Current Reviews in Musculoskeletal Medicine (2019) 12:181–189
https://doi.org/10.1007/s12178-019-09557-3

OUTCOMES RESEARCH IN ORTHOPEDICS (O AYENI, SECTION EDITOR)

Outcomes Associated with Return to Sports Following Osteochondral Allograft Transplant in the Knee: a Scoping Review

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Published online: 29 April 2019

Abstract

Purpose of Review The purposes of this review were to report the currently validated outcomes for OCA transplant patients, discuss the benefits and challenges associated with "return to sports" as an outcome measure, and summarize the currently available data on patients' ability to return to sports after OCA transplant.

Recent Findings College athletes may take less time than professionals to return to basketball, but there are many factors that can influence this timeframe. Player productivity is decreased ~ 40% and future career length is only 1 to 2 years following return to play. When evaluating all OCA transplant patients, 75–88% of patients return to sport and 38–80% return to their previous level of play at approximately 8–10 months following surgery. Overall graft failure rates are low (0–9.4%) but are based on limited short- to medium-term data.

Summary Data on the return to professional and college sports after OCA transplant is limited. Surgeons should consider collecting patient outcomes across multiple domains and contributing data to aggregate databases to allow for better quality outcome data to be reported.

Keywords Osteochondral allograft transplant · Return to sports · Patient-reported outcome

Introduction

Injury to articular cartilage produces symptoms of swelling, pain, restrictions on activity, and potentially mechanical symptoms [1]. These cartilage injuries may increase the likelihood of developing osteoarthritis (OA) earlier in life [2]. Chondral lesions are found in over 60% of knee arthroscopies and localized defects are identified in about 20% of cases [3, 4]. There are many cartilage restoration options for these lesions including microfracture [5], abrasion arthroplasty [6], augmented microfracture (e.g., AMIC[1]) [7, 8], seeded autologous chondrocytes (e.g., MACI[2]) [9, 10], osteochondral autograft transfer (OATs) [11], and osteochondral allograft transplant (OCA) [12–17]. Large lesions and lesions with bone loss, however, may be best treated with an OCA transplant [13]. The benefits of OCA transplant include the fact that it is a structural graft of mature hyaline cartilage and bone, which is size matched and allows for a single transplant for lesions > 1 cm in diameter with no harvest site morbidity[18•]. While OCA grafts are relatively immune privileged due to their avascular and aneural nature, immune conversion can infrequently occur. Patient-reported outcomes and failure rates, however, are similar between those with conversion and those who do not develop antibodies [19].

The bulk of available OCA transplant outcome data comes from the USA where there are multiple graft procurement companies and tissue banks that can make fresh osteochondral allograft tissue available for clinical use. Any overview of patients' return to sports activity after receiving an OCA transplant is therefore based on US patients and the types of sports activities in which they are involved. While fresh allograft tissue is available in Canada [20] and other countries [21], its use is much more limited due to the challenges of consent and procurement. It is hoped that a recently published cost-effectiveness analysis will help pave the way for more widespread use both in the USA and around the world [22].

[1] AMIC: Autologous Matrix-Induced Chondrogenesis

[2] MACI: Matrix-Associated Autologous Chondrocyte Implantation

This article is part of the Topical Collection on *Outcomes Research in Orthopedics*

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The use of cartilage restoration procedures such as OCA transplant continues to grow [23]. The volume of epidemiology literature reporting cartilage injuries and defects in athletes [24–26] continues to grow along with the literature reporting on the outcomes of OCA transplant in young patients and athletes [27••,28, 29, 30••, 31••, 17]. When these cartilage defects become symptomatic, the goals of cartilage restoration surgery include the resolution of pain, prevention of further cartilage degeneration or damage, return to (pre-injury) activity/sport/function, and improvement in quality of life (QOL) [32•]. Studies therefore need to assess and track all of these outcomes. Niemeyer et al. asked 118 patients having autologous chondrocyte implantation (ACI) about their post-surgery expectations for their knee. Of these patients, 70% expected a return to pain-free sports participation at some level, while 20% expected to have a pain-free return to high-impact sports [33]. Given these expectations, it is important for surgeons to possess data that can be used in the pre-surgical education of patients so that realistic expectations can be set and agreed to by both the surgeon and patient. Not only do patients want to know when or if they will be able to get back to their pre-injury sports, but they should ideally also have an understanding of how the level of activity that they return to will impact the longevity of their OCA graft, and the consequences of a failed graft. This ultimately allows them to make educated decisions about their short- and long-term activity goals post-operatively and how these goals will affect their optimum quality of life. The purposes of this paper were to review the outcome measures used to evaluate outcomes after OCA transplantation in the knee and review the currently available literature focusing on patients' abilities to return to sports, recreational activities, and work following this cartilage restoration surgery.

