Changes in Cross-sectional Area and Signal Intensity of Healing Anterior Cruciate Ligaments and Grafts in the First 2 Years After Surgery

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Background: The quality of a repaired anterior cruciate ligament (ACL) or reconstructed graft is typically quantified in clinical studies by evaluating knee, lower extremity, or patient performance. However, magnetic resonance imaging of the healing ACL or graft may provide a more direct measure of tissue quality (ie, signal intensity) and quantity (ie, cross-sectional area).

Hypotheses: (1) Average cross-sectional area or signal intensity of a healing ACL after bridge-enhanced ACL repair (BEAR) or a hamstring autograft (ACL reconstruction) will change postoperatively from 3 to 24 months. (2) The average cross-sectional area and signal intensity of the healing ligament or graft will correlate with anatomic features of the knee associated with ACL injury.

Study Design: Cohort study; Level of evidence, 2.

Methods: Patients with a complete midsubstance ACL tear who were treated with either BEAR (n = 10) or ACL reconstruction (n = 10) underwent magnetic resonance imaging at 3, 6, 12, and 24 months after surgery. Images were analyzed to determine the average cross-sectional area and signal intensity of the ACL or graft at each time point. ACL orientation, stump length, and bony anatomy were also assessed.

Results: Mean cross-sectional area of the grafts was 48% to 98% larger than the contralateral intact ACLs at all time points ($P < .01$). The BEAR ACLs were 23% to 28% greater in cross-sectional area than the contralateral intact ACLs at 3 and 6 months ($P < .02$) but similar at 12 and 24 months. The BEAR ACLs were similar in sagittal orientation to the contralateral ACLs, while the grafts were 6.5° more vertical ($P = .005$). For the BEAR ACLs, a bigger notch correlated with a bigger cross-sectional area, while a shorter ACL femoral stump, steeper lateral tibial slope, and shallower medial tibial depth were associated with higher signal intensity ($R^2 > .40$, $P < .05$). Performance of notchplasty resulted in an increased ACL cross-sectional area after the BEAR procedure ($P = .007$). No anatomic features were correlated with ACL graft size or signal intensity.

Conclusion: Hamstring autografts were larger in cross-sectional area and more vertically oriented than the native ACLs at 24 months after surgery. BEAR ACLs had a cross-sectional area, signal intensity, and sagittal orientation similar to the contralateral ACLs at 24 months. The early signal intensity and cross-sectional area of the repaired ACL may be affected by specific anatomic features, including lateral tibial slope and notch width—observations that deserve further study in a larger cohort of patients.

Registration: NCT02292004 (ClinicalTrials.gov identifier)

Keywords: ACL; repair; bridge-enhanced ACL repair; BEAR; reconstruction; MRI; signal intensity; size

Currently, the integrity of an anterior cruciate ligament (ACL) graft or repair is quantified in clinical studies by evaluating whole knee function, lower extremity performance, and/or patient-reported outcomes. However, these measures are often influenced by factors unrelated to the ACL structure. For example, physical examinations of the knee (eg, the Lachman and pivot-shift tests) can be influenced by the injury or hypertrophy of secondary stabilizers of the knee,[16,54] as well as patient age,[32] sex,[32] and bony anatomy,[41] and are prone to observer bias. Functional testing—for example, hop testing and balance testing—can be influenced by the quality of the rehabilitation program, patient compliance, and/or fear of reinjury.[9,46] Likewise, patient-reported outcomes after ACL surgery were shown to be influenced by self-esteem levels,[10] body mass index,[35] and smoking.[35] When the success or failure of a new surgical procedure is evaluated, clinical, functional, and patient-reported outcomes may be less sensitive to the structural integrity of a healing ACL or ACL

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graft owing to these nonstructural related factors. Direct measures of graft or ligament quality, including the size and degree of tissue organization, could improve our ability to compare the ability of different surgical procedures to restore the ACL structure.

Magnetic resonance imaging (MRI) has been used in preclinical[6,7] and clinical[5,26-28] studies evaluating ACL graft quality and associated outcomes. In a large animal study, the combination of ACL graft size (a measure of tissue quantity) and signal intensity (a measure of tissue quality) as determined from specific MRI sequences was associated with the mechanical[6,7] and histologic[49] properties of the graft after ACL reconstruction (ACLR). ACL graft signal intensity (measured from 2-dimensional MRI) was shown to be predictive of anterior tibial translation 3 months after surgery but not clinical and functional outcomes at 1 year.[15] However, a 3-dimensional (3D) assessment of ACL graft signal intensity and size was shown to be predictive of a range of functional, patient-reported, and clinical outcomes 3 to 5 years after ACLR in humans.[5] These studies highlight the potential of these magnetic resonance (MR)–based parameters for their noninvasive and nondestructive nature such that MRI can be used to study changes in cross-sectional area and signal intensity of grafts and ligaments at multiple time points after surgery. This approach could be useful for the comparison of different surgical procedures or to evaluate factors (eg, notch width) influencing ligament healing after surgical treatment.

In this study, a quantitative MRI approach was used to evaluate time-dependent changes in graft size and signal intensity over the first 2 years after ACLR. This approach was also used to study structural changes for complete midsubstance ACL tears treated with a novel surgical repair procedure: bridge-enhanced ACL repair (BEAR).[38,47] Prior attempts at primary ACL repair for midsubstance ACL tears had a relatively high failure rate,[14] and previous basic and translational research suggested that it may be a premature loss of the provisional scaffold at the time of injury, owing to the location of the ACL in the synovial fluid environment.[40] BEAR aims to address that deficiency by surgically placing a substitute provisional scaffold in the gap in the midsubstance of the torn ACL to stimulate healing at the time of suture repair.[36,37] A recent safety study evaluated the first 10 patients who underwent the BEAR procedure and demonstrated similar patient-reported outcomes and anteroposterior (AP) knee laxity at 3-month and 2-year follow-up as compared with a control group treated with hamstring autograft ACLR.[38,39]

The primary objectives of this study were 2-fold. First, we utilized MRI from these 2 cohorts to compare changes over time in terms of restoring the native ligament size (average cross-sectional area) and tissue quality (normalized signal intensity). We hypothesized that there would be differences in the average cross-sectional area or average normalized signal intensity of the repaired ACL or reconstructed graft over time (ie, 3, 6, 12, and 24 months postoperatively). Second, we determined if the ligament or graft cross-sectional area and normalized signal intensity values were influenced by other anatomic features of the knee after surgery. Posterior slope of the tibial plateau, depth of the medial tibial plateau, and notch width are anatomic factors linked to increased risk of ACL injury,[18,59] graft failure,[25,52] and inferior ACLR outcomes.[21] In addition to the biomechanical role of these anatomic features on ACL/graft loading, the length of the ACL stump may be an influencing factor on the repaired ACL remodeling during healing. Thus, we hypothesized that ACL stump length, posterior tibial slopes, medial tibial plateau depth, and femoral notch size were associated with the average cross-sectional area and average normalized signal intensity of the healing ACL or ACL graft.

