Current Concepts Review

Chondral Lesions of the Knee: An Evidence-Based Approach

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- Management of chondral lesions of the knee is challenging and requires assessment of several factors including the size and location of the lesion, limb alignment and rotation, and the physical and mental health of the individual patient.
- There are a multitude of options to address chondral pathologies of the knee that allow individualized treatment for the specific needs and demands of the patient.
- Osteochondral autograft transfer remains a durable and predictable graft option in smaller lesions (<2 cm^2) in the young and active patient population.
- Both mid-term and long-term results for large chondral lesions (≥3 cm^2) of the knee have demonstrated favorable results with the use of osteochondral allograft or matrix-associated chondrocyte implantation.
- Treatment options for small lesions (<2 cm^2) include osteochondral autograft transfer and marrow stimulation and/or microfracture with biologic adjunct, while larger lesions (≥2 cm^2) are typically treated with osteochondral allograft transplantation, particulated juvenile articular cartilage, or matrix-associated chondrocyte implantation.
- Emerging technologies, such as allograft scaffolds and cryopreserved allograft, are being explored for different graft sources to address complex knee chondral pathology; however, further study is needed.

Cartilage injuries of the knee can be challenging to treat. The focus of this review is on injuries involving the femoral condyles or patellofemoral articular cartilage that result from overuse, direct trauma, malalignment, or malrotation. Cartilage lesions are commonly encountered in patients undergoing knee arthroscopy, with surgeons encountering chondral defects in up to 36% of knees[1,2]. Treatment options are variable and dependent on many factors, including patient age and activity level, location and size of the defect, meniscal status, limb alignment, concomitant knee pathologies, chronicity, and comorbidities. For example, concomitant varus-producing osteotomies are performed in the setting of lateral compartment pathology with genu valgum; valgus-producing osteotomies, for medial compartment pathology in the setting of genu varum; and tibial tubercle osteotomies, in the setting of maltracking with increased tibial tuberosity-to-trochlear groove distance of >2 cm and patella alta (a Caton-Deschamps ratio of >1.2). Regardless of the cartilage repair technique, careful patient selection and management of associated concomitant pathologies is of paramount importance to optimize the outcome.

Nonoperative treatment of symptomatic cartilage injuries is preferred at times, especially for patients with tricompartmental osteoarthritis or those who are nonsurgical candidates. Once injured, cartilage is unable to fully regenerate because of poor vascularity and the limited number of chondrocytes. While cartilage has poor natural regenerative capacity, there is potential for fibrocartilage growth or

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TABLE I Summary of Microfracture Studies within the Previous 6 Years*

Study	Study Design (Level of Evidence)	Sample Size *(no. of patients)*	Duration of Follow-up†	Lesion Size†	Primary Outcome Evaluated	Results	Failure Rate *(%)*
Brittberg et al.[105] (2018)	RCT (I)	59	5 yr	4.9 ± 2.0 cm^2	KOOS pain and function and SF-12	MF significantly worse than MACI for KOOS pain, KOOS function, modified Cincinnati, and SF-12 Physical Component	5.1
Knutsen et al.[106] (2016)	RCT (I)	40	15 yr	1.4-11.2	VAS, Lysholm, and SF-36 Physical Component	No difference between MF and ACI, significant improvement in VAS, Lysholm, and SF-36 for patients who did not have failure	32.5
Solheim et al.[45] (2018)	RCT (I)	20	16 yr (15-17 yr)	3.5 (2.0-5.0)	Lysholm (preop. and at 1, 5, 10, and 15 yr)	Mosaicplasty superior to MF	15
Dasar et al.[107] (2016)	Cohort study (III)	20	22.5 ± 4.4 mo	3.5 ± 0.9	Lysholm, Modified Cincinnati, and MOCART	MF superior to carbon fiber rod implantation	NR
Mithoefer et al.[108] (2016)	Cohort study (III)	84	23.9 mo (6-81 mo)	1.9 ± 1.7	KOOS	No difference in KOOS based on grade of osseous overgrowth after MF	16.7
Solheim et al.[109] (2017)	Cohort study (III)	52	16 yr (15-17 yr)	3.4 ± 1.0	Lysholm	Mosaicplasty superior to MF	9.6
Solheim et al.[46] (2020)	Cohort study (III)	119	Survival analysis with min. 15-yr follow-up	480 ± 290 mm^2	Lysholm score of <65 or undergoing an ipsilateral knee replacement	MF articular cartilage repairs failed more often and earlier than the OAT repairs	66
Solheim et al.[110] (2016)	Case series (IV)	110	12 yr (10-14 yr)	4.0 (1-15)	Lysholm score, VAS function, and VAS pain	Significant improvement in all scores; full return to normal function not achieved	6.36
Steadman et al.[111] (2015)	Case series (IV)	26	5.8 yr (2.0-13.3 yr)	1.8 (0.1-4.0) for MFC, 1.9 (0.3-6.0) for LFC, and 2.1 (0.1-5.7) for PAT/TRO	Lysholm, Tegner, and satisfaction	MF improved function and satisfaction in adolescents with full-thickness lesions	3.8

*RCT = randomized controlled trial, KOOS = Knee injury and Osteoarthritis Outcome Score, SF-12 = Short Form-12, MF = microfracture, MACI = matrix-assisted chondrocyte implantation, ACI = autologous chondrocyte implantation, VAS = visual analog scale, MOCART = magnetic resonance observation of cartilage repair tissue , NR = not reported, OAT = osteochondral autograft transfer, MFC = medial femoral condyle, LFC = lateral femoral condyle, PAT = patella, and TRO = trochlea. †The data are given as the mean and the standard deviation or as the mean with the range in parentheses.

stabilization of symptoms[3]. However, surgery is often indicated, especially in young, active patients with a symptomatic, full-thickness chondral lesion.

There are 4 main types of surgical procedures to consider for isolated chondral lesions in the knee: (1) chondroplasty; (2) marrow stimulation; (3) osteochondral restoration, including osteochondral autograft transfer (OAT) and osteochondral allograft transfer (OCA); and (4) cell-based repair such as autologous chondrocyte implantation (ACI) or matrix-assisted ACI (MACI). To apply patient-specific treatment strategies utilizing these procedures, an understanding of chondral knee biology coupled with evidence-based surgical techniques is necessary. As technology, graft sources, and improved surgical techniques evolve, there are many strategies to address injuries of the femoral condyles and patellofemoral articular cartilage. This review provides a critical analysis of the current, relevant literature regarding surgical treatment for both isolated femoral condylar defects and patellofemoral chondral defects of the

