

# DeNovo NT Particulated Juvenile Cartilage Implant

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**Abstract:** Biological repair of focal chondral defects represents a significant clinical challenge as cartilage lacks intrinsic healing ability. Although it can be difficult to measure the objective success of cartilage repair techniques, the primary objective is symptom relief leading to less pain and improved function for the patient. Likely, the most important key to success is proper clinical indications. Second to this, the type of cartilage treatment utilized should be based on lesion location, size, depth, and other patient factors. One such treatment is DeNovo Natural Tissue. This method relies on the ability of juvenile chondrocytes to migrate from cartilage explants after being secured in a cartilage defect. Although approximately 8700 cases have been performed since 2007, long-term clinical outcomes are not yet available. However, basic science and early clinical data are promising.

**Key Words:** cartilage repair, juvenile cartilage, particulated cartilage, chondral repair, articular cartilage injury, DeNovo Natural Tissue (NT)

(*Sports Med Arthrosc Rev* 2015;00:000–000)

Articular cartilage defects of the knee cause pain and dysfunction, and can potentially lead to further degeneration.<sup>1,2</sup> Neither the innate healing process nor surgical restoration have the ability to restore native articular hyaline cartilage. Therefore, the primary aim of treatment is symptom relief with an attempt to change the natural history of the disease being a distant second. As our understanding of cartilage biomechanics and biochemistry has advanced, cartilage restoration options have evolved to include the following techniques: debridement, primary and augmented marrow stimulation or microfracture, autologous chondrocyte implantation, osteochondral autograft transfer, osteochondral allograft implantation, and most recently, particulated juvenile cartilage allograft.<sup>3</sup>

Classical tissue engineering dogma would suggest that the treatment of choice should include a viable and metabolically active cell source, an extracellular matrix that is conductive or inductive, and an environment to support development of the desired tissue.<sup>4</sup> Although this has clinically taken the form of autologous chondrocyte implantation (ACI; Aastrom Biosciences Inc., Cambridge, MA) or matrix augmented chondrocyte implantation (Aastrom Biosciences Inc., Copenhagen, Denmark), these techniques require rigorous Food and Drug Administration approval that can be cost-prohibitive to develop. Therefore, methods that eliminate the need for this approval (351 HCT/P

pathway) have gained popularity. Utilizing minced autograft (CAIS) or allograft [DeNovo Natural Tissue (NT), Zimmer Inc., Warsaw, IN] tissue is one such method that avoids the 351 pathway as this treatment demonstrates homologous use and is minimally manipulated, which makes it eligible for the less rigorous 361 HCT/P pathway. However, while avoiding the 351 pathway can be financially beneficial to reimbursing entities, it does not increase the likelihood of reimbursement by insurance companies. This is still best achieved through continued reporting of favorable patient outcomes to support the use of the product.

The basis of the particulated cartilage technique dates to 1983 when Albrecht et al<sup>5</sup> demonstrated in a rabbit model that using fragmented cartilage improved repair tissue in osteochondral defects compared with fibrin alone. Subsequent experiments utilizing murine, ovine, and equine models further delineated the benefits of minced cartilage techniques.<sup>6–8</sup> Despite promising results from a randomized controlled trial, CAIS was ultimately discontinued.<sup>2,9</sup> Therefore, DeNovo NT is arguably the most prevalent particulate cartilage technique with over 8700 cases being performed since 2007. Although the majority of these cases involve knee defects (65%), there is increasing demand in the ankle (30%) and other constrained joints with limited access.

DeNovo NT is an allograft juvenile articular cartilage minced into 1-mm<sup>3</sup> explants. Explants are obtained from the femoral condyle of donors aged from neonates to 13 years old. Only 1 donor is included in a given package, which can include from 30 to 200 units. Each package is supplied with a lot number that is traceable to the concordant donor information. DeNovo NT is viable for 40 to 45 days from harvest, as it is a fresh allograft. DeNovo NT relies on the following 2 assumptions: chondrocytes have the ability to migrate from explants and juvenile chondrocytes offer benefits beyond their adult counterparts. Regarding the former, chondrocytes ideally will migrate from the cartilage matrix and proliferate to form neocartilage that integrates with surrounding native articular cartilage.<sup>2,3,6,10</sup> The DeNovo NT tissue is delivered with a monolayer of fibrin adhesive. The ability for cells to migrate into fibrin is dependent on the viscosity of the fibrin based on studies using an equine microfracture model.<sup>11</sup> Work from our laboratory has suggested that the ability of these cells to migrate out of the tissue into the fibrin glue and form new cartilage was no different than that seen with skeletally mature donors younger than 50 years old.<sup>12</sup>

The benefits of juvenile chondrocytes over their adult counterparts have been demonstrated in multiple laboratory studies. Cartilage gene expression changes with age, and the gene expression of juvenile cartilage is more favorable for cartilage regeneration than that of adult chondrocytes.<sup>2,13</sup> Specifically, genes that direct cartilage growth and expansion are upregulated, whereas in adult

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Disclosure: B.J.C. is a paid consultant for Zimmer Inc. The remaining authors declare no conflict of interest.

