Patient-Oriented And Performance-Based Outcomes After Knee Autologous Chondrocyte Implantation: A Timeline For The First Year Of Recovery

By: **Jennifer S. Howard**, Carl G. Mattacola, David R. Mullineaux, Robert A. English, and Christian Lattermann

Abstract

Context: It is well established that autologous chondrocyte implantation (ACI) can require extended recovery postoperatively; however, little information exists to provide clinicians and patients with a timeline for antici- pated function during the first year after ACI. Objective: To document the recovery of functional performance of activities of daily living after ACI. Patients: ACI patients (n = 48, 29 male; 35.1 ± 8.0 y). Intervention: All patients completed functional tests (weight-bearing squat, walk-across, sit-to-stand, step-up/over, and forward lunge) using the NeuroCom long force plate (Clackamas, OR) and completed patient-reported outcome measures (International Knee Documentation Committee Subjective Knee Evaluation Form, Lysholm, Western Ontario and McMaster Osteoarthritis Index [WOMAC], and 36-Item Short-Form Health Survey) preoperatively and 3, 6, and 12 mo postoperatively. Main Outcome Measures: A covariance pattern model was used to compare performance and self-reported outcome across time and provide a timeline for functional recovery after ACI. Results: Participants demonstrated significant improvement in walk-across stride length from baseline (42.0% ± 8.9% height) at 6 (46.8% ± 8.1%) and 12 mo (46.6% ± 7.6%). Weight bearing on the involved limb during squatting at 30°, 60°, and 90° was significantly less at 3 mo than presurgery. Step-up/over time was significantly slower at 3 mo (1.67 ± 0.69 s) than at baseline (1.49 ± 0.33 s), 6 mo (1.51 ± 0.36 s), and 12 mo (1.40 ± 0.26 s). Step-up/over lift-up index was increased from baseline (41.0% ± 11.3% body weight [BW]) at 3 (45.0% ± 11.7% BW), 6 (47.0% ± 11.3% BW), and 12 mo (47.3% ± 11.6% BW). Forward-lunge time was decreased at 3 mo (1.51 ± 0.44 s) compared with baseline (1.39 ± 0.43 s), 6 mo (1.32 ± 0.05 s), and 12 mo (1.27 ± 0.06). Similarly, forward-lunge impact force was decreased at 3 mo (22.2% ± 1.4% BW) compared with baseline (25.4% ± 1.5% BW). The WOMAC demonstrated significant improvements at 3 mo. All patient-reported outcomes were improved from baseline at 6 and 12 mo postsurgery. Conclusions: Patients' perceptions of improvements may outpace physical changes in function. Decreased function for at least the first 3 mo after ACI should be anticipated, and improvement in performance of tasks requiring weight-bearing knee flexion, such as squatting, going down stairs, or lunging, may not occur for a year or more after surgery.

Howard, J. S., et al. (2014). "Patient-Oriented and Performance-Based Outcomes After Knee Autologous Chondrocyte Implantation: A Timeline for the First Year of Recovery." Journal of Sport Rehabilitation 23(3): 223-234. https://doi.org/10.1123/JSR.2013-0094. Publisher version of record available at: https://journals.humankinetics.com/doi/abs/10.1123/JSR.2013-0094

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Context: It is well established that autologous chondrocyte implantation (ACI) can require extended recovery postoperatively; however, little information exists to provide clinicians and patients with a timeline for anticipated function during the first year after ACI. ***Objective:*** To document the recovery of functional performance of activities of daily living after ACI. ***Patients:*** ACI patients (n = 48, 29 male; 35.1 ± 8.0 y). ***Intervention:*** All patients completed functional tests (weight-bearing squat, walk-across, sit-to-stand, step-up/over, and forward lunge) using the NeuroCom long force plate (Clackamas, OR) and completed patient-reported outcome measures (International Knee Documentation Committee Subjective Knee Evaluation Form, Lysholm, Western Ontario and McMaster Osteoarthritis Index [WOMAC], and 36-Item Short-Form Health Survey) preoperatively and 3, 6, and 12 mo postoperatively. ***Main Outcome Measures:*** A covariance pattern model was used to compare performance and self-reported outcome across time and provide a timeline for functional recovery after ACI. ***Results:*** Participants demonstrated significant improvement in walk-across stride length from baseline (42.0% ± 8.9% height) at 6 (46.8% ± 8.1%) and 12 mo (46.6% ± 7.6%). Weight bearing on the involved limb during squatting at 30°, 60°, and 90° was significantly less at 3 mo than presurgery. Step-up/over time was significantly slower at 3 mo (1.67 ± 0.69 s) than at baseline (1.49 ± 0.33 s), 6 mo (1.51 ± 0.36 s), and 12 mo (1.40 ± 0.26 s). Step-up/over lift-up index was increased from baseline (41.0% ± 11.3% body weight [BW]) at 3 (45.0% ± 11.7% BW), 6 (47.0% ± 11.3% BW), and 12 mo (47.3% ± 11.6% BW). Forward-lunge time was decreased at 3 mo (1.51 ± 0.44 s) compared with baseline (1.39 ± 0.43 s), 6 mo (1.32 ± 0.05 s), and 12 mo (1.27 ± 0.06). Similarly, forward-lunge impact force was decreased at 3 mo (22.2% ± 1.4% BW) compared with baseline (25.4% ± 1.5% BW). The WOMAC demonstrated significant improvements at 3 mo. All patient-reported outcomes were improved from baseline at 6 and 12 mo postsurgery. ***Conclusions:*** Patients' perceptions of improvements may outpace physical changes in function. Decreased function for at least the first 3 mo after ACI should be anticipated, and improvement in performance of tasks requiring weight-bearing knee flexion, such as squatting, going down stairs, or lunging, may not occur for a year or more after surgery.