METHODS

Trial Design

Food and Drug Administration (FDA) investigational device exemption (G140151) and institutional review board approval (P0012985) were obtained before initiating the study. This interventional nonrandomized trial was registered on ClinicalTrials.gov. All patients granted their written informed consent before participating. This cohort study was designed as a parallel-assignment first-in-human trial for the BEAR technique.[38] Ten patients were enrolled in the interventional (BEAR) group and 10 in the control (ACLR) group. Enrollment was completed from February to October 2015. Patients were evaluated pre-, intra-, and postoperatively at 3, 6, 12, and 24 months. A detailed description of the trial was reported previously

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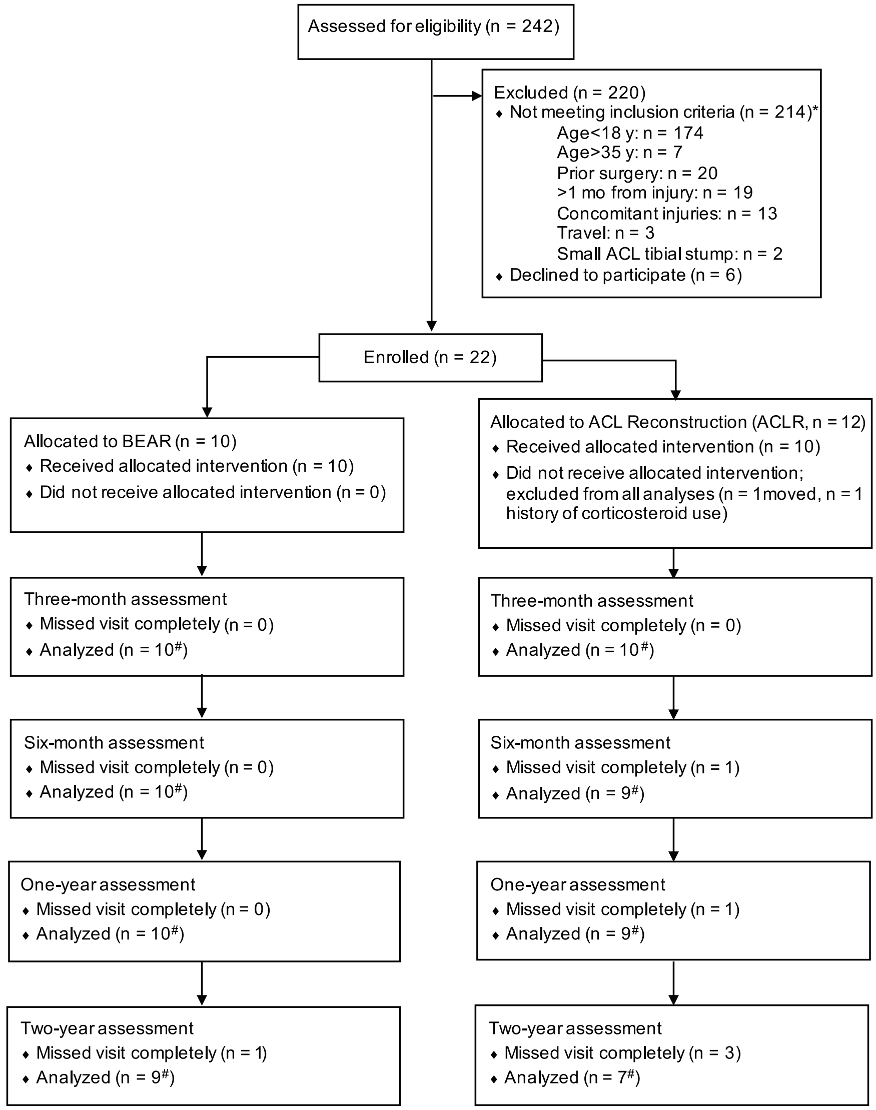


Figure 1. Flow diagram of patient recruitment and follow-up.[38] *The number of patients not meeting inclusion criteria total >214, as some patients met >1 exclusion criterion. #Not all patients completed every component of the follow-up assessments. Sample sizes with data for analysis for each component are available in the figures and tables. ACL, anterior cruciate ligament; BEAR, bridge-enhanced ACL repair.

with the clinical and functional outcomes at 3-month and 2-year follow-up.[38,40]

Participants

Patients aged 18 to 35 years with a complete midsubstance ACL tear who were <1 month from injury were eligible for enrollment in the BEAR group.[38] Patients with a complete ACL tear who were within 3 months of injury were eligible to enroll in the ACLR group, all of whom received an autograft hamstring tendon graft.[38] Patients with a partial ACL tear were not eligible for participation. Patients were excluded from either group if they had a history of knee surgery, history of knee infection, or other risk factors that might adversely affect healing (nicotine/tobacco use, corticosteroids in the past 6 months, chemotherapy, diabetes, inflammatory arthritis). Patients were excluded if they had a displaced bucket-handle tear of the medial meniscus that required repair; however, all other meniscal injuries were included. Additionally, patients were excluded if they had a full-thickness chondral injury, a grade 3 medial collateral ligament injury, a concurrent complete patellar dislocation, or an operative posterolateral corner injury.

