Title: A comparison of the responsiveness of four commonly used patient-reported outcome instruments at five years following matrix-induced autologous chondrocyte implantation.

Running Title: Responsiveness of patient-reported outcome instruments following MACI.

Authors: Jay R. Ebert PhD*; Anne Smith PhD‡; David J. Wood BSC MBBS, MS, FRCS, FRACS†; Timothy R. Ackland PhD, FASMF*

*School of Sport Science, Exercise and Health, University of Western Australia, Crawley, Perth, Western Australia, 6009.
‡The School of Physiotherapy and Curtin Health Innovation Research Institute, Curtin University, Bentley, Perth, Western Australia, 6102.
†School of Surgery (Orthopaedics), University of Western Australia, Crawley, Perth, Western Australia, 6009.

This research has received funding from the National Health and Medical Research Council (ID254622 and ID1003452), the Hollywood Private Hospital Research Foundation (RF31 and RF050). This research was approved by the University of Western Australia (RA/4/3/0464) and the Hollywood Private Hospital (HPH145) Human Research Ethics Committees (HREC).

Correspondence to: Dr Jay R. Ebert, The School of Sport Science, Exercise and Health (M408), The University of Western Australia, 35 Stirling Highway, Crawley, 6009, Western Australia. Phone: +61-8-6488-2361; Fax: +61-8-6488-1039; E-mail: jay.ebert@uwa.edu.au.
A comparison of the responsiveness of four commonly used patient-reported outcome instruments at five years following matrix-induced autologous chondrocyte implantation.

ABSTRACT

Background: Patient-reported outcome (PRO) instruments are employed to assess outcome following matrix-induced autologous chondrocyte implantation (MACI), though the PRO most responsive to change following surgery remains unknown.

Purpose: The aim of this paper was to compare the responsiveness of four commonly used PRO instruments at five years following MACI.

Study Design: Cross-sectional study.

Methods: The Knee Injury and Osteoarthritis Outcome Score (KOOS), the Lysholm score, the Tegner activity scale and the Short Form Health Survey (SF-36) were administered to 104 patients before and at five years after MACI knee surgery. The Self-administered Patient Satisfaction Scale was employed at five years to investigate each patient’s overall level of satisfaction, as well satisfaction with relieving pain, improving the ability to perform daily activities, recreational activities and participate in sport. The effect size (ES) and standardized response mean (SRM) were used to compare PRO responsiveness. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the extent to which PRO changes were associated with satisfaction. The minimal clinically important difference (MCID) according to the criterion of patient satisfaction was identified as the PRO instrument change score maximizing classification accuracy.

Results: The most responsive PRO measures were the KOOS Sport/Rec (ES: 1.63, SRM: 1.43) and QOL (ES: 1.37, SRM: 1.18) subscales. The least responsive were the SF-36 MCS
(ES: 0.38, SRM: 0.40) and the Tegner (ES: 0.91, SRM: 0.59). Of the 104 patients, 54 (51.9%) reported being ‘very satisfied’, 38 (36.5%) ‘somewhat satisfied’, 8 (7.7%) ‘somewhat dissatisfied’ and 4 (3.9%) ‘very dissatisfied’. ROC curve analysis was performed using ‘very satisfied’ as the responder criterion. The strongest association was between the change in KOOS Sport/Rec with satisfaction for improving the ability to perform recreational activities (AUC: 0.756, 95% CI: 0.663 to 0.849), and the change score maximizing prediction accuracy (MCID) was 40 (sensitivity: 69%, specificity: 76%).

**Conclusion:** The Sport/Rec and QOL KOOS subscales were the most responsive PRO measures and were most predictive of satisfaction. This information will provide a guide as to the improvements required in pertinent PRO measures in order to produce a satisfied patient, while allowing researchers to better structure trials in these patients using PRO instruments most relevant.

**Keywords:** matrix-induced autologous chondrocyte implantation, patient-reported outcome measures, post-operative assessment.
What is known about this subject: Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated good clinical efficacy for the repair of full thickness articular cartilage defects in the knee. Patient-reported outcome measures (PROs) have been employed to assess patient outcome following MACI, considered an excellent and non-invasive way of evaluating outcome. While many of these PROs employed have been validated in the use of other knee surgeries, few have been evaluated with respect to MACI surgery, and the most ideal PRO that best reflects pain, symptoms, and functional outcome most relevant to patients is yet to be determined. This is an area that requires investigation to allow better evaluation of MACI surgery with respect to those outcomes most important to these patients.

What this study adds to existing knowledge: Patient-reported outcome measures (PROs) have been employed to assess post-operative patient outcome following MACI. These PROs have proven useful; though require some validation in their use specifically with MACI surgery. Furthermore, at present we do not know which of these commonly used PROs best reflect those areas of post-operative outcome most important to the MACI patient. This research allows a reflective and accurate evaluation of MACI surgery with respect to those outcomes most important to these patients, and enables therapists and researchers to better structure research trials in these patients using the most responsive PROs.
INTRODUCTION

Matrix-induced autologous chondrocyte implantation (MACI) has become an established technique for the repair of full thickness chondral defects in the knee. A range of evaluation tools have been employed to assess the post-operative status of both the patient and repair tissue following ACI, including: radiological assessment using high-resolution magnetic resonance imaging (MRI) to assess the morphological and biochemical status of tissue repair, histological assessment to assess the quality of hyaline-like tissue repair and subjective, patient-reported outcome (PRO) measures to evaluate the improvement in pain, symptoms, function and overall surgical satisfaction.

