for assessing clinical outcomes (up to 7 points for patient recruitment, investigator independent from surgeon, and independent patient completion of outcomes), and description of subject selection process (up to 8 points for clear and unbiased selection criteria and >80% recruitment rate).<sup>87</sup>

Level of evidence was evaluated based on criteria from the Centre for Evidence Based Medicine<sup>4</sup> and was used to characterize the quality, quantity, and consistency of the included studies. Using this taxonomy, the quality of the evidence for the included studies was determined and a grade of recommendation was generated for the use of each PRO as a measure of ACI treatment effect. Consistent level 1 studies yields a grade of A.<sup>4</sup> A grade of B results from consistent level 2 or 3 studies or extrapolations from level 1 studies.<sup>4</sup> A grade of C is given for level 4 studies or extrapolations form level 2 or 3 studies, and a grade of D is the result of level 5 evidence or inconsistent or inconclusive evidence regardless of the level of evidence.<sup>4</sup>

Methodological quality assessment and the rating of the level of evidence were assessed independently by two investigators. Discrepancies in scoring were discussed until a consensus score was agreed upon.

### *Data Extraction*

The primary outcome variables of interest were scores on 6 specified PROs: the IKDC, Lysholm Knee Scale, MCKRS, KOOS, WOMAC, and SF-36 PCS. From each study all data that could be used for the calculating of effect sizes for PROs was extracted.

### Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Score (SF-36 PCS):

The entire SF-36 is frequently used as a global measure of health-related quality of life (HRQOL) in all patient populations.<sup>64</sup> It is also commonly used as a criterion reference scale in many studies validating region and disease specific scales.<sup>25, 26, 78, 85, 103, 136, 147, 148</sup> Traditional scoring of the SF-36 involves 8 individual sub-scales<sup>1</sup> but the SF-36 has also been reported as 2 summary physical and mental scores or as a single score.<sup>64</sup> Test-retest reliability for SF-36 PCS has a reported ICC value of 0.92 to 0.95 among former articular cartilage patients (minimum 5 years post-ACI surgery).<sup>58</sup> SF-36 PCS evaluates physical knee function across a variety of activities ranging from activities of daily living such as dressing and bathing to general questions about more demanding activities such as climbing stairs, walking more than a mile or participating in strenuous sports. However, unlike the IKDC the SF-36 does not address specific joint functions such as landing, pivoting, or starting and stopping. The SF-36 uses a normative based scoring system under which 50 represents an average score based on historical data.<sup>1</sup>

### Lysholm Knee Scale (Lysholm):

The Lysholm scale contains 8 items that are scored as a single scale.<sup>96, 168</sup> For overall score, measures of internal reliability are consistent across authors ranging from 0.65 to 0.73.<sup>25, 26, 85, 168</sup> The Lysholm has been documented as having high test-retest reliability across a variety of knee patients including those undergoing microfracture for

treatment of articular cartilage defects<sup>85</sup> with ICC values ranging from 0.89 to 0.97.<sup>25, 26, 103, 104, 136, 168</sup> Specifically, this scale evaluates knee symptoms – locking, stability, pain, and swelling – in addition to function during common low to moderate activities including walking, stair climbing and squatting. Unlike the IKDC, KOOS, or SF-36 PCS no part of the Lysholm addresses sport participation or knee function during sporting activities.

#### Modified Cincinnati Knee Rating System (MCKRS):

The Cincinnati Knee Rating System in its full form has undergone multiple revisions and been presented in various modified formats since its introduction.<sup>124-128</sup> While the original scale is more complex, a modified version of the Cincinnati Knee Rating System that has been commonly used to evaluate ACI patients consists of one to three simple questions asking patients to rate their perception of their knee, their pain, and their swelling on a 0 (severe) to 10 (normal knee/No problems) scale with descriptive references provided for all even values.<sup>31</sup> Because of the variation in Modified Cincinnati Knee Rating Systems reported in the literature only the MCKRS presented by Browne et al. was included in this review.<sup>31</sup> To avoid inappropriate comparison of various versions of MCKRS, studies that were included were required to either publish the scale directly in the manuscript or provide a clear reference for its use. Reliability for a version of the MCKRS has been evaluated in a population of former ACI patients where an ICC of 0.80 to 0.91 was observed; however, caution should be used in interpreting this value as no reference was provided for what version of the MCKRS was evaluated.<sup>58</sup>



Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC):

The WOMAC is a disease specific instrument evaluating pain, stiffness, and function typically in an osteoarthritic (OA) patient population.<sup>18, 19</sup> This instrument may be presented in a visual analogue scale format or as Likert type scales. A total score can be calculated by combining the pain, stiffness, and function subscales. An ideal score is zero, representing no disability, while the worst possible total score is 96 points (20 points pain, 8 points stiffness, 68 points function). Test-retest reliability among former ACI patients for the individual subscales and for the total WOMAC score has been reported to have ICC values ranging from 0.75 to 0.93.<sup>58</sup> While all cartilage repair patients do not have OA, most experience the joint swelling, crepitus, pain, and loss of function that typically characterizes OA and which the WOMAC evaluates. This instrument does not require high level strenuous physical activity to achieve maximum scores. By focusing on evaluating low to moderate demand activities of daily living (sitting, bathing, rising from sitting, household chores, etc.), the WOMAC may be an appropriate PRO among patients who do not desire to return to high level activity.

International Knee Documentation Committee Subjective Knee Form (IKDC):

The IKDC is a 20 item instrument that was developed by reviewing existing patient report instruments to create a consensus form that could be used to document changes in HRQOL over time for patients with various knee problems.<sup>76</sup> The IKDC is typically scored as a single scale instrument representing symptoms, activity, and sports function as a single construct.<sup>77</sup> Test-retest reliability has been observed among former ACI patients (minimum of 5 years post ACI) with ICC values ranging from 0.91 to 0.93.<sup>58</sup> Of the scores included in this review the IKDC evaluates the highest level of function with questions regarding jumping, pivoting, squatting, and stopping and starting quickly.

### Knee Injury and Osteoarthritis Outcome Score (KOOS):

The KOOS consists of 42 questions with 5 item Likert-type response choices covering the domains of activities of daily living (17 questions), symptoms (7 questions), pain (9 questions), knee related quality of life (4 questions), and sports and recreation (5 questions).<sup>148</sup> The KOOS was originally developed for use with patients with anterior cruciate ligament injuries, meniscus injuries, or post-traumatic osteoarthritis and contains all of the questions included in the WOMAC.<sup>148</sup> Each subscale is scored out of 100 possible points with 100 representing no knee problems. A total KOOS score is also occasionally reported out of a possible 100 points. In its initial reliability evaluation among knee patients ICC values ranged from 0.75 to 0.93 across all subscales.<sup>148</sup> The Dutch version of the KOOS, yielded ICC values of 0.87 to 0.95 for individual subscales and 0.97 for the overall KOOS among articular cartilage patients.<sup>17</sup> The existence of multiple subscales within the KOOS allows for the evaluation of varying levels of function from activities of daily living to sports activities within a single outcomes instrument. While the multiple subscales can be cumbersome to compare across groups, unlike the IKDC or the Lysholm they allow the identification of treatment effects in individual domains relating to pain, symptoms, function, and quality of life.

### *Data Analysis*

For each outcome score, individual pre- to postoperative effect sizes were calculated using bias-corrected Hedge's *g* with 95% confidence intervals (CI). Separate meta-analyses were then performed to provide a summary response for each PRO at individual specified time points. For the purposes of analysis, follow-up time points were grouped into 4 categories, Time Point I (less than 1 year); Time Point II (1 year to less than 2 years); Time Point III (2 years to less than 4 years); and Time Point IV (4 years or

greater). For each meta-analysis, a random effects model was employed. In comparison to the fixed effect model, the random effects model provides a more conservative summary effect by estimating the mean effect size and confidence interval for the distribution of all relevant true effect sizes.<sup>24</sup> We chose this model specifically because the effect sizes and confidence intervals analyzed in each meta-analysis were generated from independent studies that utilized similar, but nonuniform methods.<sup>24</sup>

Individual measures across the multiple studies were pooled from the included studies using a bias-corrected Hedges'  $g$ <sup>24</sup> and 95% confidence intervals to examine the magnitude and precision of the difference between pre- and postoperative PRO scores. Most studies made multiple comparisons across separate time points. Each comparison was treated independently within the statistical analyses of the measurement parameters. All effect sizes, 95% CIs, and Z-distribution p-values were calculated in Comprehensive Meta Analysis (Comprehensive Meta Analysis Version 2.0, Biostat, Englewood, NJ). It is important to note that Hedges'  $g$  is a standardized effect, which creates a unitless measure which is also corrected to represent an effect that exists on a parametric distribution. Across the parameters, the standardized effects were pooled for each PRO using meta-analyses conducted in Comprehensive Meta Analysis. A positive effect size indicated improvement in postoperative PRO score compared to preoperative score. Effect sizes for which confidence intervals did not overlap were considered to be significantly different. To interpret the strength of the effect sizes, Cohen's guidelines were used.<sup>36</sup> Values were interpreted as small if they were between 0.20 and 0.49, moderate if between 0.50 and 0.79, and values of more than 0.80 were interpreted as large.<sup>36</sup>

## Assessment of Publication Bias

To assess the likelihood of publication bias, a funnel plot of all measures included in the study was generated by plotting standard error against Hedge's  $g$  effect size for each included study. To assess the robustness of the observed overall effects of the variations in study design on PRO score, Orwin's Fail-Safe  $N$  test was employed.<sup>132</sup> For this test a Hedge's  $g$  effect size of 0.1 was assumed for all missing studies, or studies excluded due to publication bias, and the number of missing studies necessary to reduce the overall mean effect size for each instrument to a 0.4 was calculated. These values of were chosen to determine how many studies demonstrating a negligible effect (0.1) would be needed to be added to the existing sample of studies to result in a small (0.4) overall mean effect.

## Results

### *Study Selection*

The initial literature search yielded 216 results. Application of inclusion and exclusion criteria resulted in the inclusion of 42 articles.<sup>14, 16, 23, 27, 31, 41, 42, 44, 48, 50, 54, 55, 65-67, 69, 84, 86, 89, 98, 100, 107, 108, 112, 115, 118, 121-123, 129, 133, 135, 137, 146, 149-152, 158, 171, 185, 186</sup> Study selection and inclusion is depicted in Figure 1.1. Those studies included in the study are summarized seen in Table 1.1. A total of 2016 patients with a mean age of approximately 34.5 yrs are reported on in the included studies. Overall, 16 studies reported outcomes using the IKDC, 11 studies used the KOOS (2 reporting only total KOOS scores), 18 studies reported values for the Lysholm, 12 studies used the MCKRS, 9 studies reported SF-36 PCS values, and only 2 studies meeting the inclusion criteria utilized the WOMAC.

### *Methodology Scoring and Level of Evidence*

The mean modified Coleman Methodology Score for all included articles was 50.9  $\pm$  9.2, with a range of 35 to 68. Overall, the least reported parameters were of inclusion of MRI outcomes, inclusion of histological outcomes, and description of subject selection process. CEBM level of evidence was 2b for 38 articles and 1b for 4 articles included. Based on the consistent reporting of level 2 studies a grade B recommendation was made for the use of the IKDC, KOOS, Lysholm, MCKRS, SF-36 PCS, and WOMAC as outcome measures following ACI.<sup>4</sup>

### *Assessment of Publication Bias*

A funnel plot of all measures included in the meta-analysis portion of this study can be seen in Figure 1.2. The funnel plot displays an asymmetrical distribution of studies with a disproportionate number of studies above the mean effect size at the bottom of the funnel. These results suggest a slight publication bias towards studies demonstrating large treatment effects, particularly for studies with smaller sample sizes. However, the results of the Orwin's Fail Safe N test (Table 1.2) demonstrate that an additional 14 (SF-36 PCS) to 196 (KOOS) studies with a trivial effect size of 0.10 are necessary to reduce the mean effect size for any of the PROs to a weak value of 0.40, meaning that the observed overall effects are very robust and not likely to be artificially influenced by this potential publication bias.

**Table 1.1 Descriptive Variables for Autologous Chondrocyte Implantation Studies Included in Systematic Review and Meta-Analyses**

Study	Mean Age	Procedure Included <sup>1</sup>	Follow-up time (yrs.)	Instrument included in Review <sup>1</sup>	Total N analyzed	Lesion Locations <sup>†</sup>	Average Lesion size (or largest lesion size) (cm <sup>2</sup> )	Level of Evidence <sup>4</sup>	Modified Coleman Methodology Score <sup>87</sup>
Basad et al. 2010 <sup>14</sup>	33	MACI	.5,1.5,2	L	39	FC, Troc, Pat		1b	45
Behrens et al. 2006 <sup>16</sup>	35	MACI	2.87,5	L	33	MFC, LFC, Pat	4.08	2b	56
Bhosale et al. 2007 <sup>23</sup>	43	ACI-C w/Meniscus Allograft Transplant	1	L	8	MFC, LFC, Kissing	9.7 femoral, 3.7 tibial (median)	2b	58
Briggs et al. 2003 <sup>27</sup>	30	ACI-C	2.825	L	14	MFC, LFC, Troc, Pat	2.46	2b	43
Browne et al. 2005 <sup>31</sup>	37	ACI-P	5	M, MP, MS	87	MFC, LFC, Troc	4.9	2b	61
de Windt et al. 2009 <sup>41</sup>	35	ACI-multiple versions	3	K – Total Only	25	MFC, LFC	3.25	2b	48
Della Villa et al. 2010 <sup>42</sup>	24.3	MACI in athletic compared to non-athletic males	1, 5	I	65	MFC, LFC, Troc	2.25	2b	48
Ebert et al. 2008 <sup>44</sup>	36.9	MACI w/accelerated rehabilitation or traditional rehabilitation	0.25	K,S	62	MFC, LFC	3.3	2b	43
Ergelet et al. 2000 <sup>48</sup>	33.7	ACI-P	0.5,1	M	13	MFC, LFC, Troc, Pat	6.27	2b	35
Farr et al. 2007 <sup>50</sup>	36.9	ACI-P c/Meniscus Allograft Transplant	4.5	L,M	29	MFC, LFC, Kissing	MFC 6.36, LFC 5.35, troc 4.77, other 2.68	2b	50
Gobbi et al. 2006 <sup>54</sup>	30.5	MACI Patellofemoral	2	I	32	Pat, Troc	4.7	2b	53
Gobbi et al. 2009 <sup>55</sup>	31.2	MACI Patellofemoral	2,6,29	I	34	Pat, Troc	4.45	2b	40
Henderson and Lavigne 2006 <sup>57</sup>	33.6	ACI-P Patellofemoral with or without realignment	.75,1,2	I,M,S	44	FC, Troc, Pat	3.07	2b	50
Henderson et al. 2005 <sup>65</sup>	41	ACI-P	1,2	I	53	MFC, LFC, Troc, Pat	3.7	2b	57
Henderson et al. 2006 <sup>86</sup>	38.8	ACI-P with or without reoperation	3.52	I,M,S	170	MFC, LFC, Troc, Pat	3.45	2b	68
Horas et al. 2003 <sup>69</sup>	31.4	ACI-P	.5,1,2	L	20	MFC, LFC, PFJ	3.86	2b	71
Knutson et al. 2004 <sup>84</sup>	33.3	ACI-P	1,2	L,S	39	MFC, LFC	5.1	1b	55
Kon et al. 2009 <sup>86</sup>	29	MACI	5	I	40	MFC, LFC, Troc	2.2	2b	46
Kreuz et al. 2009 <sup>89</sup>	35	MACI	0.5,1,4	I,K	19	MFC, LFC, Pat	4	2b	61
Mandelbaum et al. 2007 <sup>88</sup>	37.1	ACI-P	4.91	M, MP, MS	40	Troc	4.5	2b	52

**Table 1.1 (continued) Descriptive Variables for Autologous Chondrocyte Implantation Studies Included in Systematic Review and Meta-Analyses**

Study	Mean Age	Procedure Included <sup>a</sup>	Follow-up time (yrs.)	Instrument included in Review <sup>b</sup>	Total N analyzed	Lesion Locations <sup>c</sup>	Average Lesion size (or largest lesion size) (cm <sup>2</sup> )	Level of Evidence <sup>d</sup>	Modified Coleman Methodology Score <sup>e,f,g</sup>
Marcacci et al. 2005 <sup>100</sup>	37.6	MACI	1,41,3,17	I	141	FC, Troc, Pat, TP	3.5	2b	64
McNickle et al. 2009 <sup>107</sup>	30.3	ACI-P	4,3	I,K,L	122	MFC, LFC, Troc, Pat, Troc & Pat	4.21	2b	62
Micheli et al. 2006 <sup>108</sup>	15.5	ACI-P	4,3	M,MP,MS	32	MFC, LFC	5.4	2b	38
Minas and Bryant 2005 <sup>112</sup>	36.9	ACI-P Patellofemoral	3,95	M,S,W	45	Pat, Troc, Pat & Troc, FC & Pat, FC & Troc, FC & Pat & Troc	10.45	2b	41
Mithöfer et al. 2005 <sup>115</sup>	15.9	ACI-P among adolescent athletes	3,91	L	20	MFC, LFC, Troc, Pat, TP	6.4	2b	45
Moseley et al. 2010 <sup>118</sup>	37	ACI-P	9,2	M,MP,MS	72	MFC, LFC, Troc	5.2	2b	52
Nehrer et al. 2006 <sup>121</sup>	33	MACI	1,3	I,L,M	36	MFC, LFC, Pat, TP	1.5-8 (range)	2b	39
Niemeyer et al. 2010 (a) <sup>122</sup>	39.4	ACI-C to those 40 and older and younger than 40	.5,2	I,L	74	MFC, LFC, Troc, Pat	Not reported	2b	57
Niemeyer et al. 2010 (b) <sup>123</sup>	37.4	ACI-C	0,5,1	I,L	66	MFC, LFC, Troc, Pat	4.3	2b	52
Ochi et al. 2002 <sup>129</sup>	26.4	Atelocollagen-associated ACI with periosteum flap	2	L	28	MFC, LFC, Pat	2.93	2b	45
Ossendorf et al. 2007 <sup>133</sup>	36	MACI	.5,1,2	K	40	MFC, LFC, PAT, Troc, TP	4.6	2b	61
Pascual-Garrido et al. 2009 <sup>135</sup>	31.8	ACI-P Patellofemoral	4	I,K,L,S	52	PAT, Troc, bipolar, Troc & MFC	4.2	2b	61
Peterson et al. 2010 <sup>137</sup>	33.3	ACI-P	12,8	L	58	FC, Pat	7	2b	63
Robertson et al. 2007 <sup>146</sup>	37.4	ACI-C	.5,1,2	K	27	MFC, LFC, Pat,	1-10 (range)	2b	49
Rosenberger et al. 2008 <sup>149</sup>	48.6	ACI-P over age 45	2,3	M,S,W	56	MFC, LFC, Troc, Pat, MTP, LTP	4.7	2b	39
Rue et al. 2008 <sup>150</sup>	23.4	ACI-P w/Meniscal allograft transplant	2	I, L, K	15	MFC, LFC	3.93	2b	63

**Table 1.1 (continued) Descriptive Variables for Autologous Chondrocyte Implantation Studies Included in Systematic Review and Meta-Analyses**

Study	Mean Age	Procedure Included <sup>d</sup>	Follow-up time (yrs.)	Instrument included in Review <sup>f</sup>	Total N analyzed	Lesion Locations <sup>†</sup>	Average Lesion size (or largest lesion size) (cm <sup>2</sup> )	Level of Evidence <sup>4</sup>	Modified Coleman Methodology Score <sup>§87</sup>
Saris et al. 2008 <sup>152</sup>	33.9	CCI	.5,1.5	K	51	FC	2.6	1b	54
Saris et al. 2009 <sup>151</sup>	33.9	CCI	3	K – Total Only	41	FC	2.6	1b	49
Selmi et al. 2008 <sup>158</sup>	30	MACI	1,2	I	17	FC	3	2b	44
Selmi et al. 2008 <sup>158</sup>	30	MACI	1,2	I	17	FC	3	2b	44
Tohyama et al. 2009 <sup>171</sup>	>20	Atelocollagen-associated ACI with periosteum flap	.5,1,2	L	27	MFC, LFC, Pat	3.2	2b	52
Zaslav et al. 2009 <sup>185</sup>	34.5	ACI-P following prior failed treatment w/n previous 3 years	0.5,1 ,3,4	M,K,S	150	MFC, LFC, Troc	4.63	2b	49
Zeifang et al. 2010 <sup>186</sup>	29.1	ACI-P, MACI	1	I, L, S	21	MFC, LFC	4.20	2b	42

\* MACI: Matrix Assisted Autologous Chondrocyte Implantation, ACI-C Collagen covered Autologous Chondrocyte Implantation, ACI-P: Periosteum covered Autologous Chondrocyte Implantation; CCI: Characterized Chondrocyte Implantation

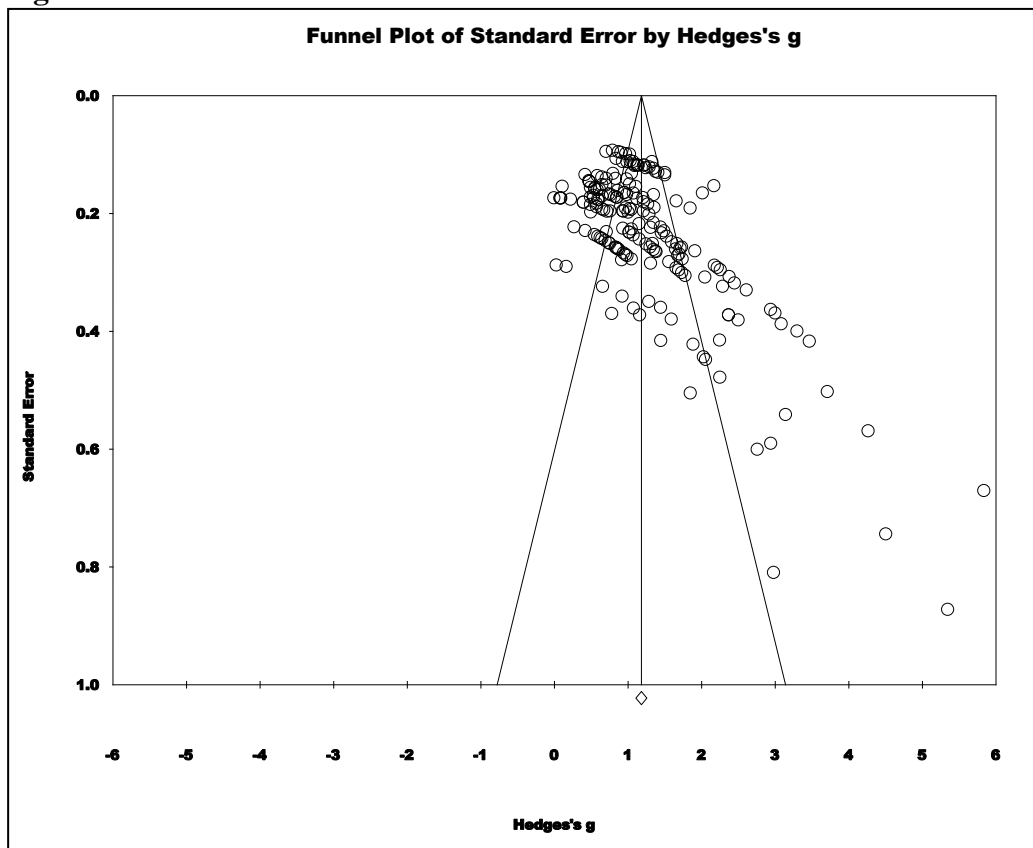
<sup>†</sup>I: International Knee Documentation Committee Subjective Knee Form (IKDC), L: Lysholm Knee Scale (Lysholm), K: Knee Injury and Osteoarthritis Outcome Score (KOOS), M: modified Cincinnati Knee Rating System (MCKRS) Patient Perspective; MP:MCKRS – Pain Scale, MS- MCKRS Swelling Scale, S: Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale (SF-36 PCS), W: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

<sup>‡</sup>FC: Femoral Condyle, Troc: Trochlear, Pat: Patellar, MFC: Medial Femoral Condyle, LFC: Lateral Femoral Condyle, TP: Tibial Plateau, PFJ: Patellofemoral Joint, MTP: Medial Tibial Plateau, LTP: Lateral Tibial Plateau

<sup>§</sup>Scored 0 to 100 with 100 representing best methodology



**Figure 1.2. Funnel Plot to Evaluate Publication Bias**



**Figure 1.2** The observed funnel plot suggests a slight publication bias towards studies demonstrating larger effect sizes, with an asymmetrical distribution of studies at the bottom of the funnel.

**Table 1.2. Orwin's Fail Safe N Analysis to Evaluate Publication Bias**

Instrument*	N†
IKDC	95
Lysholm	83
KOOS	196
MCKRS	48
SF-36 PCS	14
Overall Across All Instruments	399

\*IKDC: International Knee Documentation Committee Subjective Knee Form, Lysholm: Lysholm Knee Scale, KOOS: Knee Injury and Osteoarthritis Outcome Score. MCKRS: modified Cincinnati Knee Rating System: SF-36 PCS: Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale

†Number of studies with an effect size of 0.1 needed to reduce the overall mean effect size to 0.4

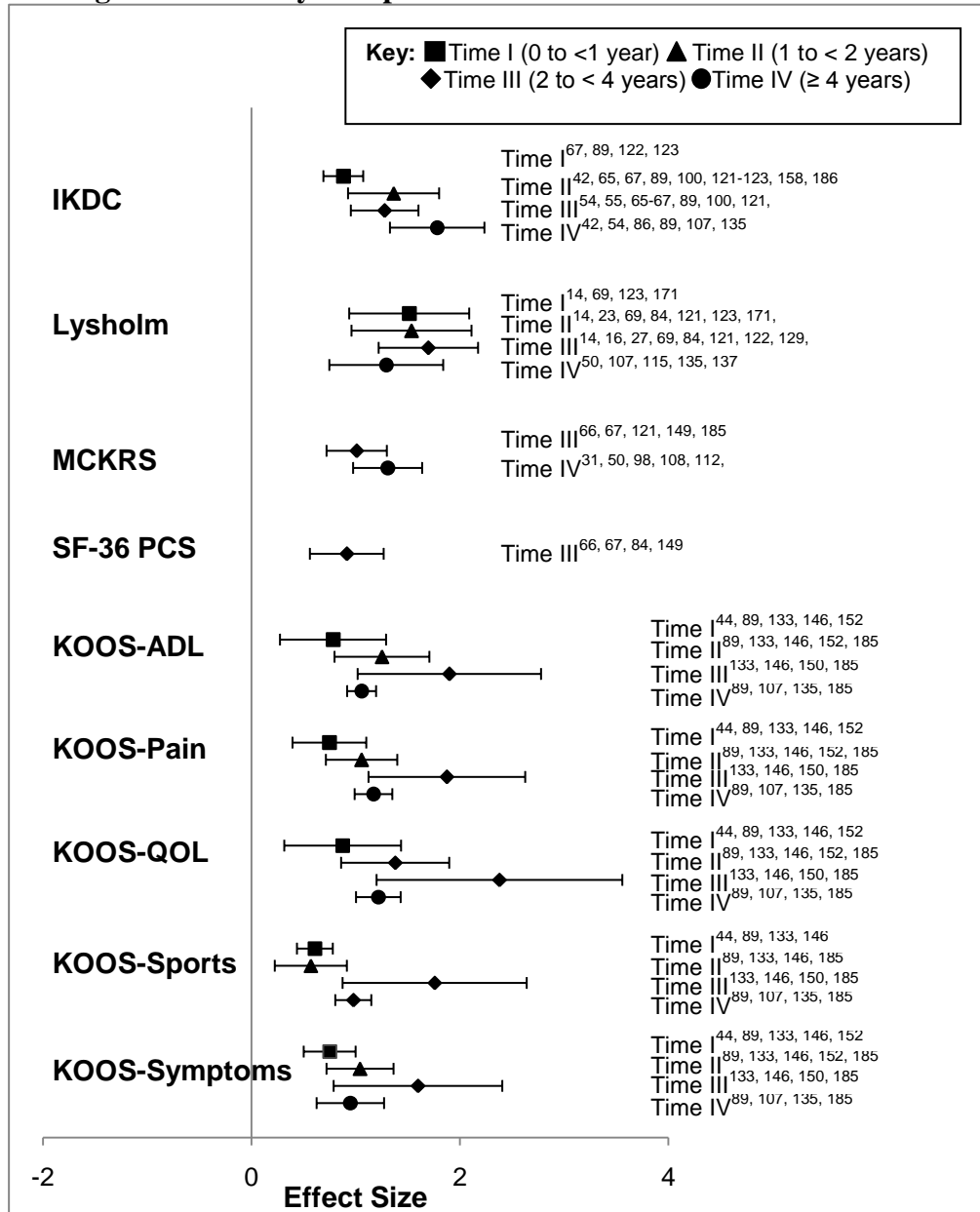
### *Responsiveness of PROs*

Mean effect sizes and 95% confidence intervals (CIs) for each instrument at each of the four time points are reported in the Forrest plot in Figure 1.3 and Figure 1.4. For an instrument to be included in the meta-analysis at a given time point a minimum of 4 individual data points must have been reported. The WOMAC did not meet this requirement at any time point, and the SF-36 PCS only met this requirement at time point III. The MCKRS could only be evaluated at time points III and IV and only the patient perception scale could be evaluated.