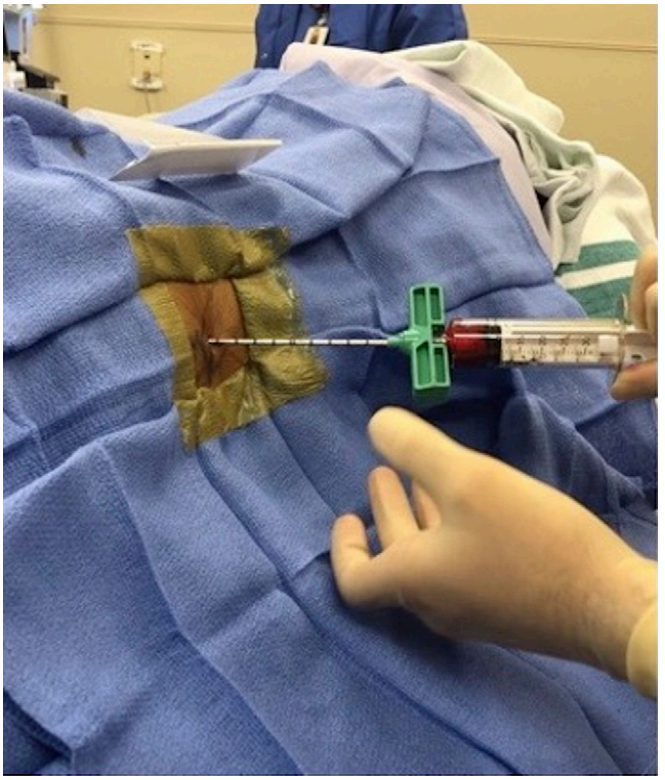

Fig. 1

With the patient in a lateral decubitus position, bone marrow aspirate for concentration is harvested from the posterior superior iliac spine in between the inner and outer tables of the iliac crest. The BMC can be later used to augment chondral procedures.

knee to provide an updated evidenced-based algorithmic treatment approach.

Marrow Stimulation

Marrow stimulation encompasses techniques with the objective of creating a healing response at the site of a cartilage defect through penetration of the subchondral plate. Mechanistically, this creates a conduit between the bone marrow and the injured cartilage surface allowing cellular elements access to the defect. Development of the technique was proposed in the 1980s using an awl, which became known as "microfracture."[4] The popularity of the technique grew because of the low cost, perceived lower morbidity, and initial results as a primary cartilage procedure, especially in young and active patients[5-7]. Contemporary views on marrow stimulation are mixed because of recent comparative studies with other repair technologies (Table I). Concerns with this procedure persist as the fibrocartilage (type-I collagen) that fills the defect is structurally weaker and insufficient compared with that of native hyaline cartilage (type-II collagen)[8]. A recent systematic review of the long-term outcomes of contemporary marrow stimulation techniques included 18 studies and 1,830 defects; failure rates were reported to range from 11% to 27% within 5 years and from 6% to 32% at 10 years[9]. Regardless of the mixed clinical results, marrow stimulation remains the most frequently performed cartilage repair procedure in the United States[9].

Marrow stimulation techniques have become refined with the addition of cellular augmentation to optimize the biologic environment for healing. Animal studies have suggested that smaller and deeper subchondral bone stimulation produces

TABLE II Summary of Clinical Decision-Making for Marrow Stimulation

Indications	Contraindications		Advantages	Disadvantages	Recommendations	Grade of Recommendation*
	Absolute	Relative				
Lesions <2 cm^2 in size, Outerbridge grade-III/IV cartilage, and lack of subchondral involvement in an active patient; and lesions confined to the femoral condyles	Infections, poor surgical candidate, inability to follow postop. rehab. protocols, end-stage osteoarthritis, or lesions of ≥2 cm^2	Smoking and/or steroid use, lower-extremity malalignment, ligamentous instability, body mass index >35 kg/m^2, or meniscal insufficiency	Low cost, arthroscopic technique, technically easy, and fast	Predominantly fibrocartilage fill, questionable long-term outcomes, and long rehabilitation time	Drilling is the preferred technique to limit damage to the subchondral plate[12]; smaller perforations closer together can maximize defect fill; augmentation with BMC or mobilized peripheral blood can optimize the healing environment[26-32]	B

*According to Wright[112], grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention; grade B, fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention; grade C, poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention; and grade I, insufficient or conflicting evidence not allowing a recommendation for or against intervention.

TABLE III Summary of OAT Studies within the Previous 6 Years*

Study	Study Design (Level of Evidence)	Sample Size *(no. of patients)*	Duration of Follow-up† *(yr)*	Mean Lesion Size†	Primary Outcome Evaluated	Results	Failure Rate
Solheim et al.[45] (2018)	RCT (I)	40 (20 MF vs. 20 OAT)	16 (15-17)	3.6 cm^2 (2-5 cm^2) of femoral condyles	Lysholm (preop. and at 1, 5, 10, and 15 yr)	At short, medium, and long term (min., 15 yr), mosaicplasty results in a better, clinically relevant outcome than MF in articular cartilage defects (2-5 cm^2) of the distal end of femur	25% at >15 yr of follow-up (1 knee replacement and 3 with poor clinical outcomes)
Solheim et al.[46] (2020)	Comparative cohort study (III)	203 (119 MF vs. 84 OAT)	Survival analysis with min. 15-yr follow-up	300 ± 110 mm^2 OAT	Lysholm score <65 or having ipsilateral knee replacement	Long-term failure rate (62% overall) was significantly higher in the MF group (66%) than the OAT group (51%)	Time to failure (mean and SD) significantly shorter in the MF group (4.0 ± 4.1 yr) than the OAT group (8.4 yr)
Matsuura et al.[52] (2019)	Case series (IV)	86 adolescents	7.2 (2.3-15.4)		IKDC and rate of return to sport, DSM (persistent symptoms for >1 yr or need for subsequent intervention), and stricter DSM criteria§	2.3% DSM with usual criterion and 12.8% with strict criterion	
Anil and Strauss[49] (2018)	Case report (V)	1	1	1.2 cm^2	Mechanical symptoms	Mechanical symptoms with walking at 8 wk with resolution of symptoms after revision of back-fill of donor sites at 1-yr follow-up	0% (100% returned to same level of sport)
Werner et al.[47] (2017)	Case Series (IV)	20	4.4 ± 1.7	1.34 (0.15-2.8)	Time to return to sport; IKDC; and Tegner	Return to sport at mean of 82.9 days (range, 39-134 days), final IKDC (mean and SD) of 84.5 ± 9.5, and final Tegner of 7.7 ± 1.9	

*RCT = randomized controlled trial, MF = microfracture, OAT = osteochondral autograft transfer, IKDC = International Knee Documentation Committee, SD = standard deviation, and DSM = donor-site morbidity. †The values are given as the mean with the range in parentheses or the mean and the standard deviation. ‡The values are given as the mean and the standard deviation, the mean with the range in parentheses, or only the mean. §Stricter DSM criteria include any symptoms, such as effusion, patellofemoral complaints, crepitation, unspecified disturbance, stiffness, pain and/or instability during activities, and osteoarthritic change.

