

# DeNovo NT Allograft

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Articular cartilage repair is a continually evolving and often controversial area of sports medicine as the result of variable outcomes, contrasting opinions, and lack of a single reliable resurfacing option in this often complex heterogeneous patient population. Although many articular cartilage lesions are asymptomatic, others cause significant disability in patients who are not optimal candidates for arthroplasty procedures. To address this subset of patients, many techniques have evolved in an effort to repair chondral or osteochondral lesions. Current techniques that are most commonly used include microfracture, autologous osteochondral transfer, autologous chondrocyte implantation (ACI), and allograft osteochondral transplantation.<sup>1-11</sup>

In general, the literature demonstrates fair to good results for these various procedures performed in appropriate patients. However, there is significant variation and controversy in the literature and amongst peers regarding the outcomes, indications for, and resultant repair tissue generated with some of these procedures. Concomitant procedures such as unloading osteotomies or realignment procedures, which may be integral to the success of an articular resurfacing procedure, also create patient heterogeneity when interpreting results. Inherent to each of the current treatment options are drawbacks or limitations, and thus, modification of these techniques vs the development of novel procedures are continually explored. More recent techniques for cartilage repair include subsequent generations of ACI, tissue-engineered constructs, as well as techniques utilizing minced or particulated cartilage fragments.<sup>12-18</sup> One of the minced cartilage techniques, termed *DeNovo* NT (natural tissue), utilizes juvenile articular cartilage and has been commercially

available since 2007. The viable articular cartilage allograft is harvested from juvenile donors, particulated into chondral fragments, and maintained in storage medium between 19°C and 26°C for up to 49 days (procurement to current expiration date). The particulated allograft chondral fragments are subsequently secured into recipient patient defects in a single-stage procedure utilizing fibrin adhesive.

## Basic Science and Rationale of Juvenile Articular Cartilage Allograft

In contrast to more mature chondrocytes where senescence is reported to proceed as a consequence of aging, juvenile chondrocytes have been shown to demonstrate greater potential for cell division and matrix production<sup>19,20</sup> (Fig. 1). A recent study has specifically demonstrated that juvenile, in contrast to adult, chondrocytes express significantly greater levels of mRNA for aggrecan and collagens type II and IX, key components of hyaline extracellular matrix.<sup>19</sup> On average, juvenile articular cartilage also contains 4-fold greater numbers of viable cells than adult articular cartilage (Fig. 2). In specifically examining fragments of chondral tissue, juvenile chondral fragments in culture produced more proteoglycans and collagen type II than mature chondral fragments.<sup>20</sup> With a greater number of chondrocytes present in the juvenile cartilage, an enhanced potential for cellular proliferation, and the ability to synthesize extracellular matrix collagen and proteoglycan, it would serve to reason then that transplantation of juvenile cartilage allograft could be effective to produce and enhance repair tissue in the treatment of chondral defects.

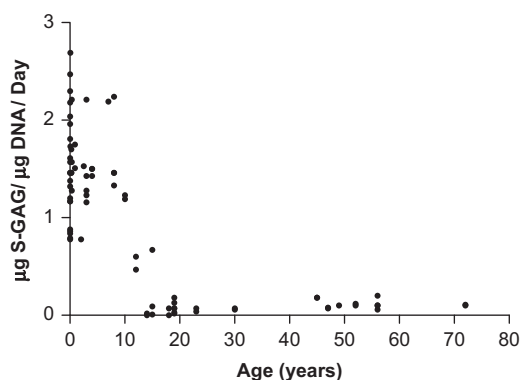
In addition to the effects of juvenile chondral tissue on this technique, the sealant used to affix the chondral fragments may also have some effect on the success of this implant. In the same study where it was demonstrated that juvenile chondral fragments have greater outgrowth potential than mature tissue, it was also demonstrated in vitro that fibrin