Keywords: cartilage, chondral repair, functional assessment, functional testing

Autologous chondrocyte implantation (ACI)[1] has become an acceptable and common treatment approach for the management of symptomatic articular cartilage defects.[2] As research regarding ACI has advanced, sizable efforts have been made to evaluate both disease- and patient-oriented outcomes after ACI. Numerous studies have evaluated the use of patient-reported outcome (PRO) measures to document the recovery of function and return to activity after ACI.[3–5] Meta-analyses of more than 43 studies have revealed large effect sizes demonstrating significant improvement for a variety of PRO scores after ACI.[5] PROs provide reliable and valid information regarding patients' perceived function and health-related quality of life.[6–13] 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.[14–19] This discordance may be due in part to the strong influence perceived pain may have on PROs. For example, PRO scores may increase even in the absence of improved function if a patient's pain has been resolved.[19–22] Recent research involving

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total-joint arthroplasty patients has provided further support for the inclusion of PBAs as part of a detailed outcomes-assessment protocol.[18–20] Combining PROs with PBAs may provide a more complete picture of clinical outcomes after ACI than the use of either type of outcome in isolation.

Few studies have used PBAs to document the return of function after ACI. Most of those that have examined either very low-demand activity such as the 6-minute-walk test[23–27] or very high-demand activity via the single-limb hop.[28] No known studies have examined the timeline for return to function after 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. A description of functional recovery during the first year after ACI is imperative to provide evidence for prescription of appropriate patient education, rehabilitation protocols, and understanding of the recovery process. Therefore, the purpose of this study was to document serial changes in knee function over 1 year after ACI using both PROs and PBAs. We hypothesized that PROs would demonstrate significant improvement from baseline at all postoperative time points. We also hypothesized that PBA measures for walking, rising from sitting, stepping up and over, and lunging would demonstrate no improvements at the 3-month time point followed, by progressive improvement at 6 months and 12 months compared with baseline measures of function.

Methods

Patients

Between July 2008 and July 2011 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; 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 before 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.

A total of 50 patients (31 male, 19 female; 35.0 ± 7.9 y; 180.34 ± 30.7 cm; 92.0 ± 20.6 kg) agreed to participate. During the enrollment period 4 patients were invited to take part in the study but declined to participate, resulting in an enrollment rate of 93% of eligible patients. Of the enrolled patients, 24 underwent ACI to the patellofemoral joint with a tibial tubercle transfer and the remaining 26 underwent ACI to the femoral condyle, of whom 4 also had a concomitant high tibial osteotomy and 2 underwent concomitant meniscal transplantation. Mean number of defects treated per patient was 1.5 ± 0.6 with an average treatment area of 8.7 ± 6.8 cm^2 (range 1.96–39.0 cm^2). All participants signed a university-approved institutional review board consent form at the time of enrollment.

Procedures

Surgical Procedures and Rehabilitation. All patients underwent a 2-step ACI procedure performed by the same surgeon (C.L.). 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 (100–200 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 miniarthrotomy. 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 (Bio-Gide®, 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 watertight 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 after surgery with considerations for defect location and concomitant procedures.[29] 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 and 12. Continuous passive motion was prescribed for all patients for 6 to 8 h/d for 6 weeks. For defects in the tibiofemoral joint, knee braces were gradually unlocked between 2 and 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 advised to abstain from high-intensity cutting or pivoting activity until at least 12 months post-ACI.

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),[11,30,31] the Western Ontario and McMaster Osteoarthritis Index (WOMAC),[10] the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form,[7] and the Lysholm Scale.[32] The SF-36,[13] IKDC,[13] Lysholm,[8] and WOMAC[8,13] have all been evaluated for reliability among cartilage patients. 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: before implantation (preoperation) and 3 months, 6 months, and 12 months postsurgery.

Performance-Based Assessments. At each time point after completing PROs each participant completed a series of 5 PBAs in a musculoskeletal-laboratory setting. All PBAs were completed using the NeuroCom Balance Master and long force plate (NeuroCom International, Clackamas, OR). This is a commercially available system designed as both a training and an 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.[33] The only exposure study participants had with the long force plate was for research testing purposes, and they were not provided feedback during testing.

The long force plate consists of a 45.72 × 152.40-cm force plate with data sampled at 100 Hz and a personal computer equipped with data-capture software (Balance Master version 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 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 (J.S.H.). 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 15 seconds of rest were permitted between trials and 30 seconds of rest between tasks. For the purposes of this article, all outcome variables are identified using the names assigned to them by the software used. Definitions for these variables are presented in Table 1. The 5 tasks were as follows:

- *Walk-Across* (Figure 1): Patients walked across the long force plate using their freely chosen standard gait speed and pattern.