A total of 242 patients presenting with an ACL injury were screened for participation in this study (Figure 1). Patients were identified as possible candidates if they scheduled an appointment in our sports medicine clinic with a new knee injury and had a MR scan confirming an ACL tear or if they contacted our research coordinator

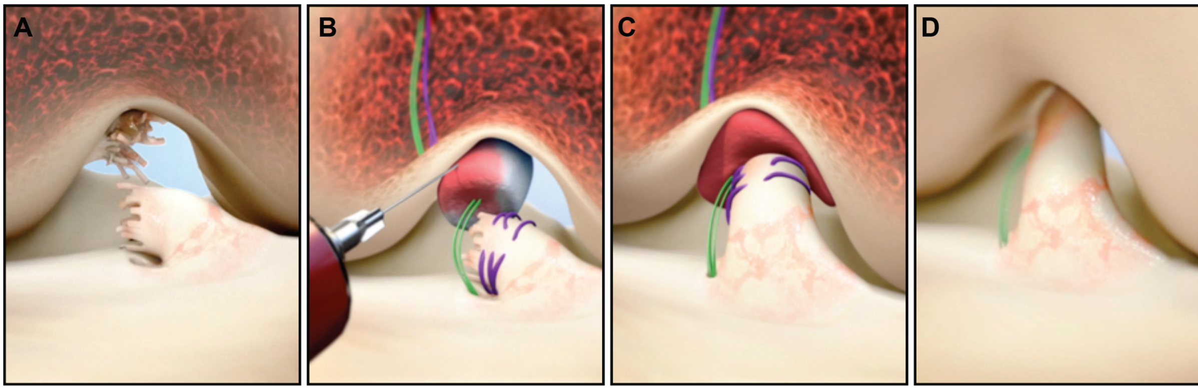


Figure 2. Stepwise demonstration of the ''bridge-enhanced ACL repair'' technique with the scaffold. In this technique, (A) the torn ACL tissue is preserved. (B) A whipstitch of No. 2 absorbable suture (purple suture) is placed into the tibial stump of the ACL. Small tunnels (4 mm) are drilled in the femur and tibia, and a suture cinch composed of a cortical button with 2 No. 2 nonabsorbable sutures (green sutures) and the No. 2 absorbable ACL sutures is passed through the femoral tunnel and the button engaged on the proximal femoral cortex. The nonabsorbable sutures are threaded through the scaffold and tibial tunnel and secured in place with a second extracortical button. The scaffold is then saturated with 10 mL of the patient's blood and (C) the tibial stump pulled up into the saturated scaffold. (D) The ends of the torn ACL then grow into the scaffold, and the ligament reunites. ACL, anterior cruciate ligament. Used with permission from Murray et al (*Orthopaedic Journal of Sports Medicine*, 2016).[38]

after hearing about the study. Of the 242 patients screened, 22 enrolled, and 2 were excluded before surgery: 1 had a history of corticosteroid use not discovered at the initial enrollment meeting, and the other elected to move to Florida for school. The primary reason for exclusion before enrollment was patient age (n = 181).[38] Details of the included patients were reported by Murray et al.[38]

The BEAR scaffold is composed of bovine extracellular matrix proteins, including collagen, and underwent extensive preclinical testing before FDA approval for this study.[47,48] The scaffold measured 22 mm in diameter by 45 mm in length. The scaffold softens when blood is added to it, making it conformable to the intra-articular notch and able to fill in the irregular contours of the gap between the torn ligament ends. The efficacy of the scaffold for stimulating ACL healing was previously demonstrated in preclinical studies.[36,37]

Surgical Procedures

Bridge-Enhanced ACL Repair. The surgical steps for the BEAR procedure are shown in Figure 2. After the induction of general anesthesia, an examination was performed to verify the positive pivot shift on the injured side and to record the Lachman test, range of motion, and pivot-shift examination results on both knees. A knee arthroscopy was performed, and any meniscal injuries were treated if present. A tibial aimer (Acufex Director Drill Guide; Smith & Nephew) was used to place a 2.4-mm guide pin through the tibia and anterior to the tibial footprint of the ACL. The pin was overdrilled with a 4.5-mm reamer (Endoscopic Drill; Smith & Nephew). A notchplasty was performed at the surgeon's discretion to visualize the femoral stump footprint as a landmark for placement of the femoral tunnel. Care was taken not to disturb the femoral footprint of the torn ACL during the BEAR procedure. A guide pin was placed anterior and inferior (within 2 mm) to the femoral ACL footprint, drilled through the femur, and then overdrilled with the 4.5-mm reamer. A 4-cm arthrotomy was made at the medial border of the patellar tendon, and a whipstitch of No. 2 absorbable braided suture (Vicryl; Ethicon) was placed into the tibial stump of the torn ACL and the free ends subsequently passed through the femoral tunnel. A suture cinch (BEAR-Cinch; Boston Children's Hospital) composed of 2 No. 2 nonabsorbable braided sutures (Ethibond; Ethicon) looped through the 2 center holes of a cortical button (EndoButton; Smith & Nephew) was used to reduce the abnormal AP laxity of the knee by (1) passing the cortical button through the femur and engaging it on the lateral femoral cortex and then (2) passing the sutures through an extracellular matrix scaffold (BEAR Scaffold; Boston Children's Hospital), the tibial tunnel, and a second cortical button. Before the suture cinch was tightened, 10 mL of autologous blood was obtained from the antecubital vein and added to the scaffold. The scaffold was then passed up along the sutures into the femoral notch, and the knee was extended. The suture cinch was tightened to reduce AP laxity of the knee, and the sutures were tied over the tibial button with maximum manual tension. The sutures from the ACL tibial stump were tightened to bring the ACL stump into the scaffold and tied over the femoral cortical button. The arthrotomy was closed in layers.

ACLR With Autologous Hamstring Tendon. A standard hamstring autograft procedure was performed with a quadrupled semitendinosus-gracilis graft looped over a continuous-loop cortical button (EndoButton; Smith & Nephew) for proximal fixation. A bioabsorbable interference screw (BioRCI HA; Smith & Nephew) was used for tibial fixation.[38] A minimal notchplasty was performed at the surgeon's discretion as needed for adequate visualization of the posterior notch for placement of the femoral tunnel starting point within the prior ACL footprint. The femoral tunnel was drilled with an anteromedial portal technique and a flexible drill system (Clancy Anatomic Cruciate Guide; Smith & Nephew).

Postoperative Rehabilitation. Rehabilitation protocols were identical in the BEAR and ACLR groups, including restricted range of motion from 0° to 50° for 2 weeks, use of a cold therapy unit, standardized physical therapy, and use of a functional ACL brace.