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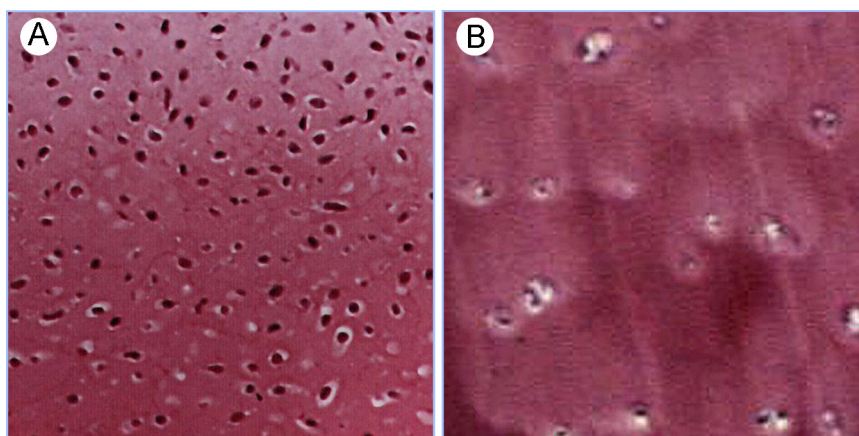


**Figure 1** Biosynthetic activity of chondrocytes as a function of age.

sealant supported chondrocyte outgrowth such that many of the adjacent fragments were connected by newly deposited extracellular matrix, suggesting that chondrocyte outgrowth is affected by the local presence of chemokines or adhesion proteins. Unpublished observations by the present authors have shown significantly greater potential for in vitro cellular outgrowth when particulated juvenile cartilage is grown on tissue culture surfaces that are treated with serum-derived adhesion proteins. By day 35, using a gap-defect model, juvenile cartilage demonstrated solid integration between adjacent fragments with an approximate distance of 0.25-0.5 mm. Histologic sectioning failed to disrupt the hyaline matrix deposited between fragments (Fig. 3). Specific to fibrin, the serum-derived sealant used in particulated juvenile chondral allograft implantation, many authors have shown suspension of chondrocytes in fibrin, both in vitro and in vivo, stimulates cellular migration and proliferation, while maintaining native synthesis of an extracellular matrix rich in type II collagen and proteoglycan.<sup>21-25</sup> The authors have seen the integration of human juvenile cartilage fragments maintained in vitro in commercial fibrin (Fig. 4). In fact, it has been reported that chondrocytes suspended in fibrin are capable of integrating with fragments of devitalized articular cartilage in vivo, suggesting that integration of particulated juvenile cartilage with chondropenic cartilage comprising a well-shouldered defect can be achieved clinically.<sup>26</sup>

Several other potential advantages exist with this technique in addition to the outgrowth potential of juvenile chondrocytes and the effects of the fibrin sealant. In contrast to the various ACI procedures, this is a single-stage procedure. There is no potential donor site morbidity. Thus far, there has not been the supply or sizing constraint as seen with fresh osteochondral allografts. The procedure does not require violation of the subchondral plate such as with microfracture, which has been shown to possibly compromise the outcomes of a subsequent ACI procedure if the marrow-stimulating procedure is unsuccessful.<sup>27,28</sup> In comparison with ACI procedures, the cost is relatively lower (currently \$4440 per packet), but is also dependent on the size of the lesion and number of packets used. Once the fibrin glue has solidified during the surgical procedure, the implant is likely somewhat more resistant to shear and compressive forces than microfracture. Finally, the technical aspects of the procedure are performed with relative ease with a minimal learning curve.

As with any tissue allograft, there is the potential for disease transmission, although this risk is mitigated by extensive serological testing and viral screening by the tissue processor. DeNovo NT is aseptically processed and cannot be terminally sterilized as this would compromise viability of resident chondrocytes. All tissue is procured and processed by American Association of Tissue Banks-accredited tissue banks. Chondral fragments are sized to 1 mm<sup>3</sup> to minimize cellular death, optimize potential for cellular outgrowth, and allow treatment of joint surfaces displaying a range of curvature. The current inclusion criterion for donor age is 29 days to 12 years, donors older than 13 years are not included in the study. An assessment of the mean age of tissue procured between 2007 and 2012 and processed for DeNovo NT packaging shows a random distribution, with a mean and standard deviation of 4.10 ± 3.66 years (range, 1 day to 12.33 years), of which nearly 50% is represented by donors <3 years. The authors are aware of cases of hypertrophy, and there is the possibility that donor's age may play a role in this, but this remains unstudied. Articular cartilage has been previously known to be immune privileged at least in part owing to chondrocytes being surrounded by a matrix that isolates them from the host immune cells.<sup>29</sup> Adkisson