Table 1 Functional Tasks Evaluated on the NeuroCom Balance Master Long Force Plate

Task	Parameters assessed	NeuroCom outcome variable	Definition
Walk-across	Characterization of gait	Stride length (cm)	Distance between contralateral heel strikes
		Stride width (cm)	Lateral distance between center of pressure (COP) of left and right foot strikes
		Walking speed (cm/s)	Speed of forward progression of the center of gravity
Weight-bearing squat	Strength, weight distribution	% body weight (BW) at 0° (full extension), 30°, 60°, and 90° of knee flexion	% BW on the involved limb at each position (test duration 0.01 s)
Sit-to-stand	Strength, weight distribution, performance time, double limb balance	Weight-transfer time (s)	Time required from start of motion while sitting (ie, increase in COP forward velocity by 5% from resting velocity) to achieve full weight-bearing standing (ie, 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
		Weight symmetry	% difference in weight supported by each limb during the weight-transfer phase
Step-up/over	Concentric strength, eccentric control, performance time	Lift-up index (%BW)	Peak vertical force occurring while stepping up onto the box as a percentage of BW
		Impact index (%BW)	Peak vertical force occurring while stepping down off the box as a percentage of BW
		Movement time (s)	Time between initial weight shift (ie, 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 posttest resting velocity)
Lunge	Concentric and eccentric control, functional range of motion, performance time	Distance (% subject height)	Length of lunge step as a percentage of subject height
		Movement time (s)	Duration of lunge phase during which lead leg is in contact with the force plate, start and stop of a trial determined by 5% change in COP velocity from pretest and posttest resting velocity
		Impact index (%BW)	Peak vertical force occurring during lunge maneuver as a percentage of BW

Note: All tasks were performed in the order presented by patients treated for articular cartilage defects to the knee.

Figure 1 — Walk-across. Outcome variables included stride width, stride length, and speed.

- *Weight-Bearing Squat* (Figure 2): Patients stood still on the force plate and force was recorded with knee-flexion angles of 0°, 30°, 60°, and 90°. The percentage of body weight on the involved limb was measured during a single trial with a duration of 0.01 second for each position. A standard goniometer was used to verify knee-joint angle at each position.
- *Sit-to-Stand* (Figure 3): Patients were seated on a 50-cm box. On 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-second trial.
- *Step-Up/Over* (Figure 4): Participants stood behind a 29-cm-high box and stepped up onto the box with their test leg, then brought their nontest leg up and over the box, and then stepped down with their test leg. Patients were instructed to complete this task as quickly as possible while still maintaining control.

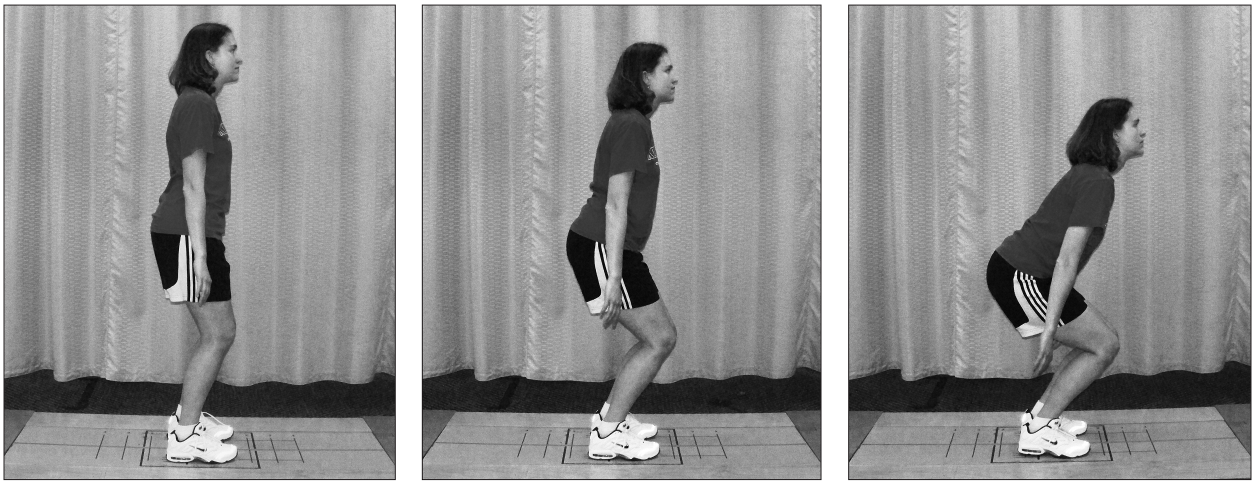

Figure 2 — Weight-bearing squat. Percentage of body weight on the involved limb was evaluated at 0° (not pictured), 30°, 60°, and 90° of knee flexion.

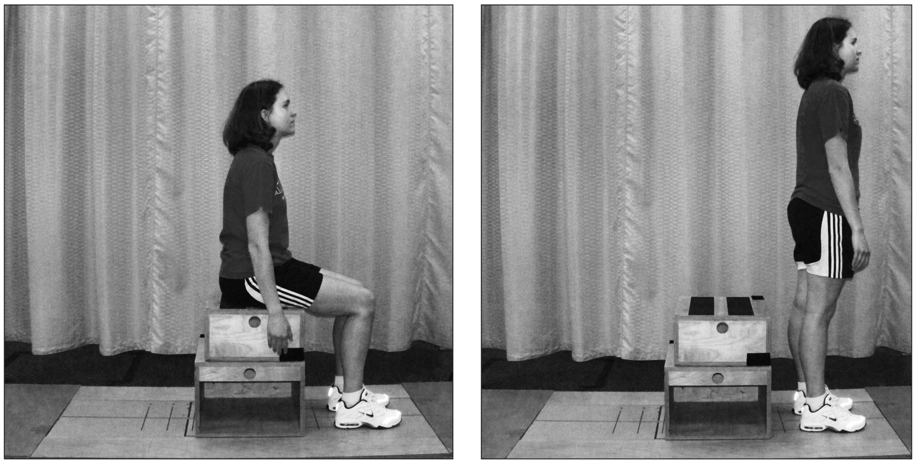

Figure 3 — Sit-to-stand. Beginning from a sitting position, participants were instructed, on receiving a visual and audio cue, to rise from sitting as quickly as possible without using hands to push off the box. Outcome measures included weight-transfer time, rising index, and weight symmetry.