TABLE IV Summary of Clinical Decision-Making for OAT*

Indications	Contraindications		Advantages	Disadvantages	Recommendations	Grade of Recommendation†
	Absolute	Relative				
1st line treatment for defects of <2 cm^2 with grade-III or IV Outerbridge cartilage and subchondral involvement in young, active patients; and lesions confined to the femoral condyles	Infections, poor surgical candidate, inability to follow postop. rehab. protocols, end-stage osteoarthritis, and lesions of ≥2 cm^2	Smoking and/or steroid use, lower-extremity malalignment, ligamentous instability, BMI of >35 kg/m^2, and meniscal insufficiency	Fast graft incorporation allowing for early rehab., greater durability of repair than MF, direct replacement of hyaline cartilage, and low comparative cost	DSM requiring secondary operation, difficult operative learning curve, and greatest benefit seen in condylar lesions	If time is a factor for return to livelihood (professional athlete, deploying soldier, etc.), consideration for the utilization of autograft should be given due to fast incorporation and early return to activities compared with alternative cartilage restorative techniques	B

*BMI = body mass index, MF = microfracture, and DSM = donor-site morbidity. †According to Wright[112], grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention.

improved fibrocartilage fill and tissue quality[10-12]. Augmentation of marrow stimulation has focused on cells with the ability to reproduce and differentiate, which are often called *stem cells*. A recent systematic review of emerging studies on cartilage repair involving stem cells found 60 clinical studies, including 9 case reports, 31 case series, 13 comparative trials, and 7 randomized controlled trials[13]. Overall, cell-based augmented treatments for cartilage repair have been safe and effective in short-term evaluation yet require further well-designed comparative studies and long-term evaluation.

Marrow stimulation may be augmented with concentrated bone marrow aspirate (BMC) or mobilized peripheral blood stem cells (Fig. 1). Clinical researchers have pioneered direct surgical implantation of BMC predominantly involving a hyaluronic acid matrix[14-25]. Development started in 2009 with a prospective clinical study of BMC in the treatment of talar osteochondral lesions and continued with a prospective knee study comparing BMC with MACI in the treatment of large patellofemoral chondral defects[23,26]. In the comparative knee study, both groups had significant improvement in the clinical scores, with no significant difference between the groups, with the exception of the International Knee Documentation Committee (IKDC) subjective score, which was better in the BMC group[26]. Subtle superiority was observed in the BMC group, including less deterioration compared with the MACI group from the 2-year to the final follow-up evaluation (at an average of 59.7 months for the MACI group and

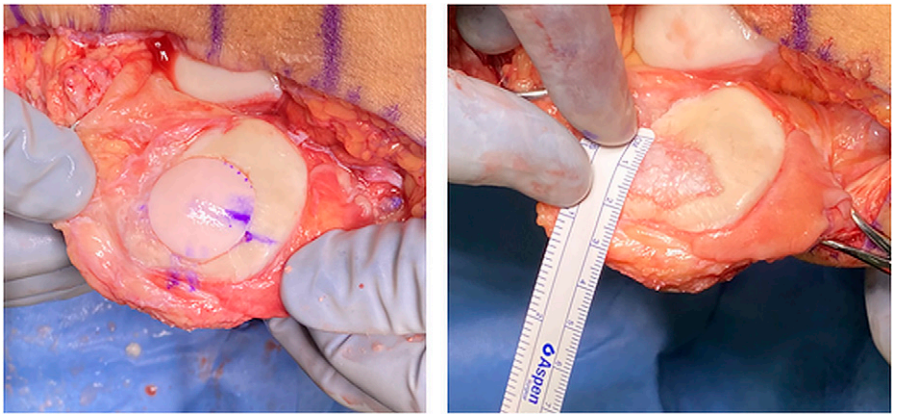

Fig. 2

Large size-matched osteochondral allograft implantation for isolated patellar osteochondral defects.

TABLE V Summary of OCA Studies within the Previous 6 Years*

Study	Study Design (Level of Evidence)	Sample Size	Duration of Follow-up†	Lesion Size† (cm^2)	Primary Outcome Evaluated	Results	Failure Rate
Tírico et al.[61] (2019)	Case control (III)	371 patients (396 knees) had primary OCA	5.5 yr (0.8-18.4 yr)	Median, 6.9 (1.8-50)	IKDC, KOOS, and satisfaction	Satisfaction rate of 88.1%, which was constant over time	NR
Gracitelli et al.[63] (2015)	Cohort study (III)	46 knees had primary OCA and 46 had revision OCA; matched for age, graft size, diagnosis, BMI, and graft location	9.7 yr (1.8-30.1 yr)	8.2 ± 3.6 for primary OCA and 8.0 ± 3.2 for revision OCA	Merle d'Aubigné-Postel, IKDC, KS-F, satisfaction, and range of motion	24% reop. rate and satisfaction of 87% for primary OCA; 44% reop. rate and satisfaction of 97% for revision OCA; survivorship of 87.4% at 10 yr for primary versus 86% after marrow stimulation	11% for primary OCA and 15% for revision OCA
Riff et al.[64] (2020)	Cohort study (III)	359 patients (92 had secondary ACI; 100, primary ACI; 88, secondary OCA; and 79, primary OCA)	43.5 ± 20.9 mo for primary OCA; 44.4 ± 27.3 mo for secondary OCA; 43.5 ± 20.9 mo for primary ACI; and 47.3 ± 23.6 mo for secondary ACI	4.96 for primary OCA, 3.96 for secondary OCA, 4.02 for primary ACI, and 4.17 for secondary ACI	Tegner, Lysholm, IKDC, KOOS, and SF-12	No difference between primary and secondary groups with regard to postop. functional scores, subjective satisfaction, reop. rate, and clinical failure rate	15% for primary OCA, 9% for secondary OCA, 8% for primary ACI, and 19% for secondary ACI
Tírico et al.[60] (2018)	Cohort study (III)	143 patients	6.0 yr (1.9-16.5 yr)	6.4 (2.3-11.5) (femoral lesions)	IKDC and satisfaction	Satisfaction rate was 89.8%; change in IKDC scores (from preop. to latest follow-up) was greater for knees with large lesions than for knees with small lesions	5.8%; overall survivorship of graft was 97.2% at 5 yr and 93.5% at 10 yr
Cameron et al.[57] (2016)	Case series (IV)	28 patients	7.0 yr (2.1-19.9 yr)	6.1 (2.3-20.0) (trochlear lesions)	Merle d'Aubigné-Postel, IKDC, KS-F, UCLA, and satisfaction	Mean Merle d'Aubigné-Postel score improved from 13.0 to 16.1; mean KS-F score, from 65.6 to 85.2; and mean IKDC total score, from 38.5 to 71.9; mean UCLA score was 7.9 postop.; and 89% were extremely satisfied or satisfied with the outcome	Graft survivorship was 100% at 5 yr and 91.7% at 10 yr
Gracitelli et al.[67] (2015)	Case series (IV)	27 patients (28 knees)	9.7 yr (1.8-30.1 yr)	10.1 (4.0-18.0) (patellar lesions)	Merle d'Aubigné-Postel, IKDC, and KS-F	Patellar allografting survivorship was 78.1% at 5 and 10 yr and 55.8% at 15 yr; 17 (60.7%) of 28 knees had further surgery; 89% of patients were extremely satisfied or satisfied	8 (28.6%) of 28 knees

continued

TABLE V (*continued*)

