

# An Autologous Cartilage Tissue Implant NeoCart for Treatment of Grade III Chondral Injury to the Distal Femur

## Prospective Clinical Safety Trial at 2 Years

Dennis C. Crawford,<sup>\*†</sup> MD, PhD, Chelsea M. Heveran,<sup>†</sup> W. Dilworth Cannon Jr,<sup>‡</sup> MD, Li Foong Foo,<sup>§</sup> MD, and Hollis G. Potter,<sup>§</sup> MD

From the <sup>†</sup>Department of Orthopaedics, Oregon Health and Science University, Portland, Oregon, the <sup>‡</sup>Department of Orthopaedic Surgery, University of California San Francisco Medical School, San Francisco, California, and the <sup>§</sup>Magnetic Resonance Imaging Division, Department of Radiology and Imaging, Hospital for Special Surgery, New York, New York

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**Background:** The healing potential of damaged articular cartilage is limited. The NeoCart is a tissue-engineered collagen matrix seeded with autogenous chondrocytes designed for the repair of hyaline articular cartilage.

**Hypothesis:** The NeoCart implant is well tolerated in the human knee.

**Study Design:** Case series; Level of evidence, 4.

**Methods:** Eight patients (treatment group) with full-thickness cartilage injury were treated with the NeoCart and evaluated prospectively. Autogenous chondrocytes provided by arthroscopic biopsy were seeded into a 3-dimensional type I collagen scaffold. The seeded scaffold was subjected to a tissue-engineering protocol including treatment with a bioreactor. Implantation of the prepared cartilage tissue patch was performed via miniarthrotomy and secured with a collagen bioadhesive. Evaluations through 24 months postoperatively included the subjective International Knee Documentation Committee questionnaire, visual analog scale, range of motion, and cartilage-sensitive magnetic resonance imaging (MRI), including quantitative T2 mapping.

**Results:** Pain scores after NeoCart implantation were significantly lower than baseline at 12 and 24 months after the procedure ( $P < .05$ ). Improved function and motion were also noted at 24 months. Six patients had 67% to 100% defect fill at 24 months with MRI evaluation. One patient had moderate (33%-66%) defect fill, and another patient had poor (less than 33%) defect fill. Partial stratification of T2 values was observed for 2 patients at 12 months and 4 patients at 24 months. No patients experienced arthrofibrosis or implant hypertrophy.

**Conclusion:** Pain was significantly reduced 12 and 24 months after NeoCart treatment. Trends toward improved function and motion were observed 24 months after implantation. The MRI indicated implant stability and peripheral integration, defect fill without overgrowth, progressive maturation, and more organized cartilage formation.

**Keywords:** cartilage repair; chondrocyte; chondral repair; articular cartilage injury

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\*Address correspondence to Dennis C. Crawford, MD, PhD, Oregon Health and Science University, Center for Health & Healing, 12th Floor, 3303 SW Bond Avenue, Portland, OR 97239 (e-mail: crawfden@ohsu.edu).

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Full-thickness cartilage injury is common in the knee.<sup>12</sup> Although mechanical pain may be addressed through removal of damaged tissue, articular cartilage has little capacity to undergo spontaneous repair, and defects may progress to degenerative joint conditions. Marrow stimulation techniques such as microfracture provide largely fibrocartilage repair,<sup>19</sup> which is known to have inferior ability to withstand shear and indentation forces.<sup>1,11</sup> While fibrocartilage repair may be an effective short-term treatment for young patients with small defects,<sup>19,20,30</sup> the essential differences in tissue quality may contribute to

the clinical deterioration noted as early as 18 months after microfracture.<sup>20</sup>

Other approaches use autologous chondrocytes in an effort to create durable hyaline repair. In autologous chondrocyte implantation (ACI), a suspension of cultured chondrocytes is injected under a periosteal cover.<sup>5</sup> This technique does not consistently achieve hyaline cartilage repair.<sup>16,19,21</sup> Furthermore, complications such as arthrofibrosis and hypertrophy of the implanted periosteum are reported.<sup>7,8,19,26,27,33</sup>

Seeding a chondrocyte population into a scaffold eschews many procedural difficulties and potential postsurgical complications that are attributed to periosteum harvest and implantation.<sup>2,10,14,37</sup> In addition, the improved structural support provided to chondrocytes by a 3-dimensional environment may promote cartilage maturation.<sup>10</sup> The NeoCart implant (Histogenics Corporation, Waltham, Massachusetts), a novel treatment for articular cartilage defects, partners a 3-dimensional type I collagen scaffold seeded with autologous chondrocytes with a tissue-engineering protocol that includes treatment with a bioreactor.<sup>17,31,35</sup> The resulting product is a proteoglycan- and glycosaminoglycan-rich, viable, and dynamic tissue-like implant. Preclinical trials, including a porcine model of full-thickness femoral cartilage injury, demonstrated that NeoCart implantation leads to hyaline-like repair cartilage, as compared with empty defects or matrix alone (Kusanagi, personal communication, 2003). Preclinical safety evaluations suggested that the NeoCart would be well tolerated in the human knee. The purpose of this report is to describe the initial experience with NeoCart therapy in a clinical population for the treatment of full-thickness cartilage injury. All data are derived from an ongoing prospective Food and Drug Administration (FDA) phase I clinical trial.