The most commonly reported PRO instruments include: the Knee Injury and Osteoarthritis Outcome Score (KOOS) to assess knee pain, symptoms, activities of daily living, sport and recreation and knee related quality of life; the Lysholm score to assess knee pain, symptoms and function; the Tegner activity scale to determine patient activity level; the Visual Analogue Scale (VAS) to determine pain frequency and/or severity; the International Knee Documentation Committee (IKDC) Subjective Knee Form designed to measure patient symptoms, function and sports activity; the Cincinnati Knee Rating System to assess overall knee function with respect to work-limitations, and; the Short Form Health Survey (SF-36) to evaluate the general health of the patient, producing a mental (MCS) and physical component score (PCS).

As outlined by Hambly and Griva, there is currently no agreement on a ‘gold standard’ PRO measure for the evaluation of cartilage repair surgery, let alone ACI. Furthermore, any knee-specific questionnaire should be validated for use specifically in that designated patient cohort such as those following knee cartilage repair, or ACI. Responsiveness is the ability of an
instrument to detect change over time in the health domain being measured. The aim of this study was to investigate the relative responsiveness of four commonly used patient-reported outcome instruments using patient-reported satisfaction as an external criterion, at five years following ACI surgery.
MATERIALS AND METHODS

Patients

104 patients (62 males, 42 females) with pre-operative and 5-year (+/- 2 months) post-operative clinical follow-up were included in this retrospective analysis. Patient recruitment was between August 2001 and June 2006 as part of two separate trials, and ethics approval was obtained from the appropriate Human Research Ethics Committees. All patients had undergone MACI to address full thickness medial or lateral femoral or tibial condylar defects (73 medial femoral; 27 lateral femoral; 1 medial tibial; 3 lateral tibial). Patients were 13-65 years of age and all underwent a structured rehabilitation program. Patients were excluded from these trials if they had a BMI > 35, had undergone a prior extensive meniscectomy or had ongoing progressive inflammatory arthritis. Patients with ligamentous instability or varus/valgus abnormalities (> 3° tibiofemoral anatomic angle) were included, provided these were addressed prior to or at the time of MACI grafting. A summary of the total patient cohort is provided in Table 1.

The MACI Surgical Technique

The MACI technique has been previously described. MACI is a 2-stage technique, where arthroscopic surgery was performed to harvest a sample of normal articular cartilage from a non weight-bearing (WB) area of the knee. After harvest, chondrocytes were isolated, cultured and seeded onto a type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) ex vivo over a 6- to 8-week period. At the time of second-stage
implantation, the chondral defect was prepared via an open mini-arthrotomy by removing all
damaged cartilage down to, but not through, the subchondral bone plate. The defect was
measured and used to shape the membrane, which was secured to the bone using fibrin glue.

Patient Reported Outcome (PRO) Measures

*The Knee Injury and Osteoarthritis Outcome Score (KOOS)*

All 104 patients completed the KOOS pre-surgery and at five years post-surgery. The KOOS
is a knee specific questionnaire which includes 42 questions in five individual subscales: Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec) and Knee Related Quality of Life (QOL). Each of these five subscales is scored from 0 (worst) to 100 (best). The KOOS has proven valid, reliable and responsive to treatment following articular cartilage repair, and has been used extensively in patients following ACI. While the minimal clinically important difference (MCID) for the KOOS has not been assessed for patients undergoing cartilage repair, or ACI, an MCID of 8-10 points has been suggested in patients following anterior cruciate ligament reconstruction.

*The Lysholm Score*

The Lysholm score was completed by all 104 patients at five years post-surgery, but by only
81 patients pre-operatively due to the late initiation of this PRO instrument. The Lysholm is
an aggregate score from 0 (worst) to 100 (best), compiled from eight individual domains: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair-climbing (10 points), squatting (5 points) and use of support (5 points). It was originally developed to assess ligamentous injury, though has been validated for knee cartilage damage and has been used extensively in patients following ACI.
The Tegner Activity Scale

The Tegner activity scale was completed by all 104 patients at five years post-surgery, but by only 80 patients pre-operatively, again due to the late initiation of this PRO instrument through our institution. The Tegner activity scale is an 11-point numerical scoring system used to determine patient work and sport activity level from 0 (sick leave/disability) to 10 (participation in competitive high demand sport at an elite level). The Tegner was also originally developed to assess ligamentous injury, though has been reported as the most widely used activity rating scale in patients with knee disorders and has been used extensively in patients following ACI.