### Responsiveness within Instruments Across Time Points

For all evaluated instruments none of the mean effect sizes or confidence intervals encompassed zero, indicating that there is evidence of positive treatment effects following ACI regardless of the PRO utilized (Figures 1.3). The IKDC was observed to have increasing responsiveness over time, as measured by Hedge's *g* effect sizes, with time point IV demonstrating a significantly greater mean effect size (mean effect size [95 CI%]: 1.78 [1.33, 2.24] than time point I (0.88, [0.69, 1.07])). The responsiveness of the Lysholm varied little across time points with mean effect sizes only ranging from 1.29 to 1.69. There was also no difference in responsiveness for the MCKRS between time points II and III. Finally, the only KOOS subscale to show improvements in responsiveness over time was the KOOS-sports and recreation subscale for which time point III (1.76 [0.87, 2.64] and time point IV (0.98 [0.81, 1.15] were significantly more responsive than time point I (0.61 [0.44, 0.78])).

**Figure 1.3. Forrest Plot of Effect Sizes by Patient Reported Outcome Among Autologous Chondrocyte Implantation Patients**



Random effects model summary mean effect sizes for each patient reported outcome instrument by time point. IKDC: International Knee Documentation Committee Subjective Knee Form, Lysholm: Lysholm Knee Scale, KOOS-ADL: Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale, KOOS-pain: Knee Injury and Osteoarthritis Outcome Score Pain subscale, KOOS-QOL: Knee Injury and Osteoarthritis Outcome Score Quality of Life subscale, KOOS-Sports: Knee Injury and Osteoarthritis Outcome Score Sports and Recreation subscale, KOOS-Symptoms: Knee Injury and Osteoarthritis Outcome Score Symptom subscale. MCKRS Patient: modified Cincinnati Knee Rating System Patient Perspective; SF-36 PCS: Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale.

**Figure 1.4. Forrest Plot of Effect Sizes by Time Point Among Autologous Chondrocyte Implantation Patients**

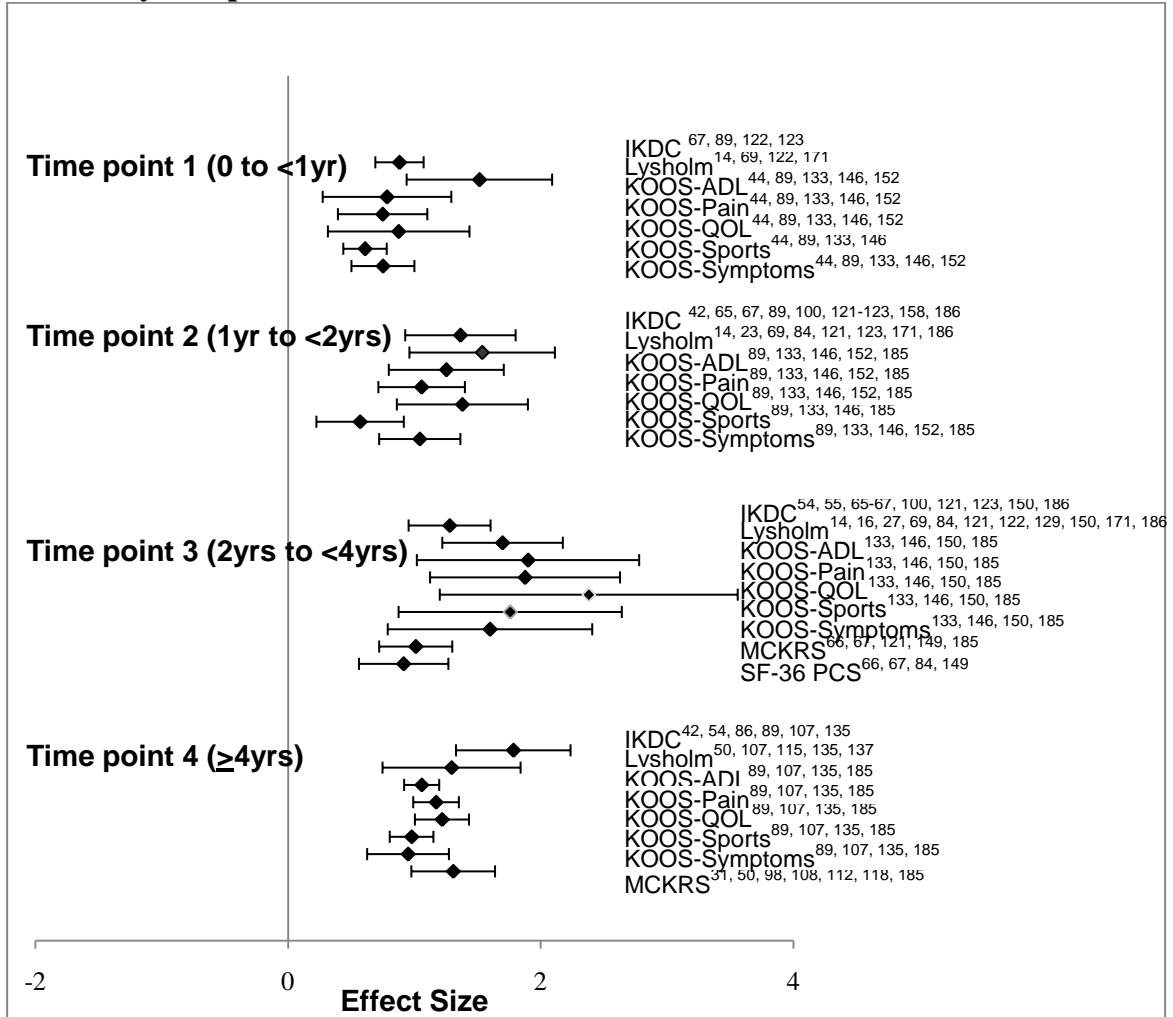


Figure 1.4. Random effects model summary mean effect sizes for each patient reported outcome instrument at each time point. IKDC: International Knee Documentation Committee Subjective Knee Form, Lysholm: Lysholm Knee Scale, KOOS-ADL: Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale, KOOS-pain: Knee Injury and Osteoarthritis Outcome Score Pain subscale, KOOS-QOL: Knee Injury and Osteoarthritis Outcome Score Quality of Life subscale, KOOS-Sports: Knee Injury and Osteoarthritis Outcome Score Sports and Recreation subscale, KOOS-Symptoms: Knee Injury and Osteoarthritis Outcome Score Symptom subscale. MCKRS Patient: modified Cincinnati Knee Rating System Patient Perspective: SF-36 PCS: Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale.

**Responsiveness by Time Point**

At time point I the Lysholm (1.52 [0.92, 2.11]) was significantly more responsive than the KOOS-sports and recreation subscale (0.61 [0.44, 0.78]) (Figure 1.4). At time

point II both the IKDC (1.37 [0.93, 1.80]) and the Lysholm (1.53 [0.96, 2.11]) were significantly more responsive than the KOOS-sports and recreation subscale (0.57 [.23, .92]). There were no significant differences between any of the instruments at time point III. Finally, at time point IV the IKDC (1.78, [1.33, 2.24]) was significantly more responsive than the KOOS-sports and recreation subscale (0.98 [.81, 1.15]).

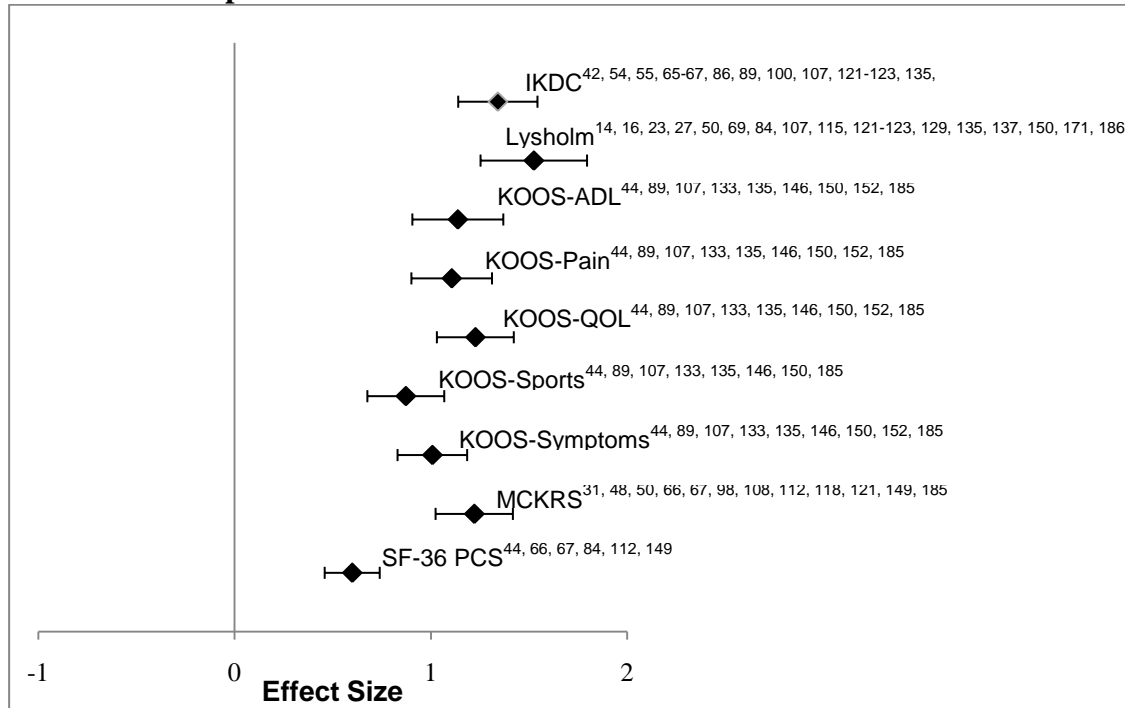
### Overall Responsiveness

The final comparison was of the overall responsiveness of each instrument with data from all available time points combined (Figure 1.5). This analysis demonstrated that overall the SF-36 PCS (0.60 [0.46, 0.74]) was significantly less responsive than all other instruments and subscales with the exception of the KOOS-sports and recreation subscale (0.87 [0.68, 1.07]). Both the Lysholm (1.52 [1.25, 1.80]) and the IKDC (1.34 [1.14, 1.54]) had overall mean effect sizes that were significantly greater than the overall mean effect size for the KOOS-sports and recreation subscale. With all time points combined the Lysholm was also significantly more responsive than the KOOS-symptoms subscale (1.01 [0.83, 1.19]).

### Discussion

The primary purpose of this study was to evaluate the responsiveness of common PROs to the treatment effects of ACI. An underlying assumption of this review was that ACI would have a common effect across studies and varying ACI procedures. While evaluating ACI efficacy was not a purpose of this review, the results of this systematic review and meta-analyses are in agreement with previous reviews documenting ACI to be a viable procedure resulting in positive patient outcomes.<sup>62, 87, 176</sup> A strength of our

**Figure 1.5. Forrest Plot of Summary Mean Effects Sizes Across all Time Points for Each Patient Reported Outcome**



Random effects model summary mean effect sizes for each patient reported outcome instrument across all time points combined. IKDC: International Knee Documentation Committee Subjective Knee Form, Lysholm: Lysholm Knee Scale, KOOS-ADL: Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale, KOOS-pain: Knee Injury and Osteoarthritis Outcome Score Pain subscale, KOOS-QOL: Knee Injury and Osteoarthritis Outcome Score Quality of Life subscale, KOOS-Sports: Knee Injury and Osteoarthritis Outcome Score Sports and Recreation subscale, KOOS-Symptoms: Knee Injury and Osteoarthritis Outcome Score Symptom subscale. MCKRS Patient: modified Cincinnati Knee Rating System Patient Perspective: SF-36 PCS: Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale

review is that we included a more comprehensive review of the available literature.

Previous systematic reviews have limited study inclusion to evaluation of randomized controlled trials,<sup>176</sup> comparisons to other cartilage treatments,<sup>62</sup> or studies of the third generation MACI version of ACI.<sup>87</sup> In previous reviews, the maximum number of included studies was 18<sup>87</sup> while the present investigation included 42 studies. Current inclusion criteria captured a wider variety of patients and defect locations representing all

surfaces of the tibiofemoral and patellofermoal joints. The large mean effect sizes and narrow confidence intervals observed in this review support the use of ACI for the generalized treatment of articular cartilage defects.

### *Responsiveness*

The results of this review demonstrate that regardless of the duration of post-operative follow-up all instruments were responsive to patient improvement following ACI; however, the IKDC and Lysholm may be more responsive than the MCKRS, KOOS, or SF-36 PCS. There was insufficient data to adequately evaluate the WOMAC.

### *Responsiveness Within Patient Reported Outcome Instruments Across Time Points*

The Lysholm demonstrated large mean effect sizes (1.30 to 1.70) with little variation across the four examined time points (Figure 1.2). The observed confidence intervals for the Lysholm at all four time points overlap by more than 50% suggesting little changes in responsiveness as time since ACI progresses. Common rehabilitation recommendations following ACI restrict return to sports participation for 12 to 18 months following surgery.<sup>9, 53, 61</sup> This delayed return to physical activity may result in lower scores on instruments that emphasize higher demand sports activity. Because the Lysholm primarily assess every day activities (walking, squatting, stair-climbing) and does not address sports activity, delayed return to higher level physical activity has little influence on Lysholm score. The lower demand activities evaluated in the Lysholm are functional goals addressed early in rehabilitation, and patients may see little improvement in these activities beyond the 1 year time point. The result is a potential ceiling effect for Lysholm scores which may explain its limited changes in responsiveness over time (i.e. confidence intervals overlap for all 4 time points). Therefore, the Lysholm scale may be

ideal for evaluating short-term outcomes or outcomes among patients not intending to return to sports, but it is less responsive to changes seen during long-term recovery as individuals return to higher demand activities.

The IKDC also demonstrated large effect sizes. However, a significant increase in mean effect size was observed between time point I and time point IV with mean effect size increasing from 0.88 to 1.78 with no overlap between confidence intervals. This difference demonstrates increased treatment effects over time when evaluating outcomes with the IKDC. Greco et al. observed a similar trend with responsiveness of the IKDC increasing between 6 and 12 months in a cohort of surgical cartilage patients.<sup>58</sup> It has previously been reported that functional and structural improvements following cartilage repair continue beyond 1 year postoperatively.<sup>22, 90, 145</sup> The observed increases in mean effect size over time may represent the IKDC's responsiveness to continual improvements in function that occur in the years following ACI surgery. The responsiveness of the IKDC to continued improvements over time can be considered a strength of this instrument and may be due to its inclusion of sporting activities. A wide variety of function can be documented with the IKDC, ranging from the inability to participate in any activity without symptoms to full participation in strenuous activities such as jumping or pivoting. The IKDC allows for continued improvement as individuals initiate return to strenuous activity and sports participation beyond the one year postoperative time point.

The KOOS-sports and recreation subscale had the lowest mean effect at time points I and II while the KOOS-symptoms subscale had the lowest mean effect of all the KOOS scales at time points III and IV. Responsiveness as evaluated by the mean effect size for the KOOS-sports and recreation subscales was significantly lower at time point I



compared to time points III and IV. These results are similar to that which was observed with the IKDC, and this progressive improvement in responsiveness over time may be related to the slow, progressive return to sports following ACI. For all other KOOS subscales no significant changes were seen for mean effect size between time points with all confidence intervals overlapping. Overall the KOOS was responsive to changes following ACI; however, the KOOS-sports and recreation subscale was the only subscale to demonstrate increasing mean effect sizes over time, suggesting that it responded to increasing treatment effects as healing progressed.

The MCKRS contains the fewest questions of the instruments included in this review, consisting of one to three questions. Only the single item of the MCKRS had sufficient data for inclusion in the meta-analyses. There was only sufficient data to evaluate the MCKRS at time point III and time point IV, limiting any conclusions that can be drawn regarding the changes in its responsiveness over time. Although the results of this review suggest that the MCKRS is responsive to changes in patient function following ACI, caution is urged regarding the use of this instrument. Many different versions of the MCKRS exist and many authors fail to reference the version of MCKRS they use. Similarly, appropriate psychometric properties for the MCKRS have rarely been reported. This made selection of appropriate studies difficult, for example, several articles were excluded at least in part because the authors did not reference the version of the MCKRS utilized, or because a different version than the one presented by Browne et al.<sup>31</sup> was utilized as an outcome measure.<sup>7, 13, 20, 21, 57, 80, 90-92, 164</sup> Due to ambiguity regarding the use of “modified” Cincinnati Knee Rating Systems the developers of the original Cincinnati Knee Rating Scale discourage the use of any modified versions.<sup>11</sup>

However, because of the frequency with which the Browne et al.<sup>31</sup> version of the MCKRS has been clearly referenced in the ACI outcomes study it was chosen for inclusion in this review.

Both the SF-36 PCS and the WOMAC had limited data available for analysis. For the SF-36 PCS there was only sufficient data for analysis of responsiveness at time point III. For this time point the SF-36 PCS did demonstrate a positive mean effect 2 to 4 years following ACI treatment with an effects size of 0.92[0.55,1.28]. There was insufficient data to include the WOMAC in any of the meta-analyses performed. Only two studies were available that utilized the WOMAC and reported sufficient data for calculating effect sizes, and even these studies failed to report results for all three WOMAC subscales.<sup>112, 149</sup> While additional studies have included the WOMAC as an outcome measure the results were only reported using non-parametric statistics and/or without the reporting of means and standard deviations, or other data necessary for calculating effect sizes.<sup>110, 111, 113, 114</sup> As a result no clear conclusions regarding the responsiveness of the WOMAC as an outcome instrument can be reached based on this review.

#### Responsiveness between Patient Reported Outcome Instruments

The Forrest plots of PRO instruments by time point can be seen in Figure 1.4, while the overall mean effect sizes across all time points can be seen in Figure 1.5. The IKDC and the KOOS- sports and recreation subscales were the only instruments to demonstrate significant changes in responsiveness over time. These changes may be related to activity restriction and gradual return to sports following ACI. The restrictions on sporting activity during the first year post-ACI may also explain the significant differences observed between the responsiveness of the KOOS-sports and recreation

subscale and the Lysholm at time points I and II (Figure 1.4). At time point II and time point IV the IKDC was more responsive than the KOOS-sports and recreation subscale. These differences may be the result of the wider range of physical functioning addressed in the IKDC as compared to the KOOS-sports and recreation subscale. At both time point III and time point IV the confidence interval surrounding the mean effect size for the MCKRS overlapped with the confidence interval for all other instruments, indicating that the responsiveness of the MCKRS was not significantly different from any other instrument evaluated. Overall and at time point III the SF-36 PCS had the lowest responsiveness as measured by mean effect size. This finding is not surprising given that the SF-36 is the only included instrument not designed specifically for the evaluation of knee function. The SF-36 may be more useful when evaluating HRQOL; while the IKDC, Lysholm, MCKRS, and all KOOS subscales, with the exception of the sports and recreation subscale, are more responsive than the SF-36 PCS to changes in knee function following ACI.

Examination of overall responsiveness without regard to individual time points demonstrates that the Lysholm and IKDC were observed to have the largest mean effect sizes with significantly greater responsiveness than the KOOS-sports and recreation subscale and the SF-36 PCS (Figure 1.5). While both the KOOS and IKDC include sports participation as components of evaluating knee function, the IKDC is significantly more responsive to overall changes in function following ACI (Figure 1.5). This overall difference, combined with the significant differences in responsiveness between the IKDC and KOOS-sports and recreation subscales at time points II and IV leads us to propose that the IKDC may be the preferred outcome instrument for evaluating long-term

outcomes following ACI, particularly among patients whose goals include return to sporting activity. Although all KOOS subscales are responsive to treatment effects following ACI, the IKDC and Lysholm are shorter instruments with single score outcomes and overall are more responsive to change than some subscales included in the KOOS. Based on these observations, the IKDC and the Lysholm may be preferable to the KOOS for documenting treatment effects following ACI.

### *Study Quality*

The mean modified Coleman Methodology score ( $50.9 \pm 9.2$ ) among studies included in this review was comparable to other recent reviews of ACI and other cartilage repair procedures. Harris et al. reported a mean modified Coleman Methodology score of 54 in 13 studies comparing ACI to other cartilage repair treatments.<sup>62</sup> Evaluation of MACI procedures resulted in observed scores of  $53.1 \pm 1.5$ .<sup>86</sup> In a general review of cartilage repair procedures using a different variation of the Coleman Methodology Score, Jakobsen et al. reported a mean score of  $43.51 \pm 12.1$ .<sup>81</sup> The slightly lower methodology score observed in our review compared to those by Harris et al.<sup>62</sup> and Kon et al.<sup>87</sup> is not surprising given the broad inclusion criteria for this review which did not seek to compare different cartilage repair techniques or different generations of ACI. Also, the present review included several studies that are over 5 years old and a general trend towards increasing study quality over time has been previously reported.<sup>62</sup> Regardless of the selection criteria utilized, this review and others demonstrate the need for improved research methodology and reporting of outcomes in future cartilage repair investigations

While the modified Coleman Methodology Score reported in this review provides a set of standardized criteria by which to evaluate cartilage research, it is not without

limitations. The scale is heavily weighted towards diagnostic, clinician based outcomes with up to 20 points of the 100 point score dependent on MRI and histological evaluation. The relationship between MRI and clinical outcome is not definitive with some authors observing low to moderate correlations between MRIs and PROs,<sup>34, 101, 146</sup> and others failing to observe such a relationship.<sup>167, 175</sup> Similarly, histological analysis can involve a wide variety of techniques and may not be ethical in cases where reoperation is not otherwise indicated. Of the 42 studies included in our review only a single study<sup>158</sup> received full credit for both histological and MRI outcomes, suggesting that the requirement of these outcomes may not be applicable in a clinical research setting.

Other areas where the included studies received less than 50% of the possible methodology points available on average were the reporting of recruitment rate (documented in only 2 studies<sup>149, 185</sup>), investigator independence, duration of follow-up, and number of different surgical procedures included. Only 8 studies clearly stated that the investigator documenting outcomes did so independently from the operating surgeon.<sup>27, 31, 84, 98, 112, 149, 152, 158</sup> To receive the full 10 points allotted for duration of study follow-up, outcomes beyond 60 months were required to be reported, a requirement that was only met by 5 studies.<sup>31, 54, 86, 118, 137</sup> Finally, only 5 studies scored a full 10 points for > 90% of subjects undergoing one surgical procedure with less than 10% undergoing concomitant procedures.<sup>16, 69, 84, 150, 158</sup> It is important to note that while common concomitant procedures such as osteotomies, meniscal allograft transplants, or ligament reconstructions reduced the overall methodological score, studies that included these procedures are much more generalizable to real clinical practice than studies of single isolated defects.<sup>46</sup>

### *Limitations*

The results of this review are limited by the quality and strength of the studies and PROs selected for inclusion. As evidenced by the low modified Coleman Methodology Score observed in this review and others, the quality of reporting in cartilage outcomes studies is variable and generally poor. Similarly, the included studies presented an expansive range of patients of various ages, with chondral defects of varying size and location, and who underwent an assortment of concomitant procedures. A random effects analysis was utilized to account for the variability between studies allowing our results to be generalized to a broad clinical population.

Numerous other PROs could have been selected for inclusion in this review; however, only the IKDC, Lysholm, MCKRS, KOOS, SF-36 PCS, and WOMAC were selected for review. As a result the conclusions drawn from this study can only be applied relative to these PROs. These PROs were chosen based on the interest of the authors, their established psychometric properties, and the frequency of their use within the articular cartilage literature.

Finally, a statistical limitation of our study is the use of multiple measures at multiple time points from within the same study populations. For studies with multiple outcome measures (Example: both IKDC and MCKRS) all evaluated outcome scores (Example: 1 year and 3 years) were included as independent measures. We acknowledge that outcome scores obtained from within the same sample are likely correlated, but given that the correlation between outcome measures and time points is rarely reported, correction for this relationship was not feasible. Fortunately, the observed mean effect sizes are so large and the confidence intervals so small for the included outcome

instruments that we do not believe this assumption violation significantly influences the overall conclusions of this review.

## **Conclusions**

Evidence for the use of ACI as a treatment for chondral defects consists primarily of level 2b observational cohort studies. The methodological quality of many of these studies is limited by the absence of diagnostic outcomes such as MRI and histological analyses, small sample size, short-follow-up, and high frequency of concomitant procedures. In addition documentation of recruitment rate and investigator independence was lacking from many studies. The IKDC, Lysholm, KOOS, MCKRS, and SF-36 PCS were all responsive to improvements in function following ACI. A positive treatment effect for ACI was observed using all instruments with follow-up time points ranging from less than one year to beyond 4 years. The Lysholm and the IKDC were the most responsive instruments across time points. The Lysholm was highly responsive as early as less-than 1 year following ACI and was consistently responsive throughout postoperative follow-up. However, this instrument may not be responsive to changes in function associated with the resumption of higher demand activities such as sports which occurs after the one year time point. For the evaluation of long-term outcomes among patients with an intent to return to physical activity, this review supports the use of the IKDC which was able to detect increasing treatment effects overtime. The use of the Lysholm and IKDC together represents a responsive combination of PRO instruments that are able to efficiently document both short term and long-term treatment effects among patients of a variety of activity levels following ACI.