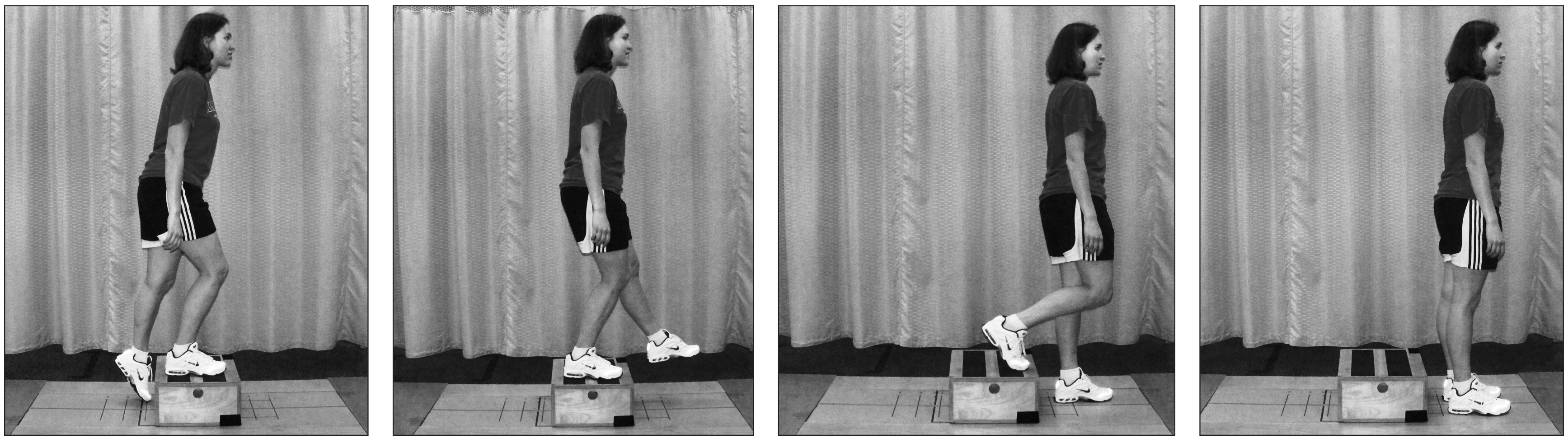

Figure 4 — Step-up/over. Beginning with both feet behind the box (not pictured), participants were instructed to step up and over the box and return to stationary standing as quickly as they could do so while still maintaining control. Outcome variables were lift-up index, impact index, and movement time.

- *Forward Lunge:* Patients in a standing position stepped forward on 1 leg, squatted down as far as possible, and then returned to the initial standing position as quickly as possible.

Previous research has investigated the global components of function assessed by the long force plate. Using factor-analysis methods, Chong[34] identified the latent functional variables assessed in several of the included tasks. He concluded that the sit-to-stand assessed the underlying factors of both agility and weight transfer, the step-up/over assessed force control, and the forward lunge assessed the underlying factor of agility.[34] In addition, walk-across stride width and stride length evaluated walking factors not well represented in the other functional tasks.[34] Outcomes using the long force plate have also previously been reported for postoperative recovery after total knee replacement.[19] Finally, the long force plate has been reported to be sensitive to functional deficits after anterior cruciate ligament reconstruction.[35] This existing literature supports the use of the long force plate as a useful tool for the assessment of lower extremity function, particularly among postoperative knee patients.

Statistical Analysis

A mixed-model analysis using a covariance pattern model with an autoregressive covariance matrix was used to compare changes in PROs and PBAs between preoperative and 3-month, 6-month, and 12-month postoperative evaluations. Significance level was set at $P \leq .05$ a priori, and when a main effect was significant, protected least-significant-difference pairwise comparisons were used to identify differences between individual time points.

Results

Six participants were declared clinical failures at or before the 1-year time point and were not medically cleared to complete functional testing at all follow-up time points; however, PRO scores were available for 4 of these patients, who had yet to undergo reoperation at the 1-year time point. An additional 5 participants were lost to follow-up. All available data for all participants at all time points were incorporated into the statistical analysis.

Patient-Reported Outcomes

There was a main effect ($P < .001$) for time for all 4 PRO instruments (Figure 5). The WOMAC ($P = .050$) was the only instrument to show significant changes between preoperation and the 3-month time point. There were significant improvements from preoperation to the 6- and 12-month follow-ups for the IKDC ($P < .001$, $P < .001$, respectively), SF36-PCS ($P = .002$, $P = .001$), Lysholm ($P < .001$, $P < .001$), and WOMAC ($P < .001$, $P < .001$).

