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Osteochondral Allograft/Autograft Transplantation (OAT)

Health Technology Assessment

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Osteochondral Allograft/Autograft Transplantation (OAT)

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Executive Summary

Introduction

Articular cartilage is a hard, white shiny material that allows the bones that coincide at joints to glide easily along each other as the joint moves. This articular hyaline cartilage is found in the knees, ankles, shoulders, elbows, and fingers. The special nature of articular cartilage, however, makes it particularly vulnerable once it becomes damaged. Articular cartilage has no blood supply, so it cannot heal on its own. This cartilage also has no nerve supply, so early injuries are not easily detected. Articular cartilage damage can involve only the cartilage (chondral) or the damage can involve both the cartilage and the underlying subchondral bone (osteochondral). If untreated, these defects or lesions are believed to lead to osteoarthritis and severe disability. A 1999 case study reported that over 900,000 Americans experience chondral lesions of the knee annually, resulting in over 200,000 surgical procedures for the high-grade lesions.[1]

More common causes of defects to the knee include trauma, repetitive microtrauma to a specific area of the joint (as may be seen in athletes) and a joint disorder with a multifactorial etiology termed osteochondritis dissecans (OCD). The majority of **osteochondral** lesions of the talus are caused by trauma, with other causes including ischemic necrosis, embolic phenomena, or ossification defects.

Surgical and non-surgical methods have been used to treat such defects. Surgical options fall into several general categories: Arthroscopic lavage/debridement, reparative or marrow-stimulating techniques and restorative techniques. Restorative techniques include autografts, allografts, and autologous chondrocyte implantation (ACI) which attempt to restore the biomechanical and physiologic cartilage functions by completely reconstructing the cartilage microarchitecture.

Transplantation of cartilage and subchondral bone into the defect is intended to replace the subchondral structure and restore the biomechanical and physiological functions of the cartilage**.** The primary goals for treatment of osteochondral injuries are to relieve pain and restore function. **Autograft** transplantation involves harvesting bone and intact articular cartilage from a non-weight bearing portion of a joint *from the patient* (i.e., autologous tissue) to fill a defect in the weight-bearing portion of the joint. **Allograft** transplants involve the transplantation of a piece of cartilage and subchondral bone *from a source outside of the patient* to fill in the osteochondral defect. Osteochondral allografts are regulated by the FDA as Human Cell or Tissue Products.

There is variability with respect to the terms used to describe osteochondral grafting with cylindrical, dowel-shaped or geometrically shaped "plugs" which are press-fit to fill defects. Definitions are also variable. In general, it appears that the term OAT (or OATS) refers to the use of one or two larger cylindrical plugs and mosaicplasty is used to describe multiple cylindrical plugs. It is often assumed that these refer to autograft procedures.

Usually the severity of symptoms, defect size and severity guide treatment. In a less active patient who is experiencing little pain and no mechanical symptoms, conservative treatment may

be appropriate. Conservative treatment may consist of non-steroidal anti-inflammatories and activity modification. Patients experiencing pain, locking, or catching may elect to have an arthroscopy to remove any articular cartilage flaps. Younger (< 50 years old), very active, or athletic patients, or those who have failed more conservative therapies may elect for a more extensive surgery such as osteochondral autograft (or allograft) transplantation (OAT) or mosaicplasty.

Based on the context provided by the Health Technology Assessment Program, for purposes of this report the acronym OAT will be used to describe the use of cylindrical, dowel-shaped or geometric-shaped plugs of osteochondral material that are press-fit into a defect and do not require the use of screws, pins, plates or other fixation devices. In general they will refer to autologous grafts and the term osteochondral allografting will be used to denote allograft with a focus on cylindrical, dowel shaped or geometric shaped plugs that do not require fixation.

This technical review assesses the evidence on this topic based on the context and key questions provided by the Washington State Health Technology Assessment Program. The following is taken from their published key questions document:

> Significant questions remain about the safety, efficacy and effectiveness, and cost effectiveness of OATS/mosaicplasty cartilage surgery. The choice of suitable patients for OATS/mosaicplasty surgery is controversial because the size and number of damage sites for which it is functional are not well defined, because the harvesting of cartilage from another site or cadaver tissue adds risk and healing issues, and because other, less invasive procedures may be equally effective in the short term (autologous chondrocyte injection). Effectiveness questions particularly center on whether the potential beneficial outcomes of long term pain and functional improvement, prevention of osteoarthritis or further joint deterioration occur with this surgical intervention.

Key questions

The following key questions were provided by the State.

When used in patients with cartilage damage:

1. What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification?
    a. What are the maximum, minimum, and optimum size (volume) of the damage that is suitable for repair using OATS/mosaicplasty?
    b. What are the maximum and optimum number of lesions that can be repaired in a single OATS/mosaicplasty procedure?
    c. Are there other considerations that make OATS/mosaicplasty suitable or unsuitable (age, mobility, comorbidities, BMI)?
    d. Is there a distinction between OATS and mosaicplasty, and a related case definition difference between the two?

e. Is there a distinction between cases where autograft versus allograft OATS/mosaicplasty is preferable?

2. What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?
3. What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)? Including consideration of short term and long term:
    a. Delay or avoidance of progression to osteoarthritis
    b. Impact on function, pain, range of motion, quality of life, activities of daily living and return to work
    c. Longevity of treatment effect
    d. Need for continuing and/or subsequent intervention
    e. Need for extended or continuing physical therapy
    f. Recovery time considering harvest site recovery issues
    g. Differential results from multiple versus single grafts, patterning for multiple grafts (linear arrangement versus circular arrangement)
    h. Differential results between allograft and autograft procedures
    i. Differential results between open and arthroscopic procedures
    j. Differential results in centers of excellence
4. What is the evidence of the safety of OATS surgery? Including consideration of:
    a. Adverse events type and frequency (peri-operative, cartilage plug detachment, cartilage rejection, graft fit, harvest site issues, development of fibrocartilage, mortality, other major morbidity such as DVT, deep infection, and excessive intraarticular bleeding)
    b. Revision/re-operation rates (if not addressed in efficacy)
5. What is the evidence that OATS surgery has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age
    c. Psychological or psychosocial co-morbidities
    d. Baseline functional status: e.g. type of injury or lesion, extent of cartilage damage, specific damage site size, number of damage sites
    e. Other patient characteristics or evidence based patient selection criteria, especially comorbidities of diabetes and high BMI
    f. Provider type, setting or other provider characteristics
    g. Payor/ beneficiary type: including worker's compensation, Medicaid, state employees
6. What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty? Including consideration of:
    a. Costs (direct and indirect) and cost effectiveness
    b. Short term and long term

Methods for evaluating comparative effectiveness

Studies for inclusion were based on the following Patients-Intervention-Comparators-Outcomes, (PICO) summary.

Study Component	Inclusion	Exclusion
Participants	• Persons with cartilage damage	•
Intervention	• Osteochondral autograft transfer system (OATS) • Osteochondral allograft transplantation (OAT-like procedures using dowels, cylinders, plugs) • Mosaicplasty	• Synthetic materials, artificial cement (e.g. Trufit plug, SaluCartilage, Chondrocushion, Hemicap or others) • Perichondrial arthroplasty • Osteochondral grafts as part of plate or screw systems or extensive reconstruction or that use plates, screws or pins for fixation • Cell-based repair (e.g. ACI) • Paste grafting (minced cartilage – allograft or autograft) • Non-FDA approved
Comparators	• Autologous chondrocyte implantation (ACI) • Microfracture surgery • Abrasion arthroplasty • Chondroplasty • Biologic resurfacing • Non-surgical interventions (e.g. physical therapy, viscosity supplementation) • Placebo • Combination of OATS with other procedures (e.g. ACL repair, meniscus transplant/repair, knee alignment, others)	• Non-FDA approved materials • Synthetic materials, artificial cement
Outcomes	• Pain relief • Functional outcomes measures (e.g. Cincinnati Knee Score, Knee Society Score, Lysholm score, WOMAC, American Orthopaedic Foot and Ankle Society, Ankle Osteoarthritis Scale ROM) • Quality of life (e.g. SF-36) • Reoperation • Progression to osteoarthritis • Complications/adverse events • Donor site morbidity and recovery	
Study Design	• Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be sought as the primary evidence base for questions of efficacy, effectiveness and safety. • Validation/reliability studies in the population of	• Case reports • Case series of < 18patients with allograft; case series of <30 patients with autograft unless designed specifically to evaluate safety

	interest for Question 2 • For question 4, safety, case series will be considered if adequate information not available from comparative studies. For inclusion, such studies must specifically evaluate complications, adverse events • Cost effectiveness studies assessing both costs and outcomes (Question 6)	• Cost-only studies • Studies of graft storage and preservation and cell viability • Laboratory studies of cell viability • Studies of the feasibility of diagnostic tests
Publication	• Full-length studies published in English in peer reviewed journals, published HTAs or publically available FDA reports • Full formal economic analyses (e.g. cost-utility studies) published in English in HTAs or in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study that do not report on different outcomes • Single reports from multicenter trials • Studies reporting on the technical aspects of these procedures • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

A formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments was done. This report focuses on the highest quality of evidence available (high quality comparative studies and full economic evaluations) that are published in English in peer-reviewed journals or publicly available FDA reports.
Pertinent studies were critically appraised using the Spectrum Research, Inc. Level of Evidence (LoE) system, which evaluates the methodological quality based on study design as well as factors that may bias studies. An overall Strength of Evidence (SoE) combines the LoE and related assessment of potential for bias, with consideration of the number of studies across different populations and the magnitude and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results

Summary by key question

Information on determination of overall strength of evidence is found in the appendices.

Key question 1: What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification**?**

Consistent or agreed-upon case definitions:

- There is variability with respect to the terms used to describe the various procedures and how they are defined. No specific agreed-upon case definitions were found. Treatment

algorithms (only available for the knee) cite case series. Lesion size and classification appear to be key criteria for assessing treatment options (after ligament and meniscus stability, lesion location and other factors have been determined).

- **Autograft (OAT or mosaicplasty)**: Based on inclusion/exclusion criteria for randomized studies for knee lesions, the most consistent characteristics defining cases for inclusion were: symptomatic (5/5 studies), isolated (4/5 studies) full-thickness lesions or Outerbridge or ICRS grades 3 or 4 lesions (4/5 studies). Exclusion criteria in three of the five studies included knee joint instability or ligamentous deficiency. The mean ages of participants in all studies was <45 years old.
- **Osteochondral allograft (dowel, cylinder, plug)**: No prospective comparative studies were found and limited information is available from three case series. Cases were defined as symptomatic in all three studies.
- Studies designed to evaluate clinical decision-making based on patient or lesion characteristics were not found.
- **Talus**: Only one comparative study was available. Pain and presence of a full thickness lesion as inclusion criteria are consistent with criteria described above for the knee.
- No studies pertaining to other anatomical regions meeting the inclusion criteria were found.

Evidence of validity and reliability (lesion classification systems):

- No validity studies of the Outerbridge or ICRS lesion grading systems in the population of interest were found.
- Overestimation of lesion size by arthroscopy compared with open evaluation was reported in one clinical study. Inexperienced clinicians had less accurate measures.
- Two clinical studies evaluated the reliability of the ICRS grading system using arthroscopy. One study reported 80.9% agreement between arthroscopic and open assessment of grade. Only one study (the smallest) reported chance-adjusted agreement between raters and suggests that there is only fair to slight agreement between raters.
- Inter-rater reliability of the Outerbridge classification was evaluated in one study. The overall agreement beyond chance for the video tapes where surgeons were to discriminate between grades 2 and 3 was moderate (κ range 0.41-0.57). The authors did not apparently evaluate grade 4 lesions to any large extent and thus, application to a case definition which may focus on grades 3 and 4 lesions is not clear.
- No studies for anatomical regions other than the knee were found.

Key question 2: What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?

- Review of the properties of outcomes measures used in included comparative studies is limited to those measures that were examined in samples drawn from the target population (patients with articular cartilage damage). Of these measures, five have been validated in this population:
    - International Cartilage Repair Society (ICRS) cartilage repair assessment

- Lysholm Knee Scoring Scale (LKSS)
- Modified Cincinnati Knee Rating System (MCRS)
- International Knee Documentation Committee subjective knee form (IKDC SKF)
- Knee Injury Osteoarthritis Outcome Score (KOOS)

Four patient-reported and one clinician-based outcomes measures commonly used in studies of patients with cartilage defects in the knee have undergone psychometric analysis in these patients:

- None of the five instruments were adequately tested for validity. Content validity was inadequate for all instruments, primarily because patients with chondral lesions were not involved in item selection in that particular study. Criterion validity was not tested in these studies for any instruments, likely because of the lack of a gold standard criterion. Tests of construct validity were hampered by definitional problems and small sample sizes.
- Reliability was inadequately tested for the three outcome measures that were tested for internal consistency. None of the studies performed factor analysis to assess potential dimensions. While good internal consistency was shown for the KOOS and the ICRS, internal consistency for these instruments was inadequate as too few patients/raters were tested. Similarly, high values for reproducibility were found for the IKDC, the LKSS, and the MCKRS in samples that were too small to meet quality criteria.
- Studies that assessed responsiveness showed strong effect sizes for change from pre-operative to post-operative scores on the IKDC, MCKS, LKSS, and KOOS. However, quality criteria also require that these effect sizes be supported by comparison of the minimally important clinical difference with the smallest detectable difference, analysis of receiver operating curves, or other supporting analysis. Only one study,[2] which analyzed the IKDC and MCKS, met this criterion.
- The minimal clinically important difference (MCID) for pre-op to post-op improvement was determined in one study to be from 6.3 points (6 months follow-up) to 16.7 points (12 month follow-up) on the IKDC and 14.0 points (6 months) and 26.0 points (12 months) on the MCKRS. The MCID was not reported for any other measures in patients with cartilage damage.

Key question 3: What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)?

Efficacy: Summary of findings for autograft OAT/mosiacplasty in the knee

Two small RCTS (LoE IIb) in younger populations compared OAT with microfracture and three RCTs (or quasi RCTs, LoE IIb) compared OAT/mosaicplasty with ACI in general (older) populations. There were substantial differences in patient populations, lesion sizes, comparators and outcomes measures used across studies, making it difficult to draw overall conclusions.

Function:

- Compared with microfracture (MF), OAT was associated with better patient-reported (based on ICRS), and clinician-reported (based on HSS) functional outcomes in young athletes and children based on two small RCTs (total n = 104).[3,4]

- For comparisons with ACI, three poor quality RCTs in general (older) populations reported functional outcomes. Two small, poor quality RCTs suggest that function based on patient-reported outcomes (LKSS and a modification of it) was better for OAT compared with ACI, however statistical significance was reached in only one of the RCTs[5] (n = 40) and in the other RCT,[6] conclusions are difficult given the significant loss to follow-up (50%). The largest RCT[7] (n = 100) reported that a significantly smaller proportion of participants receiving mosaicplasty had excellent or good results based on the author's modification of the Cincinnati Rating Scale. One of the smaller RCTs reported no significant differences in the Meyer score. Both these studies included substantial proportions of participants who had prior surgeries (94% and 45% respectively).

Longevity of treatment effect

Three small RCTs provided data to assess the longevity of treatment effects:

- Compared with microfracture (MF), in young athletes (n = 57) initial improvements in function (based on ICRS and HSS scores) in OAT recipients were sustained or slightly improved up to 36 months with sustained statistical differences between OAT and MF. Among children (n = 47) receiving OAT, following initial improvement at 12 months, ICRS scores decreased slightly, but remained stable up to 48 months. Scores for MF recipients waned substantially after 12 months and the statistical differences in treatment effects between OAT and MF were sustained over time.
- Compared with ACI, in a general population (n = 40) functional scores for both OAT and ACI increased over time for the Lysholm, Tegner and Myers scores; however, only for the Lysholm Knee Scoring Scale were significant differences between treatment sustained over time favoring OAT.

Return to work or pre-injury activity levels

- Two RCTs reported on this. In both young athletes and children, a greater proportion of patients treated by OAT versus MF had returned to pre-injury activity levels at specified time points as follows: for young athletes at 6.5 months – OAT: 93% had returned versus MF: 52%; and in children at 11.7 (OAT) and 14.1 (MF) months – OAT: 84% had returned to activity versus MF: 32%).

Differential results between open and arthroscopic procedures or other factors

- No studies directly compared the effects of open versus arthroscopic procedures.
- No data were available from RCTs regarding the effect of OAT/mosaicplasty on the following: delay or avoidance of progression to osteoarthritis, pain, range of motion, quality of life, activities of daily living, the need for continuing and/or subsequent intervention, the need for extended or continuing physical therapy, recovery time considering harvest site recovery issues, differential results from multiple versus single

grafts or patterning for multiple grafts, differential results between allograft and autograft procedures, and differential results in centers of excellence.

Effectiveness: Summary of findings for autograft OAT/mosiacplasty in the knee and ankle
There were substantial differences in patient populations, comparators and outcomes measures used across studies. All studies are likely affected by confounding by indication. Given the high potential for bias in these studies, no firm conclusions can be drawn.

OAT versus matrix assisted chondrocyte transplantation (MACT) (Knee):

- One small study (N =18) eported a significant difference in mean post-operative score (assessed by Modified Lysholm Knee Scoring Scale) between treatment arms favoring MACT. In general, clinician- and patient-reported functional outcomes as well as quality of life measures were comparable between treatment arms. Differences in pre-operative function (which were not assessed) could be influencing differences (or lack thereof) in post-operative function.

OAT/mosaicplasty in combination with another versus other treatment alone (Knee):

- OAT plus ACL reconstruction versus ACL reconstruction alone: there were no differences in improvement in any functional outcomes between treatment groups in one study (N =53).[8]
- OAT plus realignment versus realignment alone: improvement in range of motion appeared to be substantially greater among patients treated by OAT with realignment; however, there was no difference in improvement in the other functional outcome assessed in one study (N =49).[9]

Effectiveness: Summary of findings for allograft (using dowel, cylinder, plug)
Osteochondral allograft (OA) using dowel, cylindrical or geometric shaped plugs which did not require use of plates, screws or other hardware were considered to be most consistent with the autograft OATS procedure. Two small comparative studies (LoE III) and six case series (LoE IV) of such procedures provide the focus.

- Comparative studies:
  - No statistically significant differences between treatment groups were reported for most outcomes measures across two small studies (N = 70 total).
  - Tegner scores were improved for OA recipients compared with loose body removal and arthroscopic reduction and internal fixation in one study, and SF-12 Mental Component Scores were significantly improved in patients who received OA and MAT compared with OA and ACI in the other.
- Case series:
  - Various patient-reported, clinician-based outcomes and quality of life measures were used across studies and generally indicated improved function following the allograft procedure compared with pre-operative values.
  - One study (N = 65) reported a 91% survival rate of grafts at 5 years and 76% at both 10 and 15 years.

Key question 4: What is the evidence of the safety of OATS surgery?

Reporting of procedural and longer-term outcomes was inconsistent, even among the randomized controlled trials. Some complications, such as donor site morbidity, might be undetected unless specifically targeted for evaluation. Differences across studies in patient characteristics and (for comparative studies) comparative procedures, coupled with small numbers of patients in some studies, create misleading percentages for various complications. Because a large proportion of patients had surgery on the joint prior to the graft procedure and/or had other surgery at the same time as the graft procedure, complications and failed results cannot necessarily be attributed to a single procedure. In case series, the lack of a comparison group prevents drawing conclusions about the effects of these procedures on longer-term problems such as development of arthritis.

Safety: Osteochondral autograft transplantation (OAT/mosaicplasty)

Three RCTs, three nonrandomized comparative studies, and five case series of osteochondral autograft are summarized as follows:

- Surgical complications (infection, deep vein thrombosis, and hemarthrosis) are infrequent (<7%) and effectively treated in the short term.
- Re-operations following failed procedures were not uncommon across all studies. In three RCTs, revisions of OAT procedures were rare and were performed significantly less often than revisions following microfracture (1% vs. 33%). Other procedures such as debridement and release of adhesions were performed after graft surgery in 8% of OATs patients in RCTs. In case series, rates of all re-operations following OATs were 17% across seven case series, for a variety of procedures including arthroscopic debridement, revision or replacement grafting, meniscectomy, joint fusion, and total knee arthroplasty.
- Rates of donor site morbidity were 10% in two RCTs and 11% across three case series. In five case series that specifically examined donor site morbidity, two studies, both of young male competitive athletes, reported no long-term morbidity. The other three studies reported significant impact on pain and function up to four years post-surgery, as well as MRI findings suggestive of incipient arthritis.
- MRI findings from one RCT included the presence of subchondral cysts in 8% of OATS patients, a rate significantly lower than that of microfracture patients (33%). The significance of these cysts is unknown, however, as they may be a consequence of heat production during drilling. Other MRI findings from case series include the presence of bone marrow edema in half of patients (decreasing to 15% over approximately two years) and synovitis with joint effusion in 73% of patients (decreasing to 23%).
- None of the RCTs reported on progression of osteoarthritis. In three case series that detected progression of osteoarthritis radiographically, progression of osteoarthritis occurred in 30% of patients across studies; however, without a comparison group and information on potential confounding factors, it is not possible to determine the influence of the graft procedure.
- No deaths directly attributable to OAT were found in the studies reviewed. Most of these procedures were conducted among patients who were relatively young (< 50 years old).

Safety: Osteochondral allograft (OA) transplantation (OAT-like procedure with dowel, cylindrical or plugs without hardware use)

The findings of two nonrandomized comparative studies and six case series of osteochondral allograft transplantation are summarized below:

- Only two studies reported on surgical complications, which were rare (one infection and one hyperergic reaction).
- Rates of all re-operations following OA were 12.5% across seven studies, for a variety of procedures including arthroscopic debridement, revision or replacement grafting, meniscectomy, ligament reconstruction, and unicompartmental or total knee arthroplasty.
- Although two studies assessed arthritis on radiographs at follow-up, neither study could determine whether these findings represented progression from pre-operative levels.
- The rate of graft failure was 21% in two studies that used radiographs to detect collapse or fragmentation of the graft[10] or other indicators of failure including sclerosis or joint narrowing. [11]
- Allograft transplantation carries an extremely small potential risk of disease transmission from the donor tissue, which is strenuously screened, tested, and sterilized. [12,13]The last reported case of disease transmission from allograft tissue of any type occurred in 2002, before the advent of nucleic acid testing and polymerase chain reaction, when an anti-HCV–negative donor was the source of HCV infection for 8 of 30 recipients of organs or tissues.[14] No study of disease transmission related to osteochondral allograft was found in our search.
- No deaths directly attributable to allograft procedures were found in the studies reviewed.

Key question 5: What is the evidence that OATS surgery has differential efficacy or safety issues in sub populations?

Efficacy/efficacy: Autograft OAT/Mosaicplasty

- None of the RCTs assessed differential efficacy based on gender, psychological/psychosocial co-morbidities, provider type or payer/beneficiary type.
- Direct comparisons within RCTs are limited.
    - Age: One RCT reported that younger athletes (< 30 years) had better functional outcomes than older athletes.[3]
    - Defect size: Two RCTs reported that functional outcomes were comparable among patients who received OAT regardless of defect size, but among patients who received microfracture (MF), those with defects lager than 2 cm^2 had worse functional outcomes.[3,4]
    - Defect type: One RCT reported that patients with full thickness articular cartilage defects had significantly better functional outcomes than did patients with osteochondritis dissecans (OCD) defects ($p = 0.04$).[3]
    - Defect location: One RCT reported that MF patients with lesions in the central part of the medial femoral condyle (MFC) had worse clinical results than patients with lesions in other areas of weight-bearing parts of the knee joint (based on ICRS score) ($P < 0.05$); however, there was no association between lesion location and clinical results among OAT patients ($P < 0.85$).[3] One additional RCT reported that among patients with lesions of the medial femoral condyle, a greater

proportion of patients treated by ACI had an excellent or good result, compared to patients treated by mosaicplasty.

- Indirect comparisons across RCTs may suggest that patient and clinician-reported functional outcomes were better for OAT/mosaicplasty among younger patients and among patients with no prior surgical intervention. However, such comparisons should be interpreted cautiously given differences in the populations studied, study quality, and the comparators used.
- From nonrandomized studies there is limited evidence on differential effectiveness.
    - No direct comparisons for any factor were made in nonrandomized comparative studies.
    - Case series and prognostic studies indirectly suggest that younger patients may experience better function and be able to return to sports. A systematic review of primarily case series suggests OAT recipients return to sport earlier than those receiving other treatments. Better functional outcomes may occur with one plug versus multiple plugs based on two small studies. Lesion location may influence outcome.

Efficacy/efficacy: Osteochondral allograft transplantation using OAT-like procedures (dowel/cylinder/plug)

- There were no RCTs of allografts. There were conflicting results from two case series with regard to the influence of sex on outcomes. In one series, patients with grafts implanted ≤ 28 days after procurement may have better outcomes and those with neutral alignment may have better scores. Small sample size needs to be considered.

Safety: No evidence from direct assessments was found

- None of the comparative studies (RCTs or cohort studies) directly assessed differential safety by any patient factors, lesion characteristics or other factors.
- Several case series indicated that older patients may have more risk of allograft failure.
- Although there may be differential allograft failure for lesions of different etiology, the small numbers of patients with lesions of different causes makes comparisons difficult.
- Results of two case series suggested that grafts of larger lesions, which require larger and/or more grafts, are more likely to fail.
- There is conflicting information regarding the influence of the number and size of plugs on donor site morbidity for autograft recipients.
- In one larger series (N=123), significantly more persons on Workers' Compensation experienced allograft failure.
- It is difficult to disentangle the differential effects of lesion size, number of grafts, and lesion etiology. Larger lesions require a greater number of grafts, and lesion etiology can also be related to lesion size. Lesions caused by osteochondritis dissecans tended to be larger than posttraumatic lesions, and larger lesions required a greater number of plugs.

Key question 6: What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty?

No full economic studies directly addressing the cost-effectiveness of either autograft or allograft osteochondral transplantation as described in this report were found.

Summaries of overall strength of evidence (SoE) by key question

Table 1. Summary of evidence for Key Question 1: Case Definition

Key Question 1: Consistent or agreed upon case definitions; evidence of reliability and validity		
	SoE	**Conclusions/Comments**
	No evidence	• There is variability with respect to the terms used to describe the various procedures and how they are defined. • No specific agreed-upon case definitions were found. Treatment algorithms (only available for the knee) provide no citations or cite case series. • Lesion size and classification appear to be key criteria for assessing treatment options (after ligament and meniscus stability, location and other factors have been determined).
Autograft – RCT inclusion criteria	**No evidence**	• The most consistent characteristics defining cases for inclusion in the included RCTs were: symptomatic (5/5 studies), isolated (4/5 studies) full-thickness lesions or Outerbridge or ICRS grades 3 or 4 lesions (4/5 studies). Exclusion criteria in three of the five studies included knee joint instability or ligamentous deficiency. The mean ages of participants in all studies was <45 years old.
Allograft	**No evidence**	• No prospective comparative studies were found. From three (reportedly prospective) case series, cases were defined as symptomatic. Few specific inclusion/exclusion criteria were provided.
Validity and reliability	**Very low**	• No validation studies in the population of interest were found for any specific case definition or for the primary lesion classification schemes (Outerbridge, ICRS). • Overestimation of lesion size by arthroscopy compared with open evaluation was reported in one clinical study. • Only one of two clinical studies evaluating the reliability of the ICRS grading system evaluated agreement beyond chance and the agreement was fair to slight. • One study reported moderate agreement between surgeons in discriminating between Outerbridge grades 2 and 3.

Table 2. Summary of Evidence for Key Question 2: Outcomes Measures

Key Question 2: Validated instruments for measuring treatment outcomes		
	SoE	Conclusions/Comments

Measures	**Very low**	Four patient-reported and one clinician-based outcomes measures commonly used in patients with cartilage defects in the knee have undergone psychometric analysis in these patients. Measures: • International Cartilage Repair Society (ICRS) cartilage repair assessment • Lysholm Knee Scoring Scale (LKSS) • Modified Cincinnati Knee Rating System (MCRS) • International Knee Documentation Committee subjective knee form (IKDC SKF) • Knee Injury Osteoarthritis Outcome Score (KOOS)
Validity	**Very low**	None of the five instruments were adequately tested for validity.
Reliability	**Very low**	Reliability was inadequately tested as sample sizes were small and did not meet the quality criteria.
Responsiveness	**Very low**	Only one study, which analyzed the IKDC and MCKS, met this criterion.
MCID	**Very low**	The MCID for pre-op to post-op improvement was determined in one study for both the IKDC and the MCKRS.

Table 3. Summary of Evidence for Key Question 3: Efficacy and Effectiveness

Key Question 3: Efficacy and effectiveness - AUTOGRAFT		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus microfracture		
Efficacy	**Low**	• **Two poor quality RCTs** (N=104 total), one in young athletes, the other in children. • **Function**: OAT was associated with statistically better patient-reported and clinician-reported outcomes. • **Longevity of treatment effect:** Differences between treatments remained significant up to the last follow-up (maximum 48 months). Functional scores in young athletes improved for OAT recipients up to 36 months. In children following initial improvement at 12 months, ICRS scores decreased slightly, but remained stable up to 48 months. • **Return to activity:** A greater proportion of patients treated by OAT versus MF had returned to pre-injury activity levels at pre-specified time points.
Effectiveness	**No evidence**	• No nonrandomized comparative studies were found.
AUTOGRAFT: OAT/mosaicplasty versus autologous chondrocyte implantation (ACI)		
Efficacy	**Low**	• **Two poor quality RCTs** in general (older) populations were found. One enrolled >40% of participants who had prior surgeries (N =140 total). In the **other RCT,** ≥50% of persons did not receive treatment (n treated = 23/44 randomized), as authors reported "spontaneous improvement" in the six months following initial debridement. • **Function:** Patient-reported outcomes were better for OAT/mosaicplasty but statistical significance was not uniformly achieved in the two small RCTS. In the largest RCT (n = 100) a significantly smaller proportion of participants receiving mosaicplasty had excellent or good outcomes (author's modification of the Cincinnati Rating Scale) and one of the smaller RCTs reported no significant differences in the Meyer score. Both

Key Question 3: Efficacy and effectiveness - AUTOGRAFT		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus microfracture		
		these studies included substantial proportions of participants who had prior surgeries. Differences in outcomes measures used makes comparison across studies difficult. • **Longevity of treatment effect:** In one study (N =40), functional scores for both OAT and ACI increased over time for the Lysholm, Tegner and Myers scores; only for the Lysholm Knee Scoring Scale were significant differences between treatment sustained over time favoring OAT.
Effectiveness	**No evidence**	• No nonrandomized comparative studies for this comparison were found.

Key Question 3: Efficacy and Effectiveness –AUTOGRAFT- EFFECTIVENESS		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus various treatments **Nonrandomized comparative studies**		
Effectiveness: ANKLE	**Very Low**	• No randomized controlled trials were found so efficacy cannot be evaluated. • One small poor quality cohort (N= 32) reported differences in functional outcomes (assessed by AOFAS or SANE Scores) between OAT and chondroplasty or OAT and microfracture; however, 24-hour post-operative pain was greater among patients treated by OAT.
Effectiveness: **KNEE**	**Very low**	• Four small, poor quality nonrandomized studies compared OAT alone or in combination with other procedures. Confounding by indication was present in all and heterogeneity across studies precludes effective comparison across them. • For most functional outcomes, there were no differences between treatment groups. o In one small (N =18) study, post-operative mean Modified Lysholm score was significantly less for OAT versus matrix assisted chondrocyte transplantation (MACT). o Range of motion appeared to be substantially greater among patients treated by OAT with realignment versus realignment alone in another study (n =49)

Key Question 3: Efficacy and Effectiveness - ALLOGRAFT		
	SoE	**Conclusions/Comments**
Osteochondral allograft using primarily press-fit dowel/cylinder or plug (not requiring hardware)		
Efficacy	**None**	• No randomized controlled trials were found.
Effectiveness	**Very low**	• Comparative studies: No statistically significant differences between treatment groups were reported for most outcomes measures across two small studies (N = 70 total). Tegner scores were improved for OA recipients compared with loose body removal and arthroscopic reduction and internal fixation in one study, and SF-12 Mental Component Scores were significantly improved in

Key Question 3: Efficacy and Effectiveness - ALLOGRAFT		
	SoE	**Conclusions/Comments**
Osteochondral allograft using primarily press-fit dowel/cylinder or plug (not requiring hardware)		
		patients who received OA and MAT (meniscal allograft transplantation) compared with OA and ACI in the other. • Case series of >19 patients which primarily used press-fit plugs (dowel/cylinder/geometric) without use of fixation • Various patient-reported, clinician based outcomes and quality of life measures were used across studies and generally indicated improved function and quality of life following the allograft procedure compared with pre-operative values. • One study reported a 91% survival rate of grafts at 5 years and 76% at both 10 and 15 years (N =65).

Table 4. Summary of Evidence for Key Question 4: Safety

Key Question 4: Safety		
	SoE	**Conclusions/Comments**
Autograft		
	Low	• Data from three RCTs, 3 nonrandomized comparative studies, and 5 case series of osteochondral autograft transfer were used • Surgical complications (infection, deep vein thrombosis, and hemarthrosis) are infrequent (<7%). • In 3 RCTs, revisions of OAT procedures were performed significantly less often than revisions following microfracture (1% vs. 33%). Re-operations following OATs were 17% across seven case series (variety of procedures). • Rates of donor site morbidity were 10% in two RCTs and 11% across three case series. • No deaths directly attributable to OAT were found in the studies reviewed.
Allograft		
	Low	• Rates of all re-operations following OATs were 12.5% across seven studies. • Rate of graft failure was 21% in two studies that used radiographs. • Allograft transplantation carries an extremely small potential risk of disease transmission. No study of disease transmission related to osteochondral allograft was found in our search.

Table 5. Summary of Evidence for Key Question 5: Differential efficacy, effectiveness and safety

Key Question 5: Differential Efficacy, Effectiveness and Safety		
	SoE	**Conclusions/Comments**
Efficacy	**Low**	• Direct comparisons within RCTs are limited and may suggest that age, defect size, and defect location may influence outcomes • Indirect comparison of factors is challenging given differences in the populations studied, study quality the comparators used.
Effectiveness	**Very low**	• No direct comparisons for any factor were made in nonrandomized

Key Question 5: Differential Efficacy, Effectiveness and Safety		
	SoE	**Conclusions/Comments**
		comparative studies • Indirect comparisons based on case series of **autograft** OATS/mosaicplasty suggest that younger patients may experience better function and be better able to return to sports. Better functional outcomes may occur with one plug versus multiple plugs based on two small studies. Lesion location may influence outcome. • **Allograft**: Limited information from two case series is conflicting with regarding the influence of gender.
Safety	**Very low**	• No comparative studies of autograft or allograft transplantation assessed differential safety • Results of case series of autograft and allograft transplantation suggested that older patients may have more risk of graft failure and that grafts of larger lesions were more likely to fail.

Table 6. Summary of Evidence for Key Question 6: Economic

Key Question 6: What is the evidence of cost implications and cost-effectiveness		
	SoE	**Conclusions/Comments**
	No evidence	• No full economic studies directly addressing the cost-effectiveness of either autograft or allograft osteochondral transplantation as described in this report were found.

Appraisal

Rationale

This technical review will assess the evidence on this topic based on the context and key questions provided by the Washington State Health Technology Assessment Program. The following is taken from their published key questions document:

> Significant questions remain about the safety, efficacy and effectiveness, and cost effectiveness of OATS/mosaicplasty cartilage surgery. The choice of suitable patients for OATS/mosaicplasty surgery is controversial because the size and number of damage sites for which it is functional are not well defined, because the harvesting of cartilage from another site or cadaver tissue adds risk and healing issues, and because other, less invasive procedures may be equally effective in the short term (autologous chondrocyte injection). Effectiveness questions particularly center on whether the potential beneficial outcomes of long term pain and functional improvement, prevention of osteoarthritis or further joint deterioration occur with this surgical intervention.

Objective

The primary aim of this assessment is to systematically review, critically appraise and analyze available research evidence comparing the efficacy, effectiveness and safety of autograft and allograft OAT/mosiacplasty procedures. Available information on the economic impact of this will also be summarized and critically appraised.

Key questions

When used in patients with cartilage damage:

1. What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification?
    a. What are the maximum, minimum, and optimum size (volume) of the damage that is suitable for repair using OATS/mosaicplasty?
    b. What are the maximum and optimum number of lesions that can be repaired in a single OATS/mosaicplasty procedure?
    c. Are there other considerations that make OATS/mosaicplasty suitable or unsuitable (age, mobility, comorbidities, BMI)?
    d. Is there a distinction between OATS and mosaicplasty, and a related case definition difference between the two?
    e. Is there a distinction between cases where autograft versus allograft OATS/mosaicplasty is preferable?

2. What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?

3. What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)? Including consideration of short term and long term:
    a. Delay or avoidance of progression to osteoarthritis
    b. Impact on function, pain, range of motion, quality of life, activities of daily living and return to work
    c. Longevity of treatment effect
    d. Need for continuing and/or subsequent intervention
    e. Need for extended or continuing physical therapy
    f. Recovery time considering harvest site recovery issues
    g. Differential results from multiple versus single grafts, patterning for multiple grafts (linear arrangement versus circular arrangement)
    h. Differential results between allograft and autograft procedures
    i. Differential results between open and arthroscopic procedures
    j. Differential results in centers of excellence

4. What is the evidence of the safety of OATS surgery? Including consideration of:
    a. Adverse events type and frequency (peri-operative, cartilage plug detachment, cartilage rejection, graft fit, harvest site issues, development of fibrocartilage, mortality, other major morbidity such as DVT, deep infection, and excessive intraarticular bleeding)
    b. Revision/re-operation rates (if not addressed in efficacy)

5. What is the evidence that OATS surgery has differential efficacy or safety issues in sub populations? Including consideration of:
    a. Gender
    b. Age
    c. Psychological or psychosocial co-morbidities
    d. Baseline functional status: e.g. type of injury or lesion, extent of cartilage damage, specific damage site size, number of damage sites
    e. Other patient characteristics or evidence based patient selection criteria, especially comorbidities of diabetes and high BMI
    f. Provider type, setting or other provider characteristics
    g. Payor/ beneficiary type: including worker's compensation, Medicaid, state employees
6. What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty? Including consideration of:
    a. Costs (direct and indirect) and cost effectiveness
    b. Short term and long term

Primary outcomes

The focus of this report is on patient-centered outcomes. Patient-reported and clinician-based outcomes measures as well as quality of life outcomes are the emphasis for the evaluation of efficacy, effectiveness and where applicable, safety. Specific outcomes measures are further

described in results from key question #2. Although the gold standards for assessing regeneration of tissue following grafting procedures are second-look arthroscopy and cartilage biopsy, these were considered intermediate outcomes. [In addition, these procedures were generally done in fewer than 60% of the participants in included studies and were frequently done for the evaluation of extended symptoms or other concerns. Thus, data from these were not considered reliable.]

For safety, information on complications, revisions, donor site morbidity, adverse events, repeat procedures, persistent pain and progression to arthritis was sought. For full economic evaluations, incremental cost-effectiveness ratios are desirable.

Key considerations highlighted by clinical experts

Interventions:
Over the past several decades, a variety of methods have been developed to treat full-thickness cartilage defects. Although several systematic reviews [15-17] have sought to evaluate the published literature to consider recommendations for options which may be best for treating specific lesions, most have concluded that there is limited high quality evidence on which to base clinical decisions. Most surgeons consider the indications for treatment of lesions with autograft versus allograft to be different. In general, choices of when to use what treatment are controversial and influenced primarily by surgeon experience and preferences.[18]

Practice patterns and recommendations may have changed since the earlier trials have been published. Performing immediate marrow stimulation or OAT/mosaicplasy may be more in line with current practice versus waiting six months for performing a definitive procedure. Thus, some result from the Dozin trial[6] may not reflect more current practice.

Based on the existing literature, some experts have stated that "the prime indication for mosaicplasty is for chondral or osteochondral lesions in the range of 1-4 cm^2".[19] Some have suggested that the low success rates for mosaicplasty observed in the trial by Bentley[7] may be in part be due to the mean lesion size being greater than the recommended 4 cm^2 as well as use of non-standard postoperative recommendations for weight-bearing and passive motion device use.[20]

Patient considerations:
A variety of patient characteristics must be considered when determining what repair procedure may be best. The procedure choice should be tailored to the patient. Lesion size and extent of the defect are key considerations. Lesion location and etiology must be considered. The patient's symptoms, activity level, age and BMI are considered important in assessing patient suitability for a given repair option. Younger patients who are not overweight are considered the best candidates for OAT (allograft or autograft). In addition, stability of the ligaments and the

meniscus of the knee are important considerations. In patients with injuries of these structures, concurrent or staged procedures may be frequently performed with the osteochondral transplantations. Athletes are a group for which OAT (allograft or autograft) is considered a good option for osteochondral defect repair, depending on other presenting features. Active patients experience a faster return to activity following osteochondral transplantation and seem to be very satisfied with their results.

Professional considerations

OAT using cylindrical (dowel) plugs requires special tools (e.g Arthrex OATS set). For autograft OAT, the main disadvantage is the availability of grafts and the technical demands of the procedure. [21] Allograft offers the advantage of greater availability of graft material without issues related to donor site problems. Larger grafts can be taken from cadaver donors and allografting is considered to be preferable for large lesions.

Clinical study considerations

Designing and executing high quality clinical studies for orthopedic surgical procedures for osteochondral defect repair may be challenging. The low frequency of isolated symptomatic focal defects, frequent comorbidities, documentation of techniques and products are a few of these challenges. None-the-less, there is a need for high quality studies. The International Cartilage Repair Society (ICRS) has made recommendations for addressing methodological limitations of studies on cartilage repair.[22]

Washington State utilization and cost data

Information in this section was provided by the Washington State Health Technology Assessment Program.

Mosaicplasty data presented below represents only "knee" procedures, which can be identified by procedure code (see Related Medical codes below). "Day of surgery" charges were used in all calculations.

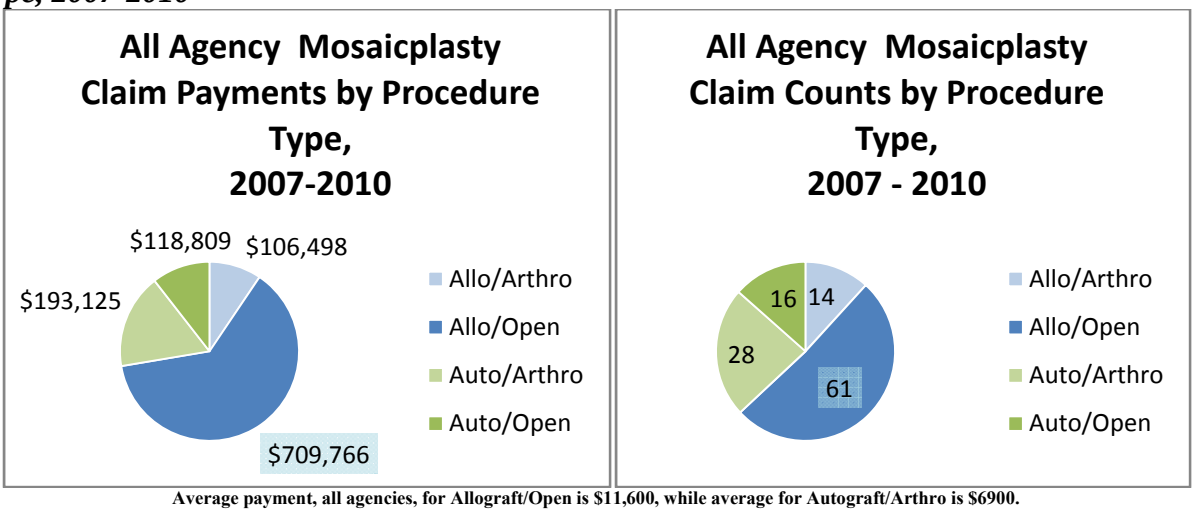
State Agency Data 1: Combined Agency Mosaicplasty Costs and Counts, 2007-2010

Member/ Claimant Counts	2007	2008	2009	2010	4 yr Total
PEB	4	5	5	6	20
L&I	18	17	19	21	73
DSHS	2	2	1	2	7
All Agencies	**24**	**24**	**25**	**29**	**100**

Total Amount Paid	2007	2008	2009	2010	4 yr Total
PEB	$36,111	$78,893	$115,758	$72,266	$303,028
L&I	$180,701	$181,999	$196,137	$237,408	$796,245
DSHS	$11,558	$13,392	$3,886	$90	$28,926
All Agencies	**$228,370**	**$274,284**	**$315,781**	**$309,764**	**$1,128,199**
Average Paid per Member	**2007**	**2008**	**2009**	**2010**	**4 Year Average**
PEB	$9,028	$15,779	$23,152	$12,044	$15,151
L&I	$10,039	$10,706	$10,323	$11,305	$10,907
DSHS	$5,779	$6,696	$3,886	$45	$4,132
All Agencies	**$9,515**	**$11,429**	**$12,631**	**$10,682**	**$11,282**

PEB - Public Employee Benefits
L&I - Department of Labor and Industry
DSHS - Department of Social and Health and Services

State Agency Data 2: All Agency Mosaicplasty Claim Payments and Counts by Procedure Type, 2007-2010

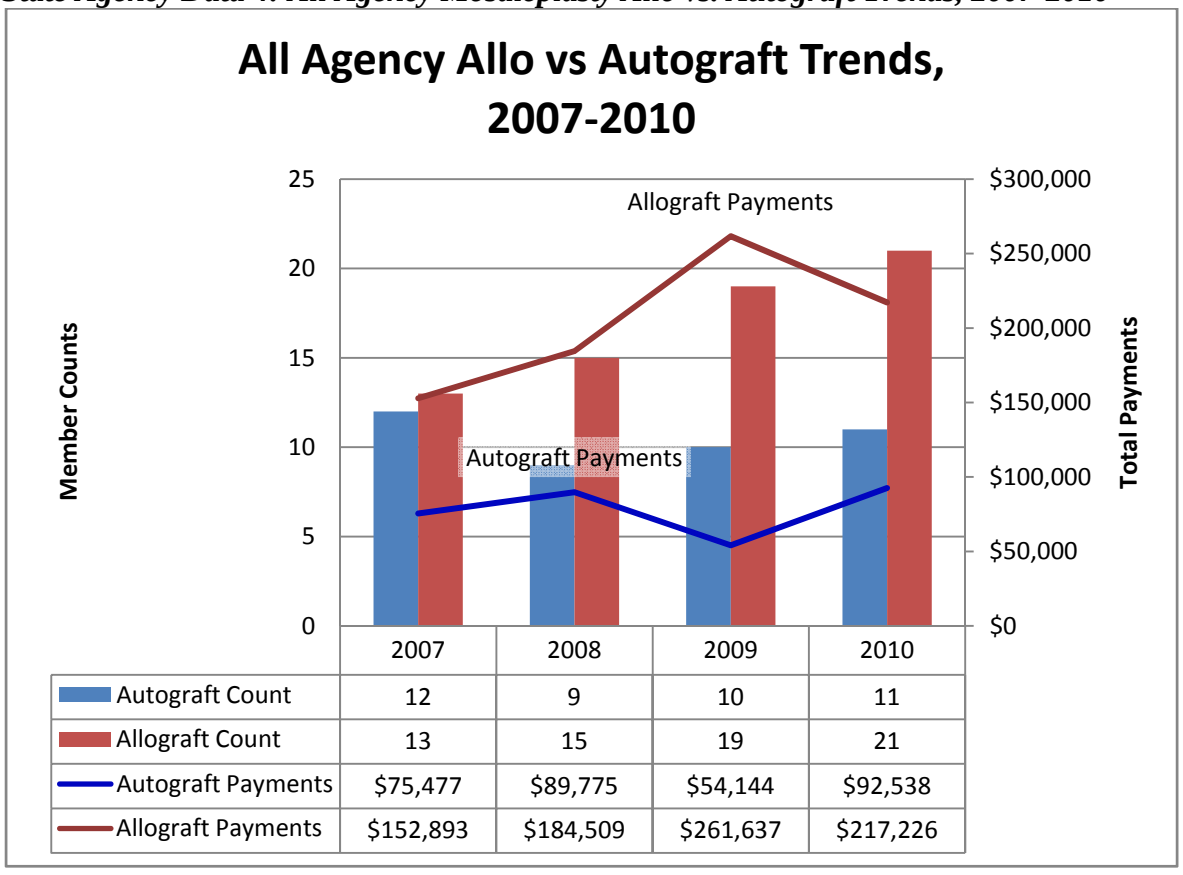


Average payment, all agencies, for Allograft/Open is $11,600, while average for Autograft/Arthro is $6900.