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1 cartilage, genes that control structural integrity of cartilage  
 2 are upregulated.<sup>2,13,14</sup> The ability of juvenile chondrocytes  
 3 to produce and maintain matrix is increased through  
 4 increased metabolic activity, cell density, proliferation rate,  
 5 and outgrowth.<sup>15,16</sup> Animal models have also shown sig-  
 6 nificant improvements in gross arthroscopic grading, his-  
 7 tology, and immunochemistry at 1-year after implantation  
 8 compared with untreated animals.<sup>2,7</sup>

9 These benefits are tempered by some potential con-  
 10 cerns based on work in our laboratory.<sup>12</sup> The cartilage  
 11 pieces tended to be relatively heterogenous with some pieces  
 12 being subjectively discolored or having nonviable cells.  
 13 Also, the benefit of the smaller explants (1 mm<sup>3</sup>) is ques-  
 14 tioned as adult chondrocytes from larger explants (3 mm  
 15 diameter) performed just as well in vitro. Lastly, the  
 16 availability and use of juvenile tissue will always represent a  
 17 concern.

18 Unlike procedures that require cellular expansion,  
 19 DeNovo NT has the ability to be performed as a single-  
 20 stage procedure. However, several factors need to be taken  
 21 into account if this is to be recommended. First, patients  
 22 that have never undergone surgery can benefit from  
 23 debridement alone, as not all patients that undergo ACI  
 24 proceed with implantation due to clinical improvement.  
 25 Secondly, the ability to accurately evaluate the extent of  
 26 cartilage lesions based on standard and even advanced  
 27 magnetic resonance imaging (MRI) techniques is difficult.  
 28 Therefore, one should consider the use of DeNovo NT  
 29 similar to that of a fresh osteochondral allograft with  
 30 regard to the treatment algorithm. Specifically, the diag-  
 31 nostic arthroscopy with debridement is used to confirm  
 32 indications, determine defect size and depth, and possibly  
 33 provide clinical benefit. In this light, it is difficult to support  
 34 using DeNovo NT as a first-line or single-stage procedure  
 35 without diagnostic arthroscopy. Benefits of DeNovo NT  
 36 include lack of donor-site morbidity and decreased risk of  
 37 allogeneic response. The latter has been demonstrated  
 38 in vivo as juvenile chondrocytes do not elicit a lymphocyte  
 39 proliferation response.<sup>2,13,14</sup>

41 **INDICATIONS**

42 Indications for the use of DeNovo NT are similar to  
 43 other cell-based cartilage restoration procedures and  
 44 include the following.<sup>3</sup>

- 45 • Patient 18 to 55 years old.
- 46 • Symptomatic articular cartilage defect.
- 47 • Defects are ICRS grade 3 + or above (an ICRS grade 3  
 48 defect is defined as extending through at least 50% of the  
 49 total depth but not into the subchondral bone).
- 50 • Minimal to no bone loss.
- 51 • Lesion is 1 to 5 cm<sup>2</sup> in size (postdebridement).
- 52 • BMI under 30 to 34 kgm<sup>2</sup>.

53 **RELATIVE CONTRAINDICATIONS<sup>3</sup>**

- 54 • Bipolar lesion.
- 55 • ICRS grade 1 or 2.
- 56 • Subchondral bone edema.
- 57 • Uncorrected menisectomy or malalignment.
- 58 • Osteochondritis dessicans with >6mm subchondral  
 59 bone loss.