Performance-Based Assessments

All PBAs demonstrated changes over time (Table 2). For the walk-across task there was a significant increase in stride length observed at both the 6- and 12-month time points compared with preoperation (6-month, $P = .002$;

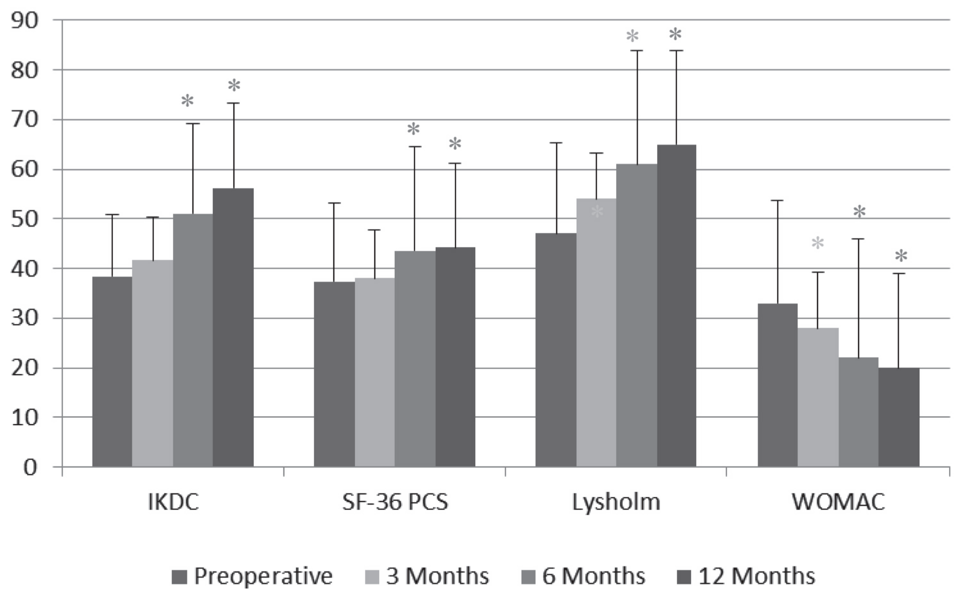

Figure 5 — Patient-reported outcome scores. Abbreviations: IKDC, International Knee Documentation Committee Subjective Knee Evaluation Form; SF-35 PCS, 36-Item Short-Form Health Survey Physical Component Scales; WOMAC, Western Ontario and McMaster Osteoarthritis Index. IKDC and Lysholm are scored from 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 represent higher levels of function. The WOMAC is scored from 96 to 0, with 0 representing no disability. Error bars represent standard deviations. *$P \leq .05$ compared with preoperative time point.

Table 2 Patient-Reported and Performance-Based Assessments Over 12 Months After Autologous Chondrocyte Implantation, Mean (SD)

Test	Preoperative	3 mo	6 mo	12 mo
Walk-across				
width (% height)	10.1 (2.8)	9.7 (2.5)	9.7 (2.1)	9.5 (2.5)
length (%height)	42.0 (8.9)	42.1 (10.5)	46.8 (8.1)*†	46.9 (7.6)*†
speed (cm/s)	82.6 (16.8)	87.7 (24.6)	88.2 (19.3)	94.5 (18.2)
Double-limb squat (% BW)				
0°	48 (5)	48 (3)	49 (3)	49 (5)
30°	48 (8)	43 (6)*	45 (6)*	46 (5)
60°	47 (8)	42 (7)*	44 (6)*	45 (6)†
90°	48 (6) †	44 (5)*	46† (6)	46 (6) †
Sit-to-stand				
weight-transfer time (s)	0.51 (0.26)	0.39 (0.32)*	0.36 (0.19)*	0.33 (0.20)*
rise index (% BW > 100%)	23.3 (9.4)	22.0 (8.5)	24.0 (8.4)	24.6 (8.8)
involved/uninvolved symmetry (toward uninvolved)	–6.2 (17.6)	–13.7 (15.2)*	–9.9 (9.8)	–8.37 (12.3)
Step-up/over				
lift-up index (% BW > 100%)	41.0 (11.3)	45.0 (11.7)*	47.0 (11.3)*	47.3 (11.6)*
time (s)	1.49 (0.33)†	1.67 (0.69)*	1.51 (0.36) †	1.40 (0.26) †
impact (% BW)	47.6 (17.0)†	54.9 (18.2)*	54.1 (19.3)*	50.7 (16.9)
Forward lunge				
distance (% height)	44.9 (7.1)	46.8 (19.1)	50.5 (19.0)	51.3 (23.8)
impact index (% BW)	24.4 (7.0)†	21.8 (6.7)*	24.4 (7.4) †	27.2 (10.4) †
time (s)	1.39 (0.43)†	1.51 (0.44)*	1.34 (0.28)†	1.29 (0.39)†
Patient-reported outcomes				
IKDC	38.43 (12.50)	41.62 (15.68)	51.10 (18.34)*†	56.21 (20.64) *†
SF-36 PCS	37.39 (8.79)	37.98 (9.83)	43.50 (9.16)*†	44.22 (11.28) *†
Lysholm	47 (18)	54 (21)	61 (23) *†	65 (24) *†
WOMAC	33 (17)†	28 (17)*	22 (19) *†	20 (19) *†

Abbreviations: BW, body weight; IKDC, International Knee Documentation Committee Subjective Knee Evaluation Form; SF-35 PCS, 36-Item Short-Form Health Survey Physical Component Scales; WOMAC, Western Ontario and McMaster Osteoarthritis Index.

*Significantly different from preoperative time point. †Significantly different from 3-month time point.

12-month, $P = .005$) and when compared with 3-month values (6-month, $P < .001$; 12-month, $P = .001$). There was no main effect for time for stride width ($P = .663$) or walking speed ($P = .051$).

For the weight-bearing squat, a main effect for time was observed for squatting at 30° ($P < .001$), 60°, and 90°. Post hoc analyses revealed decreases in weight distribution on the surgical limb between preoperation (48% body weight) and 3 months (43% body weight, $P = .020$) and 6 months (45% body weight, $P = .020$) for squatting at 30°. Decreased weight bearing was also observed between preoperation and 3 months ($P < .001$) and preoperation and 6 months ($P = .048$) for squatting at 60°. Similarly, squatting weight-distribution asymmetries were observed at 90° relative to baseline at 3 months ($P < .001$) Although not statistically different from preoperative values, at the 12-month time point mean weight distributions remained below preoperative values at 30°, 60°, and 90°.