State Agency Data 3: All Agency Top 10 Diagnosis Codes, 2007-2010

Diagnosis Description	Payment Total	% Total Payments	Claim Count	% Total Claims
OSTEOCHONDRIT DISSECANS	$407,860	36.2%	41	41.0%
ACQ DEFORMITY NEC	$90,104	8.0%	10	10.0%
BONE & CARTILAGE DIS NEC	$73,789	6.5%	5	5.0%
OSTEOCHONDROPATHY NOS	$59,277	5.3%	7	7.0%
CHONDROMALACIA	$49,253	4.4%	7	7.0%
CHONDROMALACIA PATELLAE	$43,727	3.9%	7	7.0%
INT DERANGEMENT KNEE NOS	$37,551	3.3%	5	5.0%
JOINT DIS NOS-L/LEG	$34,614	3.1%	4	4.0%
DERANGEMENT MENISCUS NEC	$33,385	3.0%	2	2.0%
SPRAIN OF KNEE LEG NOS	$31,163	2.8%	3	3.0%

State Agency Data 4: All Agency Mosaicplasty Allo vs. Autograft Trends, 2007-2010



State Agency Data: Mosaicplasty ER Visit Codes, 2007-2010

In L&I data, 5 claimants (out of 73 total) which had 12 emergency room visits on one or more days in the 7 days after surgery.
DSHS data, consisting of only 7 claims for mosaicplasty, included 2 emergency room visits for 2 patients, one two days after surgery, and one 4 days after surgery.

Related Medical Codes			
Code Type	**Codes**	**Short Description**	**Additional Info**
Comorbidity	ICD-9		
	715-715.9	Osteoarthritis	Comorbidity
Treatments	CPT		
	27415	Osteochondral allograft, knee, open	Mosaicplasty
	27416	Osteochondral autograft(s), knee, open (eg. mosaicplasty) (includes harvesting of autografts)	Mosaicplasty
	29866	Arthroscopy, knee, surgical; osteochondral autograft(s) (eg. mosaicplasty) (includes harvesting of the autografts)	Mosaicplasty
	29867	Arthroscopy, knee, surgical; osteochrondral allograft (eg mosaicplasty)	Mosaicplasty

1. Background

1.1 The condition

Articular cartilage is a hard, white shiny material that allows the bones that coincide at joints to glide easily along each other as the joint moves. This articular hyaline cartilage is found in the knees, ankles, shoulders, elbows, and fingers. The special nature of articular cartilage, however, makes it particularly vulnerable once it becomes damaged. Articular cartilage has no blood supply, so it cannot heal on its own. This cartilage also has no nerve supply, so early injuries are not easily detected. Articular cartilage damage can involve only the cartilage (chondral) or the damage can involve both the cartilage and the underlying subchondral bone (osteochondral). If untreated, these defects or lesions may lead to osteoarthritis and severe disability.

Osteochondral defects

A 1999 case study reported that over 900,000 Americans experience chondral lesions of the knee annually, resulting in over 200,000 surgical procedures for the high-grade lesions.[1] The natural history of chondral lesions is unknown, but some studies have shown that shown that cartilage injuries have over a 50% chance of becoming symptomatic. The clinical progression depends upon many factors, including the lesion location, size, and depth, in addition to patient comorbidities and previous surgical treatments.[21] Although the association is as yet unproven, results of one study suggest that knee cartilage defects might play a role in early knee osteoarthritis.[23]. One longitudinal study showed that the risk factors for the progression of cartilage defects were similar to the risk factors for knee osteoarthritis.[24]

In a retrospective analysis of 25,124 knee arthroscopies between 1989 and 2004, chondral lesions were found in 60% of the arthroscopies.[25] Of these chondral lesions, 67% were classified as localized focal osteochondral or chondral lesions, 29% as OA, 2% as osteochondritis dissecans (OCD), and 1% as other types. A prior knee injury was confirmed in 90% of these cases. In another study of 993 consecutive knee arthroscopies, articular cartilage pathology was found in 66% of patients, with 11% of these knees showing localized, full-thickness lesions.[26]

There are several ways in which the articular cartilage can be damaged. **Trauma** is one cause: a sudden or direct blow to the cartilage, such as falling directly onto the knee joint, can cause a chondral lesion. In the above-mentioned analysis of 25,124 knee arthroscopies, the onset of symptoms was of a traumatic, non-contact origin in 58% of the cases, with 45% of the cases connected with a sport.[25]

Another cause is a repetitive **microtrauma** to one specific area of the joint. Flanigan (2010) conducted a systematic review and found the prevalence of chondral defects in athletes' knees to be 36%.[27] Paley (2000) found that the prevalence of high-grade articular cartilage injury in high-

level overhand throwing athletes, including baseball and football players, was 17% in throwers, all located near the insertion of the supraspinatus tendon.[28] In an examination of 1,802 young baseball players 8–12 years of age, 27% had elbow tenderness and/or vagus stress pain. Overall, 6.7% of the total participants were found to have osteochondral lesions, although less than one-third of the symptomatic patients received diagnostic radiographs.[29]

A less common cause of chondral lesions is a condition known as **osteochondritis dissecans** (OCD). Although the etiology remains unclear, it is likely multifactorial, with family history, growth disorders, ischemia, trauma, repetitive microtrauma[30], abnormal ossification, and ischemia [Hixon 2000] theorized as possible factors. A focal area of subchondral bone undergoes necrosis, with the overlying cartilage remaining fully or partially intact. As the necrotic bone is resorbed, the cartilage loses its supporting structure and the bony fragment can be displaced into the joint space [Hixon 2000]. OCD is most commonly found in the knee, although it can also be found in the elbow, ankle and hip. Although the exact prevalence of OCD is unknown, one study conducted in Sweden reported that OCD was twice as common in men as in women and the highest incidence was found in subjects between the ages of 10 and 20 years old.[31] In a study of 76 knee joints 33 years after a diagnosis of OCD, 79% of the patients who had been diagnosed with OCD as adults progressed to osteoarthritis.[32]

Chondromalacia patellae (CP) is a spectrum of abnormalities, including softening, swelling, and fissuring of the articular hyaline cartilage of the patella. The articular cartilage degenerates due to an unstable collagen structure, resulting in abnormal stresses being transferred from the elastic, shock-absorbing cartilage to the subchondral bone.[33] In the past, the term chondromalacia patellae has been indiscriminately used, referring to any anterior knee pain.[34] Currently, CP can be arthroscopically classified into four stages. This condition is most common in young women and its progression to OA is unknown.[35]

The majority of **osteochondral lesions of the talus** are caused by trauma, with other causes including ischemic necrosis, embolic phenomena, or ossification defects. These lesions occur more frequently in men and people 20–35 years of age.[36,37] Little is known about the progression of osteochondral lesions of the talus to osteoarthritis.[38] **Osteochondral defects of the shoulder** are less common than those of the lower extremities. These defects are often symptomatic and, if left untreated, can progress to glenohumeral osteoarthritis.[39]

Osteochondral defect evaluation

The Outerbridge cartilage lesion classification system was initially developed in 1961 to describe chondromalacia patellae and was later adapted as a classification system for all chondral surfaces. This system combines the extent and size of cartilage damage and classifies lesions in the following way:[40]

Outerbridge Grade	Pathology
0	Normal cartilage
I	Softening and swelling of articular cartilage
II	Fragmentation and fissuring of articular cartilage affecting an area of less than 0.5 inches
III	Fragmentation and fissuring of articular cartilage affecting an area greater than 0.5 inches
IV	Cartilage erosion to bone

The International Cartilage Repair Society (ICRS) lesion classification system classifies lesions based on the defect dimensions, grade and depth, and location. The dimension and region of knee involvement are reported separately. Lesions are classified in the following way[41]:

ICRS Grade	Pathology
1	Normal
2	Lesions extending down to less than 50% of cartilage depth
3	Cartilage defects extending down to greater than 50% of cartilage, including calcified cartilage damage, exposed subchondral bone, or full-thickness delamination
4	Osteochondral lesion violating the subchondral plate, superficial or deep bony involvement

Creighton (2006) describes a treatment algorithm for symptomatic focal chondral lesions as follows: use of the ICRS system to classify the defect, a physical exam and thorough patient history to discern previous injuries and symptom-provoking activities, and diagnostic imaging, including an MRI.[21] The magnitude of the symptoms and extent of the lesion determine the appropriate treatment. For highly symptomatic patients, non-surgical treatment is generally ineffective. This report recommends a surgical regimen based on a number of factors, including patient characteristics and defect size, location, and depth.

1.2 The technologies and comparators

Overview of treatment of osteochondral defects

Surgical and non-surgical methods have been used to treat osteochondral defects. Surgical options fall into several general categories described below:

- Arthroscopic lavage/debridement, which resects all unstable cartilage back to a stable rim to remove loose flaps of cartilage that mechanically impinge on the joint and cause inflammation.
- Reparative or marrow stimulating techniques (e.g., subchondral drilling, abrasion arthroplasty, microfracture), which penetrate the subchondral bone and expose the underlying vascular cancellous bone leading to the formation of reparative tissue.

- Restorative techniques (e.g., autografts, allografts or synthetic materials, autologous chondrocyte implantation [ACI]), which attempt to restore the biomechanical and physiologic cartilage functions by completely reconstructing the cartilage microarchitecture.

Usually the severity of symptoms guides treatment. In a less active patient who is experiencing little pain and no mechanical symptoms, conservative treatment may be appropriate. Conservative treatment consists of non-steroidal anti-inflammatories and activity modification. Patients experiencing pain, locking, or catching may elect to have an arthroscopy to remove any articular cartilage flaps. Younger (< 50 years old), very active, or athletic patients, or those who have failed more conservative therapies may elect for a more extensive surgery known as osteochondral autograft (or allograft) transfer system (OATS) or mosaicplasty.

Technology: Osteochondral autograft and allograft

There is variability with respect to the terms used to describe osteochondral grafting with cylindrical, dowel-shaped or geometrically-shaped "plugs" which are press-fit to fill defects. For autograft procedures, the following terms have been used: osteochondral autograft transfer System (OATS), osteoarticular transfer system (OATS), osteochondral autologous graft transplantation (OATS), osteochondral autograft transplantation (OAT), autologous osteochondral transplantation (AOT) and mosaicplasty among the most common. Regarding allograft, the general term "osteochodral allograft" (OCA) has been used but appears to encompass a wide range of different techniques which include cylindrical, dowel-shaped plugs which are press-fit similar to what is described for OATS as well as shell/fragment grafts which use pins, screws or plates. Definitions are also variable. In general, it appears that the term OAT (or OATS) refers to the use of one or two larger cylindrical plugs and mosaicplasty is used to describe multiple cylindrical plugs. It is often assumed that these refer to autograft.

For purposes of this report the acronym OAT will be used to describe the use of cylindrical, dowel-shaped or geometric-shaped plugs of osteochondral material that are press fit into a defect and do not require the use of screws, pins, plates or other fixation devices. In general they will refer to autologous grafts and the term osteochondral allografting will be used to denote allograft with a focus on cylindrical, dowel-shaped or geometric-shaped plugs that do not require fixation.

Osteochondral autograft (or allograft) transplantation (OAT) or mosaicplasty involve transplantation of cartilage and subchondral bone into the defect to facilitate the growth of new tissue. These procedures can be done open or arthroscopically and are sometimes combined with other joint operations such as arthroscopic debridement or anterior cruciate ligament (ACL) repair.

Several trademarked products are available for the treatment of osteochondral defects, including the following:

- The Arthrex Allograft OATS® (Osteochondral Autograft Transfer System) consists of the surgical instrumentation necessary to perform an osteochondral transplantation and cortical/cancellous cadaveric donor bone from Allograft Tissue Systems, Inc. (ATSI) [Arthrex, 2011]. It was registered in 2005 as a medical device (surgical instrument) (registration number 3008831).[42]
- Zimmer® Chondrofix® Osteochondral Allograft is an osteochondral allograft, which consists of decellularized hyaline cartilage and cancellous bone from cadaveric donor joints, for the treatment of Grade III or IV full-thickness, focal osteochondral lesions.[43] It was registered in 2011 as a Biological Product (registration number 4013730).[44] It is not included as part of this report.

Osteochondral autograft transfer system (OATS) involves harvesting bone and intact articular cartilage from a non-weight bearing portion of a joint *from the patient* (i.e., autologous tissue) to fill a defect in the weight-bearing portion of the joint. This procedure can be performed through a small arthrotomy or arthroscopically, depending upon the defect location. First, unstable or loose chondral fragments are removed and the lesion edges are debrided back to stable, healthy cartilage. The base of the lesion is abraded down to subchondral bone and the number of grafts needed is determined. Next, the donor site is chosen, the peripheral parts of both femoral condyles at the level of the patellofemoral joint as one example. An appropriate size tubular chisel is introduced perpendicular to the donor site and the chisel is tapped into the donor site for 15–25 mm to remove one or two dowel-shaped plugs. The chisel is removed and the plug(s) is pushed out of the chisel. At the defect site, a universal drill guide is tapped in perpendicular to the base of the defect and an appropriate size drill creates a tunnel. After a dilator is inserted to create a conical-shaped recipient tunnel, the plug(s) is inserted through the guide into the defect in a press-fit manner. If the transplant is successful, the implanted bone and cartilage will incorporate into its new environment. Multiple studies have shown that autograft plugs retain their hyaline cartilage after being implanted, making this technique an improvement over microfracture and other marrow-stimulating techniques. However, this is a technically demanding procedure and is limited to treating defects < 4 cm^2 because of donor tissue limitations.[26]

Osteochondral allograft transplants involve the transplantation of a piece of cartilage and subchondral bone *from a source outside of the patient* to fill in the osteochondral defect. This technique is a viable option to autograft OATS for large defects. Either fresh or cryopreserved (previously frozen) allogenic tissue is used and are typically obtained from cadaver cartilage. Osteochondral allografting offers the advantage of providing a structurally mature articular cartilage matrix with viable chondrocytes with no accompanying size limitations and/or host donor site morbidity. It has been suggested that tissue matching is not necessary because the

transplanted chondrocytes are isolated in the cartilage matrix and not exposed to host immune surveillance[45]; however, a percentage of patients become antibody positive after allograft transplantation, possibly due to a subchondral bone immunoresponse.[41] Chondrocyte suppression has been mentioned as an issue with frozen grafts.[46]

Osteochondral allografts are regulated by the FDA as Human Cell or Tissue Products (HCT/P), as defined in section 361 of the Public Health and Service Act.[47] This act authorizes the FDA to create and enforce regulations to prevent the introduction, transmission, or spread of communicable diseases. All tissue banks must register with the FDA, which allows the FDA to inspect facilities at any time without notice. Tissue banks provide donor screening, tissue recovery, processing, storage, and distribution. Some tissue banks are certified by the American Association of Tissue Banks (AATB). Potential donors undergo screening, which includes a physical examination, comprehensive medical history, and social risk review. This information is compared against criteria that exclude individuals with high-risk behaviors. FDA's current Good Tissue Practice (CGTP) requires that recovered tissue to be distributed must be negative for HIV-1 NAT (nucleic acid testing), HCV (hepatitis C) NAT, and hepatitis B core antibody (total). It is further required that tissue banks record the complete history of the handling of the tissue and label the tissue with a distinct identification code that is linked to the donor. No allograft tissue is released until all information is evaluated by a team of medical specialists and the tissue bank's medical director. Once these experts deem the tissue to be safe, it undergoes various processing techniques to reduce the risk of disease transmission.[48,49] FDA regulations are limited to manufacturers of HCT/Ps only, not to hospitals or surgery centers performing allograft tissue transplantation. Manufacturers of HCT/Ps are required to report to the FDA certain serious adverse reactions[50]; however, hospitals and surgery centers are not required to report any adverse events to the FDA.[47]

Standards for the storage and issuing of transplanted tissue for hospitals, critical access hospitals, ambulatory office-based surgery, and outpatient centers are implemented by the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organization).[47] These standards advise organizations to develop procedures addressing the critical issues of tissue acquisition and storage and create a bidirectional tracing of the tissue from the donor or source facility to the recipient and vice versa. The organization must also have a process to investigate and report adverse events. Additionally, the AABB (American Association of Blood Banks) has published a document giving guidance on dealing with human tissue.[51] Allograft tissue can be fresh (maintained at 4° C in a culture medium for up to 28 days) or frozen (maintained at -40° C for years). The transplantation technique is similar to that of OATS, with an additional step of gradually warming the allograft tissue.[45]

A variation of allograft transplantation uses shell (or small fragment) rather than dowel-shaped plugs for larger lesions with an asymmetric pattern located in areas not amenable to dowel plugs.[52,53] A freehand technique is used to remove a graft to match the defect and bioabsorbable

pins or low-profile interfragmentary screws are often used to fix the graft. Although this is a technically demanding procedure, it has been suggested that using these thin shell allografts might have the advantage of reduced immunogenicity.[41]

Mosaicplasty is based on the same concept as OAT. However, multiple small plugs (autograft or allograft) are used. An informal differentiation between OAT and mosaicplasty is that OAT involves the use of 1–2 larger plugs and mosaicplasty involves multiple smaller plugs.[16,54] When these multiple plugs are moved into a damaged area the result is a mosaic appearance.

Indications and Contraindications

Based on clinical experience, Farr described the" ideal" patient for all cartilage restoration techniques as having a BMI < 35 kg/m^2, with realistic expectations, willing to adhere to postoperative rehabilitation protocols, with localized cartilage defects, symptomatic, and with all relevant comorbidities (e.g., malalignment) identified and corrected in a staged or concomitant procedure.[41]

Indications and contraindications for the three procedures are listed in the following tables. The Evidence for these indications is from primarily from case series.

Indications		
OAT autograft	**Mosaicplasty**	**Allograft**
small (< 2 – 4 cm^2)lesions [12,15,26,41,45]	small or medium-sized (1 – 4 cm^2) focal chondral and osteochondral defects[55]	large (> 1– 2.5 cm^2) lesions,[12,41,45,46,53,56] uncontained lesions[41]
shallow (≤ 10 – 15 mm deep) lesions[12,26]	weight-bearing surfaces of the femoral condyles, patellofemoral joint, talus, tibia, caput and capitulum humeri, and the femoral head[55]	lesions with bone and/or cartilage loss[12,41,45]
unstable OCD lesions[12]		isolated defects due to OCD or trauma[46,52,53,56]
less active patients, age < 50 years, with stable ligaments and normal alignment[12]		lesions due to avascular necrosis [Latterman 2008; Bugbee, 2002]
		salvage of a tibial plateau fracture or femoral condyle fracture [Bugbee, 2002]
		select cases of unicompartmental tibiofemoral OA[56] or multifocal OA[53]
		patellofemoral disease[53,56]
		treatment after the failure of other cartilage repair/restoration treatments such as microfracture, ACI, or mosaicplasty[12,53,56]
		knee: posttraumatic and degenerative lesions associated with intra-articular tibial plateau fractures[53]

Indications		
OAT autograft	**Mosaicplasty**	**Allograft**
		ankle: resurfacing of the tibiotalar joint secondary to post-traumatic arthritis, osteonecrosis, OCD lesions of the talus not amenable to other treatment, and reconstruction following excision of tumors of calcaneus and talus[53]
		hip and shoulder: young patients with osteonecrosis of both the femoral head and humeral head, as well as large osteochondral lesions associated with glenohumeral dislocation and instability[53]

Contraindications		
OATS autograft	**Mosaicplasty**	**Allograft**
patellar or bipolar lesions or lesions with bone loss[41]	defects deeper than 10 mm [Hangody 2002]	with inflammatory disease (rheumatoid arthritis, crystal-induced arthropathy)[53]
	generalized arthritis (rheumatoid and/or degenerative)[57]	progression multicompartmental osteoarthritis[53]
	lack of appropriate donor area[57]	corticosteroid-induced osteonecrosis[41,46,52,53]
	tumor or infection[57]	tumor or infection[46]
	age > 50 years[57]	medical condition that might affect the incorporation of allograft tissue (i.e., insulin-dependent diabetes mellitus)[46]
		BMI > 30 kg/m^2 [46]
		age > 50 years[46]

Safety and complications

Limitations of autograft OATS and mosaicplasty include the availability of donor grafts, the integration of donor-donor and donor-recipient hyaline cartilage interface, and the ability of the techniques to handle different sizes and depths of defects. Surgical complications include hemarthrosis, effusion, pain, and septic or thromboembolic complications. Donor site morbidity has also been a concern, with complications at the donor site including pain, degenerative changes, and postoperative hematomas.[26] Additional potential safety concerns with allograft transplantation include disease transmission and an immunogenic response.[26] In a CDC analysis of allograft-associated infections (AAI) in the FDA's MedWatch adverse events reporting system, bone allografts, including bone products such as bone chips and cancellous cubes, constituted 8% of the 83 reported AAIs.[58]

Comparators: other treatment options for osteochondral defects

Some researchers suggest that surgical procedures should be considered only for adult, symptomatic patients who have failed non-surgical therapies.[26] Based on clinical experience, other researchers claim that untreated lesions can progress to symptomatic degeneration of the

joint, so early surgical intervention is necessary to restore normal joint congruity and prevent further injury.[45]

Absolute contraindications for any articular knee repair treatment include untreated mechanical malalignment, ligamentous laxity, and deficient menisci.[59]

Non-surgical interventions: Non-surgical treatments of osteochondral defects include nonsteroidal antiflammatory drugs (NSAIDs), viscosupplementation, bracing, weight loss, and rehabilitation.[26] Although these treatments might provide symptomatic relief, there is no evidence that any of these treatments provide a structural improvement of the lesions.

The primary surgical comparators for OATS/mosaicplasty include the following:

Chondroplasty: This term refers to the mechanical or thermal reshaping of uneven articular cartilage by debriding chondral flaps and fibrillated articular cartilage while avoiding damage to healthy surrounding cartilage. It encourages formation of new scar cartilage or fibrous cartilage to aid in healing.

Abrasion chondroplasty/arthroplasty: This involves the use of a curette, burr, or shaver to loosen chondral edges and the calcific sclerotic base of a chondral defect, removing 1–3 mm of bone. The exposed vascularity provides a tissue bed for blood clot attachment. This in turn permits scar tissue to grow, which is necessary for the formation of cartilage cells needed to provide joint surface stability and strength. However, removing so much subchondral bone has been questioned. A retrospective study showed that 33% of patients receiving this treatment had worse postoperative functional outcomes compared to preoperative functional outcomes.[26]

Microfracture surgery: This technique is similar to drilling and abrasion arthroplasty in that it attempts to recruit bone marrow cells to form repair tissue in the cartilage defect, yet without bone removal.[26] Loose or marginally attached cartilage is debrided back to a stable rim, forming a perpendicular edge that forms a well-shouldered lesion. An awl is used to perforate the subchondral bone, making holes 3–4 mm apart. Blood and bone marrow seep out of fractures creating a blood clot that releases cartilage-building cells. Repair tissue is generally a mixture of hyaline and fibrocartilage.[26] In order to contain the cells in the defect, microfracture has been combined with a chondrogide membrane in a technique called Autologous Matrix Induced Chondrogenesis (AMIC).[60] A mixture of cancellous bone, fibrin glue, and the patient's serum is applied to the defect, providing a collagen matrix.

Indications: Best results for this treatment are indicated for grade III or IV focal articular surface lesions without bone loss that are surrounded by normal articular cartilage in a young patient.[61]

Contraindications: This treatment is contraindicated in situations including significant subchondral bone loss, malalignment, bipolar lesions, or a high risk of noncompliance with postoperative rehabilitation protocols.[61]

Autologous chondrocyte implantation (ACI): During the initial procedure, the patient's own chondrocytes are removed arthroscopically from a non-weight-bearing area from either the intercondylar notch or the superior ridge of the medial or lateral femoral condyles. The approximately 10,000 cells that are originally harvested are grown *in vitro* for 6 weeks until the population reaches 10–12 million cells. After this cell proliferation period, the patient undergoes a second surgery in which a periosteal flap is applied over the defect site and millions of dedifferentiated chondrocytes are surgically injected into the defect. Advantages of this treatment are short operating time, minimal invasiveness, and easier access to difficult sites. Complications include symptomatic hypertrophy, disturbed fusion, delamination, and graft failure. Reports of complications from using periosteal patches have led to an alternative procedure, Matrix-Induced Chondrocyte Implantation (MACI), which uses a porcine-derived collagen bilayer that is seeded with the patient's harvested chondrocytes.[26]

Indications: The initial FDA approval in 1997 was for "the repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear) caused by acute or repetitive trauma" [FDA 1997 Approval Letter][62]. A revision was issued in 2000 restricting the use "in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure" [FDA 2000 Carticel letter March 2000].[63] Non-comparative studies have demonstrated efficacy in additional populations, including patients younger than 18 years old and over 45 years old; patients with large, bipolar, and patellofemoral defects; and patients needing concurrent surgeries such as meniscus transplant.[22] However, to date, few comparative studies have examined the efficacy of ACI compared to another treatment. Off-label use has been expanded to treatment of chondral defects in the ankle, shoulder, elbow, wrist, and hip.[61]

Contraindications: Suboptimal results are found with malalignment, ligament instability, and meniscus deficiency not treated concurrently or in a staged manner.[61]

Biologic resurfacing: Partial replacements and stem-less implants have been developed that are particularly attractive for use in young patients.[64] These implants preserve anatomy and leave open various options for subsequent revision surgery. These newer implants provide the ability to adjust them to the cortical rim of the resected humeral head and offer a variety of anatomic head sizes.

Synthetic materials: Synthetic cartilage constructs may be an alternative to biological resurfacing and are considered Class II or III medical devices for FDA approval.[65] Synthetic resorbable polymers (e.g., PolyGraft™ BGS, TruFit® [cylindrical plug], TruGraft™ [granules]) have been proposed for the repair of osteochondral articular cartilage defects. Synthetic bone void fillers can be categorized into ceramics, polymers and composites. Their use in humans as an alternative for allograft or autograft for the repair of osteochondral defects has not been well evaluated. These are not included in the scope of this report.

1.3 Clinical guidelines

National Guideline Clearinghouse (NGC)
A search of the National Guidelines Clearinghouse for guidelines that addressed osteochondral autograft transplantation (OATS), osteochondral allograft, or mosaicplasty retrieved 22 potential current guidelines, three of which provided specific guidance. A variety of keyword searches were performed, including "*osteochondral autograft transfer,*" "*mosaicplasty,*" "*OATS,*" "*chondral OR osteochondral,*" "*allograft*" and "*Osteochondritis Dissecans.*"

American Academy of Orthopaedic Surgeons (AAOS) (2009)[66]:
The treatment of glenohumeral joint osteoarthritis: guideline and evidence report (NGC: 007581)
AAOS was unable to recommend for or against the use of osteoarticular allograft or autograft for the treatment of glenohumeral arthritis due to lack of studies of sufficient quality.

Work Loss Data Institute (2008)[67]:
Shoulder (acute & chronic)
A summary provided by the NGC indicates that OATS was considered as a treatment for workers with occupational shoulder disorders and not recommended. This guideline is in the process of being updated.

Work Loss Data Institute (2007)[68]:
Knee & leg (acute & chronic)
A summary provided by the NGC indicates that OATS and mosaicplasty were considered as treatments for workers with knee and leg ailments for relieving pain and improving function. OATS was recommended; mosaicplasty was not recommended. This guideline is in the process of being updated.

National Institute for Health and Clinical Excellence (NICE)
The National Institute for Health and Clinical Excellence (NICE) provides guidance on health technologies and clinical practice for the National Health Service in England and Wales. A variety of keyword searches were performed, including "*osteochondral autograft transfer,*" "*mosaicplasty,*" "*OATS,*" "*chondral OR osteochondral,*" "*allograf*" and "*Osteochondritis Dissecans.*" One guideline was found, *Mosaicplasty for knee cartilage defects 2006*, and is summarized as follows[69]:

- Current evidence suggests that there are no major safety concerns regarding the use of mosaicplasty for the treatment of knee cartilage defects; however, procedure-related and long-term complications are inadequately reported in studies.
- Some evidence exists for short-term efficacy, but data is inadequate regarding long-term efficacy.

NIH Consensus Statement

No consensus statement was found for osteochondral autograft transplantation (OAT), osteochondral allograft, or mosaicplasty.

Professional societies/other (Not indexed in NGC)

American Academy of Orthopaedic Surgeons (AAOS)

One additional guideline was found that addressed osteochondral autograft transplantation (OATS), osteochondral allograft, or mosaicplasty: *The diagnosis and treatment of osteochondritis dissecans: guideline and evidence report, 2010*.[30] AAOS was unable to recommend for or against osteochondral transplantation using allo- or autograft techniques in symptomatic skeletally mature patients with an unsalvageable fragment or osteochondritis dissecans lesion. This recommendation is based on four Level IV studies.

International Cartilage Repair Society (ICRS)

One paper was found that detailed a cartilage repair treatment algorithm for the knee: *Cartilage Injuries in the Adult Knee: Evaluation and Management, 2011*.[70] Note that this paper does not include treatment guidelines. OATS is recommended for lesions < 2 cm^2 in size and osteochondral allografts are recommended for lesions > 2 cm^2. The use of OATS for lesions between 2 and 6 cm^2 is of questionable benefit and is not recommended because of donor site morbidity.

The ICRS issued a consensus statement on conducting clinical research in articular cartilage repair, *Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair: International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care, 2011*.[22] Note that this statement does not include treatment guidelines. The consensus statement details methodological recommendations on study design and endpoint definition, patient recruitment, control group considerations, documentation of results, validated patient-reported outcome instruments, and inclusion/exclusion criteria.

The ICRS has also issued a recommendation document detailing patient-reported outcome instruments for articular cartilage repair procedures, *ICRS Recommendation Document : Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects, 2011*.[71] This statement does not include treatment guidelines. Instruments examined include the International Knee Documentation Committee (IKDC) Subjective Knee Form, the Knee injury and Osteoarthritis and Outcome Score (KOOS), the Lyshlom Scoring Scale, various patient-reported health-related quality of life measures, the Tegner Activity Rating Scale, and the Marx Activity Rating Scale.

Washington State Department of Labor and Industries

The Medical Treatment Guidelines, developed by the Office of the Medical Director in collaboration with practicing physicians and advisors, are intended to be used as educational tools for medical providers or are used by the department in the Utilization Review program and claim management process to promote best practices and improve the health of injured workers. A 2003 *Review criteria for knee surgery* indicates the following guideline for osteochondral autograft (mosaicplasty or OATS procedure)[72]:

- Conservative care: medication OR physical therapy, AND
- Subjective: joint pain AND swelling, AND

- Objective: Failure of previous subchondral drilling/microfracture; large full-thickness chondral defect < 3 cm diameter and 1 cm depth on weight-bearing part of medial/lateral femoral condyle AND knee is stable with intact fully functional menisci and ligaments AND normal knee alignment and joint space AND body mass index < 35, AND
- Imaging: chondral defect on the weight-bearing part of the medial/lateral femoral condyle on MRI or arthroscopy.

Google and Google Scholar
A keyword search on terms including "clinical guidelines" AND "osteochondral autograft transfer", "mosaicplasty," "OATS," " osteochondral," "allograft" and "Osteochondritis Dissecans" retrieved two guidelines and a book reference addressing osteochondral autograft transplantation (OAT), osteochondral allograft, or mosaicplasty:

- **State Government of Queensland, Q-Comp, The Worker's Compensation Regulatory Authority of Queensland** *Clinical guidelines for the Queensland workers' compensation scheme, Knee, 2008.*[73]

  A review of a selection of clinical guidelines or treatment protocols by other medical organizations or governmental bodies and each guidelines' relevance to the worker's compensation sector. Includes the Washington State Department of Labor and Industries Guidelines, 2003, detailed in this section.

- **American College of Rheumatology** *Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee, 2000.*[74]
  At the time of this report autologous osteochondral plugs (mosaicplasty) were being investigated for the repair of focal chondral defects. This procedure was not indicated in the treatment of patients with osteoarthritis.

- **Akhavan et al.** *Cartilage repair and replacement: from osteochondral autograft transfer to allograft*. In, *Arthritis & arthroplasty: the knee, T.E. Brown, 2009.*[12]
  A summary of the indications, surgical pearls, published outcomes, and future developments of the four most widely used surgical techniques used to treat focal, high-grade lesions of the knee, including:
  Osteochondral Autograft Transfer
  - ideal for symptomatic, focal, Outerbridge grade III or IV chondral lesions of weight-bearing femoral condyles,
  - suited for well-contained chondral defects < 4cm^2,
  - best results seen in less active patients < 50 years old with stable ligaments and normal alignment,
  - histologic analysis of repair tissue shows greatest content of hyaline-like cartilage of any repair technique,
  - technically demanding and commercially available instrumentation required, and
  - donor site morbidity might be an issue.

  Osteochondral Allograft Transfer
  - generally reserved for large lesions > 2 cm^2 associated with cavitary defects and bone loss,

- good choice in patients with symptomatic osteochondritis dissecans lesions, especially of the lateral aspect of the medial femoral condyle, for which prior attempts at native fragment fixation have failed,
- suitable for the revision of failed cartilage repair strategies,
- no donor site morbidity,
- radiographs of the knee with a radiographic sizing marker are necessary for allograft source to provide a size-matched hemicondyle,
- increased expense for the fresh osteochondral allograft and technical difficulty compared with other techniques, and
- possible risk of disease transmission or immunologic reaction.

No clinical guidelines relating to osteochondral autograft transplantation (OATS), osteochondral allograft, or mosaicplasty were found in the following organizations' resources:

- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Institute for Clinical Systems Improvement (ICSI)
- Ontario Health Technology Advisory Committee (OHTAC)
- Osteoarthritis Research Society International (OARSI)
- U.S. Food and Drug Administration (FDA)
- U.S. Army Institute of Surgical Research
- American Association of Hip and Knee Surgeons
- The Clinical Orthopaedic Society
- The Association of Bone and Joint Surgeons, Clinical Orthopaedics and Related Research
- The American Academy of Physical Medicine and Rehabilitation
- The New Zealand Guidelines Group
- American College of Physicians
- Canadian Task Force on Preventive Health Care

1.4 Previous systematic reviews/technology assessments

Many previous technology assessments (HTA) and systematic reviews (SR) concluded that the results from studies were inconclusive or evidence was insufficient to give recommendations on choice of treatment, partially due to short follow-up periods and the poor quality of some of the studies. Adverse outcomes were not reported in many of the reviews; however, donor site morbidity for osteochondral autografts was mentioned as a concern in several of the reviews. Most studies called for additional high quality studies comparing different cartilage repair techniques with longer follow-up periods. The primary focus of most of the reviews was not on OAT.

Some reviews discussed the influence of patient characteristics, lesion size, or lesion location on outcomes. Harris 2010 found that younger, more active patients with smaller isolated defects on the medial femoral condyle got the best outcome regardless of the treatment.[75] Osteochondral

allograft therapy was found to have a higher risk of failure for patients over 50 years of age with bipolar defects, malalignment, and worker's compensation.[41] One review found better clinical outcomes in patients under 30 years old regardless of the treatment.[15]

Some inconsistency was found in recommending treatment based on lesion size. One SR recommended OAT or ACI for larger lesions (> 2.5 cm^2) and single-plug OAT or microfracture for smaller lesions (< 2.5 cm^2).[15] One HTA[76] found that OAT was as good or better than marrow stimulation for small lesions, while another SR[77] found that any treatment worked well for small defects. An SR on athletes found that there was a higher return to sports after OATS or microfracture for smaller lesions (< 2cm^2) compared with larger lesions.[78]

Regarding the location of lesions, multiple HTAs/SRs analyzed some of the same studies and concluded that using ACI in treating lesions of the medial femoral condyle leads to better clinical outcomes compared with mosaicplasty.[79-82] However, in analyzing some of the same studies, Harris 2010 found that because of small sample sizes there was no evidence that the lesion location predicted better outcome after any treatment. Within a subpopulation of athletes, a better clinical outcome was seen with OAT on the lateral femoral condyle.[78]

There was inconsistent use of terminology when referring to the three treatments included in the current HTA, with some reviews not specifying the treatment as allo- or auto-graft and other reviews using OAT and mosaicplasty interchangeably. Lesion size and number of lesions was not reported for many of the studies. Most previous technology assessments and systematic reviews included studies of the knee joint, two reviews covered the talus, and one covered the elbow.

Multiple HTAs/SRs summarized many of the same studies that are included in this HTA.[15,16,75,77,79-83] Some reviews found evidence suggestive of ACI being a superior treatment than OAT or mosaicplasty.[15,77] Other reviews found that all treatments lead to improvement.[75,83] And the remaining reviews found no significant difference between the treatments or felt that evidence was insufficient to make any recommendations.

Please refer to interpretive notes for the tables regarding evidence base assesement and critical appraisal performed in the various reviews.

Table 7. Overview of previous technology assessments

Overview of previous technology assessments of osteochondral autograft transplantation (OAT), osteochondral allograft, or mosaicplasty

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Clar (2005)[79] (commissioned by NHS R&D Health Technology Assessment Programme on behalf of National Institute for Health and Clinical Excellence) *Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation*	1966 – June 2004	• ACI • mosaicplasty (autograft) • OCT	<u>ACI compared with mosaicplasty</u> • 1 RCT (%f/u NR, 12, 24 months); N = 100; mean lesion size: 4.66 cm^2 (1.22 – 12.2) <u>ACI compared with OCT</u> • 1 quasi-RCT (% f/u NR, 3, 6, 12, 24 months); N = 40; mean lesion size: 3.75 cm^2 (3.2 – 5.6) <u>Mosaicplasty</u> • 1 case series (3 – 6 years); N = 652 (578 on the knee); mean lesion size NR	Yes: no quality of evidence scores were stated	• Primary focus of HTA was on ACI • Quasi-RCT used alternate assignment as randomization • This review is an update to the Jobanputra 2001 HTA	**Efficacy:** Overall conclusion is that more research is necessary. Long-term results are absent, so the development of osteoarthritis and the rate of knee replacements are unknown at this time. Results from the 2 RCTs are inconclusive, with the RCT showing little difference in treatment groups at 24 months and the quasi-RCT showing significantly better clinical results on one outcome measure in the ACI group. The case series showed a 90% success rate in the mosaicplasty patients. **Safety:** The RCT reported some adverse effects, but not by treatment group. The quasi-RCT reported similar complication rates in the mosaicplasty and ACI groups (60%). The case series reported a 6% complication rate among all mosaicplasties. **Economic:** Insufficient evidence regarding cost effectiveness of ACI compared with mosaicplasty; longer term outcomes are required. Authors unable to produce a reliable cost per QALY due to lack of data.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Washington State Department of Labor and Industries (2002)[76] *Autologous Chondrocyte Implantation (ACI) Technology Assessment*	from 1998	• ACI • microfracture • debridement • alternative surgical treatments, including osteochondral allo- or auto-grafts	4 studies of unspecified type (% f/u NR, f/u period NR); N = NR; mean lesion size NR	NR	• Primary focus of HTA was on ACI • Autografts and allografts are covered in the Alternative Surgical Treatments section	**Efficacy:** The following results are briefly described: • Osteochondritis dissecans may respond well to grafting • In 3 studies, 63% – 86% of patients report good to excellent graft results for up to 7.5 years • 1 study reports that grafting may be as good or better than marrow stimulation for small lesions **Safety:** not addressed in this report for OATS, allografts, or mosaicplasty **Economic:** not addressed in this report for OATS, allografts, or mosaicplasty
Jobanputra (2001)[84] (commissioned by NHS R&D Health Technology Assessment Programme on behalf of National Institute for Health and Clinical Excellence) *Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review*	1966 – 2000	• Mosaicplasty • ACT	Mosaicplasty 1 case series (% f/u NR , ≥ 3 years); N = 57; mean lesion size NR	Yes: all studies in HTA were case series or cohorts of patients without controls	• Primary focus of HTA was on ACT	**Efficacy:** Review states that mosaicplasty appears to produce exceptional results, with 95% of patients returning to normal activity and only 3.5% of patients requiring an additional surgical procedure. However, this conclusion is based on one case series with a relatively small study population and short follow-up period. **Safety:** not addressed in this report for OATS, allografts, or mosaicplasty **Economic:** not addressed in this report for OATS, allografts, or mosaicplasty

f/u: follow-up NR: not reported ACI: Autologous chondrocyte implantation ACT: autologous chondrocyte transplantation; OCT: osteochondral cylinder transplantation

* Percent follow-ups were not given for any studies. Actual time of follow-up is reported unless otherwise specified.

† Only studies including the primary interventions of the current HTA are described. N reflects numbers as reported in original studies.
‡Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence. The quality of the RCTs is based on the following criteria: randomization, allocation concealment, handling of missing data/LTF, intent-to-treat analysis, power calculation, blinding, timing of outcome assessments, post-operative rehabilitation, eligibility criteria, treatment group similarity at baseline, point estimates/measure of variability for primary outcome measure, sponsoring by manufacture; rating of A (all criteria met), B (≥ 1 criteria partially met), or C (≥ 1 criteria not met) (Clar, 2005); clinical outcomes including patient input before/after surgery and adverse effects (grade A), clinical outcomes including patient input before/after surgery but no adverse effects (grade B), clinical outcomes including patient after surgery only (grade C), and clinician/radiography input (no patient input) (grade D) (Jobanputra, 2001).

Table 8. Overview of previous systematic reviews.