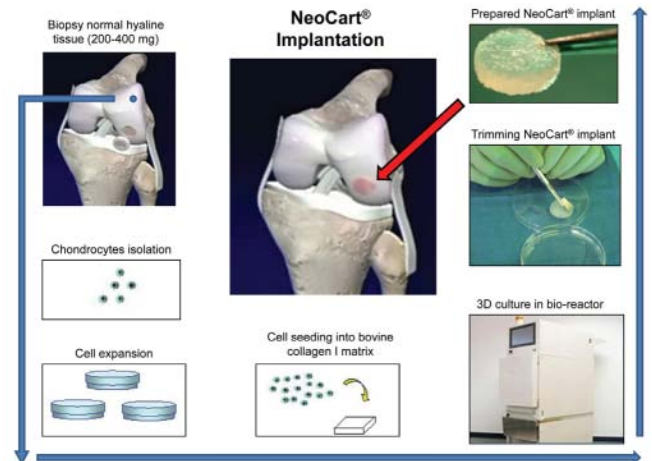
## MATERIALS AND METHODS

### Study Population

This FDA- and Institutional Review Board (IRB)-approved phase I prospective clinical trial was designed to evaluate safety as well as early clinical and radiographic outcomes of the NeoCart implant. Ten patients were enrolled at 2 investigational sites. Written consent was obtained from all patients. Eligible patients were between 18 and 55 years of age, had a symptomatic grade III (full-thickness) cartilage lesion of the femoral condyle, and otherwise satisfied inclusion and exclusion criteria (see Appendix, available in the online version of this article at <http://ajs.sagepub.com/supplemental/>).

### Study Design

NeoCart development is summarized in Figure 1. After screening and consent, all patients underwent arthroscopic evaluation of the cartilage defect and surrounding structures. Articular cartilage (200-400 mg) was taken at the time of arthroscopy from a nonweightbearing portion of

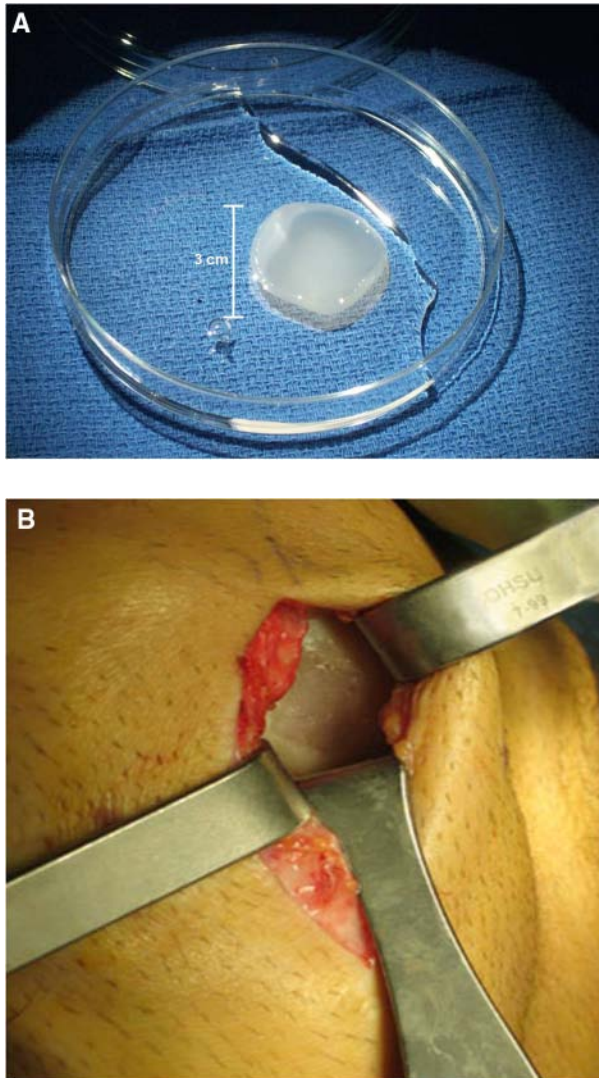


**Figure 1.** NeoCart production and implantation. Chondrocytes are harvested via arthroscopic biopsy and seeded into a bovine type I collagen matrix. Ex vivo maturation in a bioreactor provides the implant, which is surgically fixed to the damaged area with CT3 bioadhesive.

the femoral condyle or from the femoral notch of the ipsilateral knee. The subchondral bone was not penetrated. One patient had ACL reconstruction with hamstring tendon autograft at the time of arthroscopy. Five patients underwent arthroscopic debridement, and one patient had removal of a loose body. The biopsy specimen was packaged for sterile transport and shipped to Histogenics Corporation for processing.

The biopsy specimen was processed to yield chondrocytes for NeoCart. Chondrocytes were expanded and seeded into a bovine type I collagen 3-dimensional honeycomb matrix. The seeded scaffold was processed in a bioreactor in which culture conditions, including hydrostatic pressure, induced chondrocytes to synthesize cartilage glycoproteins. Subsequent static culture further encouraged chondrocyte expression. The total implant development averaged  $67 \pm 18$  days.

The NeoCart implantation procedure was performed successfully in 8 of 10 patients. The implant bed was prepared by debridement of the damaged chondral tissue, including removal of the calcified cartilage. Surgical goals included avoiding both penetration of the subchondral bone and osseous bleeding. The NeoCart was then cut to size and secured within the defect bed (Figure 2). The first 2 implantation procedures were deemed unsuccessful as a result of damage to the NeoCart from suturing and intraoperative motion testing. In subsequent procedures (the 8 reported patients), the NeoCart was secured without sutures, using only a thin layer of CT3 (Histogenics), a proprietary tissue adhesive polymer composed of collagen and polyethylene glycol components, spread below and atop the NeoCart implant. Intraoperative manipulation of the surgical knee was subsequently limited to bringing the knee into full extension for incision closure. A knee immobilizer was used for  $10 \pm 2$  days after implantation at all times.