The Short Form Health Survey (SF-36)

The SF-36 was completed by all 104 patients pre-surgery and at five years post-surgery. It evaluates the general health of the patient and includes 36 questions spanning eight health domains: physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, social functioning, vitality, mental health, bodily pain and general health perceptions. It produces a mental (MCS) and physical component score (PCS), whereby the domains within each score are summed, weighted, and transformed to fall between 0 (worst possible health, severe disability) and 100 (best possible health, no disability). The feasibility of general health systems in cartilage repair patients has been supported, while the SF-36 has been used in patients following ACI. The MCID for the SF-36 has not been assessed for cartilage repair patients, though a 12% improvement from baseline has been demonstrated as MCID in lower limb osteoarthritic patients.

Patient Satisfaction

Patient satisfaction was assessed in all patients at five years post-surgery using the validated Self-administered Patient Satisfaction Scale, as described by Mahomad et al. This
questionnaire has been used previously following knee arthroplasty\textsuperscript{36, 51, 59} and MACI,\textsuperscript{15, 16} and includes five separate questions assessing satisfaction with MACI for i) relieving knee pain, and improving the ability to perform ii) normal daily, iii) recreational and iv) sporting activities and v) overall satisfaction on a 4 point scale (‘very satisfied’, ‘somewhat satisfied’, ‘somewhat dissatisfied’ or ‘very dissatisfied’) (see Appendix 1). A combined ‘Summary Satisfaction Score’ was calculated as the mean of the responses to the five questions, transformed to a 0 to 100 point scale with 100 points reflecting maximal satisfaction.\textsuperscript{39} The Self-administered Patient Satisfaction Scale has been found to be internally consistent and have convergent validity with clinical measures and functional health status instruments, in a sample of 1700 patients undergoing total knee or hip arthroplasty who were evaluated pre-operatively and at 12 weeks and 12 months post-surgery.\textsuperscript{39} This instrument’s measurement properties have not been evaluated in articular cartilage repair to date.

Statistical Analysis

Internal responsiveness reflects the ability of each instrument to change in response to a treatment assumed to be efficacious,\textsuperscript{26} and is commonly measured by calculating a standardized change score known as an effect size. Two different effect size measures were used to evaluate the internal responsiveness of each PRO; Cohen’s effect size [\( ES = \frac{\text{mean change score}}{\text{SD (baseline)}} \)] and standardized response mean [\( \text{SRM} = \frac{\text{mean change score}}{\text{SD (change score)}} \)]. Confidence intervals were calculated for each measure using the bias-corrected bootstrap method using 10,000 samples with replacement.\textsuperscript{17} Spearman’s rank correlation coefficients were calculated between the change scores for each PRO to assess the extent to which changes in various PRO measures represented change in similar constructs.
External responsiveness reflects the extent to which changes in a health scale relate to changes in a reference measure of health status. To evaluate the external responsiveness of each instrument, receiver operating characteristic (ROC) curve analysis was performed to quantify and compare the extent to which PRO instrument changes were discriminatory for report of being ‘very satisfied’ versus the other three response categories within in each domain, using a non-parametric approach to calculate area under the curve (AUC) and corresponding 95% confidence intervals. Where ROC curve analysis estimated that a PRO change score was reasonably discriminatory and statistically significant (i.e. AUC > 0.7 with lower bound CI > 0.5), a measure of minimal clinically important change was estimated by determining the magnitude of the change score that best discriminated between patients reporting being ‘very satisfied’ versus the other three response categories (i.e. determining the cut-off point that maximizes sensitivity and specificity for identifying those patients that are ‘very satisfied’). The PRO change score maximizing classification accuracy using the optimal cut-point method, i.e. the change score closest to the point (0,1) on the top left hand corner of the ROC graph. The ‘very satisfied’ category was chosen as the external criterion for treatment response as there were only small numbers of patients reporting dissatisfaction with the procedure. A test of equality of ROC curve areas was performed for the PROs for each satisfaction question with the maximum AUC values. In addition, Tobit regression analysis with bootstrapped confidence intervals was performed to estimate the standardized effect of the change of each PRO on the overall combined satisfaction score, as the distribution of this variable was left-skewed with 29 of 104 (27.9%) observations censored at the upper bound of 100.
The pre- and post-operative values and change scores for each PRO, along with corresponding ES and SRM, are displayed in Table 2. The largest ES and SRM were observed for the KOOS Sport/Rec subscale (SRM=1.43, 95%CI: 1.16-1.73), followed by the KOOS QOL subscale (SRM=1.18, 95%CI: 0.93-1.41) and Lysholm scale (SRM=1.11, 95%CI: 0.89-1.34). The smallest ES and SRM were observed for the MCS subscale of the SF-36 (SRM=0.40, 95%CI: 0.22-0.58).