Study	Study Design (Level of Evidence)	Sample Size	Duration of Follow-up†	Lesion Size† (cm^2)	Primary Outcome Evaluated	Results	Failure Rate
Tírico et al.[68] (2019)	Case series (IV)	143 patients	6.7 yr (1.9-16.5 yr)	6.3 (2.3-13.0) (allograft area and 6.5-mm thickness)	IKDC, KOOS, and satisfaction	Satisfaction rate of 89%; IKDC pain and function scores improved significantly at latest follow-up; KOOS scores for symptoms, pain, ADL, sports and recreational activities, and QOL improved significantly	8%; 26% had further surgery; survivorship of allograft was 95.6% at 5 yr and 91.2% at 10 yr
Davey et al.[62] (2019)	Case series (IV)	9 patients had revision OCA	4.5 ± 3.2 yr	4.0 (IQR = 0)	VAS, IKDC, KOOS, Lysholm, SF-12, and Kellgren and Lawrence scale	89% graft survivorship rate with no significant changes in radiographic progression of arthritis at 4.5 yr	11%; 50% reop. rate
Wang et al.[113] (2018)	Case series (IV)	43 patients	3.5 yr (2.0 to 7.5 yr)	4.2 (1.2 to 7.1)	SF-36, KOS-ADL, IKDC Subjective Knee Score, and Cincinnati Overall Symptom Assessment	Worse clinical outcomes for those with BMI of >30 kg/m^2; significant improvements ($p < 0.05$) in SF-36 Physical Function, SF-36 Pain, KOS-ADL, IKDC Subjective Knee Score, and Cincinnati Overall Symptom Assessment	9%; 40% reop. rate

*OCA = osteochondral allograft transfer, IKDC = International Knee Documentation Committee, KOOS = Knee injury and Osteoarthritis Outcome Score, NR = not reported, BMI = body mass index, KS-F = Knee Society-Function, ACI = autologous chondrocyte implantation, SF-12 = Short Form-12, UCLA = University of California Los Angeles, KOS = Knee Outcome Score, ADL = activities of daily living, QOL = quality of life, IQR = interquartile range, and VAS = visual analog scale. †The values are given as the mean, with the range in parentheses, unless otherwise indicated. ‡The values are given as the mean, with the range in parentheses, or as the mean and the standard deviation.

54.2 months for the BMC group), with both the MACI and BMC techniques showing similarly complete filling of cartilage defects (76% versus 81%, respectively). Another developing technique involves the application of mobilized autologous peripheral blood stem cells, leveraging the same stem cell source that is used in bone marrow transplantation[27-32]. After 3 days of

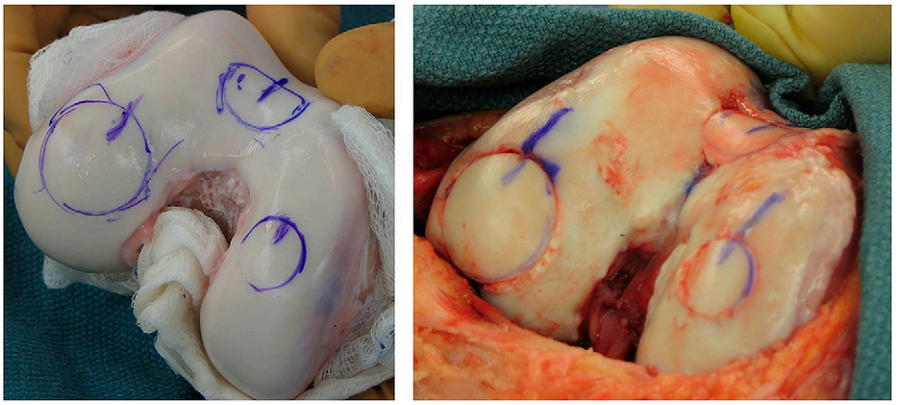

Fig. 3

Multifocal osteochondral allograft implantation with corresponding grafts taken from a size-matched donor.

TABLE VI Summary of Clinical Decision-Making for OCA

Indications	Contraindications		Advantages	Disadvantages	Recommendations	Grade of Recommendation†
	Absolute	Relative*				
1st line treatment for defects of ≥2 cm^2 with grade III or IV Outerbridge cartilage; 1st line treatment for lesions with subchondral involvement; and osteonecrosis	Infections, poor surgical candidate, inability to follow postop. rehab. protocols, and end-stage osteoarthritis	Smoking and/or steroid use, lower-extremity malalignment, ligamentous instability, BMI of >35 kg/m^2, and meniscal insufficiency	Versatile method that can be used anywhere in the knee, defects do not need to be contained, outcomes not affected by prior procedure, and can treat large chondral lesions	Graft availability, revision options limited, high secondary reop. rate, cost, difficult operative learning curve, and long recovery period to allow for complete radiographic graft incorporation	Can be used in both primary and revision cartilage restoration procedures with reliable results of both chondral and osteochondral lesions; BMC can be used as adjuvant[54]; and return to high-level impact activities and sporting events should be withheld for at least 1 yr	B

*Relative contraindications according to Cavendish et al.[54]. BMI = body mass index. †According to Wright[112], grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention.

dosing with filgrastim (a bone marrow stimulant), peripheral blood stem cells are harvested from the peripheral circulation by apheresis, a blood collection process developed for bone marrow transplantation. This produces a large yield of stem cells, which can be aliquoted and cryopreserved. The results are promising, including the potential to heal large chondral defects, with histological samples suggesting a cartilage repair more consistent with hyaline cartilage as opposed to fibrocartilage[27,29,31-35]. Multicenter comparative studies are needed to ultimately determine how emerging stem-cell cartilage technologies perform in contrast to established techniques (Table II).

Osteochondral Autograft Transfer

OAT utilizes grafts that are taken from lesser-weight-bearing portions of the knee and transferred to more weight-bearing portions of the knee[36]. Because of the use of autograft, osseous integration is faster and more reliable than osteochondral allograft and has the advantage of transferring hyaline cartilage. Ideal candidates are young, healthy, and active and have lesions that are ≤3 cm^2 in size[37]. Results are more consistently reproduced when lesions are confined to the femoral condyles; however, although less studied, trochlear and patellar cartilage-based OATs have shown durable improvement in outcomes[38-42].