**Figure 2.** A, The NeoCart implant. B, The implant in situ, viewed via miniarthrotomy.

### Rehabilitation Program

Unrestricted active or passive range of motion was encouraged after the knee immobilizer was discontinued. Patients used a continuous passive motion machine for a minimum of 6 hours a day during the 6 weeks after immobilizer use. For the first 6 weeks after implant surgery, patients were nonweightbearing. Unrestricted weightbearing was allowed afterward, with patients restricted to rehabilitation analogous to femoral condylar microfracture and ACI type protocols.<sup>3,15,38</sup>

### Assessment of Clinical and MRI Outcomes

Clinical evaluations were conducted preoperatively, at 6 and 12 weeks, and at 6, 12, and 24 months after implantation. Each evaluation included routine reporting of the

visual analog scale (VAS) pain score at rest, completion of the International Knee Documentation Committee (IKDC) subjective questionnaire, and measurement of knee range of motion. An MRI was performed at 12 weeks and 12 and 24 months after implantation. Two patients had an additional MRI at 2 and 4 weeks, and 3 patients had MRI between 7 and 9 months after implantation.

All MRI images were obtained on a clinical 1.5-T MRI unit (Signa HD Excite or HDx, General Electric Healthcare, Milwaukee, Wisconsin) using a standard receive-only 8-channel phased array or quadrature knee coil (in vivo extremity coil, InVivo Coporation, Orlando, Florida). Images were obtained using a previously validated fast spin echo pulse sequence for assessing articular cartilage.<sup>34</sup> Coronal, axial, and sagittal fast spin echo images were performed using a repetition time (TR) of 3500 to 6000 milliseconds, echo time (TE) of 34 milliseconds (effective), field of view (FOV) of 14 (axial) to 16 (sagittal) cm, matrix of 512 × 256 (axial) to 384 (sagittal), slice thickness of 3 mm (coronal) to 4 mm (sagittal) with no gap, receiver bandwidth (over the entire frequency range) of 31.25 kHz, at 2 excitations. An additional fat-suppressed fast spin echo sequence (Chemsat, General Electric Healthcare) was obtained in the sagittal plane using an effective TE of 45 milliseconds, matrix of 256 × 224, and slice thickness of 4 mm with no gap. Echo train length varied between 6 and 12. Cartilage morphological characteristics were evaluated using a previously reported series of imaging parameters including signal intensity of the repair cartilage relative to the surrounding cartilage (hypointense, isointense, or hyperintense, measured using a standardized region of interest [ROI] in the center of the repair with a standard of deviation on an MRI workstation), gross appearance (depressed, flush, or proud), the presence or absence of hypertrophy or displacement, subchondral edema (mild [ $<1 \text{ cm}^2$ ], moderate [ $1\text{-}2 \text{ cm}^2$ ], or severe [ $>2 \text{ cm}^2$ ]), bony overgrowth (absence or presence), interface with adjacent cartilage (absence, presence, size of fissure [ $<2 \text{ mm}$  or  $>2 \text{ mm}$ ]), percentage of fill based on both coronal and sagittal images (0%-33%, 34%-66%, or 67%-100%), integrity of adjacent cartilage (modified International Cartilage Repair Society [ICRS] classification),<sup>6</sup> integrity of opposing cartilage (modified ICRS classification), fat pad scarring (mild, moderate, or severe), and synovial reaction (none, mild, moderate, severe).<sup>7</sup>

T2 mapping was performed using a multislice, multi-echo, modified Carr Purcell Meiboom Gill (CPMG) pulse sequence, which uses interleaved slices and tailored refocusing pulses to minimize contribution from stimulated echoes.<sup>24</sup> Standard T2-mapping pulse sequence parameters used were a TR of 800 milliseconds, 8 echoes sampled using sequential multiples of the first TE (9-10 milliseconds), FOV of 16  $\text{cm}^2$ , matrix of 256 to 384 × 256, providing a minimum in-plane resolution of 254  $\mu$  in the frequency direction by 312  $\mu$  in the phase direction, by slice resolution of 2.0 to 3.0 mm with no gap, and a receiver bandwidth of 62.5 kHz. After image acquisition, data sets were analyzed on a pixel-by-pixel basis with a 2-parameter weighted least-squares fit algorithm, assuming a monoexponential fit (Functool 3.1, General

TABLE 1  
Patient and Lesion Demographics<sup>a</sup>

Case No.	Sex	Age at Implant, y	Body Mass Index	Location of Injury (distal femur)	Size of Injury, cm	Time Since Injury, y	Previous Surgeries of the Ipsilateral Knee <sup>b</sup>
1010	M	25	28	Medial condyle	1.9 × 1.5	>2	ACL reconstruction; Partial meniscectomy and debridement
3001	M	43	27	Medial condyle	1.0 × 2.0	>2	ACL reconstruction
3002	F	43	24	Lateral condyle	1.0 × 1.2	>20	Removal of loose body; Debridement and removal of loose body
3003	M	43	28	Medial condyle	1.4 × 2.0	>25	Partial meniscectomy (2); Meniscus repair (2)
3004	M	34	38	Medial condyle	1.0 × 2.0	0.5	None
3006	M	46	29	Medial condyle	1.5 × 2.0	>6	Arthroscopic debridement (2)
3007	F	46	20	Medial condyle	1.1 × 1.6	0.75	Partial meniscectomy and debridement
3008	F	26	25	Lateral condyle	1.3 × 1.3	>3	None
Mean (range)		38 (25-46)	27 (20-38)		1.3 × 1.7	>7	1.5 (0-4)

<sup>a</sup>M, male; F, female; ACL, anterior cruciate ligament.

<sup>b</sup>Not including arthroscopic biopsy harvest.