Overview of previous systematic reviews of knee osteochondral autograft transplantation (OAT), osteochondral allograft, or mosaicplasty

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Benthien (2011)[85] *We do not have evidence based methods for the treatment of cartilage defects in the knee*	2002 – 2007	• OATS • ACI/MACI • microfracture	133 studies (including all 4 procedures) %f/u NR, 24 months; N = 6920; mean lesion size NR	Yes: 10 LOE I studies, 5 LOE II studies, 7 Level III studies, 111 Level IV studies; mean modified Coleman score for OATS studies = 50, the lowest score for all procedures	• This review was conducted to evaluate if any of the most common and well-documented articular resurfacing procedures are evidence based.	**Efficacy:** No operative procedure proved superior based on increase in Lysholm Score (as reported in 24 studies): MACI had largest median increase (34 points), OATS had second largest increase (32 points). Choosing and applying a commonly used score (such as the Lysholm knee function score) does not necessarily lead to a higher quality level of evidence for studies. **Safety:** not addressed in this report **Economic:** Review briefly describes one study's conclusion that the average costs for ACI were lower than mosaicplasty; however more prospective studies were recommended.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Farr (2011)[41] *Clinical Cartilage Restoration: Evolution and Overview*	NR	• Marrow stimulation • Osteochondral allograft • Osteochondral autograft • ACI	5 studies of unknown type (allograft) % f/u NR, f/u period NR; N = NR; mean lesion size NR	NR	• This is a selective review, not a systematic review. Study quality was not assessed, EMBASE and Google Scholar were not searched. • With a few exceptions there is a paucity of high quality Level I RCT studies.	**Efficacy:** The results of osteochondral allografts have been promising, with improved knee function scores, normal tissue repair, and low failure rates. Indications for optimal use for autografts include femoral lesions < 2.5 cm^2; for allografts, lesions with bone and cartilage loss and large uncontained lesions. Suboptimal outcomes for autografts include patellar or bipolar lesions or lesions with bone loss; for allografts, bipolar lesions or diffuse osteoarthritis. **Safety:** not addressed in this report **Economic:** An undefined analysis concluded that it might be more cost effective in the long term to use osteochondral allograft or cell-based therapies for larger lesions.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Harris (2010)[75] *Autologous chondrocyte implantation: a systematic review*	1950 – Feb. 2010	• OATS/ mosaicplasty (autograft) • ACI • microfracture	OATS (mosaicplasty) compared with ACI • 1 RCT (%f/u NR, 24 months); N = 40; mean lesion size 3.8 cm^2; 98% of subjects with a single lesion • 1 RCT (%f/u NR, f/u time 36); N = 44; mean lesion size 1.9 cm^2; 99% of subjects with a single lesion	Yes: the two OATS studies had an average Coleman score of 50 out of a possible 100 (poor quality); overall quality of all studies in the review improved with more recent publication dates.	• Primary focus of review was on ACI. • Review included studies of lesions of Outerbridge grade III or IV. • The second RCT experienced 32% LTF or non-completion of intended treatment, so large attritional bias prevented summary of outcomes.	**Efficacy:** OATS, ACI, and microfracture all provide short-term success regarding cartilage repair; more rapid improvement is seen with OATS compared with ACI, but OATS is limited by donor site morbidity. **Safety:** failure in 7.1% of patients and arthrofibrosis in 2.5% of patients in mosaicplasty treatment group **Economic:** not addressed in this report
Vasiliadis (2010)[82] *Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee*	1950 – 2008	• Mosaicplasty (autograft) • ACI • CCI • microfracture	Mosaicplasty compared with ACI • 1 RCT (%f/u NR, 12 months); N = 100; mean lesion size: 4.66 cm^2 (1.22 – 12.2) • 1 RCT (49% f/u, 12 months); N = 47; mean lesion size: mosaicplasty 1.9 cm^2, ACI 2.0 cm^2 • 1 quasi-RCT (%f/u NR, 24 months); N = 40; mean lesion size: mosaicplasty 3.63 cm^2, ACI 3.86 cm^2	Yes, no quality of evidence scores were stated	• Primary focus of review was on ACI. • Evidence presented is of limited validity based on quality of studies. • The second RCT experienced high (23%) LTF due to spontaneous improvement after the first surgery. • An additional publication (Vasiliadis, Wasiak, Salanti 2010) is an update to this review, but provides no additional studies of OATS, mosaicplasty, or allografts.	**Efficacy:** Insufficient evidence to draw conclusions on the use of ACI compared to other treatments. An exploratory meta-analysis was done, but no conclusion was drawn due to significant heterogeneity (I^2 = 79%). **Safety:** 60% of patients in both treatment groups experienced complications at 24 months in one study. Another study reported no adverse events. The complication rates reported in the update (Vasiliadis, Wasiak, Salanti 2010) differ slightly, possibly due to the definition of complication. **Economic:** not addressed in this report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Vavken (2010)[77] *Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: a systematic review of controlled trials*	NR	• ACI • OATS (autograft) • microfracture • abrasion	<u>OATS compared with ACI</u> • 1 RCT (%f/u NR, 24 months, 5% attrition); N = 40; mean lesion size: 4.4 cm^2 • 1 RCT (%f/u NR, 24 months, 5% attrition); N = 40; mean lesion size: OATS 3.6 cm^2, ACI 3.9 cm^2 • RCT (%f/u NR, 19 months, 0% attrition); N = 100; mean lesion size: 4.66 cm^2 • 1 RCT (%f/u NR, 25 months, 15.9% attrition); N = 34; mean lesion size: OATS 1.9 cm^2, ACI 2.0 cm^2	Yes: all 4 studies LOE II	• Primary focus of review was on ACI.	**Efficacy:** No clear recommendation can be made regarding the efficacy of OATS compared with the other treatments, although some evidence is suggestive of better clinical outcomes for ACI compared with OATS. There is great inconsistency in methodological quality and findings, and the fairly small absolute differences between treatment groups raise questions about the findings' clinical importance. **Safety:** not addressed in this report. **Economic:** not addressed in this report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Bekkers (2009)[15] *Treatment selection in articular cartilage lesions of the knee: a systematic review*	NR	• OATS (autograft) • ACI • microfracture	<u>OATS compared with microfracture</u> • 1 RCT (%f/u NR, 6/12/24/36 months); N = 60; mean lesion size: OATS 2.80 ± 0.65 cm^2, microfracture 2.77 ± 0.68 cm^2 <u>Mosaicplasty compared with ACI</u> • 1 RCT (%f/u NR, 12/19 months); N = 100; mean lesion size: 4.66 cm^2 (1 – 12.2)	Yes: 2 LOE 1b studies; Coleman scores ranged from 74 – 86	• Review primarily included studies of lesions of Outerbridge grade III or IV. • The first RCT comprised papers on the same study published in different journals – the first published article was summarized. This study's population comprised competitive or highly trained athletes. • 2 excluded LOE 2b studies showed similar results compared with included studies.	**Efficacy:** For lesions > 2.5 cm^2, ACI or OATS provide better outcome; for lesions < 2.5 cm^2 microfracture is preferred. ACI shows significantly better short-term (1 year) clinical and macroscopic outcomes than mosaicplasty, but superior clinical results were not sustained at longer follow-ups. Both OATS and microfracture groups showed significant improvement in clinical outcome from baseline, with OATS patients having significantly higher scores at the longest 3 follow-ups. OATS or ACI provide better results for active patients with large articular lesions compared with microfracture. Younger patients (< 30 years) benefit more from any cartilage treatment compared with older patients. **Safety:** not addressed in this report. **Economic:** not addressed in this report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Mithoefer (2009)[86] *Return to sports participation after articular cartilage repair in the knee: scientific evidence*	1966 – May 2009	• OATS (autograft and allograft) • ACT • microfracture	5 OATS (autograft) and 1 OATS (allograft) study (a mixture of case series and RCT studies): (% f/u NR, 42 ± 10 month f/u); N = 261; mean lesion size: 2.4 ± 0.2 cm^2	Yes: Coleman scores for autograft studies averaged 71 ± 2 (out of a maximum of 100 points)	• Review primarily included studies of lesions of Outerbridge grade III or IV.	**Efficacy OATS (autograft):** Rate of return to sports was highest in OATS compared to other treatments. Continued participation in sports was lower in OATS compared with ACT. Significantly higher percentage of OATS patients with good to excellent results and higher percentage of OATS patients with normal repair tissue compared with microfracture. Within OATS group, younger athletes (< 30 years) or those with lesions on lateral femoral condyle had significantly higher rate of return to sports and better clinical outcomes. **Efficacy OATS (allograft):** Absence of data regarding sports participation. **Safety:** no significant technique-specific complications reported for OATS (autograft). **Economic:** not addressed in this report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Nakamura (2009)[80] *Cell-based therapy in articular cartilage lesions of the knee*	1994 – January 2009	• OATS (autograft) • ACI • microfracture	Mosaicplasty compared with ACI • 1 RCT (%f/u NR, 12 months); N = 100; mean lesion size: 4.66 cm^2 (1.22 – 12.2) • 1 RCT (%f/u NR, 36 months); N = 47; mean lesion size: 1.925 cm^2 (range NR) • 1 RCT (%f/u NR, 24 months); N = 40; mean lesion size: 3.75 cm^2 (3.2 – 5.6)	Yes: all 3 studies LOE II	• Primary focus of review was on cell-based therapies (ACI/MACI). • One systematic review that included OATS was also briefly summarized (Magnussen, 2008), but non-cell-based therapies were not described.	**Efficacy:** Overall, no difference between cell-based treatment and OATS. One study reported significantly better cartilage repair in the ACI group, but only 30% of the total study population received an arthroscopy. The same study also reported better clinical outcomes with ACI in the medial femoral condylar defect subgroup, but this analysis was an unplanned subgroup analysis. **Safety:** not addressed in this report. **Economic:** not addressed in this report.
Magnussen (2008)[16] *Treatment of focal articular cartilage defects in the knee: a systematic review*	1966 to 2007	• OATS (autograft) • MACI • microfracture	OATS compared with ACI • 1 RCT (%f/u NR, 12 months); N = 100; mean lesion size: 4.66 cm^2 (1 – 12.2) • 1 RCT (%f/u NR, 24 months); N = 40; mean lesion size: 3.75 cm^2 (3.2 – 5.6) OATS compared with microfracture • 1 RCT (%f/u NR, 36 months); N = 60; mean lesion size: 2.8 cm^2 (1 – 4)	Yes: 2 LOE I studies, 1 LOE II study	• Review included only OATS studies of isolated lesions of Outerbridge grade III or IV. • One study's subjects were limited to competitive or well-trained athletes. • Review reported a follow-up to clinical outcome of > 95% for all studies, but did not report number of study participants eligible, only those enrolled, we are unsure of true follow-up.	**Efficacy:** No treatment had consistently superior results compared to other treatments. The relatively short follow-up severely limits interpretation of the data. Significant differences in outcome or donor site morbidity might not be detected at short follow-up periods. **Safety:** Superficial wound infection, deep venous thrombosis, and hemarthrosis appeared most commonly in the OATS group. **Economic:** not addressed in this report.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Ruano-Ravina (2006)[83] *Autologous chondrocyte implantation: a systematic review*	1994 – 2004	• ACI • microfracture • OCT/mosaicplasty (auto- or allograft not specified)	<u>OCT/mosaicplasty compared with ACI</u> • 1 RCT (%f/u NR, 24 months); N = 40; mean lesion size NR • 1 RCT (%f/u NR, 19 months); N = 100; mean lesion size NR	Yes: both RCTs LOE I	• Primary focus of review was on ACI. • 4 systematic reviews also briefly discussed, focusing on ACI treatment	**Efficacy:** No evidence available that ACI is more effective than other treatments. OCT/mosaicplasty and ACI both lead to improvements. Interpretation of the findings is complicated by the heterogeneous study designs, standardization and indications for treatment, short follow-up, location of the lesion(s), a large patients' age range, and different outcomes measures used. **Safety:** In the second RCT, all 5 patellar mosaicplasties failed. **Economic:** not addressed in this report for OCT or mosaicplasty

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Jakobsen (2005)[17] *An analysis of the quality of cartilage repair studies*	NR	• ACI • microfracture • OATS (autograft) • Autologous periosteal transplanatation	<u>OATS compared with other procedures</u> 24 studies of unknown type; % f/u NR, f/u period NR; N = NR; mean lesion size NR	Yes: average Coleman Methodology scores for 24 OATS studies was 39.3 (12 – 65) compared with overall average of 43.5 (40.3 – 46.7)	• Primary focus of review was to assess the methodological quality of cartilage repair studies and the possible correlation of the study quality with outcomes. • Authors cautioned that this report was not a meta-analysis of well-done RCTs.	**Efficacy:** No significant differences were found between the four procedures regarding Lysholm scores or percentages of good/excellent results, and large variations were seen for each outcome within each treatment type. Excluding RCTs, the average Lysholm score (estimated from graph) for OATS is 91 (85.7 – 95.3) compared with an overall average for all procedures 86.6 (81.1 – 92.2). An estimated 92% (85.8 – 95.2) of OATS patients had good/excellent outcome compared with an overall average of 86.4% (83.1 – 89.7). **Safety:** not addressed in this report **Economic:** not addressed in this report

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
National Institute for Health and Clinical Excellence (NICE) (2005)[81] *Interventional procedure overview of mosaicplasty for knee cartilage defects*	NR	• Autologous osteochondral mosaicplasty • Cylinder condrocyte transplant	<u>Mosaicplasty compared with ACI</u> • 1 RCT (%f/u NR, 19 months); N = 100; mean lesion size 4.66 cm^2 <u>Mosaicplasty</u> • 1 case series (% f/u NR , ≤ 10 years); N = 831; graft size 2.7 – 8.5 mm • 1 case series (% f/u NR , f/u period NR); N = 21; mean lesion size 4.6 cm^2; 1 – 12 grafts • 1 case series (% f/u NR , 3 years); N = 57; lesion size 1 – 8.5 cm^2; mean 8 (3 – 17) grafts • 1 case series (% f/u NR , 3 years); N = 52; mean lesion size 4.9 cm^2; mean 6 grafts	No	• This is a rapid review of the medical literature and specialist opinion, not a rigorous systematic review. • 2 of the case series report on the same study population	**Efficacy:** Comparison across studies is made difficult by considerable variation in the outcome measures used. The RCT reported no significant difference in excellent/good results except when examining lesion repair of the medial condyle, where a significantly higher percentage of ACI patients had excellent/good results compared with mosaicplasty patients. In the large case series, the proportion of patients having excellent/good clinical outcome ranged from 79% – 92% at maximum of 10 year follow-up. Specialist advisors' opinion: efficacy might vary depending on the size of the area of defect cartilage to be repaired. **Safety:** In general, procedural and long-term complications are inadequately reported. The RCT reported some adverse effects, but not by treatment group **Economic:** not addressed in this report

OATS: osteochondral autograft transfer; OCT: osteochondral cylinder transplantation; ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; ACT: autologous chondrocyte transplantation; CCI: characterised chondrocyte implantation; RCT: randomized controlled trial; LOE: level of evidence; LTF: lost to follow-up; f/u: follow-up; NR: not reported
*Only studies including the primary interventions of the current HTA are described except as noted. N reflects numbers as reported in original studies; latest follow-up time given for some studies. N indicates total enrolled participants (Magnussen, 2008); follow-up time is reported for primary clinical outcome (Magnussen, 2008).
†Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence. Authors assessed the risk of bias (methodological quality) according to Cochrane recommendations (Vasiliadis, 2010; Bekkers, 2009); level of evidence based on an adaptation of the Centre for Evidence-Based Medicine (Oxford, UK) guidelines by the Journal of Bone and Joint Surgery (Vavken, 2010; Nakamura, 2009); level of evidence based on published guidelines of the Journal of Bone and Joint Surgery and a modified Coleman Methodology Score (maximum score of 100) (Benthien, 2011; Magnussen 2008; Jakobsen 2005); quality of RCTs based on the Delphi list (Harris, 2010 ACI); degree of possible bias based on a modification of the Coleman methodology score (Harris, 2010 ACI; Bekkers, 2009; Mithoefer, 2009); quality of studies assessed using the United States Preventive Services Task Force classification (Ruano-Ravina, 2006).

Table 9. Overview of previous systematic reviews of talus osteochondral autograft transplantation (OATS), osteochondral allograft, or mosaicplasty

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Zengerink (2010)[37] *Treatment of osteochondral lesions of the talus: a systematic review*	1966 – 2006	• OATS (autograft) • excision/curettage /BMS/autogenous bone graft • TMD • ACI • retrograde drilling • fixation	9 OATS studies (1 RCT, 8 of unspecified study types) • %f/u NR, f/u period NR; N = 243; mean lesion size NR	Yes: 52 studies in review scored total of 28 out of a possible 104 points using NOS scale	• Differs from an earlier review, which had 1 study on OATS, with a success rate of 94%. • Successful treatment defined by original study author or by scoring system of Thompson and Loomer.	**Efficacy:** OATS is not recommended as treatment of choice due to knee morbidity, but no definitive conclusions can be drawn because of the diversity in studies and variability in treatment results. OATS studies' weighted success rate of 87% (74% - 100%) compared with 85% (46% – 100%) for BMS and 76% (70% – 92%) for ACI. **Safety:** Morbidity of donor knee joint 12% (0% - 37%) of patients. **Economic:** not addressed in this report for OATS, allografts, or mosaicplasty.

Assessment (year)	Lit search dates	Procedure(s) evaluated	Evidence base available*	Critical appraisal†	Comments	Primary conclusions
Tol (2000)[87] *Treatment strategies in osteochondral defects of the talar dome: a systematic review*	1966 – 1998	• OATS • Excision and curettage • Excision, curettage and drilling • Cancelous bone grafting	1 OATS unspecified study type • %f/u NR, 19 months (12 – 28); N = 11; mean lesion size NR	No	• No details of OATS outcomes are described in the review.	**Efficacy:** No definitive conclusions can be drawn due to lack of RCTs, variability in treatment results, and the great diversity of pre- and postoperative classifications. However, the report states that the results of OATS are encouraging. **Safety:** not addressed in this report for OATS, allografts, or mosaicplasty. **Economic:** not addressed in this report for OATS, allografts, or mosaicplasty.

OATS: osteochondral autograft transfer;ACI: autologous chondrocyte implantation; BMS: bone marrow stimulation; TMD: transmalleolar drilling; f/u: follow-up; NR: not reported
* Only studies including the primary interventions of the current HTA are described. N reflects numbers as reported in original studies.
†Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence. Authors assessed the methodological quality according to the Newcastle-Ottawa Scale (NOS) adjusted for case series (Zengerink, 2010).

1.5 Medicare and representative private insurer coverage policies

There currently is no National Coverage Decision for osteochondral autograft transplantation (OAT), osteochondral allograft, or mosaicplasty published from the Centers for Medicare and Medicaid Services (CMS). Coverage policies from selected bell-weather payers are somewhat consistent for coverage of these procedures. In general, small, localized lesions are covered in cases with significant symptoms or disabling pain and prior arthroscopic/surgical treatment. There is variation among payers regarding which affected joints are covered and how auto- and allograft procedures are covered. Table 10 provides an overview of policy decisions.

- Medicare
  The Centers for Medicare and Medicaid Services have no published National Coverage Determinations (NCD) for osteochondral autograft/allograft transplantation (OATS) or mosaicplasty.
- AETNA
  Aetna has two policies covering autograft and allograft transplantation separately: Osteochondral Autografts (Mosaicplasty, OATS) and Allograft Transplants of the Extremities.

Autografts[88]

Aetna considers osteochondral autografts medically necessary for the repair of small (less than or equal to 1 cm^2) focal chondral defects of articulating cartilage of the leg (ankle, hip, knee), which are causing significant symptoms that have not been relieved by appropriate non-surgical therapies.

All of the following procedures are considered experimental and investigational and are ineligible for coverage because their effectiveness has not been established:

- Autologous osteochondral mosaicplasty for the treatment of articular cartilage defects or lesions,
- Hybrid autologous chondrocyte implantation/osteochondral autograft transfer system (OATS) technique for the treatment of osteochondral defects,
- OATS for the treatment of articular cartilage defects or lesions, and
- Osteochondral autograft transplantation to repair chondral defects of the elbow, shoulder, or other joints.

Note: This policy specifies eligibility for a single small plug for a small lesion. The broad resurfacing of larger areas with multiple plugs of autogenous articular cartilage, e.g. mosaicplasty and OATS, is experimental and investigational.

Allografts[89]

Osteochondral allograft transplantation of the knee is medically necessary when the following selection criteria are met:

- Avascular necrosis lesions of the femoral condyle, *or*
- Non-repairable stage 3 or 4 osteochondritis dissecans, *or*
- Otherwise healthy, active, non-elderly patients who have failed previous arthroscopic procedures or are not candidates for such procedures, *or*
- Treatment of an isolated, traumatic injury that is a full-thickness depth (grade 4) lesion, preferable surrounded by normal, healthy tissue and the opposing articular surface is generally free of disease or injury.

The following are considered experimental and investigational:

- Indications for the knee other than those listed above,
- Osteochondral allograft of the talus, elbow, patella, patella-femoral ligament, and shoulder, and
- The use of the TruFit Plug.

- CIGNA[90]

  CIGNA considers EITHER of the following procedures as medically necessary for the repair of a single, focal, full-thickness articular cartilage defect involving the weight-bearing surface of the distal femur:
  - osteochondral autograft transplant (e.g., OATS and mosaicplasty) for a chondral defect that is between 1–2.5 cm in diameter or $\leq$ 2.5 cm^2 total, or

- osteochondral allograft transplant for a chondral defect that is > 2 cm^2 total.

ALL of the following criteria must be met for coverage:

- disabling localized knee pain unresponsive to conservative treatment and/or prior arthroscopic or other surgical repair,
- MRI imaging or arthroscopy demonstrating a chondral defect on the weight-bearing portion of the lateral/medial femoral condyle or trochlear region of the knee,
- normal knee alignment,
- stable knee with functionally intact menisci and ligaments,
- no evidence of arthritis on the corresponding tibial surface,
- normal appearance of hyaline cartilage surrounding the borders of the defect, and
- the individual is not currently a candidate for total or partial knee replacement.

An osteochondral autograft/allograft transplant for the treatment of articular cartilage defects on any joint surface other than the femur is not covered because this treatment is considered experimental, investigation, or unproven.

- Premera Blue Cross (Washington and Alaska)[91]
  Premera considers OATS/mosaicplasty or allograft medically necessary to repair focal (localized centrally or isolated) chondral defects of the knee and ankle.
  OATS/mosaicplasty or allograft is considered not medically necessary to repair chondral defects of the knee or ankle that are not focal.

  OATS or allograft is considered to be investigational for chondral defects of other articulating surfaces, such as the patella, hip, elbow, or shoulder.

  Generally accepted criteria for the knee include symptomatic cartilaginous defect in the weight-bearing surface of the medial, lateral, or trochlear area of the femoral condyle:

  - clinically significant symptoms (cartilage injury) that are unresponsive to physical therapy, conservative treatment, or prior arthroscopic or other surgical repair procedure,
  - the knee must be stable and aligned, or undergoing simultaneous stabilization,
  - there is no evidence of osteoarthritis or inflammatory disease.

  Generally accepted criteria for the ankle include a focal defect and symptomatic significant symptoms, which may include pain, swelling, and possible clicking as documented in chart notes.

  In some situations, if the focal chondral defect is associated incidentally at the time of arthroscopy, the decision to undergo osteochondral autografting can be made at the time of arthroscopy.

Table 10. Overview of payer technology assessments and policies.

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
Centers for Medicare and Medicaid Services (CMS)	N/A	N/A	No NCDs or LCDs for the region that includes Washington State	• N/A
Aetna (2010) *Clinical Policy Bulletin: Osteochondral Autografts (Mosaicplasty, OATS) Number 0637, last review 10/15/2010* *Clinical Policy Bulletin: Allograft Transplants of the Extremities Number 0364, last review 6/15/2010* [Aetna, 2010]	NR	<u>Autograft</u> 43 total references form the basis of the policy, with descriptions of: • 1 Assessment • 7 Reviews • 1 Guideline • 1 Technical Evaluation • 1 RCT • 2 Retrospective studies • 1 Cohort study • 2 Case series • 3 undefined studies <u>Allograft</u> NR	<u>Autograft</u> Osteochondral autografts are medically necessary for the repair of small (1 cm^2 or less) focal chondral defects of articulating cartilage of the leg (ankle, hip, knee), which are causing significant symptoms that have not been relieved by appropriate non-surgical therapies. All of the following procedures are considered experimental and investigational and are ineligible for coverage because their effectiveness has not been established: • Autologous osteochondral mosaicplasty for the treatment of articular cartilage defects or lesions, • Hybrid autologous chondrocyte implantation/osteochondral autograft transfer system (OATS) technique for the treatment of osteochondral defects, • OATS for the treatment of articular cartilage defects or lesions, and • Osteochondral autograft transplantation to repair chondral defects of the elbow, shoulder, or other joints. Note: eligibility is specified for a single small plug for a small lesion. The broad resurfacing of larger areas with multiple plugs of autogenous articular cartilage, e.g. mosaicplasty and OATS, is experimental and investigational. <u>Allograft</u> Osteochondral allograft transplantation of the knee is medically necessary when the following selection criteria are met: • Avascular necrosis lesions of the femoral condyle, *or* • Non-repairable stage 3 or 4 osteochondritis dissecans, *or* • Otherwise healthy, active, non-elderly patients who have failed previous arthroscopic procedures or are not candidates for such procedures, *or* • Treatment of an isolated, traumatic injury that is a full-thickness depth (grade 4) lesion, preferable surrounded by normal, healthy tissue	<u>Autograft</u> *Mosaicplasty* • There were no studies found comparing mosaicplasty with other established procedures. • There is a lack of long-term follow-up data on the durability of the repaired/transplanted tissues or on potential complications associated with multiple donor sites. *OATS* • No studies were found that compared OATS with other established therapies. • Majority of evidence is from retrospective/case series studies on chondral lesions of the knee. • Results are encouraging from early follow-up from these studies. Well-designed prospective studies with long-term follow-up are needed to establish the effectiveness of these treatments. CPT codes if selection criteria is met: 27416, 29866 HCPCS codes if selection criteria is met: J7330, S2112. <u>Allograft</u> • Evidence is mixed regarding the viability of freeze-dried allografts compared to deep-frozen allografts. • The policy primarily discusses allografts for ACL reconstruction. • A case series reported on the use of bipolar fresh osteochondral allograft (BFOA) for the treatment of ankle arthritis and concluded that further

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
			and the opposing articular surface is generally free of disease or injury. The following are considered experimental and investigational: • Indications for the knee other than those listed above, • Osteochondral allograft of the talus, elbow, patella, patella-femoral ligament, and shoulder, and • Use of the TruFit Plug.	research is needed regarding the immunological behavior of the transplanted cartilage. CPT codes if selection criteria is met: 27415, 29867
Cigna (2010) *Osteochondral grafts for articular cartilage repair (autografts, allografts, and synthetic grafts) Coverage Policy Number 0197, 10/15/2010*	NR	<u>Autografts</u> Unspecified numbers of retrospective and prospective case series, RCTs, non-randomized controlled/comparative trials, and published reviews. <u>Allografts</u> Unspecified number of case series.	EITHER of the following procedures is medically necessary for the repair of a single, focal, full-thickness articular cartilage defect involving the weight-bearing surface of the distal femur: • osteochondral autograft transplant (e.g., OATS and mosaicplasty) for a chondral defect that is between 1 – 2.5 cm in diameter or ≤ 2.5 cm^2 total, or • osteochondral allograft transplant for a chondral defect that is > 2 cm^2 total. ALL of the following criteria must be met for coverage: • disabling localized knee pain unresponsive to conservative treatment and/or prior arthroscopic or other surgical repair, • MRI imaging or arthroscopy demonstrating a chondral defect on the weight-bearing portion of the lateral/medial femoral condyle or trochlear region of the knee, • normal knee alignment, • stable knee with functionally intact menisci and ligaments, • no evidence of arthritis on the corresponding tibial surface, • normal appearance of hyaline cartilage surrounding the borders of the defect, and • individual is not currently a candidate for total or partial knee replacement. An osteochondral autograft/allograft transplant for the treatment of articular cartilage defects on any joint surface other than the femur is not covered because this treatment is considered experimental, investigation, or unproven.	<u>Autografts</u> • Osteochondral autologous transplantation seems to offer good short- to intermediate-term results for full-thickness lesion of the femoral condyle based on a large body of evidence in peer-reviewed scientific literature. • The ideal candidate for osteochondral autograft femoral transplants is of age 45 or younger; who has chondral defects with sharp, definite borders surrounded by normal-appearing hyaline cartilage; has a unipolar defect from 2 – 2.5 cm in extent; normal mechanical alignment; and a stable knee. <u>Allografts</u> • Osteochondral allografting seems to offer relief to pain and improved joint function for select patients based on a limited number of studies evaluating short- to intermediate-term outcomes. • Allograft size is not well-delineated in the medical literature. • Evidence supports the use of allografts in patients who are physically active, have failed standard medical/surgical treatments, and are too young to be suitable candidates for TKA. CPT codes when medically

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
				necessary: 27415, 27416, 29866, 29867.
Premera Blue Cross (WA and AK) (2010) *Osteochondral Allografts and Autografts (OATS) in the Treatment of Articular Cartilage Lesions Number CP.MP.PR.7.01.506, 5/10/2011*	NR	Focus of evidence presented is on osteochondral autografts: • 12 Case Series • 1 Comparative study • 1 Systematic Review • 1 Guideline	OATS/mosaicplasty or allograft is considered medically necessary to repair focal (localized centrally or isolated) chondral defects of the knee and ankle. OATS/mosaicplasty or allograft is considered not medically necessary to repair chondral defects of the knee or ankle that are not focal. OATS or allograft is considered to be investigational for chondral defects of other articulating surfaces, such as the patella, hip, elbow, or shoulder. Generally accepted criteria for the knee include symptomatic cartilaginous defect in the weight-bearing surface of the medial, lateral, or trochlear area of the femoral condyle: • clinically significant symptoms (cartilage injury) that are unresponsive to physical therapy, conservative treatment, or prior arthroscopic or other surgical repair procedure, • the knee must be stable and aligned, or undergoing simultaneous stabilization, • there is no evidence of osteoarthritis or inflammatory disease. Generally accepted criteria for the ankle include a focal defect and symptomatic significant symptoms, which may include pain, swelling, and possible clicking as documented in chart notes. In some situations, if the focal chondral defect is associated incidentally at the time of arthroscopy, the decision to undergo osteochondral autografting can be made at the time of arthroscopy.	Autografts • The majority of studies examining OATS or mosaicplasty in the knee or ankle are the less powerful case series. • The case series on knee and ankle OATS and mosaicplasty procedures consistently report decreased pain and increased knee function for patients, with several studies reporting complication rates of 17% – 23%. Good results were found in visual inspection of the graft site(s) for both procedures. The OATS procedure seems to work best for small- to medium-sized defects. • In an SR examining the effectiveness of different treatments for osteochondral defects of the talus, although OATS had the highest success rate compared with 2 other treatments it was not recommended as the primary treatment of choice because of observed knee morbidity. The authors stated that additional sufficiently powered trials need to be conducted. • One comparative study found significantly improved results in knee function in mosaicplasty patients compared with abrasion arthroplasty patients. • The cited Guideline presents patient selection criteria based on medical literature evidence and expert opinion. Allografts • This procedure has a long clinical history in treating knee joint pathology, so

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
				evidence for its efficacy is not presented in this policy. HCPCS codes: J7330, S2112

*Medicare does not report the current evidence available. N/A: Not Available; NR: Not Reported; NCD: National Coverage Determinations; LCD: Local Coverage Determinations; RCT: Randomized Controlled Trial; TKA: Total Knee Replacement
HCPCS: Healthcare Common Procedure Coding System; CPT: Current Procedural Terminology

2. The Evidence

2.1 Methods of systematic literature review

2.1.1 Focus and inclusion/exclusion criteria

The State's technology description which accompanied the key questions is as follows:

- Osteochondral Autograft Transfer System surgery is a graft procedure that uses one or more "plugs" of healthy cartilage to fill in damaged areas. It can be done as an open or arthroscopic procedure, and is sometimes combined with other joint operations such as arthroscopic debridement or ACL repair. The grafted cartilage is harvested from another area within the joint, and the harvest site as well as the repair site need to heal properly, so a period of physical therapy is required after the operation.
- Osteochondral Allograft Transplant Surgery is a graft procedure similar to Osteochondral Autograft Transfer System, but using graft material from preserved cadaver cartilage. There is some indication that allograft cartilage does not integrate as well, and transplantation involves some risk of infection. However, adequate healthy cartilage tissue is not always available within the joint under repair.
- Mosaicplasty is a more generic term that covers either Osteochondral autograft or allograft, open or arthroscopic.

The State's interest is in OATS/mosiacplasty as a specific procedure. Thus, the focus of this report is on cylindrical, dowel shaped or geometric shaped plugs of osteochondral material (autograft or allograft) that are press fit into a defect and do not require the use of screws, pins, plates or other fixation devices.

The following table summarizes the inclusion and exclusion criteria for this report.

Table 11. Summary of inclusion and exclusion criteria (PICO)

Study Component	Inclusion	Exclusion
Participants	• Persons with cartilage damage	•

Intervention	• Osteochondral autograft transfer system (OATS) • Osteochondral allograft transplantation (OAT-like procedures using dowels, cylinders, plugs) • Mosaicplasty	• Synthetic materials, artificial cement (e.g. Trufit plug, SaluCartilage, Chondrocushion, Hemicap or others) • Perichondrial arthroplasty • Osteochondral grafts as part of plate or screw systems or extensive reconstruction or that use plates, screws or pins for fixation • Cell-based repair (e.g. ACI) • Paste grafting (minced cartilage – allograft or autograft) • Non-FDA approved
Comparators	• Autologous chondrocyte implantation (ACI) • Microfracture surgery • Abrasion arthroplasty • Chondroplasty • Biologic resurfacing • Non-surgical interventions (e.g. physical therapy, viscosity supplementation) • Placebo • Combination of OATS with other procedures (e.g. ACL repair, meniscus transplant/repair, knee alignment, others)	• Non-FDA approved materials • Synthetic materials, artificial cement
Outcomes	• Pain relief • Functional outcomes measures (e.g. Cincinnati Knee Score, Knee Society Score, Lysholm score, WOMAC, American Orthopaedic Foot and Ankle Society, Ankle Osteoarthritis Scale ROM) • Quality of life (e.g. SF-36) • Reoperation • Progression to osteoarthritis • Complications/adverse events • Donor site morbidity and recovery	
Study Design	• Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be sought as the primary evidence base for questions of efficacy, effectiveness and safety • Validation/reliability studies in the population of interest for Question 2 • For question 4, safety, case series will be considered if adequate information not available from comparative studies. For inclusion, such studies must specifically evaluate complications, adverse events • Cost effectiveness studies assessing both costs and outcomes (Question 6)	• Case reports • Case series of < 18 patients with allograft ; case series of <30 patients with autograft unless designed specifically to evaluate safety • Cost-only studies • Studies of graft storage and preservation and cell viability • Laboratory studies of cell viability • Studies of the feasibility of diagnostic tests
Publication	• Full-length studies published in English in	• Abstracts, editorials, letters

	peer reviewed journals, published HTAs or publically available FDA reports • Full formal economic analyses (e.g. cost-utility studies) published in English in a HTAs or in a peer-reviewed journal published after those represented in previous HTAs.	• Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • Studies reporting on the technical aspects of these procedures • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

2.1.2 Data sources and search strategies

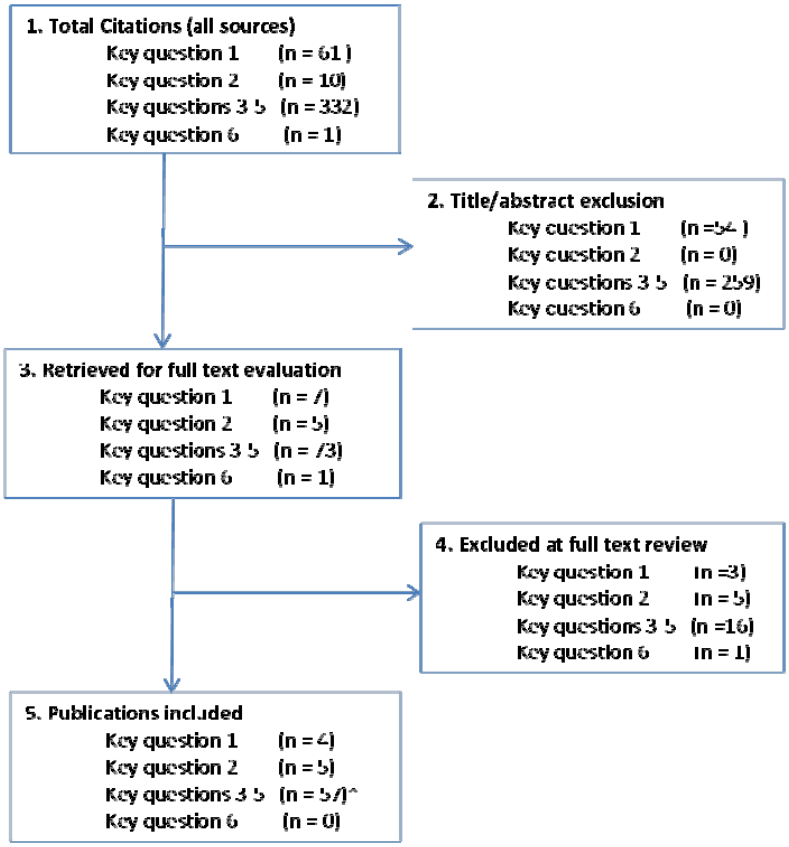
The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any unresolved disagreement between screeners resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Electronic databases searched included PubMed, EMBASE, ClinicalTrials.gov, *The Cochrane Library*, AHRQ, National Guideline Clearinghouse and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. Reference lists of all eligible studies were also searched. The search strategies are shown in Appendix B. The figure below shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

Search strategy and study selection

The search strategy used for this report is found in Appendix B. Additional information on article selection and excluded articles can be found in Appendices A-C.

Figure 1. Flow chart showing results of literature search



* includes 19 case series on shell/fragment grafting procedures that are briefly summarized

From a list of 332 potentially relevant citations a total of 57 reports were included based on the search strategies outlined in Appendix A. This includes19 case series on shell/fragment grafting procedures that are briefly summarized but systematic reviews, information from reviews or guideline are not included.

Studies of massive allografts used for structural purposes were excluded. The indication for these procedures (skeletal reconstruction e.g. following tumor resection) is very different from the indications for OAT, as is the procedure. The transplant procedure itself procedure itself is substantially different, as massive allografts normally require fixation, unlike the press-fit plugs used in OAT.

2.1.3 Data extraction

Reviewers extracted the following data from the included comparative clinical studies that provided primary evidence for this report: study population characteristics, study type, study period, patient demographics and characteristics, study interventions, follow-up time, study outcomes, adverse events, and other complications. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. For full economic

studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

2.1.4 Study quality assessment methods: Level of evidence (LoE) evaluation

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine,[92] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[93] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[94] Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Details of the Level of Evidence (LoE) methodology are found in Appendix D. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix E. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence for the relevant question or topic is determined. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group[93] for the development of clinical guidelines. Details are provided in Appendix D.

2.2 Quality of literature available

With the exception of the five randomized controlled trials which compared OAT/mosaicplasty using autograft with other surgical options, the primary evidence base consists of case series (LoE IV). Over 160 case series were found via the search strategy.

Studies retained

For Key Question 1, Three studies of reliability were included and evaluated.[95-97]

For Key Question 2, Five studies evaluating the properties of outcomes measures were included.[2,98-101]

Autograft: For Key questions 3-5 related efficacy, effectiveness and safety of autograft OAT/mosaicplasty, data from five randomized controlled trials[3-7], seven comparative studies of autograft[8,9,25,102-105] and 15 case series were included [55,106-117] were included.

Given that comparative studies were available for autograft procedures to evaluate questions of efficacy and effectiveness, case series were not considered except to provide additional summary/rate information related to safety and complications. Case series for evaluation of safety were limited to those with >30 participants and those identified via specific searches for safety-related factors or designed explicitly to evaluate safety and complications. Eleven case series reports by Hangody and colleagues on the same underlying patient population were found.

The 2008 publication[55] was felt to have the most complete data (N = 1097 procedures) on this population and safety outcomes are summarized. An additional four case series of autograft contained subanalyses exploring differential safety or efficacy with respect to patient, lesion or procedural factors was included.[118-121]

Allograft: No high quality comparative studies of allograft OATS-like procedures were found. Two poor-quality (LOE III) comparative studies were found.[122,123] Six case series (LoE IV) with a minimum of 18 patients who received dowel, cylinder or geometric "plug" allografts that did not require routine screw or plate fixation were included.[10,11,124-127]

Another 19 case series (LoE IV) which used small fragment or shell autograft plugs which included hardware fixation are only briefly summarized. Although they use "plugs" of allograft material they are different from the OATS/mosiacplasty type press-fit grafting and use hardware/fixation devices. Numerous publications on allograft use which appear to report on the same population (based on authorship and methods descriptions) were found.

2.2.2 Critical appraisal and level of evidence evaluation

Details of the Level of Evidence (LoE) methodology are found in Appendix D. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix E. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment. Additional critical appraisal is also contained in Appendix E.

The included RCTs were all considered LoE IIb, indicating poor quality for an RCT and greater opportunity for bias. Only one study had a sample size of >50. The appendix contains additional critical appraisal information on these studies.

The quality of reliability studies for Key Question 1 related to lesion size and determination of classification was LoE III for two studies and LoE II for the third.

All comparative non-randomized studies were LoE III. Treatment allocation was based on lesion characterization and severity in all cases. Thus, all had significant potential for bias, particularly confounding by indication. In addition, sample sizes were small. LoE for individual studies is found in the Appendix E.

All case series are LoE IV. Most of the case series were retrospective and the percentage of eligible patients who were followed up was generally not clear. Multiple publications were from the same author groups and it was difficult to evaluate potential for overlap in patients across reports. Although some reports indicated that data were acquired prospectively, the study design and analyses are generally retrospective.

2.3 Description of study population

Population description – studies of autografts

Five randomized controlled trials (RCTs) or quasi-RCTs addressed the efficacy of OATS/mosaicplasty in the knee[3-7] and no RCTs were found that addressed the efficacy of OATS/mosaicplasty in the ankle. Of these studies, two compared mosaicplasty to autologous chondrocyte implantation (ACI),[6,7] two compared osteochondral autologous transplantation (OAT) to microfracture (MF),[3,4] and one compared what the authors termed osteochondral cylinder transplantation to ACI.[5]

The following table summarizes the patient populations from randomized controlled trials and is described in the text below.

Table 12. Summary of population, osteochondral defect and intervention characteristics for RCTs (or quasi-RCTs) comparing OAT/mosaicplasty (autograft) with other repair procedures

Study	Mean age (years)	% male	Population	Mean defect size (range)*	Grade; description †	No. plugs (range); plug size	% prior surgery	Open or Arthroscopic
OAT vs. MF‡								
Gudas 2005 N = 57	24.3	61.4%	Athletes	2.8cm^2 (1-4 cm^2) 70% were 2-4 cm^2	ICRS 3 or 4; Single OCD or full thickness articular cartilage	4.3 (3-6); 5.5 mm	none	OAT and MF arthroscopic
Gudas 2009 N = 47	14.3	60.0%	Children	2-4 cm^2 80% OAT and 95% MF ≤ 3 cm^2	Single OCD; ICRS OCD grade 3 or 4	4.7 (3-7); 5-6 mm	none	OAT and MF arthroscopic
OAT vs. ACI‡								
Horas (2003) N =40	33.4	57.5%	General, unspecified	3. 75 cm^2 (2.2-5.6 cm^2)	Single; full thickness w/o osseous lesion; single traumatic event	NR; NR	OAT 10% ACI 35%	OAT - open ACI open
Mosaicplasty vs. ACI‡								
Bentley (2003) N = 100	31.6	57%	General, unspecified	4.66 cm^2 (1 - 12.2 cm^2)	Trauma 46%; OCD 19%; chondromalacia patellae 14%, other 21%	NR; 4.5 mm as possible	94% (mean 1.5)	Open
Dozin (2005) N = 44§	28.7	61.4%	General, unspecified	1.93 ± 0.03 cm^2 (NR)	Focal; Outerbridge III/IV w/o bone injury/loss;	NR; NR	none	Open

OAT = osteochondral autologous transplantation or osteochondral cylinder transplantation; MF = microfracture; ICRS = International Cartilage Repair Society;
ACI = autologous chondrocyte implantation; NR = not reported ; OCD = osteochondritis dissecans.
*Defect size as reported
†Grade or classification of lesion or description provided by author
‡OAT or mosaic plasty as designated by the study authors; ACI is a 2-stage procedures requiring intervention at 2 times
§Dozin randomized 44 participants but only 23/44 actually received treatment due to "spontaneous improvement" during the 6 months between examination/debridement and scheduled surgery.

The majority of participants in all studies were male. Studies comparing OATS/mosaicplasty with ACI were composed of participants that were older compared with those that used microfracture as a comparator. Four of the five studies included patients with isolated lesions

only; number of lesions is not clear in the fifth study. Mean defect sizes ranged from 1.9-4.6 cm^2, with the largest study (Bentley) reporting the largest defect sizes, up to 12.2 cm^2.[7] Although the Gudas studies[3,4] call their autograft procedure OATs, some might refer to it as mosaicplasty since multiple plugs were used. It is also probable that multiple plugs were used in the studies by Bentley[7] and Horas[5] given the defect sizes; however, this cannot be confirmed because they do not report details on the numbers or sizes of plugs used. Therefore, it is possible that all studies (with the possible exception of Dozin given the smaller lesion size in that study[6]) could be considered consistent with mosaicplasty. None of the studies described transplant configuration or arrangement.

Gudas 2005

- Population of young athletes
- Over 70% of participants had lesion sizes 2-4 cm^2 and the majority of lesions were located in the medial femoral condyle in the central portion (57% and 59% respectively for OAT, MF) based on sagittal plane (MRI or radiography)
- Arthroscopic only

Gudas 2009

- Population of children who had ICRS grade III or IV osteochondral dissecans
- Arthroscopic only

Bentley 2003

- Etiology of defects differed between treatment groups, raising some questions regarding the success of randomization. Etiology for mosaicplasty and ACI respectively was trauma 52%, 41%; OCD 12%, 24%; chondromalacia patellae 5%, 14%; other 31%, 14%)
- Anatomic distribution also differed between treatment groups. For mosaicplasty and ACI groups respectively distributions were medial femoral condyle 69%, 45%, patella 12%, 38%, lateral femoral condyle 12%, 25%
- Over 90% of participants had a prior surgical intervention
- Open only

Dozin 2005

- Surgery was performed in 50% and 54% of those randomized to mosaicplasty and ACI respectively as authors reported "spontaneous improvement" occurred in patients following the initial arthroscopic examination and debridement
- Open only

Horas 2003

- 20% of OATs patients and 35% of ACI patients had prior surgical procedure
- ACI open, OAT open

Population description – allograft studies

Six case-series were included that reported outcomes following OATS using cylindrical/dowel-shaped allografts. Three of these studies used dowel-shaped allografts only.[125-127] The other

three studies used primarily dowel-shaped allografts but also allowed for the use of other types of grafting with and without minimal fixation (i.e. shell allograft, mushroom-shaped allograft).[10,11,124] For the purposes of this report, these two groups are reported separately.

Table 13. Summary of population, osteochondral defect and intervention characteristics for case series reporting clinical outcomes following OATS using dowel-shaped allografts.