OAT has most often been compared with either the use of microfracture or ACI, without direct comparison with OCA. When ranking cartilage restoration procedures, Riboh et al. performed a meta-analysis that found OAT most consistently reproduced hyaline-like tissue at the recipient site compared with ACI and microfracture[41,43]. In addition, OAT

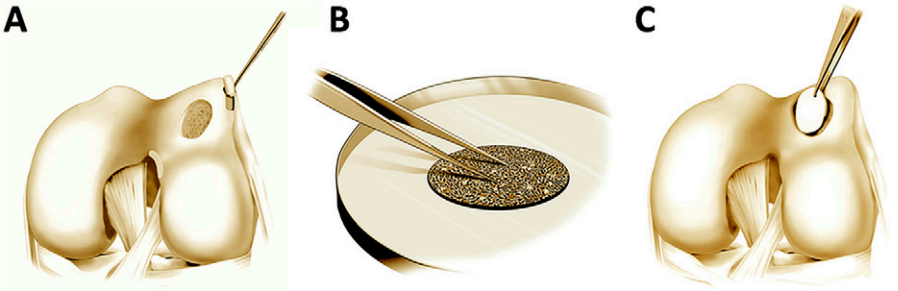

Fig. 4

Figs. 4-A, 4-B, and 4-C Drawings of the 2-stage process of MACI. **Fig. 4-A** A biopsy of the lesser-weight-bearing region of the knee is obtained. **Fig. 4-B** The chondrocytes are cultured and grown with implantation into a collagen-based matrix. **Fig. 4-C** Reimplantation of the chondrocytes into the knee.

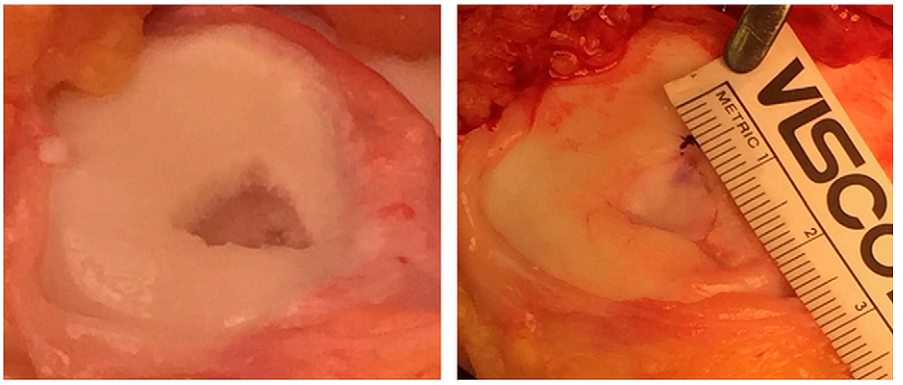

Fig. 5
MACI used for focal cartilage defects of the patella.

demonstrated a lower reoperation rate than microfracture at both 5 and 10 years postoperatively. OAT has been reported to offer durable results with maintenance of clinical benefits at >10 years of follow-up. In a large systematic review, Jones et al. found that minimal clinically important difference (MCID) values for IKDC, Lysholm, and visual analog scale for pain (VAS pain) scores were maintained for >10 years, demonstrating the durability of this surgical technique when patients are selected carefully[44]. Solheim et al. reported significantly higher Lysholm scores in a Level-I randomized controlled trial comparing OAT and microfracture at a minimum 15-year follow-up[45]. A separate retrospective cohort survival analysis found that the OAT cohort had greater durability than microfracture (8.4 versus 4.0 years)[46]. A purported benefit of OAT is the ability to have accelerated rehabilitation because of early graft integration and early weight-bearing. Werner et al. reported an average return to the same level of sport and activity at <3 months with use of OAT, which was significantly less than other cartilage replacement strategies[47] (Table III).

There are limitations to the use of autograft as a source, with size being a principal one, because lesions of >3 cm^2 are at risk of having symptomatic donor-site morbidity, pain, and symptoms[37]. Garretson et al. performed a biomechanical study that demonstrated that the optimum harvest site was just proximal to the medial sulcus terminalis followed by the lateral aspect of the trochlea because these locations have the lowest contact pressures[48]. Regardless, cases of patients who had early mechanical symptoms secondary to donor-site morbidity have been reported, with recommendations for back-filling with osteochondral allograft plugs to reduce pain and mechanical symptoms[49,50]. The rate of donor-site morbidity has been reported to range from 2.3% to 12.6%[51-53], with the most common symptoms being patellofemoral disturbances and crepitation (Table IV).

Osteochondral Allograft Transplantation

OCA is typically used in young and active patients with focal defects ≥2 cm^2 in size[54,55]. Historical limitations of OCA include varied graft cost, graft availability, and, although at an extraordinarily low rate,

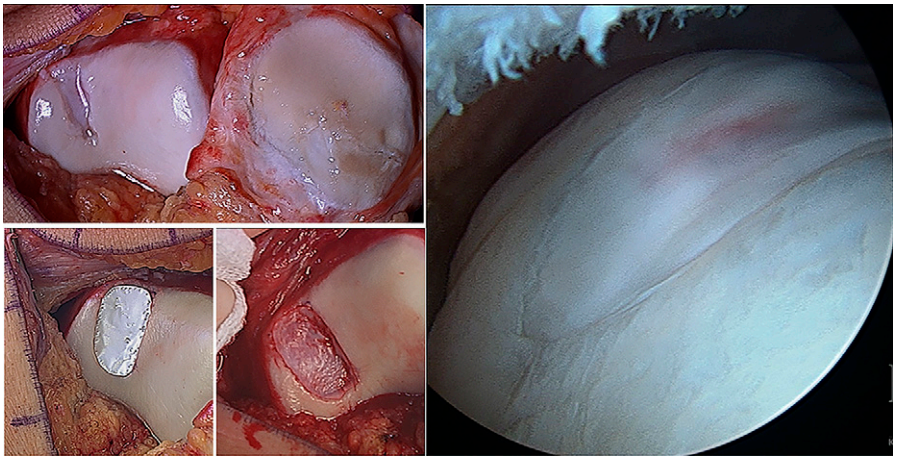

Fig. 6
A trochlear defect treated with MACI. (Photographs are courtesy of Alison P. Toth, Duke University Orthopaedics.) Corresponding defects are identified (top left), foil is used to appropriately size the MACI graft (bottom left), the MACI graft is implanted (bottom center), and second-look arthroscopy shows the healed articular surface (right).