The correlations between the PRO instrument change scores are presented in Table 3. Change in KOOS Pain displayed the highest correlations with change in KOOS ADL and the Lysholm Scale. Change in KOOS Symptoms displayed the highest correlations with change in KOOS Pain, KOOS ADL and the Lysholm Scale. Change in KOOS ADL displayed the highest correlations with change in KOOS Pain, KOOS ADL and the Lysholm Scale. Change in KOOS Sport/Rec displayed modest correlations with change in KOOS QOL and the Lysholm Scale. Change in KOOS QOL displayed the highest correlations with KOOS Pain, while change in the Tegner activity scale and SF-36 MCS, did not correlate with any other PRO. All PRO change scores correlated statistically significantly at 0.4 or above with at least one other change score with the exception of the Tegner and SF-36 MCS, which displayed no association with any other change scores.

The response frequencies for each of the five satisfaction questions are displayed in Table 4. The combined overall Satisfaction scores ranged from 0 to 100, with a mean of 76.2±25.6 and a median of 83.3 (IQR: 36.7). The estimated AUCs from the ROC analyses are presented in...
Table 5 and the best two discriminators for each satisfaction question are displayed in Figure 1 (see Appendix 2). KOOS Sport/Rec and QOL displayed values considered to indicate reasonable discrimination of ‘responders’ as classified by being ‘very satisfied’. However, test of equality for AUC revealed no significant difference between the three maximum values for each satisfaction question (p=0.188 to 0.761). The optimal cut-off scores for those AUC values estimated to be > 0.7 are also presented in Table 5. For example, an improvement in KOOS Sport/Rec score of 45 points or more can be considered to be the most reliable cut-off score for indication of being very satisfied with the MACI procedure for improving the ability to participate in sport.

The estimates of the change in Satisfaction score for a one standard deviation change in each of the PRO instruments is displayed in Table 6 (Appendix 3). For example, it was estimated that an increase of one standard deviation in the change score of KOOS Sport/Rec was associated with an increase in Satisfaction score of 18.2 points, or 23.5 points when adjusted for baseline score. The adjusted estimates are substantially larger in the case of many PROs and the least difference between adjusted and unadjusted estimates was observed for KOOS Sport/Rec and QOL. This reflects the lower baseline scores of the latter two PROs which allowed for greater improvement, with a ceiling effect for some of the PROs at five years post-surgery (e.g. KOOS ADLs) which limited the improvement that could be attained.
This analysis evaluated the responsiveness of four commonly used PRO instruments to change following MACI. The most responsive PRO measures to post-operative improvement were the KOOS Sport/Rec and QOL subscales, and these two subscales were the most predictive of patient satisfaction. This is supported by the work of Hambly and Griva who demonstrated that these two subscales were reported highest in importance and more frequently experienced than the other KOOS domains in cartilage repair patients. Roos et al. summarized the effect sizes of various PRO measures used to evaluate cartilage repair and, together with research by both Bekkers et al. and McNickle et al., demonstrated the Sport/Rec and QOL subscales to be the most responsive of the five KOOS subscales.

The KOOS Pain subscale also exhibited a large effect size, and has demonstrated responsiveness in other cartilage repair studies as reported by Roos et al. However, in this study change in KOOS Pain was not predictive of being very satisfied with the surgery. Taken together, this may mean that improvement in pain is less important for patient satisfaction than improvement in function. Articular cartilage repair patients have been likened to those suffering from osteoarthritis, whereby symptoms (and pain) experienced may have persisted over a prolonged period of time. Certainly, the mean duration of symptoms in this analysis was 8.4 years, unlike those following ACL reconstruction who generally experience an acute trauma and undergo immediate subsequent reconstruction. Therefore, while pain was not predictive of satisfaction at five years in this analysis, it may still be a dominant symptom in patients with cartilage defects which is responsive to surgery, and as such remains an important construct to evaluate pre- and post-surgery.
The KOOS Symptoms and ADL subscales also exhibited large effect sizes\textsuperscript{13} though, as demonstrated in this analysis and reported previously by Roos et al.,\textsuperscript{48} were less responsive than the other KOOS subscales in the context of cartilage repair.\textsuperscript{7, 42, 48, 61} While the KOOS ADL subscale did correlate significantly with other KOOS domains, the Lysholm and the PCS subscale of the SF-36, it was not predictive of patient satisfaction. Hambly and Griva\textsuperscript{24} reported that cartilage repair patients did not view ADL to be of importance, nor was restriction of ADL frequently experienced. MACI patients are typically younger and improved function in sport and recreational activities may be more relevant than improved function in relatively simple daily life activities.\textsuperscript{14, 24} However, it would appear as though while the KOOS ADL demonstrates statistical improvements as early as three months after second-generation ACI,\textsuperscript{34} KOOS Sport/Rec does not improve statistically until beyond four years.\textsuperscript{34} Therefore, both are important following cartilage repair to evaluate early and long-term functional improvement. Overall, the change scores reported in this study for the KOOS are well over the minimal detectable change (MDC) reported for KOOS Pain (6), Symptoms (5), ADL (7), Sport/Rec (12) and QOL (7),\textsuperscript{7} indicating capture of real change.