Study	Mean age (yrs)	% male	Population	Defect size*	Description, grade †	No. plugs (size)	Prior Surgery (%)	Open or Arthroscopic
Dowel/cylindrical shaped allograft only								
LePrade (2009) N = 23	30.9	56.5	General, unspecified	4.8 cm^2 (3.1–9.6)	OCD: 60.9%; localized full-thickness chondral defect: 39.1%; femoral condyles; symptomatic	1 (NR)	87.0% had previous surgeries	Open
McCulloch (2007) N = 25	35	72.0	52% on workers' compensation	Primary: 5.2 cm^2 (2.3–10.5); Secondary: 2.3 cm^2 (0.8–4.0)	Degenerative: 36.0%; traumatic: 32.0%; OCD: 24.0%; osteonecrosis: 8.0%; femoral condyles; symptomatic	Varied by patient [Primary: 4.0 cm^2 (1.8–7.1); Secondary: 1.8 cm^2 (0.6–3.1)]	96.0% had previous surgeries	Mini-open‡
Williams (2007) N = 19	34	68.4	General, unspecified	6.0 cm^2 (1.2–15.0);	OCD: 68.4% localized full-thickness chondral defect: 26.3%; osteonecrosis: 5.3%; femoral condyles; symptomatic	NR (NR)	89.5% had previous surgeries (mean 2 per patient, range 0–4)	Arthroscopic
Dowel/cylindrical-shaped allograft plus other types of grafting								
Bakay (1998)§ N = 33	48	NR	General, unspecified	NR	Osteoarthritis: 42.4%; traumatic: 33.3% chondromalacia: 15.2%; OCD: 9.1%; femoral condyle, tibial condyle, and patella	1–3 (NR)	NR	NR
Emmerson (2007)** N = 64	28.6	70.3	General, unspecified	NR	OCD type 3 or 4: 100%; femoral condyle	NR (7.5 cm^2)	100% had previous surgeries (mean 1.7 per knee)	Open or mini-open
Görtz (2010)†† N = 22	24.3	27.3	General, unspecified	NR	Steroid-induced osteonecrosis: 100%; Modified Ficat/Arlet stages III-IV (advanced); femoral condyle	1, 53.6% 2, 32.1% 3, 14.3% (mean total surface area 10.8 cm^2)	50% had previous surgeries (mean 1.5 per knee)	Open or mini-open
Allograft using press-fit dowels versus ARIF versus loose-body removal								
Pascual-Garrido (2009)								
Allograft, n = 16	34 ‡‡	NR	Adults (age ≥ 20 years)	2.4 ± 0.9 cm^2	Adult OCD 100%; femoral condyle	NR (size: 18–25 mm diameter; depth: 6–8	NR	NR

						mm)		
ARIF, n = 15	34‡‡	NR	Adults (age ≥ 20 years)	2.1 ± 0.5 cm^2	Adult OCD 100%; femoral condyle	n/a	NR	Arthroscopic
Loose-body removal, n = 9	34‡‡	NR	Adults (age ≥ 20 years)	2.1 ± 0.6 cm^2	Adult OCD 100%; femoral condyle	n/a	NR	NR

ARIF = arthroscopic reduction and internal fixation; ACI = autologous chondrocyte implantation; OCD = osteochondritis dissecans; MF = microfracture; n/a = not applicable; NR = not reported.
*Defect size as reported.
†Grade or classification of lesion or description provided by author.
‡Associated procedures included 10 mensical transplantations, 4 opening wedge high tibial osteotomies, and 1 removal of previous osteotomy plate.
§Femoral condyles: dowel-shaped plugs press-fit without additional metal fixation; tibial condyles: shell allograft plugs press-fit with AO screw; and patella: mushroom-shaped grafts press-fit without additional metal fixation.
**For small and medium-sized lesions, a dowel technique was used; for larger lesions, a shell allograft technique was used.
††Shell allografts were used in 67.9% (19/28) of knees and dowel-shaped plugs were used in 32.1% (9/28) of knees.
‡‡Mean age of entire study population (n = 46); mean ages were not reported separately for each group.

In the studies of dowel-shaped allografts there were a total of 67 patients, the majority of which were male. Mean ages were similar across studies, ranging from 31 to 35 years. In one study, a little over half of the participants were on Workers' Compensation.[126] All lesions were located on the femoral condyles and the most frequent cause was osteochondritis dissecans followed by full-thickness chondral defects. The size of the defect ranged from 4.8 to 6.0 cm^2 and the number of plugs/allografts used varied. Over 85% of patients in all studies had undergone prior surgery. The extent to which prior surgical intervention may have influenced outcomes is unknown. Different surgical approaches were used in all three studies to include open, mini-open, and arthroscopic. All grafts were placed with use of a press-fit technique that did not require internal fixation. One study reported associated procedures performed at the time of grafting including meniscal transplantations, open wedge high tibial osteotomies, and removal of prior hardware.[126] Following surgery, patients in two studies were allowed touchdown weight bearing with the assistance of crutches or a brace for a minimum of six to eight weeks and in the third study patients were to remain non-weight-bearing for at least eight weeks. All patients used a continuous passive motion machine during the immediate postoperative period and were started on a supervised rehabilitation program.

In the studies of grafts of varying shapes (including cylindrical) , the population characteristics were heterogeneous across the studies. There were 119 total patients. Mean patient age in one study was greater compared to the other two studies: 48 years versus 28 and 24 years. The percentage of male patients varied across studies with males comprising 70% in one study, 24% in another, and not reported in the third. Etiology of the lesion was different for each study with osteoarthritis and trauma being the primary causes (76%) in one study and osteochondritis dissecans type 3 or 4 and steroid-induced osteonecrosis accounting for all lesions in the second and third studies, respectively. Lesion location was isolated to the femoral condyle in two studies whereas the third study treated lesions on the femoral and tibial condyles as well as the patella. The mean defect size was not reported in any of the studies and the number of plugs/allografts used ranged from one to three as reported by two studies. All patients in one study and 50% in another had undergone prior surgery; the third study did not report on prior surgery. Two of the studies used an open or mini-open approach; the type of approach could not be determined for the third study. Bakay et al used dowel-shaped plugs press-fit without additional fixation for treatment of lesions on the femoral condyles, shell allograft plugs press-fit

with AO screw for the tibial condyle, and mushroom-shaped grafts press-fit without additional fixation for the patella.[11]; shell allograft plugs press-fit with AO screw for the tibial condyle; and mushroom-shaped grafts press-fit without additional metal fixation for the patella.[11] For small and medium-sized lesions, Emmerson et al used a dowel technique; for larger lesions, a shell allograft technique was used.[124] In Gortz et al, shell allografts were used in 67.9% of knees and dowel-shaped plugs were used in 32.1%.[10]Gortz et al, shell allografts were used in 67.9% of knees and dowel-shaped plugs were used in 32.1%.[10] Postoperative care for all studies included the use of continuous passive motion, touchdown or protected weightbearing for the first few months, and routine physical therapy.

2.4 Description of study outcomes

The focus of this report is on patient-centered outcomes. Patient-reported and clinician-based outcomes measures as well as quality of life outcomes are the emphasis for the evaluation of efficacy, effectiveness and, where applicable, safety. Specific outcomes measures are further described in results from key question #2. Although the gold standards for assessing regeneration of tissue following grafting procedures are second-look arthroscopy and cartilage biopsy, these were considered intermediate outcomes. [In addition, these procedures were generally done in fewer than 60% of the participants in included studies and were frequently done for the evaluation of extended symptoms or other concerns. Thus, data from these were not considered reliable.]

For safety, information on complications, revisions, donor site morbidity, adverse events, repeat procedures, persistent pain and progression to arthritis was sought. For full economic evaluations, incremental cost-effectiveness ratios are desirable.

3. Results

3.1 Key question 1: What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification?

Background
There is variability with respect to the terms used to describe osteochondral grafting with cylindrical, dowel-shaped or geometrically shaped "plugs" which are press-fit to fill defects. For autograft procedures, the following terms have been used: osteochondral autograft transfer system (OATS), osteoarticular transfer system (OATS), osteochondral autologous graft transplantation (OATS) osteochondral autograft transplantation (OAT), autologous osteochondral transplantation (AOT) and mosaicplasty among the most common. Regarding allograft, the general term "osteochodral allograft" (OCA) has been used but appears to encompass a wide range of different techniques which include cylindrical, dowel-shaped plugs which are press-fit similar to what is described for OATS as well as shell/fragment grafts which use pins or screws. The terms "mega-OATS" and massive OATS have been used. Arthrex uses

the term "Allograft OATS® (Osteochondral Autograft Transfer System)" and OATS has also been referred to as Ostoechondral Allograft/Autograft Transfer System. Smith & Nephew and Arthrex have specialized tools and arthroscopic systems (which are trademarked) for creating and fitting cylindrical, dowel-shaped plugs.
Definitions are also variable. In general, it appears that the term OAT (or OATS) refers to the use of one or two larger cylindrical plugs and mosaicplasty is used to describe multiple cylindrical plugs.[16]

The primary goals for treatment of osteochondral injuries are to relieve pain and restore function. A number of sources acknowledge that there is a lack of methodologically rigorous controlled trials for guiding clinical treatment decisions and determining which may be the best options for treating patients with symptomatic osteochondral injuries to achieve those goals.[15,18,41] Cited evidence in most review articles describing which repair procedures may be most appropriate for a given patient comes from case series and one systematic review (described below). Treatment algorithms related to treatment of joints other than the knee were not found.

Guidelines from the International Cartilage Repair Society (ICRS) on the conduct and design of studies on knee cartilage repair advise that the ideal patient for clinical RCTs of articular cartilage repair *in general* (i.e. any repair option) is young with a symptomatic focal, full-thickness chondral or osteochondral defect (ICSR grade 3 or 4) surrounded by normal cartilage in an otherwise healthy knee.[22] The authors state that "indication criteria for articular cartilage repair studies continue to evolve." The table below summarizes their current recommendations for indications, contraindications and considerations:

Summary of current recommendations for articular cartilage repair

Indications	Contraindications	Special considerations
• Symptomatic • Focal full or near-full thickness (IRCRS Grades 3 and 4) of the femoral condyle, trochlea, patella • Primary or secondary cartilage repair	• Advanced degenerative joint changes (joint space narrowing >50%) • Uncorrected axial malalignment >5° for femoral defects • Uncorrected patellar maltracking or instability for patellofemoral lesions • Uncorrected ligamentous instability • Age >60 years • Limited patient adherence • Tumor • Infection • Inflammatory arthopathy • Systemic cartilage disorder	• Defect size >2-4 cm^2 (for marrow stimulation, osteochondral authograft) • Body mass index >30 • Mild joint degeneration (joint space narrowing <50%) • Uncontained chondral lesions (depending on techniques used) • Recent medical treatments/surgery • Asymptomatic defects • Bipolar defects.

A selective review by Farr et al. likewise describes the ideal (Farr's wording) patient for repair (in general) as having a symptomatic, localized cartilage defect, a BMI <35 kg/m^2, and willing to adhere to postoperative rehabilitation protocols.[41] They suggest that relevant comorbidities related to alignment, meniscal or ligament deficiencies be addressed in staged or concomitant procedures and factors such as activity level, age, lesion size, location and chondral status also be considered.

Treatment algorithms from review and instructional articles provide similar advice and do not provide evidence-based case definitions or cite evidence supporting the decision tree for

determining characteristics that point to the best treatment options. (Citations of supporting evidence are generally not provided or, in one case refer to case series). All of these articles describe treatment options for knee lesions.[12,26,45] From these treatment algorithms, after assessing alignment, ligament stability and meniscal deficiency, recommendations for use of OAT (autograft) versus osteochondral allograft (there is no mention of mosaicplasty specifically) are primarily based on lesion size and classification and whether the patient is "high demand" or "low demand" regarding their physical activity. Some authors suggest that OATS (autograft) is indicated for lesions < 4 cm^2 and osteochondral allograft (OCA) for deep lesions > 4 cm^2 depending on patient profile.[26] The American Academy of Orthopedic Surgeons (AAOS) instructional course provides the following algorithm for focal chondral lesions of the femoral condyle and patellofemoral joint. It is adapted here to reflect choice of OATS (autograft) versus osteochondral allograft (OCA) based on lesion size and patient activity.[45]

Table 14. Treatment algorithm for focal chondral lesions (adapted from Cole, 2009)[45]

	Femoral Condyle				Patellofemoral Joint			
	Lesion size		Lesion size		Lesion size		Lesion size	
	< 2-3 cm^2	> 2-3 cm^2	< 2-3 cm^2	> 2-3 cm^2	< 2-3 cm^2	> 2-3 cm^2	< 2-3 cm^2	> 2-3 cm^2
DEMAND	High	Low	High	Low	High	Low	High	Low demand
First line treatment	OATS	OATS	OCA	OATS (possible option) OCA (best option)	Neither OATS nor OCA	OATS and OCA possible options	OCA	Neither OATS nor OCA
Second line treatment	OCA is an option				OCA is an option			

The following table provides an overview of the lesion classification systems used in included comparative studies of knee osteochondral repair. Lesion classification is one consideration in determining treatment options.

Table 15. Classification schemes for osteochondral defects that were used in the included comparative studies on knee repair

Outerbridge Classification	Grading system for joint cartilage breakdown: • Grade 0 - normal • Grade I – cartilage with softening and swelling • Grade II – a partial thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter • Grade III – fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm • Grade IV – exposed subchondral bone	The higher the grade, the greater the severity of injury.
ICRS Classification	Grading system for joint cartilage breakdown: • Grade 0 – normal • Grade 1 – nearly normal: o A. Superficial lesions with soft indentation and/or o B. Superficial fissures and cracks • Grade 2 – abnormal: lesions extending down to <50% of cartilage depth • Grade 3 – severely abnormal: o A. Cartilage defects extending down >50% of cartilage depth o B. As well as down to calcified layer	The higher the grade, the greater the severity of injury.

	○ C. Down to but not through the subchondral bone ○ D. Down to but not through the subchondral bone with blisters included • Grade 4 – severely abnormal: through the subchondral bone	
ICRS OCD Classification	Grading system osteochondritis dissecans (OCD): • Grade OCD I – stable, continuity: softened area covered by intact cartilage • Grade OCD II – partial discontinuity, stable on probing • Grade OCD III – complete discontinuity, "dead in situ", not dislocated • Grade OCD IV – dislocated fragment, loose within the bed or empty defect ○ >10 mm in depth is B-subgroup	The higher the grade, the greater the severity of injury.

Strategy to answer Key Question 1

The first step was to identify and compare the inclusion/exclusion criteria from randomized studies included in this report. Because no randomized studies of allografts were available, information was taken from prospective case series. Inclusion/exclusion criteria of clinical trials were used because these criteria define a subpopulation of patients thought to have the condition. Prospective studies were chosen because retrospective studies only have available those criteria that were collected at baseline while prospective studies are able to state *a priori* all the criteria that best identify the population for which OATS/mosaicplasty (autograft or allograft) may be most appropriate. One way to assess whether there is an agreed-upon case definition is to compare these criteria.

A PubMed search was done to identify studies which were explicitly designed to evaluate the clinical decision-making for diagnosis and treatment of osteochondral defects. Studies comparing the feasibility of MRI for use in evaluation of osteochondral lesions were excluded. Studies evaluating populations which primarily consisted of participants with ligamentous or meniscal lesions were excluded as were those focused on evaluation of osteoarthritis or rheumatoid arthritis. As standard x-ray and arthroscopic sizing and grading of lesions is used to determine treatment options, studies of the validity and reliability of arthroscopic grading and determination of lesion size in individuals with chondral or osteochondral defects were sought for grading systems used in included comparative studies.

Summary

Consistent or agreed-upon case definition:

- There is variability with respect to the terms used to describe the various procedures and how they are defined. No specific agreed upon case definitions were found. Treatment algorithms (only available for the knee) cite case series. Lesion size and classification appear to be the primary criteria for assessing treatment options (after ligament and meniscus stability have been determined).
- Autograft (OAT or mosaicplasty): Based on inclusion/exclusion criteria for randomized studies for knee lesions, the most consistent characteristics defining cases for inclusion were: symptomatic (5/5 studies), isolated (4/5 studies) full-thickness lesions or Outerbridge or ICRS grades 3 or 4 lesions (4/5 studies). Exclusion criteria in three of the five studies included knee

joint instability or ligamentous deficiency. The mean ages of participants in all studies was <45 years old.
- Osteochondral allograft (dowel, cylinder, plug): No prospective comparative studies were found and limited information is available from three case series. Cases were defined as symptomatic in all three studies. One study explicitly stated that criteria included patients with OCD or full-thickness lesions; the other two listed these as characteristics of the populations. (Authors state that data were collected prospectively, however, it is likely that all of these were retrospective analyses.)
- One poor quality study evaluating a treatment algorithm failed to provide data by treatment group. Studies designed to evaluate clinical decision-making based on patient or lesion characteristics were not found.
- Talus: Only one comparative study was available. Pain and presence of a full thickness lesion as inclusion criteria are consistent with criteria described above for the knee.
- No studies pertaining to other anatomical regions meeting the inclusion criteria were found.

Evidence of validity and reliability
- No validity studies of the Outerbridge or ICRS lesion grading systems in the population of interest were found.
- Overestimation of lesion size by arthroscopy compared with open evaluation was reported in one clinical study. Inexperienced clinicians had less accurate measures.
- Two clinical studies evaluated the reliability of the ICRS grading system. One study reported 80.9% agreement between arthroscopic and open assessment of grade. Only one study (the smallest) reported chance-adjusted agreement between raters and suggests that there is only fair to slight agreement between raters evaluating lesions arthroscopically.
- One clinical study evaluated the inter-rater reliability of the Outerbridge classification. The overall agreement beyond chance for the video tapes where surgeons were to discriminate between grades 2 and 3 was moderate (κ range 0.41-0.57). The authors did not apparently evaluate grade 4 lesions to any large extent and thus, application to a case definition which may focus on grades 3 and 4 lesions is not clear.
- No studies for anatomical regions other than the knee were found.

DETAILED RESULTS:

Inclusion criteria from comparative studies of OAT/mosaicplasty (autograft)

Inclusion criteria from the five included randomized controlled trials comparing OATS/mosaicplasty (autograft) with other treatment options in the knee are summarized in the table below. Overall, common inclusion criteria were:
- Mention of and/or description of symptoms including pain, locking of the joint, swelling
- Isolated defects, usually on a weight-bearing surface of the femoral condyle
- Full thickness cartilage lesions; lesions classified as ICRS 3 or 4 or Outerbridge III or IV lesions
- Three studies specified lesion sizes for inclusion; two specified that lesions be less than 4 cm^2 in two different populations. In all but one study, mean lesion sizes reported were ≤ 4 cm^2.

- All populations were less than 45 years old; one population was of children only
- In three of the five studies, eligible persons had stability of the knee and/or absence of alignment, ligament or meniscus problems.
- Two studies explicitly excluded individuals with degenerative or rheumatoid joint changes.
- Three studies excluded persons who had had prior surgeries.

Table 16. Summary of inclusion/exclusion criteria from included RCTs of autograft OAT/mosaicplasty

	OATS/MOS vs. Microfracture		OATS/MOS vs. ACI		
	Gudas 2005[3]	Gudas 2009[4]	Bentley 2003[7]	Dozin 2005[6]	Horas 2003[5]
INCLUSION CRITERIA					
Pain			persistent		
"Symptomatic"	yes	yes	yes	yes	yes
Activity reduction			yes		
Isolated/single defect/focal	yes	yes		yes	yes
Defect location	Weight-bearing surface med or lat condyle	med or lat condyle	no criterion specified	Weight-bearing surface of femoral condyle or patella	Weight-bearing surface of femoral condyle
Defect size	1-4 cm^2	2-4 cm^2	>1 cm diameter *	≥ 1 cm^2	(Mean 3.75 cm^2, not listed as criterion)
Lesion grade/characteristic	ICRS 3/4 or full thickness cartilage	Grade 3/4 OCD	Trauma, OCD, chondromalacia	Outerbridge III/IV w/o bone loss	full thickness w/o osseous lesion
Age	<40 yrs	<18 yrs		16-40 yrs	18-45 yrs
Clinical symptoms			giving way, locking, catching, swelling		pain with weight-bearing or squatting, locking, catching, swelling
History- single traumatic event				Single traumatic or repetitive low impact injury	yes
Other patient characteristics	althletes;Tegner I/II				
No prior surgery	yes	yes		yes	
EXCLUSION CRITERIA					
Lesion size	>4 cm2				
Ligament deficient knee	yes				
Knee joint instability				yes	yes
Matching lesion-opposing tibial surface					yes
Osteochondral tumor/neoplasia				yes	yes
Axial malalignment				yes	yes
Skeletal immaturity					yes
Degenerative or rheumatoid joint				yes	yes

Overweight				yes	
Injury to/loss of subchondral bone				yes	
ACL injury or meniscal damage				yes	
HIV, HBV or HCV (viral) infection				yes	
Activity	Tegner III/IV				

MOS = mosaicplacy; Yes = author stated this as an inclusion or exclusion criterion; Blank indicates that nothing was specified
* This is listed as a "criteria for grafting" but authors do not specify that this was an inclusion criterion. Mean lesion size across treatment arms was 4.66 cm^2.

One non-randomized comparative study evaluating OATS in the talus was found.[103] The inclusion/exclusion criteria were as follows.

Inclusion criteria	**Exclusion criteria**
• Pain or limited function despite minimum 6 months non-surgical management • Ferkel class 2b (full thickness with overlaid fragment), 3 (lesion without fragment displacement) and 4 lesions (free loose fragment) • Primary cases only (no previous surgical treatment for lesions • Lesions confirmed by MRI and arthroscopy	• Lesions < 1 cm^2 • Bipolar ("kissing") lesions • Diffuse arthritic change • Associated ankle disease (3.g. fracture) • Far posterior or central lesions not readily amenable to arthroscopic management

No comparative studies involving use of OATS/mosaicplasty (autograft or allograft) for the treatment of osteochondral defects for other joints were found.
No prospective comparative studies on the use of allograft were found. Information from three small case series on allograft that primarily focused on procedures that were most consistent with autograft OATS (i.e. those using dowel/cylinder or plugs without use of hardware) is provided in the table below. Although all three studies reported that patients were prospectively enrolled into a registry or database, it is not clear that the study was designed prior to enrollment or that inclusion/exclusion criteria were set *a priori*. It is likely that the study design and analysis are retrospective. Limited information was provided in these three studies. No inclusion/exclusion criteria with respect to age, history of trauma, prior surgeries, BMI or weight were specified in any of these studies. Overall, common inclusion criteria were:

- Mention of and/or description of symptoms
- Two of the three studies stated that only patients with isolated lesions were included.
- Two of the three specified inclusion of patients with OCD or full-thickness lesions and the third described these as indications for the procedure.
- Two of the three excluded participants with ligamentous deficiency, malalignment or knee instability.
- Only one study described lesion size as an inclusion criterion (>3 cm^2).

Table 17. Summary of inclusion/exclusion criteria from prospective case series of allograft using cylinder, dowel or plug

	Laprade 2009[125]	**McCulloch 2007[126]**	**Williams 2007[127]**

INCLUSION CRITERIA			
Pain			
"Symptomatic"	yes	yes	yes
Activity reduction			
Isolated/single defect/focal	yes		yes
Defect location	femoral condyle	femoral condyle	femoral condyle
Defect size	> 3 cm2	criterion not stated; indication described as >2cm2	no criteria listed; mean lesion size was 6.02 cm2 (range, 1.21 to 15.00 cm2
Lesion grade/characteristic	OCD, full-thickness cartilage	described as indication not inclusion criteria full-thickness cartilage (degenerative, OCD, osteonecrosis, traumatic)	full-thickness, OCD, osteonecrosis
Age			
EXCLUSION CRITERIA			
Multiple lesions			yes
Lesion size			
Ligament deficient knee			yes
Knee joint instability	yes		yes
Matching lesion-opposing tibial surface	yes - "kissing" lesion of the corresponding articular cartilage surface		
Osteochondral tumor/neoplasia			
Axial malalignment	yes		yes-severe lower extremity malalignment
Degenerative or rheumatoid joint	more than minor peripheral osteophytes or joint-space narrowing		
Overweight			
Injury to/loss of subchondral bone			
ACL injury or meniscal damage	no (most had concurrent operations)		ligamentous instability

Studies identifying factors for treatment selection

One systematic review[15] sought to identify factors for treatment selection for repair of articular cartilage lesions of the knee and included four RCTs, two of which compared OATS/mosaicplasty to an alternative treatment. (This review is summarized previously with other systematic reviews). These two RCTs are included in this HTA.[3,7] The authors concluded that lesion size, activity level and patient age should be considered in selecting treatment. For defects > 4 cm^2, clinical improvement was worse for OAT compared with ACI (based on Bentley 2003)[7] and for medium-sized lesions (~2.8 cm^2) OAT led to better clinical outcomes compared with microfracture (based on Gudas 2005).[3]

One poor quality study (LoE III) sought to create a clinical algorithm for treating patients with traumatic full thickness osteochondral lesions of the knee based on lesion size and Tegner score.[18] The population consisted of 65 patients who were treated for ICRS grade 3B, 3C, 4A or

4B cartilage injuries who were observed at 12 months following surgery. The study appears to be retrospective and no patient characteristic data were provided. Mosaicplasty (n = 24) was used in lesions up to 4 cm^2, microfracture for lesions > 4 cm^2 in patients with Tegner ≤ 3 (n = 26) and bone marrow transplant with periosteum flap (n = 15) for lesions > 4 cm^2 in patients with Tenger ≥ 4 or lesions > 8 cm^2 . Results were not separated out for these groups. Across groups, 49 patients were classified as normal, 24 as nearly normal and 3 abnormal based on the IKDC 2000 Knee Examination form. No conclusions regarding the effectiveness of mosaicplasty based on lesion size are possible from this study.

Studies evaluating validity and reliability of x-ray or arthroscopic evaluation and defect size or classification

No studies evaluating the validity and reliability of lesion size with standard x-ray were found. Arthroscopy is considered by many to be the "gold standard" for grading of osteochondral lesions and a number of systems for grading osteochondral lesions have been described. Those systems used for determining case definitions for the randomized comparative studies of knee repair were the Outerbridge Classification and International Cartilage Repair Society (ICRS) classification for joint cartilage breakdown and for osteochondritis dissecans (OCD). Other non-randomized studies of the knee employed the Noyes Classification. No studies designed to evaluate the validity of these classifications in the population of interest were found. Reliability studies for the Outerbridge and ICRS cartilage classifications were found but none were found for the Noyes classification. The Ferkel and Hepple classification systems for talar lesions were reported in included studies but no validity or reliability studies were found.

Lesion size

One clinical study [Niemeyer] compared arthroscopic with open assessment (as the gold standard) of lesion size in 407 patients (n = 450 focal cartilage defects) who underwent ACI.[96] The mean age was 35.7 ± 9.2 years. Other patient demographic information was not provided. Subanalyses based on surgeon experience were done for the following groups: inexperienced (<100 knee arthroscopies), experienced (100-1000 knee arthroscopies) and expert (>1000 knee arthroscopies). A scaled arthroscopic instrument with 5mm increments was compared with open assessment using a ruler having 1 mm increments. It is not clear to what extent raters were blinded. The level of evidence rating for this reliability study was III.

Table 18. Summary of results comparing lesion size in patients undergoing ACI: Arthroscopic versus open evaluation (from Niemeyer)[96]

Defect size	**Arthroscopic**	**Open**		**P-value**
Mean defect size (± sd)	5.69 (± 1.81)	4.54 (± 2.11)		p <0.001
	Number lesions (%) (n = 450)	**Mean over or under estimation**	**Direction**	
Small (≤ 4.0 cm^2)	233 (51.8)	1.64 cm^2 (± 1.05)	Over	p < 0.01*
Medium (>4.0 cm^2 to <6.0 cm^2)	171 (38.0)	0.91 cm^2 (± 1.15)	Over	p < 0.01*
Large (> 6.0 cm^2)	46 (10.2)	-0.36 cm^2 (± 2.22)	Under	p < 0.01*

* authors report thes p-value for all comparisons between groups of defect sizes)

The mean defect size was significantly greater for arthroscopic determination compared with open assessment. Small and medium size defects tended to be overestimated by arthroscopic methods while larger defects were underestimated and there was greater variability in measurement for these defects (see table above). Accuracy was less among inexperienced surgeons versus experienced surgeons ($p = 0.006$) and versus experts ($p < 0.001$) with no significant difference between experienced and expert surgeons. They do not provide statistics to assess the role of agreement by chance between raters.

[Overestimation of lesion size arthroscopically was also reported in a plastic knee simulation model.[128] This study did not meet the inclusion criteria as it was not done on humans in a clinical setting but is briefly summarized for context. Lesions of varying size were drawn on five surfaces on five plastic knee models (25 lesions total) and three observers made three sets of measurements arthroscopically which were compared with images scanned into a computer. The authors described the accuracy, intra- and inter-rater reliability as poor. They suggest that smaller defects and surgeon experience influence accuracy.]

Lesion grading

Two clinical studies that evaluated the reliability of arthroscopic determination of lesion severity using the ICRS grading system[96,97] and one using the Outerbridge classification[95] were found. In general, the degree (%) of concordance does not account for the role of chance agreement and is not a good index of reliability.

ICRS: The Niemeyer study (LoE III) described above also compared arthroscopic versus open methods for determining ICRS lesion grade of in 407 patients (n = 450 focal cartilage defects) in patients who underwent ACI.[96] This was not designed as a formal validation study, but provides some insight into the accuracy of ICRS grading arthroscopically versus open evaluation as a standard. They reported on the percentage of correct classification based on lesion location. Data for individual raters were not provided. Overall, 80.9% of lesions were correctly classified. The authors state that no statistically significant differences were found based on lesion location or with respect to the accuracy of grading between inexperienced, experienced or expert surgeons. They do not provide kappa or other statistics to assess the role of agreement beyond chance between raters.

Table 19. Summary of results comparing ICRS grade in patients undergoing ACI: Arthroscopic versus open evaluation (from Niemeyer)[96]

Lesion location	Number lesions (%) (n = 450 total)	Correctly classified* n (%)	Underestimate 1 grade	Overestimate 1 grade	Overestimate 2 grades
Medial femoral condyle	195 (43.3)	161 (82.6)	7	26	1
Lateral femoral condyle	38 (0.08)	28 (73.7)	5	5	0
Patella	158 (35.1)	132 (83.5)	16	10	0
Trochlea	59 (13.1)	44(74.6)	7	8	0

*open evaluation was considered the gold standard

Spahn et al. evaluated inter-rater reliability for arthroscopically determined ICRS grade in 14 cartilage areas in 16 patients (n = 224 areas) who had not undergone prior surgery.[97] The mean

age was 45.3 ± 14.9 years (22-68 years old) and nine patients were male. None of the patients received OAT/mosaicplasty (autograft or allograft). Documentation of grade was done anonymously and raters were blinded to each other's grading. The study was rated as LoE II, but the small number of patients should be noted.

This evaluation reported fair to slight agreement between raters based on both overall percent agreement and the Cohen (Fleiss) Kappa Index for multiple raters. Data for individual raters was not presented. The results are summarized below.

Summary of agreement on ICRS classification from arthroscopic evaluation (Spahn)[97]

Agreement between clinicians	N = 16 patients n = 224 areas
	n (%)
Complete agreement - all 4 clinicians	39 (17.4)
Agreement between 3 clinicians	84 (37.5)
Agreement between 2 clinicians	101 (45.1)
Difference of 1 grade	101(46.9)
Differences of 2 grades	39 (17.4)
Differences of 3 grades	41 (18.3)

Table 20. Summary of Cohen (Fleiss) Kappa Index for multiple investigators by anatomic region (Spahn)[97]

Region Evaluated	κ
Femoral condyles	
medial (mean bearing zone)	0.193
medial margin	0.116
lateral (mean bearing zone)	0.309
lateral margin	0.111
Tibial plateau	
medial (mean bearing zone)	0.168
medial margin	0.164
lateral (mean bearing zone)	0.020
lateral margin	0.085
Patella	
medial	0.052
central	0.300
lateral	0.170
Trochlea	
medial	0.292
central	0.255
lateral	0.234

Modified Outerbridge classification: One clinical study (LoE III) evaluated inter-rater reliability based on sets of videotapes taken during arthroscopy.[95] For 22 videotapes, only lesions that were considered to be grade 2 or 3 were included to determine whether surgeons could differentiate between the grades. The other 31 video tapes apparently focused on patients who underwent ACL reconstruction and did not include many severe chondral defects. It is difficult from the way their methods are written to ascertain precisely what differentiated the sets of video tapes.

The overall agreement beyond chance for the videotapes where surgeons were to discriminate between grades 2 and 3 was moderate (κ range 0.41-0.57). The authors did not apparently evaluate grade 4 lesions to any large extent and thus, application to a case definition which may focus on grades 3 and 4 lesions is not clear.

Table 21. Summary of results for interrater agreement on the Outerbridge Classification from Marx[95]

Interrater agreement for 31 lesions *with* Grade 2 and 3 lesions combined		
Location	**Observed agreement**	**κ**
Lateral articular lesions		
Femoral condyle	0.94	0.86
Tibial plateau	0.81	0.51
Patellar	0.93	0.80
Trochlear	0.9	0.71
Medial articular lesions		
Femoral condyle	0.93	0.84
Tibial plateau	0.87	0.34
Patellar	0.94	0.87
Trochlear	0.92	0.76
Interrater agreement for 22 lesions *without* Grade 2 and 3 lesions combined		
Cartilage grade	**Observed agreement %**	**κ**
1	3.4	0.45
2	22.3	0.41
3	38.1	0.52
4	3.4	0.52
Overall	67.2	0.47

The kappa statistic is generally interpreted using the following:

Kappa statistic interpretation

κ	**Interpretation (Landis and Koch)***
Below 0	Less than chance agreement
0.00 – 0.20	Slight agreement

0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 1.00	Almost perfect agreement

*Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

[A small study on cadaveric knees also found that interrater reliability for the Outerbrigde classification was moderate, (κ coefficient 0.52) even though there was substantial intra-observer agreement (κ coefficient =0.80).[129] This study did not meet the inclusion criteria as it was not done on humans in a clinical setting but is briefly summarized for context. Cadaveric knees (N = 6) (67 years; 16.7% male) underwent arthroscopy and then arthrotomy and were graded by 9 surgeons. Overall accuracy was 68%, but varied by location. The arthroscopy grade was higher than arthrotomy grade 63% of the time. The κ coefficient between 2 physicians in practice >5 years was = 0 .72 and between physicians in practice <5 years it was 0.50.]

3.2 Key question 2: What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?

The goals of OAT/mosaicplasty include improving function and restoring activity in people with osteochondral lesions. The procedure is often a salvage operation for younger patients in order to avoid total knee arthroplasty. Outcomes determined by patient-and clinician-reported measures provide the focus of this section.

Review of the properties of instruments is limited to those measures that were used in included comparative studies (primarily RCTs) and examined in samples drawn from the target population (patients with articular cartilage damage). Of these measures, five have been validated in this population:

- International Cartilage Repair Society (ICRS) cartilage repair assessment
- Lysholm Knee Scoring Scale (LKSS)
- Modified Cincinnati Knee Rating System (MCRS)
- International Knee Documentation Committee subjective knee form (IKDC SKF)
- Knee Injury Osteoarthritis Outcome Score (KOOS)

SUMMARY:

- Four patient-reported and one clinician-based outcomes measures commonly used in patients with cartilage defects in the knee have undergone psychometric analysis in these patients.
    - None of the five instruments were adequately tested for validity. Content validity was inadequate for all instruments, primarily because patients with chondral

lesions were not involved in item selection in that particular study. Criterion validity was not tested in these studies for any instruments, likely because of the lack of a gold standard criterion. Tests of construct validity were hampered by definitional problems and small sample sizes.

- Reliability was inadequately tested for the three outcome measures that were tested for internal consistency. None of the studies performed factor analysis to assess potential dimensions. While good internal consistency was shown for the KOOS and the ICRS, internal consistency for these instruments was inadequate as too few patients/raters were tested. Similarly, high values for reproducibility were found for the IKDC, the LKSS, and the MCKRS in samples that were too small to meet quality criteria.

- Studies that assessed responsiveness showed strong effect sizes for change from pre-operative to post-operative scores on the IKDC, MCKS, LKSS, and KOOS. However, quality criteria also require that these effect sizes be supported by comparison of the minimally important clinical difference with the smallest detectable difference, analysis of receiver operating curves, or other supporting analysis. Only one study, which analyzed the IKDC and MCKS, met this criterion.[2]

- The minimal clinically important difference (MCID) for pre-op to post-op improvement was determined in one study to be from 6.3 points (6 months follow-up) to 16.7 (12 month follow-up) on the IKDC and 14.0 points (6 months) and 26.0 (12 months) on the MCKRS. The MCID was not calculated for any other measures in patients with cartilage damage.

Detailed results

Nineteen functional outcome measures were used in comparative studies of OAT/mosaicplasty in the knee: seven clinician-reported measures and 11 patient-reported measures. Three measures were used in studies of the ankle: one clinician-reported measure and two patient-reported measures. Details are given in Appendix F.

Review of the properties of these instruments is limited to those measures that were examined in samples drawn from the target population (patients with articular cartilage damage). Of these measures, five have been validated in this population:

- International Cartilage Repair Society (ICRS) cartilage repair assessment
- Lysholm Knee Scoring Scale (LKSS)
- Modified Cincinnati Knee Rating System (MCRS)

- International Knee Documentation Committee subjective knee form (IKDC SKF)
- Knee Injury Osteoarthritis Outcome Score (KOOS)

These five instruments are described below and summarized in Appendix F.

The instruments were evaluated based on the following quality criteria:[130,131]

- **Validity.** Validity evaluates whether an outcome instrument measures what it was intended to measure.[130] We evaluated three aspects of validity:
  - *Content validity* evaluates whether the outcomes of interest are comprehensively represented by the questions in the instrument.[130,131] We gave the studies credit if there was a clear description of each of the following: the aim of the outcome measure, the target population, the concepts being assessed, and the method by which the items were selected. In addition, the population of interest (and either investigators or experts) should have been involved in item selection.[131]
  - *Criterion validity* refers to whether the scores relate to a "gold standard" on the same theme[130,131]; for credit, we looked for a correlation with the gold standard of at least 0.70.[131]
  - *Construct validity* evaluates whether scores relate to other measures in accordance with specific hypotheses that are theoretically derived. The instrument of interest and another related outcome measure may have convergent (high correlation if they measure similar concepts) or divergent (low correlation if they measure different concepts) validity with one another.[130,131] For credit, specific hypotheses need to be stated, and 75% or more of the results should be consistent with these hypotheses as tested in at least 50 patients.[131]
- **Reliability** evaluates of the extent to which repeated measurements in stable patients (test-retest) yield similar responses.[130] There are two aspects of reliability:
  - *Internal consistency* assesses whether the items in the questionnaire are correlated, in that they evaluate the same concept.[131] Questions should correlate highly with one another and with the overall (sub)scale score.[130] For credit, factor analysis should be performed on a minimum of 100 patients to determine whether the construct is uni- or multidimensional; Cronbach's alpha should range from 0.70 to 0.95 for each subscale, which is an indication of good internal consistency.[131]

- *Reproducibility* measures whether patients can be differentiated from each other in spite of measurement error (relative measurement error).[130,131] For credit, the ICC (intraclass correlation coefficient) or weighted Kappa coefficient should be ≥ 0.70 when measured in at least 50 patients. The Pearson correlation coefficient is not an adequate measurement of reliability, as it does not account for systematic differences.[131]

- **Responsiveness** assesses whether a questionnaire is able to detect clinically important changes over time (i.e., the score changes with the status of the patient).[130,131] For credit, ***one*** of the following should be demonstrated:
  1. SDC < MIC,[131] where:
     - SDC (smallest detectable change) = 1.96 x √2 x SEM (standard error of measurement); thus the SDC is the smallest intraperson change in score that should be interpreted as "real" change, or change greater than measurement error.[131]
     - MIC (minimal important change) is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management".[131] MIC may also be written as MCID (minimal clinically important difference).

  2. MIC should be outside the limits of agreement (LOA)[131]
     LOA = mean change in scores of repeated measurements ± 1.96 x standard deviation of the changes[131]
  3. RR (responsiveness ratio) > 1.96 [131]
  4. AUC ≥ 0.70 [131]
     AUC (area under the ROC (receiver operating characteristics) curve) measures whether a questionnaire is able to differentiate between patients who have and have not changed, as measured by some other criteria (usually the patient's own perception of change).[131]

- **Floor or ceiling effects** are absent if the lowest or highest possible score, respectively, was reached by less than 15% of patients. Credit is given if no floor or ceiling effects are found in a sample size of 50 patients or more.[131]

- **MCID** (minimal clinically important difference, see MIC under responsiveness above for definition) assesses whether the authors reported the MCID for the questionnaire based on comparisons with patient-reported evaluation of overall outcome (i.e., function).

A summary of the five instruments is found in Appendix F, and detailed quality assessment information is provided below.

Table 22. Quality assessment of outcome measures evaluated in persons with osteochondral defects

	Validity			Reliability				
Instrument	**Content validity**	**Criterion validity**	**Construct validity**	**Internal consistency**	**Reproducibility**	**Floor/ceiling**	**Responsiveness**	**MCID**
Patient-reported outcomes								
International Knee Documentation Committee subjective knee form (IKDC SKF) [Greco]	NR	NR	NR	NR	-	+/-	+	+
Lysholm Knee Scoring Scale* (LKSS)[Kocher, Smith HJ 2009]	NR	NR	-	-	+/-	+/-	-	NR
Knee Injury Osteoarthritis Outcome Score (KOOS) [Bekkers]	NR	NR	-	-	-	-	-	NR
Modified Cincinnati Knee Rating Systen (MCKRS) [Greco]	NR	NR	NR	NR	-		+/-	+
Clinician-reported outcomes								
International Cartilage Repair Society (ICRS) cartilage repair assessment † [Smith GD 2005, Vandenborne 2007]	NR	NR	-	-	-	NR	NR	NR

Table adapted from Lodhia et al. (2011)[78] and Terwee et al. (2007)[122]
NR = not reported
"+" indicates criteria were met, "+/-" indicates the quality assessment was inadequate or indeterminate, "-" indicates the criteria were not met; NR indicates the quality assessment was not reported or performed.
*Two studies [Kocher, Smith HJ] evaluated the LKSS
†Two studies [Smith GD 2005, Vandenborne 2007] evaluated the ICRS cartilage repair assessment

THE INTERNATIONAL KNEE DOCUMENTATION COMMITTEE SUBJECTIVE KNEE FORM (IKDC SKF)

The International Knee Documentation Committee (IKDC) was composed of international knee experts from the American Orthopedic Society for Sports Medicine and the European Society for Sports Traumatology, Knee Surgery and Arthroscopy.[132] The subjective knee form was developed by the IKDC to assess symptoms and functioning in patients with a variety of knee

disorders.[133] The form consists of 18 questions that measure symptoms (pain, stiffness, swelling, joint locking, and joint instability) and functioning in daily activity and in sports (ability to run, stop and start, climb stairs, kneel, rise from a chair). Scores on this measure range from 0 to 100, with 100 indicating no limitation in patient function.

Greco et al. conducted a study that assessed reliability and responsiveness of the IKDC SKF among patients with articular cartilage lesions.[2] Patients between 18 and 65 years of age were included in two cohorts. A treatment cohort of 73 patients with a primary diagnosis of an articular cartilage defect of the knee were scheduled for surgery to repair the defect (autologous chondrocyte implantation (ACI), abrasion arthroplasty, microfracture, or cell therapy). A second cohort comprised 64 patients who had been treated with ACI for an articular cartilage defect of the knee at least 5 years before the study began.

In the treatment cohort, patients completed the IKDC SKF along with the SF-36, modified Cincinnati Knee Rating Scale (MCKRS), and Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Six and 12 months after surgery, patients completed these same outcome measures along with a subjective rating of change in knee function from baseline on a 7-point global rating scale (endpoints much worse and much better). Fifty-one of the 73 (70%) recruited participants (mean age 36.6 years, 61% male) completed the follow-up assessments. Patients in the stable cohort were sent packets containing the instruments and were included if their condition was relatively stable (MCKRS was less than 5, MCKRS changed >2 points since their rating five years after ACI, or they reported additional knee injury or surgery). These included patients completed the same outcome measures at 6 and 12 months after baseline measures were returned (49/64 (76%) completed both follow-ups). Mean age in this group was 43.8 years, and 62% were male.

Quality assessment of the IKDC SKF:

- *Content validity* for patients with osteochondral lesions was not demonstrated in this study, as patients with this condition were not involved in item selection during the development of the outcome measure.
- *Criterion validity* was not tested in this study, as no standard was identified.
- *Construct validity* was not measured.
- *Reliability*
  - *Internal consistency* was not measured.
  - *Reproducibility* was not adequately demonstrated for the IKDC SKF, as this study tested reproducibility in fewer than 50 patients. Test-retest reliability was assessed by comparing three administrations of the instruments at baseline, 6 months, and 12 months. However, this analysis was limited to 17 patients in the stable cohort

who reported that their status was unchanged at the 12-month follow-up. The ICC (intraclass correlation coefficients) were 0.91 at 6 months and 0.93 at 12 months.

- *Responsiveness* was demonstrated with change between pre-operative and post-operative scores among the treatment cohort.
  - Patients improved by 11.5 points on the IKDC SKF at 6 months (effect size 0.76), and 19.4 points at 12 months (effect size 1.06).
  - The area under the ROC was .75 at 6 months and 0.78 at 12 months, meeting the quality criterion of AUC > 0.70.
  - A second quality criterion, that smallest detectable difference (SDD) < minimal important change (MIC), was met for the 12-month follow-up but not for the 6-month follow-up. At 6 months, MIC was less than SDD (6.3 vs. 15.6), and at 12 months MIC was greater than SDD (16.7 vs. 13.7).

- Floor effects were not reported, while ceiling effects were absent for the IKDC SKF.

- *Minimal clinically important difference (MCID*) was defined by calculating the sensitivity and specificity of change scores to determine the optimal score that discriminated between patients who rated themselves as improved and not improved. The MCID for pre-post improvement was 6.3 points at 6 months and 16.7 points at 12 months.

LYSHOLM KNEE SCORING SCALE (LKSS)

The Lysholm Knee Scoring Scale (LKSS)[134] was originally designed to assess ligament injures in the knee, but has been used for a variety of conditions, including chondral disorders.[99] The scale contains eight 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). Of the overall score of 100, 95 to 100 indicates an excellent result; 84 to 94, a good result; 65 to 83, a fair result; and <65, a poor result.

The LKSS has been evaluated in two studies of patients with articular cartilage damage. Kocher et al. examined psychometric properties among a heterogenous group of 1657 patients (mean age 44, 61% male) with various types of traumatic and degenerative chondral lesions.[99] The LKSS was administered pre-operatively and at 3, 6, and 12 months after surgery, with yearly follow-ups thereafter. In a subset of 57 patients (Group B, mean age 44, 61% male), the LKSS was administered twice preoperatively, no more than four weeks apart, in order to demonstrate reproducibility. A second subset of 248 patients (Group C, mean age 40, 67% male), also completed the SF-12, the WOMAC, and the Tegner activity scale before surgery.