TABLE VII Summary of MACI Studies within the Previous 6 Years*

Study	Study Design (Level of Evidence)	Sample Size *(no. of patients)*	Duration of Follow-up†	Lesion Size† *(cm^2)*	Primary Outcome Evaluated	Culture Time and Matrix Scaffold	Failure Rate
Brittberg et al.[105] (2018)	RCT (I)	65	5 yr	5.1 ± 3 cm^2	KOOS pain and function	Seeded at a density of ≥500,000 cells/cm^2 and ≤1 million cells/cm^2	1.5% (n = 1)
Hoburg et al.[114] (2019)	Cohort study (III)	71 (29 adolescents and 42 young adults)	63.3 mo (3.5-8.0 yr) for adolescents and 48.4 mo (3.8 to 4.3 yr) for young adults	4.6 ± 2.4 in adolescents and 4.7 ± 1.2 in young adults	KOOS, IKDC, Lysholm, MOCART, and time to treatment failure	NR	3% (n = 1) for adolescents and 5% (n = 2) for young adults
Müller et al.[84] (2020)	Cohort study (III)	20 without previous BMS and 20 with previous BMS	6, 12, 24, and 36 mo	5.40 ± 2.6 (2-15) in Group 1 and 4.82 ± 2.0 (2-10) in Group 2	IKDC and VAS	Cultivation time was approx. 3-4 wk; seeded on a collagen type-I/III biphasic scaffold	0% for Group 1 and 30% (n = 6) for Group 2
Ebert et al.[80] (2017)	Case series (IV)	31	1, 2, 3, 6, 12, and 24 mo	2.52 (1.00-5.00)	KOOS, Lysholm, Tegner, VAS, SF-36 Health Survey, active knee motion, 6-min. walk test, and limb symmetry indices	Cultured for approximately 4 to 8 wk; seeded onto a type-I/III collagen membrane	6.5% (n = 2)
Gille et al.[115] (2016)	Case series (IV)	38	16 yr (15-17 yr)	3.6 (1.5-8.75)	Lysholm, IKDC, and Tegner	Cultured for 4 wk; seeded (approx. 1 million cells/cm^2) on rough side of porcine collagen type-I/III matrix	0%
Kon et al.[116] (2016)	Case series (IV)	32	2, 5, and 10 yr	4.45 ± 2.1	IKDC, VAS, and Tegner	Hyalograft C	12.5% (n = 4)

*RCT = randomized controlled trial, KOOS = Knee injury and Osteoarthritis Outcome Score, IKDC = International Knee Documentation Committee, MOCART = magnetic resonance observation of cartilage, NR = not reported, BMS = bone marrow stimulation, SF-36 = Short Form-36, and VAS = visual analog scale for pain. †The values are given as the mean, with the range in parentheses, or as the mean and the standard deviation.

disease transmission[54,55]. The reported overall failure rate (defined as graft removal or conversion to arthroplasty) has been reported to range from 8% to 50% when lesions treated throughout all areas of the knee are included[2,54-59]. However, recent studies have demonstrated improvement in survivorship and sustained patient satisfaction for up to 15 and 20 years[59-61]. Davey et al. demonstrated that, in patients who had repeat revision of OCA and a mean follow-up of 4.5 years, the failure rate was 11% (1 of 9 patients), demonstrating the efficacy of OCA even in difficult cartilage defects[62]. Gracitelli et al. reported no difference in failure rates in a large cohort study, in which primary OCA (11%) and OCA after a marrow stimulation procedure (15%) were compared[63]. Despite low failure rates, they found that 24% of patients in the primary group compared with 44% of patients in the secondary group required a secondary reoperation, such as an arthroscopic lysis of adhesions and chondroplasty. Additionally, 87% of patients in the primary group and 97% in the secondary group reported satisfaction at a minimum follow-up of 2 years[63].

TABLE VIII Summary of Clinical Decision-Making for MACI*

Indications	Contraindications		Advantages	Disadvantages	Recommendations	Grade of Recommendation‡
	Absolute†	Relative				
1st line treatment for defects of ≥2 cm^2 with grade III/IV Outerbridge cartilage[81,84] 2nd line treatment for lesions ≤2 cm^2 in size[81]	Infections, inflammatory arthritis, inability to follow postop. rehab. protocols, and end-stage osteoarthritis	Uncontained and bipolar tibiofemoral lesions, lower-extremity malalignment, ligamentous instability, patellofemoral instability and/or maltracking, and meniscal insufficiency	Elastic membrane can conform to variously shaped defects; consistency of cellular implant makeup and method of application; and can treat large chondral lesions	2-stage procedure; ex vivo cell expansion; cost; and invasive (mini-arthrotomy required)	MACI should be used as 1st-line therapy for lesions >2 cm^2 in size[70,72] because of the additional cost and the invasive nature of MACI, this technique may not be suitable for patients with smaller defects, and other options should be considered in defects <2 cm^2 in size[73,81,85-87]	B

*MACI = matrix-assisted autologous chondrocyte implantation. †Absolute contraindications according to Hinckel and Gomoll[81]. ‡According to Wright[112], grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention.

OCA and ACI have been the most common methods used to address large lesions after failed marrow stimulation. Riff et al. found no difference in outcomes when primary OCA and ACI were compared in the treatment of large lesions or in revision cases[64]. Furthermore, there was no difference between the groups with respect to functional outcome scores, subjective satisfaction, reoperation rates, and clinical failures. While the cost of OCA can be concerning, it has been reported to be a highly cost-effective treatment modality when accounting for quality-adjusted life years[65].

The patellofemoral joint (PFJ) has been reported to have chondral defects in approximately 33% of knees undergoing arthroscopy[2]. Multiple recent systematic reviews[2,53,55,59,66] have demonstrated sustained improvement in outcome scores, durable graft survivorship (13% to 16% failure rate at 5 years), and increased patient satisfaction when OCA was used in the treatment of PFJ defects (Fig. 2). Because of the difficult biomechanics of this joint, resulting from the increased shear forces and strain across the joint, reliable outcomes with cartilage restoration procedures are particularly difficult to achieve. However, Gracitelli et al. demonstrated that isolated patellar defects treated by OCA have a survivorship of 78.1% at 10 years and 55.8% at 15 years of follow-up[67]. Cameron et al. showed overall increased survivorship when isolated trochlear defects were treated, with 100% survivorship at 5 years and 91.7% at 10 years of follow-up[57] (Table V).

Technically, Tírico et al. described a modified OCA technique utilizing thin plugs, with an average thickness of 6.3 mm, in 187 patients (200 knees) at a mean follow-up of 6.7 years[68]. The purported benefits of this technique allow for reliable clinical outcomes (8% rate of failure and 89% rate of satisfaction at 10 years of follow-up) without increasing compromise of the subchondral bone. Although BMC is often utilized to aid in graft integration and chondral growth[55], Wang et al. found no increase in osseous integration, decreased cystic changes, or other bone, cartilage, and ancillary feature changes based on magnetic resonance imaging (MRI) features of the Osteochondral Allograft MRI Scoring System[69] (Fig. 3, Table VI).