***CHAPTER 2: RELIABILITY OF FORCE PLATE BASED PERFORMANCE MEASURES FOR EVALUATION OF PATIENTS RECEIVING TREATMENT FOR KNEE ARTICULAR CARTILAGE DEFECTS***

**INTRODUCTION**

With any form of medical treatment the ability to accurately and objectively document outcomes is of the utmost importance. This is particularly true in areas with new and emerging therapies such as the treatment of articular cartilage defects. Within this rapidly evolving field a variety of different outcomes can be used to evaluate treatment success. The types of outcomes collected can be classified as disease oriented, patient oriented, or performance based outcomes. Disease oriented outcomes are those that are of primary interest to the clinician. Disease oriented outcomes include elements such as Magnetic Resonance Imaging, graft biopsy, range of motion, or swelling. Patient oriented outcomes emphasize health related quality of life and focus on the ability to return to work, social, and recreational activities, and are commonly collected using patient reported outcome instruments (PROs) such as pen and paper questionnaires. Finally, performance based outcomes/assessments (PBAs) focus primarily on activities or functional tasks such as squatting, walking, hopping, or performing a standardized series of movements that can be objectively quantified by a measurement of kinematic or kinetic variables (e.g. distance, time, pressure, force, repetitions). All three types of outcomes are relevant in determining the successfulness of treatment and should be included in any comprehensive outcomes study. Regardless of the type of outcome being considered it is imperative that the method being used to measure it is reliable.



In the existing literature the predominant outcome measure for articular cartilage treatment via autologous chondrocyte implantation (ACI) has been patient oriented outcomes documented using PROs.<sup>21, 29, 31, 44, 49, 51, 86, 90, 98, 108, 115, 116, 149, 185</sup> Common PRO instruments including the Lysholm scale<sup>85</sup>, International Knee Documentation Committee Subjective Knee Form<sup>58</sup>, modified Cincinnati Knee Rating System<sup>58</sup>, Knee Osteoarthritis Outcomes Score<sup>17</sup>, and Western Ontario and McMaster Universities Osteoarthritis Index<sup>58, 147</sup> have been evaluated for reliability among cartilage patients.

One common form of disease oriented outcome evaluation is grading of the articular cartilage from direct visualization during a second look or follow-up arthroscopy. The reliability of multiple visual inspection scales have been evaluated among articular cartilage and specifically ACI patients.<sup>161, 174</sup> In general, observational evaluation of articular cartilage via arthroscopy has acceptable intrarater reliability (ICC = 0.65<sup>174</sup> to 0.94<sup>161</sup>), but interrater reliability and agreement may be highly variable and specific to each individual group of raters (ICC = 0.52<sup>32</sup> to 0.83<sup>161</sup>).<sup>32, 102, 161, 174</sup> These disease oriented outcomes are one of the few outcomes that have been specifically applied to an ACI patient population. However, they are also the least practical outcome measure to universally collect on ACI patients. In medical practice a second look arthroscopy cannot ethically be performed routinely. These follow-up surgeries will only be performed in patients who report dissatisfaction with treatment outcomes or new injury, resulting in a biased sample. Research is ongoing into less invasive assessment techniques such as magnetic resonance imaging to reliably document cartilage healing and structure.<sup>83, 95, 140</sup> While these techniques may provide a quality evaluation of tissue structure and healing, they are not cost effective across large populations, and physical structure may not always relate to pain and function levels.

Performance based testing, particularly of the lower extremity, has been suggested as part of a comprehensive rehabilitation program for several years.<sup>12, 63</sup> However, there are few clear cut recommendations as to what form lower extremity PBAs should take. The ultimate goal of performance based testing is to assess function by recreating forces similar to those the body experiences during normal activity or participation.<sup>94</sup> This form of outcomes assessment is relatively new within the ACI literature and is only known to have been reported in three outcome studies thus far.<sup>44, 146, 172</sup> In these studies the 6 minute walk test<sup>44, 47, 146</sup> and a series of single limb hopping tasks<sup>172</sup> were the assessments evaluated. The reliability for these tests or any other PBA has not been established among patients undergoing articular cartilage repair of the knee.

PBA measures should at minimum have the potential to be evaluated pre-operatively and at long-term (e.g.  $\geq 1$  year) follow-up. Ideally a measure will also be suitable for repeated testing throughout the recovery process. The NeuroCom Balance Master<sup>®</sup> and long force plate(LFP) (NeuroCom International, Clackamas, OR) together are a commercially available system designed both as a training and evaluation tool for functional and balance tasks.<sup>5</sup> This system has the ability to provide immediate feedback to clinicians and patients regarding quality of task performance for a variety of activities of daily living (ADLs). Additionally, performance values are saved in individual patient files for easy comparison to evaluate progress over time. Tasks that are part of the LFP testing protocol that simulate ADLs and have potential as ACI outcome measures include the unilateral stance, weight bearing squat, sit-to-stand, rhythmic weight shift, step-up and over, and the forward lunge. These outcome measures are of low to moderate demand and should be feasible for performance by ACI patients throughout much of the recovery process. However, for these tasks to be useful as assessments, they must be reliable

across time points to document changes in function following surgical treatment.

Therefore, the purpose of this study was to evaluate the reliability of a series of force plate based PBAs among ACI patients.

## **METHODS**

### **Participants**

Twenty-one patients (12 males, 9 females, age  $36.4 \pm 6.8$  years, weight  $93.8 \pm 21.1$  kg, height  $175.9 \pm 12.1$  cm) being treated for articular cartilage defects to the knee participated in this study. Prior to study enrollment all patients provided institutional review board approved informed consent. This was a repeated measures study design with subjects tested 2 times within the same data collection period to evaluate test-retest reliability. To assess the reliability of measures at various stages of treatment, patients were either enrolled at their preoperative appointment prior to undergoing ACI (n=9) or at their 1 year follow-up appointment following ACI (n=12). Nine participants (4 preoperative) were undergoing treatment for defects to the tibiofemoral joint, while 12 participants (5 preoperative) underwent treatment to the patellofemoral joint that included tibial tubercle transfer in addition to ACI.

### **Performance Based Assessments (PBAs):**

Each participant completed a series of seven functional tasks performed on the LFP.<sup>5</sup> The LFP consists of a 45.72 cm x 152.40 cm force plate with data sampled at 100 Hz and a personal computer equipped with data capture software (Balance Master ver. 8.1). These functional tasks were selected because of their direct relationship to activities

of daily living and the feasibility of patients being able to complete the task at each testing time point (Table 2.1). Tests were completed for both testing sessions in the order presented in Table 2.1, which was determined to be from least to most demanding based on patient reporting of difficulty during pilot testing. All testing was administered by the same investigator (JSH). For all single limb tests the uninvolved limb was tested first. Three successful trials of each task were performed, except for the Weight Bearing Squat which consisted of a single trial at each joint angle and the Rhythmic Weight Shift which consisted of one trial at each speed in each direction. Approximately 15s of rest was provided between each trial and 30s of rest between each task. Following a minimum of a 15 minute rest period all tests were repeated on the same day. Before, and after each testing session participants were asked to verbally rate their knee pain on a 0-10 scale. Changes of more than 2 points between the start of testing sessions were considered to represent a meaningful change in pain and these participants were excluded from the reliability analysis. All outcome variables are identified using the names assigned to them by the software used, and are defined in Table 2.1. The seven tasks are described below.

*Walk Across:* Patients walked across the LFP using their freely chosen standard gait speed and pattern.

*Weight Bearing Squat:* Patients stood still on the force plate at the initial measure was recorded with knee flexion angles of 0°, 30°, 60°, and 90° as tolerated (0°). They then flexed their knees and held positions at 30°, 60°, and 90° as tolerated. The percentage of body weight on the involved limb was measured during a single trial with a duration .01s for each position. A standard goniometer was used to verify joint angle at each position.

**Table 2.1 Functional tasks evaluated on the NeuroCom Balance Master® Long Force Plate.** All tasks were performed in the order presented by patients treated for articular cartilage defects to the knee.

Task	Parameter Assessed	NeuroCom Outcome Variable	Definition		
<b>Walk Across</b>	Characterization of Gait	Stride Length (cm)	Distance between contralateral heel strikes		
		Stride Width (cm)	Lateral distance between center of pressure of left and right foot strikes		
		Walking Speed (cm/s)	Speed of forward progression of the center of gravity (COG)		
<b>Weight Bearing Squat Unilateral Stance</b>	Proprioception, Strength Balance	% Body Weight (BW) at 0° (full extension), 30°, 60°, and 90° of knee flexion Center of Gravity (COG) Sway Velocity (deg/s)	% BW on the involved limb at each position (test duration .01s) Angular displacement (angle between the center of pressure to theoretical COG vector and horizontal vector) divided by the 10s duration of the trial		
<b>Sit To Stand</b>	Strength and Double Limb Balance	Weight Transfer time (s)	Time required from start of motion while sitting (i.e. increase in center of pressure(COP) forward velocity by 5% from resting velocity) to achieve full weight bearing standing (i.e. forward velocity drops to within 5% of standing resting velocity)		
		Rising Index (%BW)	Peak vertical force exerted through the legs when rising to full standing relative to stationary vertical standing force		
		COG Sway Velocity (deg/s)	Angular displacement (angle between the center of pressure to theoretical COG vector and horizontal vector) divided by the time to rise and the first 5s following rising		
		Weight Symmetry	% Difference in weight supported by each limb during the weight transfer phase		
		On-Axis Velocity (deg/s)	Average speed of movement in the target direction		
<b>Rhythmic Weight Shift</b>	Postural Control	Directional Control (ratio)	Ratio of movement in the intended direction to extraneous movement away from the intended direction		
		<b>Step-up/Over</b>	Concentric Strength and Eccentric Control	Lift-up Index (%BW) Impact Index (%BW) Movement Time (s)	Peak vertical force occurring while stepping up onto the box as a percentage of body weight Peak vertical force occurring while stepping down off the box as a percentage of body weight Time between initial weight shift (i.e. change in COP velocity by 5%) and contact with force plate on opposite side of box (determined by COP velocity dropping to within 5% of post-test resting velocity)
		<b>Lunge</b>	Concentric and Eccentric Control, Functional Range of Motion	Distance (% subject height) Movement Time (s) Impact Index (%BW)	Length of lunge step as a percentage of subject height Duration of lunge phase during which lead leg is in contact with the force plate. Start and stop of a trial is determined by 5% change in COP velocity from pre-test and post-test resting velocity. Peak vertical force occurring during lunge maneuver as a percentage of body weight

*Unilateral Stance:* Patients stood on each leg and maintained their balance for 10 s with their eyes open. They begin with the non-weight bearing leg flexed at about 60-80° and with their hands on their hips. If patients touched down, or their legs touched each other, testing was stopped and the trial was discarded. Testing of a condition was discontinued if a participant experienced three consecutive failed trials. Testing was repeated for both legs with the patients' eyes closed.

*Sit to Stand:* Patients were seated on a 50cm box. Upon both visual and audio signal from the computer they rose to full standing as quickly as possible without using their hands, and then maintained a steady stance for the remainder of the 10 s trial.

*Rhythmic Weight Shift:* Patients stood on the force plate and shifted their center of gravity (COG) rhythmically left to right or front to back between targets at 1s, 2s, and 3s intervals. Both visual and audio cues were provided for pacing, as was visual feedback for the position of the COG. One trial consisted of three complete cycles between targets. One trial was completed at each speed/direction combination.

*Step-Up/Over:* Participants stood behind a 29cm high box and stepped up onto the box with their test leg, then brought their non-test leg up and over the box, and then stepped down with their test leg. This was performed as quickly as possible while still maintaining control.

*Forward Lunge:* Patients in a standing position stepped forward on one leg and squatted down as far as comfortably possible, and then returned to the initial standing position as quickly as possible.

## **Statistical Analysis**

Outcome variables were averaged for the three trials on the involved limb for each task, except for the Weight Bearing Squat and the Rhythmic Weight Shift. For the Weight Bearing Squat a single trial at each joint angle was examined. For the Rhythmic Weight Shift on axis velocity and directional control were averaged across speeds for each direction (right-to-left and front-to-back) to provide a composite score for each variable in each direction. The descriptive statistics of minimum, maximum, mean and standard deviation (SD) were used to summarize the data. Intraclass correlations (ICC(2,1)) were used to evaluate the test re-test reliability of each outcome measure. For unilateral tests, only the reliability of the involved (surgical) limb was analyzed. All tests with ICC greater than or equal to 0.75 were considered to have acceptable reliability as a PBA for documenting outcomes following ACI. Standard error of measurement ( $SEM=SD(\sqrt{1-ICC})$ ) values were also calculated to provide a clinical context to the data by reporting the response stability in the actual units of measures.<sup>138</sup> The SEM represents the range of scores that can be expected on re-testing. PASW 18.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

## **RESULTS**

### **All Patients**

The resulting descriptive and reliability statistics are reported in Table 2.2. No patients were excluded from the analysis due to changes in self-reported pain between testing sessions. ICC values when all patients were analyzed as one group ranged from 0.38 to 0.94. For the Walk Across, both stride length and speed demonstrated acceptable

**Table 2.2 Descriptive Data and Reliability Statistics for Performance Based Assessments Among Autologous Chondrocyte Implantation Patients Pre and 12 Months Post Operatively**

Test Variable*	Preoperative					12 Months Postoperative					All Patients Combined				
	Min	Max	Mean (SD)	ICC (2,1)	SEM	Min	Max	Mean (SD)	ICC	SEM	Min	Max	Mean (SD)	ICC	SEM
<b>Walk Across</b>															
Width (cm)	9.6	23.5	17.8(4.0)	0.76	1.9	7.6	27.4	17.8 (3.6)	0.68	2.0	7.6	27.4	17.8 (3.6)	0.68	2.1
Length (cm)	58.0	99.5	79.8(18.2)	0.99	0.8	58.2	100.1	83.1 (11.6)	0.92	3.3	58.2	100.1	81.9 (14.0)	0.96	2.7
Speed (cm/s)	65.8	103.8	84.1(10.1)	0.62	6.3	68.3	117.7	90.8 (12.5)	0.82	5.4	68.3	117.7	88.4 (11.9)	0.76	5.0
<b>Weight Bearing Squat (%BW)</b>															
0°	35	51	46(4)	0.32	3	43	56	48 (3)	0.55	2	43	56	47 (3)	0.47	2
30°	28	52	43(6)	0.54	4	39	56	46 (3)	0.14	3	39	56	45 (5)	0.38	4
60°	23	57	45(8)	0.42	6	40	57	46 (4)	0.65	3	40	57	46 (6)	0.49	4
90°	20	52	45(9)	0.87	3	39	53	47 (3)	0.34	3	39	53	46 (6)	0.75	3
<b>Unilateral Stance (COG Sway Velocity (deg/s))</b>															
Eyes Open	0.50	1.40	0.81(0.21)	0.78	0.10	0.60	1.70	0.89 (0.24)	0.74	0.12	0.60	1.70	0.86 (0.23)	0.75	0.12
Eyes Close	1.20	4.10	2.13(0.70)	0.78	0.33	1.20	3.20	1.98 (0.51)	0.74	0.26	1.20	3.20	2.05 (0.59)	0.77	0.28
<b>Sit to Stand</b>															
Weight Transfer Time (s)	0.25	2.23	0.59(0.38)	0.35	0.31	0.15	0.80	0.27 (0.12)	0.41	0.09	0.15	0.80	0.41 (0.30)	0.48	0.22
Rise Index (% BW≥100%)	15	53	28(12)	0.98	2	8	42	23 (9)	0.90	3	8	42	25 (11)	0.94	3
COG Sway Velocity (cm/s)	0.60	5.10	3.40(1.15)	0.55	0.77	1.30	6.40	4.48 (1.20)	0.58	0.78	1.30	6.40	4.02 (1.27)	0.61	0.79
<b>Rhythmic Weight Shift</b>															
On Axis Velocity Left-Right Composite (deg/s)	4.90	7.80	5.96(0.83)	0.93	0.22	5.00	8.60	6.05 (1.03)	0.91	0.31	5.00	8.60	6.02 (0.93)	0.92	0.27
On-Axis Front-Back Composite (deg/s)	2.90	6.20	4.02(0.87)	0.84	0.35	2.80	4.80	3.76 (0.44)	0.75	0.22	2.80	4.80	3.86 (0.64)	0.82	0.27
Directional Control Left-Right Composite (%)	81	94	86(3)	0.45	2	79	90	86 (3)	0.80	1	79	90	86 (3)	0.62	2
Directional Control Front-Back Composite (%)	74	88	82(4)	0.66	2	54	87	75 (7)	0.52	5	54	87	78 (7)	0.62	4
<b>Step Up/Over</b>															
Lift-up Index (% BW≥100%)	24	65	43(11)	0.88	4	25	67	49 (12)	0.98	2	25	67	46 (12)	0.93	3
Time (s)	1.14	2.48	1.55(0.38)	0.95	0.08	0.95	2.00	1.41 (0.29)	0.89	0.09	0.95	2.00	1.47 (0.33)	0.92	0.09
Impact (% BW)	19	61	42(14)	0.92	4	34	88	54 (14)	0.84	5	34	88	49 (15)	0.89	5



**TABLE 2.2 (continued) Descriptive Data and Reliability Statistics for Performance Based Assessments Among Autologous Chondrocyte Implantation Patients Pre and 12 Months Post Operatively**

Forward Lunge	42	54	47 (3)	0.79	1	38	56	48 (5)	0.85	2	48 (4)	0.84	2
Distance (% height)	17	34	25 (6)	0.84	2	13	38	24 (7)	0.75	3	24 (6)	0.78	3
Impact Index (% BW)	0.82	1.75	1.38 (0.29)	0.94	0.07	0.85	2.14	1.22 (0.32)	0.91	0.10	1.29 (0.31)	0.93	0.09
Time (s)	94	231	155 (33)	0.82	14	88	224	131 (32)	0.90	10	141 (34)	0.88	11.74
Impulse (%BW x s)													

\* See Table 2.1 for details regarding each variable. Standard Error of the Measurement (SEM); Intraclass Correlation Coefficient<sub>2,1</sub> (ICC); Center of Gravity (COG); Percentage of Body Weight (%BW).

reliability ( $ICC \geq 0.75$ ). For the Weight Bearing Squat only squatting at  $90^\circ$  of knee flexion demonstrated acceptable reliability. Both eyes open and eyes closed Unilateral Stance on the involved limb showed acceptable reliability. For the Sit-to-Stand only the rise force met the reliability standard. Both left-right and front-back composite on axis velocity for the Rhythmic Weight Shift were reliable. The Step Up/Over was reliable for lift-up index, movement time, and impact index. Finally, distance, impact index, movement time, and impulse were reliable for the Forward Lunge.

### **Preoperative vs. Postoperative**

Among preoperative patients ICC values ranged from .32 to 0.99. Among patients 12 months post ACI, ICC values ranged from .14 to .98. The Weight Bearing Squat at  $90^\circ$  was observed to be reliable in the preoperative group ( $ICC=0.87$ ), but not in the postoperative group ( $ICC=0.34$ ). Walk Across speed (pre  $ICC=0.62$ , post  $ICC=0.82$ ) and Rhythmic Weight Shift left-right directional control composite score (pre  $ICC=0.45$ , post  $ICC=0.80$ ) were the only variables observed to have acceptable reliability in the postoperative group but not in the preoperative group. For the remaining variables observed to have acceptable reliability across groups ICC values differed by less than 0.10 between preoperative and postoperative patients.

### **DISCUSSION**

The purpose of this study was to investigate the reliability of a series of tests using the NeuroCom Balance Master<sup>®</sup> long force plate among knee cartilage patients. These tests represent potential performance based outcomes to serially evaluate treatment progress and success following ACI or other cartilage repair and restoration procedures. For each

of the tests evaluated, at least one outcome variable was observed to have acceptable reliability with  $ICC \geq 0.75$ . Overall the most reliable task was the Step Up/Over and the least reliable task was the Weight Bearing Squat.

To our knowledge this is the first study to evaluate the reliability of LFP measures in a pathologic knee population. NeuroCom International has previously reported reliability among healthy participants for all of the tests evaluated with the exception of the Rhythmic Weight Shift.<sup>3</sup> This reliability consisted of Pearson product moment correlation coefficients ( $r$ ) calculated “by performing linear regression analysis.”<sup>3</sup> One limitation to the use of these simple linear analysis tests is that systematic differences cannot be detected between testing sessions, which may occur due to a learning effect. Other authors using the NeuroCom system have frequently referenced these correlation values as being acceptable.<sup>6, 180, 183</sup> Despite the limitations of the NeuroCom International data, the correlation coefficients they report are similar to those we observed with  $r$  values ranging from 0.35 to 0.93.<sup>3</sup>

Elsewhere in the literature, “Good to excellent”<sup>173</sup> reliability for the unilateral stance and forward lunge among healthy participants was referenced by Willems et al.<sup>184</sup> Additionally, independent intertester and intratester reliability has been established in active females for the Step-Up/Over and the Forward Lunge with ICC values ranging from 0.59 to 0.93.<sup>119</sup> It should be noted that the ability to interpret and generalize these authors’ findings is limited due to the use of ICC equation (3,k). By definition reliability calculated using model 3 is only applicable for the examiner for whom the reliability has been calculated and cannot be generalized to other potential examiners.<sup>160</sup> Finally, the use of only healthy, female participants in this study limits its generalizability to more diverse clinical populations including knee patients.

Despite the differences between studies, a comparison between our results and Naylor and Romani<sup>119</sup> demonstrates similar reliability values, even in the presence of different performance means. Both studies reported acceptable intratester reliability for these measures. Compared to Naylor and Romani we observed slightly higher ICCs for lift-up index (0.93 our study vs. 0.68 to 0.79) and impact index (0.89 our study vs. 0.83) and identical values for movement time (0.92).<sup>119</sup> Similar results were seen for the Forward Lunge where ICCs ranging from 0.72 to 0.93 were observed, while Naylor and Romani reported values from 0.71 to 0.93. Furthermore, differences between patients with a known pathology and healthy participants represent a level of face validity for these NeuroCom tests. For example, when comparing our results to those reported by Naylor and Romani lower functional scores were observed among our pathologic patients than their healthy female controls.<sup>119</sup> During the Step Up/Over our patients demonstrated lower lift-up index (46% vs 48% to 54%) and impact index values (49% vs. 55% to 65%), but longer movement times (1.47s) compared to the healthy athletic female participants (1.03 to 1.09s).<sup>119</sup> During the Forward Lunge ACI patients demonstrated shorter lunge distance (48% vs. 53% to 57%) and lower impact index (24% vs. 39 to 42%), but longer movement time (1.29s vs. 0.73s to 0.77s) in comparison to those values reported among healthy, athletic females.<sup>119</sup> Despite these performance differences, similar reliability was observed in our study compared to that previously reported for all forward lunge variables with both studies demonstrating reliability above the 0.75 threshold for lunge distance, impact index, movement time and impulse.

The outcome measures where reliability fell below the *a priori* threshold of 0.75 were Walk Across width; Weight Bearing Squat at 0°, 30°, and 60°; Sit to Stand weight transfer time and center of gravity sway velocity; and the Rhythmic Weight Shift

directional control moving left-right or front-back. For the Weight Bearing Squat the variability of this task may be higher than the other tasks evaluated due to the nature of the data collected. Unlike other measures where the average of three trials is recorded as the outcome variable, per the NeuroCom protocol, only a single trial at each position is recorded for the Weight Bearing Squat. Furthermore, the testing protocol for the Weight Bearing Squat captures the percentage of weight bearing for only a single data point at the time the test is initiated. The averaging of multiple trials at each position may improve the reliability of this test. A similar effect may exist with the Rhythmic Weight Shift where the computer software is designed to collect only one trial at each speed. Lower reliability values were also observed for width of the Walk Across task (ICC=0.68). This task demonstrated a learning effect as our participants had a 2.6 cm narrower stride during the second testing session. Narrowing of the stride is considered to represent improved function as an individual becomes comfortable with a narrower base of support.<sup>3</sup> Therefore, this improvement may be a result of individuals becoming more comfortable with the testing apparatus and laboratory environment over time, thus reducing our reliability values. Since the Walk Across was the first overall test, the reliability of this test may be improved by providing participants with more time to acclimate to the testing procedures.

One goal of this study was to examine the reliability of LFP tasks across levels of function within the same patient population. This was investigated by including both preoperative and 12 month postoperative patients in the study population. Although there were some differences in reliability between preoperative and postoperative groups, in general outcome measures that were observed to be reliable in one group were reliable in the other. The exceptions to this were the Walk Across speed, Weight Bearing Squat at

90°, and Rhythmic Weight Shift right-left directional control composite score. Each of these had ICC values ranging from 0.62 to 0.76 when examined across groups and potential threats to reliability that have already been discussed. Specifically, the Walk Across and Rhythmic Weight Shift reliability may have increased over time due to a potential learning effect among 12 month patients who had more experience with these tasks due to previous exposure as part of an ongoing outcomes study. Overall for each task, with the exception of the Weight Bearing Squat, at least one outcome variable was observed to have acceptable reliability among both preoperative and postoperative patients.

### **Limitations**

Patients were evaluated preoperatively and one year postoperatively, hence reliability at interim time points cannot be assessed. Reliability was assessed intraday as it was anticipated that the greatest threat to reliability would be a learning effect for the tests utilized, hence any interday effects have not been investigated. In this study we examined reliability of the long force plate measures, and did not evaluate the responsiveness of these measures to treatment progress.

### **CONCLUSION**

PBAs have the potential to provide further insight into patient outcomes following ACI. However, PBAs must be reliable to be effective for evaluating patient progress over time. The NeuroCom Balance Master<sup>®</sup> Long Force Plate is capable of reliably evaluating ACI patient performance of movements utilized during ADLs. Lower extremity function was most reliably assessed by the step up/over and lunge tasks for which ICC values

ranged from 0.78 to 0.93, demonstrating consistent evaluation in a pathologic knee population. Additionally, select outcome variables associated with the Walk Across, Weight Bearing Squat, Unilateral Stance, Sit to Stand, and Rhythmic Weight Shift were also observed to have acceptable reliability ( $ICC \geq 0.75$ ). Furthermore, this instrument demonstrated reliability across a variety of levels of function among both preoperative patients and those one year post ACI surgery.

## ***CHAPTER 3: PATIENT ORIENTED AND PERFORMANCE BASED OUTCOMES FOLLOWING KNEE AUTOLOGOUS CHONDROCYTE IMPLANTATION***

### **INTRODUCTION**

Autologous chondrocyte implantation (ACI)<sup>28</sup> has become an acceptable and common treatment approach for the management of symptomatic articular cartilage defects.<sup>61</sup> As research regarding ACI has advanced sizable efforts have been made to evaluate both disease and patient oriented outcomes following ACI. Numerous studies have evaluated the utilization of patient reported outcomes (PROs) to document the recovery of function and return to activity following ACI.<sup>74</sup> Meta-analyses of more than 43 studies have revealed large effect sizes demonstrating significant improvement for a variety of PRO scores following ACI.<sup>74</sup> PROs provide reliable and valid information regarding patients' perceived function and health related quality of life (HRQL). An alternative to PROs is the use of performance based assessments (PBAs) to document outcomes. PBAs provide a direct, objective measure of patient function and involve measures of performance such as time, distance, or force for specified tasks or movements. The relationship between PROs and PBAs has previously been reported as low to moderate among a variety of knee patients.<sup>52, 79, 82, 117, 120, 159</sup> Recent research involving total joint arthroplasty patients has provided further support for the inclusion of PBAs as part of a detailed outcomes assessment protocol.<sup>79, 117, 166</sup> The combining of PROs with PBAs may provide a more complete picture of clinical outcomes after ACI than the utilization of either type of outcome in isolation.