In a cross-sectional study, Smith et al.[100] evaluated measurement properties of the LKSS using a Rash model. Subjects were 157 patients with symptomatic cartilage defects (mean age 37, 67% male) who had been recruited from hospitals in the UK and Norway into a multi-center RCT of ACI compared to several other treatments from 18 hospitals in UK and Norway (2 hosp). All patients had had at least one previous procedure on the same defect which had failed to relieve symptoms. Patients completed the LKSS within 3 months prior to randomization and surgery. At the same time, an independent assessor (a physiotherapist based at each hospital) carried out a semi-structured interview, a physical examination and functional tests with the patient. Based on information and observations from this assessment, and without looking at the patient's own scores, the assessor also completed the LKSS. Results were analyzed using a Rasch model, a different approach than the traditional properties of reliability and validity. With this analysis, response patterns are tested against an expected unidimensional model which defines the measurement; the data must fit model expectations if linear measurement is to be achieved. In this study, the authors re-ordered and removed items and collapsed response categories in order to achieve ordered thresholds on all items, consistent with the underlying model.

Quality assessment of the LKSS:

- *Content validity* for patients with osteochondral lesions was not reported in either study. One study[99] discussed content validity in terms of mean, standard deviation, and floor and ceiling effects, but these characteristics do not meet the definition of content validity of the quality criteria.

- *Criterion validity* was not tested in either study, as no standard was identified. Kocher et al. presented correlations between the LKSS, SF-12, WOMAC, and Tegner scales as evidence of criterion validity (*r*s from 0.346 to 0.814), but there is no evidence that any of these comparative scales represent a gold standard for knee functioning.

- *Construct validity* was inadequate.
    - In the Kocher et al. study,[99] the authors set out nine hypotheses (which they defined as "constructs") that proposed relationships between LKSS scores and a variety of other indicators. None of the other indicators were standardized measures of knee function. Four of the nine indicators were characteristics of the lesions (Outerbridge grade, number of affected surfaces, presence of meniscal tears, previous knee surgery) and five were 10-point single indicators that measured activity, ADL, difficulty working or with sports, and overall assessment of knee function. All of these indicators were significantly correlated with LKSS scores from 0.3 to 0.475 in the subset of 248 patients.
    - The Smith et al. study[100] did not evaluate construct validity in the conventional sense (by relating scores to other measures). Instead, internal

construct validity was demonstrated by revising the scale to fit a unidimensional Rasch model.

- *Reliability*
  - *Internal consistency* did not meet quality criteria.
    1. The internal consistency of the LKSS was 0.65 in 1657 patients in one study,[99] falling short of the quality criterion of 0.70. No factor analysis was performed.
    2. Internal consistency in the second study was 0.70 in 157 patients as measured by the person separation index (PSI) produced by Rasch modeling. Model fit ensured that the scale was unidimensional, however, these assessments are based on a revised scale in which some items were collapsed or dropped to fit the Rasch model.[100]

  - *Reproducibility* was demonstrated in one study; however, high consistency in the second study was based on a revised scale.
    1. Kocher et al.[99] assessed reproducibility of the LKSS with a test-retest procedure in 57 patients, with the two administrations separated by no more than 4 weeks. The ICC for the overall score was 0.91, with high ICCs for most subscales (pain 0.61, instability 0.82, locking 0.97. stair-climbing 0.67, limp 0.82, use of support 0.98, swelling 0.94, squatting 0.91). The overall score and the scores for six of the eight subscales meet quality criteria (ICC>0.70).
    2. In the second study of the LKSS,[100] reproducibility was assessed by calculating ICCs of patient-reported and clinician-reported scores, which ranged from 0.86 to 0.93). However, these calculations are based on a revised scale in which some items were collapsed or dropped to fit the Rasch model.

- *Responsiveness* was not adequately demonstrated.
  - Responsiveness was not assessed in one of the two studies.[100]
  - Korcher et al.[99] compared pre-operative scores on the LKSS to post-operative scores collected a mean of 51.2 months after treatment with microfracture (248 patients). The effect size for the overall LKSS was 1.16, with moderate to strong effect sizes for subscales (pain 1.3, swelling 1.2, limping 13, squatting 1.3, instability 0.21, use of support 0.59, stair-climbing 0.75, locking 0.55).
  - Despite strong effect sizes, the quality criteria used for evaluation require that one of four criteria be demonstrated: smallest detectable change (SDD) < minimal important change (MIC), MIC outside the limits of agreement,

responsiveness ratio >1.96, or area under the ROC >0.70. None of these criteria were met.

- Floor and ceiling effects were adequate for the overall (total) LKSS score. No floor or ceiling effects were found in one study,[100] and in the second study there were no patients who achieved the lowest possible score and 7% who achieved the highest possible score on the LKSS.[99] Some of the subscales demonstrated unacceptable floor and ceiling effects in the Kocher et al. study[99]: the highest possible score was reported by 19% of patients on the swelling subscale, 32% for limping, 67% for instability, 55% for support, and 62% for locking. Considering floor effects, the lowest possible score was reported by 26% for pain, 52% for squatting, and 19% for stair-climbing. Several subscales of the LKSS therefore do not meet quality criteria (less than 15% of patients achieving the highest or lowest possible scores).

- *Minimal clinically important difference (MCID*) was not evaluated in either study.

KNEE INJURY OSTEOARTHRITIS OUTCOME SCORE (KOOS)

The Knee Injury Osteoarthritis Outcome Score (KOOS) was developed to assess patient-reported knee pain, symptoms, function, and quality of life in young and middle-aged patients with ACL injury, meniscus injury, or post-traumatic osteoarthrisis.[135] The instrument includes all of the questions on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as well as additional questions developed from literature review, patient groups, and a pilot study. The five dimensions of the KOOS are scored separately: pain (9 items), symptoms (7 items), functioning in activities of daily life (17 items), sport and recreation functioning (5 items), and quality of life (4 items). All items are scored from 0-4, and the score in each domain is transformed to a scale from 0 to 100, with zero representing severe knee problems and 100 representing no problems.

The KOOS has been evaluated in one retrospective study of patients with symptomatic focal cartilage lesions.[15] Sixty patients who had been treated with either autologous chondrocyte implantation (ACI) or microfracture were contacted to participate, and 46 patients agreed (77%). These patients were mailed two sets questionnaires that included the KOOS (in Dutch) and other instruments that measured similar constructs (LKSS, SF-36, EQ-5D), and were instructed to complete one questionnaire and the second two days later. Completed questionnaires were received from 40 patients (mean age 35, 70% men) at an average post-operative time of 32 months.

Quality assessment of the KOOS:

- *Content validity* for patients with osteochondral lesions was not demonstrated in this study, as patients with this condition were not involved in item selection during the development of the outcome measure.
  - The purpose of the KOOS is to evaluate short- and long-term patient-relevant outcomes following knee injury.
  - The instrument was based on the WOMAC Osteoarthritis Index, a literature review, consultation of a panel of patients, and a pilot study. In the original development of the instrument, patients were consulted and a pilot study of questionnaires that assessed symptoms of ACL injury and of osteoarthritis. These procedures were performed to ensure content validity for patients with ACL injury, meniscus injury, and early osteoarthritis.
  - The KOOS was designed to evaluate pain, functioning, and quality of life. It reports separate scores that distinguish function in activities of daily living from that in sports and recreation. The questions adequately evaluate these different domains and include activities that cover a wide range of abilities. For example, the ADL subscale evaluates a patient's ability to sit as well as the ease with which they are able to perform heavy domestic duties (shoveling snow, scrubbing floors).
  - Items were selected based on the input from patients with ACL injuries and osteoarthritis. However, the target population was <u>not</u> involved in the item selection, which is necessary for demonstration of content validity.

- *Criterion validity* was not tested in this study, as no standard was identified.

- *Construct validity* was inadequate due to small sample size.
  - Construct validity was examined by comparing scores on subdomains of the KOOS with *a priori* hypothesized corresponding domains of the other instruments administered: KOOS symptoms with SF-36 physical functioning, KOOS pain with SF-36 bodily pain and EQ-VAS, KOOS ADL with the complete SF-36 instrument, KOOS sport and recreation with the LKSS, and KOOS QoL with EQ-5D.
  - Spearman's rank correlation coefficients were 0.585 for symptoms, 0.661 for pain, 0.558 for ADL, 0.70 for sport/recreation, and 0.43 for QoL. Although these coefficients were moderate to high and consistent with hypotheses, the patient sample was too small (<50) to meet quality criteria.

- *Reliability*
  - *Internal consistency* was inadequate due to small sample size and lack of factor analysis.
    1. Factor analysis was not performed.

2. Cronbach's coefficient alpha was calculated for the overall KOOS score and for each of the five domains on 40 patients, and ranged from 0.74 to 0.96 (overall: $\alpha = 0.96$; pain: $\alpha = 0.88$; symptoms: $\alpha = 0.74$; function ADL: $\alpha = 0.95$; function sport/recreation: $\alpha = 0.89$; QoL: $\alpha = 0.90$). For credit to be given, factor analysis should be performed on at least 100 patients and Cronbach's alpha should range from 0.70 to 0.95 for each subscale.

- *Reproducibility* was not adequately demonstrated for the KOOS, as this study tested for reliability in fewer than 50 patients. The test-retest reliability of KOOS subdomains and total score was assessed by comparing two administrations of the instruments separated by 2 days. The ICC (intraclass correlation coefficients) were high: 0.97 for the overall KOOS,0 .95 for symptoms, 0.92 for pain, 0.87 for function/ADL, 0.89 for sport/recreation, and 0.95 for QoL.

- *Responsiveness* was not adequately demonstrated.
  - Responsiveness was evaluated with data from a separate study: a randomized controlled trial of 36 patients in which characterized chondrocyte implantation was compared to microfracture. Patients completed the KOOS and the Marx activity rating scale (ARS) at baseline and at 36 months follow-up. Standardized response mean (SRM; mean change in score from baseline to follow-up divided by the standard deviation of the mean change)
  - Effect sizes were 0.91 for the overall KOOS, 0.72 for symptoms, 0.82 for pain, 0.70 for functional ADL, .98 for sport/recreation, and 1.32 for QoL. SRMs were 0.85 for the overall KOOS, 0.61 for symptoms, 0.71 for pain, 0.75 for functional ADL, 0.87 for sport/recreation, and 0.76 for QoL.
  - Despite these strong effect sizes, the quality criteria used for evaluation require that one of four criteria be demonstrated: smallest detectable change (SDD) < minimal important change (MIC), MIC outside the limits of agreement, responsiveness ratio >1.96, or area under the ROC >0.70. None of these criteria were met.

- Floor or ceiling effects were inadequately evaluated due to small sample size (<50). No patients had the lowest possible score, and the proportion of patients reaching the highest possible score ranged from 2.6% to 10.3% of patients across the subdomains and was 2.6% for the total KOOS score.

- *Minimal clinically important difference (MCID*) was not evaluated in this study.

MODIFIED CINCINNATI KNEE RATING SYSTEM (MCKRS)

The Cincinnati Knee Rating System (CKRS)[136] is was developed as a functional measure specifically for the knee. The original form of the scale incorporated both clinical parameters and patient ratings on six subscales covering subjective ratings, activity level, clinical examination, stability, radiographic findings, and function testing. A modified version, the Modified Cincinnati Knee Rating System (MCKRS), incorporates patient input only and incorporates measures of pain, swelling, giving way, and other knee symptoms; overall activity level and ability to walk, climb stairs, run, and jump/twist.[137] Scores range from 6 to 100, with higher scores representing better functioning.

Greco et al.[2] conducted a study that assessed reliability and responsiveness of the IKDC SKF among patients with articular cartilage lesions (see above section on the IKDC SKF for study description).

Quality assessment of the MCKRS:

- *Content validity* for patients with osteochondral lesions was not demonstrated in this study, as patients with this condition were not involved in item selection during the development of the outcome measure.
- *Criterion validity* was not tested in this study, as no standard was identified.
- *Construct validity* was not measured.
- *Reliability*
  - *Internal consistency* was not measured.
  - *Reproducibility* was not adequately demonstrated for MCKRS, as this study tested for reliability in fewer than 50 patients. Test-retest reliability of subdomains and total score was assessed by comparing three administrations of the instruments at baseline, 6 months, and 12 months. However, this analysis was limited to 17 patients in the stable cohort who reported that their status was unchanged at the 12-month follow-up. The ICC (intraclass correlation coefficients) were 0.91 at 6 months and 0.80 at 12 months.
- *Responsiveness* was demonstrated with change between pre-operative and post-operative scores among the treatment cohort.
  - Patients improved by 13.1 points on the MCKRS at 6 months (effect size .60), and 21.7 points at 12 months (effect size 1.09).
  - The area under the ROC was 0.72 at 6 months and 0.75 at 12 months, meeting the quality criterion of AUC >0.70.
  - A second quality criterion, that smallest detectable difference (SDD) < minimal important change (MIC), was met for the 12-month follow-up but not for the 6-month follow-up. At 6 months, MIC was less than SDD (14.0 vs. 15.3), and at 12 months MIC was greater than SDD (26.0 vs. 22.8).

- Floor reports are not reported, and while ceiling effects were reported to be present, the data were not provided in the paper.

- Minimal clinically important difference (MCID) was defined by calculating the sensitivity and specificity of change scores to determine the optimal score that discriminated between patients who rated themselves as improved and not improved. The MCID for pre-post improvement was 14.0 points at 6 months and 26.0 points at 12 months follow-up.

THE INTERNATIONAL CARTILAGE REPAIR SOCIETY (ICRS) CARTILAGE REPAIR ASSESSMENT SYSTEM

The International Cartilage Repair Society (ICRS) cartilage repair assessment[138,139] is a part of the ICRS Cartilage Injury Evaluation Package. The entire evaluation package is composed of a patient-reported section (injury questionnaire, IKDC subjective knee evaluation) and a section completed by the surgeon (six clinician-reported instruments, including the Cartilage Repair Assessment). Cartilage repair is assessed arthroscopically on three subscales:

- degree of defect repair (4 points, where 0=0% repair of defect depth and 4=in level with surrounding cartilage)
- integration to border zone (4 points, where 0=less than ¼ of graft integrated with surrounding cartilage and 4=complete integration with surrounding cartilage)
- macroscopic appearance (4 points, where 0=total degeneration of grafted area and 4=intact smooth surface)

The assessment score can range from 0-12 points, with higher scores indicating better repair:

- 0-3 points: Grade IV (severely abnormal)
- 4-7 points: Grade III (abnormal)
- 8-11 points: Grade II (nearly normal)
- 12 points: Grade I (normal)

The ICRS cartilage repair assessment has been tested in two studies in which surgeons rated images or video clips of patient arthroscopies.[101,140] In van den Borne et al., 7 observers rated 101 videos and prints that had been made during a follow-up arthroscopy 12 months after previous surgery for cartilage repair.[101] All images were blinded by a unique randomized number and were presented in random order. Four of the observers were orthopedic surgeons with extensive experience in cartilage surgery, one was an arthroscopy fellow, one an orthopedic surgery resident, and one a clinical research manager with a non-medical background. These observers judged the images twice, at an interval of 4 weeks, using both the ICRS cartilage repair assessment and the Oswestry Arthroscopy Score (OAS).

The second study[140] also assessed both the ICRS assessment and the OAS. Videos of five post-repair arthroscopies were assessed by 6 orthopedic surgeons who had an interest in cartilage

repair. The videos were selected to represent spectrum of macroscopic appearance, from good to poor. Scoring was repeated after a 2-month or 6-week interval (this interval is reported inconsistently). Observers also answered two questions to assess face validity and content validity (whether the scoring methods are a reasonable way to objectively assess cartilage repair, and which parameters are the most important in assessment of cartilage repair).

Quality assessment of the ICRS cartilage repair system:

- *Content validity* for patients with osteochondral lesions was not assessed in these studies.
  - Content validity was not assessed in one study.[101]
  - The second study[140] reported that it assessed content validity by asking the 6 observers to rank order the importance of the six parameters assessed by the ICRS instrument. However, such ordering would not constitute content validity.
- *Criterion validity* was not tested in either study, as no standard was identified.
- *Construct validity* was assessed in both studies, although it was called "equivalence reliability" in both studies. Pearson correlations between the ICRS instrument and the OAS were 0.94 in one study[101] and 0.88 in the second study.[140] However, there were less than ten raters in each of these studies, and quality criteria require at least 50 patients, which would correspond to raters in this case.

- *Reliability*
  - *Internal consistency* was inadequate due to small sample size and lack of factor analysis. Smith et al. report a Cronbach's alpha of 0.91 for the ISCR instrument[140]; however this represents less than 50 observations (6 videos and 5 observers), and no correction for repeated measures within persons is reported. Alpha was 0.79 in van den Borne et al.'s study of 7 raters and 101 images,[101] but this parameter may not incorporate a correction for within-person consistency across image ratings.
  - *Reproducibility* was inadequate due to small sample size. ICC for test-retest reliability in van den Borne et al. was 0.73, and inter-observer reliability was 0.62.[101] The ICC for test-retest reliability was 0.94 and inter-rater reliability ICC was 0.83 in Smith et al.[140] Although these coefficients are strong, they were based on based on only 6 observations in each of 5 observers and thus do not meet quality criteria.
- *Responsiveness* was not assessed in either study.
- *Floor or ceiling effects* were not assessed in either study.
- *Minimal clinically important difference (MCID*) was not evaluated in either study.

3.3 Key question 3: What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)?

Including consideration of short term and long term:

a. Delay or avoidance of progression to osteoarthritis
b. Impact on function, pain, range of motion, quality of life, activities of daily living and return to work
c. Longevity of treatment effect
d. Need for continuing and/or subsequent intervention
e. Need for extended or continuing physical therapy
f. Recovery time considering harvest site recovery issues
g. Differential results from multiple versus single grafts, patterning for multiple grafts (linear arrangement vs. circular arrangement
h. Differential results between allograft and autograft procedures
i. Differential results between open and arthroscopic procedures
j. Differential results in centers of excellence

AUTOGRAFT

Summary

Efficacy: autograft OAT/mosiacplasty in the knee

Two small RCTS in younger populations compared OAT with microfracture and three RCTs (or quasi RCTs) compared OAT/mosaicplasty with ACI in general (older) populations. All studies used autograft. There were substantial differences in patient populations, comparators and outcomes measures used across studies.

- **Function:**
  - Compared with microfracture (MF), OAT was associated with significantly better patient-reported (based on ICRS), and clinician-reported (based on HSS) functional outcomes in young athletes and children based on two small RCTs (total n = 104).[3,4]
  - For comparisons with ACI, three poor quality RCTs in general (older) populations reported on functional outcomes. Two small RCTs suggest that function based on patient-reported outcomes (LKSS and a modification of it) was better for OAT compared with ACI, however statistical significance was reached in only one of the RCTs (n = 40)[5] and in the other RCT,[6] conclusions are difficult given the significant loss to follow-up (50%). The largest RCT (n = 100) reported that a significantly smaller proportion of participants receiving mosaicplasty had excellent or good results based on the author's modification of the Cincinnati Rating Scale. The average lesion size in this study was greater than that in the other studies. One of the small studies reported no significant differences in the

Meyer score. Two studies included substantial proportions of participants who had prior surgeries (94% and 45% respectively).

Conclusions across studies are difficult given the substantial differences in patient populations, comparators and outcomes assessed between the studies.

- **Longevity of treatment effect:** Three small RCTs provided data to assess the longevity of treatment effects.[3-5]
    - Compared with microfracture (MF), in young athletes (n = 57) initial improvements in function (based on ICRS and HSS scores) in OAT recipients were sustained or slightly improved up to 36 months with sustained statistical differences between OAT and MF. Among children (n = 47) receiving OAT, following initial improvement at 12 months, ICRS scores decreased slightly, but remained stable up to 48 months. Scores for MF recipients waned substantially after 12 months and the statistical differences in treatment effects between OAT and MF were sustained over time, favoring OAT.
    - In a general population (n = 40) functional scores for both OAT and ACI increased over time for the LKSS, Tegner and Meyers scores; however, only for the LKSS were significant differences between treatment sustained over time favoring OAT.

- **Return to work or pre-injury activity levels**: Two studies reported on the effect of OAT/mosaicplasty on return to pre-injury activity levels.[3,4] In both young athletes and children, a greater proportion of patients treated by OAT versus MF had returned to pre-injury activity levels at specified time points (at a mean of 6.5 months – OAT: 93% versus MF: 52%; at 11.7 months (OAT) and 14.1 months (MF) – OAT: 84% versus MF: 32%).

- **Differential results between open and arthroscopic procedures:** No studies directly compared the effects of open versus arthroscopic procedures; however, indirect comparison of results from the two RCTs which used open procedures[6,7] and the two RCTs which used arthroscopic procedures[3,4] may suggest that the functional and clinical outcomes for OAT were better for arthroscopic procedures. This should be interpreted cautiously given the differences in populations and outcomes assessed between the studies.

- No data were available from RCTs regarding the effect of OAT/mosaicplasty on the following: delay or avoidance of progression to osteoarthritis, pain, range of motion, quality of life, activities of daily living, the need for continuing and/or subsequent intervention, the need for extended or continuing physical therapy, recovery time considering harvest site recovery issues, differential results from multiple versus single grafts or patterning for multiple grafts, differential results between allograft and autograft procedures, and differential results in centers of excellence.

Detailed results

a) Delay or avoidance of progression to osteoarthritis
None of the RCTs reported on the effect of OATS/mosaicplasty on delay or avoidance of progression to osteoarthritis.

b) Impact on function, pain, range of motion, quality of life, activities of daily living and return to work

Function
The assessment of function differed across studies. All of the five RCTs reported on the impact of OATS/mosaicplasty based on patient-reported functional outcomes,[3-7] and two of five RCTs reported the impact of OATS/mosaicplasty based on clinician-based functional outcomes.[3,5]

Five RCTs provided data from patient-reported functional outcomes but assessed them using five different questionnaires: the Modified Cincinnatti Knee Rating Scale (MCKRS), International Cartilage Repair Society Scale (which appears to be the IKDC SKF that is part of the ICRS evaluation package), the LKSS, the Tegner Activity Score and a Modified Lysholm Score. Details of these measures have been provided in previous sections and in the appendices.

The results are presented in Tables 23 and 24 and described below. Information on patient and lesion characteristics for these studies can be found in Table 12.

Table 23. Results of patient-reported functional outcomes from RCTs*

Outcome Measure	Author	Time	Results		P-value
International Cartilage Repair Society Score (ICRS)† Range: unknown Authors report higher score indicates better function	Gudas (2005)‡		**OAT (n = 28)**	**MF (n =29)**	
			Mean ± SD		**P-value** §
		pre-op	50.7 ± 4.05	50.8 ± 4.07	> 0.05
			Mean Change Score (%)**		
		12 mos	35.2 (69.2)	24.8 (48.8)	< 0.03
		24 mos	37.3 (73.6)	25.2 (47.6)	< 0.001
		36 mos	38.3 (75.5)	24.2 (47.6)	< 0.001
	Gudas (2009)††		**OAT (n=25)**	**MF (n=22)**	
			Mean ± SD		**P-value** §
		pre-op	51	51	> 0.05
			Mean Change Score (%)**		

	12 mos	41 (80.4)	35 (68.6)	NR
	24 mos	43 (84.3)	24 (47.1)	NR
	36 mos	33 (64.7)	13 (25.5)	< 0.001
	48 mos	32 (62.7)	12 (23.5)	< 0.05

Lysholm Knee Scoring Scale (LKSS)	Horas (2003)	**OAT (n = 20)**	**ACI (n =20)**	
Range: 0 - 100		**Mean ± SD**		**P-value** §
Higher score = greater function	pre-op	28.45	24.9	> 0.05
		Mean Change Score (%)**		
	3 mos	-0.5 (-1.8)	2.65 (10.6)	NR
	6 mos	25 (87.9)	20.85 (83.7)	≤ 0.015
	12 mos	39.8 (139.9)	32.6 (130.9)	≤ 0.001
	24 mos	44.25 (155.5)	41.85 (168.1)	≤ 0.012

Modified Lysholm Knee Scoring Scale‡‡	Dozin (2005)§§	**Mosaic (n = 22)*** **	**ACI (n =22)*** **	
Range: 0 - 100		**No. of cases (%)**		**P-value†††**
Excellent: 95 - 100	12 mos	Complete success‡‡: 15 (68.2)	Complete success‡‡: 10 (45.5)	0.12
Good: 84 - 94		Partial success‡‡: 2 (9.1)	Partial success‡‡: 5 (22.7)	
Fair: 65 - 83		Failure‡‡: 0 (0)	Failure‡‡: 1 (4.5)	
Poor: <65		LTFU: 5 (22.7)	LTFU: 6 (27.2)	

Tegner Activity Scale (TAS)	Horas (2003)***	**OAT (n = 20)**	**ACI (n =20)**	
Range: 0 - 10		**Mean ± SD**		**P-value‡**
10: Competitive sports	pre-op	1.6	1.6	> 0.05
0: Sick leave or disability		**Mean Change Score (%)****		
	3 mos	-0.05 (-3.1)	-0.05 (-3.1)	> 0.05
	6 mos	1.95 (121.9)	1.35 (84.4)	> 0.05
	12 mos	3.4 (212.5)	2.65 (165.6)	> 0.05
	24 mos	3.6 (225.0)	3.5 (218.8)	> 0.05

Modified Cincinnati Knee Rating Scale	Bentley (2003)	**Mosaic (n = 42)**	**ACI (n = 58)**	
Range: 0 -100		**No. of cases (%)**		**P value‡‡‡**
Excellent: 80-100 ‡‡‡	12 mos	Excellent: 9 (21.4)	Excellent: 23 (39.7)	0.02
Good: 55-79 ‡‡‡		Good: 20 (47.6)	Good: 28 (53.8)	
Fair: 30-45 ‡‡‡		Fair: 6 (14.3)	Fair: 7(12.1)	
Poor <30 ‡‡‡		Poor: 7 (16.7)	Poor: 0 (0)	

Acronyms: SD=standard deviation; LTFU=lost to follow-up

* All data and P-values are as reported in original articles unless noted by authors

† The authors do not provide a reference for this questionnaire nor do they indicate what questions are included on the scale; the authors suggest that a higher score indicates better results

‡ 60 patients were randomized/treated but data only reported on 57 who had follow-up evaluation

§ P values compare mean score in OATS group to means core in ACI or MF at the specified time-point

** Calculated as the difference and % change in mean score from pre-op

†† 50 patients were randomized/ treated, but data only reported on 47 who had follow-up evaluation

‡‡ Modified Lysholm Knee Score: the Lysholm Knee Symptom Score was modified by eliminating the instability category. Categories are defined using the combination of cut-points and self-report of improvement: Failure: score< 60; Partial success: score of 60-90, Complete success: score of 90-100 or report of subjective improvement; Second scores were available for 10 patients who did not receive treatment; p-value compares all 5 categories. Of those completing a second LKSS 15/17 (88.2%) and 10/16 (62.5%) for mosaicplasty and ACI respectively had "complete success" based authors Table 3 with a corresponding RR (95% CI) of. 1.4 (0.93, 2.14) p = 0.12.

§§ Although 47 were randomized, 2 were actually determined to be ineligible, and one refused treatment and was LTFU

*** Of the 44 randomized participants, only 23 had surgery; 14 patients did not have surgery because they reported improvement after arthroscopy; of the 14 reporting improvement, 10 completed a second Lysholm Knee Scoring Scale; therefore, f/u data was available on n=37 patients, 10 of which did not receive treatment; 20% of the OATS and 35% of the ACI group had a prior surgical intervention

†††We calculated the P value using Fisher's exact to compare the distribution of patients who achieved complete success vs. Partial success/failure (based on the Modified Lysholm Knee Scoring Scale and report of spontaneous improvement); the P value reported by authors in original manuscript (P=0.295) compared the distribution of patients among 5 categories including the 3 categories of Modified LKSS, LTFU and subjective improvement.

‡‡‡ These cut-points reported by Bentley et al. differ from the validated cut-points for the Modified Cincinnati Rating Scale; We calculated the P value using Chi sq to compare the distribution of patients with excellent/good repair to fair/poor repair between OATS/ Mosaic and MF/ACI; however, the P value reported by authors in original manuscript differed substantially(P=0.28) (94% of participants had a prior surgical intervention);

- In two RCTs in younger populations (young athletes[3] and children[4]), OATS was associated with greater function compared with MF, based on the authors' description of the ICRS score. [The authors provide no reference or description of how the ICRS score was determined; if they used the ICRS "Cartilage Injury Evaluation Package," it includes the IKDC Subjective Knee Form (as well as the ICRS classifications and repair assessment system forms). In the IKDC Subjective Knee Form, higher scores indicate better function.] Authors did not report what might constitute a clinically significant difference in ICRS score. (Table 23)
    - In athletes,[3] patients who received OAT had consistently higher ICRS scores indicating better function than patients who received MF. Differences in mean ICRS score between OAT and MF were significant at all time points (12, 24 and 36 months). The difference in change in ICRS score between treatments was apparent and statistically significant at 12 months and sustained through the last follow-up at 36 months.
    - In children,[4] patients who received OAT had consistently higher ICRS scores indicating better function than patients who received MF. Differences in mean ICRS score between OAT and MF were not reported at 12 or 24 months, but were statistically significant at 36 and 48 months. In OAT and MF treatment arms, the mean change score was greatest at either 12 (MF) or 24 months (OATS), and decreased at later time points, more so for MF than for OATS.
    - In both of these studies, the improvement on ICRS scores exceeded the minimal clinically important difference (MCID) established in a study of the validity of this scale (see earlier section on Measurement for details). The MCID for this scale is a 16.7-point increase at one year post-surgery from pre-surgery levels. In these two studies,[3,4] the mean improvement at 12 months was 35 and 42 points, respectively.

- In three poor quality RCTS/quasi-RCTs (LoE IIb) in general (older) populations comparing OAT/mosaicplasty to ACI, conclusions regarding which treatment leads to better function are not clear. In two of these studies,[7] {Horas, 2003 #817 a substantial proportion of participants had a prior surgical intervention . (Table 23)
    - Bentley et al.[7] reported that a greater proportion of ACI patients had excellent or good functional outcomes at 12 months (as assessed by the Modified Cincinnati Rating Scale) compared with patients who had received mosaicplasty [risk difference (RD) (95%CI) comparing mosaicplasty to ACI = 19% (3%, 35%), relative risk (RR) (95%CI) = 0.79 (0.63, 0.98; p = 0.02]. Ninety-four percent of participants had a prior surgical intervention. The mean lesion size treated in this study was 4.66 cm^2 (1- 12.2 cm^2), compared with other studies with lesion sizes which ranged from 1.93 cm^2 to 3.75 cm^2. (Table 12 lists lesion sizes for all studies.)
    - Horas et al.[5] reported that patients who received OAT had better function at all time points (3, 6, 12 and 24 months) compared with patients who received ACI, based on the Lysholm Knee Scoring Scale (LKSS). The authors do not report what may constitute a clinically meaningful change in the LKSS, and the validation/reliability studies for this measure do not provide a minimal clinically important difference (MCID). Although the authors conclude that recovery was slower following ACI versus OAT and the figure suggests higher mean values for OAT earlier in time, no formal statistical comparison of the curve slopes (i.e. rate of recovery) was presented. The p-values presented appear to relate to the statistical differences between mean values for the study groups at the same time points, not the rate of recovery.
    - Horas et al.[5] also reports higher levels of self-reported physical activity, as measured by the Tegner Activity Score, at 3, 6, 12 and 24 months for both OATS and ACI; however, there were no statistically significant differences between treatment groups at any time point.
    - In Dozin et al.,[6] a higher proportion of mosaicplasty patients experienced "complete success" at 12 months, based on the Modified Lysholm Knee Scoring Scale; however, the difference in the proportion of patients experiencing "excellent" function (LKSS > 90, described as complete success by the authors) was not significantly different between treatment arms [RR (95% CI) = 1.4 (0.93, 2.14) p = 0.12] (see table). [Thresholds used in the Dozin paper differ from thresholds set for the validated Modified Lysholm Knee Scoring Scale]. In this study, only 23 of the participants who had originally been randomized had surgery (14 experienced improvement after initial arthroscopy). For statistical testing, the authors included 10 of the 14 patients who did not have surgery who also completed a follow-up LKSS; thus, it is unclear to what extent mosaicplasty may be responsible for the differences in function.

Two RCTS/quasi-RCTs reported clinician-based functional outcomes, but used different questionnaires: the Hospital for Special Surgery (HSS) Score and the Meyers Score. Details of these measures have been provided in previous sections and in the appendices.

Table 24. Results of clinician-reported functional outcomes from RCTs*

Outcome Measure	Author	Time	Results		P value
Hospital for Special Surgery Score	Gudas (2005)†		**OAT (n = 28)**	**MF (n =29)**	
Range: 0 - 100			**Mean ± SD**		**P value‡**
Excellent: 85- 100		pre-op	77.9 ± 6.23	77.2 ± 8.12	> 0.05
Good: 70-84			**Mean Change Score (%)§**		
Fair: 60-69		12 mos	10.1 (13.0)	5.8 (7.5)	< 0.05
Poor: <60		24 mos	13.1 (16.8)	4.8 (7.5)	< 0.01
		36 mos	13.1 (16.9)	3.4 (4.4)	< 0.01
Meyers Score	Horas (2003)		**OAT (n = 20)**	**ACI (n =20)**	**P value‡**
Range: 0 - 18			**Mean ± SD**		
Excellent: 18		pre-op	7.85	7.2	> 0.05
Good: 15 - 17			**Mean Change Score (%)§**		
Fair: 12 - 14		3 mos	0 (0)	1.3 (18.1)	> 0.05
Poor: < 12		6 mos	5.9 (75.2)	4.85 (67.4)	> 0.05
		12 mos	8.05 (102.5)	6.95 (96.5)	> 0.05
		24 mos	8.9 (113.4)	8.7 (120.9)	> 0.05

Acronyms: SD = standard deviation; LTFU=lost to follow-up

* All data and P-values are as reported in original articles unless noted by authors

† 60 patients were randomized/treated but data only reported on 57 who had follow-up evaluation

‡ P values compare mean score in OATS group to means core in ACI or MF at the specified time-point

§ Calculated as the difference and % change in mean score from pre-op

- In one RCT in young athletes,[3] OAT was associated with higher function compared with MF, as assessed by clinicians using the Hospital for Special Surgery Score. Differences in mean HSS score between OAT and MF were statistically significant at each time point (12, 24 and 36 months). For OATS patients, the mean change in HSS score was greatest at 24 months, and sustained to 36 months; however, for MF patients, the mean change in HSS score was greatest at 12 months, and decreased at 24 and 36 months (see table).
- In an RCT in the general (older) population, comparing OAT/mosaicplasty to ACI, conclusions regarding which treatment leads to better function are not clear. In this study, a substantial proportion of participants had a prior surgical intervention.
    - Horas et al.[5] reported no statistically significant differences in clinician-based functional outcomes (based on the Meyers Score) between patients receiving OATS and ACI. For both OATS and ACI patients, the mean change in Meyers score increased at each time point (3, 6, 12 and 24 months) (Figure 3). Slight improvement at 24 months was reported by 2/39 (10%) of ACI patients and 3/40 (15%) of OAT patients with 85% of both ACI and OAT patients reporting substantial improvement at 24 months (the authors do not report how this was assessed). Forty-five percent of participants had a prior surgical intervention.

Pain
In all RCTs, pain was assessed as part of either patient-reported (International Cartilage Repair Society Scale, Lysholm Knee Scoring Scale, Modified Lysholm Score, Modified Cincinnati Rating Scale) or clinician-based (Hospital for Special Surgery Score, Meyers Score) functional outcomes measures; however, data for the pain subscale portion of these questionnaires was not presented separately and therefore cannot be assessed separately. Anecdotal information was provided in one quasi-RCT,[5] which reported that one of the 20 (5%) patients who received ACI complained of an increase in pain in the treated knee, and 5 out of 7 OAT patients who had grafts harvested from the posterior aspect of the femoral condyle had pain when squatting.

Persistence of pain in non-randomized studies is discussed under key question 4 on safety.

Range of motion
In three of the five RCTs[3,5,7] range of motion was assessed as part of the clinician-based functional outcomes measures; however, data for the range of motion subscale portion of these questionnaires was not presented separately and therefore cannot be assessed separately.

Quality of life
None of the RCTs reported on the effect of OAT/mosaicplasty on quality of life.

Activities of daily living
None of the RCTs reported on the effect of OAT/mosaicplasty on activities of daily living aside for aspects of this that are imbedded in the functional measures used.

Return to work or pre-injury activity levels
None of the RCTs reported on the effect of OAT/mosaicplasty on return to work, however, two RCTs reported the effects of OAT on return to pre-injury activity level.[3,4] Authors do not provide detail regarding how this was assessed.

In an RCT among young athletes[3] 26 of the 28 (93%) athletes who received OAT returned to sports activities at their pre-injury level at an average of 6.5 months, compared with only 15 of 29 (52%) who received MF [RD (95% CI) = 41% (21%, 62%), RR (95%CI) = 1.8 (1.2, 2.6); p = 0.0008]. Return to pre-injury activity level was only assessed at one time point; therefore, it is unclear whether one treatment group was able to return function earlier than the other treatment group. Gudas et al. also reported that "others showed a decline in sports activity level because of a lifestyle change; and others limited activities for fear of a new injury,"[3] however, no data were provided.

In an RCT among children,[4] 21 of 25 (84%) patients who received OAT achieved pre-injury activity levels at 11.7 months after surgery, while only 7 of 22 (32%) patients who received MF achieved pre-injury activity levels at 14.1 months [RD (95% CI) = 52% (28%, 76%), RR (95% CI) = 2.6 (1.4, 5.0); p = 0.0004]. Furthermore, 81% of OAT patients who achieved pre-injury activity levels at 11.7 months were practicing sports at the same level after 4.2 years, while only 43% of MF patients who achieved pre-injury activity levels at 14.1 months remained at the same level after 4.2 years [RR (95% CI) = 1.9 (0.8, 4.6); p=0.14].[4] Since return to pre-injury activity

level was only assessed at one time point, which differs by 3 months between treatment arms, it is not possible to conclude whether one treatment group was able to return function earlier than the other treatment group or to what extent the longer time frame influenced this.

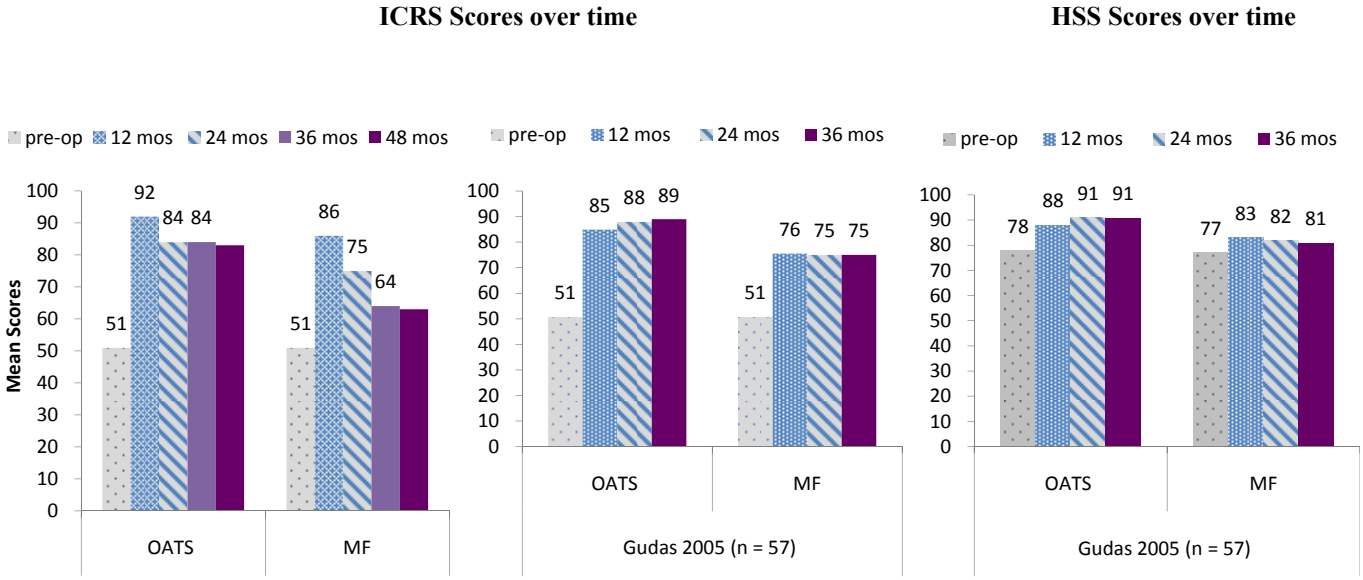
No data on return to work or pre-injury activity levels was reported in RCTs in general (older) populations.

c) Longevity of treatment effect
The longest follow-up in any of the RCTs was 48 months, thus there is limited information on duration of treatment effect beyond this time from these studies. Three RCTs assessed patient and/or clinical functional outcomes over multiple time points[3-5] for a minimum of 24 months, and up to 36[3] or 48 months.[4] (Figures 2 and 3)

- In two RCTs in young populations (young athletes[3] and children[4]), the treatment effect in general was sustained for individuals receiving OAT with some differences noted in the two populations.
  - In 57 athletes,[3] patients who received OAT had a greater improvement in function (as determined by mean ICRS and HSS Scores) at all time points than patients who received MF. Among patients who received OAT, improvement in function from baseline (ICRS and HSS Scores) was reported at each time point (12, 24 and 36 months), with the maximum improvement reported at 36 months. Among patients who received MF, the initial improvement in patient-reported function (ICRS Score) at 12 months was sustained at 24 and 36 months; however the maximum improvement in clinician-based function (HSS Score) was reported at 12 months, and the effect waned very slightly (2 points) by 36 months. Mean ICRS and HSS Scores were significantly higher among OAT patients at all time points.
  - In 47 children,[4] patients who received OAT had a greater improvement in function (as determined by mean ICRS Score) at all time points than patients who received MF; however, the improvement in function waned over time in both treatment groups. Among patients who received OAT, the maximum improvement in function was reported at 24 months (mean score 92), which waned modestly (mean 84) by 36 months but remained stable to 48 months. Among patients who received MF, the maximum improvement in function was reported at 12 months, and the effect waned more substantially at 24, 36 and 48 months. Mean ICRS Score were significantly higher among OAT patients at 36 and 48 months (not assessed at 12 and 24 months).
- In one RCT in a general (older) population of 40 participants,[5] the longevity of the treatment effect was comparable among patients receiving OAT and ACI. Patients who received OAT had either a somewhat greater (based on mean LKSS and Meyers Scores) or comparable (based on mean TAS Score) initial improvement in function at 3 months than patients who received ACI. In both OAT and ACI patients, functional outcomes scores continued to improve at subsequent time points, with the maximum improvement in functional outcomes being comparable and reported at 24 months for both treatment arms (based on mean LKSS, TAS, and Meyers Scores over time). There were no statistically significant differences in mean TAS or Meyers Scores between treatment

arms at any time; however, mean LKSS was significantly higher for OAT patients at 6, 12, and 24 months. Over 40% of participants had a prior surgical intervention.

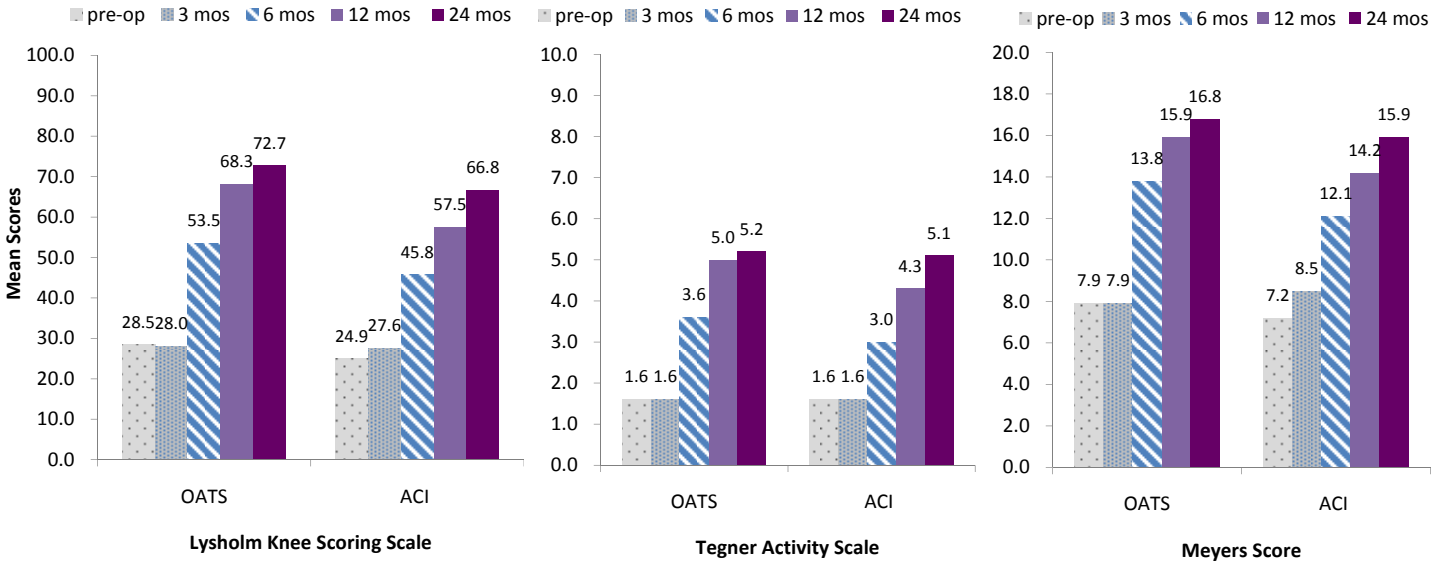
Figure 2. Mean scores for patient-reported (ICRS) and clinician-reported (HHS) measures over time.



ICRS = International Cartilage Repair Society score, HHS = Hospital for Special Surgery Score; MF = microfracture; LKSS = Lysholm Knee Scoring Scale; TAS = Tegner Activity Scale.

Figure 3. Mean scores for patient-reported (LKSS and TAS) and clinician-reported (Meyers) measures over time.