Magnetic Resonance Imaging

MRI was acquired preoperatively (n = 10, BEAR; n = 10, ACLR) and postoperatively at 3 months (n = 10, n = 10), 6 months (n = 10, n = 8), 12 months (n = 9, n = 6), and 24 months (n = 9, n = 7). With a 3T scanner (Tim Trio; Siemens) and a 15-channel knee coil, the following sequences were obtained: coronal proton density fast spin echo with fat suppression (PD FSE; repetition time/echo time [TR/TE] = 3000/19 milliseconds, 16-cm field of view [FOV], 3-mm slice thickness, 0.3 gap, 284 × 384 matrix, echo train length = 4), sagittal isotropic 3D proton density fast spin echo (SPACE: TR/TE = 1000/39 milliseconds, 16-cm FOV, 0.5-mm slice reconstruction, 320 × 320 matrix, echo train length = 74), and a 3D constructive interference in steady state (CISS; TR/TE = 14/7 milliseconds, flip angle = 35°, 16-cm FOV, 80 × 512 × 512 [slice × frequency × phase]). Images with the CISS sequence were also acquired of the contralateral knee at 24 months (n = 7, BEAR; n = 7, ACLR) after surgery, and 3D SPACE images were reformatted in the coronal and axial planes.

Imaging Outcomes

The following parameters were quantified from the MRI stack for the BEAR and ACLR groups.

Ligament Tissue Parameters. Repaired ACLs, reconstructed grafts, and contralateral intact ACLs were manually segmented from the sagittal CISS image stack to create a 3D model of the structure with the use of commercially available software (Mimics 17.0; Materialize).[5] The model was used to measure the ligament volume and length, which were then used to calculate the mean ACL cross-sectional area (volume/length). This approach was performed to avoid measurement challenges associated with inconsistent selection of the axial oblique slice to quantify the ACL cross-sectional area in its midsubstance. The mean grayscale value across the ligament voxels for each patient was also extracted and normalized to the patient-specific grayscale value of the femoral cortical bone to minimize interscan variability.[5,6] The normalized grayscale value was defined as ligament signal intensity. The segmentations were done by an experienced examiner (A.M.K.). To assess the reliability of the measurements, a subset of 20 repaired and 18 reconstructed ligaments was also segmented by an independent examiner.[13]

Anatomic Parameters. All other anatomic measurements were performed with MRI viewing software (Osirix Viewer v 8.5; Pixmeo SARL). These included tunnel and ligament insertion positions, sagittal elevation angle, ACL stump length, tibial slopes and depth, and femoral notch width as described in turn (Appendix Figure A2, available in the online version of this article).

Tunnel and Ligament Insertion Positions. The sagittal PD FSE MRI obtained at 3 months was used to document the locations of the femoral and tibial tunnels for the BEAR and ACLR knees.[15] For femoral tunnels, the first sagittal slice showing the tunnel on the lateral condyle was selected, and the width and height of the lateral condyle were measured. The distances from the center of the tunnel to the back and bottom of the condyle were measured and normalized to the width and height of the lateral condyle to quantify the location of the femoral tunnel in AP and superior-inferior directions. With the same images, the most medial slice showing the tibial tunnel was used to measure the width of tibia. The distance between the tibial tunnel center and the front of the tibia was also measured and then normalized to the tibial width to quantify the tibial tunnel AP location. Similar methods were used to quantify the location of the ACL femoral and tibial insertions with preoperative MRI.

Ligament Sagittal Elevation Angle. ACL or graft elevation angles in the sagittal plane were measured with the 3D CISS MR scans obtained at 24 months. Briefly, the longitudinal axis of the tibia was established via the technique described by Hudek et al[19] in a central sagittal slice in which the tibial attachment of the posterior cruciate ligament, the intercondylar eminence, and the anterior and posterior tibial cortices appeared in a concave shape. Then, 2 circles were fitted to the tibial head: a cranial circle touching the anterior, posterior, and cranial tibial cortex and a caudal circle touching the anterior and posterior tibial cortex. The line connecting the center of the 2 circles was defined as the longitudinal tibial axis. The line perpendicular to the longitudinal axis of the tibia was then established as the reference for measuring the sagittal elevation angle of the ACL or graft. The ligament longitudinal axis was defined as the line passing through the center of the tissue parallel to the anterior and posterior edges of the ligament. The ligament sagittal elevation angle was measured as the angle between the longitudinal axis of the ligament and the reference line. This method was used previously to measure the multiplanar orientation of human ACL graft.[53]

ACL Stump Length. Preoperative sagittal PD FSE MRI of the injured knee was used to measure the ACL stump length at the femoral and tibial sides. Femoral stump length was defined as the linear distance from the center of the ACL femoral insertion to the most distal fibers of the femoral remnant. Similarly, the tibial stump length was defined as the linear distance from the center of the ACL tibial insertion to the most superior fibers of the tibial remnant. Stump lengths were then normalized to the ACL length, measured as the linear distance between the center of the femoral and tibial insertions in the same MRI scans.[11]

Tibial Slopes and Depth. The posterior slopes of the medial and lateral tibial plateaus were measured from the 3-month sagittal PD FSE MR scans of the injured knee.[17,19] The posterior slopes of the tibial plateaus were measured in a sagittal slice at the center of each medial and lateral plateau as the angle between a line that joined the peak points on the anterior and posterior rims of the plateau and a line perpendicular to the longitudinal axis of the tibia.[17] The medial tibial depth was also measured as the perpendicular distance between a line connecting the anterior and posterior rims of the medial tibial plateau and the deepest point of the medial plateau in the same slice that the medial slope was measured.[17]

Femoral Notch Width. Notch width was measured parallel to a line along the most inferior aspects of the femoral condyles in an axial slice corresponding to the front of the notch. At each time point, notch width was measured at multiple spots from middle to the bottom of the notch, and the maximum value was used as notch width.[45] The measurements were done on preoperative and 3-month PD FSE MRI of the injured knee. Notchplasty was defined as the difference between the notch width measured on the postoperative MRI and that measured on the preoperative MRI.

Statistical Analysis

Imaging outcomes were summarized with descriptive statistics. Two-sample t tests were used to compare the baseline anatomic parameters between the ACLR and BEAR groups. Mixed linear models with Bonferroni post hoc tests were used to compare the ligament cross-sectional area and signal intensity at each time point and with the contralateral intact ACL. This analysis was done to address missing data points during longitudinal follow-ups. The model had a random intercept and slope. Time was used as the fixed effect in the model to assess time-dependent changes in the outcomes. Paired-samples t tests were used to compare the ACL insertion, tunnel locations, and ligament sagittal elevation between pre- and postsurgery or between the surgical and contralateral knees. Two-sided P values are reported and considered significant when $P < .05$. Univariate linear regression analyses were performed to assess the associations between anatomic predictors and cross-sectional area or signal intensity of the repaired ACLs or reconstructed grafts at 24 months. Analyses were performed with statistical software (Prism v 7.0; GraphPad Software Inc).