Cell-Based Articular Cartilage Restoration Techniques

ACI is a 2-stage procedure for treating large full-thickness cartilage defects[70]. At its most fundamental level, the procedure consists of a diagnostic arthroscopy for measurement of the cartilage defect and biopsy of lesser-weight-bearing articular surfaces of the knee. The harvested chondrocytes are then cultured ex vivo and implanted back into the knee during the second stage[70-73]. A depiction of this procedure can be seen in Figure 4. Initially, the original ACI techniques consisted of injecting the cultured cells under a periosteal patch or a collagen membrane[1,74,75]. However, periosteal patch hypertrophy, high reoperation rates for debridement, bulky sutures, and cell leakage negatively contributed to the overall outcomes of the ACI procedure compared with more traditional OCA and bone marrow stimulation (BMS) techniques[76-79]. These issues prompted the development of a third-generation MACI technique[79,80]. The MACI technique differs from its predecessors in that it involves culturing the harvested chondrocytes for 3 to 4 weeks and directly seeding the cells into a type-I/III collagen

TABLE IX Summary of PJAC Studies within the Previous 6 Years*

Study	Study Design (Level of Evidence)	Sample Size	Mean Duration of Follow-up	Mean Lesion Size† (cm^2)	Primary Outcome Evaluated	Outcome	Failure Rate
Wang et al.[95] (2018)	Case series (IV)	27 patients (30 knees with patellofemoral defects)	3.8 yr	2.14 ± 1.23	MRI, KOOS, IKDC, KOOS-ADL, and Marx	69% lesion fill on MRI, morphologic differences persist; improved IKDC and KOS-ADL; and no change in Marx	0%
Grawe et al.[94] (2017)	Case series (IV)	45 patients	6, 12, and 24 mo	2.1 ± 1.2 (0.4-5)	MRI cartilage fill	85% of patients at 12 mo displayed good to moderate fill of the graft; at 24 mo, patient age demonstrated negative correlation with mean T2 relaxation times of the deep and superficial graft	2% (n = 1)

*PJAC = particulated juvenile allograft cartilage, MRI = magnetic resonance imaging, KOOS = Knee injury and Osteoarthritis Outcome Score, IKDC = International Knee Documentation Committee, and KOS-ADL = Knee Outcome Survey-Activities of Daily Living. †The values are given as the mean and the standard deviation, with the range in parentheses.

scaffold matrix, which is subsequently fixated into the chondral defect with fibrin glue[74,75,80-83] (Figs. 5 and 6).

In a recent systematic review, Schuette et al. reported that MACI significantly improved the Knee injury and Osteoarthritis Outcome Score (KOOS), Short Form-36 (SF-36), and Tegner scores from baseline for both tibiofemoral and patellofemoral defects[75]. Overall, there was a 9.7% treatment failure rate, with a significantly higher failure rate in the 442 patients with tibiofemoral defects compared with the group of 136 patients with patellofemoral defects[75].

Regarding the use of MACI after failure of primary BMS, Müller et al. reported that MACI improved IKDC and VAS scores in both patients treated with and those treated without primary BMS[84]. However, the authors noted that patients with primary BMS had significantly worse outcomes and higher failure rates because of compromise of the subchondral plate[84], which was consistent with the findings of previous studies investigating the use of ACI as second-line therapy for large lesions[63,73,85-87] (Table VII).

It has also been recommended that MACI should be used as a first-line therapy for lesions ≥2 cm^2 in size[70,72]. A randomized controlled trial evaluating 5-year outcomes of MACI and microfracture techniques demonstrated that MACI yielded significantly higher KOOS pain and function scores and a nonsignificantly lower failure rate[70]. However, the efficacy of MACI over microfracture has yet to be established in defects <2 cm^2 in size[74,88,89], and future studies are needed to definitively determine the value of MACI over OCA for larger cartilage defects[72] (Table VIII).

Particulated Juvenile Allograft Cartilage

Particulated juvenile allograft cartilage (PJAC) (DeNovo Natural Tissue [NT]; Zimmer Biomet) represents a second-generation cartilage treatment due to its off-the-shelf capability and limited immunogenic response. This system consists of minced live cartilage allograft from juvenile donors that contains chondrocytes within their native extracellular matrix, conveying a theoretically increased proliferative potential. The minced cartilage utilizes 1 to 2-mm cubes, allowing chondrocytes to diffuse from their extracellular matrix to form new hyaline-like cartilage[90]. Because PJAC does not require a biopsy, this can be performed as a single-stage procedure. Despite these benefits, the graft remains expensive and is still seen as experimental by various insurance companies; thus, consideration of its use must be made on a case-by-case basis.

The technique requires preparing the surface by removing the calcified cartilage layer and establishing well-defined, stable borders around the defect followed by placement of the PJAC such that the fragments are spaced 1 to 2 mm apart. Each packet of PJAC covers an area 2.0 to 2.5 cm^2 in size[72]. The surface is then secured with a final layer of fibrin glue and should be recessed from the surrounding native cartilage by 1 mm to prevent graft dislodgement. Graft hypertrophy has been reported in up to 33% of cases, requiring revision arthroscopic debridement[91]. Graft displacement may occur if stable peripheral walls are not established, the graft is not recessed appropriately, or

TABLE X Summary of Clinical Decision-Making for PJAC*

Indications†	Contraindications		Advantages	Disadvantages	Recommendations	Grade of Recommendation‡
	Absolute	Relative				
Lesions of 2-6 cm^2 with grade-III or IV Outerbridge changes; minimal to no bone loss or subchondral involvement; and 2nd-line treatment for lesions of <2 cm^2	Infections, inflammatory arthritis, inability to follow postop. rehab. protocols, and end-stage osteoarthritis	Uncontained and bipolar lesions, lower-extremity malalignment, ligamentous instability, PFJ instability and/or maltracking, and meniscal insufficiency	Single-stage procedure, consistency of cellular implant makeup and method of application, can treat large chondral lesions, and uncontained lesions can be covered in collagen type-I/III membranes[117]	Concern for graft stability or dislodgement, graft hypertrophy, cost, invasive (mini-arthrotomy required), and depth of >6 mm requires bone-grafting[117,118]	PJAC can be used as 1st line therapy for lesions of ≥2 cm^2; because of additional cost and invasive nature of PJAC, this technique may not be suitable for patients with defects of <2 cm^2	C

*PJAC = particulated juvenile allograft cartilage, PFJ = patellofemoral joint. †Indications are according to several studies[93,95,119,120]. ‡According to Wright[112], grade C indicates poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention.

intraoperative mobilization is initiated before the fibrin glue is sealed (Table IX).