Few studies have utilized PBAs to document the return of function following ACI. Those that have, have either examined very low demand activity such as the 6 minute walk test,<sup>44, 45, 146</sup> or very high demand activity via the single-limb hop.<sup>172</sup> No known studies have examined the timeline for return to function following ACI using low to moderate demand PBAs that recreate the demands and stresses of common activities of daily living such as squatting, rising from sitting, or going up and down stairs, in addition to walking. Nor has the relationship between PROs and PBAs been examined in an ACI patient population. An accurate description of functional recovery during the first year following ACI is imperative to provide evidence for prescription of appropriate patient education, rehabilitation protocols, and understanding of the recovery process. Furthermore, an understanding of the relationship between PROs and PBAs will provide key information regarding the importance of collecting varying types of outcomes in future cartilage repair research. At present PROs are the accepted standard for functional outcomes in cartilage research; however, if PRO scores are not correlated with PBAs then both outcome measures may be necessary to document both perceived and physical changes in patient function following ACI. Therefore, the purpose of this study was to document serial changes in knee function over one year following ACI using both PROs and PBAs and to explore the relationship between PROs and PBAs during recovery following ACI. It was hypothesized that PROs would demonstrate significant improvement from baseline at all postoperative time points. It was also hypothesized that PBA measures for walking, rising from sitting, stepping up/over, and lunging would demonstrate no improvements at the 3 month time point followed by progressive improvement at 6 months and 12 months as compared to baseline measures of function. Finally, it was hypothesized that a significant relationship ( $P \leq 0.05$ ) would exist between

all PRO scores and performance measures for walking, rising from sitting, stepping up/over, and lunging at all time points with both forms of assessment demonstrating positive improvements over time.

## **METHODS**

### **Patients**

Beginning in July 2009 patients were prospectively recruited from an active cartilage center. Inclusion criteria were planned ACI surgery to the medial or lateral femoral condyle, trochlea, or patella; willingness to participate and no uncorrectable contraindications to ACI such as extensive degenerative joint disease, insufficient meniscus, or unstable knee; and ability to ambulate without use of assistive devices. There were no exclusions based on limb malalignment if the malalignment was corrected prior to or at the time of surgery via high tibial osteotomy or tibial tubercle transfer. Similarly, patients undergoing concomitant or staged ligament reconstruction to correct joint instability were also eligible for study participation. Patients undergoing concomitant meniscal transplant were excluded.

A total of 29 patients (17 males, 12 females,  $36.3 \pm 6.9$  yrs,  $174.4 \pm 9.6$  cm,  $90.4 \pm 19.4$  kg) agreed to participate. Three patients were invited to take part of the study, but declined to participate resulting in an enrollment rate of 90%. Of the enrolled patients 13 underwent ACI to the patellofemoral joint with a tibial tubercle transfer and the remaining 16 underwent ACI to the medial femoral condyle, of which 4 also had a concomitant high tibial osteotomy. Mean number of defects treated per patient were  $1.38 \pm 0.6$  with an

average treatment area of  $6.6 \pm 2.5 \text{ cm}^2$  (range 2.3 to 13.0  $\text{cm}^2$ ). All participants signed a university approved IRB consent form at the time of enrollment.

### **Surgical Procedures and Rehabilitation**

All patients underwent a two-step ACI procedure performed by the same surgeon (CL). During the first procedure a limited chondroplasty was performed and the lesion was evaluated arthroscopically. At this time a biopsy was obtained from the intracondylar notch (100 to 200 mg cartilage). This sample was sent to a commercial laboratory where it was cultured and expanded (Carticel, Genzyme Corp, Cambridge, MA). In a second surgical procedure chondrocyte implantation was performed using a mini-arthrotomy. First the defect or defects were prepared using a curette to debride down to the subchondral plate with stable edges. A type I/III collagen membrane (Chondro-Gide<sup>(R)</sup>, Geistlich Biomaterials, Wohousen, Switzerland) was shaped to match the defect. Sutures and fibrin glue (Tisseel, Baxter Healthcare Corp., Deerfield, IL) were used to adhere the membrane over the defect to form a water tight seal. The chondrocytes in suspension were then injected beneath the membrane into the defect through a small portal remaining at the edge of the collagen membrane. The portal was then closed and sealed with sutures and additional fibrin glue.

All patients followed standardized rehabilitation protocols following surgery.<sup>93</sup> All patients were braced in full extension and were non-weight bearing for 2 weeks postoperatively. Toe-touch weight bearing was permitted from 2 to 4 weeks with partial weight bearing from 4 to 6 weeks and progression to full weight bearing between weeks 6 to 12. Continuous passive motion was prescribed for all patients for 6 to 8 hours per day for 6 weeks. For defects in the tibiofemoral joint knee braces were gradually unlocked

between 2 to 4 weeks as quadriceps control was gained. For defects to the patellofemoral joint knees were braced in full extension for weight bearing through 4 weeks postoperative and then were gradually unlocked as quadriceps control was gained between weeks 4 and 6. Once good quadriceps control was gained all patients were transitioned to a hinged knee sleeve. All patients were recommended to abstain from high intensity cutting or pivoting activity until at least 12 months post ACL.

### **Patient Reported Outcomes**

The PROs used in this study were the Medical Outcomes Study – 36 Item Short Form Health Survey Physical Component Scales (SF-36 PCS),<sup>105, 106, 179</sup> the Western Ontario and McMaster Osteoarthritis Index (WOMAC),<sup>18</sup> the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form,<sup>77</sup> and the Lysholm scale.<sup>96</sup> The SF-36,<sup>58</sup> IKDC,<sup>58</sup> Lysholm,<sup>85</sup> and WOMAC<sup>58, 85</sup> have all been evaluated for reliability among cartilage patients. The SF-36 PCS was included to serve as a measure of HRQL. The IKDC and Lysholm are region specific instruments that focus on knee function, while the WOMAC is a disease specific instrument focusing on degenerative joint disease covering pain, stiffness, and function. A researcher independent of the treating physician reviewed each instrument with the patients and was available to answer any questions they may have had. All PROs were completed at the following time points: prior to implantation (preoperation), 3 months, 6 months, and 12 months post-surgery.

### **Performance Based Assessments**

At each time point after completing PROs each participant completed a series of 6 PBAs in a musculoskeletal laboratory setting. All PBAs were completed using the NeuroCom Balance Master<sup>®</sup> and long force plate (LFP) (NeuroCom International,

Clackamas, OR). This is a commercially available system designed both as a training and evaluation tool for function and balance tasks, and it has the ability to provide immediate feedback to clinicians and patients regarding quality of task performance for a variety of activities of daily living (ADLs).<sup>5</sup>

The LFP consists of a 45.72 cm x 152.40 cm force plate with data sampled at 100 Hz and a personal computer equipped with data capture software (Balance Master ver. 8.1). These functional tasks were selected because of their direct relationship to activities of daily living and the feasibility of patients being able to complete the task at each testing time point (Table 2.1). Tests were completed in the order presented at all time points. This order was subjectively determined during pilot testing to be from least to most demanding. All testing was administered by the same investigator (JSH). For all single limb tests the uninvolved limb was tested first. Three successful trials of each task were performed (except for the Weight Bearing Squat which consisted of a single trial at each joint angle). Approximately 15s of rest was permitted between each trial and 30s of rest between each task. For the purposes of this manuscript all outcome variables are identified using the names assigned to them by the software utilized. Definitions for these variables are presented in Table 2.1. The six tasks are described below.

*Walk Across:* Patients walked across the LFP using their freely chosen standard gait speed and pattern.

*Weight Bearing Squat:* Patients stood still on the force plate at the initial measure was recorded with knee flexion angles of 0°, 30°, 60°, and 90° as tolerated (0°). They then flexed their knees and held positions at 30°, 60°, and 90° as tolerated. The percentage of body weight on the involved limb was measured during a single trial with a duration .01s

for each position. A standard goniometer was used to verify knee joint angle at each position.

*Unilateral Stance:* Patients stood on each leg and maintained their balance for 10 s with their eyes open. They begin with the non-weight bearing leg flexed at about 60-80° and with their hands on their hips. If patients touched down, or their legs touched each other, testing was stopped and the trial was discarded. Testing of a condition was discontinued if a participant experienced three consecutive failed trials. Testing was repeated for both legs with the patients' eyes closed.

*Sit to Stand:* Patients were seated on a 50cm box. Upon both visual and audio signal from the computer they rose to full standing as quickly as possible without using their hands, and then maintained a steady stance for the remainder of the 10 s trial.

*Step-Up/Over:* Participants stood behind a 29cm high box and stepped up onto the box with their test leg, then brought their non-test leg up and over the box, and then stepped down with their test leg. This was performed as quickly as possible while still maintaining control.

*Forward Lunge:* Patients in a standing position stepped forward on one leg and squatted down as far as comfortably possible, and then returned to the initial standing position as quickly as possible.

### **Statistical Analysis**

Separate repeated measures ANOVAs were used to compare changes in PROs and each force plate assessment between preoperative, 3 month, 6 month, and 12 month postoperative evaluations. The significance level was set at  $p \leq 0.05$  *a priori* and when a main effect for time was evident pairwise comparisons with a Bonferonni adjustment to

correct for multiple comparisons were used to identify differences between individual time points. In addition to evaluating for statistical differences, changes between performance values at the preoperative time point and each follow-up time point were also compared to minimal detectable change (MDC) values. The MDC values were calculated from a concurrent study evaluating the reliability of long force plate measures in ACI patients (Chapter 2).<sup>73</sup> A Pearson product moment correlation was used to examine the relationship between PROs and PBAs at each time point. Relationships with R-values above .90 were considered to have a high correlation, 0.71 to 0.90 was moderate, and 0.40 to 0.71 was low.<sup>169</sup> For all correlations a significance level of  $p \leq 0.05$  was set *a priori*.

## **RESULTS**

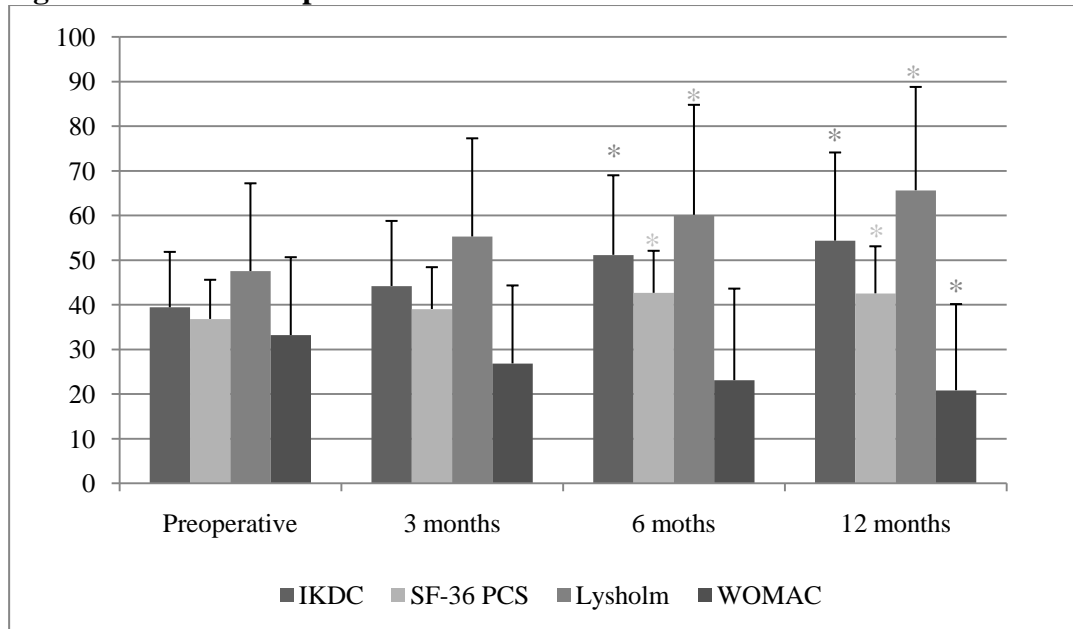
Six participants were declared clinical failures at or before the one year time point and were not medically cleared to complete functional testing at all time points. An additional five participants were lost to follow-up. Finally, one participant failed to complete preoperative force plate testing and another participant was lost to follow-up at the 6 month time point, but returned to the study at the 12 month time point. As a result full PBA data was only available for 16 subjects. Full PRO data was available for 21 patients including 4 patients who were declared failures at the 12 month time point.

### **Patient Reported Outcomes**

There was a main effect for time for all four PRO instruments (Figure 3.1). There were significant improvements from preoperation to 12 month follow-up for the IKDC ( $p = 0.012$ ), SF36-PCS ( $p = 0.011$ ), Lysholm ( $p = 0.002$ ), and WOMAC ( $p = 0.013$ ). The

IKDC ( $p = 0.50$ ) and the Lysholm ( $p = 0.008$ ) also improved significantly between preoperation and 6 months postoperatively. There were no significant changes between preoperation and the 3 month time point for any of the PRO instruments.

**Figure 3.1. Patient Reported Outcome Scores**



\* $p \leq 0.05$  compared to preoperative time point. IKDC and Lysholm are scored from 0 to 100 with 100 representing an ideal score. SF-36 PCS uses a norm-based scoring system where 50 represents a mean score with a standard deviation of 10 and higher scores representing higher levels of function. The WOMAC is scored 96-0 with 0 representing an ideal score.

### Performance Based Assessments

The only PBAs to demonstrate changes over time were the Walk Across, Weight Bearing Squat, and Step Up/Over (Table 3.1). There was a significant increase in stride length observed between the 3 month and 6 month time points ( $p = 0.025$ ) for the Walk Across task. There were no significant changes in stride width or walking speed. For the Weight Bearing Squat a main effect for time was observed for squatting at 30°, 60°, and 90°. Post-hoc analysis revealed decreases in weight distribution on the surgical limb between preoperation (50% body weight) and 3 months (45% body weight,  $p = 0.05$ ) for



**Table 3.1. Patient Reported and Performance Based Assessments Over 12 Months Following Autologous Chondrocyte Implantation**

Test Variable	Preoperative		3 Months		6 Months		12 Months		Minimal Detectable Change
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
<b>Walk Across</b>									
Width (% height)	10.1	1.9	10.6	1.6	9.6	1.9	9.8	2.4	2.3
Length (% height)	42.3	7.2	41.8	10.3	47.5 <sup>†‡</sup>	7.1	48.3 <sup>‡</sup>	6.4	3.0
Speed (cm/s)	78.5	9.6	84.4	17.1	85.7	21.8	93.6 <sup>‡</sup>	11.4	11.50
<b>Double Limb Squat (% Body Weight (BW))</b>									
0°	49	3	48	2	49	3	48	3	5
30°	50	3	45*	5	46	5	46	3	8
60°	50	4	43*	5	44*	5	46	4	8
90°	52	6	45 <sup>‡</sup>	5	48	6	48	4	6
<b>Unilateral Stance (Center of Gravity(COG) Sway Velocity (deg/s))</b>									
Eyes Open	0.88	0.33	0.88	0.16	0.83	0.21	0.83	0.30	0.23
Eyes Close	1.76	0.60	2.99	3.48	1.79	0.36	1.84	0.50	0.21
<b>Sit to Stand</b>									
Weight Transfer Time (s)	0.38	0.38	0.39	0.27	0.39	0.27	0.29	0.10	0.43
Rise Index (% BW>100%)	25.2	9.9	21.7	7.1	24.5	7.5	25.5	8.6	5.04
COG Sway Velocity (cm/s)	4.12	1.19	4.80	1.50	4.56	1.81	4.30	1.25	1.56
Inv/Uninv Symmetry (-towards uninvolved)	-2.67	16.77	-11.27	14.28	-10.67	8.24	-7.33	9.08	11.16
<b>Step Up/Over</b>									
Lift-up Index (% BW>100%)	39.8	10.3	47.9 <sup>‡</sup>	12.1	50.0 <sup>‡</sup>	12.1	48.2 <sup>‡</sup>	10.1	6.0
Time (s)	1.39	0.25	1.67 <sup>‡</sup>	0.67	1.44	0.28	1.40	0.28	0.18
Impact (% BW)	50.2	13.8	54.0	20.5	59.6	21.0	56.5	14.4	9.7
<b>Forward Lunge</b>									
Distance (% height)	45.8	7.1	45.0	6.4	48.3	5.9	47.5	5.4	3.2
Impact Index (% BW)	24.4	7.4	21.8	6.4	24.0	4.9	23.9	7.5	5.8
Time (s)	1.23	0.38	1.52 <sup>‡</sup>	0.60	1.33	0.19	1.29	0.31	0.17

**Table 3.1. (continued) Patient Reported and Performance Based Assessments Over 12 Months Following Autologous Chondrocyte Implantation**

Test Variable	Preoperative		3 Months		6 Months		12 Months		Minimal Detectable Change
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
<b>Patient Reported Outcomes</b>									
IKDC	40.48	14.26	43.96	14.94	52.41*	18.98	54.87*	20.10	13.70 <sup>58</sup>
SF-36 PCS	37.05	10.25	40.01	9.60	43.49*	10.07	43.04*	10.54	6.60 <sup>58</sup>
Lysholm	47	22	55	23	64*	23	66*	24	15.80 <sup>85</sup>
WOMAC	32	19	27	19	22	21	20*	20	15.30 <sup>58</sup>

\*significantly different from preoperative time point, †significantly different from 3 month time point, ‡Change from preoperative greater than MDC

squatting at 30°. Decreases were also observed between preoperation and 3 months ( $p = 0.002$ ) and preoperation and 6 months ( $p = 0.02$ ) for squatting at 60°. At both the 3 month time point (43% body weight) and the 6 month time point (44% body weight) a lower percentage of body weight was placed on the surgical limb compared to squatting at the preoperative time point (50% body weight). Although not statistically different from preoperative values, at the 12 month time point mean weight distribution remained below preoperative values at 0° ( $49 \pm 3\%$  vs.  $48 \pm 3\%$ ), 30° ( $50 \pm 3\%$  vs.  $46 \pm 5\%$ ), 60° ( $50 \pm 3\%$  vs.  $46 \pm 5\%$ ), and 90° ( $52 \pm 6\%$  vs.  $48 \pm 4\%$ ). Finally, there were significant increases in lift-up force between preoperation ( $40 \pm 10\%$  body weight) and 6 months ( $50 \pm 12\%$  body weight) for the Step Up/Over. No other Step Up/Over variables changed significantly over one year following ACI.

Comparison of changes between preoperative and postoperative follow-up values to MDC values demonstrated measurable changes in performance for the Walk Across, Weight Bearing Squat, Step Up/Over, and Forward Lunge (Table 3.1). Between preoperation and the 3 month time point measurable decreases in weight distribution (7% body weight) on the involved limb were observed for squatting at 90°. During the same time period increases were observed for lift-up force (8.1% body weight) and performance time (0.28s) for the Step Up/Over, and for performance time (0.29s) for the Forward Lunge. Between preoperation and the 6 month time point Walk Across stride length increased by 5.2% of body height and Step Up/Over lift-up index increased by 11.2%. Finally, between preoperation and the 12 month follow-up Walk Across stride length increased by 6% of body height while walking speed increased by 15.1 cm/s and Step Up/Over lift-up index increased by 8.16% body weight.

## **Relationship Between Patient Reported Outcomes and Performance Based Assessments**

Across all time points there were 54 significant correlations with absolute R values ranging from 0.38 to 0.73. All significant correlations are presented in Table 3.2. Correlations occurred between each of the four evaluated PROs and the Walk Across, Unilateral Stance, Weight Bearing Squat, Sit-to-Stand and Forward Lunge functional tasks. At no time point did any of the PROs correlate to outcome measures for the Step Up/Over. Among PBA outcome measures there were 14 measures correlated to the IKDC score at varying time points (absolute R value range: 0.38 to 0.61), 18 to SF-36 PCS score (0.38 to 0.73), 8 to Lysholm score (0.38 to 0.64), and 14 to total WOMAC score (0.38 to 0.64). There were 17 correlations between PRO scores and PBA outcome measures at the preoperative time point (0.38 to 0.66), 7 at the 3 month time point (0.45 to 0.72), 10 at the 6 month time point (0.44 to 0.66), and 20 at the 12 month time point (0.48 to 0.73). There were no PRO scores or PBA measures that were consistently correlated to each other across all 4 time points.

## **DISCUSSION**

The primary purpose of this study was to provide a timeline for recovery that could be utilized by both patients and physicians in managing expectations regarding postoperative recovery of function. A summary timeline of the functional recovery observed in the first year following ACI can be seen in Figure 3.2. Improvements in patients' self-reported function were observed as early as 6 months following ACI using the IKDC and Lysholm outcome scores. In addition to these PROs, the SF-36 PCS and WOMAC also demonstrated improvements one year following ACI. In contrast, some

**Table 3.2. Correlations Between Performance Based Assessments and Patient Reported Outcomes By Follow-up Time Point**

Task	Preoperative				3 Months Postoperative			
	IKDC	SF-36 PCS	WOMAC	Lysholm	IKDC	SF-36 PCS	WOMAC	Lysholm
<b>Walk Across</b>								
Width	-	-0.38	0.50*	-	-	-0.50	-	-
Length	0.43	0.47	-0.66*	-	-	-	-	-
Speed	0.38	-	-	-	-	-	-0.45	-
<b>Weight Bearing Squat</b>								
0 degrees	-	-	-	0.38	-	-	-	-
30 degrees	0.42	-	-0.46	0.53*	-	-	-	-
60 degrees	-	-	-	0.46	-	-	-	-
<b>Unilateral Stance</b>								
Eyes open COG Sway	-	-0.44	-	-	-	-	-	-
Eyes closed COG SV	-0.46	-	-	-	-	-	-	-
<b>Sit-to-Stand</b>								
Rise Force	-	-	-0.38	-	-	-	-	-
Involved/ Uninvolved rise symmetry COG Sway	-	0.40*	-	-	-	0.49	-	-
<b>Lunge</b>								
Impact Index	-	0.45	-	-	0.53*	0.72*	-0.51*	-
Distance	-	-	-	-	-	0.50	-	-
Time	-	-	-	0.51	-	-	-	-

All presented correlations are significant at the  $p \leq 0.051$  level, (\* $p < 0.01$ )

**Table 3.2. (continued) Correlations Between Performance Based Assessments and Patient Reported Outcomes By Follow-up Time Point**

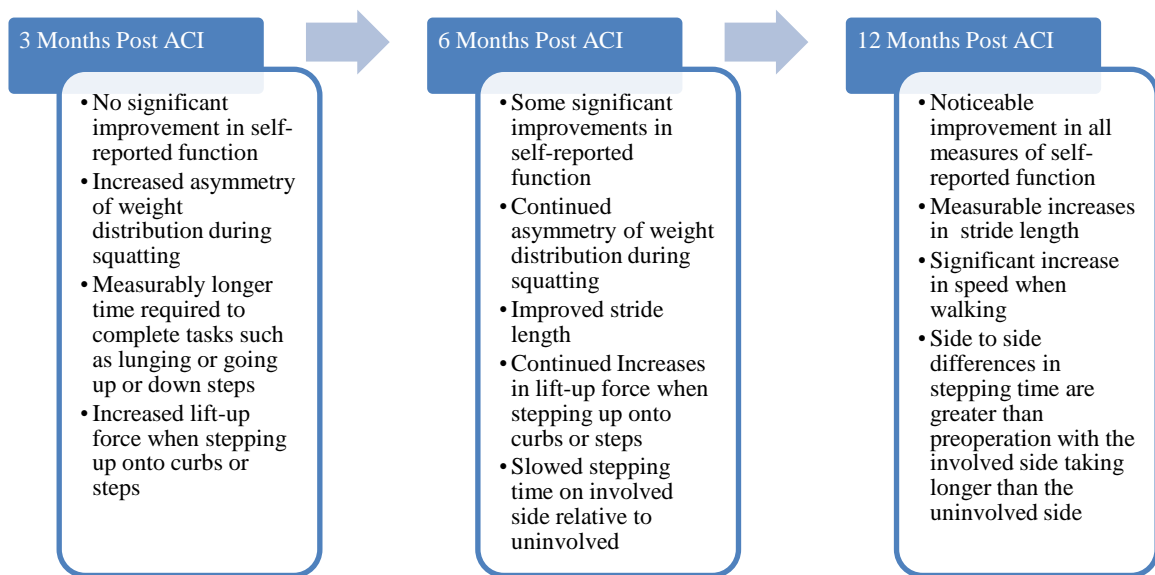
Task	6 Months Postoperative				12 Months Postoperative			
	IKDC	SF-36 PCS	WOMAC	Lysholm	IKDC	SF-36 PCS	WOMAC	Lysholm
<b>Walk Across</b>								
Width	-	-	-	-	-	-	-	-
Length	-	-	-	-	-	-	-	-
Speed	-	-	-	-	0.58	0.56	-0.54	-
<b>Weight Bearing Squat</b>								
0 degrees	-	-	-	-	-	-	-	-
30 degrees	0.44	0.59*	-0.52	-	-	-	-	-
60 degrees	-	-	-	-	-	-	-	-
<b>Unilateral Stance</b>								
Eyes open COG Sway	-	-	-	-	-0.54	-0.67*	0.64*	-0.64*
Eyes closed COG SV	-	-	-	-	-0.59*	-0.73*	0.58	-0.64*
<b>Sit-to-Stand</b>								
Rise Force	-	-	-	-	-	-	-	-
Involved/ Uninvolved rise symmetry COG Sway	-	-	-	-	0.61*	0.61*	-0.63*	0.50
<b>Lunge</b>								
Impact Index	0.62*	0.60*	-0.66*	0.61*	-	-	-	-
Distance	0.45	0.45	-0.51	-	-	-	-	-
Time	-	-	-	-	-	-0.48	-	-

All presented correlations are significant at the  $p \leq 0.051$  level, \* $p < 0.01$ )

decreases in performance based function relative to preoperative values were seen at the 3 and 6 month time points with decreased performance values for squatting, lunging, and stepping. Beginning at 6 months, increases in stride speed and length were observed; however, the difference between performance time for the involved side relative to the uninvolved side was greater at the 12 month time point than at the preoperative time point for the Step Up/Over. Overall, these results suggest that patients may experience physical benefits such as decreased pain and symptoms as early as 6 months following

ACI, but significant improvement in functional performance of complex tasks such as squatting, stepping, and lunging may not occur until 12 months or longer following ACI.

**Figure 3.2. Timeline of Functional Recovery Following Autologous Chondrocyte Implantation**



### Patient Reported Outcomes

PROs have frequently been utilized to report functional outcomes following ACI. The observed results suggest that patients should not expect significant improvement prior to the 6 month time point, and that in some cases, such as with the WOMAC, improvements may not be appreciable until one year post ACI. The lack of significant improvement in PRO scores at the 3 month time point is in agreement with previous research by Henderson and Levigne and Ebert et al.<sup>44, 67</sup> However, both of these authors observed decreases in self-reported function using the IKDC<sup>67</sup> and SF-36 PCS<sup>44, 67</sup> at the three month time point, while we observed slight, but non-significant increases. In contrast Tohyama et al. did observe significant improvements in Lysholm scores as early as 3 months following treatment with atelocollagen-associated ACI.<sup>171</sup>

The improvements observed among patients in IKDC, Lysholm, and SF-36 PCS scores at 6 months were similar to the outcomes observed by Niemeyer et al. for the IKDC<sup>122</sup> and both Niemeyer et al. and Kreuz et al. for the Lysholm.<sup>89, 122</sup> Other authors have observed even larger improvements in IKDC<sup>171</sup> and Lysholm<sup>14</sup> scores as early 6 months following ACI. The failure to observe improvements in the WOMAC at the 6 month time point in the current study is similar to other authors observations of no improvement at 6 months in IKDC<sup>67, 89</sup> or SF-36 PCS<sup>67</sup> scores. There have been no reports of WOMAC scores for periods of less than 1 year for comparison to the present results.