60 **PRESENTATION AND PHYSICAL EXAMINTION**

61 Patients with focal chondral defects of the knee pres-  
 62 ent with pain correlating to the location of the defect and

63 sometimes complain of locking or catching. Patients with  
 64 patellofemoral defects complain of anterior and activity-  
 65 related knee pain with flexion, such as using stairs or sitting  
 66 for prolonged periods of time. A patient may point to the  
 67 front of the patella and explain that the pain is deep to this  
 68 point (one finger sign). Patients with tibiofemoral lesions  
 69 complain of pain with weight-bearing along the joint line  
 70 corresponding to the location of the defect. One can also  
 71 palpate the distal femoral condyle directly with the knee in  
 72 flexion or hyperflexion. Swelling is an important part of the  
 73 subjective examination that would suggest that the patient  
 74 has a significant defect.

75 The physical examination should focus on determining  
 76 the specific location at which provocative maneuvers fur-  
 77 ther define the patient's pain. Specifically, examination  
 78 maneuvers may be focused more on the patellofemoral joint  
 79 as opposed to the tibiofemoral joint based on the patient's  
 80 presentation. Start with inspection of the patient's align-  
 81 ment, as significant valgus may be associated with lateral  
 82 patellar tracking from increased Q-angle. Along with this,  
 83 check for the presence of a J-sign with increased lateral  
 84 patellar subluxation with extension. Secondly, have the  
 85 patient perform a single-leg squat. Observe dynamic valgus  
 86 and internal rotation that are habitual and may improve  
 87 with physical therapy. Also patients may have coronal  
 88 plane "instability" where they have difficulty keeping their  
 89 patella in line with their foot. Occasionally, patients will  
 90 state at what point during the squat the pain comes about,  
 91 note this angle and determine whether it correlated with the  
 92 findings on advanced imaging. Although an effusion is an  
 93 important examination finding, patients may have  
 94 abstained from activities that cause this before their visit.  
 95 Therefore, measure their quadriceps circumference as effu-  
 96 sions can cause quadriceps deactivation. The patellar grind  
 97 test (placing downward force on the patella during flexion  
 98 and extension) can also signal patellofemoral defects. In  
 99 addition, it is important to assess the patient for mala-  
 100 lignment, patellar tilt, and patellar apprehension.<sup>1</sup>

101 **PREOPERATIVE IMAGING<sup>1</sup>**

102 **Radiographs**

- 103 • AP standing: anterior tibiofemoral arthritis, fractures,  
 104 other lesions.
- 105 • PA standing (flexion weight-bearing): femoral condyles  
 106 (including osteochondritis dessicans), posterior tibiofe-  
 107 moral osteoarthritis.
- 108 • Lateral: patella alta, patella baja, trochlear dysplasia.
- 109 • Axial view: patellofemoral joint space narrowing, tilt,  
 110 and trochlear or patellar dysplasia.
- 111 • Mechanical axis: determine whether significant valgus is  
 112 contributing to lateral patellar subluxation for possible  
 113 distal femoral osteotomy.

114 **MRI (All Patients)**

- 115 • Assessment of soft tissues: cartilage integrity and quality  
 116 (dGEMERIC, fast spin echo, or other cartilage-specific  
 117 sequences).
- 118 • Subchondral bone edema.
- 119 • Ventral height, trochlear depth, sulcus angle, lateral  
 120 trochlear inclination.
- 121 • Defect depth.
- 122 • Associated pathology: TT-TG distance, meniscus status,  
 123 ligament status.

## 1 Computed Tomography

- Alternative to MRI for patients with significant bone loss or cystic changes.
- Alternative to MRI for measuring TT-TG distance for patients with planned tibial tubercle osteotomy.

## 7 SURGICAL TECHNIQUE

9 As a viable tissue, DeNovo NT has a limited shelf life of 44 days; therefore, it typically needs to be ordered before surgery. One package of DeNovo NT will cover an approximately 2.5 cm<sup>2</sup> defect, so larger defects may require multiple packages.<sup>3</sup>

15 The DeNovo NT procedure begins with a standard diagnostic arthroscopy to look for unexpected contraindications or concomitant pathology, even if the patient recently underwent a diagnostic arthroscopy. Next, the defect is accessed through an arthrotomy (Fig. 1). For a patellofemoral or lateral femoral condyle defect, a lateral arthrotomy is used; the medial vastus-sparing approach is used for defects in other locations.<sup>3</sup>

23 The defect is prepared through debridement until healthy tissue is reached and the walls are vertical (Fig. 2). After the defect is entirely clear of diseased tissue, the calcified cartilage layer is carefully removed without entering the subchondral bone.<sup>3</sup> If the subchondral bone is violated and bleeding occurs, use fibrin with digital pressure at the base of the defect to decrease bleeding.