Horas 2003 (n = 40)



d) Need for continuing and/or subsequent intervention
The need for continuing and/or subsequent intervention is covered under safety.

e) Need for extended or continuing physical therapy
All RCTs included a post-surgical rehabilitation protocol, which included standardized physical therapy; however, none of the RCTs reported on the effect of OATS/Mosaicplasty on the need for extended or continuing physical therapy beyond that which was provided by the protocol.

f) Recovery time considering harvest site recovery issues
None of the RCTs provided data related to donor site recovery, and none report outcomes by donor site. Donor site morbidity is covered in the section on safety and adverse events.

There is little evidence to suggest that overall recovery time differed by treatment. In young athletes, time to maximum patient-reported functional improvement (as determined by mean change in ICRS over time) was comparable between OAT and MF treatment groups, based on mean scores reported by authors at specified follow-up times (see table).[3] However, maximum clinician-based functional improvement was achieved faster for MF than for OATS (as determined by mean change in HSS over time), although MF patients experienced lower overall improvement in function than OAT patients).[3] In children, time to reach maximum patient-reported functional improvement was comparable between treatment arms.[4] This information is based on the specified time points for follow-up and it is not known if recovery was faster prior to the first time point.

In older general populations, time to maximum patient-reported functional improvement (as determined by mean change in LKSS and TAS scores over time) and clinician-based functional improvement (as determined by mean change in Meyers Score) was comparable between OAT and ACI treatment groups. [5]

g) Differential results from multiple versus single grafts, patterning for multiple grafts (linear arrangement vs. circular arrangement)
Only two of the five RCTs reported the mean number of grafts used[3,4] and in both studies, multiple grafts were used; therefore, there are no data available to assess the differential results from multiple versus single grafts. No studies reported any information regarding the arrangement of plugs.

h) Differential results between allograft and autograft procedures
All RCTs used autograft procedures; therefore, there are no data available to assess the differential results effect of OATS/mosaicplasty between allograft and autograft procedures in the same underlying population.

i) Differential results between open and arthroscopic procedures
No studies directly compared the effects of open versus arthroscopic procedures. Indirect comparisons across studies are problematic due to heterogeneity across studies with regard to population characteristics, lesion sizes, comparative treatments and outcomes measures used. It is not possible to disentangle the influence of these factors from the potential effects of open versus arthroscopic approaches. The table below summarizes functional outcomes at final follow-up for studies based on surgical approach (see table below).

Summary of functional outcomes for studies using open versus arthroscopic procedures:

	Open			Arthroscopic		
	Author	**Summary of results**	**Outcome measure**	**Author**	**Summary of results**	**Outcome measure**
Patient-reported functional outcomes	Dozin 2005	Comparable outcomes	% Complete Success on Modified LKSS at 12 months Mosaic: 88.2% ACI: 62.5% P = 0.12	Gudas 2009	Better outcomes for OAT	Mean ICRS at 48 months OAT: 83 MF:63 P<0.05
	Horas* 2003	Better for OAT for LKSS, Comparable for TAS	Mean LKSS at 24 months OAT: 72.7 ACI: 66.8 P ≤ 0.012 Mean TAS at 24 months OAT: 5.1 ACI: 5.2 P >0.05	Gudas 2005	Better outcomes for OAT	Mean ICRS at 36 months OAT: 89 MF:75 P<0.001
	Bentley 2003*	Worse for mosaic	% Good or excellent on Modified CRS at 12 months Mosaic: 69% ACI: 93.5% P = 0.02			

Clinician-based functional outcomes	Horas* 2003	Comparable outcomes	Mean Meyers Score at 24 months OAT: 16.8 ACI: 15.0 P > 0.05	Gudas 2005	Better outcomes for OAT	Mean HSS at 36 months OAT:91 MF:81 P<0.01

LKSS = Lysholm Knee Scoring Scale, TAS = Tegner Activity Scale, HSS = Hospital for Special Surgery Score; ICRS = International Cartilage Repair Society Score, CRS = Cincinnati Knee Rating Scale
*45% (Horas) and 94 % (Bentley) of participants had a previous surgical intervention

j) Differential results in centers of excellence

None of the RCTs reported on the differential effectiveness of OATS/mosaicplasty in centers of excellence. No other studies addressing this were found.

ALLOGRAFT

Summary

Osteochondral allograft (OA) using dowel, cylindrical or geometric shaped plugs which did not require use of plates, screws or other hardware were considered to be most consistent with the autograft OATS procedure. Two small comparative studies (LoE III) and six case series (LoE IV) of such procedures provide the focus. An additional 19 case series (LoE IV) that used primarily shell/fragment osteochondral allograft with bioabsorbable pins, screws/pins or plates were considered to be procedurally different are briefly summarized in the detailed results.

- Comparative studies: No statistically significant differences between treatment groups were reported for most outcomes measures across two small studies (N = 70 total). Tegner scores were improved for OA recipients compared with loose body removal, and arthroscopic reduction and internal fixation in one study,[122] and SF-12 Mental Component Scores were significantly improved in patients who received OAT and MAT compared with OAT and ACI in the other study.[123]
- Case series:
  - Various patient-reported and clinician-based outcomes and quality of life measures were used across studies and generally indicated improved function and quality of life following the allograft procedure compared with pre-operative values.
  - One study reported a 91% survival rate of grafts at 5 years and 76% at both 10 and 15 years.

Detailed results

Pascual-Garrido et al 2009 published a comparative study of 52 adults with OCD of the knee who were at least 20 years old (mean age 34 years (± 9.5)).[122] Comparisons were done between arthroscopic reduction and internal fixation (ARIF, n = 15) osteochondral allografting using press-fit dowels (n = 16) and loose body removal (LBR n = 9) with a total of 40 patients. Authors state that multivariate analysis was done to find predictors of improvement in the LKSS, but do not mention adjusting for baseline differences between groups. Pre-operative scores on

the Knee Injury and Osteoarthritis Outcome Score (KOOS), Activities of Daily Living (ADL), and SF-12 for the osteochodral allograft (OA) group were statistically lower than scores for both the ARIF and LBR groups. They do not appear to have adjusted for multiple comparisons. Mean follow-up period was 4.0 ± 1.8 years.

A second study compared combined meniscal allograft transplantation (MAT) and ACI with combined MAT and OA.[123] Thirty patients, 58.1% male, with a mean age of 29.9 years were included, and 31 procedures were performed (16 MAT + ACI and 15 MAT + OAT). The ACI and OA groups were significantly different in age (23.4 versus 36.8 years; $P < .001$) and size of chondral defect (3.9 vs.5.5 cm^2; $p = .03$). Preoperative scores for the ACI group were significantly higher than for OA group in several outcomes scoring systems (LKSS, Noyes symptom, IKDC, KOOS pain, KOOS symptom, KOOS ADL, and KOOS quality of life). Authors reported the mean change score (percentage increase), in addition to absolute outcomes scores, in order to control for this difference. Mean follow-up period was 3.1 years.

No statistically significant differences between treatment groups were reported for most patient-reported and quality of life measures at last reported follow-up in either study. In the study by Pascual-Garrido et al.,[122] patients treated with OA graft showed greater improvement on the Tegner activity scale compared with those who had LBR or ARIF; however improvement was significantly worse for OA recipients on the KOOS Sport and the KOOS quality of life measures. Of note, patient treatment was based on lesion size and stability, leading to likely confounding by indication. In the study by Rue et al.,[123] only the SF-12 Mental Component Score changed significantly among patients treated with OA and MAT compared with ACI and MAT, suggesting improved quality of life (Table 25).

Table 25. Comparison of outcomes following OATS and various other knee procedures

Pascual-Garrido et al 2009	**Allograft (n = 16)**			**ARIF (n = 15)**			**Loose body removal (n = 9)**			***P*-Value between treatments**
	Pre-op score	Mean change score	*P*-value	Pre-op score	Mean change score	*P*-value	Pre-op score	Mean change score	*P*-value	
FUNCTION										
Patient-reported										
Tegner	0	6	< .001	2	1	.43	1	4	.03	**.03***
LKSS	25	12	.02	28	14	.01	32	12	.11	.95
IKDC	31	14	.004	37	16	.01	37	21	.002	.63
KOOS										
–Symptoms	59	8	.27	54	26	< .001	55	16	.18	.29
–ADL	57	10	.20	72	14	.02	70	17	.03	.83
–Sport	32	14	.04	29	51	< .001	30	47	.002	**.01†**
PAIN										
KOOS–Pain	52	22	.002	65	16	.01	65	13	.09	.59
QUALITY OF LIFE										
SF-12										
–Mental	49	8	.41	53	3	.13	54	0	.94	.26
–Physical	41	2	.09	36	5	.002	36	7	.02	.33
KOOS–QoL	29	10	.06	25	28	.03	26	39	< .001	**.03‡**
Rue et al 2008	**MAT + OAT (n = 15)**			**MAT + ACI (n = 16)**						***P*-Value**

	Pre-op score (± SD)	Mean change score	*P*-value	Pre-op score (± SD)	Mean change score	*P*-value		**between treatments**
FUNCTION								
Patient-reported								
Tegner	4.4 ± 3.7	1.8	.03	5.5 ± 2.9	1.8	.03		ns
LKSS	42.0 ± 14.5	26.2	.001	55.0 ± 16.0	24.4	< .001		ns
IKDC	31.4 ± 12.8	25.7	< .001	45.5 ± 8.2	21.5	< .001		ns
Noyes								
–Sports activity	47.3 ± 39.0	20.4	.04	61.8 ± 26.0	19.3	.02		ns
–Symptoms	4.5 ± 1.8	2.6	< .001	6.2 ± 1.4	2.4	< .001		ns
KOOS								
–Symptoms	49.2 ± 17.9	15.9	.01	63.5 ± 11.3	16.9	< .001		ns
–ADL	60.9 ± 23.3	23.4	.003	82.6 ± 8.3	14.8	< .001		ns
–Sport	20.8 ± 14.8	21.9	.001	29.6 ± 16.8	40.8	< .001		ns
PAIN								
KOOS–Pain	47.3 ± 15.5	25.8	< .001	62.9 ± 11.9	26.0	< .001		ns
QUALITY OF LIFE								
SF-12								
–Mental	52.6 ± 11.3	3.1	.14	58.2 ± 6.4	-3.5	.16		**.04**
–Physical	37.0 ± 8.2	5.2	.08	40.6 ± 6.3	5.0	.009		ns
KOOS–QoL	13.9 ± 17.5	27.4	< .001	35.7 ± 13.5	32.2	< .001		ns

ADL: activities of daily living; ARIF: Arthroscopic reduction and internal fixation; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; LKSS: Lysholm knee function scoring scale; Mental: Mental Component Summary; Physical: Physical Component Summary; SF-12: Short Form-12; Tegner: Tegner activity level rating scale.
*For comparison between allograft and ARIF.
†For comparisons between allograft and ARIF and allograft and loose body removal.
‡For comparison between allograft and loose body removal.

Case series of dowel-shaped/cylindrical allografts (without use of hardware)

Function

Patient-reported outcomes

Four patient-reported outcome measures were used across the three studies and all indicated improved function following the allograft procedure. The International Knee Documentation Committee (IKDC) knee scoring system was reported by two studies in a total of 48 patients.[125,126] The mean preoperative IKDC score of 40 improved by 23 points (57.5%) at a mean of 3 years follow-up ($p < .05$), an improvement that exceeds the MCID for this scale (16.7 at one year). One study reported outcomes using the Activities of Daily Living Scale of the Knee Outcome Survey in 19 patients.[127] Mean scores increased by 14 points from pre-operative values (56 ± 24) at a mean of 4 years follow-up, translating to a 25% improvement in function, $p < .05$. Another study used the Knee Injury and Osteoarthritis Outcome Score (KOOS) to measure functional outcomes in 25 patients.[126] Significant improvement was seen in all three function categories of the measure at 2.9 years follow-up: the other disease-specific symptoms score (39.1%), the ADL score (33.7%), and the sports score (156%); $p = .001$, $p < 0.0001$, and $p < 0.0001$, respectively. This same study also reported outcomes using the Lysholm Knee Scoring

Scale (LKSS) and found a mean improvement of 71.8%, translating to a mean 28 points increase from baseline scores ($p < .0001$).

One study reported outcomes using a modified Cincinnati knee rating score.[125] There were 23 patients with a mean follow-up of 3 years. Mean preoperative values for the overall score, the function score, and the symptoms score were 49.2, 27.3, and 21.9, respectively. At final follow-up, these scores had improved by 19.8 ($p < 0.02$), 9.2 ($p < 0.01$), and 10.6 points ($p < 0.03$), translating to percent mean improvements of 40.2%, 33.7% and 48.4%, respectively.

Pain

Only one study reported pain using the Pain score of the KOOS measure.[126] Mean pain scores in the 25 patients improved by 30 points or 69.8% ($p <0 .001$) from baseline at a mean 2.9 years follow-up.

Quality of Life

Two studies reported quality of life (QoL) in their patients. The SF-36 was reported in 19 patients with a mean of 4 years follow-up.[127] Mean preoperative values for the overall score, the Physical Component Score (PCS), and the Mental Component Score (MCS) were 51 ± 23, 32 ± 10 and 46 ±13, respectively. All scores improved significantly at final follow-up with the MCS showing the least percent improvement: 6.5% ($p = .01$) versus 25.0% ($p < .005$) and 29.4% ($p < 0.005$) for the PCS and overall scores, respectively. Another study used the SF-12 to measure QoL in 25 patients. Mean percent improvements in the PCS and the MCS at a mean of 2.9 years follow-up were 11.1% ($p = .01$) and 11.8% ($p = 0.05$), respectively.[126] This latter study also reported the KOOS QoL score which improved by 127% from a mean baseline score of 22 points, $p < 0.0001$.

Patient Satisfaction

One study reported overall patient satisfaction by asking their 25 patients three general questions.[126] When asked how satisfied they were with their results (for example, daily activity, functionality) the patients reported an average of 84% satisfaction (range, 25%–100%). Regarding the function of the affected/operated knee, patients responded that the affected knee was an average of 79% (range, 35%–100%) functionally compared with good knee. Lastly, 80% of patients reported that they would repeat the surgery, 8% reported they would not repeat the procedure and 12% declined to answer.

Objective evaluations

One study reported effusion rating, passive extension, and functional testing (single-leg hop test) in 20 patients (87%) with greater than 2 years follow-up.[125] At follow-up, the effusion rating was normal in all 20 patients compared with 1 (5%) rated as normal, 17 (85%) rated as nearly normal and 2 (10%) as abnormal preoperatively, $p <0 .001$. For the single-leg hop test, no patients were rated as normal preoperatively and only 4 (20%) were rated as nearly normal. Significant improvement was seen in the functional test at follow-up with 11 (55%) patients rated normal, 8 (40%) rated nearly normal and only 1 (5%) rated abnormal, $p < 0.001$. No significant difference was seen in passive extension from preoperative to postoperative assessment, with 18 (90%) rated patients as normal or nearly normal at both time points. Another study reported range of motion (ROM) and quadriceps size in the affected knee in 25

patients.[126] No significant differences were seen between preoperative and mean 2.9 year follow-up values for either measure: 123º versus 127º and 47.2 cm versus 46.2 cm, respectively.

Associated procedures

One study compared function, pain and QoL between three groups of patients according to associated procedures received during OATS[126]: allograft only (n = 11), allograft and meniscus transplantation (n = 10), and allograft and high tibial osteotomy (n = 4). As expected, a number of significant differences between preoperative and follow-up scores were seen in all three groups. However, there were no significant subjective score comparisons between the groups ($p > 0.05$). There was no control for potentially confounding factors, thus the estimate of any effect is uncertain. See Table 25.

Failure

The rate of graft failure was 7.5% (5/67 knees) at a mean follow-up of 3.5 years across the three studies. Four failures were due to graft collapse resulting in a subsequent operation in one study[127] and one was secondary to allograft fragmentation in another.[126] No graft failures were encountered in the third study.{LaPrade, 2009 #245}

Conversion to total knee arthroplasty (TKA)

Only one knee (1.5%) required a conversion to TKA 2 years following allograft placement.[127] This knee was also considered a clinical failure and pathologic examination upon graft retrieval demonstrated articular cartilage fragmentation and necrotic bone.

Case series in which dowel-shaped grafts as well as other types were used (Table 26)

Failure

The rate of graft failure was 21.3% across two studies with a total of 47 knees and mean follow-up of 3.5 years.[10,11] In one of the studies,[10] failure was reported in 14 of the 28 total knees with longer-term radiographic follow-up with failure defined as resorption, fragmentation and collapse of the allograft. In the second study,[11] failure was defined as defined as sclerosis, narrowing or obliteration of joint space, or formation of osteophytes, and the authors note that the age of each patient in whom the operation was unsuccessful was over 45 years (mean 53 years).

Conversion to knee arthroplasty

Need for a subsequent knee arthroplasty was reported in 4 of 93 patients (4.3%) across two studies with a mean follow-up of 6.6 years[10,124]; 3 of these were total knee arthroplasties (TKA) and one was a unicompartmental knee arthroplasty performed after 5 years.[124] Time to arthroplasty for the three TKAs ranged from 3 to 8 years postoperative.

Excellent or good result

Two studies reported rates of 66.7% and 72.3% for patients scoring excellent or good on the Bentley score[11] or the Merle d'Aubigné-Postel hip score,[124] respectively. There were 33 and 65 patients in each study and mean follow-up periods were 1.6 and 7.7 years, respectively. Patients in the study with the lower success rate were older compared to the other study patients: mean 48 years (range, 21–64) versus 29 years (range, 15–54).

Survivorship

One study[124] of 64 patients (66 knees), with a mean age of 28.6 years, and mean follow-up of 7.7 years reported 5- and 10-year survival rates of 91% (95% CI 83% to 99%) and 76% (95% CI 62% to 90%) respectively based on Kaplan-Meier analysis. The 15 year survival was the same as the 10 year survival.

Function

Patient-reported outcomes

One study reported outcomes using the IKDC knee score function scale.[10] In 22 patients with a mean follow-up of 5.5 years, function scores more than doubled from a preoperative value of 3.5 to 8.3 postoperatively, translating to a mean percent improvement of 137% ($p = 0.002$).

Clinician-reported outcomes

Two studies with a total of 86 patients with a mean follow-up of 6.6 years reported functional outcomes using the Merle d'Aubigné-Postel hip score.[10,124] Postoperatively, scores increased a mean of 3.7 points from baseline (12.6 points), translating to a 29.3% improvement; $P < .01$. One study used the Knee Society function score to evaluate its 22 patients.[10] By a mean follow-up of 5.5 years, score had increased from 60 preoperatively to 85.7, translating to an improvement in function of 42.8% ($p = 0.005$).

Pain

One study reported pain using the IKDC knee score pain scale in 22 patients with a mean follow-up of 5.5 years.[10] Mean pain scores improved by 5.1 points from baseline, translating to a 71.8% mean improvement in pain ($p < .001$).

Table 26. Summary of outcomes in case series following OATS using primarily dowel-shaped allografts

Studies using dowel-shaped allografts*†						
	No. Studies	**No. knees**	**Mean age years (range)**	**Mean follow-up years (range)**	**Risk, % (95% CI)‡**	
FAILURE§	3 [Williams, LePrade, McCulloch]	67	33.3 (16–49)	3.5 (1.8–5.7)	7.5 (3.2, 16.3)	
CONVERSION TO TKA	3 [Williams, LePrade, McCulloch]	67	33.3 (16–49)	3.5 (1.8–5.7)	1.5 (0.3, 8.0)	
	No. Studies	**No. patients**	**Mean age years (range)**	**Mean follow-up years (range)**	**Mean pre-op score (± SD)**	**Mean change score (% mean change)**
PATIENT REPORTED						
IKDC knee scoring system	2 [LePrade, McCulloch]	48	33.0 (16–49)	3 (1.9–5.6)	40.0	23.0 (57.5)
ADL Scale of the Knee Outcome Survey	1 [Williams]	19	34 (19–49)	4 (1.8–5.7)	56 ± 24	14 (25.0)
KOOS	1 [McCulloch]	25	35 (17–49)	2.9 (2–5.6)		
Other disease-specific symptoms					46	18 (39.1)

score						
ADL score					56	27 (48.2)
Sports score					18	28 (156)
LKSS	1 [McCulloch]	25	35 (17–49)	2.9 (2–5.6)	39	28 (71.8)
Modified Cincinnati knee-rating score	1 [LePrade]	23	30.9 (16–47)	3 (1.9–4)		
Overall score					49.2	19.8 (40.2)
Function score					27.3	9.2 (33.7)
Symptoms score					21.9	10.6 (48.4)
PAIN						
KOOS – pain score	1 [McCulloch]	25	35 (17–49)	2.9 (2–5.6)	43	30 (69.8)
QUALITY OF LIFE						
SF-36	1 [Williams]	19	34 (19–49)	4 (1.8–5.7)		
Total score					51 ± 23	15 (29.4)
Physical Component Score					32 ± 10	8 (25.0)
Mental Component Score					46 ± 13	3 (6.5)
SF-12	1 [McCulloch]	25	35 (17–49)	2.9 (2–5.6)		
Physical Component Score					36	4 (11.1)
Mental Component Score					51	6 (11.8)
KOOS – QoL score	1 [McCulloch]	25	35 (17–49)	2.9 (2–5.6)	22	28 (127)

Studies using dowel-shaped plugs and other allograft types**

	No. Studies	No. knees	Mean age years (range)	Mean follow-up years (range)	Risk, % (95% CI)†
FAILURE††	2 [Bakay, Gortz]	47	38.5 (16–64)	3.5 (0.8–19.6)	21.3 (12.0, 34.9)
CONVERSION TO TKA‡‡	2 [Emmerson, Gortz]	93	27.3 (15–54)	6.6 (2–22)	4.3 (1.7, 10.5)
SUCCESS (% good/excellent)					
Bentley score	1 [Bakay]	33	48 (21–64)	1.6 (0.8–3.2)	66.7 (49.6, 80.3)
Merle d'Aubigné-Postel hip score	1 [Emmerson]	65	28.6 (15–54)	7.7 (2–22)	72.3 (60.4, 81.7)
SURVIVORSHIP	1 [Emmerson]	65	28.6 (15–54)	7.7 (2–22)	
5 years					91 (83, 99)
10 & 15 years(same for both times)					76 (62, 90)

	No. Studies	No. patients	Mean age years (range)	Mean follow-up years (range)	Mean pre-op score (± SD)	Mean change score (% mean change)
PATIENT REPORTED						
IKDC knee score - function	1 [Gortz]	22	24.3 (16–44)	5.5 (2.1–19.6)	3.5	4.8 (137)
CLINICIAN BASED						
Merle d'Aubigné-Postel hip score	2 [Gortz, Emmerson]	86	27.5 (15–54)	6.6 (2–22)	12.6	3.7 (29.3)
Knee Society function score	1 [Gortz]	22	24.3 (16–44)	5.5 (2.1–19.6)	60	25.7 (42.8)
PAIN						
IKDC knee score - pain	1 [Gortz]	22	24.3 (16–44)	5.5 (2.1–19.6)	7.1	5.1 (71.8)

ADL: activities of daily living; IKDC: International Knee Documentation Committee; KOOS: Knee injury and Osteoarthritis Outcome Score; TKA: total knee arthroplasty.
*Of the three studies included in the table, one used an open approach [LePrade], one a mini-open approach [McCulloch] and one an arthroscopic approach [Williams].
†The study by McCulloch et al
‡All confidence intervals, excluding those reported for survivorship, were calculated by Spectrum Research, Inc.
§Failure was due to graft collapse resulting in subsequent operation in one study [Williams], was secondary to allograft fragmentation in one study [McCulloch], and the third study only stated that "no graft failure was encountered". [LePrade]
**Of the three studies included, two used an open or mini-open approach [Emmerson, Gortz] and one did not report the approach used [Bakay].
††Failure was reported in 14/28 knees with longer-term radiographic following in one study [Gortz] with failure defined as resorption, fragmentation, and collapse of the allograft. In the second study, failure was defined as fragmentation of the allograft [Bakay].
‡‡Includes one unicompartmental knee arthroplasty.

Summary of outcomes with respect to associated procedures following OATS using primarily dowel-shaped allografts [McCulloch 2007][126]

Outcome measure	Isolated Allograft (n = 11)	Allograft + MTx (n = 10)	Allograft + HTO (n = 4)

	Pre-op score (mean ± SD)	Mean change score (% change)	*P*-value	Pre-op score (mean ± SD)	Mean change score (% change)	*P*-value	Pre-op score (mean ± SD)	Mean change score (% change)	*P*-value
LKSS	34 ± 20	26 (76.5)	.008	47 ±16	21 (44.7)	.013	30 ±19	52 (173)	.002
IKDC	26 ± 8	33 (127)	.003	36 ±14	19 (52.8)	.017	22 ±13	40 (182)	.003
KOOS Pain	40 ±15	20 (50.0)	.004	49 ±12	26 (53.1)	.005	38 ±15	43 (113)	.003
KOOS Symptom	43 ± 21	19 (44.2)	.03	54 ±15	9 (16.7)	ns	36 ±28	39 (108)	.03
KOOS ADL	48 ± 20	30 (62.5)	.004	70 ±17	15 (21.4)	.028	43 ±27	47 (109)	.01
KOOS Sport	17 ± 11	33 (194)	.007	20 ±16	19 (95.0)	.032	15 ±13	39 (260)	.02
KOOS QoL	24 ±18	35 (146)	.007	19 ±21	22 (116)	.012	22 ±13	23 (105)	.02
SF-12 PCS	38 ± 8	2 (5.3)	ns	37 ±9	5 (13.5)	ns	29 ±5	9 (31.0)	ns
SF-12 MCS	53 ±14	3 (5.7)	ns	53 ±10	4 (7.5)	ns	43 ±9	18 (41.9)	.02

HTO: high tibial osteotomy; IKDC: International Knee Documentation Committee; KOOS:Knee injury and Osteoarthritis Outcome Score; LKSS: Lysholm Knee Scoring Scale; MCS: Mental Component Summary; MTx: meniscus transplantation; ns: not statistically significant; PCS: Physical Component Summary; SF-12: Short Form-12.

Case series of shell/fragment allograft

Nineteen case series were found that reported clinical outcomes following fresh osteochondral allograft transplantation for the treatment of articular cartilage defects of the knee. Based on the specific type of allograft used and the method of fixation, studies were divided into two separate groups for the purpose of results reporting: seven which employed fresh osteochondral shell allografts with fixation using absorbable pins[141-147] and 12 which used fresh osteochondral allografts with rigid fixation achieved using cancellous screws.[148-159] The results of both allograft groups should be interpreted with caution as many of the evaluations appear to have been conducted in the same patient populations and it was impossible to decipher the extent of overlap between reports. Furthermore, the heterogeneity of measures and definitions of failure/clinical success used across the studies makes comparisons difficult.

Knee allograft

Shell allograft with pin fixation (Table 27)

Seven case series were found which reported the use of osteochondral shell allografts with fixation using press fit and absorbable pins.[141-147] There were a total of 328 patients (352 knees/grafts) with mean ages ranging from 34 to 39 years (15–70 years). The percent male varied widely across studies (range, 29.7%–71.4%). Lesion etiology was predominantly trauma, followed by osteochondritis/avascular necrosis (AVN) and chondromalacia. Mean follow-up ranged from to 6 or more years across the studies.

Clinical Success

Clinical success was reported by four studies and ranged from 70.1% to 82.9% over a mean of 1 to 6.3 years follow-up.[141-143,145] The definition of clinical success varied across the studies.

Modified D'Aubigné and Postel

Five studies reported outcomes using the Modified D'Aubigné and Postel score.[141-144,147] Good or excellent overall results were achieved in 69.1% to 87.1% of patients across the studies over a mean of 2.6 to 6.3 years follow-up.

Failure

Failure rates across seven studies ranged from 11.8% to 32.0% over a mean of 1 to 6 or more years follow-up, with the latter in patients with AVN. Failure definitions varied across the studies.

Allograft with screw fixation (Table 28)

Twelve case series were found which reported the use of fresh osteochondral allografts with rigid fixation achieved using cancellous screws.[148-152,154-159] There were a total of 1039 patients (1048 knees/grafts) with mean ages ranging from 27 to 57 years (11–78 years). The percent male ranged from 45.0%–80%. Lesion etiology was predominantly trauma, followed by osteochondritis and osteoarthritis. Mean follow-up ranged from 2.9 to 12 years across the studies.

Clinical success

One study reported clinical success, defined as a postoperative score (unnamed clinician-reported measure) equal to or greater than 75 points and no subsequent surgery other than a realignment procedure, in only 55.6% of patients at a mean 6 years follow-up.[156]

Knee scores

Good or excellent results using the Modified Hospital for Special Surgery (HSS) Score were reported in 80.0% to 85.7% of patients across three studies,[148,151,154] all with greater than 5 years follow-up. One study reported knee outcomes using the Mount Sinai Hospital Knee Evaluation with good or excellent results occurring in 53.6% of the patients at 6 years follow-up.[149] A Knee Assessment Scoring System was used in another study and mean preoperative scores were 47.3, improving to 65.1 by a mean follow-up of 3.8 years. The proportion of patients with good/excellent score was not reported by this last study.

Failure

Failure rates across nine studies ranged from 14.3% to 35.4% over a mean follow-up period of 5 to 12 years.[148,150-152,154-158]

Survival rate

Overall, five studies reported survival rates.[150-152,158,159] At five years, survival ranged from 75% to 95% across four studies; at 10 years, 64% to 85% across five studies; at 15 years, 63% to 74% across four studies; and at 20 years, two studies reported survival rates of 46% and 66%.

Radiographic arthritic changes

Two studies evaluated patients for arthritic changes at means of 10.9 and 12 years postoperative, with moderate/severe arthritis seen in 52.0% and 40.0% of the patients, respectively. In all cases, the cause of the lesion was trauma.[154,158]

Table 27. Clinical outcomes following fresh osteochondral shell allografts with fixation using press fit and absorbable pins.

Outcome	No. Patients (no. knees)	Mean age in years (range)	% Male	No. of knees with outcome (%)	Etiology of lesion (%)	Mean Follow-up in years (range)
Failure						
Bugbee 1999*	97 (97)	34 (15–68)	NR	15 (15.5)†	Trauma: 65.9; Osteochondritis: 13.2; AVN: 11.0; Chondromalacia: 8.8	4.2 (2–12.3)
Chu 1999‡	55 (55)	35.6 (15–68)	NR	9 (16.4)	NR	6.3 (1–12.3)
Convery 1994§	37 (38)**	35 (15–68)	29.7	9 (24.3)	Trauma: 67.8; Osteochondritis or AVN: 24.1; Chondromalacia: 8.1	4.4 (2–8)
Convery 1991*	36 (37)	35 (15–68)	30.6	4 (11.8)††	Trauma: 62.2; Osteochondritis: 21.6; steroid-induced AVN: 16.2	≤ 6 years (NR)
Kusnick 1987‡‡	24 (41)	33 (16–67)	41.7	7 (17.1)	Ischemic necrosis: 48.8; chondromalacia: 24.4; osteochondritis: 22.0; trauma: 4.9	1 (0.2–2.3)
Meyers 1989§§	58 (59)	38.7 (15–70)	38.5	9 (22.5)***	Arthritis: 30.5; Trauma: 23.7; Osteochondritis: 20.3; Chondromalacia: 16.9; AVN: 8.5	2.6 (1–10)
Meyers 1985†††	21 (25)	NR (16–50)	71.4	8 (32.0)	AVN due to: steroids 47.6, alcoholism 33.3, fracture 19.0	NR (0.8–5.3)
Clinical Success						
Bugbee 1999‡‡‡	97 (97)	34 (15–68)	NR	68 (70.1)	Trauma: 65.9; Osteochondritis: 13.2; AVN: 11.0; Chondromalacia: 8.8	4.2 (2–12.3)
Chu 1999§§§	55 (55)	35.6 (15–68)	NR	45 (81.8)	NR	6.3 (1–12.3)
Convery 1994 ****	37 (38)**	35 (15–68)	29.7	28 (75.7)	Trauma: 67.8; Osteochondritis or AVN: 24.1; Chondromalacia: 8.1	4.4 (2–8)
Kusnick 1987††††	24 (41)	33 (16–67)	41.7	34 (82.9)	Ischemic necrosis: 48.8; chondromalacia: 24.4; osteochondritis: 22.0; trauma: 4.9	1 (0.2–2.3)
Modified D'Aubigné and Postel – Good/excellent						
Bugbee 1999	97 (97)	34 (15–68)	NR	67 (69.1)	Trauma: 65.9; Osteochondritis: 13.2; AVN: 11.0; Chondromalacia: 8.8	4.2 (2–12.3)
Chu 1999	55 (55)	35.6 (15–68)	NR	42 (76.4)	NR	6.3 (1–12.3)
Convery 1994	37 (38)**	35 (15–68)	29.7	28 (75.7)	Trauma: 67.8; Osteochondritis or AVN: 24.1; Chondromalacia: 8.1	4.4 (2–8)
Convery 1991	36 (37)	35 (15–68)	30.6	26 (76.5)††	Trauma: 62.2; Osteochondritis: 21.6; steroid-induced AVN: 16.2	≤ 6 years (NR)
Meyers 1989‡‡‡‡	58 (59)	38.7 (15–70)	38.5	27 (87.1)	Arthritis: 30.5; Trauma: 23.7; Osteochondritis: 20.3; Chondromalacia: 16.9; AVN: 8.5	2.6 (1–10)

AVN: avascular necrosis; NR: not reported.
*Failure not defined.
†Eight of these patients were rated as poor OR failures; unclear whether these represent the same result.
‡Failure defined as a knee rating of fair or poor and radiographic evidence of absorption or collapse of transplant.
§Failure not defined. Authors state that many of the patients were not local and telephone evaluations for long-term follow-up were necessary. In these cases, the patient's assessment, work, recreational activities, and any functional imitations were determined and a subjective rating of success/failure made.
**Only the 37 patients with > 2 years follow-up were included in analysis; this is out of an original cohort of 87 patients (90 knees).
††Out of the 34 patients (94%) followed.
‡‡Failure defined using unspecified clinical and radiographic criteria.
§§Failure defined as a poor clinical rating was and radiographic evidence of absorption or collapse of the transplant or of narrowing of the joint space.
***In the 39 patients (40 knees) followed.

†††Failure defined as continued moderate or severe pain after weight-bearing was resumed or collapse of the transplant.
‡‡‡Clinical success defined as a knee rating of excellent, good, or fair.
§§§Clinical success defined as a knee rating was excellent, good, or fair and radiographic evidence of graft incorporation.
****Clinical success defined as a knee rating of excellent or good.
††††Clinical success defined using unspecified clinical and radiographic criteria.
‡‡‡‡Knee scores reported only in the 31 knees that were not failures.

Table 28. Clinical outcomes following fresh osteochondral allografts with rigid fixation achieved using press fit and cancellous screws.

Outcome	No. Patients (no. knees)	Mean age in years (range)	% Male	No. of knees with outcome (%)	Etiology of lesion (%)	Mean Follow-up in years (range)
Failure						
Aubin 2001*	60 (60)	27 (15–47)	80	12 (20.0)	Trauma: 60.0; Osteochondritis: 28.0; ON: 10.0; OA: 2.0	> 5 (NR)
Beaver 1992†	91 (92)	41.9 (17–75)	56	13 (14.3)	Trauma: 100	5.7 (0.3–14.5)
Ghazavi 1997‡	123 (126)	35 (15–64)	65.9	18 (14.3)	Trauma: 88.1; Osteochondritis: 11.9	7.5 (2–22)
Gross 2002‡§	72 (72)	NR	NR	12 (20.0)**	NR	10 (NR)
Gross 2005††	125 (125)	35.2 (15–64)	61.6	20 (16.0)	Trauma: 80.8; Osteochondritis: 13.6; ON: 4.8; OA: 1	10.9 (NR)
Kandel 1985‡‡	100	NR (16–75)	45..5	22 (22.0)	OA: 68.2; ON: 27.3; Osteochondritis: 4.5	NR
McDermott 1985§§	100	48 (11–78)	60	29 (29.0)	Trauma: 53.3; OA: 26.7; ON: 15.6; Osteochondritis: 4.4	6.0 (0.5–13)
Oakshott 1988***	108	57 (16–75)	NR	18 (16.7)	OA, 61.1; ON, 33.3; Osteochondritis: 5.6	2.9 (1.1–7.7)
Shasha 2003††	67 (67)	42.8 (16–69)	45.0	23 (35.4)†††	Trauma: 100	12 (NR)
Survival Rate (%)						
At 5 years						
Beaver 1992	91 (91)	41.9 (17–75)	56	75	Trauma: 100	5.7 (0.3–14.5)
Ghazavi 1997	123 (126)	35 (15–64)	65.9	95	Trauma: 88.1; Osteochondritis: 11.9	7.5 (2–22)
Mohamed 1992	91 (92)	41.9 (17–75)	56.0	75	Trauma: 100	5.7 (0.3–14.5)
Shasha 2003	67 (67)	42.8 (16–69)	45.0	95	Trauma: 100	12 (NR)
At 10 years						
Beaver 1992	91 (91)	41.9 (17–75)	56	64	Trauma: 100	5.7 (0.3–14.5)
Ghazavi 1997	123 (126)	35 (15–64)	65.9	71	Trauma: 88.1; Osteochondritis: 11.9	7.5 (2–22)
Gross 2002*	72 (72)	NR	NR	85†	NR	10 (NR)
Mohamed 1992	91 (92)	41.9 (17–75)	56.0	64	Trauma: 100	5.7 (0.3–14.5)
Shasha 2003	67 (67)	42.8 (16–69)	45.0	80	Trauma: 100	12 (NR)
At 15 years						
Beaver 1992	91 (91)	41.9 (17–75)	56	63	Trauma: 100	5.7 (0.3–14.5)
Gross 2002*	72 (72)	NR	NR	74†	NR	10 (NR)
Mohamed 1992	91 (92)	41.9 (17–75)	56.0	63	Trauma: 100	5.7 (0.3–14.5)
Shasha 2003	67 (67)	42.8 (16–69)	45.0	65	Trauma: 100	12 (NR)
At 20 years						
Ghazavi 1997	123 (126)	35 (15–64)	65.9	66	Trauma: 88.1; Osteochondritis: 11.9	7.5 (2–22)
Shasha 2003	67 (67)	42.8 (16–69)	45.0	46	Trauma: 100	12 (NR)

Clinical Success						
McDermott 1985‡‡‡	100	48 (11–78)	60	50 (55.6)	Trauma: 53.3; OA: 26.7; ON: 15.6; Osteochondritis: 4.4	6.0 (0.5–13)
Modified HSS score						
Good/excellent						
Aubin§§§	60 (60)	27 (15–47)	80	40 (83.3)	Trauma: 60.0; Osteochondritis: 28.0; ON: 10.0; OA: 2.0	> 5 (NR)
Ghazavi 1997	123 (126)	35 (15–64)	65.9	108 (85.7)	Trauma: 88.1; Osteochondritis: 11.9	7.5 (2–22)
Gross 2005****	125 (125)	35.2 (15–64)	61.6	84 (80.0)	Trauma: 80.8; Osteochondritis: 13.6; ON: 4.8; OA: 1.0	10.9 (NR)
Mount Sinai Hospital Knee Evaluation						
Bayne 1985††††	28 (28)	NR	NR		Trauma: 53.6; Spontaneous ON: 21.4; Steroid-induced ON: 10.7; osteochondritis: 14.3	4.8 (2–10)
Good/excellent				15 (53.6)		
Radiographic Arthritic Changes						
None/Mild						
Gross 2005	38	NR	NR	18 (48.0)	NR	10.9 (NR)
Shasha 2003	35	NR	NR	21 (60.0)	Trauma: 100	12 (NR)
Moderate/Severe						
Gross 2005	38	NR	NR	20 (52.0)	NR	10.9 (NR)
Shasha 2003	35	NR	NR	14 (40.0)	Trauma: 100	12 (NR)

NR: not reported; OA: osteoarthritis; ON: osteonecrosis.
*Failure defined as need for additional surgery including graft removal, unicompartmental arthroplasty, and total knee arthroplasty.
†Failure defined as less than ten points improvement in modified HSSS knee score after operation, or the need for revision operation (other than for removal of implants), or the patient's opinion that the knee was worse than before the allograft procedure.
‡Failure defined as a decrease in clinical knee score after procedure or need for revision surgery.
§Gross et al 2002 reported the same results as Ghazavi 1997; these were not included. The results of a more recent study were also reported in the Gross et al 2002 article and the results for that population are presented here.
**Failure reported in the 60 patients who completed the study.
††Failure defined as graft removal, need for arthroplasty, or HSS score of less than 70.
‡‡Study population was comprised of 22 patients out of 100 who had failed allografts. Demographics are for these 22 patients only. This study was included only for the failure rate.
§§Failure defined as reoperation (not including realignment) for whatever cause.
***Study population was comprised of 18 patients out of 108 who had failed allografts. Demographics are for these 18 patients only. This study was included only for the failure rate.
†††Out of the 65 (97%) patients followed.
‡‡‡A successful result was defined as one where the postoperative score was equal to or greater than 75 points and the patient had not had subsequent surgery other than a realignment procedure.
§§§Modified HSS outcomes were reported in the 48 patients without failures.
****Modified HSS outcomes were reported in the 105 patients without failures.
††††Bayne et al 2008 also reported outcomes for patients following proximal tibial osteotomy (n = 10) and arthrotomy, debridement and drilling (n = 5) but only those for patient who underwent allograft are reported.

3.4 Key question 4: What is the evidence of the safety of OATS surgery?

Including consideration of:

- Adverse events type and frequency (peri-operative, cartilage plug detachment, cartilage rejection, graft fit, harvest site issues, development of fibrocartilage, mortality, other major morbidity such as DVT, deep infection, and excessive intraarticular bleeding)
- Revision/re-operation rates (if not addressed in efficacy)

Complications of osteochondral transfer surgery include short-term, perioperative events such as infection and bleeding,[21,53] sequelae such as pain and loss of function, and re-operations due to the failure of the procedure. Autograft transfer also poses the risk of donor site morbidity, since harvesting osteochondral tissue from a healthy joint site can lead to pain or joint locking at the donor site.[41,160] Articular cartilage removed from the healthy donor site is replaced by fibrocartilage, which has inferior properties to hyaline cartilage, and it is unknown whether this cartilage degenerates over time.[161] Using allografts for transplantation eliminates the potential for donor site morbidity, but poses potential risks of disease transmission and immunologic reaction, although these risks are extremely small.[12,41,53,161]

To assess safety of these procedures, safety outcomes were summarized from 1) the results of the comparative studies discussed previously; 2) the findings of case series that met inclusion criteria; and 3) findings of case series that that focused on reporting of specific complications or were expressly designed to look at safety or adverse events.

Although comparative studies, especially randomized controlled trials, may provide a more rigorous examination of outcomes, these studies are few and incorporate relatively short follow-up periods (a maximum of four years for RCTs of osteochondral grafts). In addition, such studies often do not include a sufficient number of participants to detect rare complications and adverse events. Case series were therefore used to examine safety outcomes for autograft and allograft transfer procedures, although the level of evidence for case series is low. Many of these studies incorporated longer-term follow-up and included a larger number of patients. However, many aspects of case series limit the conclusions that can be drawn. Many (from 30-100%) of the patients in these studies had had previous unsuccessful surgeries on the problematic joint, and many (up to 80%) also had concurrent procedures at the time of the graft transfer (most commonly ACL reconstruction, meniscal transplant, and high tibial osteotomy to correct alignment problems). As a result, complications and failed results cannot necessarily be attributed to a single procedure. Moreover, without a comparison group who did not receive graft surgery, it is not possible to draw conclusions about the effects of these procedures on longer-term sequelae such as development of arthritis. Many of the case series that were reviewed did not provide follow-up rates or information on retrospective or prospective data collection, and

summaries of findings were complicated by a great deal of overlap in patient samples from studies at two large surgical centers.

Procedural and long-term complications have been described as "inadequately reported" in the literature, [81] and the present report found a great variability in reporting of complications. Several studies did not report on complications, leaving it unclear if those complications had not occurred or if they had occurred but were not mentioned.

Summary of findings of safety outcomes for osteochondral autograft transplantation (OAT/mosaicplasty)

With the caveats described above in mind, a summary of the findings of three RCTs, three nonrandomized comparative studies, and five case series of osteochondral autograft transfer follows.

- Surgical complications (infection, deep vein thrombosis, and hemarthrosis) are infrequent (<7%) and effectively treated in the short term.
- Re-operations following failed procedures were not uncommon across all studies. In three RCTs, revisions of OAT procedures were rare and were performed significantly less often than revisions following microfracture (1% vs. 33%). Other procedures such as debridement and release of adhesions were performed after graft surgery in 8% of OATs patients in RCTs. In case series, rates of all re-operations following OATs were 17% across seven case series, for a variety of procedures including arthroscopic debridement, revision or replacement grafting, meniscectomy, joint fusion, and total knee arthroplasty.
- Rates of donor site morbidity were 10% in two RCTs and 11% across three case series. In five case series that specifically examined donor site morbidity, two studies, both of young male competitive athletes, reported no long-term morbidity. The other three studies reported significant impact on pain and function up to four years post-surgery, as well as MRI findings suggestive of incipient arthritis.
- MRI findings from one RCT included the presence of subchondral cysts in 8% of OATS patients, a rate significantly lower than that of of microfracture patients (33%). The significance of these cysts is unknown, however, as they may be a consequence of heat production during drilling.[111] Other MRI findings from case series include the presence of bone marrow edema in half of patients (decreasing to 15% over approximately two years) and synovitis with joint effusion in 73% of patients (decreasing to 23%).
- None of the RCTs reported on progression of osteoarthritis. In three case series that detected progression of osteoarthritis radiographically, progression of osteoarthritis occurred in 30% of patients across studies; however, without a comparison group and evaluation of potential confounders, the influence of the graft procedure is not known.

- No deaths directly attributable to OAT were found in the studies reviewed. Most of these procedures were conducted among patients who were relatively young (<50 years).