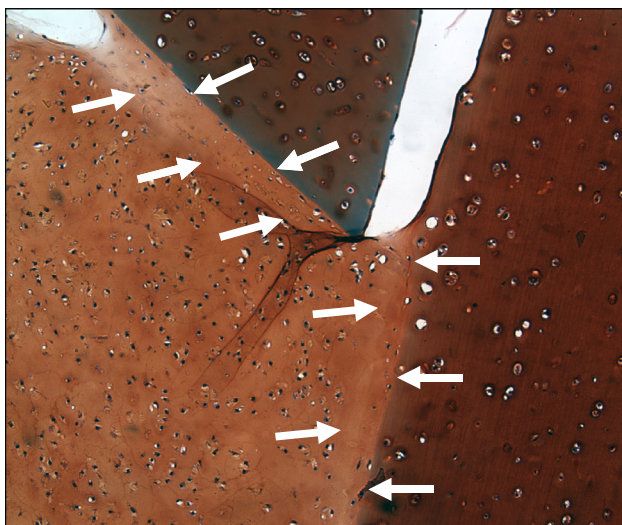


**Figure 2** Comparison of chondrocyte density in human juvenile (A) and adult (B) articular cartilage. (Color version of figure is available online.)

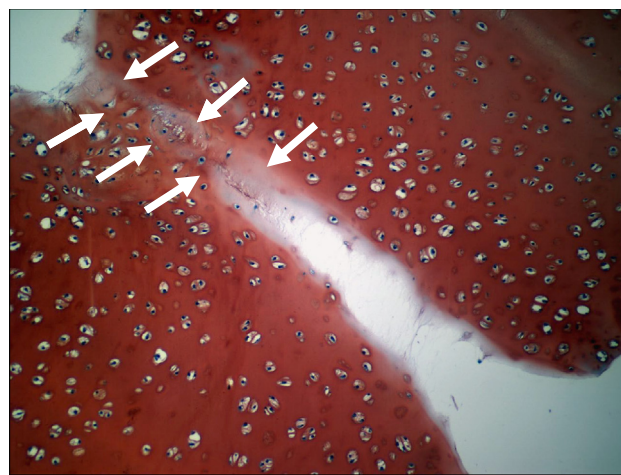
et al. have also reported that isolated juvenile chondrocytes are immune privileged, and there are no reports of immunogenic responses to the tissue thus far.<sup>30</sup>

## Indications

Cartilage injury represents a spectrum of disease with both patient- and lesion-specific factors affecting treatment and prognosis. Different treatment algorithms have been proposed which attempt to direct treatment based on these factors. There is enduring controversy and contrasting opinion, however, regarding the optimal treatment of symptomatic cartilage lesions. Most surgeons develop personal treatment preferences guided by training, published literature and outcome data, education conferences, expert opinion, and personal experience. As a recently developed cartilage-repair technique, the role of *DeNovo* NT has not been clearly defined. Currently, *DeNovo* NT has been utilized in more than 5000 patients since its introduction in 2007. Its primary clinical applications to date have been in the knee and ankle. Indications for this procedure are still in evolution and certainly subject to debate vs other repair options. As with virtually all articular cartilage-repair procedures, focal, unipolar, nondegenerative, full-thickness cartilage defects in younger individuals without uncorrected malalignment or maltracking would likely have better outcomes compared with others. This population, therefore, represents the best indications for this procedure. It may, however, be used in more than 1 lesion, but is not intended for generalized chondral disease such as in osteoarthritis. Although *DeNovo* NT has been utilized successfully for chondral lesions throughout different locations of the knee, the authors' have found it to be quite useful in addressing patella defects which can be clinically challenging.<sup>31</sup> More traditional options are generally less successful in the patella as compared with other areas of the knee.<sup>32-38</sup> Thus far, this technique seems to yield reasonably good results and yet is a relatively



**Figure 3** Integration of 3 adjacent fragments of *DeNovo* NT observed at day 35 of culture. (Color version of figure is available online.)