Across all PROs we observed improvements when preoperative scores were compared to scores 12 months following ACI surgery. These results are in agreement with the findings of others when utilizing the IKDC,<sup>42, 65, 67, 89, 121, 122, 158, 186</sup> Lysholm,<sup>89, 121, 122, 171, 186</sup> SF-36 PCS,<sup>67</sup> and WOMAC<sup>111, 113</sup> scores 1-year following ACI. Regardless of which outcome instrument is used, the IKDC, Lysholm, SF-36 PCS, or the WOMAC, both clinicians and patients can anticipate improvements in self-perceived function during the first year following ACI.

### **Performance Based Assessments**

Limited improvements in PBAs were observed 1-year following ACI (Table 3.2.). In general, a decrease in physical performance was observed at 3 and 6 months postoperatively, followed by a return towards baseline at 12 months following ACI. This pattern of decreased function followed by gradual return of function was particularly true for the Weight Bearing Squat, Step Up/Over, and Lunge. The only measures to show positive improvements at or within the 12 month time point were Walk Across stride



length and speed, and Step Up/Over lift-up index. These results suggest that improvements for simpler, less demanding tasks, such as walking or going up steps can be seen as early as 6 to 12 months following ACI. However, for more complex tasks, particularly those that require eccentric quadriceps control - such as squatting, going down steps, or lunging - meaningful changes in function may not be observed within the first year following ACI. From the results of this study it is unclear as to whether further improvements in function, particularly for more complex tasks occurs over long-term follow-up following ACI.

Decreases in physical performance at the 3 month time point have been previously observed with the 6 minute walk-test following matrix-induced autologous chondrocyte implantation (MACI)<sup>44, 45</sup> and characterized chondrocyte implantation (CCI).<sup>146</sup> Similar to our results, other researchers have observed slight improvements in walking performances at the 6 month<sup>45</sup> and 12 month<sup>45, 146</sup> time points that continue to improve at 24 month follow-up.<sup>45, 146</sup> During laboratory gait analysis improvements in gait speed and stride length, without significant changes in stride width, were observed over 12 months following MACI.<sup>43</sup> These results support our observation that, after an initial decrease in function, both patients and physicians can anticipate improvements in gait beginning around the 6 month time point following ACI.

In examining more dynamic tasks, Van Assche et al. observed decreased functional performance for a series of hopping and strength tasks (single-limb hop, cross-over hop, 6 m timed hop, and isometric knee extension strength) at 6 months following CCI and no significant improvements were observed as late as 24 months after CCI.<sup>172</sup> For example, these authors observed a 9% decrease in the single-leg hopping limb symmetry index

through 24 months following surgery.<sup>172</sup> These results are in agreement with our observations demonstrating an initial decrease in function for more dynamic tasks such as squatting, stepping, and lunging with few or no significant or measurable improvements in functional performance at the 12 month time point following ACI.

Normative values for some LFP variables for the Weight Bearing Squat, Unilateral Stance, Step Up/Over, and Forward Lunge have been published by the system manufacturer.<sup>3</sup> This normative data is presented by age group with individuals ages 20 to 39 (n = 74) and individuals ages 40 to 59 (n = 47) being the most appropriate groups for comparison to the current cohort. In comparing values observed in the present study to this historical data from healthy individuals some general observations can be made. For the Weight Bearing Squat normative data is only available for the standing (0°) position. Normative values for weight asymmetry in this position ranged from  $0.6 \pm 3.1\%$  to  $1.4 \pm 3.1\%$  body weight. These values were similar to those seen for ACI patients with asymmetries ranging from  $0.7 \pm 3.0\%$  (at 6 months) to  $2.4 \pm 2.3\%$  (at 3 months). For the Unilateral Stance the values observed among ACI patients throughout treatment for both the eyes open ( $0.8 \pm 0.2$  to  $0.9 \pm 0.3$  deg/s) and closed ( $1.8 \pm 0.6$  to  $3.0 \pm 3.5$  deg/s) conditions were similar to those observed among both normative age groups (eyes open:  $0.7 \pm 0.1$  to  $0.9 \pm 0.3$ , eyes closed  $1.9 \pm 0.7$  to  $2.9 \pm 1.1$  deg/s). For the Step Up/Over lift up index preoperative values ( $39.8 \pm 10.3\%$  body weight) began below normative values ( $46.9 \pm 14.1\%$  body weight to  $50.2 \pm 15.5\%$  body weight) but rose to normative values at all follow-up time points ranging from  $47.9 \pm 12.1\%$  body weight at 3 months to  $50.0 \pm 12.1\%$  body weight at 6 months. Similar values were also observed between ACI patients and healthy norms for Step Up/Over impact index. However, normative data for Step

Up/Over time ( $1.20 \pm 0.2s$  to  $1.3 \pm 0.3s$ ) trended to be lower than ACI patients at any time point ( $1.4 \pm 0.3s$  to  $1.7 \pm 0.7s$ ). For the Forward Lunge, impact index ( $21.8\% \pm 6.5\%$  body weight to  $24.4 \pm 7.4\%$  body weight) was lower at all testing points compared to the normative data ( $36.0 \pm 14.6\%$  body weight to  $42.2 \pm 15.3\%$  body weight). Also, Forward Lunge contact time was slower in ACI patients ( $1.2 \pm 0.4s$  to  $1.5 \pm 0.6s$ ) than has been previously reported among healthy individuals ( $1.0 \pm 0.2s$  to  $1.1 \pm 0.2s$ ). One variable that did approach normative values ( $48.3 \pm 8.6\%$  height to  $53.4 \pm 7.8\%$  height) was Forward Lunge distance which increased from  $45.8 \pm 7.1\%$  height at preoperation to  $48.3 \pm 5.9\%$  height at the 6 month time point.

In comparison to normative data<sup>3</sup> it can be observed that some LFP variables were normal at baseline and return to that level by the 12 month time point. These include the Weight Bearing Squat at  $0^\circ$ , Single limb stance, and Step Up/Over impact index. Other variables including the Step Up/Over lift-up index and Forward Lunge distances are below normative values preoperatively but increase to normal ranges by 12 months postoperative. Finally, some variables are below normal ranges preoperatively and remain so at the 12 month time point. These include the Step Up/Over time and Forward Lunge time and impact index.

Across the literature and within our study sample, improvements in gait relative to the preoperative time point have been observed as early as 6 months following ACI. However, improvements in more dynamic activities such as squatting, lunging, stepping, and hopping have not been observed within the first 12 months following ACI in the present study or elsewhere. These results support existing theory that although

improvements in self-report measures may occur early postoperatively, maximal defect healing and functional improvement continues beyond 12 months following ACI.<sup>22, 90, 145</sup>

### **Relationship Between Patient Reported Outcomes and Performance Based Outcomes**

Low to moderate correlations were observed between various PROs and PBAs at each of the 4 time points with no PRO/PBA pairing correlating consistently across all time points. The limited relationships observed between PROs and PBAs among ACI patients is similar to that which has been previously reported among patients with other lower extremity pathologies. Among anterior cruciate ligament patients (ACL)<sup>120, 144</sup> IKDC scores have been observed to have little ( $R=.28$ )<sup>159</sup> to no<sup>82</sup> relationship to single-leg hop, triple hop, cross-over triple hop, or vertical jump performance. Similarly, the Lysholm has been observed to have a low ( $R = 0.36$ )<sup>159</sup> to non-significant<sup>52, 120</sup> correlation to the single-leg hop or figure 8 run among ACL patients. In a longitudinal study of total knee patients Mizner et al. observed low and variable correlations ( $R= -0.07$  to  $-0.29$ ) between the SF-36 bodily pain subscale and performance on the six-minute walk test, timed up and go test, and stair climbing test.<sup>117</sup> These patients were evaluated preoperatively and 1 month and 12 months postoperatively. Similar to the present study, none of the correlations between the SF-36 bodily pain scale and the performance measures were consistently significant across time points.<sup>117</sup> Finally, in the only other study reporting the relationship between a LFP assessment and a PRO, Jacobs et al. did not observe a significant relationship pre or postoperatively between a modified Step Up/Over lift-up index and Knee Society pain or function scores.<sup>79</sup> Despite our attempts to select PBAs that included activities addressed in the PROs (Ex. walking, going up and

down steps, rising from sitting, and squatting) no consistent relationships were observed between these two methods of assessing function.

Overall the results of this study suggest poor concurrent validity between PROs and PBAs. It has been proposed that PRO instruments may be disproportionately influenced by pain,<sup>79, 97, 165, 166</sup> and this is one possible explanation for the slight trend of improvement in PRO scores observed as early as 3 months (Figure 3.1) despite significant decreases in physical function. These findings are in agreement with the work of Mizner et al.<sup>117</sup> and Parent and Moffett<sup>134</sup> both of which observed that in the acute phase of recovery following total knee arthroplasty patients subjectively over estimated their functional capabilities. Similar to the present study, improvement or no change in PRO scores was observed during early postoperative follow-up despite concurrent decreases in objective measures of physical performance.<sup>117, 134</sup>

The variability of the correlations across time in this study and elsewhere is particularly important and suggests that different latent variables may contribute to the self-appraisal process used to complete PRO forms at varying times during clinical follow-up. These variations in appraisal criteria are in agreement with response shift theory which proposes that over time changes in personal evaluation standards and perspective may result in changes to self-evaluation scores independent of true physical changes in function.<sup>139, 163</sup> One proposed solution to the disconnect between PROs and PBAs is that patients complete some form of PBA prior to completing PROs.<sup>40</sup> This methodology provides patients with an additional sample of experiences from which to evaluate their physical capabilities and may improve the accuracy of the self-appraisal process.<sup>139</sup> In the present study we chose to have patients complete all PROs prior to

testing PBAs. This was done so that PBA performance would not influence PRO scores, and our results could be compared to other ACI outcome studies which to date have predominantly utilized PRO scores as primary outcome measures and have rarely included PBAs. However, our results support the use of both forms of assessment when evaluating changes in function following ACI. Furthermore, future research should consider evaluating PBAs prior to having patients complete PROs to possibly improve PRO accuracy and better describe post-operative changes in function.

### **Limitations**

A limitation of this study is the inclusion of a diverse ACI patient population. The study sample included individuals undergoing treatment for lesions to the patella, trochlea, and/or femoral condyle many of which also underwent concomitant realignment procedures. Because of this variability, the presented timeline for recovery is not specific or precise for any one defect location and/or realignment procedure. Instead a broad pattern of recovery has been presented that can be generalized to a variety of defect patterns and sizes.

An additional limitation of this study is the lack of outcomes beyond 12 months post-ACI. However, the purpose of this study was to provide a descriptive time line for changes in self-perceived function and functional recovery in the first year following ACI. This time line is intended to describe when patients can expect improvements in activities of daily living and when patients will perceive a benefit from the surgery, two key pieces of information that may be valuable to patients and physicians when deciding if and when to undergo ACI. Future examination of these outcome variables for a longer period (> 1

year) will provide more information regarding the long term course of recovery following ACI.

## **CONCLUSIONS**

This study presents a descriptive timeline for changes in both PROs and PBAs during the first 12 months following ACI and also describes the relationship between PRO and PBA scores. Self-perceived changes in function were observed as early as 6 months following ACI while performance based measures of function demonstrated functional deficits compared to preoperative levels at both the 3 and 6 month time points. Specifically, patients demonstrated increased asymmetry of weight distribution when squatting and longer performance times for lunging and stepping activities. At the 12 month time point performance improvements were seen for walking speed and stride length: however, Step Up/Over time and Forward Lunge impact index and time remained below previously reported norms. Overall, it was observed that patients' perceptions of functional improvements may outpace true physical changes in function. This observation was further supported by the limited and inconsistent correlations existing between PROs and PBAs. These results suggest that the relationship between patient's self ratings and physical abilities may vary over time and be largely influenced by independent factors. Therefore, both PROs and PBAs should both be utilized to comprehensively assess outcomes following ACI.

## **CHAPTER 4: INFLUENCE OF RESPONSE SHIFT ON PATIENT REPORTED OUTCOMES FOLLOWING AUTOLOGOUS CHONDROCYTE IMPLANTATION**

### **INTRODUCTION**

A variety of outcome measures are frequently used in clinical research to document treatment effectiveness. While it may be possible to document changes in clinical measures such as strength or range of motion, it is difficult to quantify abstract concepts such as function or health related quality of life (HRQL). To assess function or quality of life, patients are often asked to evaluate their well-being using a self-report instrument or questionnaire to document patient reported outcomes (PROs). PROs are used to document temporal changes such as between pre- and post-treatments. However, PROs may be influenced by response shift.<sup>155</sup> *Response shift is the phenomenon by which an individual's self-evaluation of a construct changes due to a change in internal standards of measurement (recalibration), a change in values or priorities (reprioritization), or a personal redefinition of the target construct (reconceptualization).*<sup>163</sup> Response shift may interfere with the ability to detect change in a construct with accuracy. Examples of response shift are observed among the terminally ill where patients' physical health deteriorates, yet their self-reported HRQL remains stable.<sup>156, 162, 181</sup> It has been hypothesized that these changes may be a result of changing values, standards and priorities.<sup>155</sup> For example, patients become more focused on time with family than work productivity. Response shift has been documented in cases of terminal and chronic disease or illness.<sup>60, 170, 178, 181</sup> Only three known studies have examined response shift in an orthopedic population.<sup>10, 141, 142</sup> In two response shift was observed among knee arthroplasty patients 6 months and 12 months postoperatively.<sup>141,</sup>



<sup>142</sup> In the third, response shift was observed among articular cartilage patients undergoing microfracture treatment.<sup>10</sup> Based on these results, it is possible that patients undergoing knee surgery for localized articular cartilage damage may also experience response shift.

Treatment of articular cartilage injuries represents a complex and challenging problem for both orthopedic surgeons and rehabilitation specialists. If not treated appropriately, defects to the hyaline cartilage can become increasingly painful and disabling. This is particularly true for lesions of the knee where biomechanical stresses result in both shear and compressive forces during normal activities of daily living.<sup>38</sup> Chondral lesions have been observed in as many as 63% of knee arthroscopies; therefore, effective treatment and rehabilitation is important.<sup>39</sup> One of the emerging forms of treatment for chondral defects is the use of cultured chondrocytes in the procedure known as autologous chondrocyte implantation (ACI).<sup>28</sup>

In the twenty years since its conception ACI has been performed on thousands of patients with degenerative and traumatic cartilage lesions.<sup>61</sup> While early results for ACI outcomes are promising, the existing literature primarily reports outcomes using PROs.<sup>21, 29, 31, 44, 49, 51, 86, 90, 98, 108, 115, 116, 149, 185</sup> Although PROs are used frequently in orthopedic and rehabilitation literature, the traditional pre-post-test research designs used may be influenced by response shift phenomenon. If the PROs frequently used to evaluate ACI outcomes are subject to a response shift, then reported outcomes may under- or over-estimate the effectiveness of existing articular cartilage treatments. The extended preparation and rehabilitation required for ACI may make patients undergoing this procedure particularly prone to response shift. ACI is a two step surgical procedure. During the first surgery a cartilage biopsy is obtained from which cells are cultured and

then a minimum of 4 weeks later implanted into the defect during a second surgery.<sup>28</sup> In many cases patients have a history of prolonged knee pain and multiple previous surgeries prior to undergoing ACI. After undergoing ACI, current rehabilitation protocols recommend patients remain non-weight bearing for 6 to 12 weeks and maximum improvements may not be seen until 1-2 years following surgery.<sup>143</sup> It is possible that this extended period of functional limitations, combined with the inherent expectations associated with surgery, may result in a response shift.

It has been recommended that performance based assessments (PBAs) be included in response shift studies to provide an additional reference of physical function. Schwartz et al. suggests that differences in performance based measures and self-evaluations may represent response shifts experienced by individuals in response to physical or emotional changes in health.<sup>157</sup> There is limited to no documentation of PBAs in the previous literature regarding response shift among orthopedic knee patients.<sup>141, 142</sup>

Accurate documentation of *change* is vital to evaluating patient progress. If methods of documenting change do not accurately reflect the constructs they claim to measure then interventions intended to address those constructs cannot be accurately evaluated. If PRO instruments used to evaluate function in ACI patients are influenced by a response shift, then reported changes in function over time may be inaccurate. The purpose of this study is to determine if patients undergoing ACI experience response shift. It was proposed to verify a response shift via the then-test method and comparison to objective PBAs. It was hypothesized that there will be evidence of a response shift using the following PROs: the Medical Outcomes Study – 36 Item Short Form Health Survey Physical Component Scale (SF-36 PCS), the Western Ontario and McMaster

Osteoarthritis Index (WOMAC), and the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form. It was also hypothesized that outcomes evaluated by the Lysholm Knee Scale (Lysholm) would not be influenced by response shift. The IKDC, WOMAC, and SF-36 rely heavily on subjective evaluations of quality of task performance, physical function, and pain levels which may be influenced by reprioritization, recalibration, and reconceptualization. Therefore, it is anticipated that these scales will be influenced by response shift. For example, the perception of mild pain for someone who has had chronic pain may be recalibrated following surgical intervention. It is not anticipated that the Lysholm scale will demonstrate a response shift because of its focus on the capacity to perform specific tasks rather than the ease or pain associated with task performance.

## **METHODS**

### **Patients**

Patients were prospectively recruited from an active cartilage center. Inclusion criteria were the following: planned ACI surgery to the medial or lateral femoral condyle, trochlea, or patella; willingness to participate and no uncorrectable contraindications to ACI such as extensive degenerative joint disease, insufficient meniscus or unstable knee. There were no exclusions based on limb malalignment if the malalignment was corrected prior to or at the time of surgery via high tibial osteotomy or tibial tubercle transfer. Similarly, patients undergoing concomitant or staged ligament reconstruction to correct joint instability were also eligible for study participation. Patients undergoing concomitant meniscal transplant were excluded.

A total of 29 patients (17 males, 12 females,  $36.3 \pm 6.9$  yrs,  $174.4 \pm 9.6$  cm,  $90.4 \pm 19.4$  kg) agreed to participate. Three patients declined to participate resulting in an enrollment rate of 90%. Of the enrolled patients 13 underwent ACI to the patellofemoral joint with a tibial tubercle transfer and the remaining 16 underwent ACI to the femoral condyle, of which 4 also had a concomitant high tibial osteotomy. The mean number of defects treated per patient was  $1.38 \pm 0.6$  with an average treatment area of  $6.6 \pm 2.5$  cm<sup>2</sup> (range 2.3 to 13.0 cm<sup>2</sup>) as measured intraoperatively. All participants signed a university approved IRB consent form.

### **Surgical Procedures and Rehabilitation**

All patients underwent a two-step ACI procedure performed by the same surgeon (CL). During the first procedure a limited chondroplasty was performed and the lesion was evaluated arthroscopically. At this time a biopsy was obtained from the intracondylar notch (100 to 200mg cartilage). This sample was sent to a commercial laboratory where it was cultured and expanded (Carticel, Genzyme Corp, Cambridge, MA). In a second surgical procedure chondrocyte implantation was performed using a mini-arthrotomy. First the defect or defects were prepared using a curette to debride down to the subchondral plate with stable edges. A type I/III collagen membrane (Chondro-Gide<sup>(R)</sup>, Geistlich Biomaterials, Wohousen, Switzerland) was shaped to match the defect. Sutures and fibrin glue (Tisseel, Baxter Healthcare Corp., Deerfield, IL) were used to adhere the membrane over the defect to form a water tight seal. The chondrocytes in suspension were then injected beneath the membrane into the defect through a small portal remaining at the edge of the collagen membrane. The portal was then closed and sealed with sutures and additional fibrin glue.

All patients followed standardized rehabilitation protocols following surgery.<sup>93</sup> All patients were braced in full extension and were non-weight bearing for 2 weeks postoperatively. Toe-touch weight bearing was permitted from 2 to 4 weeks with partial weight bearing from 4 to 6 weeks and progression to full weight bearing between weeks 6 to 12. Continuous passive motion was prescribed for all patients for 6 to 8 hours per day for 6 weeks. For defects in the tibiofemoral joint, knee braces were gradually unlocked between 2 to 4 weeks as quadriceps control was gained. For defects to the patellofemoral joint, knees were braced in full extension for weight bearing through 4 weeks postoperative and then were gradually unlocked as quadriceps control was gained between weeks 4 and 6. Once good quadriceps control was gained all patients were transitioned to a hinged knee sleeve. All patients were recommended to abstain from high intensity cutting or pivoting activity until at least 12 months post ACI.

## **Outcome Measures**

### *Patient Reported Outcomes*

The PROs used in this study were the SF-36 PCS,<sup>105, 106, 179</sup> the WOMAC,<sup>18</sup> the IKDC,<sup>77</sup> and the Lysholm.<sup>96</sup> The SF-36,<sup>58</sup> IKDC,<sup>58</sup> Lysholm,<sup>85</sup> and WOMAC<sup>58, 85</sup> have all been evaluated for reliability among cartilage patients. The SF-36 PCS was included to serve as measures of health related quality of life (HRQL). The IKDC and Lysholm are region specific instruments that focus on knee function, while the WOMAC is a disease specific instrument focusing on degenerative joint disease covering pain, stiffness, and function. Reliability has been previously established for all of these instruments.<sup>18, 77, 85, 103, 105, 147</sup> A researcher independent of the treating physician reviewed each instrument with the patients and was available to answer any questions they may have had. All PROs

were completed at the following time points: prior to implantation, 6 months, and 12 months post-surgery.

#### *Performance Based Assessments*

At each time point after completing PROs each participant completed a series of 6 PBAs in a musculoskeletal laboratory setting. All PBAs were completed using the NeuroCom Balance Master<sup>®</sup> and long force plate (LFP) (NeuroCom International, Clackamas, OR). This is a commercially available system designed both as a training and evaluation tool for function and balance tasks, and it has the ability to provide immediate feedback to clinicians and patients regarding quality of task performance for a variety of activities of daily living (ADLs).<sup>5</sup>

The LFP consists of a 45.72 cm x 152.40 cm force plate with data sampled at 100 Hz and a personal computer equipped with data capture software (Balance Master ver. 8.1, NeuroCom International, Clackamas, OR). These functional tasks were selected because of their direct relationship to activities of daily living and the feasibility of patients being able to complete the task at each testing time point (Table 2.1). Tests were completed for both testing sessions in the order presented in Table 2.1, which was determined to be from least to most demanding based on patient reporting of difficulty during pilot testing. All testing was administered by the same investigator (JSH). For all single limb tests the uninvolved limb was tested first. Three successful trials of each task were performed, except for the Weight Bearing Squat which consisted of a single trial at each joint angle and the Rhythmic Weight Shift which consisted of one trial at each speed in each direction. Approximately 15s of rest was provided between each trial and 30s of rest between each task. For the purposes of this manuscript all outcome variables are

identified using the names assigned to them by the software utilized. Definitions for these variables are presented in Table 2.1. The six tasks are described below.

*Walk Across:* Patients walked across the LFP using their freely chosen standard gait speed and pattern.

*Weight Bearing Squat:* Patients stood still on the force plate and the initial measure was recorded with knee flexion angles of 0°, 30°, 60°, and 90° (as tolerated 0°). They then flexed their knees and held positions at 30°, 60°, and 90° as tolerated. The percentage of body weight on the involved limb was measured during a single trial with a duration .01s for each position. A standard goniometer was used to verify knee joint angle at each position.

*Unilateral Stance:* Patients stood on each leg and maintained their balance for 10 s with their eyes open. They begin with the non-weight bearing leg flexed at about 60-80° and with their hands on their hips. If patients touched down, or their legs touched each other, testing was stopped and the trial was discarded. Testing of a condition was discontinued if a participant experienced three consecutive failed trials. Testing was repeated for both legs with the patients' eyes closed.

*Sit to Stand:* Patients were seated on a 50cm box. Upon both visual and audio signals from the computer they rose to full standing as quickly as possible without using their hands, and then maintained a steady stance for the remainder of the 10 s trial.

*Step-Up/Over:* Participants stood behind a 29cm high box and stepped up onto the box with their test leg, then brought their non-test leg up and over the box, and then stepped down with their test leg. This was performed as quickly as possible while still maintaining control.

*Forward Lunge*: Patients in a standing position stepped forward on one leg and squatted down as far as comfortably possible, and then returned to the initial standing position as quickly as possible.

### **Assessment of Response Shift**

A variety of methodological and statistical approaches have been proposed for the measurement of response shift using self-report instruments.<sup>8, 56, 71, 88, 109, 130, 131, 153</sup> One of the most common approaches is the *Then-test Method* (Figure 4.1).<sup>70, 71</sup> This approach is identical to a traditional pre-test/post-test method with the exception that subjects complete an additional “then-test” assessment at the same session as their post-test assessment. For the then-test subjects are instructed to assess how they were at the time of the pre-test, prior to the intervention. The rationale for this design is that subjects will provide responses from the same frame of reference and calibration standards to both the then-test and the post-test by completing them at the same time. In a pre/post design *traditional change (TC)* is the difference between post-test and pre-test scores and is the only variable of interest. With the then-test method, response shift is calculated as the difference between the then-test and the pre-test and the *response shift adjusted change (RSAC)* is considered to be the difference between the post-test and the then-test.

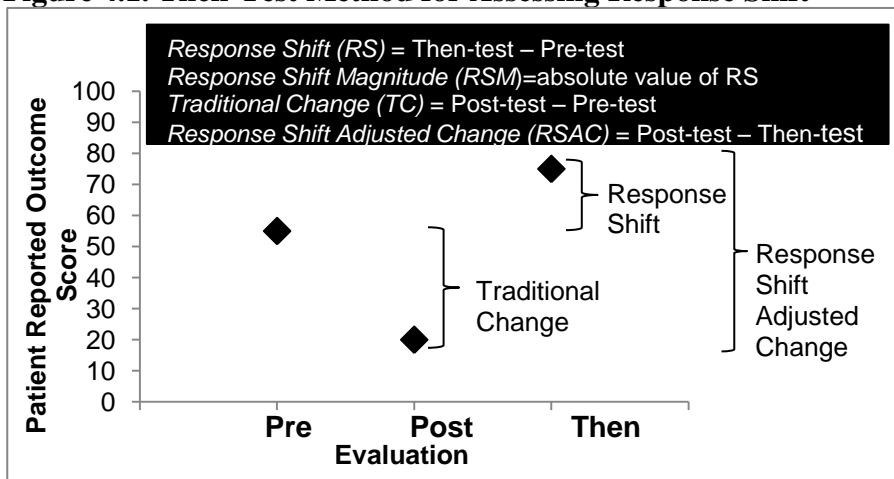
A limitation of the then-test method is that a response shift will only be detected on the group level if the direction of the response shift experienced is the same for the majority of patients. A group effect for response shift has the potential to influence overall study interpretation and may result in over or under reporting of outcomes when only traditional change is examined and response shift is not taken into consideration.

Because numerous personal and environmental factors can influence patient perspective,



it may be necessary to evaluate effects of response shift at the individual level. On an individual level, response shift can influence HRQL and may be clinically relevant to the care and management of individual patients.<sup>72</sup> This may be particularly true in the case of cartilage patients where few diagnostic tools are readily available to evaluate the healing process, and subjective reporting of symptoms and perceived progress are the primary clinical indicators of treatment outcome. In the present study response shift will also be examined on the individual level by evaluating the magnitude of the response shift occurring without regard for the direction.