The sit-to-stand demonstrated the earliest positive effects of surgery, with decreased weight-transfer time at 3 months (P = 0. 016) compared with preoperation. Weigh-transfer time continued to improve at 6 months ($P = .05$) and 12 months ($P = .002$).

For the step-up/over, there were significant increases in lift-up force between preoperation and the 3- ($P = .003$), 6- ($P = .005$), and 12-month ($P = .010$) follow-up time points. Time required to complete the step-up/over was also increased at 3months ($P = .009$) but returned to baseline at later time points. Similarly, step-up/over impact index was increased over preoperation values at 3 months ($P = .001$) and 6 months ($P = .034$), possibly demonstrating a loss of eccentric control when stepping down from the box.

Finally, results for the forward lunge showed a significant decrease in impact index (peak vertical ground-reaction force) at 3 months ($P = .007$) but returned to preoperative levels and began to increase at the 6- and 12-month time points. Similar to the step-up/over, forward-lunge time was slower at the 3-month time point ($P = .006$) but gradually became faster at subsequent evaluations.

Discussion

The primary purpose of this study was to provide a timeline for recovery that could be used by both patients and clinicians in managing expectations regarding postoperative recovery of function. A summary timeline of the functional recovery observed in the first year after ACI can be seen in Figure 6. Overall, these results suggest that patients may experience physical benefits such as decreased pain and symptoms as early as 3 months after ACI, but some facets of functional performance may initially decline after surgery, with significant improvements in functional performance of complex tasks such as squatting and stepping not occurring until 12 months, or perhaps longer.

Patient-Reported Outcomes

PROs have frequently been used to document functional outcomes after ACI.[3–5] The observed results suggest that patients may experience functional improvements for simple activities of daily living such as those evaluated by the WOMAC as early as 3 months after ACI. However, data from the other self-reported outcome instruments used suggest that patients should not expect significant improvement before the 6-month time point. The lack of significant improvement in most PRO scores at the 3-month time point is in agreement with previous research by Henderson and Levigne[36] and Ebert et al[23] However, those authors observed decreases in self-reported function using the IKDC[36] and SF-36 PCS[23,36] at the 3-month time point, while we observed slight but nonsignificant increases. In contrast, Tohyama et al[37] reported significant improvements in Lysholm scores as early as 3 months after treatment with atelocollagen-associated ACI.

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[38] and both Niemeyer et al[38] and Kreuz et al[39] for the Lysholm. Other authors have observed even larger improvements in IKDC[37] and Lysholm[40] scores as early as 6 months after ACI.

Across all PROs we observed improvements when preoperative scores were compared with scores 12 months after ACI surgery. These results are in agreement with the findings of others when using IKDC,[36,38,39,41–45] Lysholm,[37–39,41,42] SF-36 PCS,[36] and WOMAC[46,47] scores 1 year after 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 after ACI.

Performance-Based Assessments

Limited improvements in PBAs were observed 1 year after ACI (Table 2.). In general, a decrease in physical performance was observed at 3 and 6 months postoperatively, followed by a return toward baseline at 12 months after ACI. This pattern of decreased function followed by gradual return/improvement of function was particularly true for the weight-bearing squat, step-up/over, and lunge. The only measures to show positive improvements from preoperative levels at or within the 12-month time period were walk-across stride length, sit-to-stand weight-shift time, and step-up/over lift-up index. These results suggest that improvements for simpler, less demanding

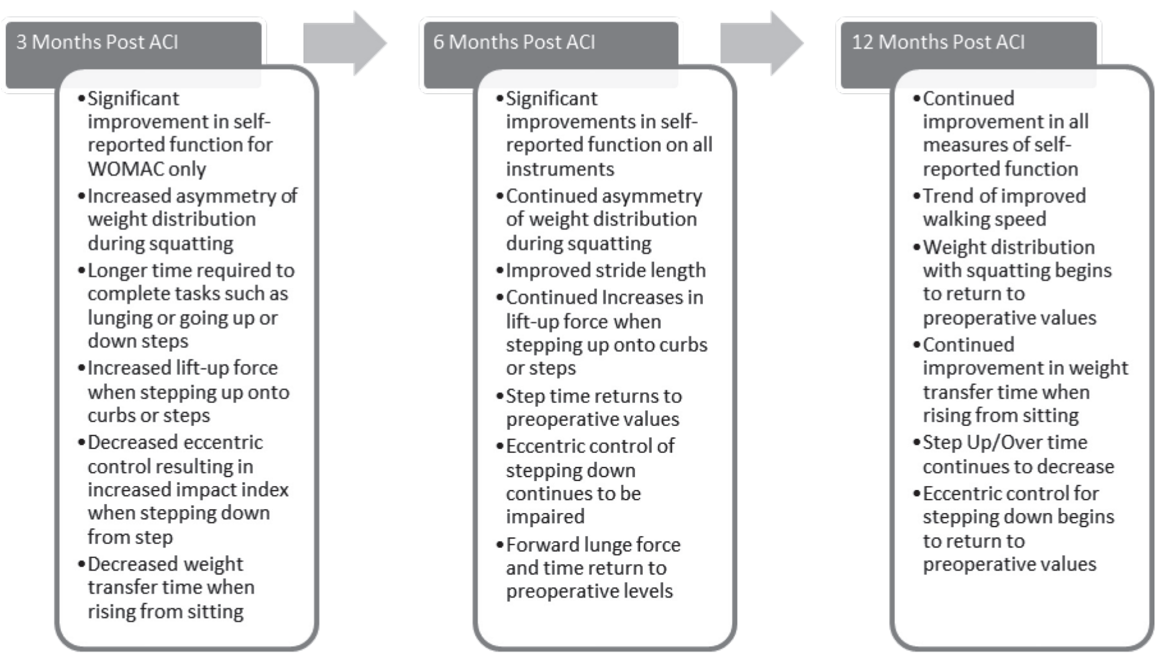

Figure 6 — Timeline of functional recovery after autologous chondrocyte implantation.

tasks such as walking or going up steps can be seen as early as 6 to 12 months after 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 after ACI.