29 DeNovo NT can be implanted through several methods. The authors prefer to prepare the implant either on the back table or directly in the defect. Regardless of this technique, preparation of the implant is identical. Excess media is first aspirated from the DeNovo NT package, leaving the minced cartilage pieces. If preparing the implant directly in the defect (typically for the trochlea), the minced cartilage pieces are placed directly into the defect and should sit approximately 1 mm lower than the surrounding cartilage shoulders to minimize compressive load and shear forces on the repair. The area is immediately covered with fibrin glue. Alter the operating table (Trendelenburg) or flex the knee to aid in gravity-assisting fibrin placement. When the glue has set, the knee is moved through range of motion to ensure stability of the implant.<sup>3,17</sup>

45 Alternatively, DeNovo NT can be applied by an extra-articular method. Pressing a thin piece of sterile foil against the base and walls of the defect creates a negative mold



65 **FIGURE 1.** Exposure of a patellar defect through an arthrotomy.



83 **FIGURE 2.** Debridement of a patellar defect.

85 (Fig. 3). DeNovo NT is transferred into the mold with the pieces spread evenly apart. Fibrin glue is used to fill the rest of the mold up to 1 mm from the top (Fig. 4). As the mold sets (3 to 10 min), fresh fibrin glue is applied to the defect's base. Finally, the implant is removed from the mold and is placed into the defect (Fig. 5). Another layer can be used over the implant for stability, ensuring the fibrin is not excessively proud compared with the surrounding cartilage. Again, the knee should be moved through range of motion to ensure stability of the implant.

95 Unpublished data from our laboratory demonstrates that the likelihood of cartilage technologies displacing that rely on fibrin glue for adhesion increases with defect size and leaving the fibrin proud relative to the surrounding cartilage. The former has been addressed by surgeons placing a collagen patch, similar to that used in second-generation ACI, over the implant. The later can be addressed through meticulous technique, ensuring the defect is not over-filled.

## 105 POSTOPERATIVE PROTOCOL

107 Following the DeNovo NT procedure, it is important to protect the cartilage repair process by following proper rehabilitation protocols to allow for cartilage integration



129 **FIGURE 3.** Sterile foil placed in a patellar defect to create a negative mold for DeNovo Natural Tissue placement.



**FIGURE 4.** Fibrin being added to the DeNovo Natural Tissue in the negative mold.

and ensure tissue stability. Specific rehabilitation protocols are based on the location of the defect.<sup>3</sup>

**Patellofemoral Compartment Rehabilitation Protocol**

- **Weight-bearing:** weight-bearing as tolerated with brace locked in extension if no osteotomy, limit weight-bearing to non-weight-bearing 0 to 2 weeks and partial at 2 to 4 weeks if osteotomy is performed.
- **Brace:** locked in extension for weight-bearing for at least 2 weeks, increase by 20 degrees each week until full and then discontinue.
- **Range of motion:** continuous passive motion (CPM) performed out of brace for 6 hours per day from 0 to 45 degrees for 3 weeks, then increase by 5 to 10 degrees per



**FIGURE 5.** Final DeNovo Natural Tissue implant placed in the patellar defect with fibrin placed over the implant.

day until at 90 degrees by 6 weeks, discontinue thereafter.

- **Exercises:** weeks 1 to 4: quadriceps sets and straight leg raise with hamstring isometrics; weeks 4 to 10: isometric closed chain exercises with balance and bike at 8 weeks; 6 to 8 months: fast walking on a treadmill, light plyometric activity, and limited high-impact activities; advance as tolerated as long as symptoms do not reoccur.

**Femoral Condyle Rehabilitation Protocol**

- **Weight-bearing:** non-weight-bearing 0 to 2 weeks, foot flat weight-bearing 2 to 6 weeks (30 to 40 pounds with use of 1 crutch), full weight-bearing with normal gait at 6 to 12 weeks.
- **Brace:** locked in full extension (remove for CPM or manually cycle leg and exercise) for 0 to 2 weeks, gradually unlock brace as lower extremity control returns from 2 to 4 weeks and then discontinue.
- **Range of motion:** CPM performed out of brace for 6 to 8 hours per day at 1 cycle/min, beginning at 0 to 30 degrees and increasing 5 to 10 degrees per day as tolerated, patient should gain at least 90 degrees by week 4 and 120 to 130 degrees by week 6 or manually cycle the leg.
- **Exercises:** weeks 0 to 2: quadriceps sets, straight leg raise, hamstring isometrics (perform with brace if inadequate quadriceps control); weeks 2 to 6: begin progressive closed chain exercises and open chain exercises with emphasis on the quadriceps and core muscles; weeks 6 to 10: progress bilateral closed chain strengthening, begin open chain knee strengthening while avoiding loading terminal open chain exercises, biking with minimal load for 30 minutes per day as tolerated; weeks 10 to 12: progress closed chain exercises using resistance less than the patient’s body weight, progress to unilateral closed chain exercises, begin balance activities, biking with a progressive load for 30 minutes per day as possible; months 3 to 6: advance bilateral and unilateral closed chain exercises with emphasis on concentric/eccentric control, continue with biking, stair master and treadmill, and progress balance activities.