RESULTS

The baseline characteristics of both groups were previously reported.[38] In summary, the 2 groups were similar with regard to age, sex, race, and body mass index. The mean age was 24 years in both groups. The majority of the injuries in both groups were noncontact and occurred during sports participation. The normalized tibial stump length (tibial stump length/total ACL length) as measured on MRI was 49.4% ± 11.4% (range, 31%-64%) for the BEAR group and 53.9% ± 11.4% (range, 31%-68%) in the ACLR group. The quadrupled hamstring tendon grafts measured 8 or 9 mm in diameter at surgery. The anatomic parameters for the ACLR and BEAR groups were also similar in terms of posterior tibial slope, medial tibial depth, and preoperative notch size (Table 1).

TABLE 1
Anatomic Features as Determined From the Magnetic Resonance Scans for the Patients Undergoing BEAR and ACLR With Autograft Hamstring Graft[a]

Measurement	BEAR (n = 10)	ACLR (n = 10)	*P* Value
Normalized stump length,[b] %			
Femoral	45.6 ± 10.9	38.8 ± 7.3	.117
Tibial	49.4 ± 11.4	53.9 ± 11.4	.361
Tibial slope, deg			
Lateral	6.1 ± 2.5	6.9 ± 2.1	.439
Medial	4.6 ± 2.5	5.9 ± 2.7	.291
Medial tibial depth, mm	2.0 ± 0.8	2.0 ± 0.7	.881
Preoperative notch width, mm	18.6 ± 1.9	18.8 ± 3.2	.888

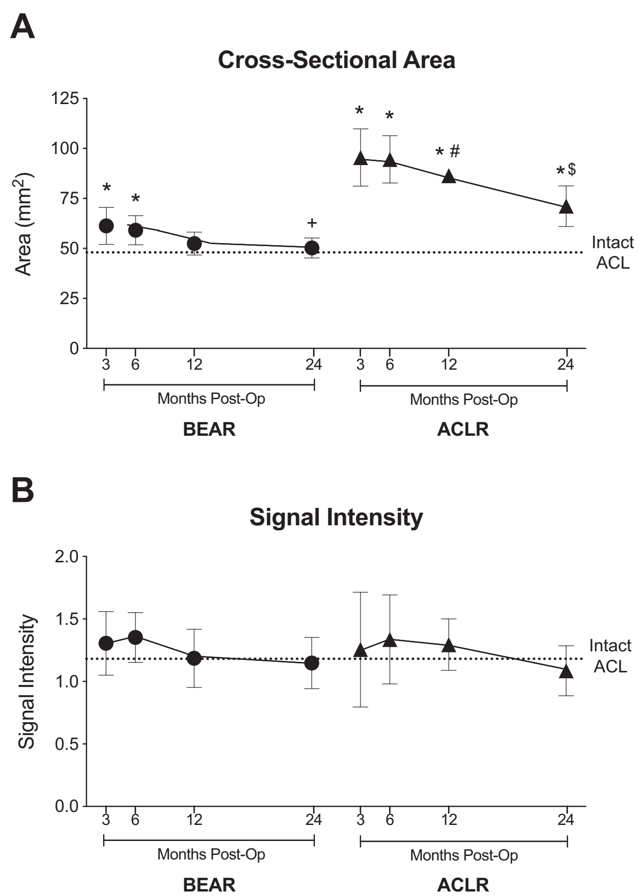
[a]Values are presented as mean ± SD. ACL, anterior cruciate ligament; ACLR, anterior cruciate ligament reconstruction; BEAR, bridge-enhanced ACL repair.
[b]Normalized to the ACL length.

Time-Dependent Changes in Cross-sectional Area

The cross-sectional area measurements from the MRI were highly reproducible (intraclass correlation coefficient, 0.959). The time-dependent changes in ACL or graft cross-sectional area are shown in Figure 3A. The ACL/graft cross-sectional area underwent significant changes within the first 2 years in both groups (BEAR: F = 6.0, df = 31.8, P = .001; ACLR: F = 28.4, df = 22.1, $P < .001$). At 3 months, the grafts had approximately double the cross-sectional area of the contralateral intact ACL ($P < .001$). Between 3 and 24 months, the ACL grafts decreased in cross-sectional area; however, they remained 48% larger than the native ACL at 24 months (P = .002). The ACLs treated with BEAR were 28% larger than the contralateral intact ACL at 3 months (P = .003). While the cross-sectional area of the repaired ACL remained significantly larger than that of the contralateral intact ACL at 3 and 6 months (P = .019), it became similar in size at 12 and 24 months after surgery ($P > .9$).

Time-Dependent Changes in Signal Intensity

The signal intensity measurements were highly reproducible (intraclass correlation coefficient, 0.909). The time-dependent changes in ACL or graft signal intensity are shown in Figure 3B. The ACL/graft signal intensities did not significantly change within the first 2 years in either group (BEAR: F = .7, df = 25.9, P = .605; ACLR: F = 2.4,



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	Intact ACL	Months Post-Op 3	6	12	24
BEAR	N = 7	N = 10	N = 10	N = 9	N = 9
ACLR	N = 7	N = 10	N = 8	N = 6	N = 7

Figure 3. Time-dependent changes in ACL/graft (A) cross-sectional area and (B) signal intensity. (C) Sample size for each treatment group at every time point. Intact ACL values are from the contralateral intact knee imaged at 24 months. Mean ± SD. *$P < .02$ for comparisons with the contralateral intact ACL. +Smaller repaired ACL cross-sectional area at 24 months vs 3 months (P = .023). $Smaller reconstructed graft cross-sectional area at 24 months vs 3 months ($P <$ .001) and 6 months (P = .002). #SDs are smaller than the symbol (±2.2 mm^2). ACL, anterior cruciate ligament; ACLR, ACL reconstruction; BEAR, bridge-enhanced ACL repair.

df = 32.2, P = .075). The BEAR and ACLR groups had a slightly higher mean ligament signal intensity at 3 months when compared with the contralateral intact ACL, but these differences were not statistically significant ($P > .4$) (Figure 3B). The mean signal intensity of the repaired ACLs and reconstructed grafts trended to a maximum at 6 months before reduction to the levels seen in the contralateral intact ACL at 24 months, although none of these changes were statistically significant ($P > .1$).