**Figure 4** In vitro integration of *DeNovo* NT suspended in fibrin sealant. (Color version of figure is available online.)

straightforward single-stage procedure.<sup>12,31,39-41</sup> It is not yet clear what role this technique may play in the setting of osteochondral lesions with osseous defects, but the authors and others have utilized *DeNovo* NT with associated subchondral bone loss or cystic change less than 5-6 mm. Appropriate lesion size also has so far been poorly defined.

## Surgical Technique

There are 2 general techniques which may be utilized when implanting the *DeNovo* NT graft into a defect. Both are described because each may have advantages in different settings. The first, which is termed the “foil template” technique, was originally advocated as the technique of choice.<sup>42</sup> This technique essentially utilizes a foil mold to create a *DeNovo* NT or fibrin glue–composite graft which is subsequently implanted and fixed into the defect with fibrin glue. An alternative technique, which is technically easier when it is possible to be utilized, bypasses the foil mold and directly implants the *DeNovo* NT cartilage tissue into the defect.

Defect preparation is identical with both methods. Typically a tourniquet is placed and may or may not be inflated based on surgeon discretion. A miniarthrotomy is performed to access the defect. Of note, patella defects may be accessed through a relatively small incision and the patella can be partially or fully everted by extending the arthrotomy both proximally and distally through the relatively smaller skin incision. Utilizing both a No. 15 blade and sharp curettes, the lesion is debrided to leave a relatively healthy, contained defect if possible (Fig. 5). Remove the calcified cartilage layer from the base of the defect without damaging the subchondral bone plate. Any subchondral cysts or bone defects are debrided to healthy bone as well. Subchondral bone bleeding should be stopped if present. Unlike the preparation of a defect for ACI, however, hemostasis may be achieved with the fibrin glue which is also utilized for graft fixation. Subchondral bone loss less than 6 mm can be filled with either localized autologous bone graft or *DeNovo* NT graft. It should



**Figure 5** The lesion is debrided to relatively healthy tissue leaving a contained, well-shouldered defect. (Color version of figure is available online.)

be noted, however, that the effect of layering the *DeNovo* NT graft is poorly understood and likely not recommended, so anything deeper than 6 mm should probably be bone grafted.

### “Foil Template” Technique

The “foil technique” utilizes a thin sterile foil to make a mold of the recipient defect. Although this technique can be utilized for any defect, it is especially useful for more posterior condylar defects in which gravity may be working against you and cause the chondral fragments to fall out or displace when attempting to place them directly from the packet into the defect.

Following defect preparation, a thin piece of sterile foil is pressed into the defect paying particular attention to replicate the well-bordered vertical peripheral walls (Fig. 6). A flat-ended rod or freer elevator may be helpful in this preparation. The foil defect template is then taken to the back table to create the *DeNovo* NT graft or fibrin glue–composite implant.

Open the *DeNovo* NT packet carefully so that the cartilage fragments do not inadvertently spill out (Fig. 7). Using an 18-gauge needle or angiocath tip and syringe, aspirate and discard the fluid medium so that the cartilage fragments remain. The tip of a sterile sponge or gauze can be helpful in completing this step. Transfer the *DeNovo* NT cartilage fragments into the foil mold evenly dispersing them across the base of the mold. Remove any remaining medium fluid from the foil by gently poking a few small holes into the base of the foil and allowing it to drain out.