Decreases in physical performance at the 3-month time point have been previously observed with the 6-minute-walk test after matrix-induced autologous chondrocyte implantation (MACI)[23,25] and characterized chondrocyte implantation (CCI).[24] Similar to our results, other researchers have observed slight improvements in walking performances at the 6-month[25] and 12-month[24,25] time points that continued to improve at 24-month follow-up.[24,25] During laboratory gait analysis, improvements in gait speed and stride length, without significant changes in stride width, were observed over 12 months after MACI.[48] These results support our observation that, after an initial decrease in function, patients and physicians can anticipate improvements in gait beginning around the 6-month time point after ACI.

In examining more-dynamic tasks, Van Assche et al[28] observed deceased functional performance for a series of hopping and strength tasks (single-limb hop, crossover hop, 6-m timed hop, and isometric knee-extension strength) at 6 months after CCI and no significant improvements as late as 24 months after CCI. For example, those authors observed a 9% decrease in the single-leg-hopping limb-symmetry index through 24 months after surgery. These results are in agreement with our observations demonstrating an initial decrease in function for more dynamic tasks such as squatting and stepping, with few or no significant or measurable improvements in functional performance at the 12-month time point after ACI.

In comparison with normative data[49] it can be observed that some long-force-plate variables are below preoperative levels at baseline but approach or achieve age-group normative values during the first year of postoperative recovery. These include the step-up/over lift-up index and forward-lunge distance. However, other variables such as step-up/over and forward-lunge times are below normal at baseline, become more abnormal at the 3-month time point, and despite some improvement continue to be below normative levels at the 1-year mark. These results suggest that although patients may have improvements in the ability to successfully perform the task, they continue to do so at a slower pace.

Across the literature and within our study sample, improvements in gait relative to presurgery have been observed as early as 6 months after ACI.[25] However, improvements in more-dynamic activities such as squatting, lunging, stepping, and hopping have not been observed within the first 12 months after ACI in the current study or elsewhere.[28] These results support existing theory that although improvements in self-report measures may occur early postoperatively, maximal defect healing and functional improvement continue beyond 12 months after ACI.[50–53]

The occurrence of changes in self-report measures of function before changes in performance-based measures of function may be a result of the large influence that pain levels have been observed to have on PRO scores.[19–22] 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 toward 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 alone.

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 whom also underwent concomitant realignment procedures. In addition, rehabilitation compliance was not tracked, and all patients were free to work with a physical therapist of their choice. Because of this variability, the presented timeline for recovery is not specific or precise for any 1 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 timeline for changes in self-perceived function and functional recovery in the first year after ACI. This timeline is intended to describe when patients can expect improvements in activities of daily living and when they will perceive a benefit from the surgery, 2 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 y) will provide more information regarding the long-term course of recovery after ACI.

Conclusions

This study presents a descriptive timeline for changes in both PROs and PBAs during the first 12 months after ACI. Self-perceived changes in function were observed as early as 3 months after ACI, while performance-based measures of function demonstrated functional deficits compared with preoperative levels at both the 3- and 6-month time points. Specifically, patients demonstrated increased asymmetry of weight distribution when squatting and rising from sitting, decreased vertical ground-reaction-force production during lunging, and longer performance times for lunging and stepping activities. At the 12-month time point, performance improvements were seen for walking speed, sit-to-stand weight-transfer time, and step-up/over lift-up index; 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. The present results, combined with those in the literature, provide important information for both physicians and rehabilitation specialists to consider when working with cartilage patients who desire to return to high-level physical activity. Clearly, recovery can be lengthy, and intense rehabilitation (beyond the existing standard of care) may be necessary to improve beyond or even restore to preoperative levels of dynamic function.

Acknowledgments

We would like to thank the University of Kentucky Center for Applied Statistics for their assistance with data analysis. This research was supported by the University of Kentucky Center for Clinical and Translational Science through grant number UL1RR033173 from the National Center for Research Resources (NCRR); funded by the Office of the Director, National Institutes of Health (NIH); and supported by the NIH Roadmap for Medical Research. In addition, co-author C.L. is supported by the NIH-NIAMS 1K23AR060275-01A1 (2012-2017). The content is solely the responsibility of the authors and does not necessarily represent the official views of NCRR and NIH.

Conflict of Interest: Independent of the presented research, co-author C.L. serves as a consultant for Sanofi/Genzyme Corp and Zimmer Inc.