Outcomes

To best capture the overall change in patient ability after any knee surgery, it has been suggested that measures of general health, knee specific symptoms and abilities, and patient activity level should be assessed [34]. In a study of five high impact journals that publish studies involving cartilage restoration, Makhni et al. looked at how patient outcomes were reported across the domains of pain, satisfaction, progression of osteoarthritis and degeneration, objective knee function, subjective knee function, and patient-reported outcomes (PROs) [32•]. Only 39% of studies reported a measure of post-operative pain and only 30% reported a measure of patient satisfaction. While PROs were the most commonly reported outcome measure (96% of studies), there were 24 different PROs identified and only four of these were consistently used across more than 20% of the studies (IKDC[3] in 58%, KOOS[4] in 39%). Presently, only the IKDC, KOOS, and Lysholm Knee Score have been validated for use in patients with cartilage defects [37–40]. The modified Merle d'Aubigne Postel score has also been commonly reported in the OCA transplant literature given its historical use in a large ongoing database dating back to the 1980s [41, 42]. As there were no available validated PROs for knee patients at that time, the Merle d'Aubigne Postel hip score was modified for use in knee patients but has not been validated (personal communication, Dr. William Bugbee, 2019) [42].

In 122 studies reporting on the treatment of cartilage defects in the knee, only 14% provided data on patients' ability to return to sport. Eleven percent reported the level of activity to which patients were able to return, and only 6.6% reported how long it took patients to return to that level of activity [32•]. The limited use of this outcome is unfortunate given these factors are of common interest to patients when considering OCA transplant surgery.

In addition to asking patients outright about whether or not they have returned to their pre-injury level of sporting activity, the Tegner Activity Scale and the Marx Activity Rating Scale are two other frequently reported outcome measures that focus on sport-related activity level and may be surrogate scores for return to play outcomes [43, 44]. The Tegner was originally developed to accompany the Lysholm Knee Scoring Scale which focused more on knee-related symptoms [44]. The Tegner uses a 0–10 scale developed by having patients with ACL injuries rate how hard they felt a certain activity, of which most are sports examples, would be to perform. The Tegner has been shown to have acceptable psychometric properties, test-retest reliability, and floor-ceiling effects. It has the ability to measure moderate to large changes in activity level but may not be sensitive enough to detect smaller changes [34]. While studies have shown that significant improvements in the Tegner score following cartilage surgery [34], others have suggested that it may not appropriately rank athletes at the top end of the scale where, for example, (inter)national soccer is rated a 10 but competitive level basketball is only rated a 7 [45]. Balzas et al. further discuss this factor related to the high peak loads and shear forces placed on articular cartilage and cartilage transplants during repetitive jump landing in a sport-like basketball [27••]. Additionally, studies that include a large age range in their patient population should take into account that there may be an age effect resulting in a decrease of 0.8 (95% CI: 0.4, 1.1) points on the Tegner scale for each 10-year increase in age. On top of the age effect, females tend to score 0.7 (95% CI: 0.4, 1.0) points lower than their male counterparts [46].

[3] International Knee Documental Committee (IKDC) score [35]

[4] Knee Injury and Osteoarthritis Outcome Score (KOOS) [36]

The Marx Activity Score was initially developed to be a quick self-administered rating scale for patients' activity level that was not based on specific sports [43]. This therefore allows for the comparison of patients participating in different sports or activities. This score focuses primarily on the most challenging activities for the knee, those being running, cutting, decelerating, and pivoting [43]. This scale is therefore less useful for sports such as cycling and cross-country skiing, which do not involve these types of movements. In this manner, the Marx scale can be useful for evaluating the abilities and performance of athletes returning to sports such as basketball, soccer, and football, but there would be a type of floor-effect for athletes returning to sports like cycling or cross-country skiing. Scores for these athletes may be low at both pre-injury and return to play time points thereby negating its ability to differentiate changes in ability. These athletes may have fully returned to their pre-injury activity level while scoring relatively low on this scale. The Marx Activity Score should therefore be used as an adjunct to reporting return to play outcomes such as the proportion of patients returning to their previous level of activity and the time required to return to that level.