Tunnel and Ligament Insertion Position

For the repaired group, the 4.5-mm tunnels used to place the suture cinch were not located within the femoral or tibial footprints, consistent with the surgical protocol for tunnel placement. The femoral tunnels were located anterior and inferior (closer to the bottom of the condyle) to the native ACL insertion ($P < .02$) (Appendix Figure A1, A and B, available online). The 4.5-mm tibial tunnel for the suture cinch was also anterior to the tibial footprint of the native ACL ($P < .001$) (Appendix Figure A1C). The repaired ACL had the same sagittal elevation angle as the contralateral intact ACL (49.8° ± 3.2° vs 49.8° ± 1.7°, P = .796) and coursed from insertion site to insertion site rather than from the femoral to tibia tunnel of the suture cinch. For the reconstructed group, the center of the 9-mm femoral tunnel was anterior to the center of the femoral insertion site ($P < .001$) (Appendix Figure A1A) and in the same superior-inferior location as the native ACL insertion site (P = .795) (Appendix Figure A1B). The 9-mm tibial tunnels were slightly posterior to the tibial footprint of the native ACL (P = .003) (Appendix Figure A1C). The reconstructed grafts coursed from tibial to femoral tunnels and were more vertical than the contralateral intact ACL (55.8° ± 2.6° vs 49.3° ± 1.0°, P = .005).

Associations Between Anatomic Features of the Knee and Repaired ACL Cross-sectional Area and Signal Intensity

The regression analyses for the associations between the anatomic features of the knee and the repaired ACL cross-sectional area and normalized signal intensity at 24 months after surgery are presented in Table 2. For healing ligaments (BEAR group), the normalized femoral stump length, lateral tibial slope, and medial tibial depth were significantly correlated with the signal intensity of the repaired ligament (Figure 4) ($P < .05$ for all associations), while the pre- and postoperative notch size and performance of a notchplasty were predictive of the cross-sectional area of the repaired ligament at 24 months postoperatively (Figure 5) ($P < .05$ for all associations).

A longer femoral stump before surgery was associated with a lower signal intensity (closer to normal ligament) of the BEAR ligament (Figure 4A), as were a smaller lateral tibial slope and larger medial tibial depth (Figure 4, B and C). A longer tibial stump was not associated with a lower signal intensity or larger cross-sectional area (Table 2) ($P > .12$).

The pre- and postoperative width of the notch as well as the extent of notchplasty (notch enlargement) correlated with increased cross-sectional area of the repaired ACL at 24 months (Figure 5).

Associations Between Anatomic Features of the Knee and ACL Graft Cross-sectional Area and Signal Intensity

The regression analyses for the associations between the anatomic features of the knee and the ACL graft cross-

TABLE 2
Regression Coefficients for the MRI-Based Predictors of the Repaired ACL at 24 Months: Cross-sectional Area and Signal Intensity[a]

	Cross-sectional Area			Signal Intensity		
	β (95% CI)	R^2	*P* Value	β (95% CI)	R^2	*P* Value
Contralateral intact ACL						
Signal intensity	–0.66 (–36.52 to 35.20)	.00	.964	0.64 (–0.49 to 1.76)	.30	.204
Cross-sectional area	0.42 (–0.74 to 1.57)	.15	.395	0.01 (–0.03 to 0.06)	.11	.457
Normalized stump length[b]						
Femoral	–0.15 (–0.74 to 0.44)	.05	.566	–0.01 (–0.03 to 0.00)	.46	**.045**
Tibial	0.09 (–0.51 to 0.68)	.02	.746	0.01 (0.00 to 0.03)	.30	.129
Tibial slope						
Lateral	0.11 (–2.37 to 2.59)	.00	.919	0.07 (0.01 to 0.12)	.57	**.019**
Medial	0.44 (–1.77 to 2.66)	.03	.651	0.05 (0.00 to 0.11)	.39	.075
Medial tibial depth	–0.21 (–7.07 to 6.66)	.00	.945	–0.17 (–0.32 to –0.01)	.48	**.039**
Notch width						
Preoperative	3.51 (0.39 to 6.64)	.50	**.033**	0.05 (–0.09 to 0.18)	.09	.434
Postoperative	1.89 (0.76 to 3.03)	.69	**.006**	0.01 (–0.05 to 0.08)	.03	.639
Amount of notchplasty	3.06 (1.17 to 4.95)	.68	**.007**	0.01 (–0.10 to 0.11)	.01	.852

[a]For all, n = 9 (except normalized signal intensity and cross-sectional area of the contralateral intact ACL, n = 7). Significant associations are highlighted in bold, $P < .05$. β is a regression slope, representing change in the outcome per unit change in the predictor. ACL, anterior cruciate ligament; MRI, magnetic resonance imaging.
[b]Normalized to total ACL length.

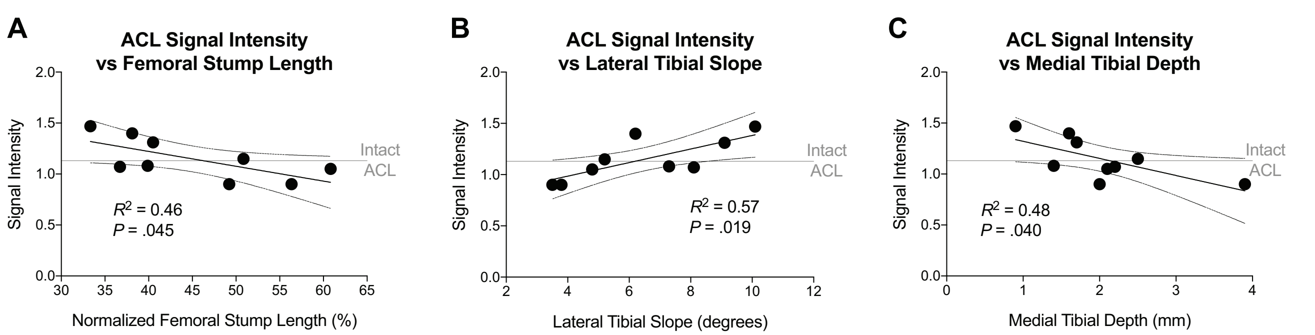

Figure 4. Associations between BEAR ACL signal intensity at 24 months with (A) femoral stump length (normalized to ACL length), (B) lateral tibial slope, and (C) medial tibial depth. n = 9. Dotted lines represent the 95% CIs. Horizontal line represents the mean signal intensity of the contralateral intact ACL. ACL, anterior cruciate ligament; BEAR, bridge-enhanced ACL repair.

sectional area and signal intensity at 24 months after surgery are presented in Table 3. None of the anatomic features of the knee were predictive of either graft cross-sectional area or signal intensity at postoperative 24 months.