Gently apply the fibrin glue product so the mold is filled approximately 75% of the way to the top (Fig. 8). The fragments would thus become fixed within the fibrin adhesive once they dry in 5–10 minutes. With a deeper defect, such as in the patella, you may wish to layer the *DeNovo* fragments by repeating these steps. Once dry, the completed graft may be



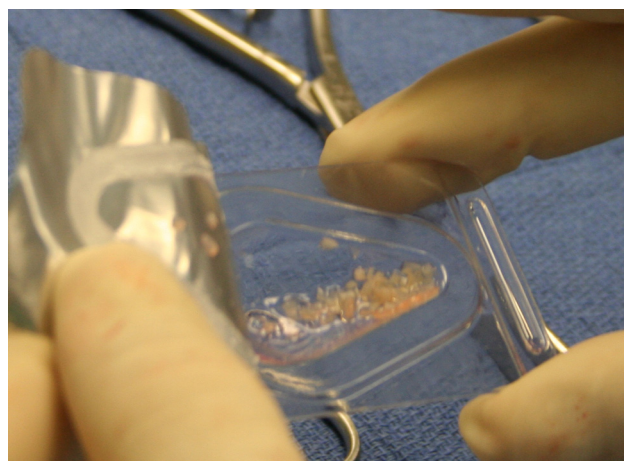
**Figure 6** A thin piece of sterile foil is pressed into the defect paying particular attention to replicate the well-bordered vertical peripheral walls. Figure used with permission from Zimmer Holdings Inc (Warsaw, IN). (Color version of figure is available online.)

lifted off the foil template with an elevator. It is important to identify the orientation of the graft relative to the recipient site when it is not obvious. Marking the “North” end of the foil and graft with a surgical marking pen may be useful. Ensure the recipient site is dry by dabbing with a surgical gauze.

Place a thin layer of fibrin adhesive to the recipient site. Gently implant the *DeNovo* NT graft in the proper orientation so that it fits properly. Typically you would need to dry off excessive fibrin adhesive. You also want to make sure the graft is slightly recessed (approximately 0.5 mm) below the native articular surface. A number of instruments including a finger can assist in applying light pressure and maintaining reduction of the graft within the defect until it is dry (typically 5–10 minutes). Once you are sure the adhesive is completely dry, you may bring the joint through a gentle range of motion.

### “Direct” Technique

Quite simply the *DeNovo* NT cartilage fragments are placed directly into the prepared defect where they are secured with



**Figure 7** The packet is opened carefully to avoid spilling the fragments. (Color version of figure is available online.)

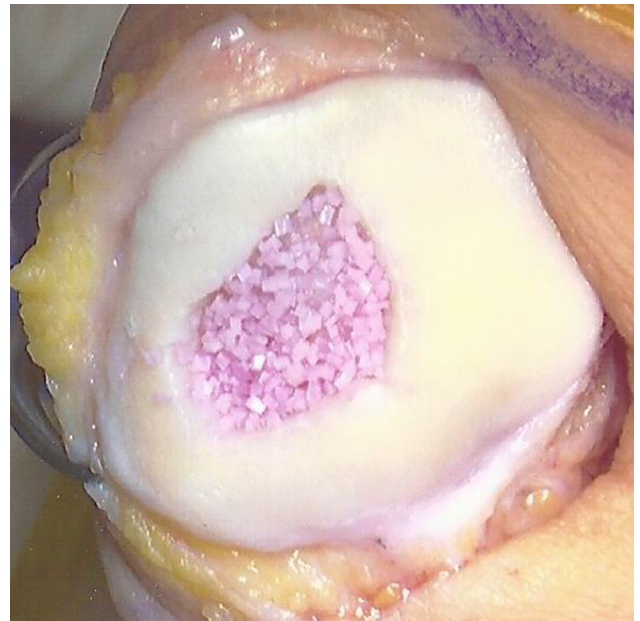


**Figure 8** Creating the *DeNovo* NT composite implant within the foil mold. Figure used with permission from Zimmer Holdings Inc (Warsaw, IN). (Color version of figure is available online.)