Return to Activity Outcomes

While the reporting of OCA transplant outcomes continues to grow, the number of surgeons having a sufficient volume of patients and focused tracking of return to sports data to publish is limited. In fact, the data is limited to retrospective case series involving the practices of three large volume OCA transplant centers in the USA [27••, 29, 30••, 31••].

Studies that limited their inclusion to high school, college, and professional sports had lower mean ages (19–23 years old) [27••, 30••] compared to those that included recreational and working patients (30–33 years old) [29, 31••, 47]. Additional demographic data including BMI, follow-up period, number of previous surgeries, mean defect size, and defect location are included in Table 1.

College and Professional Sports

Across these four studies, there were only five athletes identified as "professional" [27••, 29] (including four basketball players) and 21 collegiate-level players [27••, 29, 30••]. Neilsen et al. had a category of "highly competitive athletes" but the inclusion of professional or college-level athletes in this group was not further identified [31••]. The data on return to play after OCA transplant in college or professional-level athletes is therefore extremely limited. Of the four NBA players, three of them returned to play at a median of 20 months (range 10–26 months), while one was cleared for return to play but remained an unsigned free agent [27••]. Of

Table 1 Studies reporting return to play/sports after osteochondral allograft transplant in the knee

Lead author	Journal	Year	Surgeon database	Population	Sample size	Age (years)	Male (%)	Follow-up (years)	BMI (kg/m^2)	Previous surgery (%)	Mean size (mm^2)	Location
Balzas	OJSM	2018	Williams	College 64% Professional 36%	11	22.8	82	Min 1	24.8	64	509	LFC 43% Trochlea 36%
Krych	AJSM	2012	Williams	Recreational 74% College 23% Professional 2%	43	33 ± 10	70	2.5	27.9 ± 4.1	58	725 ± 236	MFC 40% LFC 40% Trochlea 2% Multiple 18%
McCarthy	Arthros	2017	Cole	High school College Professional	13	19.2 ± 2.8 (15–26)	54	5.9 ± 2.5 (2.2–9.6)	22.7 ± 6	100	450 ± 174	MFC 60% LFC 40%
Neilsen	AJSM	2017	Bugbee	All who participated in sports	142	31.2	58.4	6 (1–15.8)	NR	89	820 ± 520	NR
Shaha	AJSM	2013	Military	Military	38	29.8 ± 5.3	90.9	4.1 (0.6–8.9)	27.6 ± 2.7	76	502 ± 132	MFC 66% LFC 34%

LFC lateral femoral condyle, *MFC* medial femoral condyle, *Arthros* arthroscopy, *NR* not reported the seven collegiate players in the same study, six were eligible to return to play and five of them did so at a median of 8 months. One player had surgery after graduation and therefore did not return. While this sample is clearly limited in size, there is a notable difference in the time to return to sport between the college and professional basketball players. Two players had complications, including a graft failure requiring revision with a freeze-dried allograft (returned to play at 26 months) and one had septic arthritis requiring multiple arthroscopic procedures and returned to play at 20 months after the index procedure. This clouds the comparison on return to play time but raises the question of other factors that may play a role in the timing of return to sport. Examples of these factors may include player psychological readiness, contract obligations/limitations, level of performance required to gain playing time, pressure from team staff to rejoin the team, and financial factors etc.

In addition to the rate and timing for return to play, Balzas et al. reported publicly available player productivity data on six professional or Division I/II college basketball players. There was a general non-significant trend for decreasing productivity of approximately 40% across all measures (minutes played, points, rebounds, assists, steals, blocks). These six players only played one or two more years at their previous level of play after their OCA transplant [27••].