References

1. 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. PubMed doi:10.1056/NEJM199410063311401
2. 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. PubMed doi:10.1177/0363546505281918
3. Harris JD, Siston RA, Pan X, Flanigan DC. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am*. 2010;92 (12):2220–2233. PubMed doi:10.2106/JBJS.J.00049
4. Harris JD, Erickson BJ, Abrams GD, et al. Methodologic quality of knee articular cartilage studies. *Arthroscopy.* 2013;29(7):1243–1252.
5. Howard JS, Lattermann C, Hoch JM, Mattacola CG, Medina McKeon JM. Comparing responsiveness of six common patient-reported outcomes to changes following autologous chondrocyte implantation: a systematic review and meta-analysis of prospective studies. *Cartilage.* 2013;4(2):97–110. doi:10.1177/1947603512470684
6. Roos EM, Engelhart L, Ranstam J, et al. ICRS recommendation document: patient-reported outcome instruments for use in patients with articular cartilage defects. *Cartilage.* 2011;2(2):122–136. doi:10.1177/1947603510391084
7. 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. PubMed
8. 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;86-A(6):1139–1145. PubMed
9. 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-A(10):1459–1469. PubMed
10. 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. PubMed
11. 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. PubMed doi:10.1097/00005650-199401000-00004
12. Roos EM, Klassbo M, Lohmander LS. WOMAC osteoarthritis index: reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and McMaster Universities. *Scand J Rheumatol*. 1999;28(4):210–215. PubMed doi:10.1080/03009749950155562
13. 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. PubMed doi:10.1177/0363546509354163
14. 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. PubMed doi:10.1055/s-2007-1024766
15. 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. PubMed doi:10.2519/jospt.1997.26.6.324
16. 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. PubMed doi:10.1007/s001670050141
17. 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):267–272.
18. Mizner RL, Petterson SC, Clements KE, Zeni JA, Jr, 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*. 2011;26(5):728–737. PubMed doi:10.1016/j.arth.2010.06.004
19. Jacobs CA, Christensen CP. Correlations between knee society function scores and functional force measures. *Clin Orthop Relat Res*. 2009;467(9):2414–2419. PubMed doi:10.1007/s11999-009-0811-0
20. 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. PubMed doi:10.2522/ptj.20060002
21. Maly MR, Costigan PA, Olney SJ. Determinants of self-report outcome measures in people with knee osteoarthritis. *Arch Phys Med Rehabil*. 2006;87(1):96–104. PubMed doi:10.1016/j.apmr.2005.08.110
22. Stratford PW, Kennedy DM. Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *J Clin Epidemiol*. 2006;59(2):160–167. PubMed doi:10.1016/j.jclinepi.2005.07.012
23. 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. *Osteoarthritis Cartilage*. 2008;16(10):1131–1140. PubMed doi:10.1016/j.joca.2008.03.010
24. 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. PubMed doi:10.1016/j.knee.2006.11.009
25. 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. doi:10.1177/1947603510362907
26. Ebert JR, Fallon M, Ackland TR, Wood DJ, Janes GC. Arthroscopic matrix-induced autologous chondrocyte implantation: 2-year outcomes. *Arthroscopy.* 2012;28(7):952–964.
27. Ebert JR, Robertson WB, Woodhouse J, et al. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. *Am J Sports Med*. 2011;39(4):753–763. PubMed doi:10.1177/0363546510390476
28. 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. PubMed doi:10.1007/s00167-009-0955-1
29. Lattermann C. UK Center for Cartilage Repair and Restoration. 2011. http://ukhealthcare.uky.edu/rehab-protocol/#.UGuk55jAcdc. Accessed October 2, 2012.
30. 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. PubMed doi:10.1097/00005650-199303000-00006
31. 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. PubMed doi:10.1097/00005650-199206000-00002
32. 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. PubMed doi:10.1177/036354658201000306
33. Balance Master Family: Balance Master. 2011; http://www.onbalance.com/products/Balance-Master/detail.php#balance. Accessed February 18, 2011.
34. Chong RK. Factor analysis of the functional limitations test in healthy individuals. *Gait Posture*. 2008;28(1):144–149. PubMed doi:10.1016/j.gaitpost.2007.11.005
35. Mattacola CG, Jacobs CA, Rund MA, Johnson DL. Functional assessment using the step-up-and-over test and forward lunge following ACL reconstruction. *Orthopedics*. 2004;27(6):602–608. PubMed
36. 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. PubMed doi:10.1016/j.knee.2006.04.006
37. 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. PubMed doi:10.1007/s00776-009-1384-1
38. 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. PubMed doi:10.1177/0363546510376742
39. 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. *Arthritis Res Ther*. 2009;11(2):R33. PubMed doi:10.1186/ar2638
40. 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. PubMed doi:10.1007/s00167-009-1028-1
41. 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. PubMed doi:10.1177/0363546509351499
42. 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. PubMed doi:10.1016/j.ejrad.2005.08.005
43. 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. PubMed doi:10.1177/0363546509348490
44. 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. PubMed doi:10.1016/j.knee.2004.07.002
45. 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. PubMed doi:10.1302/0301-620X.90B5.20360
46. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop Relat Res*. 2001;(391 Suppl)S349–S361. PubMed doi:10.1097/00003086-200110001-00032
47. Minas T, Chiu R. Autologous chondrocyte implantation. *Am J Knee Surg*. 2000;13(1):41–50. PubMed
48. 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. PubMed doi:10.1016/j.clinbiomech.2010.07.004
49. NeuroCom International Inc. *Balance Master Systems Clinical Operations Guide*. Clackamas, OR: Author; 2008.
50. 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):1261–1268. PubMed doi:10.1177/0363546507300693
51. 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–R73. PubMed doi:10.1186/ar613
52. 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(Suppl 1):131S–138S. PubMed doi:10.1177/0363546509350555
53. Niethammer TR, Müller P, Safi E, et al. Early resumption of physical activities leads to inferior clinical outcomes after matrix-based autologous chondrocyte implantation in the knee. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(6):1345–1352. PubMed