Summary of findings of safety outcomes for osteochondral allograft transplantation (using dowel, cylindrical press-fit plugs without hardware)

To summarize the findings of two nonrandomized comparative studies and six case series of osteochondral allograft transplantation:

- Only two studies reported on surgical complications, which were rare (one infection and one hyperergic reaction).
- Rates of all re-operations following OA were 12.5% across seven studies, for a variety of procedures including arthroscopic debridement, revision or replacement grafting, meniscectomy, ligament reconstruction, and unicompartmental or total knee arthroplasty.
- Although two studies assessed arthritis on radiographs at follow-up, neither study could determine whether these findings represented progression from pre-operative levels.
- The rate of graft failure was 21% in two studies that used radiographs to detect collapse or fragmentation of the graft[10] or other indicators of failure including sclerosis or joint narrowing.[11]
- Allograft transplantation carries an extremely small potential risk of disease transmission from the cadaveric tissue, which is strenuously screened, tested, and sterilized.[12,13] The last reported case of disease transmission from allograft tissue of any type occurred in 2002, before the advent of nucleic acid testing and polymerase chain reaction, when an anti-HCV–negative donor was the source of HCV infection for 8 of 30 recipients of organs or tissues.[14] No study of disease transmission related to osteochondral allograft was found in our search.

Autograft OAT/mosaicplasty: RCTs

Of the five RCTs of OAT/mosaicplasty in the knee, one[6] did not report on complications, and one[7] did not report complications separately by treatment group. Of the three remaining studies, two[3,4] compared OAT to microfracture, and the third[5] compared OAT to ACI.

Reoperation

Over the three RCTs that reported outcomes by treatment group, rates of reoperation (other than diagnostic arthroscopy) were 1/53 (1%) for OATS, 17/51 (33%) for microfracture, and 1/20 (5%) for ACI. The single re-operation following OATS was a replacement of one of the existing plugs, the single re-operation following ACI was OATS, and the re-operations for microfracture were either OATS or ACI.

Evaluation arthroscopy

Arthroscopy to evaluate cartilage repair was performed on 13/53 (24.5%) OAT cases and 24/51 (47%) microfracture patients in two studies. Arthroscopy for persistent symptoms was performed on 4/20 (20%) OAT patients and 5/20 (25%) ACI patients in one study.[5]

Other arthroscopic procedures
In two studies,[3,5] 4 of 48 OAT patients (8%), 1/29 microfracture patients (3%), and 2/20 (10%) ACI patients underwent subsequent arthroscopic procedures including debridement, release of adhesions, and spongialization.

Donor site morbidity
Donor site morbidity (diagnosed by pain on squatting) was reported for 5/48 (10%) OAT patients across two RCTs.[3,5]

Joint stiffness
Joint stiffness or arthrofibrosis was reported in two studies,[3,5] and occurred in OAT/MOS, microfracture, and ACI in 13%, 3%, and 15% of cases respectively.

Infection
Infection occurred in 5.5% of 73 OATS procedures in the three RCTs that reported complications by treatment group, with no reports of infection for microfracture or ACI.

Hemarthrosis
Bleeding in the joint was reported in 2 of 20 OATS procedures (10%) in one study.[5]

Joint swelling/effusion
Joint swelling, reported in two studies,[4,5] occurred in 3/45 (6.6%) OATS patients, 10/22 (45%) microfracture patients, and 3/20 (15%) ACI patients.

MRI findings
One study[3] reported that 8% of OATS patients and 33% of microfracture patients showed subchondral cysts on postoperative MRI.

Table 29. Summary of complications and re-operations in RCTs of osteochondral autograft transplantation (OAT)

		OAT/mosaicplasty		MF		ACI	
Complication	**Study**	**N**	**Cases (%)**	**N**	**Cases (%)**	**N**	**Cases (%)**

		OAT/mosaicplasty		MF		ACI	
Reoperation for revision*	Gudas (2005)	28	1 (3.6)	29	8 (27.6)		
	Gudas (2009)	25	0	22	9 (40.9)		
	Horas (2003)	20	0			20	1 (5)
Evaluation arthroscopy	Gudas (2005)	28	8 (28.6)	29	8 (27.6)		
	Gudas (2009)	25	5 (20)	22	16 (73)		
Diagnostic arthroscopy†	Horas (2003)	20	4 (20)			20	5 (25)
Other arthroscopic procedures‡	Gudas (2005)	28	0	29	1 (3.4)		
	Horas (2003)	20	4 (20)			20	2 (10)
Donor site morbidity	Gudas (2005)	28	0	N/A			
	Horas (2003)	20	5 (25)			20	0
Joint stiffness	Gudas (2005)	28	0	29	1 (3)		
	Horas (2003)	20	6 (30)			20	3 (15)
Infection	Gudas (2005)	28	2 (7)	29	0		
	Gudas (2009)	25	1 (4)	22	0		
	Horas (2003)	20	1 (5)			20	0
Hemarthrosis	Horas (2003)	20	2 (10)			20	0
Joint swelling/ effusion	Gudas (2009)	25	2 (8)	22	10 (45)		
	Horas (2003)	20	1 (5)			20	3 (15)
Subchondral cyst (MRI)	Gudas (2005)	25	2 (8)	21	7 (33)		

OAT: osteochondral autologous transplantation; ACI: autologous chondrocyte implantation; MF: microfracture
*Includes revision of same procedure (e.g., plug replacement) and substitute repair procedure
† For persistent symptoms or new injuries
‡ Debridement, release of adhesions, spongialization
# 95% confidence interval of risk difference excludes zero

Autograft OAT/mosaicplasty: non-randomized comparative studies

Three non-randomized comparative studies were reviewed; one of these was a retrospective chart review that reported on re-operations but not on surgical complications.[102] Two of the studies [102,104] were of the knee, and one of the ankle.[103]

Reoperation

In the three non-randomized studies, rates of reoperation (other than diagnostic arthroscopy) were low: 1/35 OAT procedures and 1/60 ACI procedures in two studies of the knee[102 104] and 1/11 chondroplasties in one study of the ankle.[103] No revisions were reported for 9 microfracture procedures and 12 OAT in the single ankle study.[103]

Diagnostic arthroscopy
Diagnostic arthroscopies for patients with persistent symptoms were performed on 7 of 40 (17%) of patients who had received abrasion chondroplasty to the knee in one study, with no diagnostic arthroscopies for OATS or ACI patients.[104]

Other procedures
Arthroscopic debridement was performed on 4 of 27 OATS patients (14%) in two studies (one ankle[103] and one knee.[104] In one study of the knee,[102] 30% of 20 mosaicplasty patients and 36% of 53 ACI patients underwent an "unanticipated arthroscopy," the purpose of which was not defined. In the same study, 5% of mosaicplasty patients and 15% of ACI patients underwent joint manipulation under anesthesia.

Donor site morbidity
No donor site morbidity was reported in any of the non-randomized studies.

Joint stiffness
Joint stiffness was reported in 2/12 (17%) of OAT patients in one study of the ankle.[103]

Other peri-operative complications
No infection or hemarthrosis was reported in these studies.

MRI findings
One study that compared OAT, ACI, and abrasion chondroplasty in the knee included findings from MRI.[104] Slight medullary edema occurred in 3/15 (20%) OAT, 3/3 (100%) ACI, and none of the 40 abrasion chondroplasties. In MRI of the 40 patients with abrasion chondroplasties, subchondral cysts were observed in 9 patients (22.5%) and arthrosynovitis was found in 28 patients (70%).

Table 30. Summary of complications and re-operations in non-randomized comparative studies of osteochondral autograft transplantation in the knee

		OAT/ MOS		ACI		MF		ACP	
Complication	**Study**	**N**	**Cases (%)**	**N**	**Cases (%)**	**N**	**Cases (%)**	**N**	**Cases (%)**
Reoperation for revision*	Derrett (2005)	20	1 (5)	53	1 (2)				

		OAT/ MOS		ACI		MF		ACP	
	Macarini (2003)	15	NR	7	NR			40	NR
Diagnostic arthroscopy†	Macarini (2003)	15	0	7	0			40	7 (17.5)
"Unanticipated" arthroscopy	Derrett (2005)	20	6 (30)	53	19 (36)				
Arthroscopic debridement	Macarini (2003)	15	2 (13)	7	0			40	0
MUA	Derrett (2005)	20	1 (5)	53	8 (15)				
Joint swelling/ effusion‡	Macarini (2003)	15	3 (20)	3	3 (100)			40	0
Subchondral cyst/geode‡	Macarini (2003)	15	0	3	0			40	9 (22.5)
Arthrosynovitis‡	Macarini (2003)	15	0	3	0			40	28 (70)

OAT: osteochondral autologous transplantation; MOS: mosaicplasty; ACI: autologous chondrocyte implantation; MF: microfracture; ACP: abrasion chondroplasty; MUA: manipulation under anesthesia
* Includes repeat of same procedure and substitute repair procedure
† For persistent symptoms or new injuries
‡ MRI findings

Table 31. Summary of complications and re-operations in non-randomized comparative studies of osteochondral autograft transplantation in the ankle

		OAT/ MOS		ACI		MF		CP	
Complication	**Study**	**N**	**Cases (%)**	**N**	**Cases (%)**	**N**	**Cases (%)**	**N**	**Cases (%)**
Reoperation for revision*	Gobbi (2006)	12	0			9	0	11	1 (9)
Arthroscopic debridement	Gobbi (2006)	12	2 (16.6)			9	0	11	0
Joint stiffness	Gobbi (2006)	12	2 (16.6)			9	0	11	0

OAT: osteochondral autologous transplantation; MOS: mosaicplasty; ACI: autologous chondrocyte implantation; MF: microfracture; CP: chondroplasty;
* Includes repeat of same procedure and substitute repair procedure

Autograft OAT/mosaicplasty: case series

Fifteen case series of osteochondral autograft transplantation met inclusion criteria and are included in this review. Nine of these series included procedures on the knee,[106,108-113,117,162] 4 on the ankle,[107,116,163,164] one on both knee and ankle,[114] and one included procedures largely from the knee and ankle but some procedures on hip, elbow, and shoulder. [55]

Re-operation other than hardware removal
Re-operation rates following graft procedures were 3-28% in seven studies of the knee and 3-28% in three studies of the ankle. Subsequent procedures included arthroscopic debridement, meniscectomy, high tibial osteotomy to correct joint alignment, and revision grafting or ACI due to graft failure. In one study of 50 ankle patients, [164] two subsequently had joint fusion, and two out of 30 patients had total knee arthoplasty in a second study. [110]

Diagnostic arthroscopy
In five studies of the knee, diagnostic arthroscopy was performed on 7-39% of patients, while in one study of the ankle the rate was 9%.

Donor site morbidity
Rates of donor site morbidity were 6-17% in three studies of the knee,[111,113,162] 2-9% in 2 studies of the ankle,[107,116] and 3% in one study[55] at both sites. One study [55] used the Bandi scoring system[165] to indicate donor site morbidity, while in the remaining studies it was indicated by pain and/or crepitation at the donor site.

Infection
Perioperative infection occurred in 2-4% of cases in 3 studies of the knee, 3% in one study of the ankle, and .4% in 1 study of both knee and ankle.

Hemarthrosis
Rates of hemarthrosis were 2-7% in three studies of the knee and 5% in one study of multiple sites. In one study of the knee, [113] hemarthrosis was aspirated in 13 out of 29 knees, but it is not clear why this rate is higher than in other studies.

Deep vein thrombosis
Deep vein thrombosis occurred in .4-3% of patients across three studies of the knee and one study of multiple sites.

Osteoarthritis progression
Development or progression of arthritis was examined radiographically in three studies of the knee. In a study of 33 knee patients,[109] 29 radiographs were evaluated at a mean of 63 months post-surgery using a four-grade classification. Of 12 patients without osteoarthritis at baseline, four (33%) had developed signs of arthritis at the last follow-up examination, and 13 of 17

patients (76%) of patients without osteoarthritis at baseline showed progression of arthritis (15 of the 17 deteriorated by one grade). Osteoarthritic progression was also reported in a study of 29 knee patients with follow-up from 6-12 years (mean 8.1 years). [113] Pre-operatively, 19 patients had no signs of osteoarthritis, 6 patients had grade I, and four patients had grade II. At follow-up, 17/29 patients (58%) maintained the same stage of osteoarthritis as preoperatively and 12/29 (42%) had worsened about one stage. In contrast, no arthritis was found at a mean follow-up of four years in a series of 36 knee patients who had no generalized arthritic changes at baseline.[108]

MRI findings

A study of 55 patients who received grafts in either knee or ankle[114] reported on several findings from MRI performed from 3 months to 3 years post-surgery. Joint effusion was found in 42 of 55 (76%) of patients in the first year after surgery, with mild effusion in 29 patients and severe effusion in 13 patients. In the first post-operative year (3-11 months; 55 patients), MRI for 51% of patients showed bone marrow edema in or around the transplanted cylinders, and 73% shows synovitis with joint effusion. These percentages decreased to 17% and 33% respectively in year 2 (12-23 months; 30 patients) and to 15% and 23% respectively in year 3 (24-36 months; 13 patients). Eight of 105 cylinders (8%) transplanted into 6 of 55 patients (11%) were assessed as showing complete or partial osteonecroses (6 cylinders in 4 of 45 knee patients, and 2 cylinders in 2 of 10 ankle patients). Half of these osteonecroses (4/8) were observed in the first 12 months and the remaining four were observed at 12-24 months.

Table 32. Summary of complications and re-operations in case series of osteochondral autograft transplantation

Complication	No. studies	N	Cases (%)
KNEE			
Reoperation*	7 [106,110-113,117,162]	272	47 (17)
Diagnostic arthroscopy†	5 [106,108,110,111,117]	216	54 (25)
Donor site morbidity	3 [111,113,162]	108	11 (10)
Infection	3 [111,112,117]	157	5 (3)
Hemarthrosis	4 [110,111,113,117]	178	18 (10)
Deep vein thrombosis	3 [109,112,117]	138	3 (2)
Osteoarthritis progression	3 [108,109,113]	98	29 (29.5)
Edema or sclerosis on MRI	1 [162]	27	17 (71)
ANKLE			

Complication	No. studies	N	Cases (%)
Reoperation*	3[107,163,164]	128	44 (34)
Donor site morbidity	2[107,116]	155	11 (7)
Infection	1[116]	112	3 (3)
COMBINED SITES			
Reoperation	NR		
Diagnostic arthroscopy†	1[55]	1097	98 (9)
Donor site morbidity	1[55]	1097	98 (9)
Infection	1[55]	1097	4 (.4)
Hemarthrosis	1[55]	1097	56 (5)
Deep vein thrombosis	1[55]	1097	4 (.4)
Joint swelling/ effusion/edema‡	1[114]	55	42 (76)
Osteonecrosis of grafts‡	1[114]	55	6 (11)

*Other than hardware removal; procedures included revision or replacement for graft failure, debridement, tibial osteotomy, joint fusion, total knee arthroplasty
† For persistent symptoms or new injuries
‡ MRI findings

Allograft (dowel/cylindrical OAT-like plugs): cohort studies

Two non-randomized comparative studies of osteochondral allograft transplantation in the knee were reviewed.[122,123] One of the studies[122] did not report on surgical complications, and the other[123] reported that no surgical complications occurred. Across the two studies, re-operations for reasons other than hardware removal were performed in two of 30 OATS patients (6%) and 4 of 18 ACI patients (22%). In one study of 30 patients, [123] 1/14 (7%) of OATS patients and 3/15 (20%) of ACI patients underwent subsequent arthroscopic debridement. In the second study,[122] revision procedures were performed on 6 of the 43 patients: one of 3 ACI procedures was revised with OATS; one of 9 loose body removal procedures was followed by microfracture, 3 of 15 arthroscopic reduction and internal fixation were revised with OATS and microfracture, and one OATS patient subsequently received total knee arthroplasty. Because these are non-randomized comparisons, the results are confounded by indication: that is, patients with more or less severe disease may be treated with different procedures. Therefore, drawing conclusions from comparisons as to the safety of these procedures would be unwise.

Allograft (dowel/cylindrical OAT-like plugs): case series

Six case series of osteochondral allograft transplantation, all of which included only patients with procedures on the knee, met inclusion criteria and are included in this review.[10,11,124-127]

Reoperation
Re-operation rates for reasons other than hardware removal or diagnostic arthroscopy were 4-26% in five studies.[10,124-127] Subsequent procedures included arthroscopic debridement, meniscectomy, ligament reconstruction, and revision grafting due to graft fragmentation or collapse. Five out of 161 patients in these five case series had unicompartmental or total knee arthroplasty.

Other procedures
One of 23 patients (4%) in one study[125] underwent diagnostic arthroscopy, and one of 19 patients (5%) in one study underwent manipulation under anesthesia.[127]

Infection
Infection was reported in one of 23 patients (4%) in one study.[125]

Osteoarthritis
Presence of arthritis was examined radiographically in two studies with follow-up at 2-3 years.[124,126] Arthritis was present in 2 of 22 patients (8%)[126] and 24 of 29 patients (83%).[124] However, neither study claimed that osteoarthritis was a result of the allograft procedure or stated that these findings represented progression from baseline.

Radiographic findings
Two studies used radiographs to detect graft failure. Bakay et al.[11] reported graft failure in 8 of 33 patients (24%), with failure defined as sclerosis, narrowing or obliteration of joint space, or formation of osteophytes. Graft failure occurred in 2 of 14 patients (14%) of a second study[10] in which graft failure was defined as resorption, collapse, or fragmentation of the osseous portion of the allograft. Subchondral cysts were detected radiographically in 5% of patients in one study.[124]

Table 33. Summary of complications and re-operations in cohort and case series of osteochondral allograft transplantation

Complication	No. studies	N	Cases (%)
Reoperation*	7[10,122-127]	191	24 (12.5)
Diagnostic	1[125]	23	1 (4)

arthroscopy†			
MUA	1[127]	19	1 (5)
Infection	1[125]	23	1 (4)
Graft failure‡	2[10,11]	47	10 (21)
Subchondral cysts	1[124]	29	5 (17)

MUA: manipulation under anesthesia
*Other than hardware removal; procedures included revision or replacement for graft failure, debridement, meniscectomy, ligament reconstruction, unicompartmental or total knee arthroplasty
† For persistent symptoms or new injuries
‡ defined as either 1) resorption, collapse, or fragmentation of the osseous portion of the allograft [Görtz] or sclerosis, narrowing or obliteration of joint space, or formation of osteophytes [Bakay]

Results of case series that explicitly examined safety outcomes

The initial literature search yielded several case series that explicitly examined selected safety outcomes but that did not meet our inclusion criteria (n>30 for autograft and n>20 for allograft).

Donor site morbidity (autograft)
Five case series examined donor site morbidity in autograft transfer to the elbow[166,167] or ankle.[116,168,169] In studies of OATS in the knee, healthy cartilage is taken from non-load-bearing areas of the same knee joint. In these studies, however, cartilage plugs were taken from the knee and transplanted to other locations, making donor site morbidity in the knee easier to differentiate.

Two of the five studies[166,167] showed minimal symptoms in the donor knee, with nearly all patients symptom-free at follow-up. These two studies differed from the other three in several characteristics:

- Patients in these two studies were young (aged 11-22), male competitive athletes, all of whom returned to their previous level of competitive sports. Given the youth and physical condition of these individuals, the likelihood of comorbidities that interfere with healing is low. Moreover, their motivation to return to competition was likely to produce more diligent rehabilitation efforts.
- In these two studies the harvest site voids were not left empty but were packed with bone wax[166] or bone grafts from the recipient elbow site[167] to reduce post-operative bleeding. The potential effects of such a procedure on cartilage regeneration are unknown.[166,167]
- In these two studies, grafts were harvested from the contralateral knee for transplantation into the elbow, while the other studies used the ipsilateral knee as the harvest site for transplantation into the ankle. In studies in which the donor and recipient sites are on the

same side of the body, it is possible that subjective ratings of the donor knee might be influenced by pain and function deficits in the recipient ankle.

In the three remaining studies, a significant proportion of patients had pain or functional problems with the donor knee. For example, more than half of patients in one study had pain in their knee at follow-up periods from 4-7 years,[169] and LKSS scores in two other studies[116,168] revealed from 8% to 36% to patients experiencing poor knee results at follow-ups up to 10 years.

Findings from MRI and single photon emission computed tomography in one study[169] showed that all patients had some abnormalities in the donor knee (see Table 34), including narrowed or missing cartilage, disrupted or missing subchondral bone plates, subchondral cysts, and joint space narrowing. Radiological findings and self-reported pain (VAS scale of 0-10) were moderately correlated (r=.42). Such findings might be interpreted as incipient osteoarthritis.[169]

It has often been suggested that the risk of morbidity at the donor size is higher for larger graft sizes (greater than 300-400 mm^2.[55,106,112] It is difficult to compare graft size across studies given the inconsistencies in reporting the total area of the transplanted grafts. However, in the largest case series of donor site morbidity,[116] the number of grafts and the total size of the harvested plugs were not related to scores on either the Lysholm or WOMAC scales. A small study of 11 patients[169] reported that patients with excellent results did not differ from those with good/poor results in terms of the number of grafts harvested (3.0 vs. 2.8) or the total surface area of plugs harvested (57.8 mm^2 vs. 62.1 mm^2).

Table 34. Summary of case series of donor site morbidity

	N	Mean age (range)	Follow-up in months	Plug harvest procedure	Knee	Findings
Iwasaki (2007)*[166]	11	14 (11-22)	12-65	NR	Contra-lateral	LKSS: Mean 99.6; all patients graded as excellent IKDC objective: all normal MRI: 6/9 had 50-100% defect fill; 4/9 had normal or nearly normal signal. No subchondral bone marrow edema ROM: 11/11 had full extension and flexion Joint effusion: 8/11 at 1-5 weeks post-op; none at F/U Other: 1/11 slight pain with stair climbing
Nishimura (2011)*[167]	12	14.4 (12-17)	24+	Mini-arthro-tomy	Contra-lateral	Knee pain (0-10): Mean .8 at 1 month, 0 at 6 months; 10/12 pain-free at 3 months Joint effusion: 7/12 at 1 month, 0 at 3 months LKSS: Mean 96.3 at 3 months, 100 thereafter Radiographs: No arthritis at 24 months Other: 2 knee pain and swelling upon exercise at 3 months; resolved at 6 months
Paul (2009)[116]	112	32 (16-57)	25-124	NR	Ipsi-lateral	LKSS: Mean 89 ± 17; 45% 98-100, 19% 92-97, 13% 82-91, 14% 66-81, 8% <66 WOMAC: Mean 5.5 ± 1; 91% minimal disease, 7%

	N	Mean age (range)	Follow-up in months	Plug harvest procedure	Knee	Findings
						mild, 1% moderate, 1% severe
Reddy (2007)[168]	11	31 (19-51)	7-77	Arthro-scopic or arthro-tomy	Ipsi-lateral	LKSS: Mean 81; 5/11 95-100, 2/11 84-94, 4/11 <65 Other: Patients with good or poor LKSS scores cited instability, pain, difficulty squatting, limping
Valderrabano (2009)[169]	12	27	43-91	NR	Ipsi-lateral	Knee pain (0-10): Increased from 0 to 2.0 postoperatively; 5/12 no pain at F/U, 5/12 mild pain, 2/12 severe pain Other: 1 joint swelling, 1 giving-way symptoms MRI Cartilage: 1/12 normal, 4/12 intact or signal-altered cartilage, 7/12 partially narrowed cartilage, 1/12 completely missing cartilage. MRI Subchondral bone plate: 4/12 intact, 5/12 partially disrupted, 1/12 completely missing MRI Cysts: 1/12 none; 6/12 small/ 3/12 large MRI bone bruising: 9/12 SPECT-CT: 12/12 abnormal appearance: 5/12 joint space narrowing, 5/12 subchondral bone plate disruption, 1/12 subchondral bone plate completely absent, 12/12 cysts (4 small, 8 large)

SPECT-CT: single photon emission computed tomography–computed tomography; LKSS: Lysholm Knee Scoring Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; IKDC: International Knee Documentation Committee; NR=not reported
* Patients were young, male competitive athletes
† Contrateral knee
‡ Ipsilateral knee

Immune response (allograft)

Allografts are not matched between donor and recipient in blood or tissue type. Although osteochondral allografts are often stated to be immunoprivileged, some patients become antibody positive after osteochondral allograft transplantation.[41]

Two case series[170,171] examined immune response in patients who underwent knee surgery and received fresh osteochondral allografts for indications other than skeletal reconstruction. In a study of 14 patients (mean age 38, range 24-55),[170] patients received donor tissue within 12 hours of donor expiration, and sera were obtained a mean of 85 months (12-130 months) after the allograft procedure. Control sera were obtained from 14 healthy controls with no history of transfusion of immunological disorder. Eight (57%) of the 14 patients developed antibodies to cartilage-specific protein measured by Western blot tests (compared to 2/14 (14%) controls). Of the eight antibody-positive patients, reactivity was low for five, moderate for two patients, and strong for one. A limitation of the study is the variation in times of collection of sera, but the authors report that reactivity and collection time were unrelated.

A second study examined the association of immunologic response to MRI findings in patients who received fresh osteochondral allografts in the knee.[171] The 36 patients (mean age 36, range 15-60) had a total of 44 allografts in 36 knees, with 6 knees receiving more than a single graft. Graft material was transplanted within 7 days of procurement. Patients were screened for serum anti-human leukocyte antigen antibodies before surgery and 2-36 months postoperatively, and were divided into antibody-positive (n=11) and antibody-negative (n=25) groups. MRI imaging was performed from 3 to 36 months post-operatively. Compared to antibody-negative patients, antibody-positive patients had significantly more host marrow edema (72 vs. 25 mm, p<.002), larger graft host interface (1.7 mm vs. 1.1 mm, p<.03), a greater percentage of abnormal graft marrow (73% vs. 48%, p<.04), and a greater likelihood of graft surface collapse (27% vs. 0%, p<.03). The antibody-positive and antibody-negative groups were similar in age, sex, donor age, graft surface area, and time after surgery, decreasing the possibility that confounding patient factors are responsible for group differences in MRI findings.

Although these studies indicated that immune reactions occur to both cartilage-specific proteins and leukocyte antigens, the relevance of these findings is unknown. Neither of these studies investigated the association of immune reactions to functional outcomes, although MRI findings suggest that antibody development interferes with healing.

3.5 Key question 5: What is the evidence that OATS surgery has differential efficacy or safety issues in sub populations?

Including consideration of:

a. Gender
b. Age
c. Psychological or psychosocial co-morbidities
d. Baseline functional status: e.g. type of injury or lesion, extent of cartilage damage, specific damage site size, number of damage sites
e. Other patient characteristics or evidence based patient selection criteria, especially comorbidities of diabetes and high BMI
f. Provider type, setting or other provider characteristics
g. Payor/beneficiary type: including worker's compensation, Medicaid, state employees

Summary

For autograft OAT/mosaicplasty

- None of the RCTs assessed differential efficacy based on gender, psychological/psychosocial co-morbidities, provider type or payer/beneficiary type.
- Direct comparisons within RCTs are limited.
    - Age: One RCT reported that younger athletes (< 30 years) had better functional outcomes than older athletes.[3]

  - Defect size: Two RCTs reported that functional outcomes were comparable among patients who received OAT regardless of defect size, but among patients who received microfracture (MF), those with defects larger than 2 cm^2 had worse functional outcomes.[3,4]
  - Defect type: One RCT reported that patients with full-thickness articular cartilage defects had significantly better functional outcomes than did patients with osteochondritis dissecans (OCD) defects ($p = 0.04$).[3]
  - Defect location: One RCT reported that MF patients with lesions in the central part of the medial femoral condyle (MFC) had worse clinical results than patients with lesions in other areas of weight-bearing parts of the knee joint (based on ICRS score) ($p < 0.05$); however, there was no association between lesion location and clinical results among OAT patients ($p < 0.85$).[3] One additional RCT reported that among patients with lesions of the medial femoral condyle, a greater proportion of patients treated by ACI had an excellent or good result, compared to patients treated by mosaicplasty.

- Indirect comparisons across RCTs may suggest that patient and clinician-reported functional outcomes were better for OAT/mosaicplasty among younger patients and among patients with no prior surgical intervention. However, such comparisons should be interpreted cautiously given differences in the populations studied, study quality, and the comparators used.
- From nonrandomized studies there is limited evidence on differential effectiveness.
  - No direct comparisons for any factor were made in nonrandomized comparative studies.
  - Case series and prognostic studies indirectly suggest that younger patients may experience better function and be able to return to sports. Better functional outcomes may occur with one plug versus multiple plugs based on two small studies. Lesion location may influence outcome.

For allograft osteochondral grafting using OAT-like procedures (dowel/cylinder/plug)

- There were no RCTs. No information on differential effectiveness is available from nonrandomized studies.

Safety

- None of the comparative studies (RCTs or cohort studies) directly assessed differential safety by any patient factors, lesion characteristics or other factors.
- Several case series indicated that older patients may have more risk of allograft failure.
- Although there may be differential allograft failure for lesions of different etiology, the small numbers of patients with lesions of different causes makes comparisons difficult.
- Results of two case series suggested that grafts of larger lesions, which require larger and/or more grafts, are more likely to fail.
- There is conflicting information regarding the influence of the number and size of plugs on donor site morbidity for autograft recipients.
- In one larger series (N=123), significantly more persons on Workers' Compensation experienced allograft failure.

- It is difficult to disentangle the differential effects of lesion size, number of grafts, and lesion etiology. Larger lesions require a greater number of grafts, and lesion etiology can also be related to lesion size. Lesions caused by osteochondritis dissecans tended to be larger than posttraumatic lesions, and larger lesions required a greater number of plugs.

Detailed results

Evidence from RCTs/quasi-RCTs - Efficacy

There were five RCTs/quasi-RCTs comparing autograft OAT/mosaicplasty procedures with other surgical options. There were no randomized studies comparing osteochondral allograft procedures (dowel/cylinder graft or other) with other surgical options.

Gender

None of the RCTs reported on the differential efficacy or safety of OATS/mosaicplasty among males and females.

Age

Only one RCT directly compared the efficacy of OATS versus MF among younger and older patients.[3] Gudas et al. reported that in both MF and OATS, younger (<30 years) athletes had better functional outcomes than older athletes (p=0.008); however, no data were provided.

Of the five RCTs or quasi-RCTs addressing the efficacy of OATS/mosaicplasty in the knee, two were conducted in younger patients (mean age < 25 years), and three were conducted in older patients (mean age ≥ 25 years; however, mean age for all three studies was approximately 30 years and only one study included patients > 45 years of age[7]). Indirect comparison across studies may suggest that patient- and clinician-reported functional outcomes were better for OAT/mosaicplasty among younger patients. However, due to heterogeneity across studies with regard to population characteristics, comparative treatments and outcomes measures used, it is not possible to disentangle the influence of these factors from the potential effects of age. Thus, comparisons across studies must be interpreted with caution. The table below summarizes functional outcomes at final follow-up for studies based on age. (Table 35)

Table 35. Summary of functional outcomes for studies using younger and older populations

	Mean age ≥ 25 years			Mean age < 25 years		
	Author	Summary of results	Outcome measure	Author	Summary of results	Outcome measure
Patient-reported functional outcomes	Dozin 2005	Comparable outcomes	% Complete Success on Modified LKSS at 12 months Mosaic: 88.2% ACI: 62.5% P = 0.12	Gudas 2009	Better outcomes for OAT	Mean ICRS at 48 months OAT: 83 MF:63 P<0.05
	Horas 2003	Better outcomes for OAT	Mean LKSS at 24 months OAT: 72.7 ACI: 66.8	Gudas	Better	Mean ICRS at 36 months

			P ≤ 0.012	2005	outcomes for OAT	OAT: 89 MF:75 P<0.001
	Horas 2003	Comparable outcomes	Mean TAS at 24 months OAT: 5.2 ACI: 5.1 P > 0.05			
Clinician-based functional outcomes	Bentley 2003*	Worse for mosaic	% Good or excellent on Modified CRS at 12 months Mosaic: 69% ACI: 93.5% P = 0.02	Gudas 2005	Better outcomes for OAT	Mean HSS at 36 months OAT:91 MF:81 P<0.01
	Horas 2003	Comparable outcomes	Mean Meyers Score at 24 months OAT: 16.75 ACI: 15.90 P > 0.05			

*94 % of participants had a previous surgical intervention

Psychological or psychosocial co-morbidities
None of the RCTs reported on the differential efficacy or safety of OATS/mosaicplasty among subpopulations defined by psychological or psychosocial co-morbidities.

Baseline functional status (type of injury or lesion, extent of cartilage damage, specific damage site size, number of damage sites)

Anatomical characteristics of defect
Only one RCT directly compared the efficacy of OATS versus MF among patients with different types of defects.[3] Gudas et al. reported that patients with full-thickness articular cartilage defects had significantly better functional outcomes (according to ICRS) than did patients with osteochondritis dissecans (OCD) defects (p = 0.04); however, no data were provided.

Defect size
Two RCTs directly compared the efficacy of OATS versus MF among patients with different sizes of defects.[3,4] In both studies, patients who received OAT had comparable functional outcomes regardless of defect size; however, among patients who received MF, patients with defects larger than 2 cm^2 had worse functional outcomes than patients with smaller defects ($p < 0.05$).[3,4] No data were provided in either study, and the authors did not indicate what measure of clinical results were being compared.

The mean lesion size in all but one study was less than 4.0 cm^2. It is difficult to draw conclusions based on indirect comparisons across studies given differences in the populations studied, study quality, and the comparators used.

Location of defect
Two RCTs directly compared the efficacy of OATS versus MF among patients with different locations of defects.[3,7] Gudas et al. reported that MF patients with lesions in the central part of medial femoral condyle (MFC) had worse functional outcomes (presumably based on the IKDC SKF that is part of the ICRS evaluation package) than patients with lesions in other areas of weight-bearing parts of the knee joint ($p < 0.05$); however, there was no association between

lesion location and functional outcomes among OAT patients (p<0.85).[3] Bentley et al. reported that among patients with lesions of the MFC, a greater proportion of patients treated by ACI had an excellent or good result, compared to patients treated by mosaicplasty. Among patients with lesions of the lateral femoral condyle or patella, there were no significant differences in the proportion of patients who had excellent or good results between treatment groups, and there were insufficient numbers of patients with lesions in the trochlea and lateral tibial plateau to compare the effects of mosaicplasty and ACI.[7]

Table 36. Functional outcomes by defect location, as reported in Bentley et al. (ref Bentley)

Lesion Site	Cincinnati Rating System	Mosaic (n=42) %	ACI (n=58) %	*P* value*
Medial femoral condyle (MFC) (n=53)	Excellent: 80-100 †	20%	46%	*P*=0.032
	Good: 55-79 †	52%	42%	
	Fair: 30-45 †	14%	12%	
	Poor <30 †	14%	0%	
Lateral femoral condyle (LFC) (n=18)	Excellent: 80-100 †	40%	54%	*P*=0.182
	Good: 55-79 †	0%	38%	
	Fair: 30-45 †	40%	8%	
	Poor <30 †	20%	0%	
Patella (n=25)	Excellent: 80-100 †	0%	25%	*P*=0.076
	Good: 55-79 †	60%	60%	
	Fair: 30-45 †	0%	15%	
	Poor <30 †	40%	0%	
Trochlea (n=3)	Excellent: 80-100 †	50%	0%	*P*=NA
	Good: 55-79 †	50%	100%	
	Fair: 30-45 †	0%	0%	
	Poor <30 †	0%	0%	
Lateral tibial plateau (n=1)	Excellent: 80-100 †	0%	0%	*P*=NA
	Good: 55-79 †	100%	0%	
	Fair: 30-45 †	0%	0%	
	Poor <30 †	0%	0%	
* *P* values calculated by authors using Mann Whitney U test for non-parametric data; compares the distribution of patients with excellent/good to fair/poor functional outcomes between Mosaic and ACI				
† The cut points reported by Bentley et al. differ from the validated cut points for the Modified Cincinnati Rating Scale				

Other patient characteristics or evidence-based patient selection criteria, especially comorbidities of diabetes and high BMI

None of the RCTs directly compared the efficacy of OAT/mosaicplasty among subpopulations defined by other patient characteristics or evidence-based patient selection criteria. However, among the five RCTs or quasi-RCTs addressing the efficacy of OATS/mosaicplasty in the knee, three RCTs were conducted in patients with no prior surgical intervention,[3,4,6] and two were conducted in patients who had a prior surgical intervention.[5,7] Indirect comparison across these studies may suggest that patients with no prior surgical intervention experience better functional outcomes from OAT/mosaicplasty. However, due to heterogeneity across studies with regard to population characteristics, comparative treatments and outcomes measures used, it is not possible to disentangle the influence of these factors from the potential effects of age and comparisons

across studies must be interpreted with caution. The table below summarizes functional outcomes at final follow-up for studies based on the inclusion of a substantial proportion of participants with previous surgeries. (Table 37)

Table 37. Summary of functional outcomes for studies in patients with and without prior surgical intervention

	Prior surgical intervention			No prior surgical intervention		
	Author	Summary of results	Outcome measure	Author	Summary of results	Outcome measure
Patient-reported functional outcomes	Horas 2003 (45% had prior surgery)	Better outcomes for OAT	Mean LKSS at 24 months	Gudas 2005	Better outcomes for OAT	Mean ICRS at 36 months
			OAT: 72.70			OAT: 89
			ACI: 66.75			MF:75
			P < 0.012			*P* < 0.001
		Comparable outcomes	Mean TAS at 24 months	Gudas 2009	Better outcomes for OAT	Mean ICRS at 48 months
			OAT: 5.20			OAT: 83
			ACI: 5.20			Mosaic: 63
			P > 0.05			*P* < 0.001
				Dozin 2005	Comparable outcomes	% Complete Success on Modified LKSS at 12 months
						Mosaic: 88.2%
						ACI: 62.5%
						P = 0.12
Clinician-based functional outcomes	Bentley 2003 (94% had prior surgery)	Worse for mosaic	% Good or excellent on Modified CRS at 12 months	Gudas 2005	Better outcomes for OAT	Mean HSS at 36 months
			Mosaic: 69%			OAT: 91.1 ± 4.15
			ACI: 93.5%			MF: 80.6 ± 4.55
			P = 0.02			*P* < 0.01
	Horas 2003	Comparable outcomes	Mean Meyer Score at 24 months			
			OAT: 16.75			
			ACI: 15.90			
			P > 0.05			

LKSS = Lysholm Knee Scoring Scale; ICRS = International Cartilage Repair Society; OAT = Osteochondryl Autograft Transplantation; ACI = Autologous Chondrocyte Implantation; MF = Microfracture; Mosaic = Mosaicplasty; TAS = Tegner Activity Score; CRS = Cincinnati Rating Scale; HSS = Hospital for Special Surgery

Provider type, setting or other provider characteristics
None of the RCTs reported on the differential efficacy or safety of OAT/mosaicplasty among subpopulations defined by provider type, setting or other provider characteristics.

Payer/beneficiary type: including worker's compensation, Medicaid, state employees
None of the RCTs reported on the differential efficacy or safety of OAT/mosaicplasty among subpopulations defined by payer/beneficiary type.

Evidence from non-randomized studies - effectiveness
Autograft OAT/mosaicplasty
No direct comparisons for any factor were made in nonrandomized comparative studies.

Five case series were identified that looked at outcomes following OATS or mosaicplasty (autograft) in various subpopulations: by patient characteristics (age and gender), preoperative status (chronicity, arthritis grade, and previous procedures), and surgical procedure (lesion location, concurrent procedures, and number of plugs). One study consisted solely of athletes. As none of the studies were comparative, only indirect assessment of the influence of various factors is possible.

Age
In one case series of knee mosaicplasties, a significantly higher percentage (80%) of younger patients (16–30 years old) had excellent/good ICRS scores compared with older (≥ 30 years old) patients (75%) (p = .02).[121] Based on indirect comparisons, younger athletes (described below) may return to sport more quickly and have better functional outcomes.

Lesion characteristics- number, location, number of plugs
Andres et al. looked at outcomes based on the number of lesions and type of treatment in 22 patients.[118] This study found that patients with OAT treatment of one knee lesion had significantly better WOMAC scores (14.9 ± 6.9, p = 0.002) and VAS pain scores (3.8 ± 1.2, p = 0.025) compared with patients who had > 1 lesion and were treated with OATS/debridement (WOMAC: 51.7 ± 26.2; VAS: 6.6 ± 2.3).

Baltzer et al.[107] examined outcomes based on the number of osteochondral plugs transplanted in 43 ankle mosaicplasties. A higher percentage of patients receiving one plug (53%) achieved a full ROM within 24 months compared with patients receiving two plugs (20% in > 24 months) and three plugs (0% in > 24 months); however, this study experienced significant loss to follow-up.

One study of knee mosaicplasties found that a higher percentage of patients with acute lesions (83%) had excellent/good ICRS scores compared with patients with chronic lesions (76%), although this did not achieve statistical significance.[121]

Marcacci et al.[121] found that a significantly higher percentage of patients receiving lateral condyle mosaicplasties (100%) had excellent/good ICRS scores compared with patients receiving medial condyle mosaicplasties (65%) (p = 0.003); however, the lateral lesion subgroup consisted mostly of younger patients. This same study also found that a higher percentage of patients receiving medial condyle mosaicplasties (22%) were unable to return to sports compared with patients receiving lateral condyle mosaicplasties (0%).

In athletes, lesion location may influence outcomes as well (see below).

Athletes
A systematic review by Mithoefer of studies which focused on return to sports after cartilage repair was found and summarized in the background to this report.[78] The review combined data from RCTs and case series from different patient populations. Thus, only indirect assessment is possible for OATS (autograft) compared to other treatments. Continued participation in sports was lower in OATS compared with ACI (autologous chondrocyte implantation). Findings

showed a significantly higher percentage of OATS patients with good to excellent results and higher percentage of OATS patients with normal repair tissue compared with microfracture. Within the OATS group, younger athletes (< 30 years) or those with lesions on the lateral femoral condyle had a significantly higher rate of return to sports and better clinical outcomes. No data for osteochondral allograft procedures were presented.

In the largest case series evaluating athletes (n = 354), those over 30 years old had worse (lower) HSS scores compared with patients under 30 years old.[120] This study also reported that among all knee and ankle patients, a higher percentage of younger patients (63%), mainly < 30 years old, returned to the same level of sports activity. A lower percentage of older patients (28%), mainly > 30 years old, returned to a lower level of sports activity. A higher percentage of patients with more severe osteoarthritis (OA) at baseline (Grades I-II) had their OA worsen (30%) compared with patients with less severe OA at baseline (Grade 0) (12%) (p = NR). These authors also reported that patients with patellar mosaicplasties experienced the smallest improvement in HSS scores compared with femoral or tibial mosaicplasties. No significant differences in outcomes between men and women were found. Limited data to support some of the results statements were available.

Previous and concurrent surgical interventions
Two studies examined outcomes based on whether or not the patient had had previous surgeries.[121,172] One study (n=14) of ankle mosaicplasties found no significant differences between patients with and without previous mosaicplasties in pain level or return to sports.[172] Pain levels (VAS) for patients with and without previous mosaicplasty were 4.1 and 2.6 for overall pain, 4.8 and 2.9 for ankle pain, and 3.4 and 1.7 for donor knee pain (all *p*s=NS). 50% of patients with previous mosaicplasties returned to playing sports at pre-surgery levels, compared to 33% of patients without previous mosaicplasties. Another study of knee mosaicplasties (n = 37) also found no significant differences in the percentage with excellent/good ICRS scores among patients with previous articular cartilage repair surgeries (74%) compared with patients with no previous surgery (83%) (p = ns).[121]

The Marcacci 2005 study (n= 37) looked at outcomes for patients who did or did not receive a surgical procedure concurrent with their OATS or mosaicplasty procedure.[121] This study found that patients receiving a procedure concurrent with their knee mosaicplasty had a higher percentage (96%) of excellent/good ICRS scores compared with patients who did not have a concurrent procedure (50%) (p = 0.007).

Allograft: Differential effectiveness
Limited information from case series is available. As none of the studies were comparative, only indirect assessment of the influence of various factors is possible.

Gender
Two studies investigated whether outcomes following OATS with dowel-shaped allografts differed according to gender. One study found no significant differences in Cincinnati knee scores and International Knee Documentation Committee (IKDC) knee scores at 3 years follow-up between male and female patients (no data provided).[125] In a second study, although mean

SF-36 scores increased significantly for both males (baseline: 58 ± 21; latest follow-up: 73 ± 16) and females (36 ± 22; 52 ± 33) ($p < 0.05$), male gender was found to correlate with better SF-36 scores at the time of follow-up (r = 0.452, $p < 0.05$).[127] Furthermore, men had a significant improvement in the mean Activities of Daily Living Scale score (58 ± 25 to 76 ± 16) ($P < 0.05$) whereas the mean score for women only changed marginally from 53 ± 23 to 58 ± 30 ($p = .36$).

Graft Age
McCulloch et al compared outcomes in patients with grafts that were implanted at 28 days or less after procurement (n = 20) versus those implanted at greater than 28 days after procurement (n = 5).[126] Significantly higher follow-up scores were seen with fresher grafts in three subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS): Pain score (90 vs. 69; $p = .03$); Other Disease-Specific Symptoms score (81 vs. 60; $p = .04$); and Activities of Daily Living score (96 vs. 79; $p = .03$). However, the authors state that these differences are most likely due to the small sample size in the greater-than-28-days group. All other assessments were not significantly different between groups (Lysholm score, IKDC knee score, SF-12 Mental and Physical Component Scores).

Alignment
McCulloch et al compared results in patients with neutral alignment (n = 21) versus malalignment (n = 4) at final follow-up.[126] Significant differences were seen between the groups, with higher IKDC scores in the neutral compared with the malaligned group, 62 versus 39 ($p = .02$), and a greater proportion of patients stating they would repeat the surgery, 90.5% (19/21) versus 25.0% (1/4), respectively ($p < .001$). All other assessments were not significantly different between groups (Lysholm score, KOOS, SF-12 Mental and Physical Component Scores).

Differential safety
No comparative studies (RCTs or cohort studies) addressed differential safety by any patient factors or lesion characteristics.

Several case series reported that certain patient factors appeared to be related to complications or graft failure. However, none of the studies were designed to detect differential outcomes by treatment, and only two of these studies performed statistical analysis.