Of the several cartilage repair studies summarized by Roos et al.\textsuperscript{48} only one study\textsuperscript{31} reported a moderate effect size of 0.53 for the Lysholm, following periosteal-covered ACI, compared with the large effect size\textsuperscript{13} of 1.22 reported for MACI in this analysis. To the best of our knowledge, the MDC for the Lysholm has not been reported, but it is likely that the large effect observed in this study is indicative of real change. A recent review of the evidence for efficacy of one cartilage repair surgical method over another\textsuperscript{8} identified 24 studies of cartilage repair that used the Lysholm score and suggested an increase in the Lysholm was related to surgical success.\textsuperscript{8} Whilst no procedure yielded significantly greater improvements in the Lysholm score, MACI demonstrated the highest improvement overall. Despite the large effect size estimated in this study, there was not strong evidence that change in the Lysholm was
reasonably discriminatory of being very satisfied with the procedure (i.e. AUC estimate <0.7), although lower bounds of 95%CI for AUCs were above 0.5 for two of the satisfaction questions, indicating that change in Lysholm was better than chance in identifying very satisfied patients. This may be because the Lysholm differs from the KOOS in that it is a single aggregate score that incorporates several constructs.

Of the several studies summarized by Roos et al., only one study in patients following periosteal-covered ACI reported an effect size of 0.67 for the Tegner activity scale, compared with the moderate to large effect size reported in this analysis. Given that the return to sport is of high importance to younger patients undergoing cartilage repair, it may be expected that these patient-reported activity scores would be predictive of a satisfied patient. However, despite the moderate to large effect sizes estimated in this study, there was not strong evidence that change in the Tegner was reasonably discriminatory of being very satisfied with the procedure (point estimate <0.7), although lower bounds of 95%CI for AUCs were above 0.5 for three of the satisfaction questions, indicating that change in Tegner activity scale was better than chance in discriminating those patients who were very satisfied. Point estimates for responsiveness and discrimination for the Tegner activity scale were less than the KOOS Sport/Rec in this study. This may be due to the differences in the Tegner activity scale as compared to the KOOS subscales, as the Tegner asks specifically about levels of sport, recreation and work, whereas the KOOS Sport/Rec scale asks about difficulties with specific functional tasks that are components of sport, recreation and work. While the Tegner activity scale has been reported as the most widely used activity scale in patients with knee disorders, and a recent review suggested that the Tegner had the ability to measure change in activity level in a cartilage repair cohort, studies cited were outlined as being inconsistently reported and lacking methodological detail.
The feasibility of general health scoring systems in cartilage repair patients has been supported, and the SF-36 appears to be the most popular health measure. It has been suggested that both generic and disease/condition specific instruments should be employed to evaluate different aspects of recovery. In this study, the SF-36 PCS subscale exhibited a large effect size, similar to those for KOOS Pain and Symptoms. This is similar to the large effect for PCS (1.10) reported for microfracture, though a range of small to large effect sizes for PCS (0.10-1.01) have been reported for periosteal-covered ACI. Although change in the PCS was not estimated as being reasonably discriminatory of being very satisfied with MACI (point estimate <0.7), the lower bounds of 95%CI for AUCs were above 0.5 for three of the satisfaction questions, indicating that change in PCS was better than chance in discriminating very satisfied patients. These results indicate PCS is an acceptable instrument to capture patient response to MACI.

In contrast, the MCS exhibited a small effect size, did not correlate with any of the other PRO instruments and demonstrated no discriminatory utility for patient satisfaction. These results suggest that the MCS is not responsive to the improvement provided by ACI, nor is change in this PRO predictive of patient satisfaction. In a similar study investigating the responsiveness of generic and disease specific questionnaires with known adequate psychometric properties following TKR, the MCS subscale of the SF-12 exhibited the lowest effect sizes, no correlation with other knee specific PRO instruments, and change scores that were unrelated to the other instruments. Therefore, the MCS is of dubious value for inclusion in the assessment of improvement in patients undergoing cartilage repair and possibly other knee procedures.

It has been suggested that the repair tissue produced with MACI continues to develop and remodel up to three years following surgery and, therefore, this study provides data that may
evaluate a final patient outcome (five years), as opposed to many studies that investigate responsiveness over the shorter term. While it should be noted that all patients referred to our institution who underwent MACI to address isolated medial or lateral femoral or tibial condylar defects were recruited into one of two trials\textsuperscript{15, 16} (i.e. 100\%, no patients refused consent to participate), an additional 11 patients (i.e. n=115) were recruited though failed to undergo assessment at five years post-surgery. These were as a result of a participant death (n=1), interstate or overseas relocation (n=4), or being lost to follow-up (n=6). Of the 104 patients with five year assessment, the sample predominantly comprised of patients who were satisfied overall with the procedure (92 of 104, 89\%) and it is possible that those patients not providing data at five years were less satisfied. These additional data may have allowed better estimation of the magnitude of any change in scores in this group of ‘non-responders’.