DISCUSSION

Despite the similarities in patient-reported outcomes, AP laxity of the knee, and functional hop testing between the BEAR and ACLR procedures,[38] this study identified differences in how the average cross-sectional area of the reconstructed graft and repaired ACL change within 2 years after ACL surgery. The observed changes in cross-sectional area and normalized signal intensity suggest that reconstructed grafts continue to remodel over the first 2 years after surgery, whereas the remodeling of the repaired ACL primarily happens within the first year. The results highlight the ability of the BEAR procedure to restore the signal intensity and anatomic properties (ie, area and orientation) of the torn ACL to those of the native ACL, while ACLR resulted in significantly larger and more vertical grafts at 2 years. Unlike ACLR grafts, the repaired ACL size and normalized signal intensity at 24 months correlated with the preoperative ACL femoral stump length, lateral tibial slope, medial tibial depth, and femoral notch size.

The ACL grafts were significantly larger than the contralateral intact ACLs. This was previously noted on MRI performed 3 years postoperatively (>30% larger).[23,56,58] The cross-sectional area is considered a determinant of the maximum load that a structure can bear.[6,7] As such,

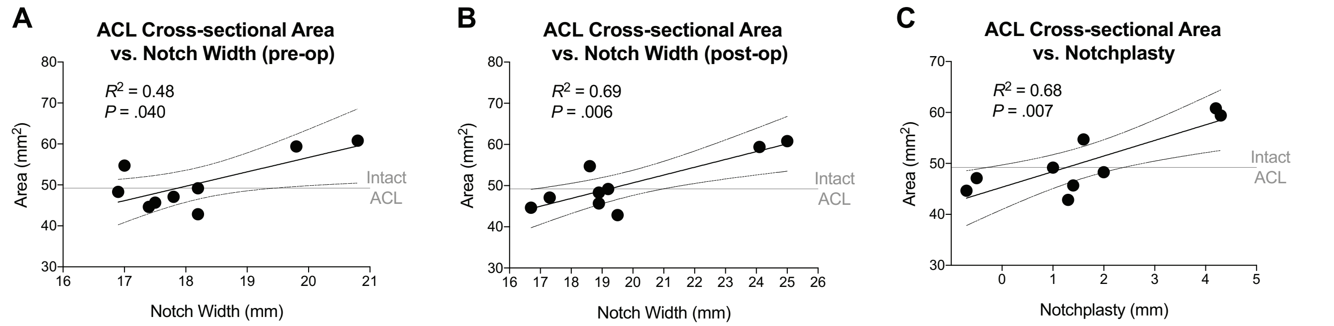

Figure 5. Associations between ACL cross-sectional area of the BEAR group at 24 months and (A) pre- and (B) postoperative notch width and (C) notchplasty. n = 9. Dotted lines represent the 95% CIs. Horizontal line represents the mean cross-sectional area of the contralateral intact ACL. ACL, anterior cruciate ligament; BEAR, bridge-enhanced ACL repair.

TABLE 3
Regression Coefficients for the MRI-Based Predictors of the Reconstructed Graft at 24 Months: Cross-sectional Area and Signal Intensity[a]

	Cross-sectional Area			Signal Intensity		
MRI-Based Predictors	β (95% CI)	R^2	*P* Value	β (95% CI)	R^2	*P* Value
Contralateral intact ACL						
Signal intensity	–11.02 (–44.45 to 22.42)	.13	.436	0.16 (–0.46 to 0.79)	.08	.529
Cross-sectional area	0.32 (–0.50 to 1.14)	.16	.368	–0.01 (–0.02 to 0.01)	.28	.224
Normalized stump length						
Femoral	0.31 (–1.12 to 1.75)	.06	.600	0.02 (0.00 to 0.04)	.53	.062
Tibial	–0.35 (–1.20 to 0.50)	.18	.339	–0.01 (–0.02 to 0.01)	.30	.203
Tibial slope						
Lateral	–2.92 (–8.06 to 2.23)	.30	.205	0.04 (–0.07 to 0.14)	.13	.418
Medial	–2.38 (–6.51 to 1.76)	.30	.200	0.05 (–0.03 to 0.12)	.33	.174
Medial tibial depth	1.27 (–17.09 to 19.62)	.01	.866	0.06 (–0.27 to 0.39)	.04	.668
Notch width						
Preoperative	1.09 (–2.50 to 4.68)	.11	.609	–0.03 (–0.09 to 0.03)	.26	.246
Postoperative	0.13 (–4.29 to 4.56)	.01	.941	–0.02 (–0.10 to 0.06)	.06	.604
Amount of notchplasty	–2.23 (–7.32 to 2.87)	.20	.312	0.04 (–0.05 to 0.13)	.20	.311

[a]For all analyses, n = 7. There were no significant associations. β is a regression slope, representing change in the outcome per unit change in the predictor. ACL, anterior cruciate ligament; MRI, magnetic resonance imaging.

this increased cross-sectional area would predict that the grafts would be able to support greater loads than the native ACL, assuming equal material properties, and thus possibly decrease the risk of graft failure when a potentially injurious load is placed upon it. We were unable to determine if an increased cross-sectional area was associated with a lower failure rate, as none of the patients in this study had a ligament failure during the study; however, prior studies reported that larger grafts promote a lower failure rate.[12,31] Last, decreases in graft cross-sectional area within the first year after surgery were previously reported,[1] although the reasons for the decrease in size of the graft over time are unknown and whether this trend will continue requires a longer-term imaging study.