Electric Healthcare). Quantitative T2 values were calculated by taking the natural logarithm of the signal decay curve in a selected ROI. The ROIs were obtained in a standardized fashion from the articular cartilage over the center of the cartilage repair, both within the deep and superficial 50% of the cartilage repair, as well as of the adjacent and opposite articular cartilage surfaces. Care was taken not to sample close to the tidemark/subchondral plate to avoid partial volume effects of sampling any misregistration due to residual chemical shift. All MRI images were evaluated by 2 experienced musculoskeletal MRI radiologists.

## Safety

Safety was assessed by physical examinations, clinical laboratory tests, and monitoring of adverse events (AEs) throughout the study period. All AEs were monitored until resolved and reported as required by each IRB and the FDA.

## RESULTS

### Patient Enrollment

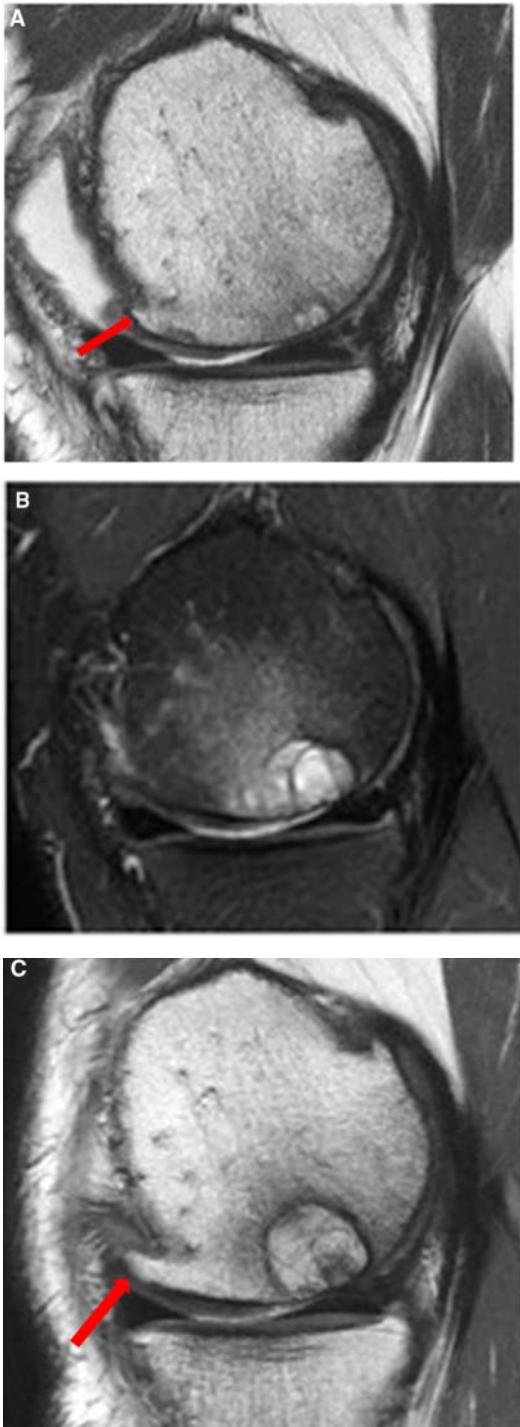
Ten patients were enrolled as the intention to treat group. The 8 patients who had the NeoCart surgically secured with CT3 alone are reported as the treatment group. For 2 other patients, the implant was damaged as a result of suturing and intraoperative motion testing. Data for these 2 patients are not reported here.

The treatment group included 3 women and 5 men, with a mean age of 38 years (range, 25-46) and a mean body mass index (BMI) of 27 (range, 20-38) (Table 1). All patients had an isolated grade III chondral injury to the

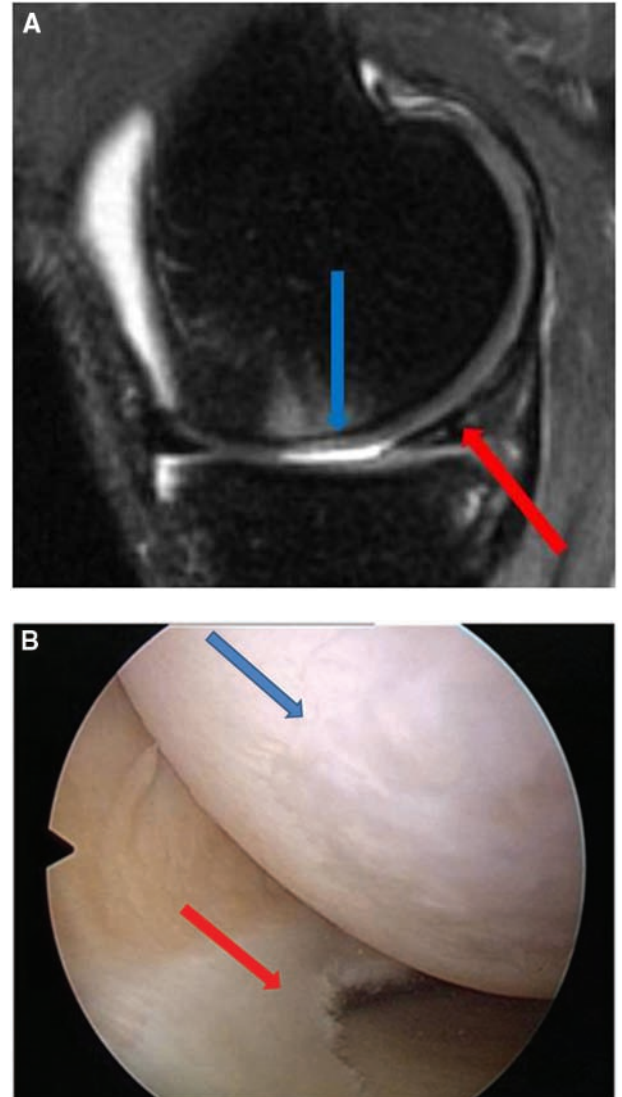
weightbearing region of either the medial or lateral femoral condyle. Injuries were typically chronic; 6 patients reported symptoms greater than 2 years before treatment. Defects were associated with trauma (n = 3), focal osteoarthritis (n = 3), prior ACL injury (n = 2), and osteonecrosis (same knee, opposite condyle) (n = 1). Defects averaged 1.3 × 1.7 cm, or 2.2 cm<sup>2</sup> (range, 1.2-3.0 cm<sup>2</sup>). No patient had prior treatment of the study defect other than arthroscopic debridement. All patients were evaluated up to or exceeding 24 months.