A number of limitations exist in this study. Firstly, we employed a patient satisfaction scale to evaluate the ability of PRO instruments to measure the perceived patient benefit of MACI, instead of the widely employed Global Rating of Change (GRC) scale\textsuperscript{30} often employed as a ‘gold standard’ indicator of treatment response. However, the advantage of the satisfaction questions used in this study is that they tapped into varying domains of satisfaction rather than an overall ‘improvement’ rating such as a GRC, which allowed a more detailed examination of those PROs most associated with each domain of satisfaction. Additionally, the reliability and validity of these GRC retrospective measures of change has been questioned.\textsuperscript{20, 43} Only moderate agreement was observed between prospectively collected PROs and patient recall of pre-operative status only three months after TKR,\textsuperscript{37} suggesting inaccurate recall by patients of prior status. Nevertheless, any measure of patient satisfaction is also likely to draw on conflicting issues such as the perceived costs and benefits of the procedure, as well as the achievement of individual patient expectations. While expectations of surgery have not been previously assessed in a MACI cohort, these patients are typically younger and hope to return
to a normally active lifestyle and, therefore, expectations may play a large role in this relatively highly functioning group. Patient expectation has been previously demonstrated as a strong predictor of satisfaction following TKR\textsuperscript{10, 40}. It would appear that given the relatively weak prediction of patient satisfaction by the improvement in PRO change scores alone in this study, as well as the known link between expectations and post-operative satisfaction, that PRO instruments incorporating information about pre-operative expectations and post-operative achievement (and lack) of those expectations would be a useful addition to examine and understand the treatment response to these procedures.

Secondly, a recent review evaluating ACI outlined a definitive list of PROs most representative of the clinically important measures of ACI effectiveness\textsuperscript{57}. We evaluated PRO instruments used routinely through our clinic and did not include other commonly used scores such as the IKDC and Cincinnati Scores. In particular, the IKDC is widely accepted in the international research community\textsuperscript{48} and has been reported as a good measure in patients undergoing articular cartilage surgery\textsuperscript{19, 24}. Tanner et al.\textsuperscript{53} have reported that the KOOS and IKDC contain the most items important to post-operative knee patients, including ACL reconstruction, meniscal tears and osteoarthritis. While the IKDC had been reported as a better clinical measure than the KOOS in patients undergoing cartilage repair\textsuperscript{19}, a more recent review found no superiority of the IKDC over the KOOS in cartilage repair patients\textsuperscript{48}. It should be noted that in a study in which cartilage repair patients evaluated the importance of items from both the KOOS and the IKDC, the KOOS Sport/Rec and QOL subscales scored highest on mean importance\textsuperscript{24}, while other studies that have compared the two PRO instruments did so in a range of cartilage repair surgeries, rather than specifically in ACI.

Thirdly, PRO measures evaluated in this study were of varied formats, including single scores (Tegner), aggregate scores (Lysholm) that combine potentially unrelated constructs, and
domain specific scores (KOOS) that provide a series of individual subscales. However, the purpose of this paper was to investigate commonly used scores in ACI evaluation, which incorporates both aggregate and individual sub-scale PRO measures. Lastly, responsiveness depends on both the variability in the change scores and the baseline values, as well as the true efficacy of the surgery. A limitation of determining a MCID for PROs is that the degree of change in a measure is often associated with the baseline state. This is the case in this study, and the reason for the association is likely to be a combination of regression to the mean, ceiling effects in some of the PROs, and possibly a true association of greater improvement in patients with lower scores at baseline. These phenomena are inseparable in this study. One method of dealing with this problem is residualizing the change score (from baseline values), which means statistically removing the relationship between the two measures over time, but generating MCIDs by using residualized change scores risks removing true meaning as well as error. Therefore, MCIDs for PROs were estimated without residualizing change scores, whilst the results from Table 6 allow a comparison of the association of change score with the overall Satisfaction score both adjusted and unadjusted for baseline scores.

To the best of our knowledge, this is the first study to investigate the relative responsiveness of commonly used PRO instruments at five years following MACI. Based on the PRO instruments employed, the most responsive measures to post-operative improvement, and most predictive of patient satisfaction, were the KOOS Sport/Rec and QOL subscales. This also suggests that an improvement in the ability to return to activity may be more important to these patients than improvement in pain alone. Additionally, this research provides the clinician with MCIDs for those PRO measures found to be predictive of a ‘very satisfied’ patient. Furthermore, these outcomes will allow better structured research trials in these patients using PRO instruments that are most responsive and reflective of items important to
post-operative MACI outcome. These results suggest that randomized controlled trials for evaluating the efficacy of cartilage repair trials could best use the change in KOOS Sport/Rec as a binary indicator of being ‘very satisfied’ with the surgical intervention, and that a change score of 40 could be used as a binary indicator of a treatment ‘responder’. These outcomes are specific to PRO measures employed within this analysis for patients undergoing MACI to the WB condyles, and further investigation of other pertinent PRO measures and other cartilage repair procedures is required.