the fibrin adhesive. As long as the defect is in a location in which gravity is not causing the fragments to fall out or become dislodged, this technique is quite straightforward. A thin layer of fibrin adhesive is placed at the base of the defect. The *DeNovo* NT fragments are carefully transferred directly onto the fibrin layer as evenly dispersed as possible (Figs. 9 and 10). Then, another layer of fibrin adhesive is used to cover the cartilage pieces and hold them in place (Fig. 11). The authors recommend that the ultimate composite graft level is just below the native surrounding articular cartilage. In regions where the defect is deeper than what can be accomplished with a single *DeNovo* NT layer, you can either place a thicker layer of *DeNovo* cartilage fragments or create individual layers by repeating the process over the initial composite layer. This situation may be encountered



**Figure 9** Utilizing the “direct” technique, fragments are implanted directly into the prepared defect. (Color version of figure is available online.)



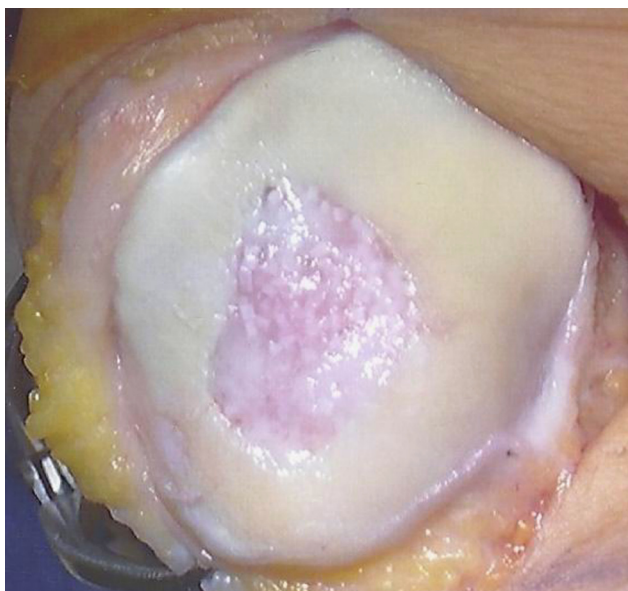
**Figure 10** *DeNovo* NT fragments are evenly dispersed into the defect within the fibrin adhesive. (Color version of figure is available online.)

with subchondral bone loss or patella lesions where the native articular cartilage is thickest. Make sure the final graft is completely dry before performing gentle range of motion to ensure stability of the graft (Fig. 12).

In the opinion of the authors, the direct technique is more reproducible and should be used when possible. However, the direct technique is dependent upon the *DeNovo* NT chondral fragments maintaining stability within the defect until they can be fixed with fibrin adhesive. This stability is primarily affected by gravity as well as the adhesiveness of the minced chondral fragments. To optimize the effect of gravity on the fragments, the table may be tilted or the patella may be fully or partially everted or both for those specific defects.



**Figure 11** An additional layer of fibrin is placed over the *DeNovo* NT fragments. (Color version of figure is available online.)



**Figure 12** The graft is allowed to dry over 5-10 minutes. Once it is dry, the knee can begin range of motion. (Color version of figure is available online.)

## Miscellaneous

As when contemplating any articular cartilage procedure, it is critical to consider other factors potentially affecting the joint which may have contributed to the development of the chondral lesion or influence the outcome of a repair procedure. As such, it may be necessary to perform concomitant realignment procedures, ligamentous reconstruction, or address meniscal deficiency.

A frequent dilemma when choosing to utilize *DeNovo* NT for the treatment of a chondral defect is how many packets should be ordered. Unfortunately, this question needs to be addressed in advance because the tissue graft cannot be sent back and refunded once shipped. The answer to this question may be difficult because it is currently unknown as to what is the optimal density of allograft tissue per unit area for a given lesion size. Currently, there is variability amongst surgeons because the answer is unknown. The recommendation from the company commercially marketing this product (Zimmer Holdings Inc, Warsaw, IN) has been “1 packet” of *DeNovo* NT per 2.5 cm<sup>2</sup>.<sup>42</sup> Many surgeons, however, including the authors, feel that probably twice this amount may be a more appropriate approximation to give the composite graft a more desirable *DeNovo* NT chondral fragment density. Other factors that play a role when ordering the graft include the following: magnetic resonance imaging scans (MRIs) often underestimate the size of articular cartilage defects and patellar articular cartilage is thicker than other locations. Thus more tissue may be required to fill patella defects relative to other sites. One word of caution is that hypertrophy has occasionally been noted, so attention should be paid to making sure that ultimately the defect is slightly underfilled by the final construct.