Return to Sports

Across all four studies, return to sport at some level was consistent and ranged from 75 to 88% [27••, 29, 30••, 31••]. Two of these studies reported the proportion of patients returning to their previous level of sports activity as 79–80% [27••, 29]; however, the study by McCarthy et al. reported a substantially lower rate of 38% [30••]. Factors that contributed to this lower rate of return to the previous level of activity included graduation from high school (presumably without a move to college level sports) and a non-cartilage re-injury to the index knee. Mean time for return to sport following OCA transplant was reported in two studies ($N = 56$ patients). The 43 athletes followed by Krych et al. returned to sports at a mean of 9.6 ± 3 months (range 7–13 months) [29]. This is similar to the time frame reported by McCarthy et al. (7.9 ± 3.5 months) [30••]. In comparison, a meta-analysis of return to sport after cartilage restoration procedures demonstrated a 58% return to sport at a mean of 9 months for microfracture patients, an 82% return to sport at a mean of 12 months for ACI, and a 93% return to sport at a mean of 5.2 months for osteochondral autograft transplant (OAT) [48•]. The higher return to sport rates and quicker timelines for OATS in these studies may be related to the smaller defects treated (means of 190–240 mm^2) and the use of autograft bone [49, 50].

Military Activity

While many patients undergo OCA transplant in hopes of improving their abilities to participate in recreational and sports activities, another subset of patients undergo these procedures with a main goal of return to work or other high-demand activities such as active military service. The military has a vested interest in the success of these grafts given the need to return service members to full active duty in order to continue their careers. Shaha et al. evaluated the records of 38 active service personnel (90.9% male, 29.8 ± 5.3 years old, BMI 27.6 ± 2.7 kg/m^2) who underwent osteochondral allograft transplant to the femoral condyle at an average of 4.1 years (range 0.6 to 8.9 years) post-surgery [47]. While they reported no graft failures or complications, only 29% of patients were able to return to full active duty and only 5% reported full return to active duty and symptom-free unrestricted sports participation.

Those who returned to full active duty did so at a mean of 12.1 ± 6.9 months (range: 7.1–27.2 months). Limited duty, defined as remaining on active duty but not deployable, or permanently accommodated with alternative fitness tests or fitness requirements, was attained in 29%, while 42% were medically removed from service due to knee symptoms that precluded them from performing their required duties. Concomitant procedures were performed in 29% (HTO [$n = 7$], tibial tubercle osteotomy [$n = 1$], and meniscus transplant ± ACL reconstruction [$n = 3$]). Previous cartilage restoration procedures included one patient who had failed autologous chondrocyte implantation and 22 patients who had microfracture. There were no significant differences in the size of the chondral lesions across the three final duty status categories (full: 552.3 mm^2 [range: 400–900 mm^2]; limited: 472.6 mm^2 [range: 255–625 mm^2]; unable to return: 488.9 mm^2 [96–625 mm^2]). SANE and KOOS scores were higher in those service members returning to full active duty. In this light, the authors recommend that the use of OCA transplant "should be approached with caution in patients who require a return to high-demand, daily physical activities." [47]

Allograft Survival/Longevity

One of the main questions that active patients want to know when discussing surgery revolves around when they should expect to be able to return to the sports and activities from which they are currently limited. As outlined above, it may be reasonable to say that about 75–88% of patients can return to their activities and can do so between 8 and 10 months following surgery [27••, 29, 30••, 31••]. While return to play is the initial goal for patients and surgeons alike, the bigger question may be how long does the OCA graft last once the patient returns to their full activity, especially if that activity involves impact activity, cutting, pivoting, or jumping.

Unfortunately, with mean follow-up of 2.5 to 6 years, the studies quoted here that evaluate return to sport do not really have sufficient follow-up time to evaluate the longevity of the OCA grafts under these activity conditions. The studies by Krych et al. and McCarthy et al. do not report a failure rate[30••]. The military study, with a mean of 4.1-year follow-up, reports that there were no failures in that population and Balzas et al. reported one of 11 patients with an early failure [27••, 47]. The study by Neilsen et al. had a mean follow-up of 6 years but the range included up to almost 16 years [31••]. In that study, failure was defined as undergoing an additional surgery for graft removal or conversion to a unicompartmental (UKA) or total knee arthroplasty (TKA). Their failure rate was 9.4% which included eight revision OCA transplants and six conversions to arthroplasty. The mean time to failure was 1.9 years, but their overall survivorship was 91% at 5 years and 89% at 10 years, suggesting that failures tend to occur early and patient outcomes are fairly well maintained once they get beyond the first 2 to 3 years following their index transplant procedure. Definitions of failure used in other studies may vary slightly but are for the most part in line with those of Neilsen et al. A 2017 systematic review of the outcomes following OCA transplant of the knee included survival analyses from studies going back over 20 years. That study demonstrated mean survival rates of 86.7%, 78.7%, 72.8%, and 67.5% at 5, 10, 15, and 20 years, respectively [18•].