## Safety

No serious AEs occurred, and no patients were discontinued from the study because of AEs. Twelve AEs were considered at least possibly related to the implant. They included normal postsurgical sequelae such as pain, swelling, and numbness at the site of incision. A subchondral cyst of dimensions 1.9 × 1.8 × 1.3 cm was noted at 12-month MRI for one patient and appeared larger at 24 months. This patient had preimplant evidence of osteonecrosis (without collapse) of the ipsilateral knee lateral condyle (medial condyle treated with the NeoCart), as well as prior ACL reconstruction (Figure 3). There were 2 severe AEs possibly related to the study implant. One involved a patellar fracture that occurred after a fall in the index knee 6 months after NeoCart treatment. Another patient suffered a meniscal tear in the index compartment within 3 months of implantation (Figure 4). The implant remained stable in both cases. No infections or study-related interventions occurred in the treatment group. Incomplete attachment was described for the initial MRIs (3 and 9 months) for 2 patients. At subsequent MRIs, these implants remained stable, with good defect fill (67%-100%) seen at both 12 and 24 months and partial stratification of T2 values observed at 24 months.



**Figure 3.** Sagittal fast inversion recovery and fast spin echo magnetic resonance images over the site of cartilage repair in a patient with osteonecrosis of the opposite femoral condyle. Persistent poor fill of the defect demonstrated by hyperintense repair cartilage is accompanied by a progressive subchondral cystic change and bone marrow edema. A, Three months after NeoCart implantation with adjacent osteophyte (arrow). B, Thirteen months after NeoCart implantation. C, Twenty-five months after NeoCart implantation. Osteophyte noted with arrow.



**Figure 4.** A, Sagittal magnetic resonance image of the NeoCart implant (gray arrow) at 12 weeks with adjacent posterior horn meniscal tear (white arrow). B, Arthroscopic image of the NeoCart implant in situ after arthroscopic meniscus debridement. The NeoCart (blue arrow) appears flush and integrated to the area of medial meniscectomy (red arrow).

Implant failures associated with the first 2 implantation procedures were considered to be AEs. To date, additional AEs for these patients include only superficial venous thrombosis of the left forearm for one patient, a complication of intravenous placement on the day of surgery.

#### Clinical Outcomes

All 10 patients completed all benchmarks through 24 months. Clinical outcomes represent the treatment group (8 patients). The VAS significantly decreased to an average of  $0.9 \pm 1.5$  at 12 months, down from  $3.3 \pm 2.8$  at baseline ( $P < .05$ ). Pain scores at 24 months remained significantly

TABLE 2  
Clinical Outcomes After NeoCart Implantation<sup>a</sup>

Assessments		Case No.							
		1010	3001	3002	3003	3004	3006	3007	3008
Visual analog scale	Baseline	5.92	3.35	1.48	1.33	0.47	6.78	0.47	6.67
	6 weeks	2.31	0.95	0.68	0.79	0.40	4.16	1.14	2.23
	3 months	0.41	1.66	0.46	0.34	0.20	6.47	5.27	2.03
	6 months	0.61	1.14	0.34	0.47	0.74	5.80	2.15	0.81
	1 year	0.00	1.08	0.54	0.07	0.34	4.59	0.27	0.13
	2 years	0.00	1.02	0.95	0.00	0.82	2.30	0.20	0.30
Range of motion, deg	Baseline	144	126	137	115	117	130	130	125
	6 weeks	140	115	125	125	105	120	125	135
	3 months	130	125	130	130	115	125	130	135
	6 months	136	140	125	135	115	125	135	135
	1 year	140	135	130	135	120	125	135	135
	2 years	145	135	125	135	130	135	140	145
International Knee Documentation Committee score	Baseline	13.79	68.97	68.97	75.86	68.60	25.29	80.46	52.87
	6 weeks	22.78	48.28	29.89	43.68	58.62	6.90	42.53	37.93
	3 months	45.78	64.37	65.52	68.97	54.02	13.79	49.43	50.57
	6 months	56.32	68.97	73.56	73.56	64.37	33.33	59.77	65.52
	1 year	72.00	89.66	87.36	100.00	62.07	34.94	62.07	81.61
	2 years	73.56	85.06	77.01	100.00	72.41	49.43	59.77	93.10

<sup>a</sup>NeoCart from Histogenics Corporation.

lower than at baseline ( $P < .05$ ). Average range of motion improved from  $128^\circ \pm 10^\circ$  at baseline to  $136^\circ \pm 7^\circ$  at 24 months. Range of motion improved in 7 of 8 patients during the study period. No patients developed arthrofibrosis. Knee function, assessed with the IKDC, improved in 7 of 8 patients from  $57 \pm 25$  at baseline to  $76 \pm 17$  at 24 months (Table 2).