Ebert JR, Fallon M, Zheng MH, Wood DJ, Ackland TR. A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weightbearing


FIGURE LEGENDS

FIGURE 1 (Appendix 2). Receiver operating characteristic (ROC) curves demonstrating the two PRO measures most predictive of satisfaction for (A) relieving knee pain, (B) improving the ability to perform activities of daily living, (C) improving the ability to return to recreational activities, (D) improving the ability to perform sporting activities, and (E) overall satisfaction.
TABLE 1. Descriptive statistics of baseline patient variables, clinical scores and surgical parameters in the 104 patients included in this analysis.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Mean (SD) or n (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.9 (11.6)</td>
<td>13 - 65</td>
</tr>
<tr>
<td>Female</td>
<td>42 (38.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>26.7 (3.9)</td>
<td>16.8 – 33.3</td>
</tr>
<tr>
<td>SF-36 (MCS)</td>
<td>51.4 (10.3)</td>
<td>23.3 – 85.6</td>
</tr>
<tr>
<td>SF-36 (PCS)</td>
<td>39.2 (9.6)</td>
<td>22.0 – 58.6</td>
</tr>
<tr>
<td>Duration symptoms (years)</td>
<td>8.4 (7.5)</td>
<td>1 - 46</td>
</tr>
<tr>
<td>Number of prior procedures</td>
<td>1.4 (1.2)</td>
<td>0 - 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical Characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect size (cm²)</td>
<td>3.2 (2.3)</td>
<td>0.6 – 10.0</td>
</tr>
<tr>
<td>Lateral compartment (vs medial)</td>
<td>30 (28.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Concomitant surgical procedure</td>
<td>14 (13.5)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

SF-36 = 36 item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score.
TABLE 2. Pre-surgery, 5-year post-surgery and change scores for the patient reported outcome instruments in 104 patients undergoing MACI.

<table>
<thead>
<tr>
<th>Patient Reported Outcome Instruments</th>
<th>Pre-surgery Mean (SD)</th>
<th>5-years Post-surgery Mean (SD)</th>
<th>Change Mean (SD)</th>
<th>Effect Size (95% CI)</th>
<th>Standardized Response Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee Specific Scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Pain</td>
<td>63.9 (19.4)</td>
<td>85.0 (13.6)</td>
<td>21.2 (20.2)</td>
<td>1.09 (0.91,1.30)</td>
<td>1.05 (0.85,1.26)</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>66.4 (19.5)</td>
<td>84.5 (14.1)</td>
<td>18.1 (20.1)</td>
<td>0.93 (0.73,1.12)</td>
<td>0.90 (0.69,1.12)</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>74.2 (19.4)</td>
<td>91.8 (10.8)</td>
<td>17.6 (19.0)</td>
<td>0.91 (0.76,1.08)</td>
<td>0.93 (0.76,1.09)</td>
</tr>
<tr>
<td>KOOS Sport/Rec</td>
<td>23.8 (24.1)</td>
<td>63.1 (27.1)</td>
<td>39.2 (27.4)</td>
<td>1.63 (1.28,2.02)</td>
<td>1.43 (1.16,1.73)</td>
</tr>
<tr>
<td>KOOS QOL</td>
<td>29.3 (21.3)</td>
<td>58.5 (23.1)</td>
<td>29.2 (24.7)</td>
<td>1.37 (1.04,1.72)</td>
<td>1.18 (0.93,1.41)</td>
</tr>
<tr>
<td>Lysholm Scale¹</td>
<td>58.4 (18.1)</td>
<td>80.4 (14.3)</td>
<td>22.0 (19.9)</td>
<td>1.22 (0.97,1.54)</td>
<td>1.11 (0.89,1.34)</td>
</tr>
<tr>
<td><strong>Activity Rating Scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegner¹</td>
<td>2.9 (1.1)</td>
<td>3.9 (1.5)</td>
<td>1.0 (1.7)</td>
<td>0.91 (0.54,1.46)</td>
<td>0.59 (0.41,0.80)</td>
</tr>
<tr>
<td><strong>Generic Health Scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>39.2 (9.6)</td>
<td>48.6 (8.2)</td>
<td>9.4 (9.4)</td>
<td>0.98 (0.77,1.21)</td>
<td>1.00 (0.82,1.19)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>51.1 (9.7)</td>
<td>54.8 (7.5)</td>
<td>3.7 (9.3)</td>
<td>0.38 (0.21,0.55)</td>
<td>0.40 (0.22,0.58)</td>
</tr>
</tbody>
</table>

¹data only available for 81 (Lysholm) and 80 (Tegner) patients only
TABLE 3. Spearman’s rank correlation coefficients between the change scores of the patient reported outcome instruments.