Autograft transplantation (OAT/mosaicplasty)

Lesion size and graft size
The authors of a case series of 52 patients noted that complications and reoperations seemed to be more frequent in patients with larger surface lesions.[111] Graft failure requiring re-operation developed in none of the 13 patients with small lesions (<2.0 cm in diameter), 3 of 25 (12%) of patients with intermediate lesions (2.0-2.9 cm diameter), and 1 of 14 (7%) of patients with large lesions (>3.0 cm). Two additional patients with large lesions had other complications (infection, postoperative stiffness). Similarly, in a case series of 30 patients, 3 of 10 procedures (30%) that

implanted 3-4 cylinders failed and required re-operation, while none of the 20 procedures that transplanted 1-2 plugs failed.[162] No statistical analysis was presented in the paper, but these proportions are significantly different by Fishers exact test (p= 0.029).

A large study (N = 200) that focused solely on donor site morbidity[116] found that the number of harvested grafts and the total size of the harvested cylinders transplanted into the talus was not related to WOMAC or LKSS scores of the *donor* knee. In contrast, another case series (n = 30) reported that crepitus in the donor knee was present in all three patients who had four grafts harvested and in none of the 27 patients with fewer grafts.[162] No statistical analysis was presented in the paper, but these proportions are significantly different by Fishers exact test (p< 0.001).

Body mass index
A case series of 200 patients with autograft transplants to the ankle found that patients with larger body mass index had significantly worse scores on the WOMAC and LKSS scale for the donor knee. No specific threshold points were described.[116]

Osteochondral allograft transplantation (using dowel/cylinder/plug)

Age
The results of three case series of allografts transplanted in the knee suggested that rates of graft failure and re-operation are higher among older patients. In a case series of 33 patients, all of the 8 patients with graft failure (fragmentation or collapse) were over 40.[11] The authors concluded that a low clinical success rate could be expected in allograft transplantation among patients over 40. However, the mean age of the full sample in this study was 48, and the proportion of successful outcomes among patients younger or older than 40 was not reported. One case series (n = 64) found that patients who underwent re-operation tended to be older (mean age 31 years) than the full sample (mean age 28.6 years), but no statistical analysis of this difference was presented.[124] A third study of 123 patients reported that five out of 18 patients older than 50 (27%) experienced failed results (defined as no functional improvement and/or re-operation), compared to 13 out of 105 patients younger than 50 (12%).[151] Although statistical analyses were presented, the results are difficult to verify given that the numbers in the paper do not add up to the sample size, and the probability level for this age comparison given in the paper ($p < 0.008$) does not agree with the results of a chi-square ($p = 0.18$) or Fishers exact test ($p = 0.14$).

Lesion size
In a case series of 64 patients (66 knees), patients who required re-operation tended to have larger lesions (mean 10.4 cm^2) than the full sample (mean 7.5 cm^2). No statistical analysis of this difference was presented.[124]

Unipolar versus bipolar grafts
A case series of 123 patients (126 knees) found a significantly greater rate of graft failure in patients with grafts at both tibial and femoral sites (4/8; 50%) compared to patients with unipolar grafts (14/188; 12%; p<.05).[151]

Joint malalignment
In a case series of 123 patients (126 knees), radiographs of 103 patients indicated that joint malalignment was associated with graft failure: of 85 well-aligned cases, 8 (9%) were clinical failures compared with six of 14 malaligned cases (43%; p=.004).[151]

Lesion etiology
Failure rates were presented by lesion etiology in a case series of 100 patients with allograft transplants to the knee.[156] Failure rates were lower among patients with lesions resulting from traumatic injury (12/48; 25%) than among patients with lesions caused by osteoarthritis (14/24; 58%) or spontaneous osteonecrosis (8/11; 73%). No statistical analysis was presented in the paper, but these proportions are significantly different by chi-square analysis (p=.002).

Workers compensation
Patients treated under workers compensation were more likely to experience failed grafts (7/21; 33%) than other patients (11/102; 11%; p<.05) in a case series of 123 patients (126 knees).[151]

3.6 Key question 6: What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty?

One poor quality full economic study that compared ACI with mosiacplasty was found but provides no evidence on the cost-effectiveness of OATS/mosaicplasty as ACI is the focus.[102] The purpose was to evaluate the cost-effectiveness of ACI. The study was performed in the UK based on National Health Service (NHS) secondary care costs. These factors, combined with the small number of mosaicplasty patients (n = 11) preclude drawing meaningful conclusions regarding the cost-effectiveness of OATS/ mosaicplasty. The study was funded by Verigen UK Limited.

Given the focus of this U.K. economic study it was not included as no information regarding the cost-effectiveness of OATS/mosiacplasty was available.

4. Summary by key question

Information on determination of overall strength of evidence (SoE) is found in the Appendix D. Summaries for the individual questions are found in the executive summary an in the corresponding sections of the report. The following tables summarize the overall strength of evidence for each key question.

Key Question 1: Consistent or agreed upon case definitions; evidence of reliability and validity		
	SoE	**Conclusions/Comments**
	No evidence	• There is variability with respect to the terms used to describe the various procedures and how they are defined. • No specific agreed-upon case definitions were found. Treatment algorithms (only available for the knee) provide no citations or cite case series. • Lesion size and classification appear to be key criteria for assessing treatment options (after ligament and meniscus stability, location and other factors have been determined).
Autograft – RCT inclusion criteria	**No evidence**	• The most consistent characteristics defining cases for inclusion in the included RCTs were: symptomatic (5/5 studies), isolated (4/5 studies) full-thickness lesions or Outerbridge or ICRS grades 3 or 4 lesions (4/5 studies). Exclusion criteria in three of the five studies included knee joint instability or ligamentous deficiency. The mean ages of participants in all studies was <45 years old.
Allograft	**No evidence**	• No prospective comparative studies were found. From three (reportedly prospective) case series, cases were defined as symptomatic. Few specific inclusion/exclusion criteria were provided.
Validity and reliability	**Very low**	• No validation studies in the population of interest were found for any specific case definition or for the primary lesion classification schemes (Outerbridge, ICRS). • Overestimation of lesion size by arthroscopy compared with open evaluation was reported in one clinical study. • Only one of two clinical studies evaluating the reliability of the ICRS grading system evaluated agreement beyond chance and the agreement was fair to slight. • One study reported moderate agreement between surgeons in discriminating between Outerbridge grades 2 and 3.

Key Question 2: Validated instruments for measuring treatment outcomes		
	SoE	Conclusions/Comments
Measures	**Very low**	Four patient-reported and one clinician-based outcomes measures commonly used in patients with cartilage defects in the knee have undergone psychometric analysis in these patients. Measures: • International Cartilage Repair Society (ICRS) cartilage repair assessment • Lysholm Knee Scoring Scale (LKSS) • Modified Cincinnati Knee Rating System (MCRS) • International Knee Documentation Committee subjective knee form (IKDC SKF) • Knee Injury Osteoarthritis Outcome Score (KOOS)
Validity	**Very low**	None of the five instruments were adequately tested for validity.
Reliability	**Very low**	Reliability was inadequately tested as sample sizes were small and did not meet the quality criteria.
Responsiveness	**Very low**	Only one study, which analyzed the IKDC and MCKS, met this criterion.
MCID	**Very low**	The MCID for pre-op to post-op improvement was determined in one study for both the IKDC and the MCKRS.

Key Question 3: Efficacy and effectiveness - AUTOGRAFT		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus microfracture		
Efficacy	**Low**	• **Two poor quality RCTs** (N=104 total), one in young athletes, the other in children. • **Function**: OAT was associated with statistically better patient-reported and clinician-reported outcomes. • **Longevity of treatment effect:** Differences between treatments remained significant up to the last follow-up (maximum 48 months). Functional scores in young athletes improved for OAT recipients up to 36 months. In children following initial improvement at 12 months, ICRS scores decreased slightly, but remained stable up to 48 months. • **Return to activity:** A greater proportion of patients treated by OAT versus MF had returned to pre-injury activity levels at pre-specified time points.
Effectiveness	**No evidence**	• No nonrandomized comparative studies were found.
AUTOGRAFT: OAT/mosaicplasty versus autologous chondrocyte implantation (ACI)		
Efficacy	**Low**	• **Two poor quality RCTs** in general (older) populations were found. One enrolled >40% of participants who had prior surgeries (N =140 total). In the **other RCT,** ≥50% of persons did not receive treatment (n treated = 23/44 randomized), as authors reported "spontaneous improvement" in the six months following initial debridement. • **Function:** Patient-reported outcomes were better for OAT/mosaicplasty but statistical significance was not uniformly achieved in the two small RCTS. In the largest RCT (n = 100) a significantly smaller proportion of participants receiving mosaicplasty had excellent or good outcomes (author's modification of the Cincinnati Rating Scale) and one of the smaller RCTs reported no significant differences in the Meyer score. Both these studies included substantial proportions of participants who had prior surgeries. Differences in outcomes measures used makes comparison across studies difficult. • **Longevity of treatment effect:** In one study (N =40), functional scores for both OAT and ACI increased over time for the Lysholm, Tegner and Myers scores; only for the Lysholm Knee Scoring Scale were significant differences between treatment sustained over time favoring OAT.
Effectiveness	**No evidence**	• No nonrandomized comparative studies for this comparison were found.

Key Question 3: Efficacy and Effectiveness –AUTOGRAFT- EFFECTIVENESS		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus various treatments Nonrandomized comparative studies		
Effectiveness: ANKLE	**Very Low**	• No randomized controlled trials were found so efficacy cannot be evaluated. • One small poor quality cohort (N= 32) reported differences in functional outcomes (assessed by AOFAS or SANE Scores) between OAT and chondroplasty or OAT and microfracture; however, 24-hour post-operative pain was greater among patients treated by OAT.

Key Question 3: Efficacy and Effectiveness –AUTOGRAFT- EFFECTIVENESS		
	SoE	**Conclusions/Comments**
AUTOGRAFT: OAT/mosaicplasty versus various treatments Nonrandomized comparative studies		
Effectiveness: **KNEE**	**Very low**	• Four small, poor quality nonrandomized studies compared OAT alone or in combination with other procedures. Confounding by indication was present in all and heterogeneity across studies precludes effective comparison across them. • For most functional outcomes, there were no differences between treatment groups. o In one small (N =18) study, post-operative mean Modified Lysholm score was significantly less for OAT versus matrix assisted chondrocyte transplantation (MACT). o Range of motion appeared to be substantially greater among patients treated by OAT with realignment versus realignment alone in another study (n =49)

Key Question 3: Efficacy and Effectiveness - ALLOGRAFT		
	SoE	**Conclusions/Comments**
Osteochondral allograft using primarily press-fit dowel/cylinder or plug (not requiring hardware)		
Efficacy	**None**	• No randomized controlled trials were found.
Effectiveness	**Very low**	• Comparative studies: No statistically significant differences between treatment groups were reported for most outcomes measures across two small studies (N = 70 total). Tegner scores were improved for OA recipients compared with loose body removal and arthroscopic reduction and internal fixation in one study, and SF-12 Mental Component Scores were significantly improved in patients who received OA and MAT (meniscal allograft transplantation) compared with OA and ACI in the other. • Case series of >19 patients which primarily used press-fit plugs (dowel/cylinder/geometric) without use of fixation • Various patient-reported, clinician based outcomes and quality of life measures were used across studies and generally indicated improved function and quality of life following the allograft procedure compared with pre-operative values. • One study reported a 91% survival rate of grafts at 5 years and 76% at both 10 and 15 years (N =65).

Key Question 4: Safety		
	SoE	**Conclusions/Comments**
Autograft		
	Low	• Data from three RCTs, 3 nonrandomized comparative studies, and 5 case series of osteochondral autograft transfer were used • Surgical complications (infection, deep vein thrombosis, and hemarthrosis) are infrequent (<7%). • In 3 RCTs, revisions of OAT procedures were performed significantly less often than revisions following microfracture (1% vs. 33%). Re-operations following OATs were 17% across seven case series (variety of procedures).

Key Question 4: Safety		
	SoE	**Conclusions/Comments**
Autograft		
		• Rates of donor site morbidity were 10% in two RCTs and 11% across three case series. • No deaths directly attributable to OAT were found in the studies reviewed.
Allograft		
	Low	• Rates of all re-operations following OATs were 12.5% across seven studies. • Rate of graft failure was 21% in two studies that used radiographs. • Allograft transplantation carries an extremely small potential risk of disease transmission. No study of disease transmission related to osteochondral allograft was found in our search.

Key Question 5: Differential Efficacy, Effectiveness and Safety		
	SoE	**Conclusions/Comments**
Efficacy	**Low**	• Direct comparisons within RCTs are limited and may suggest that age, defect size, and defect location may influence outcomes • Indirect comparison of factors is challenging given differences in the populations studied, study quality the comparators used.
Effectiveness	**Very low**	• No direct comparisons for any factor were made in nonrandomized comparative studies • Indirect comparisons based on case series of **autograft** OATS/mosaicplasty suggest that younger patients may experience better function and be better able to return to sports. Better functional outcomes may occur with one plug versus multiple plugs based on two small studies. Lesion location may influence outcome. • **Allograft**: Limited information from two case series is conflicting with regarding the influence of gender.
Safety	**Very low**	• No comparative studies of autograft or allograft transplantation assessed differential safety • Results of case series of autograft and allograft transplantation suggested that older patients may have more risk of graft failure and that grafts of larger lesions were more likely to fail.

Summary of evidence and implications

This systematic review of the literature focuses on the highest quality of literature currently available to answer the key questions. The overall quality of the literature, particularly with respect to allograft, is poor. The overall strength of evidence for the key questions ranges from no evidence to very low evidence. Thus, it is difficult to draw evidence-based conclusions regarding the key questions posed for this assessment.

Remaining questions

Evidence-based conclusions regarding which patients may most benefit from which type of grafting procedure are not clear from the literature reviewed in this report. The efficacy, effectiveness and safety of autograft and allograft transplantation procedures as described in this report are still in question given the overall poor quality of the evidence available.

References

1. Cole BJ, Frederick RW, Levy AS, Zaslav KR. Management of a 37-Year-Old Man with Recurrent Knee Pain. *J Clin Outcomes Management.* 1999;6(6):46 - 57.

2. 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.

3. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. *Arthroscopy.* Sep 2005;21(9):1066-1075.

4. Gudas R, Simonaityte R, Cekanauskas E, Tamosiunas R. A prospective, randomized clinical study of osteochondral autologous transplantation versus microfracture for the treatment of osteochondritis dissecans in the knee joint in children. *J Pediatr Orthop.* Oct-Nov 2009;29(7):741-748.

5. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. *J Bone Joint Surg Am.* Feb 2003;85-A(2):185-192.

6. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med.* Jul 2005;15(4):220-226.

7. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br.* Mar 2003;85(2):223-230.

8. Gaweda K, Walawski J, Weglowski R, Patyra M. Rehabilitation after one-stage anterior cruciate reconstruction and osteochondral grafting. *Int Orthop.* Jun 2006;30(3):185-189.

9. Gaweda K, Walawski J, Weglowski R, Drelich M, Mazurkiewicz T. Early results of one-stage knee extensor realignment and autologous osteochondral grafting. *Int Orthop.* Feb 2006;30(1):39-42.

10. Gortz S, De Young AJ, Bugbee WD. Fresh osteochondral allografting for steroid-associated osteonecrosis of the femoral condyles. *Clin Orthop Relat Res.* May 2010;468(5):1269-1278.

11. Bakay A, Csonge L, Papp G, Fekete L. Osteochondral resurfacing of the knee joint with allograft. Clinical analysis of 33 cases. *Int Orthop.* 1998;22(5):277-281.

12. Akhavan S, Miniaci A, T PM, et al. Cartilage repair and replacement: from osteochondral autograft transfer to allograft. *Arthritis & arthroplasty: The knee*: Saunders/Elsevier; 2009:334.

13. Tomford WW. Transmission of disease through transplantation of musculoskeletal allografts. *J Bone Joint Surg Am.* Nov 1995;77(11):1742-1754.

14. Tugwell BD, Patel PR, Williams IT, et al. Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor. *Ann Intern Med.* Nov 1 2005;143(9):648-654.

15. Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med.* Nov 2009;37 Suppl 1:148S-155S.
16. Magnussen RA, Dunn WR, Carey JL, Spindler KP. Treatment of focal articular cartilage defects in the knee: a systematic review. *Clin Orthop Relat Res.* Apr 2008;466(4):952-962.
17. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. *J Bone Joint Surg Am.* Oct 2005;87(10):2232-2239.
18. Slynarski K, Deszczynski J. Algorithms for articular cartilage repair. *Transplant Proc.* Jan-Feb 2006;38(1):316-317.
19. Kish G, Hangody L. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br.* May 2004;86(4):619; author reply 619-620.
20. Safran MR, Seiber K. The evidence for surgical repair of articular cartilage in the knee. *J Am Acad Orthop Surg.* May;18(5):259-266.
21. Creighton RA, Cole BJ. Autologous osteochondral transplantation: background, surgical indications, and results. In: Scott WN, ed. *Surgery of the knee*. Philadelphia: Churchill Livingstone/Elsevier; 2006.
22. Mithoefer K, Saris DB, Farr J, et al. Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair: International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care. *Cartilage.* 2011;2(2):100-121.
23. Ding C, Cicuttini F, Scott F, Cooley H, Boon C, Jones G. Natural history of knee cartilage defects and factors affecting change. *Arch Intern Med.* Mar 27 2006;166(6):651-658.
24. Wang Y, Ding C, Wluka AE, et al. Factors affecting progression of knee cartilage defects in normal subjects over 2 years. *Rheumatology (Oxford).* Jan 2006;45(1):79-84.
25. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee.* Jun 2007;14(3):177-182.
26. Shah MR, Kaplan KM, Meislin RJ, Bosco JA, 3rd. Articular cartilage restoration of the knee. *Bull NYU Hosp Jt Dis.* 2007;65(1):51-60.
27. Flanigan DC, Harris JD, Trinh TQ, Siston RA, Brophy RH. Prevalence of chondral defects in athletes' knees: a systematic review. *Med Sci Sports Exerc.* Oct 2010;42(10):1795-1801.
28. Paley KJ, Jobe FW, Pink MM, Kvitne RS, ElAttrache NS. Arthroscopic findings in the overhand throwing athlete: evidence for posterior internal impingement of the rotator cuff. *Arthroscopy.* Jan-Feb 2000;16(1):35-40.
29. Matsuura T, Kashiwaguchi S, Iwase T, Susue N, Yasui N. Epidemiology of elbow osteochondral lesion in young baseball players. *75th Annual Meeting Podium Presentations, Sports Medicine/Arthroscopy 4: ACL 2* 2008; http://www3.aaos.org/education/anmeet/anmt2008/podium/podium.cfm?Pevent=566. Accessed 8/10/2011.
30. American Academy of Orthopaedic Surgeons. The diagnosis and treatment of osteochondritis dissecans: guideline and evidence report. 2010; http://www.aaos.org/research/guidelines/OCD_guideline.pdf, 06/29/2011.
31. Linden B. The incidence of osteochondritis dissecans in the condyles of the femur. *Acta Orthop Scand.* Dec 1976;47(6):664-667.

32. Linden B. Osteochondritis dissecans of the femoral condyles: a long-term follow-up study. *J Bone Joint Surg Am.* Sep 1977;59(6):769-776.
33. Gagliardi JA, Chung EM, Chandnani VP, et al. Detection and staging of chondromalacia patellae: relative efficacies of conventional MR imaging, MR arthrography, and CT arthrography. *AJR Am J Roentgenol.* Sep 1994;163(3):629-636.
34. Doberstein ST, Romeyn RL, Reineke DM. The diagnostic value of the Clarke sign in assessing chondromalacia patella. *J Athl Train.* Apr-Jun 2008;43(2):190-196.
35. Wheeless' Textbook of Orthopaedics. Chondromalacia of the Patella. 2011; http://www.wheelessonline.com/ortho/chondromalacia_of_the_patella. Accessed 08/22/2011.
36. Wheeless' Textbook of Orthopaedics. Osteochondral Lesions of the Talus. 2011; http://www.wheelessonline.com/ortho/Talus_Osteochondral_Lesion. Accessed 08/22/2011.
37. Zengerink M, Struijs PA, Tol JL, van Dijk CN. Treatment of osteochondral lesions of the talus: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* Feb 2010;18(2):238-246.
38. Finger A, Sheskier SC. Osteochondral lesions of the talar dome. *Bull Hosp Jt Dis.* 2003;61(3-4):155-159.
39. Scheibel M, Bartl C, Magosch P, Lichtenberg S, Habermeyer P. Osteochondral autologous transplantation for the treatment of full-thickness articular cartilage defects of the shoulder. *J Bone Joint Surg Br.* Sep 2004;86(7):991-997.
40. Rodriguez-Merchan EC, Gomez-Cardero P. The outerbridge classification predicts the need for patellar resurfacing in TKA. *Clin Orthop Relat Res.* May 2010;468(5):1254-1257.
41. Farr J, Cole B, Dhawan A, Kercher J, Sherman S. Clinical Cartilage Restoration: Evolution and Overview. *Clin Orthop Relat Res.* Jan 15 2011.
42. United States Patent and Trademark Office. Trademark Electronic Search System (TESS): OATS. 2011; http://tess2.uspto.gov/bin/showfield?f=doc&state=4009:3undvt.10.1. Accessed 09/06/2011.
43. Zimmer, Inc.,. Zimmer® Chondrofix® Osteochondral Allograft Reimbursement Kit. 2011; http://www.zimmer.com/web/enUS/pdf/Chondrofix_Reimbursement_Kit_20111.pdf. Accessed 09/06/2011.
44. United States Patent and Trademark Office. Trademark Electronic Search System (TESS): CHONDROFIX. 2011; http://tess2.uspto.gov/bin/showfield?f=doc&state=4005:8ocpmq.5.1. Accessed 09/06/2011.
45. Cole BJ, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. *J Bone Joint Surg Am.* Jul 2009;91(7):1778-1790.
46. DeFranco MJ, McNickle AG, Cole BJ. Allograft Osteoarticular Resurfacing. In: M B, A A, J B, S M, J M, eds. *The Knee Joint, Surgical Techniques and Strategies*: Springer; 2011.
47. McAllister DR, Joyce MJ, Mann BJ, Vangsness CT, Jr. Allograft update: the current status of tissue regulation, procurement, processing, and sterilization. *Am J Sports Med.* Dec 2007;35(12):2148-2158.

48. American academy of orthopaedic surgeons. Bone and Tissue Transplantation 2009; http://orthoinfo.aaos.org/topic.cfm?topic=a00115. Accessed 08/22/2011.
49. Vangsness CT, Jr., Wagner PP, Moore TM, Roberts MR. Overview of safety issues concerning the preparation and processing of soft-tissue allografts. *Arthroscopy.* Dec 2006;22(12):1351-1358.
50. U.S. Food and Drug Administration. Human Cell & Tissue Products (HCT/P) Adverse Reaction Reporting. 2009; http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/ucm152576.htm. Accessed 09/06/2011.
51. Eastlund DT, Eisenbrey AB. *Guidelines for Managing Tissue Allografts in Hospitals* Bethesda, MD: American Association of Blood Banks,; 2006.
52. Caldwell PE, 3rd, Shelton WR. Indications for allografts. *Orthop Clin North Am.* Oct 2005;36(4):459-467.
53. Lattermann C, Romine SE. Osteochondral allografts: state of the art. *Clin Sports Med.* Apr 2009;28(2):285-301, ix.
54. Buschmann M. Email Response to OATS questions. In: Skelly A, ed2011.
55. Hangody L, Vasarhelyi G, Hangody LR, et al. Autologous osteochondral grafting--technique and long-term results. *Injury.* Apr 2008;39 Suppl 1:S32-39.
56. Bugbee WD. Fresh osteochondral allografts. *J Knee Surg.* Summer 2002;15(3):191-195.
57. Hangody L, Duska Z, Karpati Z. Autologous Osteochondral Mosaicplasty. *Techniques in Knee Surgery.* 2002;1(1):13-22.
58. Wang S, Zinderman C, Wise R, Braun M. Infections and human tissue transplants: review of FDA MedWatch reports 2001-2004. *Cell Tissue Bank.* 2007;8(3):211-219.
59. Alford JW, Cole BJ. Cartilage restoration, part 1: basic science, historical perspective, patient evaluation, and treatment options. *Am J Sports Med.* Feb 2005;33(2):295-306.
60. Knee Joint Surgery. Articular Cartilage: Treatment Options. 2007; http://www.kneejointsurgery.com/html/articular_cartilage/treatment_options.html. Accessed 08/24/2011.
61. Alford JW, Cole BJ. Cartilage restoration, part 2: techniques, outcomes, and future directions. *Am J Sports Med.* Mar 2005;33(3):443-460.
62. U.S. Food and Drug Administration. August 22, 1997 Approval Letter - Carticel. 1997; http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm171702.htm.
63. U.S. Food and Drug Administration. Carticel (autologous cultured chondrocytes) Dear Healthcare Professional Letter Mar 2000. 2000; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm176061.htm.
64. Elser F, Braun S, Dewing CB, Millett PJ. Glenohumeral joint preservation: current options for managing articular cartilage lesions in young, active patients. *Arthroscopy.* May 2010;26(5):685-696.
65. McNickle AG, Provencher MT, Cole BJ. Overview of existing cartilage repair technology. *Sports Med Arthrosc.* Dec 2008;16(4):196-201.
66. American Academy of Orthopaedic Surgeons. The treatment of glenohumeral joint osteoarthritis: guideline and evidence report. 2009; http://www.aaos.org/research/guidelines/gloguideline.pdf, 06/29/2011.

67. National Guideline Clearinghouse (NGC). Shoulder (acute & chronic) (Work Loss Data Institute): guideline summary. 2008, update in progress; http://www.guidelines.gov/content.aspx?id=12678. Accessed 06/30/2011.
68. National Guideline Clearinghouse (NGC). Knee & leg (acute & chronic) (Work Loss Data Institute): guideline summary. 2007, update in progress. Accessed 06/30/2011.
69. National Institute for Health and Clinical Excellence (NICE). Mosaicplasty for knee cartilage defects. 2006; http://www.nice.org.uk/nicemedia/pdf/ip/IPG162guidance.pdf. Accessed 6/27/2011.
70. Moyad TF. Cartilage Injuries in the Adult Knee: Evaluation and Management. *Cartilage.* 2011;2(3):226-236.
71. 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.
72. Washington State Department of Labor and Industries. Medical treatment guidelines: review criteria for knee surgery. 2003; http://www.lni.wa.gov/ClaimsIns/Files/OMD/MedTreat/KneeSurgery.pdf. Accessed 06/28/2011.
73. State Government of Queensland, Q-Comp: The Workers' Compensation Regulatory Authority. Clinical guidelines for the Queensland workers' compensation scheme: knee. 2008; http://www.qcomp.com.au/media/10251/knee%5B1%5D.pdf. Accessed 6/29/2011.
74. American College of Rheumatology. Recommendations for the medical management of osteoarthritis of the hip and knee. 2000, addendum 2005; http://www.rheumatology.org/practice/clinical/guidelines/oa-mgmt.asp. Accessed 06/27/2011.
75. Harris JD, Siston RA, Pan X, Flanigan DC. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am.* Sep 15 2010;92(12):2220-2233.
76. Washington State Department of Labor and Industries. Autologous Chondrocyte Implantation (ACI) Technology Assessment. 2002 Update; http://www.lni.wa.gov/ClaimsIns/Files/OMD/AciUpdate.pdf. Accessed 06/28/2011.
77. Vavken P, Samartzis D. Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: a systematic review of controlled trials. *Osteoarthritis Cartilage.* Jun 2010;18(6):857-863.
78. Mithoefer K, Hambly K, Della Villa S, Silvers H, Mandelbaum BR. Return to sports participation after articular cartilage repair in the knee: scientific evidence. *Am J Sports Med.* Nov 2009;37 Suppl 1:167S-176S.
79. Clar C, Cummins E, McIntyre L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess.* Dec 2005;9(47):iii-iv, ix-x, 1-82.
80. Nakamura N, Miyama T, Engebretsen L, Yoshikawa H, Shino K. Cell-based therapy in articular cartilage lesions of the knee. *Arthroscopy.* May 2009;25(5):531-552.
81. National Institute for Health and Clinical Excellence (NICE). Interventional procedure overview of mosaicplasty for knee cartilage defects. 2005; http://www.nice.org.uk/ip283overview. Accessed 6/27/2011, 07/28/2011.
82. Vasiliadis HS, Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. *Cochrane Database Syst Rev.* 2010(10):CD003323.

83. Ruano-Ravina A, Jato Diaz M. Autologous chondrocyte implantation: a systematic review. *Osteoarthritis Cartilage.* Jan 2006;14(1):47-51.
84. Jobanputra P, Parry D, Fry-Smith A, Burls A. Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review. *Health Technol Assess.* 2001;5(11):1-57.
85. Benthien JP, Schwaninger M, Behrens P. We do not have evidence based methods for the treatment of cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc.* Apr 2011;19(4):543-552.
86. Mithoefer K, McAdams TR, Scopp JM, Mandelbaum BR. Emerging options for treatment of articular cartilage injury in the athlete. *Clin Sports Med.* Jan 2009;28(1):25-40.
87. Tol JL, Struijs PA, Bossuyt PM, Verhagen RA, van Dijk CN. Treatment strategies in osteochondral defects of the talar dome: a systematic review. *Foot Ankle Int.* Feb 2000;21(2):119-126.
88. Aetna, Inc. Clinical policy bulletin: osteochondral autografts (mosaicplasty, OATS), number 0637. 2010; http://www.aetna.com/cpb/medical/data/600_699/0637.html. Accessed 06/20/2011.
89. Aetna, Inc. Clinical policy bulletin: allograft transplants of the knee, number 0364. 2010; http://www.aetna.com/cpb/medical/data/300_399/0364.html. Accessed 07/03/2011.
90. Cigna, Inc. Osteochondral grafts for articular cartilage repair (autografts, allografts, and synthetic grafts), number 0197. 2011; http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0197_coveragepositioncriteria_osteochondral_autograft_transplant.pdf. Accessed 06/30/2011.
91. Premara Blue Cross. Osteochondral allografts and autografts (OATS) in the treatment of articular cartilage lesions, number CP.MP.PR.7.01.506. 2011; https://www.premera.com/stellent/groups/public/documents/medicalpolicy/cmi_017594.pdf. Accessed 06/30/2011.
92. Phillips B, Ball C, Sackett D, et al. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp. 2001. Accessed December 2, 2006, 2006.
93. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *Bmj.* Jun 19 2004;328(7454):1490.
94. West S, King V, Carey TS, et.al. Systems to Rate the Strength of Scientific Evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center, Contract No. 290-97-0011): Agency for Healthcare Research and Quality, Rockville, MD; 2002.
95. Marx RG, Connor J, Lyman S, et al. Multirater agreement of arthroscopic grading of knee articular cartilage. *Am J Sports Med.* Nov 2005;33(11):1654-1657.
96. Niemeyer P, Pestka JM, Erggelet C, Steinwachs M, Salzmann GM, Sudkamp NP. Comparison of arthroscopic and open assessment of size and grade of cartilage defects of the knee. *Arthroscopy.* Jan 2011;27(1):46-51.
97. Spahn G, Klinger HM, Baums M, Pinkepank U, Hofmann GO. Reliability in arthroscopic grading of cartilage lesions: results of a prospective blinded study for evaluation of inter-observer reliability. *Arch Orthop Trauma Surg.* Mar 2011;131(3):377-381.

98. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage.* 2009;17(11):1434-1439.

99. 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.* 2004:1139-1145.

100. Smith HJ, Richardson JB, Tennant A. Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. *Osteoarthritis Cartilage.* Jan 2009;17(1):53-58.

101. van den Borne MP, Raijmakers NJ, Vanlauwe J, et al. International Cartilage Repair Society (ICRS) and Oswestry macroscopic cartilage evaluation scores validated for use in Autologous Chondrocyte Implantation (ACI) and microfracture. *Osteoarthritis Cartilage.* Dec 2007;15(12):1397-1402.

102. Derrett S, Stokes EA, James M, Bartlett W, Bentley G. Cost and health status analysis after autologous chondrocyte implantation and mosaicplasty: a retrospective comparison. *Int J Technol Assess Health Care.* Summer 2005;21(3):359-367.

103. Gobbi A, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. *Arthroscopy.* Oct 2006;22(10):1085-1092.

104. Macarini L, Murrone M, Marini S, Moretti B, Patella V. Aspects of Magnetic Resonance in the surgical treatment of osteochondral lesions of the knee. *Radiol Med.* Jul-Aug 2003;106(1-2):74-86.

105. Salzmann GM, Paul J, Bauer JS, et al. T2 assessment and clinical outcome following autologous matrix-assisted chondrocyte and osteochondral autograft transplantation. *Osteoarthritis Cartilage.* Dec 2009;17(12):1576-1582.

106. Agneskirchner JD, Brucker P, Burkart A, Imhoff AB. Large osteochondral defects of the femoral condyle: press-fit transplantation of the posterior femoral condyle (MEGA-OATS). *Knee Surg Sports Traumatol Arthrosc.* May 2002;10(3):160-168.

107. Baltzer AW, Arnold JP. Bone-cartilage transplantation from the ipsilateral knee for chondral lesions of the talus. *Arthroscopy.* Feb 2005;21(2):159-166.

108. Barber FA, Chow JC. Arthroscopic chondral osseous autograft transplantation (COR procedure) for femoral defects. *Arthroscopy.* Jan 2006;22(1):10-16.

109. Braun S, Minzlaff P, Hollweck R, Wortler K, Imhoff AB. The 5.5-year results of MegaOATS--autologous transfer of the posterior femoral condyle: a case-series study. *Arthritis Res Ther.* 2008;10(3):R68.

110. Chow JC, Hantes ME, Houle JB, Zalavras CG. Arthroscopic autogenous osteochondral transplantation for treating knee cartilage defects: a 2- to 5-year follow-up study. *Arthroscopy.* Sep 2004;20(7):681-690.

111. Jakob RP, Franz T, Gautier E, Mainil-Varlet P. Autologous osteochondral grafting in the knee: indication, results, and reflections. *Clin Orthop Relat Res.* Aug 2002(401):170-184.

112. Karataglis D, Green MA, Learmonth DJ. Autologous osteochondral transplantation for the treatment of chondral defects of the knee. *Knee.* Jan 2006;13(1):32-35.

113. Laprell H, Petersen W. Autologous osteochondral transplantation using the diamond bone-cutting system (DBCS): 6-12 years' follow-up of 35 patients with osteochondral defects at the knee joint. *Arch Orthop Trauma Surg.* May 2001;121(5):248-253.

114. Link TM, Mischung J, Wortler K, Burkart A, Rummeny EJ, Imhoff AB. Normal and pathological MR findings in osteochondral autografts with longitudinal follow-up. *Eur Radiol.* Jan 2006;16(1):88-96.
115. Marcacci M, Kon E, Zaffagnini S, et al. Arthroscopic second generation autologous chondrocyte implantation. *Knee Surg Sports Traumatol Arthrosc.* May 2007;15(5):610-619.
116. Paul J, Sagstetter A, Kriner M, Imhoff AB, Spang J, Hinterwimmer S. Donor-site morbidity after osteochondral autologous transplantation for lesions of the talus. *J Bone Joint Surg Am.* Jul 2009;91(7):1683-1688.
117. Solheim E, Hegna J, Oyen J, Austgulen OK, Harlem T, Strand T. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. *Knee.* Jan;17(1):84-87.
118. Andres BM, Mears SC, Somel DS, Klug R, Wenz JF. Treatment of osteoarthritic cartilage lesions with osteochondral autograft transplantation. *Orthopedics.* Nov 2003;26(11):1121-1126.
119. Haasper C, Zelle BA, Knobloch K, et al. No mid-term difference in mosaicplasty in previously treated versus previously untreated patients with osteochondral lesions of the talus. *Arch Orthop Trauma Surg.* May 2008;128(5):499-504.
120. Hangody L, Dobos J, Balo E, Panics G, Hangody LR, Berkes I. Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. *Am J Sports Med.* Jun 2010;38(6):1125-1133.
121. Marcacci M, Kon E, Zaffagnini S, et al. Multiple osteochondral arthroscopic grafting (mosaicplasty) for cartilage defects of the knee: prospective study results at 2-year follow-up. *Arthroscopy.* Apr 2005;21(4):462-470.
122. Pascual-Garrido C, Friel NA, Kirk SS, et al. Midterm results of surgical treatment for adult osteochondritis dissecans of the knee. *Am J Sports Med.* Nov 2009;37 Suppl 1:125S-130S.
123. Rue JP, Yanke AB, Busam ML, McNickle AG, Cole BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. *Am J Sports Med.* Sep 2008;36(9):1770-1778.
124. Emmerson BC, Gortz S, Jamali AA, Chung C, Amiel D, Bugbee WD. Fresh osteochondral allografting in the treatment of osteochondritis dissecans of the femoral condyle. *Am J Sports Med.* Jun 2007;35(6):907-914.
125. LaPrade RF, Botker J, Herzog M, Agel J. Refrigerated osteoarticular allografts to treat articular cartilage defects of the femoral condyles. A prospective outcomes study. *J Bone Joint Surg Am.* Apr 2009;91(4):805-811.
126. McCulloch PC, Kang RW, Sobhy MH, Hayden JK, Cole BJ. Prospective evaluation of prolonged fresh osteochondral allograft transplantation of the femoral condyle: minimum 2-year follow-up. *Am J Sports Med.* Mar 2007;35(3):411-420.
127. Williams RJ, 3rd, Ranawat AS, Potter HG, Carter T, Warren RF. Fresh stored allografts for the treatment of osteochondral defects of the knee. *J Bone Joint Surg Am.* Apr 2007;89(4):718-726.
128. Oakley SP, Portek I, Szomor Z, et al. Accuracy and reliability of arthroscopic estimates of cartilage lesion size in a plastic knee simulation model. *Arthroscopy.* Mar 2003;19(3):282-289.

129. Cameron ML, Briggs KK, Steadman JR. Reproducibility and reliability of the outerbridge classification for grading chondral lesions of the knee arthroscopically. *Am J Sports Med.* Jan-Feb 2003;31(1):83-86.
130. Norvell D, Dettori J, Suk M. What makes a quality outcomes instrument? In: Suk M, Hanson, BP, Norvell, DC, Helfet, DL, ed. *AO handbook of musculoskeletal outcomes measures and instruments*. Stuttgart: Thieme; 2005:7-24.
131. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol.* Jan 2007;60(1):34-42.
132. Higgins LD, Taylor MK, Park D, et al. Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form. *Joint Bone Spine.* Dec 2007;74(6):594-599.
133. 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.
134. 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.
135. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.
136. Noyes FR, Mooar PA, Matthews DS, Butler DL. The symptomatic anterior cruciate-deficient knee. Part I: the long-term functional disability in athletically active individuals. *J Bone Joint Surg Am.* 1983;65(2):154-162.
137. Agel J, LaPrade RF. Assessment of differences between the modified Cincinnati and International Knee Documentation Committee patient outcome scores: a prospective study. *Am J Sports Med.* Nov 2009;37(11):2151-2157.
138. Brittberg M, Peterson L. Introduction of an articular cartilage classification. *ICRS Newsletter.* 1998;1:5-8.
139. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res.* May 2000(374):212-234.
140. Smith GD, Taylor J, Almqvist KF, et al. Arthroscopic assessment of cartilage repair: a validation study of 2 scoring systems. *Arthroscopy.* 2005;21(12):1462-1467.
141. Bugbee WD, Convery FR. Osteochondral allograft transplantation. *Clin Sports Med.* Jan 1999;18(1):67-75.
142. Chu CR, Convery FR, Akeson WH, Meyers M, Amiel D. Articular cartilage transplantation. Clinical results in the knee. *Clin Orthop Relat Res.* Mar 1999(360):159-168.
143. Convery FR, Botte MJ, Akeson WH, Meyers MH. Chondral defects of the knee. *Contemp Orthop.* Feb 1994;28(2):101-107.
144. Convery FR, Meyers MH, Akeson WH. Fresh osteochondral allografting of the femoral condyle. *Clin Orthop Relat Res.* Dec 1991(273):139-145.
145. Kusnick C, Hayward I, Sartoris DJ, et al. Radiographic evaluation of joints resurfaced with osteochondral shell allografts. *AJR Am J Roentgenol.* Oct 1987;149(4):743-748.
146. Meyers MH. Resurfacing of the femoral head with fresh osteochondral allografts. Long-term results. *Clin Orthop Relat Res.* Jul-Aug 1985(197):111-114.

147. Meyers MH, Akeson W, Convery FR. Resurfacing of the knee with fresh osteochondral allograft. *J Bone Joint Surg Am.* Jun 1989;71(5):704-713.
148. Aubin PP, Cheah HK, Davis AM, Gross AE. Long-term followup of fresh femoral osteochondral allografts for posttraumatic knee defects. *Clin Orthop Relat Res.* Oct 2001(391 Suppl):S318-327.
149. Bayne O, Langer F, Pritzker KP, Houpt J, Gross AE. Osteochondral allografts in the treatment of osteonecrosis of the knee. *Orthop Clin North Am.* Oct 1985;16(4):727-740.
150. Beaver RJ, Mahomed M, Backstein D, Davis A, Zukor DJ, Gross AE. Fresh osteochondral allografts for post-traumatic defects in the knee. A survivorship analysis. *J Bone Joint Surg Br.* Jan 1992;74(1):105-110.
151. Ghazavi MT, Pritzker KP, Davis AM, Gross AE. Fresh osteochondral allografts for post-traumatic osteochondral defects of the knee. *J Bone Joint Surg Br.* Nov 1997;79(6):1008-1013.
152. Gross AE, Aubin P, Cheah HK, Davis AM, Ghazavi MT. A fresh osteochondral allograft alternative. *J Arthroplasty.* Jun 2002;17(4 Suppl 1):50-53.
153. Gross AE, McKee NH, Pritzker KP, Langer F. Reconstruction of skeletal deficits at the knee. A comprehensive osteochondral transplant program. *Clin Orthop Relat Res.* Apr 1983(174):96-106.
154. Gross AE, Shasha N, Aubin P. Long-term followup of the use of fresh osteochondral allografts for posttraumatic knee defects. *Clin Orthop Relat Res.* Jun 2005(435):79-87.
155. Kandel RA, Gross AE, Ganel A, McDermott AG, Langer F, Pritzker KP. Histopathology of failed osteoarticular shell allografts. *Clin Orthop Relat Res.* Jul-Aug 1985(197):103-110.
156. McDermott AG, Langer F, Pritzker KP, Gross AE. Fresh small-fragment osteochondral allografts. Long-term follow-up study on first 100 cases. *Clin Orthop Relat Res.* Jul-Aug 1985(197):96-102.
157. Oakeshott RD, Farine I, Pritzker KP, Langer F, Gross AE. A clinical and histologic analysis of failed fresh osteochondral allografts. *Clin Orthop Relat Res.* Aug 1988(233):283-294.
158. Shasha N, Krywulak S, Backstein D, Pressman A, Gross AE. Long-term follow-up of fresh tibial osteochondral allografts for failed tibial plateau fractures. *J Bone Joint Surg Am.* 2003;85-A Suppl 2:33-39.
159. Mahomed MN, Beaver RJ, Gross AE. The long-term success of fresh, small fragment osteochondral allografts used for intraarticular post-traumatic defects in the knee joint. *Orthopedics.* Oct 1992;15(10):1191-1199.
160. Matricali GA, Dereymaeker GP, Luyten FP. Donor site morbidity after articular cartilage repair procedures: a review. *Acta Orthop Belg.* Oct 2010;76(5):669-674.
161. Revell CM, Athanasiou KA. Success rates and immunologic responses of autogenic, allogenic, and xenogenic treatments to repair articular cartilage defects. *Tissue Eng Part B Rev.* Mar 2009;15(1):1-15.
162. Marcacci M, Kon E, Delcogliano M, Filardo G, Busacca M, Zaffagnini S. Arthroscopic autologous osteochondral grafting for cartilage defects of the knee: prospective study results at a minimum 7-year follow-up. *Am J Sports Med.* Dec 2007;35(12):2014-2021.
163. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Henle P, Niemeyer P. Mosaicplasty with autogenous talar autograft for osteochondral lesions of the talus after failed primary

arthroscopic management: a prospective study with a 4-year follow-up. *Am J Sports Med.* Jan 2006;34(1):55-63.

164. Scranton PE, Jr., McDermott JE. Treatment of type V osteochondral lesions of the talus with ipsilateral knee osteochondral autografts. *Foot Ankle Int.* May 2001;22(5):380-384.

165. Bandi W. Chondromalacia patellae and femoropatellar arthroplasty. *Helv Chir Acta.* 1972;39(Suppl II):1-70.

166. Iwasaki N, Kato H, Kamishima T, Suenaga N, Minami A. Donor site evaluation after autologous osteochondral mosaicplasty for cartilaginous lesions of the elbow joint. *Am J Sports Med.* Dec 2007;35(12):2096-2100.

167. Nishimura A, Morita A, Fukuda A, Kato K, Sudo A. Functional recovery of the donor knee after autologous osteochondral transplantation for capitellar osteochondritis dissecans. *Am J Sports Med.* Apr 2011;39(4):838-842.

168. Reddy S, Pedowitz DI, Parekh SG, Sennett BJ, Okereke E. The morbidity associated with osteochondral harvest from asymptomatic knees for the treatment of osteochondral lesions of the talus. *Am J Sports Med.* Jan 2007;35(1):80-85.

169. Valderrabano V, Leumann A, Rasch H, Egelhof T, Hintermann B, Pagenstert G. Knee-to-ankle mosaicplasty for the treatment of osteochondral lesions of the ankle joint. *Am J Sports Med.* Nov 2009;37 Suppl 1:105S-111S.

170. Phipatanakul WP, VandeVord PJ, Teitge RA, Wooley PH. Immune response in patients receiving fresh osteochondral allografts. *Am J Orthop (Belle Mead NJ).* Jul 2004;33(7):345-348.

171. Sirlin CB, Brossmann J, Boutin RD, et al. Shell osteochondral allografts of the knee: comparison of mr imaging findings and immunologic responses. *Radiology.* Apr 2001;219(1):35-43.

172. Haasper C, Zeichen J, Meister R, Krettek C, Jagodzinski M. Tissue engineering of osteochondral constructs in vitro using bioreactors. *Injury.* Apr 2008;39 Suppl 1:S66-76.