### MRI Outcomes

The MRI at 24 months showed 6 of 8 patients with good to complete (67%-100%) defect fill. One patient had moderate (33%-66%) defect fill, and another patient had poor (<33%) defect fill. This last patient developed a subchondral cyst adjacent to the implant. No soft tissue hypertrophy was noted throughout the study period. Two patients demonstrated partial stratification of T2 values similar to hyaline cartilage at 12 months. At 24 months, 4 of 8 patients had stratification of T2 values; however, all repairs showed prolongation of quantitative T2 values in both the superficial and deep components of the repair tissue (Figures 5 and 6).

Assessment of peripheral integration at 12 weeks found 2 patients with fissures less than 2 mm and 6 patients with fissures greater than 2 mm. Improved integration was seen in 4 of 8 patients at 12 months. At this time point, 1 implant was completely integrated with surrounding tissue, 4 had fissures less than 2 mm, and 3 had fissures greater than 2 mm. Integration continued to improve at 24 months. Two implants were completely integrated, including one that at 12 months had fissures less than 2 mm.

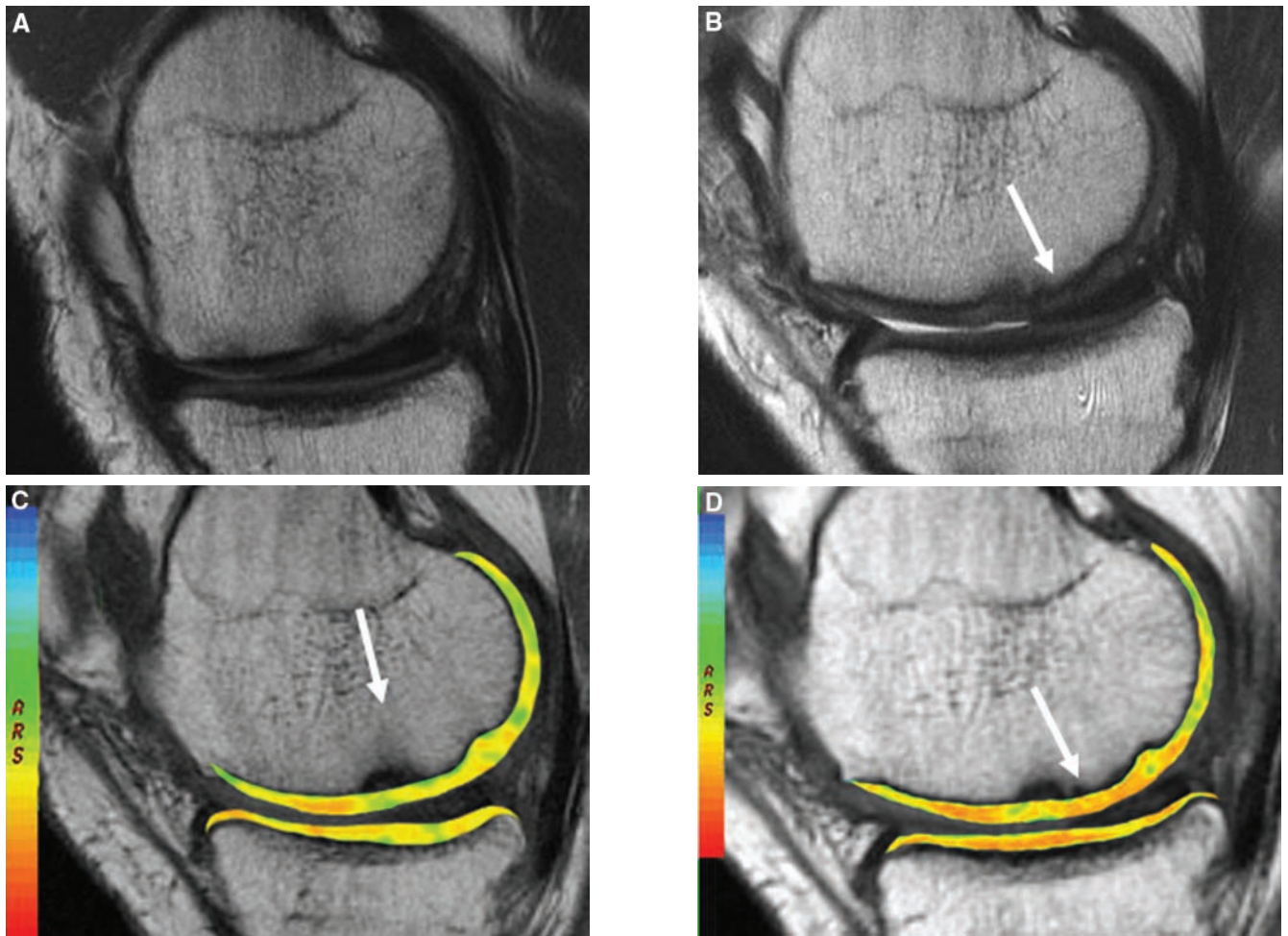
Three implants had fissures less than 2 mm, and 3 had fissures greater than 2 mm.

### DISCUSSION

Suboptimal repair of articular cartilage defects with current methods inspires investigation into the potential use of tissue-engineered cartilage. The autologous cartilage tissue implant (ACTI) NeoCart is an implantable cell/matrix-based implant with characteristics of hyaline cartilage. This product is developed from a 3-dimensional collagen scaffold seeded with autologous cells and incubated using physiological stimuli.

This study provides the first evaluation of the NeoCart in the human knee. Data collected through 24 months for all patients suggest implant safety. No serious AEs were associated with the NeoCart implant, procedures, or rehabilitation. The implant remained stable for all patients when secured with the CT3 bioadhesive alone. It was determined from the first 2 (unsuccessful) implantation procedures that suture fixation and/or immediate intraoperative motion testing may damage the NeoCart implant and cause detachment. No serious AEs were noted in the 2 patients who did not receive the implant. One underwent uneventful microfracture treatment.