<table>
<thead>
<tr>
<th>Patient Reported Outcome Measure</th>
<th>KOOS Pain</th>
<th>KOOS Symptoms</th>
<th>KOOS ADL</th>
<th>KOOS Sport/Rec</th>
<th>KOOS QOL</th>
<th>Lysholm Scale (^1)</th>
<th>Tegner (^1)</th>
<th>SF-36 PCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS Symptoms</td>
<td>0.695**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>0.745**</td>
<td>0.680**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS Sport/Rec</td>
<td>0.388**</td>
<td>0.367**</td>
<td>0.408**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOOS QOL</td>
<td>0.591**</td>
<td>0.543**</td>
<td>0.525**</td>
<td>0.500**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysholm Scale (^1)</td>
<td>0.742**</td>
<td>0.634**</td>
<td>0.667**</td>
<td>0.450**</td>
<td>0.526**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegner (^1)</td>
<td>0.073</td>
<td>0.188</td>
<td>0.227</td>
<td>0.338*</td>
<td>0.169</td>
<td>0.191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>0.454**</td>
<td>0.268</td>
<td>0.470**</td>
<td>0.376**</td>
<td>0.437**</td>
<td>0.461**</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>0.044</td>
<td>0.100</td>
<td>0.038</td>
<td>-0.054</td>
<td>-0.058</td>
<td>-0.052</td>
<td>-0.076</td>
<td>-0.121</td>
</tr>
</tbody>
</table>

\(^1\)data only available for 81 (Lysholm) and 80 (Tegner) patients

*p<0.01**p<0.001
TABLE 4. The number (%) of patients in each category of the five satisfaction questions.

<table>
<thead>
<tr>
<th>Satisfaction Question (1-5)</th>
<th>Very satisfied</th>
<th>Somewhat satisfied</th>
<th>Somewhat dissatisfied</th>
<th>Very dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1. Relieving pain</td>
<td>54 (53.9)</td>
<td>39 (37.5)</td>
<td>5 (4.8)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>2. Improving ability to perform ADLs</td>
<td>61 (58.7)</td>
<td>32 (30.8)</td>
<td>8 (7.7)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>3. Improving ability to return to recreational activities</td>
<td>55 (52.9)</td>
<td>34 (32.7)</td>
<td>10 (9.6)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>4. Improving ability to participate in sport</td>
<td>32 (30.8)</td>
<td>42 (40.4)</td>
<td>14 (13.5)</td>
<td>16 (15.4)</td>
</tr>
<tr>
<td>5. Overall satisfaction</td>
<td>54 (51.9)</td>
<td>38 (36.5)</td>
<td>8 (7.7)</td>
<td>4 (3.9)</td>
</tr>
</tbody>
</table>
TABLE 5. Receiver operating characteristic (ROC) curve analysis: area under the curve (AUC) (95% Confidence Interval) for discrimination between ‘Very Satisfied’ response category versus all other response categories combined on five satisfaction questions (estimates indicating performance better than chance, i.e. lower bound of 95% CI > 0.5, in bold; cut-off score* maximizing sensitivity and specificity if AUC estimate > 0.7).

<table>
<thead>
<tr>
<th>Patient Reported Outcome Measure</th>
<th>Relieve Pain (AUC)</th>
<th>Improve ADLs (AUC)</th>
<th>Recreation Return (AUC)</th>
<th>Sport Return (AUC)</th>
<th>Overall (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS Pain</td>
<td>.578 (.467,.690)</td>
<td>.575 (.460,.689)</td>
<td>.605 (.496,.714)</td>
<td>.579 (.456,.701)</td>
<td>.574 (.463,.685)</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>.600 (.490,.711)</td>
<td>.586 (.474,.699)</td>
<td>.615 (.507,.723)</td>
<td>.579 (.459,.699)</td>
<td>.594 (.483,.705)</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>.529 (.414,.643)</td>
<td>.552 (.436,.669)</td>
<td>.570 (.458,.681)</td>
<td>.556 (.438,.674)</td>
<td>.553 (.441,.665)</td>
</tr>
<tr>
<td>KOOS S&amp;R</td>
<td>.686 (.582,.790)</td>
<td>.750 (.654,.847)</td>
<td>.756 (.663,.849)</td>
<td>.741 (.636,.845)</td>
<td>.732 (.634,.829)</td>
</tr>
<tr>
<td>KOOS QOL</td>
<td>.681 (.578,.785)</td>
<td>.703 (.601,.805)</td>
<td>.694 (.592,.795)</td>
<td>.693 (.573,.814)</td>
<td>.710 (.609,.812)</td>
</tr>
<tr>
<td>Lysholm¹</td>
<td>.664 (.542,.785)</td>
<td>.622 (.498,.746)</td>
<td>.690 (.576,.805)</td>
<td>.630 (.498,.762)</td>
<td>.602 (.478,.726)</td>
</tr>
<tr>
<td>Tegner¹</td>
<td>.594 (.469,.718)</td>
<td>.591 (.467,.715)</td>
<td>.639 (.521,.756)</td>
<td>.696 (.568,.823)</td>
<td>.620 (.501,.739)</td>
</tr>
<tr>
<td>SF36 PCS</td>
<td>.568 (.455,.680)</td>
<td>.633 (.523,.742)</td>
<td>.650 (.544,.755)</td>
<td>.631 (.511,.751)</td>
<td>.591 (.481,.700)</td>
</tr>
<tr>
<td>SF36 MCS</td>
<td>.509 (.397,.622)</td>
<td>.556 (.443,.668)</td>
<td>0.498 (.386,.611)</td>
<td>.486 (.356,.615)</td>
<td>.474 (.362,.586)</td>
</tr>
</tbody>
</table>

¹data only available for 81 (Lysholm) and 80 (Tegner) patients only.