Factors Related to Not Returning to Sports

Across most, if not all, facets of orthopedic sports medicine, the main goal is to return the injured patient/athlete back to the highest level of activity possible. Despite the best surgical plan, surgical execution, and effort in rehabilitation, there may be other factors that will ultimately play a role in the athlete's ability to reach their goal activity level. The first factor is age. For OCA grafts, OATs and ACI, a patient age of greater than 25 years old resulted in less return to sport [29, 51]. The second significant factor was duration of symptoms. For OCA transplants, patients with symptoms for greater than 12 months had a 42 times higher odds of not returning to sports relative to those undergoing surgery following a shorter course of symptoms [29]. This data is in line with the ACI outcomes presented by Campbell et al., who reported that patients with a symptom duration of less than 12 months had a better return to sports overall, had a better return to impact sports (67% vs. 14%), and a better return to sports for adolescents (100% vs. 33%) [51].

In the study by Krych et al., there were a number of factors identified that may be related to return to sport but these secondary analyses were likely underpowered. This study suggested that multiple lesion locations and the use of multiple OCA plugs may reduce return to sport, while pre-injury sports activity four to seven times per week and participation at the professional or college level may increase the likelihood of return to sport [29]. These findings were supported by the work of Neilsen et al. and Campbell et al. [51, 31••] Additional factors associated with a decreased likelihood of returning to sport include female gender, a non-sport-related injury, a degenerative lesion, large lesion size, and a lesion located in the patella [31••].

Challenges With the Use of "Return to Sport" as a Measure of Successful Outcome

"When can I get back to playing X?" is a common question patients ask in relation to many orthopedic sports medicine surgeries. The timeframe for return to unrestricted activity and sports is a clear, objective, and important goal for the patient [32•]. For the surgeon, however, interpreting the limited data available in the literature can be a challenge. As an outcome measure, the proportion of patients who return to either any level of sport, or their previous level of sport, can be tracked. This outcome, however, may under predict the true proportion of patients who "could have" returned. Factors other than the anatomical pathology, surgical technique, and rehabilitation can play a role in the final proportion of patients returning to activity. Athletes may no longer have the opportunity to return to the same level of play. They may graduate from high school or college and therefore not be eligible for the teams on which they previously played [30••]. Professional athletes may be "cleared" for return to play, but may be without a contract or a team for which to play [27••]. Alternatively, other life decisions may also play a role. These may include starting a new career or a family, developing an interest in a different sport, or sustaining new health issues unrelated to the index knee surgery that may prevent a return to the previous level of activity [31••]. Finally, in some patients, especially given the high rate of multiple surgeries (58–100%) [27••, 29, 30••, 31••, 47], patients may feel they are capable of returning to their previous level of sports participation but may chose not to for fear of re-injury [30••]. Of the 10 players who returned to sports in the study by McCarthy et al., five did not return to their previous level. Four of these graduated from high school and one had an unrelated re-injury (meniscus). While all five of these athletes felt that they could have physically returned to their previous level, three of these five also reported that fear of re-injury prevented them from doing so [30••].

In considering return to play data, there are two additional levels of information to be considered even when the athlete returns to their previous sport level: (1) do they perform at the same skill or "productivity" level that they did before the injury?; (2) how long are they able to stay in that league or compete at that level after their return? Tracking athletic performance after return to play is challenging for studies. When tracking the performance of athletes who play at a high level, data may be available from various sources but the integrity and accuracy of that data is challenging to quantify. Data may be attained directly from the athlete's own team's internal statistics, assuming the athlete provides consent and the team agrees to supply the data. It can also be mined from publicly available sports media websites, injury and player tracking websites, and limited access injury databases usually controlled by the particular sports league. Previous studies have used game summaries, play by play documents, weekly injury reports, player profiles, player/team/league websites, press releases, and league injury databases [27••, 52–58]. While this data can be very helpful to delineate the level of successful return, the information must be taken in guarded fashion given all the factors unrelated to the success of the surgery and rehabilitation that play a role in performance (playing time, position on the roster, other injuries, contracts, team make-up and skill level, etc.). Balzas et al. tracked the return to previous level of play and player performance statistics, albeit in a small sample (6 players) of high-level basketball players [27••]. They tracked the number of seasons played after they returned, as well as a number of basketball-specific player productivity measures. The exact methods of data collection and the sources of player performance data, however, were not clearly delineated in their study.