**Figure 4.1. Then-Test Method for Assessing Response Shift**



For the then-test method patients are requested to complete an outcome instrument three times. First pre-treatment (Pre-test), again at a specified post-treatment time point (Post-test), and at that same post-treatment time point they also complete a Then-test on which they are asked to retrospectively rate how they were at the pre-treatment time point. From these three scores response shift, response shift magnitude, traditional change, and response shift adjusted change can then be calculated.

## Statistical Analysis

### *Main Outcome Measures*

The dependent variables of *Response Shift*, *Response Shift Magnitude*, *Traditional Change* and *Response Shift Adjusted Change* were calculated for the IKDC, Lysholm, SF-36 PCS and WOMAC at 6 months and 1 year following ACI as described in Figure 4.1.

### *Group Effect*

To investigate the occurrence of a group level response shift paired t-tests were used to compare then-test scores to pre-test scores for each instrument and to compare TC to RSAC for each instrument. Significant t-test results would support the occurrence of a group effect with a consistent response shift occurring across patients. A large difference between scores would support the importance of accounting for the effects of response shift and its potential influence on the over or under reporting of treatment effects with traditional pre-post outcomes.

### Proposed Statistical Tests to Validate Occurrence of a Group Level Response Shift

Pearson product moment correlations between PROs and PBAs were used to evaluate the relationship between pre-test, post-test, and then-test scores for any PRO for which a group level response shift was evident. For each PBA variable (Table 4.1) for which a significant correlation was observed separate regression equations were calculated to predict pre-operative PBAs from pre-test PROs and then-test PROs, and to predict post-operative PBAs from post-test PROs. Parameter estimates ( $\beta$ ) were then compared using 95% confidence intervals. This process was completed at both the 6 and 12 month time points. A significant change in the relationship between self-evaluation (PROs) and physical performance (PBAs) was considered evidence to verify that a response shift had occurred. Because post-test PROs and then-test PROs were completed

at the same time point postoperatively, it was anticipated that these tests would relate similarly to PBAs ( $H_0: \beta_{Post} = \beta_{Then}$ ). In contrast, pre-test PROs were completed prior to surgery, prior to the occurrence of a potential response shift, resulting in a different frame of reference and a different relationship to PBAs ( $H_0: \beta_{Pre} \neq \beta_{Post}$ , and  $\beta_{Pre} \neq \beta_{Then}$ ).

**Table 4.1. Linear Regressions Proposed to Verify Occurrence of a Response Shift**

Regression Equations
(1) $y_{PBA(pre)} = \beta_{01} + \beta_1 X_{PRO(pre)}$
(2) $y_{PBA(post6)} = \beta_{02} + \beta_2 X_{PRO(post6)}$
(3) $y_{PBA(post12)} = \beta_{03} + \beta_3 X_{PRO(post12)}$
(4) $y_{PBA(pre)} = \beta_{04} + \beta_4 X_{PRO(then6)}$
(5) $y_{PBA(pre)} = \beta_{05} + \beta_5 X_{PRO(then12)}$

Performance Based Assessment (PBA), Patient Reported Outcome (PRO), Preoperative (Pre), 6 Months Postoperative (Post6), 12 Months Postoperative (Post12), Then-Test 6 Month Postoperative (Then6), Then-Test 12 Months Postoperative (Then12)

#### *Individual Effect*

To investigate the occurrence of an individual level effect for response shift, response shift magnitude was calculated as the absolute value of the response shift for each PRO. One-sample t-tests were then used to compare the response shift magnitude to previously established minimal detectable changes (MDCs) for each PRO instrument. The MDC at 6 and 12 month follow-up has been previously established among patients a minimum of 5 years post ACI for the IKDC (15.6 points at 6 months, 13.7 points at 12 months), WOMAC (10.9, 15.3), and SF-36 PCS (3.2, 3.6).<sup>58</sup> For the Lysholm scale an MDC of 15.8 was calculated from previously published reliability and ICC values among patients awaiting surgery for chondral defects.<sup>15, 85</sup> Pearson product moment correlations

were used to evaluate the relationship between response shift (Then-test – Pre-test) and TC to determine if change in self-perceived level of function influenced response shift.

## **RESULTS**

Six participants were declared clinical failures at or before the one year time point and were not medically cleared to complete functional testing at all time points. An additional five participants were lost to follow-up. Finally, one participant failed to complete preoperative force plate testing and another participant was lost to follow-up at the 6 month time point, but returned to the study at the 12 month time point. As a result full PBA assessment data was only available for 16 subjects. At the 12 month time point full PRO data was available for 22 patients including 4 patients who were declared failures at that time point. At the 6 month time point full PRO data was available for 23 patients including 2 who were declared failures at or prior to that time point.

### **Group Level Analysis**

Main outcome measures are reported in Table 4.2. No group level effect for response shift was observed. There were no differences between Pre-test and Then-test scores for any of the PROs evaluated. There were also no differences between RSAC and TC, and none of the mean RS values exceeded previously established MDC values for the IKDC, Lysholm, SF-36 PCS, or WOMAC. Because there was no evidence of a group level response shift for any of the PROs, the proposed analyses involving correlation and regression to verify response shift with functional performance were not completed.

**Table 4.2. Main Outcome Variables for Response Shift among Autologous Chondrocyte Implantation Patients**

Measure	IKDC		Lysholm		SF-36 PCS		WOMAC	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Pre-test	39.40 (12.09)	47 (18)	36.28 (8.26)	32 (17)				
Post-test 6 Months	51.97 (17.17)	62 (23)	42.74 (9.06)	22 (19)				
Post-test 12 Months	54.32 (19.74)	66 (23)	42.52 (10.55)	21 (19)				
Then-test at 6 Months	39.92 (17.89)	40 (18)	37.22 (10.07)	37 (23)				
Then-test at 12 Months	40.39 (18.40)	44 (19)	38.31 (10.01)	36 (20)				
Response Shift at 6 Months	0.52 (18.24)	-6 (18)	0.94 (8.97)	5 (21)				
Response Shift at 12 Months	1.62 (16.79)	-12 (29)	2.28 (9.08)	-3 (19)				
Response Shift Magnitude at 6 Months	12.67 (12.86)	15 (11)	6.83 (5.71)	17* (13)				
Response Shift Magnitude at 12 Months	11.37 (12.21)	22 (22)	6.91 (6.14)	15 (11)				
Traditional Change at 6 Months	12.57 (18.36)	15 (22)	6.46 (10.08)	-10 (17)				
Traditional Change at 12 Months	14.03 (17.28)	18 (20)	5.65 (7.40)	-12 (15)				
Response Shift Adjusted Change at 6 Months	12.05 (25.98)	21 (22)	5.52 (14.01)	-15 (27)				
Response Shift Adjusted Change at 12 Months	13.74 (27.28)	21 (15)	4.35 (9.90)	-15 (2)				
Minimal Detectable Change at 6 Months	10.90 <sup>58</sup>	15.8 <sup>85</sup>	8.3 <sup>58</sup>	10.9 <sup>58</sup>				
Minimal Detectable Change at 12 Months	15.30 <sup>58</sup>	15.8 <sup>85</sup>	6.6 <sup>58</sup>	15.3 <sup>58</sup>				

\* Significantly different from MDC 6 (p = .039)

Response Shift = Then-test – Pre-test

Response Shift Magnitude = absolute value of Response Shift

Traditional Change = Post-test – Pre-test

Response Shift Adjusted Change = Post-test – Then-test

## **Individual Level Analysis**

RSM values were used to determine the number of subjects that experienced a response shift beyond the MDC at the 6 and 12 month time points for each PRO instrument. At 6 months it was observed that there was a response shift beyond the MDC for 8 patients assessed via the IKDC, 6 patients for the SF-36 PCS, 8 patients for the Lysholm, and 15 patients for the WOMAC. At the 12 month time point 6 patients for the IKDC, 9 patients for the SF-36 PCS, 9 patients for the Lysholm, and 8 patients for the WOMAC experienced response shifts that exceeded the MDC. Overall 8 patients at 6 months and 4 patients at 12 months demonstrated evidence of a response shift on at least 3 of the four instruments utilized. The only PRO to show a significant response shift at an individual level across patients was Total WOMAC score at 6 months. The mean RSM value for the WOMAC at 6 months was  $17 \pm 13$  which was significantly greater than the MDC over 6 months of 10.9 established by Greco et al.<sup>58</sup>

Finally, there were no significant correlations between TC values or RS values at 6 or 12 months for any of the PROs evaluated. These results suggest that the occurrence of a response shift is not related to overall treatment outcome as traditionally evaluated by PROs.

## **DISCUSSION**

### **Group Level Effects**

The purpose of this study was to evaluate 4 common PRO instruments for evidence of response shift in patients following ACI. Had any of those PROs demonstrated evidence of a group level response shift, linear regression analysis would

have been used to validate the occurrence of this response shift via comparison of self-report and performance based outcome measures. An example of this proposed method of analysis can be seen in Appendix B. There were no group level effects for response shift observed for the IKDC, Lysholm, SF-36 PCS, or WOMAC. These results fail to support the hypothesis that response shift would be evident for the IKDC, SF-36 PCS, and WOMAC, but the results do support the hypothesis that no response shift would be observed for the Lysholm.

Previous research in both microfracture<sup>10</sup> and total knee arthroplasty<sup>141, 142</sup> has reported the occurrence of a statistically significant response shift among patients. A significant difference between pre-test and then-test scores for the WOMAC<sup>141, 142</sup> and the SF-36 PCS<sup>141</sup> has been reported at 6 and 12 months following knee arthroplasty. Similarly, a response shift was reported using the Lysholm scale among patients a median of 34 months following microfracture for knee articular cartilage damage.<sup>10</sup> In both patient populations a positive response shift was observed, meaning that patients retrospectively rated their preoperative function lower on the then-test than they did at the original preoperative evaluations,<sup>10, 141, 142</sup> as a result RSAC demonstrated greater improvement in function than TC for at least two studies.<sup>141, 142</sup>

Upon initial review our failure to observe a group level response shift is in disagreement with the previous work<sup>10, 141, 142</sup> in orthopaedic knee patients. However, upon further examination the values observed in the present study are very similar to those reported elsewhere. In the present study mean RS values of  $-6 \pm 18$  and  $-12 \pm 29$  for the Lysholm were observed compared to a median RS of -7 (interquartile range 4 to -17) by Balain et al.<sup>10</sup> Similarly, mean RS values of  $5 \pm 21$  and  $-3 \pm 19$  were observed for the

WOMAC and  $0.94 \pm 8.97$  and  $2.28 \pm 9.08$  for the SF-36 PCS, compared to mean WOMAC RS values of  $3.79 \pm 19.52$ ,  $5.45 \pm 16.85$  and  $6.73 \pm 15.50$  and SF-36 PCS values of  $-1.66 \pm 8.05$  and  $-3.16 \pm 7.94$  reported by Razmjou et al.<sup>141, 142</sup> In all cases the mean or median differences between then-test and pre-test scores were less than the previously established MDC scores for each instrument and standard deviations or reported ranges were quite high. However, the larger samples sizes in the previous studies, ranging from 53<sup>10</sup> to 234,<sup>141</sup> resulted in statistically significant RS values, leading the authors to conclude that a response shift had occurred. By examining actual mean RS values and standard deviations it can be concluded that the group effect for response shift observed in previous studies was no more clinically meaningful than those observed in the present study. This conclusion was reiterated by the previous authors who conceded that although a statistically significant response shift had occurred, adjusting for the response shift did not change clinical conclusions regarding treatment efficacy.<sup>10, 141, 142</sup> Based on the present study and previous reports, a slight group effect for response shift may occur among postoperative orthopaedic knee patients; however, this response shift is not substantial enough on a group level to invalidate the use of traditional pre-post outcomes assessment methods.

### **Individual Level Effect**

No significant group level effect was observed for any of the PRO instruments included in this study. However, by comparing RSM values to previously established MDC values for articular cartilage patients a statistically significant response shift ( $p = 0.039$ ) was observed on an individual level for the WOMAC at 6 months. This result means that although WOMAC scores did not demonstrate a group level effect for



response shift with the majority of patients recalibrating their then-test scores in a uniform direction, the mean magnitude of change (RSM) observed on WOMAC scores did exceed MDC values. In this study's population, individual patients did exhibit a response shift. However, some patients' then-test scores recalibrated positively (Then test > Pre-test) while others shifted negatively (Then-test < Pre-test) as a result mean RS values were not statistically significant, but RSM values were. RS variability in magnitude and direction were substantial enough that there was no difference in TC and RSAC values and accounting for response shift did not alter clinical interpretation of treatment outcomes on the group level. However, RSM values suggest that WOMAC scores are susceptible to response shift on the individual patient level. If WOMAC scores are being used to track treatment progress of an individual patient, response shift should be taken into consideration.

Additional analyses using MDC values suggested that some individual patients may experience a clinically relevant response shift across PRO instruments with 8 patients at 6 months and 4 patients at 12 months observed to have RSM values exceeding MDC values on at least 3 out of 4 PROs. Utilizing RSM values instead of RS values provides a depiction of the magnitude of response shift which can be examined without regard for the direction of the response shift. The direction of the response shift is important on a group level to evaluate the influence of response shift on interpretation of overall treatment effects across patients. However, because it is clear that patients may experience either a positive or negative response shift, averaging RS values across patients may obscure the occurrence of a true, albeit non-uniform, response shift.

MDC values and minimal clinically important differences (MCID) were also utilized in previous assessments of response shift in orthopaedic knee patients. Razmjou et al. observed that 36% of patients experienced a response shift that exceeded MCID values (15 points) for the WOMAC.<sup>141</sup> In the present study it was observed that 65% of patients experienced a response shift that exceeded the 6 month MDC (10.9) for the WOMAC in articular cartilage patients. At 12 months 38% of patients experienced a response shift exceeding the 12 month MDC (15.3) for the WOMAC. Both the present study and previous research<sup>141</sup> suggest that on an individual level the WOMAC may be subject to both meaningful and measurable response shifts.

Multiple factors may contribute to the WOMAC being more influenced by response shift than the other PROs evaluated in this study. The version of the WOMAC included in this study consists of 24 items with 5 item Likert-type response choices. Response choices include “none”, “mild”, “moderate”, “severe”, or “extreme”. This type of scale can be highly subjective and may be prone to scale recalibration. Depending on the patient’s prior experiences, mild and moderate may have different meanings over time as the patient has more information and new experiences for comparison. While other PRO instruments contain some similarly structured questions, the WOMAC provides significantly less context from which the patient is asked to answer the questions. For each of the 3 domains of the WOMAC –pain, stiffness, and function – the patient is prompted with a simple statement such as “How much pain do you have...” or “What degree of difficulty do you have...” followed by a list of activities or tasks such as going up and down stairs, sitting or lying, or rising from bed. These questions do little to frame the appraisal process. In contrast, the IKDC, SF-36, and Lysholm provide a set of

parameters from which the patient is asked to evaluate themselves. They also may be provided with more objective criteria for comparative rating. For example, the SF-36 instructs patients to answer questions with respect to work or daily activities (a specific setting) in the last 4 weeks (a specific time frame) and separates physical health from emotional health (a specific aspect of health/function). Similarly, the IKDC and the Lysholm provide the patient with reference criteria creating meaningful standards around which he or she can anchor his or her internal scale. For example, the IKDC asks “What is the highest level of activity you are able to perform without significant giving way in your knee?” and in addition to providing response choices such as “very strenuous” or “strenuous” examples of each level of activity are provided, such as “very strenuous activities like jumping or pivoting as in basketball or soccer.” By placing the dysfunction of giving way in the participation context of soccer or basketball the instrument is cueing the patient to a specific sample of relevant experiences or activities from which to evaluate his or her own function. Finally, the Lysholm scale may be resistive to response shift by providing objective examples of function, such as providing set distances for how far a patient is able to walk without knee pain. The use of reference points for comparison may reduce the likelihood of Lysholm scores being subject to scale recalibration. By providing scale anchors and directing the patient towards a specific sample of experiences the IKDC, SF-36, and Lysholm appear to reduce the risk of significant variation in scale, and conceptualization between and within patients over time.

The use of scale anchors and direction toward relevant experiences to reduce the effect of response shift on PRO scores is consistent with Rapkin and Schwartz’s

previously proposed model of self-appraisal for health related quality of life.<sup>139</sup>

According to this model, when faced with an assessment question a patient completes four distinct steps to arrive at a response. The patient first establishes a frame of reference from which to consider the question. Next, a sample of specific experiences relative to that frame of reference is selected. These sample experiences are then judged against subjective standards of comparison, and finally a combinatory algorithm is applied to summarize these experiences and select a response.<sup>139</sup> The first three steps of this process present an area in which reconceptualization (change in initial frame of reference), reprioritization (change in which experiences are relevant to be sampled), and recalibration (change in standards for comparison) may occur resulting in a response shift. By providing cues to trigger a frame of reference, referring to specific experiences to sample, and/or providing set standards for comparison, PRO instruments may be able to effectively reduce the influence of response shift on outcome scores, making comparisons of scores across testing points more valid and accurate.

The WOMAC demonstrated evidence of an individual level response shift at 6 months, but not at 12 months. Performance measures and contextual factors may explain these variations in response shift over time. As discussed in Chapter 3 of this dissertation, there were very few differences in functional performance between preoperative and 12 month postoperative assessments. Significant changes were only observed for Walk Across speed and Step Up/Over lift-up force. Functional capacity at preoperative and 12 month time points was similar; the relevance of this finding is that patients are likely participating in similar activities at these time points. Furthermore, many restrictions in activity and work have or are being removed from the patient at the 12 month time point,

but may still be in place at the 6 month time point. This is particularly true for those patients involved in sports activity or manual labor. Recent activity participation, or lack thereof, has been proposed as a potential factor contributing to response shift.<sup>40</sup> At the 6 month time point patients have a sample of work, recreation, and physical therapy activities from which to choose when completing the appraisal process. This sample of experiences may be different from those available for appraisal prior to undergoing ACI or at the 12 month time point. The removal of work and physical activity restrictions, along with the natural healing process, may result in a very similar sample of experiences for appraisal at the preoperative and 12 month time points. As a result, the patient may use a similar frame of reference when completing the PROs at the preoperative and 12 month postoperative time points, resulting in little to no response shift between these time points.

Finally, no significant correlation was observed between TC values and RS. These results suggest that the occurrence of response shift is not a function of treatment success as traditionally evaluated using Pre-Post PRO scores. These results are similar to those of Balain et al. who observed no differences in any response shift variables (pre-test, then-test, TC, or RSAC scores) between groups of patients with varying levels of satisfaction following microfracture.<sup>10</sup> These observations support the importance of personal and environmental factors when considering response shift. The World Health Organization's International Classification of Functioning, Disability, and Health (ICF) seeks to model an individuals' health based on three principle components: body function and structure, activity, and participation.<sup>2</sup> However, each of these components can be influenced by contextual factors which include both personal and environmental factors.<sup>2</sup>

Personal and environmental factors may explain why among cartilage patients response shift seems to be an individual and not a group phenomenon. Unlike a terminal disease, which will inevitably impact every aspect of life, the impact of physical limitations secondary to knee surgery may vary from person to person depending on factors such as employment status, pre-injury activity level, self-image, social support, and preoperative expectations. These contextual factors have previously been referred to as “antecedents” in Spranger and Schwartz’s model of response shift and health related quality of life.<sup>163</sup> This model of response shift stresses the importance of variables such as personality, sociodemographics, access to care, physical environment, expectations, and spiritual identity on health outcomes. All of these factors may vary from person to person, further explaining the great variability in response shift observed and why evidence of a significant response shift may exist on an individual level, but not on the group level.

### **Limitations**

The use of the then-test method to evaluate response shift may be considered a limitation of this study. By asking patients to recall their level of function 6 to 12 months prior, this method may be prone to recall bias.<sup>154</sup> However, the then-test method has been demonstrated as having convergent validity with more complicated methods of evaluating response shift including structural equation modeling and analysis of covariance which require much larger samples sizes than were available in this investigation.<sup>154, 177</sup> Additional research has demonstrated that recall bias alone was unable to explain changes in then-test scores observed among cancer patients, and at least a portion of observed changes could be attributed to response shift via scale

recalibration.<sup>157</sup> Furthermore, use of the then-test method allowed for direct comparison to previous investigations of response shift in orthopaedic knee patients.

## **CONCLUSIONS**

There was no evidence of a group level effect for response shift following ACI. These results support the validity of traditional pre-test/post-test research designs in evaluating treatment effects following cartilage repair. Although some variations may be observed between TC and RSAC scores for PROs, on the group level these variations are not uniform in direction, do not exceed MDC values, and do not alter the clinical interpretation of treatment outcomes. However, there is evidence that response shifts may occur on an individual level on a patient by patient basis, and scores on the WOMAC in particular may be influenced by response shifts. Future research should examine what factors may make an individual prone to a response shift and how those factors can be utilized to provide the individual with the highest possible self-perceived health related quality of life. On a clinical level recognizing the occurrence of a response shift may be key in evaluating treatment progress for individual patients. This is particularly true for treatments such as ACI where physicians depend heavily on patient self-report and appraisal of progress because tools for diagnostic evaluation are limited and not always feasible or cost-effective.

## **CHAPTER 5: FUNCTIONAL OUTCOMES FOLLOWING ARTICULAR CARTILAGE IMPLANTATION: BALANCING PATIENT ORIENTED AND PERFORMANCE BASED MEASURES**

### **PURPOSE AND AIMS**

The purposes of the presented studies were to investigate clinical and functional outcomes following autologous chondrocyte implantation (ACI) to the knee and the methodology for documenting those outcomes. Specifically, the following aims and hypotheses were examined within this dissertation:

1. To systematically review and evaluate the responsiveness of common instruments used to measure PROs following ACI at varying time points.  
*Hypotheses: All instruments will demonstrate improved self-reported function and health related quality of life following ACI with the simplest instruments showing the greatest treatment effect.*
2. To determine among articular cartilage patients the reliability of the following NeuroCom Balance Master<sup>®</sup> long force plate assessments: Walk Across, Weight Bearing Squat, Unilateral Stance, Sit-to-Stand, Step Up/Over, and Forward Lunge tests. *Hypotheses: The reliability of all measures of time, distance, and force will demonstrate acceptable ICC values >0.75. There will be poor reliability of measures of sway and balance with ICC values <0.75.*
3. To document the clinical outcomes of ACI patients over one year following surgery utilizing both patient reported outcomes (PROs) and performance based assessments (PBAs), and to examine the relationship between PROs and PBAs. *Hypotheses: All PROs and PBAs will demonstrate an initial decrease*



*in function at the three month time point. There will be improved function at 6 months and improvements from baseline at the 12 month time point based on PRO and PBA evaluations.*

4. To determine if patients undergoing ACI experience a response shift between preoperative assessment and evaluation at 6 and 12 months postoperative.

*Hypotheses: There will be evidence of a response shift as assessed via PROs.*

*Further evidence of this response shift will be supported by changes in the relationship between PROs and PBAs over time.*

## **SUMMARY**

### **Responsiveness of Patient Reported Outcomes (PROs)**

In Chapter 1 the large body of work regarding the use of PROs following ACI was reviewed. Overall the evidence supporting the use of ACI for the treatment of cartilage defects is of poor to moderate methodological quality with included studies observed to have a mean modified Coleman Methodology score<sup>87</sup> of  $50.9 \pm 9.2$ . Additionally, the majority of studies were Level 2b prospective cohorts with only 4 Level 1b randomized controlled trials meeting the inclusion and exclusion criteria.<sup>4</sup> Despite these limitations in methodological quality and inconsistent reporting of outcome means and measures of variability, a grade B<sup>4</sup> recommendation was made for the use of the Medical Outcomes Study 36-Item Short Form Health Survey Physical Component Scale (SF-36 PCS),<sup>105, 106, 179</sup> the International Knee Documentation Committee Subjective Knee Form (IKDC),<sup>77</sup> the Lysholm Knee Scale (Lysholm),<sup>96, 168</sup> the modified Cincinnati Knee Rating System (MCKRS),<sup>31</sup> the Western Ontario and McMaster Universities Osteoarthritis Index

(WOMAC),<sup>18, 19</sup> and the Knee Injury and Osteoarthritis Outcome Score (KOOS)<sup>148</sup> as outcome measures following ACI.

To determine which PROs may be most receptive to changes in self-reported function following ACI meta-analyses were conducted to examine the responsiveness of each instrument using Hedge's *g* effect sizes over 4 postoperative time points with follow-up ranging from less than 1 year to 4 or more years after ACI. Across all time points the hypothesis was supported with the IKDC, KOOS, Lysholm, MCKRS, and SF-36 PCS all demonstrating large effect sizes and significant improvement in self-reported function and health related quality of life following ACI. There was not sufficient data to analyze the WOMAC at any of the individual time points and limited data for the SF-36 PCS and the MCKRS. The Lysholm was highly responsive as early as less than 1 year following ACI and was consistently responsive throughout postoperative follow-up. However, this instrument may not be responsive to changes in function associated with the resumption of higher demand activities such as sports which occurs after the 1 year time point. For the evaluation of long-term outcomes among patients who intend to return to physical activity, this review supports the use of the IKDC which was able to detect increasing treatment effects over time. The KOOS-sports and recreation subscale also demonstrated increasing treatment effects over time; however, the IKDC was significantly more responsive than this KOOS-subscale at time point II (between 1 and < 2 years post ACI) and at time point IV ( $\geq 4$  years post ACI). The use of the Lysholm and IKDC together represents a responsive combination of PRO instruments that are able to efficiently document both short-term and long-term treatment effects among patients of a variety of activity levels following ACI.

## **Reliability of Performance Based Assessments (PBAs)**

The use of PBAs following ACI has been limited, with only a few authors reporting functional performance for the 6 minute walk-test, the single-leg hop, and isokinetic strength measures.<sup>44, 45, 146, 172</sup> In this investigation, tasks that are part of the NeuroCom Balance Master<sup>®</sup> long force plate (LFP) (NeuroCom International, Clackamas, OR) testing protocol were evaluated for their reliability. The examined tasks included the Unilateral Stance, Weight Bearing Squat, Sit-to-Stand, Rhythmic Weight Shift, Step-Up/Over, and the Forward Lunge.<sup>3</sup> These outcome measures are of low to moderate demand, simulate activities of daily living, and are feasible for performance by ACI patients throughout much of the recovery process. Because PBA measures should at a minimum have the potential to be evaluated pre-operatively and at long-term (>1 year) follow-up, a cross-sectional sample of ACI patients at the preoperative and 1 year postoperative time point were enrolled in this study. Intraclass correlations (ICC(2,1)) were used to evaluate the test re-test reliability of each outcome measure. For unilateral tests, only the reliability of the involved (surgical) limb was analyzed. All tests with ICC greater than or equal to 0.75 were considered to have acceptable reliability as a PBA for documenting outcomes following ACI.

Overall reliability varied by task, yet at least one variable for each task demonstrated acceptable test-retest reliability. As hypothesized - force, time, and distance measures were reliable for the Weight Bearing Squat at 90°, Step-Up/Over, and Lunge with ICC values ranging from .75 to .93. Similarly, Walk Across length and speed were also reliable; however, Walk Across width was not, nor was the Weight Bearing Squat at 0°, 30° or, 60° or Sit-to-Stand rise time or center of gravity sway velocity. Contrary to the

hypothesis for balance measures, the Unilateral Stance demonstrated acceptable reliability in both the eyes open (ICC = 0.75) and eyes closed (ICC = 0.77) conditions. Overall, the selected tasks, particularly the Step Up/Over and Forward Lunge, demonstrated reliability across a variety of levels of function among both preoperative patients and those one year post ACI surgery. Furthermore, this study provided minimal detectable change values (MDC) for LFP variables to evaluate longitudinal changes in function following ACI.