Increased normalized signal intensity has been associated with histologic changes in the ACL, including the presence of inflammatory cells, actively synthesizing fibroblasts, and less collagen and blood vessel organization and orientation.[8] Signal intensity measures, which reflect the "maturation" of ligament healing, have been used to evaluate outcomes and the factors that may influence outcomes after ACLR.[24,27,28,42,44,50,51,55] In a cohort of patients undergoing ACL reconstruction, Li et al[27] showed significant correlations between signal intensity and (1) physical activity and (2) time from surgery—both of which were sex dependent. Rose and Crawford[50] compared 2 types of allografts for ACLR using signal intensity. They determined that "graft maturity" was dependent on the position of the tibial tunnel and the sagittal plane orientation of the graft, although there were no differences between the graft types (hamstring tendon vs tibialis anterior). Signal intensity measures were also used to compare graft types,[28,55] tunnel placement,[24,51] and biologic augmentation.[42,44] In this study, the signal intensity was similar in both groups, with a trend toward a higher signal intensity (more disorganized tissue) at 3 and 6 months and normalization by 12 and 24 months. These observations are consistent with a prior preclinical study of repaired ligaments, which demonstrated an improvement in the histologic ligament maturity index after surgery.[49] It is difficult to directly compare signal intensity values across studies, as the signal intensity magnitude is dependent on the hardware, sequence, sequence parameters, and normalization process selected,[7] which vary across studies. This is a limitation of using signal intensity as an outcome measure, particularly for multicenter studies. Work is currently under way to implement and optimize relaxometry methods (eg, T_2* relaxation time),[2,3,7,8] which are theoretically less dependent on hardware and postprocessing and would provide consistency across platforms, institutions, and trials.[7] While the current study used a different imaging protocol, normalization structure, and analysis technique from prior clinical studies of ACLR, the overall finding of higher signal intensity early on and normalization afterward is consistent with prior reports of (1) temporal changes in ACL graft signal intensity within 1 year after ACLR,[26] (2) decreasing signal intensity of grafts as the postoperative interval increases,[27,43] and (3) decreased metabolic activity of the grafts as assessed by positron emission tomography–MRI.[30] Moreover, normalized signal intensity measures obtained with the same hardware and sequence within a study provide insight into the integrity of the healing ligament or graft.

The more vertical sagittal orientation seen in the ACL grafts in this study is consistent with that observed for ACL grafts placed via an anteromedial portal technique (55° for grafts placed with an anteromedial portal and 64° with a transtibial technique)[57] and has been associated with increased cartilage damage in preclinical models.[20] Interestingly, the nonanatomic tunnel placement for the suture cinch used among the BEAR patients did not alter the sagittal orientation of the healing ACL, which healed with a sagittal orientation identical to that of the native ACL. On MRI, the repaired ACL was found to course from insertion site to insertion site, rather than from the femoral cinch tunnel to the tibial cinch tunnel. The insertion-to-insertion healing also suggests that the BEAR procedure may preserve the anatomy of the ACL footprints, which was shown to influence ACL tension patterns and knee biomechanics.[22]

While none of the anatomic parameters measured here influenced the graft cross-sectional area or signal intensity, several parameters significantly affected the healing ACL, including modifiable factors (notch size), nonmodifiable factors (femoral stump length, medial tibial depth), and potentially modifiable factors (lateral tibial slope). A greater notch width was associated with a bigger repaired ACL cross-sectional area. A large notch can be indicative of a larger native ACL, which can ultimately lead to a larger repaired ACL. Performance of a notchplasty had a reasonably large effect on the cross-sectional area of the healing ACL, with every millimeter of notchplasty leading to a 3-mm^2 (6%) increase in ACL cross-sectional area. This finding was most evident by observed variations in repaired ACL cross-sectional area, which was strongly correlated with the side range of postoperative notch width and notchplasty, as shown in Figure 5. As cross-sectional area is a primary determinant of the maximum load that can be withstood by the ACL, performance of a notchplasty during a BEAR procedure may be a reasonable surgical choice; however, further studies are needed to determine the long-term outcomes of adding this to the procedure.

Smaller femoral stump length, shallower medial tibial depth, and steeper posterior slope of the lateral tibial plateau resulted in significant increases in normalized signal intensity of the healing ACL. Although these features are not easily modifiable, they may potentially be considered biomarkers to predict the risk of reinjury[25,52] and inferior postoperative outcomes.[21] While the tibial stump is pulled toward the femur and into the scaffold with sutures, the femoral stump is not tensioned during the BEAR procedure. Thus, a longer femoral stump may more easily provide a greater length of low-intensity ACL fibers in the gap between the insertion points, leading to a more organized (lower signal intensity) healing ACL. Lateral tibial slope and medial tibial depth have both been shown to influence knee biomechanics[17,33,34] and ACL loading.[29,34] A steep lateral tibial slope and shallow medial tibial depth were previously associated with increased risk of ACL injury.[4,18] Increased lateral tibial slope and decreased medial depth can lead to additional AP[19,40] and rotational[19,24,58] instability and increased ACL loading, which may be detrimental to collagen organization in the early phases of healing after BEAR. If this last hypothesis were verified, the risks associated with a higher tibial slope might be mitigated by utilizing a more conservative rehabilitation protocol for these patients. Further work to investigate this hypothesis is needed.

There were several limitations to this study. The first was the small sample size in each group. This study was a first-in-human safety study of a new medical device. FDA approval for these initial safety studies is typically limited to those with small sample sizes such that few patients will suffer an adverse event if the device is found to have a high rate of failure or infection. Second, the total ACL length was quantified from the preoperative MRI. While we attempted to scan all knees in a standardized way, small differences in knee subluxation may have resulted in measurement errors in quantifying total ACL length. Third, while the association of healing ACL cross-sectional area and preoperative notch width appears to rely on the 2 patients with very large notch widths (see Figure 5A), the associations to postoperative notch width (Figure 5B) and notchplasty (Figure 5C) better depict the nature of these relationships by demonstrating small ACL areas in patients with smaller notch widths and less notchplasty and the largest ACL areas in those with bigger notch widths and more notchplasty. These graphs also show how patients with average notch width and notchplasty had an average ACL cross-sectional area. Fourth, the contralateral ACL-intact knee was imaged only at 2 years because of imaging time constraints. Longitudinal assessment of the contralateral knee could have helped to better investigate the time- and treatment-dependent changes in the treated ACL. Last, this was a cohort study rather than a randomized controlled trial. This was due to the fact that this was a first-in-human trial, and the study team and surgeons thought that there was not sufficient equipoise to ethically conduct a randomized controlled trial. Thus, the participants in the trial were allowed to choose the treatment arm they wished to be in—a study design that has the potential to introduce a selection bias. Further studies with larger numbers of patients and a randomized controlled design are planned.

In conclusion, postoperative MRI of healing ACL grafts and repaired ACLs suggests that ACL grafts with autograft hamstring tendon are larger and more vertically oriented than both the native ACL and the repaired ACL. The time-dependent changes in signal intensity suggest that the repaired ligaments and grafts undergo a period of maturation, with both groups attaining average signal intensities similar to those of the contralateral intact ACLs by 12 (repaired group) and 24 (ACLR group) months after surgery. The results here also suggest that the cross-sectional area of the repaired ACL may be affected by notch width, while the signal intensity of the repaired ACLs appeared to be correlated with specific anatomic features—observations that deserve further study in a larger cohort of patients. These findings suggest that MRI techniques can be used to noninvasively monitor the healing and maturation of ACL grafts and repaired ACLs after surgery.

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