With either technique you would need to obtain and prepare the fibrin adhesives intraoperatively before allograft

implantation. You would need to allow adequate time for the frozen or refrigerated components of the fibrin to warm as per their individual instructions.

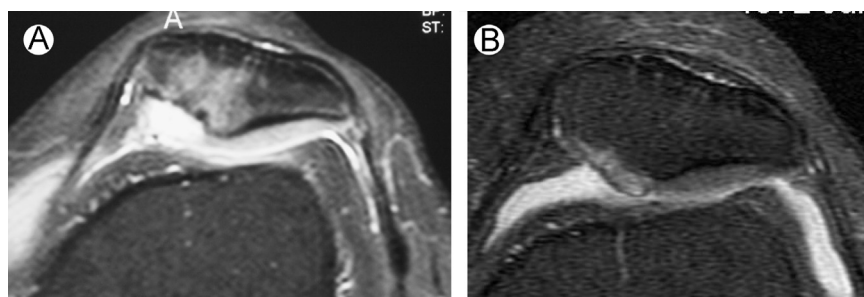
Although considered an off-label use, a commercially available type I or III collagen membrane is another potential consideration. This has been used, in conjunction with the *DeNovo* NT graft, by some surgeons to help protect larger uncontained lesions. This is the same membrane which is now commonly utilized as an off-label alternative to a periosteal patch when performing ACL. In ACL-recipient patients, this membrane has been shown to be safe; it also decreases reoperation rates owing to tissue hypertrophy as compared with autologous periosteum.<sup>43</sup> Outcomes of this technique in *DeNovo* NT patients have not yet been reported.

## Rehabilitation

The rehabilitation of *DeNovo* NT is dependent on the location, size, and stability of the implant as well as any concomitant procedures. Implant protection is initially similar to other cellular type of cartilage-repair techniques. Femoral or tibial lesions are often toe touch to 50% weight bearing for the first 6 weeks. Weight bearing is typically progressed as tolerated over 2-6 weeks after that point. More stable patella-femoral lesions may be weight bearing as tolerated locked in a brace (full extension) during ambulation for the first 6 weeks. Bracing may be discontinued once quadriceps strength is sufficient to allow ambulation without giving way. Therapy is initially focused on range of motion exercises. Continuous passive motion or biking without resistance or both are utilized for the first 6 weeks. Quadriceps sets and straight leg raises may also be done during the first 6 weeks, but quadriceps resistance exercises should be reserved until after 6 weeks. Higher patellofemoral force exercises are to be avoided for patella or trochlear lesions for at least 4-6 months. By the third month, patients may begin more aggressive strengthening and jogging, followed by agility and power work at approximately 4-5 months after the operation. Return to sports is generally deferred until 6 months or later.

## Results

The literature to date documenting results with this technique is sparse and consists of case reports. In the sports literature, there are 2 case reports or series. In a series of 4 patients, Farr and Yao documented improved clinical outcomes based on Knee Injury and Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee, and MRI evidence of graft durability in the short term.<sup>40</sup> In the original case report, Bonner et al. reported on a 36-year-old patient with an isolated full-thickness patellar defect treated with *DeNovo* NT. They also demonstrated improved outcomes on KOOS and International Knee Documentation Committee as well as MRI evidence of defect filling at the follow-up 2 years after the operation.<sup>12</sup> This patient has reported no decline in his knee pain or function at recent 5-year follow-up.