### **Application of PROs and PBAs to Evaluate Changes in Patient Function Following ACI**

As previously discussed, few studies have utilized PBAs to document the return of function following ACI.<sup>44, 45, 146, 172</sup> No known studies have examined the timeline for return to function following ACI using low to moderate demand PBAs that recreate the demands and stresses of common activities of daily living such as squatting, rising from sitting, or going up and down stairs, in addition to walking. Nor has the relationship between PROs and PBAs been examined in an ACI patient population. The purpose of this study was to provide an accurate description of functional recovery during the first year following ACI for patients, physicians and rehabilitation specialists. Furthermore, an understanding of the relationship between PROs and PBAs provides important information regarding the importance of collecting varying types of outcomes in future cartilage repair research.

It was observed that patients reported significant improvements in self-reported function on the IKDC, Lysholm, and SF-36 PCS as early as 6 months and on the WOMAC at 12 months following ACI. However, there was an initial decrease in function at the 3 month time point for several of the PBAs with asymmetrical weight

distribution during squatting and increased performance time for lunging and stepping up and over a box. At the 6 month time point performance deficits still remained, such as asymmetrical weight distribution during squatting, but small improvements were observed for Walk Across stride length. At the 12 month time point the only performance variables to demonstrate changes from the preoperative time point were Walk Across speed and stride length, and Step Up/Over lift-up index. These results support existing theory that although improvements in self-report measures may occur early postoperatively, maximal defect healing and functional improvement continues beyond 12 months following ACI.<sup>22, 90, 145</sup>

Although low to moderate correlations were observed between various PROs and PBAs at each of the 4 time points, no consistent correlations were observed between any of the PROs and PBAs across all four time points. This inconsistent to non-existent relationship between PROs and PBAs is consistent with previous literature concerning orthopedic knee patients.<sup>52, 79, 82, 117, 120, 144, 159</sup> The occurrence of changes in self-report measures of function prior to changes in performance based measures of function may be a result of the large influence pain levels have been observed to have on PRO scores.<sup>79, 97, 165, 166</sup> The lack of consistent correlations between PROs and PBAs, and the observed improvement in PRO scores in the absence of improved physical performance supports the importance of incorporating both types of outcome measures when documenting patient outcomes. The importance of a patient's own rating of function and subjective feelings towards joint health cannot be ignored. However, when considering decisions such as ability to return to work or physical activity, or to evaluate postoperative changes

in biomechanics, performance based measures provide unique information that cannot be fully and accurately captured by PROs along.

### **The Influence of Response Shift on Patient Reported Outcomes following ACI**

The final question of this dissertation examined the phenomenon of response shift among ACI patients when evaluating outcomes using the IKDC, Lysholm, SF-36 PCS, and KOOS. Response shift is the changing of an individual's frame of reference or perspective due to reprioritization, recalibration, or reconceptualization.<sup>163</sup> If response shift is occurring it may not be appropriate to compare PRO scores across time as a different set of standards and a changing appraisal process is used to respond to questions at each time point. A group level effect for response shift has the potential to result in under or over reporting of treatment effects. On an individual level, the identification of a response shift may be relevant to clinical care, particularly for therapies such as ACI where self-report of changes in symptoms and pain are the primary measure of treatment success.

Among ACI patients there was no evidence to support the hypothesis that a group level effect for response shift would be evident in the included PROs. These results support the validity of traditional pre-test/post-test research designs for evaluating treatment effects following cartilage repair on the group level. However, an individual level response shift was observed for the WOMAC at 6 months post-ACI. Response shift magnitude values for the WOMAC at 6 months were significantly different from previously identified MDC values. The WOMAC may be more prone to a response shift than other PRO instruments due to its dependence on Likert-type response scales and the failure to reference specific locations, times, or criteria that provide the patient with a

context from which to rate his or her function. These results demonstrate that although, a measurable response shift does not occur in a uniform direction following ACI, it does occur on a patient-by-patient basis with some patients over-estimating their preoperative level of function and other patients under-estimating their preoperative function.

## **SYNTHESIS OF RESULTS AND CONCLUSIONS**

The overall purpose of this dissertation was to describe functional outcomes following ACI and to examine the use of PROs and PBAs for evaluating functional outcomes following ACI. From this investigation several observations and recommendations for outcomes assessment following ACI can be made.

1. The Lysholm and the IKDC are the recommended PRO instruments for evaluating changes in self-reported function following ACI. Both instruments exhibit excellent responsiveness to functional changes following ACI with the Lysholm being most responsive to short-term changes in lower level activities such, as walking, going up and down stairs, or squatting. The IKDC demonstrated increasing responsiveness over time as patients become eligible to return to higher demand activities such as running or cutting. Furthermore, neither instrument was influenced by response shift on either the group or individual level. As a result these scores can be used for the traditional pre/post evaluation of function on a group level, or can be used to monitor changes on a patient by patient basis.
2. Patients and clinicians can realistically anticipate significant improvements in self-reported function as early as 6 months following ACI. However, some postoperative loss of function is likely to be present at the 3 and 6 month time

points for movements such as stepping, lunging, and squatting. At 6 and 12 months, improvements in walking stride length can be expected, but side to side discrepancies in performance for some activities may linger due to learned habits or continued weakness.

3. Both PROs and PBAs are needed to create a complete picture of assessment. The relationship between PROs and PBAs was inconsistent and varied across time. Significant improvements in PROs were observed in the absence of substantial changes in physical performance. PROs may be overly influenced by changes in pain levels resulting in a poor correlation with direct physical performance, even when instrument content addresses those tasks being performed.
4. Response shift does not substantially influence the interpretation of treatment outcomes when using the IKDC, Lysholm or SF-36 PCS. Response shift may influence outcomes when using the WOMAC on an individual patient level. Although, no group effects were observed for response shift, individual patients may experience a response shift and this potential for response shift further supports the use of valid and reliable PBAs as an additional outcome measure following ACI.

### **FUTURE RESEARCH**

In this dissertation the responsiveness of several PROs was reviewed and the reliability of a series of force plate based PBAs was established. A time line for recovery of function following ACI using both PROs and PBAs was presented. Future research should continue to examine the influence of factors such as defect location, defect size,



concomitant procedures, and rehabilitation parameters (such as time non-weight bearing, use of continuous passive motion, and intensity of strengthening activities) on both PRO and PBA outcomes. Additionally, longer follow-up is necessary to determine if PBAs that failed to demonstrate improvement at the 12 month time point subsequently improve as the patient is cleared for return to regular sports and physical activity. Finally, the relationship between preoperative or early postoperative PRO and PBA scores and long-term treatment success should be investigated to help in the selection of patients most likely to succeed and to recognize early clinical failures and provide them with alternative treatments.

While a significant or meaningful group level effect for response shift was not observed in this study, a subset of patients was observed to experience response shift at the individual level across multiple PRO instruments. This subset warrants further considerations as response shift can be a beneficial coping mechanism in response to disease or disability,<sup>33, 163</sup> or it may negatively impact a person's health related quality of life in the event that his or her perceived expectations of treatment or self-evaluation of function are not realistic.<sup>72</sup> Further understanding and identification of patients prone to response shift may improve outcomes assessment and assist in the improvement of patient health related quality of life of patient by patient basis.

## APPENDICES

### APPENDIX A – PATIENT REPORTED OUTCOME INSTRUMENTS

*\*These pages are meant to serve as a representation of instrument content and are formatted to fit page requirements not to serve as the actual instruments themselves.*



#### International Knee Documentation Committee Subjective Knee Form (IKDC)

\*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.



1. What is the highest level of activity that you can perform without significant knee pain?

- Very strenuous activities like jumping or pivoting as in basketball or soccer
- Strenuous activities like heavy physical work, skiing or tennis
- Moderate activities like moderate physical work, running or jogging
- Light activities like walking, housework or yard work
- Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

- |   |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |   |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---|
| Never   | 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       | Constant  |
|  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |

3. If you have pain, how severe is it?

- |   |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |   |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---|
| No pain   | 0                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       | Worst Pain Imaginable   |
|  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

- Not at all  Mildly  Moderately  Very  Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

- Very strenuous activities like jumping or pivoting as in basketball or soccer
- Strenuous activities like heavy physical work, skiing or tennis
- Moderate activities like moderate physical work, running or jogging
- Light activities like walking, housework, or yard work
- Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

- Yes  No

7. What is the highest level of activity you can perform without significant giving way in your knee?

- Very strenuous activities like jumping or pivoting as in basketball or soccer
- Strenuous activities like heavy physical work, skiing or tennis
- Moderate activities like moderate physical work, running or jogging
- Light activities like walking, housework or yard work
- Unable to perform any of the above activities due to giving way of the knee

## IKDC Continued.

### SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

- Very strenuous activities like jumping or pivoting as in basketball or soccer
- Strenuous activities like heavy physical work, skiing or tennis
- Moderate activities like moderate physical work, running or jogging
- Light activities like walking, housework or yard work
- Unable to perform any of the above activities due to knee



9. How does your knee affect your ability to:

	Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a. Go up stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Go down stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Kneel on the front of your knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Squat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Sit with your knee bent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Rise from a chair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Run straight ahead	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Jump and land on your involved leg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Stop and start quickly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



### FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

#### FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform daily activities  0 1 2 3 4 5 6 7 8 9 10 No limitation 

#### CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities  0 1 2 3 4 5 6 7 8 9 10 No limitation 

## Lysholm Knee Scale

**1. Do you have a limp?**

- No
- Slight limp or limp periodically
- Severe limp and constantly

**2. What support do you need for walking?**

- None
- Stick or crutch
- I am unable to weight bear.

**3. Does your knee lock?**

- No locking or catching sensations
- Catching sensation but no locking
- Locking - occasionally
- Locking - frequently
- Locked joint on examination (it is locked now)

**4. How unstable is your Knee?**

- It never gives way
- Rarely during athletics or other severe exertion
- Frequently during athletics
- Occasionally during daily activities
- Often during daily activities
- Every step

**5. How painful is your Knee?**

- No pain
- Inconstant and slight during severe exertion
- Marked during severe exertion
- Marked on or after walking 2km
- Marked on or after walking less than 2km
- Constant

**6. Do you have swelling in your knee?**

- None
- On severe exertion
- On ordinary exertion
- Constant

**7. Can you climb stairs?**

- No problems
- Slightly impaired
- One step at a time
- Impossible

**8. Can you squat?**

- No problems
- Slightly impaired
- Not beyond 90 degrees
- Impossible

## Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

1. In general, would you say your health is:

- Excellent  
 Very Good  
 Good  
 Fair  
 Poor

2. Compared to one year ago, how would you rate your health in general now?

- Much better now than 1 year ago  
 Somewhat better now than 1 year ago  
 About the same as 1 year ago  
 Somewhat worse now than 1 year ago  
 Much worse now than 1 year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities?

If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Lifting or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Climbing several flights of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Climbing one flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Bending, kneeling or stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Walking more than a mile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Walking several hundred yards	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Walking one hundred yards	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Bathing or dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## SF-36 Continued

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Accomplished less than you would like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Were limited in the kind of work or other activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Had difficulty performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Accomplished less than you would like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Did work or other activities less carefully than usu	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

- Not At All  
 Slightly  
 Moderately  
 Quite a Bit  
 Extremely

7. How much bodily pain have you had during the past 4 weeks?

- None  
 Very Mild  
 Mild  
 Moderate  
 Severe  
 Very Severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at All  
 A Little Bit  
 Moderately  
 Quite a Bit  
 Extremely

## SF-36 Continued

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Have you been very nervous?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Have you felt calm and peaceful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Did you have a lot of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Have you felt downhearted and depressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Did you feel worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Have you been happy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Did you feel tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time  
 Most of the time  
 Some of the time  
 A little of the time  
 None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. I am as healthy as anybody I know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. I expect my health to get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. My health is excellent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

**P:** These questions concern the amount of **pain** you are currently experiencing due to arthritis in your hips and your knees. For each situation, please enter the amount of pain you have recently experienced. How much pain do you have...

1. Walking on a flat surface	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
2. Going up or down stairs	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
3. At night while in bed	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
4. Sitting or lying	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
5. Standing upright	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme

**M:** These questions concern the amount of **joint stiffness** (not pain) you are currently experiencing due to arthritis in your hips and or knees. Stiffness is sensation of restriction or slowness in the area around which you move your joints.

6. How severe is your stiffness after first waking in the morning?	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
7. How severe is your stiffness after sitting, lying or resting later in the day?	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme

**F:** These questions concern your **physical function**. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you are experiencing due to arthritis. What degree of difficulty do you have with...

8. Descending stairs	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
9. Ascending stairs	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
10. Rising from sitting	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
11. Standing	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
12. Bending to floor	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
13. Walking on flat	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
14. Getting in/out of car	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
15. Going shopping	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
16. Putting on socks/stockings	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
17. Rising from bed	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
18. Taking off socks/stockings	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
19. Lying in bed	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
20. Getting in/out bath	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
21. Sitting	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
22. Getting on/off toilet	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
23. Heavy domestic duties	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme
24. Light domestic duties	<input type="checkbox"/> None	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe	<input type="checkbox"/> Extreme



## **APPENDIX B: PROPOSED METHOD FOR VERIFYING RESPONSE SHIFT WITH PERFORMANCE BASED ASSESSMENTS**

In the event a group level response shift had occurred a series of linear regression analyses would have been conducted to determine if the occurrence of the response shift could be validated by changes in the relationship between pre-test scores and preoperative PBAs, then-test scores and preoperative PBAs, and post-test scores and postoperative PBAs. The purpose of this appendix is to provide an example of how this proposed method of evaluating response shift would have been performed had there been evidence of a response shift.

A significant correlation was observed between pre-test IKDC score and preoperative Walk Across length ( $R = 0.43$ ,  $p = 0.024$ ) and between then-test at 6 months IKDC score and preoperative Walk Across length ( $R = 0.43$ ,  $p = 0.04$ ). The correlation between IKDC post-test score at 6 months and Walk Across length at 6 months was not significant ( $R = 0.06$ ,  $p = 0.81$ ). Because the then-test at 6 months and post-test at 6 months were completed at the same time it was theorized that both tests would be completed from the same frame of reference. If a response shift had occurred the relationship between the then-test score at 6 months and preoperative Walk Across length and the relationship between the post-test score at 6 months and 6 month Walk Across length would be similar. However, the relationship between pre-test score and pre-test Walk Across length would be significantly different. To evaluate these relationships a series of regression equations were employed (Table 4.1).

The regression model for preoperative Walk Across length as a function of pre-test IKDC was  $preoperative\ Walk\ Across\ length = 0.295 + .003(pre-test\ IKDC\ Score)$  ( $Adjusted\ R^2 = 0.15$ ). The 95% confidence interval for the intercept was 0.199 to 0.390,

while the confidence interval for the parameter estimate for IKDC score was 0.000 to 0.005. The regression model for preoperative Walk Across length as a function of 6 month then-test IKDC score was *preoperative Walk Across length = 0.335 + .002(then-test 6month IKDC Score)* (*Adjusted R<sup>2</sup> = 0.15*). The 95% confidence interval for the intercept was 0.261 to 0.410, while the confidence interval for the parameter estimate for IKDC score was 0.000 to 0.004. Given that the 95% confidence intervals for both the intercept and the parameter estimates overlap, these observations do not support the occurrence of a response shift resulting in a change in patient frame of reference between the preoperative and 6 month time points. These results are in agreement with the group level analysis that failed to identify a response shift for the IKDC or any other PRO instruments and fail to support the hypothesis that  $\beta_{Pre} \neq \beta_{then}$  where  $\beta_{Pre}$  is the parameter estimate for pre-test IKDC score and  $\beta_{then}$  is the parameter estimate for then test IKDC score at 6 months.

## REFERENCES

1. *How to Score the SF-36 Health Survey*. Boston, MA: Medical Outcomes Trust; 1994.
2. Towards a common language for functioning, disability, and health; ICF the international classification of functioning, disability, and health. *World Health Organization*. Geneva; 2002.
3. *Balance Manager Systems Clinical Operations Guide*. Clackamas, OR: NeuroCom International Inc.; 2008.
4. Oxford Centre for Evidence-based Medicine - Levels of Evidence January 12, 2011. Available at: <http://www.cebm.net/index.aspx?o=1025>. Accessed January 20, 2011.
5. Balance master family: balance master. *NeuroCom International, Inc*. Available at: <http://www.onbalance.com/products/Balance-Master/detail.php#balance>. Accessed February 18, 2011.
6. Alkjaer T, Simonsen EB, Peter Magnusson SP, Aagaard H, Dyhre-Poulsen P. Differences in the movement pattern of a forward lunge in two types of anterior cruciate ligament deficient patients: copers and non-copers. *Clin Biomech (Bristol, Avon)*. 2002;17(8):586-593.
7. Amin AA, Bartlett W, Gooding CR, et al. The use of autologous chondrocyte implantation following and combined with anterior cruciate ligament reconstruction. *Int Orthop*. 2006;30(1):48-53.
8. Armenakis AA, Feild HS, Wilmoth JN. An algorithm for assessing factor structure congruence. *Educ Psychol Meas*. 1977;37(1):213-214.
9. Bailey A, Goodstone N, Roberts S, et al. Rehabilitation after oswestry autologous-chondrocyte implantation: the OsCell protocol. *J Sport Rehab*. 2003;12(2):104-118.
10. Balain B, Ennis O, Kanen G, et al. Response shift in self-reported functional scores after knee microfracture for full thickness cartilage lesions. *Osteoarthritis Cartil*. Aug 2009;17(8):1009-1013.
11. Barber-Westin SD, Noyes FR, McCloskey JW. Rigorous statistical reliability, validity, and responsiveness testing of the Cincinnati Knee Rating System in 350 subjects with uninjured, injured, or anterior cruciate ligament-reconstructed knees. *Am J Sports Med*. 1999;27(4):402-416.
12. Barber SD, Noyes FR, Mangine R, DeMaio M. Rehabilitation after ACL reconstruction: function testing. *Orthopedics*. 1992;15(8):969-974.
13. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br*. 2005;87(5):640-645.
14. Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):519-527.

15. Beaton DE. Understanding the relevance of measured change through studies of responsiveness. *Spine*. 15 2000;25(24):3192-3199.
16. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)--5-year follow-up. *Knee*. 2006;13(3):194-202.
17. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the knee injury and osteoarthritis outcome score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthr Cartil*. 2009;17(11):1434-1439.
18. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-1840.
19. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically-important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. *J Orthop Rheum*. 1988;1:95-108.
20. Bentley G, Biant LC, Akmal M, et al. Autologous chondrocyte implantation was superior to mosaicplasty for repair of articular cartilage defects in the knee at one year. *J Bone Joint Surg Am*. 2003;85A(11):2259-2259.
21. Bentley G, Biant LC, Carrington RWJ, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br*. 2003;85(2):223-230.
22. Bhosale AM, Kuiper JH, Johnson WEB, Harrison PE, Richardson JB. Midterm to Long-Term Longitudinal Outcome of Autologous Chondrocyte Implantation in the Knee Joint. *Am J Sports Med*. 2009;37(1s):131S-138S.
23. Bhosale AM, Myint P, Roberts S, et al. Combined autologous chondrocyte implantation and allogenic meniscus transplantation: a biological knee replacement. *Knee*. 2007;14(5):361-368.
24. Borenstein M, Hedges LV, Higgins JPT, Rothstein H. *Introduction to Meta-Analysis*. 1st ed. Chichester: John Wiley & Sons, Ltd; 2009.
25. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. *J Bone Joint Surg Am*. 2006;88(4):698-705.
26. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. *Am J Sports Med*. 2009;37(5):890-897.
27. Briggs TW, Mahroof S, David LA, Flannelly J, Pringle J, Bayliss M. Histological evaluation of chondral defects after autologous chondrocyte implantation of the knee. *J Bone Joint Surg Br*. 2003;85(7):1077-1083.
28. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889-895.
29. Brittberg M, Tallheden T, Sjogren-Jansson E, Lindahl A, Peterson L. Autologous chondrocytes used for articular cartilage repair: an update. *Clin Orthop*. 2001(391):S337-348.

30. Brophy RH, Zeltser D, Wright RW, Flanigan D. Anterior cruciate ligament reconstruction and concomitant articular cartilage injury: incidence and treatment. *Arthroscopy*. 2010;26(1):112-120.
31. Browne JE, Anderson AF, Arciero R, et al. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. *Clin Orthop*. 2005(436):237-245.
32. Cameron ML, Briggs KK, Steadman JR. Reproducibility and reliability of the outerbridge classification for grading chondral lesions of the knee arthroscopically. *Am J Sports Med*. 2003;31(1):83-86.
33. Carver CS, Scheier MF. Scaling back goals and recalibration of the affect system are processes in normal adaptive self-regulation: understanding 'response shift' phenomena. *Soc Sci Med*. 2000;50(12):1715-1722.
34. Caumo F, Russo A, Faccioli N, et al. Autologous chondrocyte implantation: prospective MRI evaluation with clinical correlation. *La Radiologia Medica*. 2007;112(5):722-731.
35. Cherubino P, Grassi FA, Bulgheroni P, Ronga M. Autologous chondrocyte implantation using a bilayer collagen membrane: a preliminary report. *J Orthop Surg (Hong Kong)*. 2003;11(1):10-15.
36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Assoc; 1988.
37. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. *Scand J Med Sci Sports*. 2000;10(1):2-11.
38. Costigan PA, Deluzio KJ, Wyss UP. Knee and hip kinetics during normal stair climbing. *Gait Posture*. 2002;16(1):31-37.
39. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy*. 1997;13(4):456-460.
40. Daltroy LH, Larson MG, Eaton HM, Phillips CB, Liang MH. Discrepancies between self-reported and observed physical function in the elderly: the influence of response shift and other factors. *Soc Sci Med*. 1999;48(11):1549-1561.
41. de Windt TS, Bekkers JEJ, Creemers LB, Dhert WJA, Saris DIBF. Patient profiling in cartilage regeneration. *Am J Sports Med*. 2009;37(1s):58S-62S.
42. Della Villa S, Kon E, Filardo G, et al. Does intensive rehabilitation permit early return to sport without compromising the clinical outcome after arthroscopic autologous chondrocyte implantation in highly competitive athletes? *Am J Sports Med*. 2010;38(1):68-77.
43. Ebert JR, Lloyd DG, Ackland T, Wood DJ. Knee biomechanics during walking gait following matrix-induced autologous chondrocyte implantation. *Clin Biomech*. 2010;25(10):1011-1017.
44. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. Traditional vs accelerated approaches to post-operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI): comparison of clinical, biomechanical and radiographic outcomes. *Osteoarthr Cartil*. 2008;16(10):1131-1140.
45. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. A prospective, randomized comparison of traditional and accelerated approaches to

- postoperative rehabilitation following autologous chondrocyte implantation. *Cartilage*. 2010;1(3):180-187.
46. Engen CN, Engebretsen L, Årøen A. Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopedic practice. *Cartilage*. 2010;1(4):312-319.
  47. Enright PL. The six-minute walk test. *Respir Care*. 2003;48(8):783-785.
  48. Erggelet C, Steinwachs M, Reichelt A. The operative treatment of full thickness cartilage defects in the knee joint with autologous chondrocyte transplantation. *Saudi Med J*. 2000;21(8):715-721.
  49. Farr J. Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. *Clin Orthop*. 2007;463:187-194.
  50. Farr J, Rawal A, Marberry KM. Concomitant meniscal allograft transplantation and autologous chondrocyte implantation: minimum 2-year follow-up. *Am J Sports Med*. 2007;35(9):1459-1466.
  51. Ferruzzi A, Buda R, Faldini C, et al. Autologous chondrocyte implantation in the knee joint: open compared with arthroscopic technique. comparison at a minimum follow-up of five years. *J Bone Joint Surg Am*. 2008;90(4s):90-101.
  52. Gauffin H, Pettersson G, Tegner Y, Tropp H. Function testing in patients with old rupture of the anterior cruciate ligament. *Int J Sports Med*. 1990;11(1):73-77.
  53. Gillogly SD, Myers TH, Reinold MM. Treatment of full-thickness chondral defects in the knee with autologous chondrocyte implantation. *J Orthop Sports Phys Ther*. 2006;36(10):751-764.
  54. Gobbi A, Kon E, Berruto M, et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up. *Am J Sports Med*. 2009;37(6):1083-1092.
  55. Gobbi A, Kon E, Berruto M, Francisco R, Filardo G, Marcacci M. Patellofemoral full-thickness chondral defects treated with hyalograft-C: a clinical, arthroscopic, and histologic review. *Am J Sports Med*. 2006;34(11):1763-1773.
  56. Golembiewski RT, Billingsley K, Yeager S. Measuring change and persistence in human affairs: Types of change generated by OD designs. *J Appl Behav Sci*. 1975;12(2):133-157.
  57. Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered. *Knee*. 2006;13(3):203-210.
  58. Greco NJ, Anderson AF, Mann BJ, et al. Responsiveness of the International Knee Documentation Committee Subjective Knee Form in comparison to the Western Ontario and McMaster Universities Osteoarthritis Index, Modified Cincinnati Knee Rating System, and Short Form 36 in patients with focal articular cartilage defects. *Am J Sports Med*. 2010;38(5):891-902.
  59. Haddo O, Mahroof S, Higgs D, et al. The use of chondrocyte membrane in autologous chondrocyte implantation. *Knee*. 2004;11(1):51-55.
  60. Hagedoorn M, Sneeuw KCA, Aaronson NK. Changes in physical functioning and quality of life in patients with cancer: Response shift and relative evaluation of one's condition. *J Clin Epidemiol*. 2002;55(2):176-183.



61. Hambly K, Bobic V, Wondrasch B, Van Assche D, Marlovits S. Autologous chondrocyte implantation postoperative care and rehabilitation: science and practice. *Am J Sports Med.* 2006;34(6):1020-1038.
62. Harris JD, Siston RA, Pan X, Flanigan DC. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am.* 2010;92(12):2220-2233.
63. Harter RA. Clinical rationale for closed kinetic chain activities in functional testing and rehabilitation of ankle pathologies. *J Sport Rehab.* 1996;5(1):13-24.
64. Hays RD, Morales LS. The RAND-36 measures of health-related quality of life. *Ann Med.* 2001;33:350-357.
65. Henderson I, Francisco R, Oakes B, Cameron J. Autologous chondrocyte implantation for treatment of focal chondral defects of the knee--a clinical, arthroscopic, MRI and histologic evaluation at 2 years. *Knee.* 2005;12(3):209-216.
66. Henderson I, Gui J, Lavigne P. Autologous chondrocyte implantation: natural history of postimplantation periosteal hypertrophy and effects of repair-site debridement on outcome. *Arthroscopy.* 2006;22(12):1318-1324
67. Henderson IJP, Lavigne P. Periosteal autologous chondrocyte implantation for patellar chondral defect in patients with normal and abnormal patellar tracking. *Knee.* 2006;13(4):274-279.
68. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy.* 2002;18(7):730-734.
69. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint: a prospective, comparative trial. *J Bone Joint Surg Am.* 2003;85-A(2):185-192.
70. Howard GS. Internal invalidity in pretest-posttest self-report evaluations and a re-evaluation of retrospective pretests. *App Psych Meas.* 1979;3(1):1-23.
71. Howard GS, Schmeck RR, Bray JH. Internal invalidity in studies employing self-report instruments: A suggested remedy. *J Educ Meas.* 1979;16(2):129-135.
72. Howard JS, Mattacola CG, Howell DM, Lattermann C. Response shift theory: an application for health related quality of life in rehabilitation research and practice. *J Allied Health.* 2011;40(1):31-38.
73. Howard JS, Mattacola CG, Mullineaux DM, English RA, Lattermann C. Reliability of force plate based performance measures for evaluation of patients receiving treatment for knee articular cartilage defects. Lexington, KY: University of Kentucky; 2011.
74. Howard JS, McKeon JM, Mattacola CG, Hoch JM, Lattermann C. Systematic review and meta-analysis of patient reported outcome instruments following autologous chondrocyte implantation. Lexington, KY: University of Kentucky; 2011.
75. Hunter W. Of the structure and diseases of articulating cartilages. *Philos Transact.* 1742;42:514-521.
76. Irrgang JJ, Anderson AF. Development and validation of health-related quality of life measures for the knee. *Clin Orthop.* 2002(402):95-109.
77. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med.* 2001;29(5):600-613.