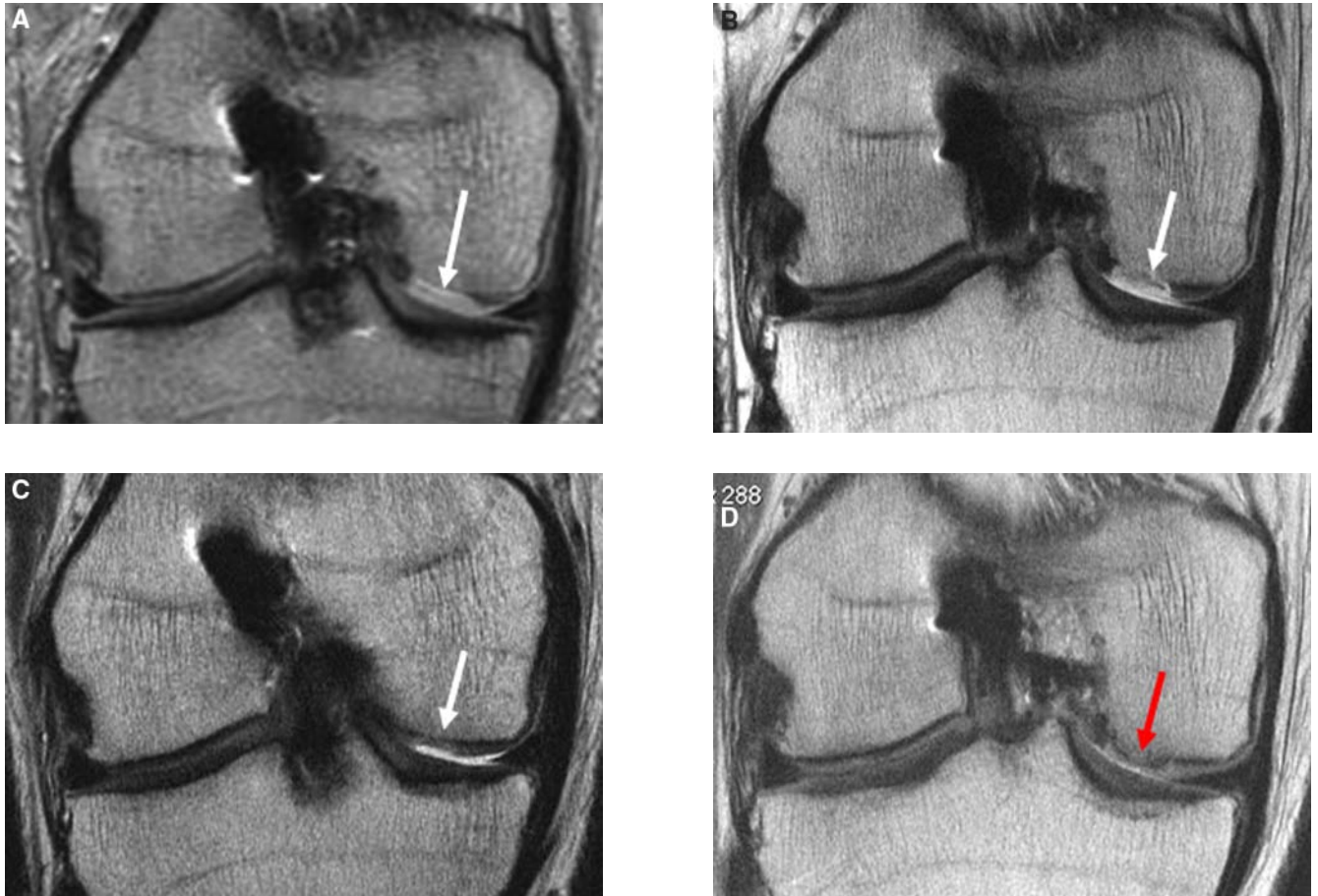
Two-year preliminary data for this small number of phase I patients suggest beneficial clinical outcomes. A significant reduction in subjective pain was observed as early as 12 months after NeoCart treatment and sustained through 24 months ( $P < .05$ ). Knee function as measured



**Figure 5.** A, Sagittal magnetic resonance images after implantation of a NeoCart patch over the medial femoral condyle. Cartilage-sensitive magnetic resonance image at 1 year demonstrates fill of the defect by repair tissue that is hyperintense relative to native cartilage. B, Good fill was maintained at 2 years, with progressive decrease in signal intensity of the repair cartilage (arrow) undergoing “maturation.” C, Corresponding T2 mapping at 1 year demonstrates prolongation of T2 values at the site of cartilage repair (arrow). D, Corresponding T2 mapping at 2 years demonstrates partial stratification of T2 values (arrow).

by the IKDC score also improved for 7 of 8 patients. The exception suffered a new meniscal tear of the index knee. All patients gained or preserved range of motion arc versus presurgery measures. This was not statistically significant but may be an important finding based on contrast with the association of cartilage restoration procedures such as ACI with potential arthrofibrosis. In a study of 169 patients treated with ACI, Minas reported a 5% incidence of arthrofibrosis.<sup>27</sup> Outcomes review of the Carticel outcomes registry, with 891 patients at the time of the authors' review, found the incidence of arthrofibrosis after ACI to be 3.1%.<sup>25</sup> Of particular interest, our 8 patients all demonstrated improvement in at least 2 of 3 key efficacy measurements: VAS pain, IKDC score, or range of motion at 12 and 24 months after NeoCart treatment. At 12 months, 3 patients improved in all 3 efficacy categories compared with baseline. By 24 months, 5 of 8 demonstrated improvement from baseline evaluation for all 3 measurements.