**Figure 13** (A) Preoperative MRI of full-thickness patellar defect. (B) Six-month postoperative MRI following cartilage repair utilizing the particulated juvenile cartilage allograft.

The authors have participated in a clinical study involving isolated patellar lesions from 15 knees in 13 patients. Some patients did undergo concomitant procedures such as medial patellofemoral ligament reconstruction or tibial tubercle transfer, but all patients underwent cartilage repair with *DeNovo* NT. Overall, good results based on International Cartilage Repair Society cartilage-repair assessment were demonstrated on MRI at minimum 6 months of follow-up (Fig. 13). Subjective scores from International Cartilage Repair Society, KOOS, Kujala, Tegner, and visual analog scale at a minimum of 6 months of follow-up also demonstrated good outcomes, with similar or slightly better scores to other cartilage-repair techniques in isolated patellar lesions.

There are also short-term case reports in the foot and ankle literature. One report in an active 30-year-old patient demonstrated she had returned to full activity by the sixth month and did not report any pain at 2 years.<sup>41</sup> A case series of 7 patients who underwent repair of osteochondral lesions of the talar dome with cylindrical demineralized cancellous allograft bone covered with particulated juvenile cartilage allograft demonstrated significant improvements in pain and function at 6 months.<sup>39</sup>

Many areas of study, however, still remain unreported. There is limited data on the histology of this allograft tissue after healing. At this point, it appears that it initially heals as a

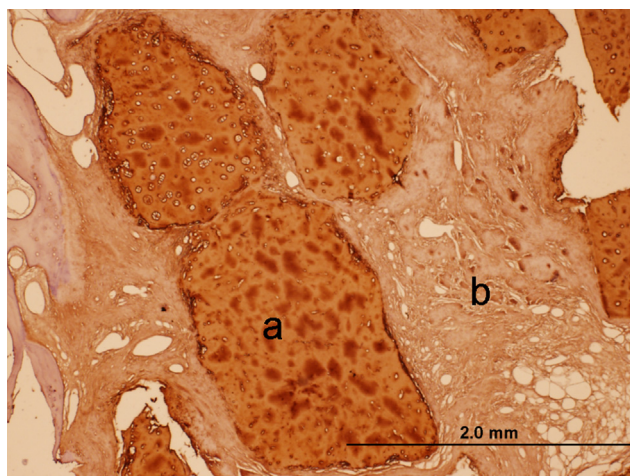
composite of the hyaline articular fragments within a bed of fibrous or fibrocartilaginous tissue. Perhaps somewhat analogous to a stone wall-type structure with the chondral fragments representing the stone and the more fibrous component representing the mortar (Fig. 14). It does appear that intimately opposed chondral fragments may heal to one another with bridging cells phenotypically similar to chondrocytes. It has yet to be shown if, and to what degree, the juvenile chondrocytes would migrate into the adjacent fibrous or fibrocartilaginous tissue and then produce extracellular matrix. Certainly, at this time, there is no evidence to suggest that there is reorganization into normal articular cartilage layer architecture. We do not have any information on the compressive strength. The fibrin likely makes the construct more resistant to shear than ACI, at least in the initial period, but the construct's resistance to shear forces over the long term is unknown.

## Summary

*DeNovo* NT is a particulated juvenile articular cartilage allograft which thus far seems to show promise in the challenging field of cartilage repair. It has many potential advantages, not the least of which is that it is a straightforward single-stage procedure. Limited reports seem to indicate relatively good early results with the demonstration of reproducible repair tissue fill by MRI in most cases. However, our enthusiasm to explore novel ideas to improve on current outcomes must also be tempered with appreciation of our past failures. Many questions remain unanswered regarding this procedure, the foremost being, does it offer reproducible advantages over alternative cartilage-repair techniques for particular patient cohorts. Further clinical studies would help better define the indications and clinical implications of this implant.

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**Figure 14** Six-month postoperative biopsy revealing particulated juvenile cartilage allograft fragments (a) within fibrous tissue (b). Note that there is bridging between fragments. (Color version of figure is available online.)

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