78. Irrgang JJ, Anderson AF, Boland AL, et al. Responsiveness of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med.* 2006;34(10):1567-1573.
79. Jacobs CA, Christensen CP. Correlations between knee society function scores and functional force measures. *Clin Orthop Relat Res.* 2009;467(9):2414-2419.
80. Jaiswal PK, Macmull S, Bentley G, Carrington RW, Skinner JA, Briggs TW. Does smoking influence outcome after autologous chondrocyte implantation?: A case-controlled study. *J Bone Joint Surg Br.* 2009;91(12):1575-1578.
81. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. *J Bone Joint Surg Am.* 2005;87A(10):2232-2239.
82. Jamshidi AA, Olyaei GR, Heydarian K, Talebian S. Isokinetic and functional parameters in patients following reconstruction of the anterior cruciate ligament. *Isokinet Exerc Sci* 2005;13(4).
83. Jaremko JL, Cheng RWT, Lambert RGW, Habib AF, Ronsky JL. Reliability of an efficient MRI-based method for estimation of knee cartilage volume using surface registration. *Osteoarthr Cartil.* 2006;14(9):914-922.
84. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee: a randomized trial. *J Bone Joint Surg Am.* 2004;86-A(3):455-464.
85. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm Knee Scale for various chondral disorders of the knee. *J Bone Joint Surg Am.* 2004;86A(6):1139-1145.
86. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M. Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. *Am J Sports Med.* 2009;37(1):33-41.
87. Kon E, Verdonk P, Condello V, et al. Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee. *Am J Sports Med.* 2009;37(1s):156S-166S.
88. Korth B, Tucker LR. The distribution of chance congruence coefficients from simulated data. *Psychometrika.* 1975;40(2):361-372.
89. Kreuz PC, Müller S, Ossendorf C, Kaps C, Erggelet C. Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte grafts: four-year clinical results. *Arthrit Res Ther.* 2009;11(2):R33-R33.
90. Kreuz PC, Steinwachs M, Erggelet C, et al. Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. *Am J Sports Med.* 2007;35(8):1262-1268.
91. Krishnan SP, Skinner JA, Bartlett W, et al. Who is the ideal candidate for autologous chondrocyte implantation? *J Bone Joint Surg Br.* 2006;88(1):61-64.
92. Krishnan SP, Skinner JA, Carrington RWJ, Flanagan AM, Briggs TWR, Bentley G. Collagen-covered autologous chondrocyte implantation for osteochondritis dissecans of the knee: two- to seven-year results. *J Bone Joint Surg Br.* 2006;88B(2):203-205.
93. Lattermann C. UK Center for Cartilage Repair and Restoration *University of Kentucky.* March 9, 2010. Available at: <http://www.ukhealthcare.uky.edu/cartilage/rehab.htm>. Accessed February 24, 2011.



94. Lephart SM, Perrin DH, Fu FH, Minger K. Functional performance tests for the anterior cruciate ligament insufficient athlete. *J Athl Train*. Spring 1991;26(1):44-45;48-50.
95. Li J, Williams JM, Zhong Z, et al. Reliability of diffraction enhanced imaging for assessment of cartilage lesions, ex vivo. *Osteoarthr Cartil*. 2005;13(3):187-197.
96. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med*. 1982;10(3):150-154.
97. Maly MR, Costigan PA, Olney SJ. Determinants of self-report outcome measures in people with knee osteoarthritis. *Arch Phys Med Rehabil*. Jan 2006;87(1):96-104.
98. Mandelbaum B, Browne JE, Fu F, et al. Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. *Am J Sports Med*. 2007;35(6):915-921.
99. Mandelbaum BR, Browne JE, Fu F, et al. Articular cartilage lesions of the knee. *Am J Sports Med*. 1998;26(6):853-861.
100. Marcacci M, Berruto M, Brocchetta D, et al. Articular cartilage engineering with Hyalograft C: 3-year clinical results. *Clin Orthop Relat Res*. 2005(435):96-105.
101. Marlovits S, Singer P, Zeller P, Mandl I, Haller Jr, Trattng S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. *Eur J Radiol*. 2006;57(1):16-23.
102. Marx RG, Connor J, Lyman S, et al. Multirater agreement of arthroscopic grading of knee articular cartilage. *Am J Sports Med*. 2005;33(11):1654-1657.
103. Marx RG, Jones EC, Allen AA, et al. Reliability, validity, and responsiveness of four knee outcome scales for athletic patients. *J Bone Joint Surg Am*. 2001;83(10):1459.
104. Marx RG, Menezes A, Horovitz L, Jones EC, Warren RF. A comparison of two time intervals for test-retest reliability of health status instruments. *J Clin Epidemiol*. 2003;56(8):730-735.
105. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994;32(1):40-66.
106. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993;31(3):247-263.
107. McNickle AG, L'Heureux DR, Yanke AB, Cole BJ. Outcomes of autologous chondrocyte implantation in a diverse patient population. *Am J Sports Med*. 2009;37(7):1344-1350.
108. Micheli LJ, Moseley JB, Anderson AF, et al. Articular cartilage defects of the distal femur in children and adolescents: treatment with autologous chondrocyte implantation. *J Pediatr Orthop*. 2006;26(4):455-460.
109. Millsap RE, Hartog SB. Alpha, beta, and gamma change in evaluation research: a structural equation approach. *J Appl Psychol*. 1988;73(3):574-584.
110. Minas T. Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am J Orthop*. 1998;27(11):739-744.
111. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop Relat Res*. 2001(391 Suppl):S349-361.

112. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. *Clin Orthop Relat Res.* 2005(436):30-39.
113. Minas T, Chiu R. Autologous chondrocyte implantation. *Am J Knee Surg.* 2000;13(1):41-50.
114. Minas T, Gomoll AH, Solhpour S, Rosenberger R, Probst C, Bryant T. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. *Clin Orthop.* 2010;468(1):147-157.
115. Mithöfer K, Minas T, Peterson L, Yeon H, Micheli LJ. Functional outcome of knee articular cartilage repair in adolescent athletes. *Am J Sports Med.* 2005;33(8):1147-1153.
116. Mithöfer K, Peterson L, Mandelbaum BR, Minas T. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. *Am J Sports Med.* 2005;33(11):1639-1646.
117. Mizner RL, Petterson SC, Clements KE, Zeni Jr JA, Irrgang JJ, Snyder-Mackler L. Measuring functional improvement after total knee arthroplasty requires both performance-based and patient-report assessments: a longitudinal analysis of outcomes. *J Arthroplasty.* In Press, Corrected Proof.
118. Moseley JB, Anderson AF, Browne JE, et al. Long-term durability of autologous chondrocyte implantation: a multicenter, observational study in US patients. *Am J Sports Med.* 2010;38(2):238-246.
119. Naylor ME, Romani WA. Test-retest reliability of three dynamic tests obtained from active females using the Neurocom Balance Master. *J Sport Rehab.* 2006;15(4):326-337.
120. Neeb TB, Aufdemkampe G, Wagener JHD, Mastenbroek L. Assessing anterior cruciate ligament injuries: the association and differential value of questionnaires, clinical tests, and functional tests. *J Orthop Sports Phys Ther.* 1997;26(6):324-331.
121. Nehrer S, Domayer S, Dorotka R, Schatz K, Bindreiter U, Kotz R. Three-year clinical outcome after chondrocyte transplantation using a hyaluronan matrix for cartilage repair. *Eur J Radiol.* 2006;57(1):3-8.
122. Niemeyer P, Köstler W, Salzmann GM, Lenz P, Kreuz PC, Südkamp N. Autologous chondrocyte implantation for treatment of focal cartilage defects in patients age 40 tears and older. *Am J Sports Med.* 2010;38(12):2410-2416.
123. Niemeyer P, Salzmann G, Steinwachs M, et al. Presence of subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after autologous chondrocyte implantation. *Arch Orthop Trauma Surg.* 2010;130(8):977-983.
124. Noyes FR, Barber SD, Mangine RE. Bone-patellar ligament-bone and fascia lata allografts for reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Am.* 1990;72(8):1125-1136.
125. Noyes FR, Matthews DS, Mooar PA, Grood ES. The symptomatic anterior cruciate-deficient knee. Part II: the results of rehabilitation, activity modification, and counseling on functional disability. *J Bone Joint Surg Am.* 1983;65(2):163-174.
126. Noyes FR, McGinniss GH, Grood ES. The variable functional disability of the anterior cruciate ligament-deficient knee. *Orthop Clin North Am.* 1985;16(1):47-67.

127. Noyes FR, Mooar LA, Barber SD. The assessment of work-related activities and limitations in knee disorders. *Am J Sports Med.* 1991;19(2):178-188.
128. Noyes FR, Mooar PA, Matthews DS, Butler DL. The symptomatic anterior cruciate-deficient knee. Part I: the long-term functional disability in athletically active individuals. *J Bone Joint Surg Am.* 1983;65(2):154-162.
129. Ochi M, Uchio Y, Kawasaki K, Wakitani S, Iwasa J. Transplantation of cartilage-like tissue made by tissue engineering in the treatment of cartilage defects of the knee. *J Bone Joint Surg Br.* 2002;84(4):571-578.
130. Oort FJ. Using structural equation modeling to detect response shifts and true change. *Qual Life Res.* 2005;14(3):587-598.
131. Oort FJ, Visser MRM, Sprangers MAG. An application of structural equation modeling to detect response shifts and true change in quality of life data from cancer patients undergoing invasive surgery. *Qual Life Res.* 2005;14(3):599-609.
132. Orwin RG. A fail-safe N for effect size in meta-analysis. *J Ed Stat.* 1983;8(2):157-159.
133. Ossendorf C, Kaps C, Kreuz PC, Burmester GR, Sittinger M, Erggelet C. Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-year clinical results. *Arthrit Res Ther.* 2007;9(2):R41-R41.
134. Parent E, Moffet H. Comparative responsiveness of locomotor tests and questionnaires used to follow early recovery after total knee arthroplasty. *Arch Phys Med Rehabil.* 2002;83(1):70-80.
135. Pascual-Garrido C, Slabaugh MA, L'Heureux DR, Friel NA, Cole BJ. Recommendations and treatment outcomes for patellofemoral articular cartilage defects with autologous chondrocyte implantation. *Am J Sports Med.* 2009;37(1s):33S-41S.
136. Paxton EW, Fithian DC, Stone ML, Silva P. The reliability and validity of knee-specific and general health instruments in assessing acute patellar dislocation outcomes. *Am J Sports Med.* 2003;31(4):487-492.
137. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med.* 2010; 38(6):1117-1124.
138. Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice.* Second ed. Upper Saddle River, NJ: Prentice Hall Health; 2000.
139. Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health Qual Life Outcomes.* 2004;2:14-14.
140. Raynauld JP, Kauffmann C, Beaudoin G, et al. Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. *Osteoarthr Cartil.* 2003;11(5):351-360.
141. Razmjou H, Schwartz CE, Yee A, Finkelstein JA. Traditional assessment of health outcome following total knee arthroplasty was confounded by response shift phenomenon. *J Clin Epidemiol.* 2009;62(1):91-96.
142. Razmjou H, Yee A, Ford M, Finkelstein JA. Response shift in outcome assessment in patients undergoing total knee arthroplasty. *J Bone Jt Surg Am.* 2006;88(12):2590-2595.

143. Reinold MM, Wilk KE, Macrina LC, Dugas JR, Cain EL. Current concepts in the rehabilitation following articular cartilage repair procedures in the knee. *J Orthop Sports Phys Ther.* 2006;36(10):774-794.
144. Risberg MA, Ekeland A. Assessment of functional tests after anterior cruciate ligament surgery. *J Orthop Sports Phys Ther.* 1994;19(4):212-217.
145. Roberts S, McCall IW, Darby AJ, et al. Autologous chondrocyte implantation for cartilage repair: monitoring its success by magnetic resonance imaging and histology. *Arthritis Res Ther.* 2003;5(1):R60-73.
146. Robertson WB, Fick D, Wood DJ, Linklater JM, Zheng MH, Ackland TR. MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years. *Knee.* 2007;14(2):117-127.
147. Roos EM, Klassbo M, Lohmander LS. WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and MacMaster Universities. *Scand J Rheumatol.* 1999;28(4):210-215.
148. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee injury and osteoarthritis outcome score (KOOS)-development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.
149. Rosenberger RE, Gomoll AH, Bryant T, Minas T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. *Am J Sports Med.* 2008;36(12):2336-2344.
150. Rue JH, Yanke AB, Busam ML, McNickle AG, Cole BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. *Am J Sports Med.* 2008;36(9):1770-1778.
151. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med.* 2009;37 (1s):10S-19S.
152. Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am J Sports Med.* 2008;36(2):235-246.
153. Schmitt N. The use of analysis of covariance structures to assess beta and gamma change. *Multivar Behav Res.* 1982;17(3):343-358.
154. Schmitt NW, Pulakos ED, Lieblein A. Comparison of three techniques to assess group-level beta and gamma change. *App Psychol Meas.* 1984;8(3):249-260.
155. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. *Soc Sci Med.* 1999;48(11):1531-1548.
156. Schwartz CE, Sprangers MAG. An introduction to quality of life assessment in oncology: the value of measuring patient-reported outcomes. *Am J Manag Care.* 2002;8(18 Suppl):S550-559.
157. Schwartz CE, Sprangers MAG, Carey A, Reed G. Exploring response shift in longitudinal data. *Psychol Health.* 2004;19(1):51-69.
158. Selmi TA, Verdonk P, Chambat P, et al. Autologous chondrocyte implantation in a novel alginate-agarose hydrogel: outcome at two years. *J Bone Joint Surg Br.* 2008;90(5):597-604.

159. Sernert N, Kartus J, Koehler K, et al. Analysis of subjective, objective and functional examination tests after anterior cruciate ligament reconstruction: a follow-up of 527 patients. *Knee Surg Sports Traumatol Arthrosc.* 1999;7(3):160-165.
160. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-428.
161. Smith GD, Taylor J, Almqvist KF, et al. Arthroscopic assessment of cartilage repair: a validation study of 2 scoring systems. *Arthroscopy.* 2005;21(12):1462-1467.
162. Sprangers MA, Schwartz CE. The challenge of response shift for quality-of-life-based clinical oncology research. *Ann Oncol.* 1999;10(7):747-749.
163. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med.* 1999;48(11):1507-1515.
164. Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up. *Arthroscopy.* 2007;23(4):381-387.
165. Stratford PW, Kennedy DM. Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *J Clin Epidemiol.* 2006;59(2):160-167.
166. Stratford PW, Kennedy DM, Woodhouse LJ. Performance measures provide assessments of pain and function in people with advanced osteoarthritis of the hip or knee. *Phys Ther.* 2006;86(11):1489-1496.
167. Takahashi T, Tins B, McCall IW, Richardson JB, Takagi K, Ashton K. MR appearance of autologous chondrocyte implantation in the knee: correlation with the knee features and clinical outcome. *Skeletal Radiol.* 2006;35(1):16-26.
168. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop.* 1985(198):43-49.
169. Thomas JR, Nelson JK. *Research Methods in Physical Activity.* Second ed. Champaign, IL: Human Kinetics Books; 1990.
170. Tierney DK, Facione N, Padilla G, Dodd M. Response shift: a theoretical exploration of quality of life following hematopoietic cell transplantation. *Cancer Nurs.* 2007;30(2):125-138.
171. Tohyama H, Yasuda K, Minami A, et al. Atelocollagen-associated autologous chondrocyte implantation for the repair of chondral defects of the knee: a prospective multicenter clinical trial in Japan. *J Orthop Sci.* 2009;14(5):579-588.
172. Van Assche D, Staes F, Van Caspel D, et al. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: a prospective randomized trial, with 2-year follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(4):486-495.
173. Van de Vlier I, Wyant K. *New Balance Master: Research to Reliability in a Healthy Population.* Ghent, Belgium: Rehabilitation Sciences and Physiotherapy, University of Ghent; 1999.
174. van den Borne MPJ, Raijmakers NJH, Vanlauwe J, et al. International cartilage repair society (ICRS) and oswestry macroscopic cartilage evaluation scores validated for use in autologous chondrocyte implantation (ACI) and microfracture. *Osteoarthr Cartil.* 2007;15(12):1397-1402.
175. Vasiliadis HS, Danielson B, Ljungberg M, McKeon B, Lindahl A, Peterson L. Autologous chondrocyte implantation in cartilage lesions of the knee: long-term



- evaluation with magnetic resonance imaging and delayed gadolinium-enhanced magnetic resonance imaging technique. *Am J Sports Med.* 2010;38(5):943-949.
176. Vasiliadis HS, Wasiak J, Salanti G. Autologous chondrocyte implantation for the treatment of cartilage lesions of the knee: a systematic review of randomized studies. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(12):1645-1655
177. Visser M, Oort F, Sprangers M. Methods to detect response shift in quality of life data: A convergent validity study. *Qual Life Res.* 2005;14(3):629-639.
178. Wagner JA. Response shift and glycemic control in children with diabetes. *Health Qual Life Outcomes.* 2005;3:38-38.
179. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
180. Waterman N, Sole G, Hale L. The effect of a netball game on parameters of balance. *Phys Ther Sport.* 2004;5(4):200-207.
181. Westerman MJ, The A-M, Sprangers MAG, Groen HJM, van der Wal G, Hak T. Small-cell lung cancer patients are just 'a little bit' tired: response shift and self-presentation in the measurement of fatigue. *Qual Life Res.* 2007;16(5):853-861.
182. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee.* 2007;14(3):177-182.
183. Wilkerson GB, Colston MA, Short NI, Neal KL, Hoewischer PE, Pixley JJ. Neuromuscular changes in female collegiate athletes resulting from a plyometric jump-training program. *J Athl Train.* 2004;39(1):17-23.
184. Willems TM, Witvrouw E, Delbaere K, Mahieu N, De Bourdeaudhuij I, De Clercq D. Intrinsic risk factors for inversion ankle sprains in male subjects: a prospective study. *Am J Sports Med.* 2005;33(3):415-423.
185. Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med.* 2009;37(1):42-55.
186. Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. *Am J Sports Med.* 2010;38(5):924-933.

## VITA

### Jennifer Sebert Howard, MS, ATC

#### I. General Information

Birthdate 03/26/1982

Place of Birth Ronceverte, West Virginia

Certificate or Specialty Board Licensure:

National Athletic Trainers Association Board of Certification #050402262

#### II. Education:

- 2007 – Present     The University of Kentucky, Lexington, KY,  
College of Health Sciences,  
Doctor of Philosophy, Rehabilitation Sciences  
Expected Completion: May 2011  
Dissertation: Clinical and Functional Assessment following  
Autologous Chondrocyte Implantation (ACI) to the Knee: The Role  
of Patient Reported Outcomes, Performance Based Assessment,  
and Response Shift
- 2004 – 2006     The University of Kentucky, Lexington, KY, College of Education,  
Master's of Science in Kinesiology and Health Promotion,  
concentration in Athletic Training
- 1996 – 2000     High Point University, High Point, NC  
Bachelor of Sciences in Athletic Training  
NATA Approved Athletic Training Curriculum

#### III. Professional Experiences:

- August 2007 – Present     Research Assistant  
Department of Orthopaedic Surgery and Sports Medicine  
Center for Cartilage Repair and Restoration  
University of Kentucky, Lexington, KY
- August 2008 – May 2009     Part-time Instructor  
College of Education  
Kinesiology and Health Promotion,  
University of Kentucky, Lexington, KY
- August 2006 – May 2007     Assistant Athletic Trainer  
Department of Athletics  
Elon University, Elon, NC

January 2005 – May 2006 Instructor  
Health and Human Performance  
Centre College, Danville, KY

August 2004 – May 2006 Graduate Assistant Athletic Trainer  
Centre College, Danville, KY

#### IV. Scholastic and Professional Honors

- |            |   |
|------------|---|
| 2005       | National Athletic Trainers' Association Research and Education Foundation Master's Scholarship        |
| 2003-2004  | High Point University Sports Medicine Academic Achievement Award                                      |
| 2000-2004  | High Point University Dean's List   |
| 2003       | Junior Marshal – Top 10% of High Point University Junior Class  |
| 2004       | Who's Who Among American Colleges and Universities  |
| 2000-2004  | All University Scholar Scholarship Recipient High Point University                                    |
| 2003, 2004 | Millis Scholar Student Athlete/Athletic Trainer 4.0 Award   |
| 2002       | American Chemical Society Cardinal Recognition Award for Outstanding Achievement in General Chemistry |
| 2002-2004  | Alpha Chi National Honor Society  |

#### V. Professional Publications and Presentations

##### a. Non-Reviewed Publications And Presentations

Accepted Speaker - Researchers' Forum: Demystifying the clinical and translational research process: Why Clinicians are vital to this process. *National Athletic Trainers' Association 62nd Annual Meeting and Clinical Symposium*, New Orleans, LA June 20, 2011.

Invited Speaker – Performance based and patient reported outcomes following autologous chondrocyte implantation. *University of Kentucky, Center for Clinical and Translational Sciences Seminar Series*, Lexington, KY. April 14, 2010.

Invited Speaker –SOCRATES Workshop: Pitfalls, perils and lessons learned from the implementation of Standardized Orthopaedic Cartilage Repair And Treatment Evaluation Software (SOCRATES) into clinical practice, *ICRS 2009 - 8th World Congress of the International Cartilage Repair Society*, Miami, FL. May 26, 2009.



Invited Speaker – Lower extremity functional assessment. *Kentucky Athletic Trainers' Society 2008 Annual Meeting and Clinical Symposium*, Highland Heights, KY. January 19, 2008.

Book Review –**Howard JS**. Functional Testing in Human Performance by Michael P. Reiman and Robert C. Manske, *NATA News*, September 2010.

**Howard JS**, Briggs D. The arch height index measurement system: a new method of foot classification clinical evaluation & testing column submission. *Athletic Therapy Today*, 11(5):56-57, 2006.

b. Refereed Abstract Presentations

**Howard JS**, Mattacola CG, Hoch JM, Lattermann C. Changes in functional performance during walking, squatting, rising, and stepping following autologous chondrocyte implantation (ACI). *9th World Congress of the International Cartilage Repair Society*; September 27, 2010, 2010; Stiges/Barcelona.

Mattacola CG, **Howard JS**, Hoch JM, Lattermann C. Comparison of knee strength pre-operatively, and at 6 and 12 months post-operatively following autologous chondrocyte implantation(ACI). *9th World Congress of the International Cartilage Repair Society*; September 27, 2010, 2010; Stiges/Barcelona.

Hoch JM, Mattacola CG, **Howard JS**, Lattermann C. Serum cartilage oligomeric matrix protein (sCOMP) is elevated in patients with knee osteoarthritis: a systematic review. *9th World Congress of the International Cartilage Repair Society*; September 27, 2010, 2010; Stiges/Barcelona.

Lattermann C, **Howard JS**, Hoch JM, Mattacola CG. Time-line for self-reported changes in function following autologous chondrocyte implantation (ACI) over one year. *9th World Congress of the International Cartilage Repair Society*; September 27, 2010, 2010; Stiges/Barcelona.

**Howard JS**, Lattermann C, Mattacola, CG. Concurrent validity of lysholm scale responses and corresponding performance based measures of function in articular cartilage patients. *National Athletic Trainers' Association 61st Annual Meeting and Clinical Symposium*, Philadelphia, PA June 23, 2010

**Howard JS**, Lattermann C, Mattacola, CG. Evaluation of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for response shift among surgical knee patients. *National Athletic Trainers' Association 60<sup>th</sup> Annual Meeting and Clinical Symposium*, San Antonio, TX June 19, 2009

**Howard JS**, Cheatham SA, James LM, Waespe DM, Lattermann C. Medial bone bridge meniscal transplantation. Can it be done anatomically without compromising the ACL footprint? *ICRS 2009 - 8th World Congress of the International Cartilage Repair Society*, Miami, FL. May 26, 2009

**Howard JS**, Fazio MA, Mattacola CG, Uhl TL. relationship of static hip range of motion to hip and knee kinematics during flight and landing. *33rd Annual Southeast Athletic Trainers' Association Clinical Symposium and Members Meeting*, Franklin, TN. February 29, 2008

**Howard JS**, Fazio MA, Mattacola CG, Uhl TL, Shapiro R, Jacobs CA. Relationship of hip and foot structure to knee and hip kinematics during landing. *58th National Athletic Trainers' Association Annual Meeting and Clinical Symposium*, Anaheim, CA. June 27, 2007

Fazio MA, **Howard JS**, Mattacola CG, Uhl TL, Jacobs CA, Shapiro R. The effect of activity type and fatigue on knee kinematics. *58th National Athletic Trainers' Association Annual Meeting and Clinical Symposium*, Anaheim, CA. June 27, 2007

**Howard JS**, Fazio MA, Mattacola CG, Uhl TL, Shapiro R, Jacobs CA. Relationship of Hip and Foot Structure to Knee and Hip Kinematics During Landing. *32nd Annual Southeast Athletic Trainers' Association Clinical Symposium and Members Meeting*, Franklin, TN. March 23, 2007

**Sebert JE**, Mattacola CG, Uhl TL. Diffuse Shoulder Pain in a Collegiate Swimmer. *J Athl Train* 41(2):S77, 2006

**Sebert JE**, Mattacola CG, Uhl TL. Diffuse shoulder pain in a collegiate swimmer. *31st Annual Southeast Athletic Trainers' Association Clinical Symposium and Members Meeting*, Atlanta, GA. March 31, 2006

c. Peer Reviewed Publications

Hoch JM, **Howard JS**, McKeon JM, Mattacola CG, Lattermann C. Serum cartilage oligomeric matrix protein (sCOMP) is elevated in patients with knee osteoarthritis: a systematic review and meta-Analysis. *Osteoarthritis Cartilage*. (Under Review).

Fazio MA, **Howard JS**, Mattacola CG, Uhl TL, Jacobs CA, Shapiro R. The effect of activity type and fatigue on knee kinematics. *Athletic Training & Sports Health Care* (Under Review)

**Howard JS**, Fazio MA, Mattacola CG, Uhl TL, Jacobs CA. Influence of structure, sex, and strength on knee and hip kinematics during landing. *J Athl Train* (In Press)

**Howard JS**, Mattacola CG, Howell DM, Lattermann C. response shift theory: an application for health related quality of life in rehabilitation research and practice. *J Allied Health*. 2011;40(1):31-8

**Howard JS**, Mattacola CG, Romine SE, Lattermann C. Continuous passive motion, early weight bearing, and active motion following knee articular cartilage repair: evidence for clinical practice. *Cartilage*. 2010;1(5):276-286.

Jennifer Sebert Howard, April 25, 2011