Good to complete defect fill (67%-100%) was observed in MRI studies for 6 of 8 patients at 24 months. While clinical outcomes and fill grade are positively correlated,<sup>29,30</sup> volume of fill has varied considerably for the microfracture procedure.<sup>9,13,29</sup> The MRI of 19 patients at an average of 3 years after microfracture evidenced that only 42% of patients had 67% to 100% defect fill, while 31% to 66% and 0% to 30% defect fill were noted in 21% and 37% of patients, respectively.<sup>13</sup> No patients had overgrowth of the NeoCart patch. By contrast, graft and periosteum hypertrophy are known complications of the ACI technique that often necessitate removal or debridement.<sup>7,8,19,33</sup> In one randomized comparison of ACI and microfracture, 25% of patients in the ACI group, as opposed to 10% of patients in the microfracture group, required arthroscopic debridement before second-look arthroscopy at 2 years.<sup>19</sup> Another comparison demonstrated an incidence of hypertrophy at 1 year after study surgery of 25% for patients receiving characterized



**Figure 6.** Coronal magnetic resonance images after implantation of the NeoCart patch over the medial femoral condyle demonstrate good fill of the cartilage defect as well as progressive decreased signal intensity of the repair tissue, approaching that of adjacent native cartilage (white arrows). A, Ten days after NeoCart implantation. B, One month after NeoCart implantation. C, Three months after NeoCart implantation. D, Eleven months after NeoCart implantation. Development of focal underlying subchondral bony remodeling is noted (arrow).

chondrocyte implantation and 8% for patients receiving microfracture.<sup>36</sup> A large study of 349 ACI procedures reported that the incidence of symptomatic hypertrophy was 15.8% for patients receiving periosteum-covered ACI (ACI-P) and only 1.9% and 4.9% for patients receiving membrane-covered ACI (ACI-C) and matrix-associated ACI (MACI), respectively.<sup>32</sup> These findings suggest that hypertrophy may be avoided by the use of collagen matrix in place of periosteum as in the NeoCart procedure.

Quantitative T2 mapping was used to assess the repair tissue. Stratification of T2 values, with shorter relaxation times in the basilar components and longer values in the superficial components, has been correlated with the organization of collagen fibrils similar to that of normal articular cartilage.<sup>7</sup> At 12 months after surgery, 25% of patients demonstrated partial T2 stratification. While the numbers are small, this figure increased to 50% at 24 months. All patients with partially stratified cartilage at 12 months maintained this pattern of stratification at 24 months.

These results are consistent with continued maturation of the NeoCart implant into hyaline-like repair cartilage. T2 stratification was not observed in 4 patients. Of these 4, one patient sustained a new meniscal tear in the index knee on return to activity, and another patient had 4 previous debridement surgeries and preimplantation radiographs that suggested early osteoarthritis. Multiple knee surgeries before cartilage restoration surgery are known to correlate with inferior clinical scores<sup>21</sup> and delayed return to sport.<sup>30</sup>

Clinical and MRI outcomes are particularly encouraging in relation to the chronicity of symptoms, age range, and BMI. Of the 8 patients receiving NeoCart treatment, 6 reported symptoms greater than 2 years previous to study surgery. In other studies, patients with chronic injuries were more likely to demonstrate less functional improvement<sup>2,13,21,29</sup> and inferior fill grade<sup>29</sup> compared with patients with acute injury. Five patients were above age 40 years at the time of index surgery. Of the 4 patients

with T2 stratification, 2 were at least 40 years of age. Younger patients, often defined as under 30 years of age, have the most success with microfracture<sup>19,20,29</sup> and ACI.<sup>2,19,21,22</sup> Patients with T2 stratification had a BMI encompassing the entire study range of 20 to 38. The only patient to not report improved knee function, as based on the IKDC score, had the lowest BMI. By contrast, a BMI greater than 30 has been shown to correlate with inferior clinical outcomes for the microfracture procedure.<sup>29</sup>

Early clinical and MRI outcomes suggest that the NeoCart therapy may be a safe and promising alternative to current restorative techniques for partial to full-thickness cartilage defects. This initial safety trial suggests that concerns such as arthrofibrosis and graft hypertrophy associated with ACI-type techniques are potentially avoided with the NeoCart technique. Comparison of NeoCart clinical outcomes with other cartilage restoration therapies such as microfracture, ACI-P,<sup>5</sup> and scaffold techniques such as ACI-C,<sup>5,14</sup> MACI,<sup>10</sup> and other scaffold techniques, for example, Hyalograft C<sup>39</sup> and Cartipatch,<sup>37</sup> is currently premature given the small number of patients in this trial. Previous comparisons of the effectiveness of these techniques for the treatment of articular cartilage injury have produced mixed results. A recent review of cartilage restoration techniques including microfracture, ACI-P, ACI-C, and MACI found no one superior cartilage restoration technique.<sup>23</sup> The authors of the review suggest that microfracture should be considered a first-line treatment, based upon findings that microfracture is not inferior to ACI techniques, may not preclude secondary treatments, and may require less planning and equipment.<sup>23</sup> Unfortunately, microfracture has been associated with a failure rate of 23% at 5 years<sup>18</sup> and a deterioration of clinical outcomes as early as 18 months after surgery.<sup>20</sup> In addition, inferior results for ACI after failed microfracture have been reported, raising concern for microfracture as a primary therapy.<sup>28</sup> Taken together, this suggests a need for an alternative first-line treatment that restores the hyaline matrix and does not violate the subchondral bone. A prospective, randomized controlled investigation comparing clinical and MRI outcomes in the NeoCart versus microfracture is currently underway.

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