As PJAC is a newer technique, mid-term and long-term clinical outcomes data are lacking, but early clinical outcomes studies have been promising. Buckwalter et al. noted improved outcome scores at short-term follow-up in a series of 17 patients[92]. Tompkins et al. observed similar favorable clinical outcomes after 28.8 months of follow-up, although patients did not return to the same level of activity[91]. Farr et al., in a prospective study, found that hyaline-like cartilage was predominant in follow-up biopsy specimens following PJAC[93]. Grawe et al. observed moderate to good fill of cartilage

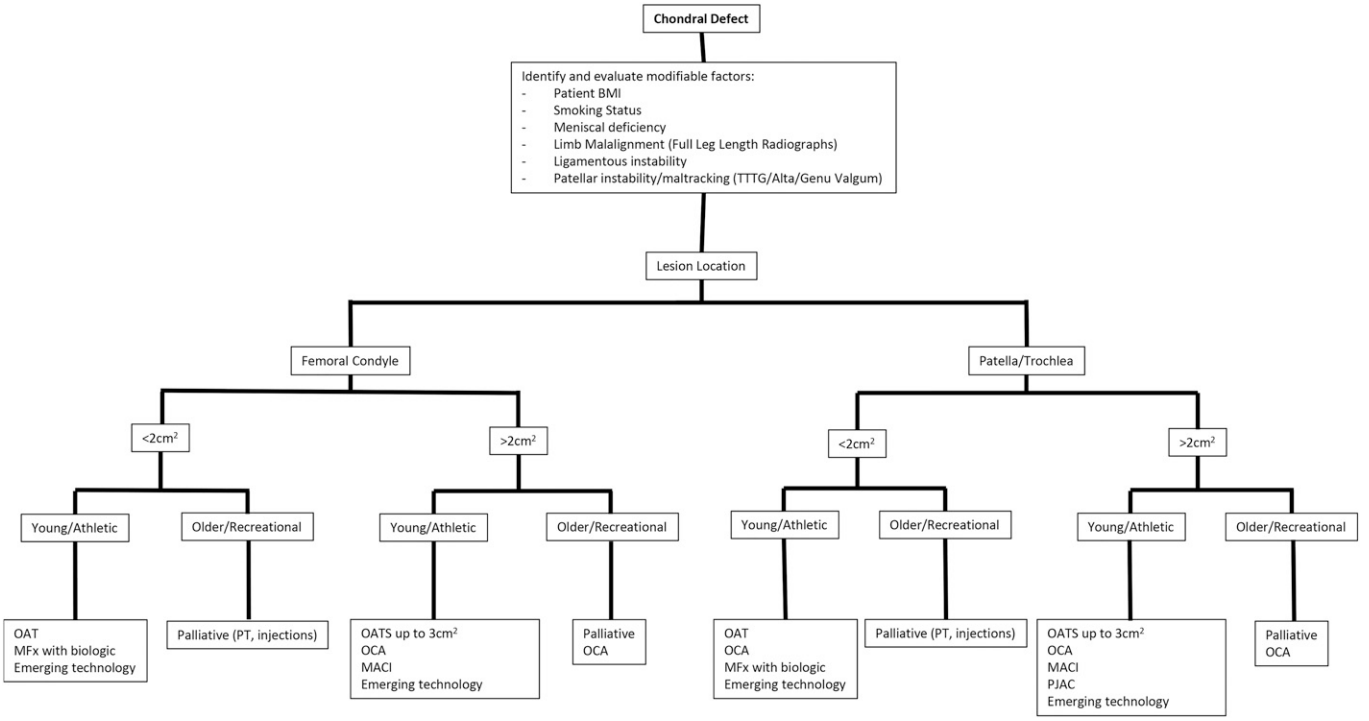

Fig. 7

Treatment algorithm for cartilage defects based on their location and size and the activity level of the patient[104]. BMI = body mass index, TTTG = tibial tubercle-trochlear groove, MFx = microfracture, and PT = physical therapy.

repair tissue in 82%, 85%, and 75% of knees at 6, 12, and 24 months, respectively[94]. Wang et al. demonstrated that 69% of the 27 patients (30 lesions) demonstrated lesion fill of >67%, with significantly improved IKDC and Knee Outcome Survey-Activities of Daily Living (KOS-ADL) scores but unchanged Marx Activity Scale scores[95]. The overall correlation between cartilage repair evaluated radiographically and subjective outcomes measures has yet to be fully established. Although initial studies have demonstrated encouraging results, the quality of evidence to support the use of PJAC is currently limited (Table X).

Emerging Allograft Technology

New biologic scaffolds of allograft cartilage have been used to enhance the biologic response to microfracture for improved cartilage repair[96]. Most of the evidence for their use is in preclinical studies with benchtop models demonstrating promising results[96-100]. BioCartilage (Arthrex) is desiccated micronized allograft cartilage extracellular matrix, which is hydrated with platelet-rich plasma (PRP) and placed in contained defects after microfracture[101]. The technique follows the principles of microfracture, ensuring removal of the calcified layers and creation of a well-contained lesion, and it is secured with a fibrin glue. Clinical outcomes following biologic scaffold augmentation are limited, but basic-science studies have shown an improved type-II collagen profile compared with microfracture. Fortier et al. evaluated BioCartilage versus microfracture alone in an equine model with two 10-mm defects using serial arthroscopic evaluation at 2, 6, and 13 months, as well as MRI and microcomputed tomography (micro-CT) at 13 months[97]. The overall International Cartilage Repair Society score for defects was significantly better for BioCartilage than microfracture alone, and there were no adverse inflammatory reactions.

Cryopreserved OCA-equivalent implants are also available and include Cartiform (Arthrex) and ProChondrix CR (Stryker). These options deliver cryopreserved chondrocytes, chondrogenic growth factors, and extracellular matrix proteins on a thin layer of subchondral bone. After microfracture is performed, the graft is sized and placed into the defect with the osseous surface oriented toward the subchondral bone. Graft fixation has been described with the use of sutures to native cartilage, anchors, and fibrin glue[102]. The cryopreserved nature of the graft allows for increased shelf life and provides a single-stage surgical option for smaller (1 to 2 cm^2), full-thickness, contained defects[102,103]. Because of the small osseous layer and thin profile, these implants are contraindicated in the presence of subchondral bone loss of >5 mm, mechanical malalignment, meniscal insufficiency, ligamentous instability, and patellar defects with maltracking. Early animal studies have shown healing of osteochondral defects and very limited case series have demonstrated the ability to generate cellular hyaline-like repair tissue and MRI evidence of graft incorporation[98,100] (Fig. 7).

Overview

As technology, graft sources, and newer surgical techniques evolve, there are a multitude of strategies to address focal articular cartilage injuries of either the patellofemoral joint or femoral condyles in the young and active patient population. Patient selection is paramount, as the mechanical (varus, valgus, malrotation, malalignment, and meniscal deficiency), biologic (smoking status, inflammatory arthropathy, and increased body mass index), and mental environments (patient resilience and willingness to comply with restrictions) need to be accounted for to optimize patient outcomes. This review serves to provide a resource for the clinician in an ever-challenging and ever-evolving field. ■

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