Limitations

Even though the volume of literature on the outcomes of OCA transplant continues to increase, there are currently only five studies ($N = 247$ patients) reporting data specifically on return to sports or high-level occupational work [27••, 29, 30••, 31••, 47]. The inclusion criteria for the studies are varied and complicated by the fact that 58–100% of patients in these studies had previous surgeries. Some studies included concomitant procedures and others did not. These five studies are all based on US data and therefore generalization outside of the US is unknown. While there are multiple studies quoting OCA survival rates, there is minimal data on how these graft survival rates are affected by increased activity level such as return to high-level sports and physical work.

Conclusions

The use of multiple outcome measures in the evaluation of surgical procedures in the knee is beneficial to capture the many facets of patient improvement. In addition to a general health questionnaire, studies of cartilage restoration procedures should include a knee specific outcome validated for this specific population, such as the KOOS, IKDC, or Lysholm knee score, and a measure of return to sports and/or activity. Specifically noting the proportion of patients who return to sports, to what level they return, and the length of time it takes for them to return to that level is beneficial. Activity scores such as the Tegner or Marx may be collected; however, the limitations of these outcomes should be recognized.

There is limited data on the return to sports outcomes for professional and college athletes. There is a suggestion of a quicker return in college athletes but there are a multitude of factors that can influence that timeframe. Limited data suggests about a 40% reduction in player productivity and a future career length of only 1 to 2 years after return to their previous level of sports. When looking at all patients undergoing OCA transplant, 75–88% of patients are able to return to some level of sport, and 38–80% of patients can return to their previous level of sports participation. This usually occurs between 8 and 10 months following surgery. The outcomes are not as good for military personnel, where only 29% of patients were able to return to full active duty and only 5% were able to return to full symptom-free unrestricted sports activity. Across all of these studies, the failure rate ranged from 0 to 9.4%, but the follow-up time frame was less than 10 years in most studies. Age greater than 25 years old and symptoms greater than 12 months resulted in lower return to play. Rates of return to (previous) sports, however, can also be affected by other more indirect life factors such as graduation from high school or college, family, career, and fear of re-injury, making an accurate assessment of the surgical and rehabilitative success a challenge.

Based on the results of this review, to follow is a list of considerations for all cartilage restoration surgeons to incorporate into their clinical practice and future OCA transplant research in order to help advance the body of knowledge that can be used to educate patients regarding cartilage restoration treatment decisions and to help guide their post-operative expectations.

1. Cartilage restoration surgeons should track their own patient outcomes with validated, disease-specific patient-reported outcome measures (e.g., KOOS) as well as other relevant functional outcomes such as return to work or sports status.
2. Surgeons and specialty societies should work towards the use of standardized outcome assessment tools to allow both a comparison of outcomes across published studies and allow the collaboration of surgeons to aggregate data in this patient population to provide more powerful outcomes data. These groups should also clarify and standardize the definition of return to sport and how the level of return will be quantified.

3. Surgeons should consider enrolling in, and contributing to, a large multi-center cartilage restoration database (e.g., International Cartilage Regeneration & Joint Preservation Society, https://cartilage.org/society/icrs-patient-registry/) to allow for the pooling of data and analysis of outcomes following (epidemiologically rare) treatments such as osteochondral allograft transplant.
4. Surgeons should continue to follow return to sport outcomes concurrently with clinical graft-related outcomes in order to provide more long-term data on graft survival that can be stratified by sport level and the biomechanical demands placed upon the knee.
5. Even though the Metric Reporting Score developed by Makhni et al. was based on expert opinion and has not been validated [32•], it represents a thoughtful approach to the collection of outcomes across a broad spectrum of domains that are important to both patients and cartilage restoration surgeons for evaluating and understanding the short- and long-term effectiveness and success of osteochondral allograft transplantation of the knee. Future studies should therefore consider including outcomes from each of these domains in order to optimally measure the breadth of outcomes in these patients.

Compliance with Ethical Standards

Conflict of Interest JAG has received research grants and consultancy fees from JRF Ortho. JAG has received financial support for attending symposia and consultancy fees from Ossur Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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