Respect the graft site with closed chain activities by avoiding loading in full extension for anterior lesions and avoiding loading in flexion greater than 45 degrees for posterior lesions.

**CLINICAL OUTCOMES**

Although clinical outcomes for DeNovo NT have only recently been reported, results so far have shown the technique to be safe and efficacious in both patellofemoral<sup>17,18</sup> and tibiofemoral lesions.<sup>9</sup> In the first prospective study evaluating patients 2 years after DeNovo NT implantation, Farr and colleagues demonstrated histologically favorable repair tissue and native-like hyaline cartilage growth of the femur; 3 of the 8 study samples had predominantly hyaline cartilage with extremely good integration of hyaline and fibrocartilage areas. In the same study, 6 of the 8 samples had higher immunopositivity for type 2 collagen than type 1 at 2-year follow-up.<sup>10</sup>

MRI findings from the same study indicated maturation of allograft tissue and increasing defect fill (43.5% ± 48.5% at 3mo to 109.7% ± 62.9% at 2y) approaching levels of normal articular cartilage.<sup>10</sup> Clinical results, including subjective knee outcome score increases, graft failure, and hypertrophy, were similar to 2-year

1 outcomes of both matrix augmented chondrocyte implan- 63  
 2 tation<sup>19</sup> and ACI.<sup>20</sup> No reoperations were necessary at 2  
 3 years for any of the patients.<sup>10</sup> 65

4 Defect fill in the patella after DeNovo NT has been 67  
 5 shown to be superior to that of ACI<sup>21,22</sup> and micro-  
 6 fracture,<sup>22</sup> and at least as good as defect fill following 69  
 7 OATS.<sup>23</sup> In a study using twice the recommended density of  
 8 DeNovo NT, Tompkins et al<sup>18</sup> showed 89% mean fill on  
 9 patellar defects (2.4 ± 1.2 cm<sup>2</sup>) at 28 months, with 2 of the  
 10 15 patients needing debridement for hypertrophy. 71

11 Cartilage technologies that can be applied through 73  
 12 arthroscopic methods are attractive with regards to more  
 13 constrained joints such as the hip and ankle that require  
 14 extensive approaches and possibly osteotomies for open  
 15 treatment. Use in the ankle has been described and is  
 16 increasing. In 1 case report by Kruse et al,<sup>24</sup> the patient  
 17 began light jogging at 4 months without pain, returned to  
 18 full activity at 6 months, and resumed full activity at 2 years  
 19 while remaining pain free. 75

## DISCUSSION

23 Although no prospective randomized controlled trials  
 24 involving DeNovo NT have been performed, short-term  
 25 studies show the procedure to be safe and effective with  
 26 significant improvement in subjective patient reported  
 27 outcomes and evidence of defect fill on MRI.<sup>3,17</sup> DeNovo  
 28 NT is the only particulated juvenile allograft 1-stage tech-  
 29 nique currently available in the United States. There are  
 30 several advantages of DeNovo NT over other options to  
 31 repair focal chondral defects. Unlike other cartilage resto-  
 32 ration procedures, DeNovo NT does not require violation  
 33 of the subchondral bone or cause donor-site morbidity.  
 34 Potential disadvantages to DeNovo NT include the possi-  
 35 bility for disease transmission or immunological rejection  
 36 of the implant; however, because cartilage is immune-  
 37 privileged, the risk of either of these adverse events is  
 38 extremely low.<sup>3,9</sup> Disease transmission can also be avoided  
 39 with proper donor screening, tissue recovery, and tissue  
 40 processing procedures.<sup>17</sup> The use of fibrin fixation with  
 41 DeNovo NT decreases the potential for graft hypertrophy;  
 42 however, this has been reported and can be corrected with  
 43 simple arthroscopic debridement.<sup>3,17,18</sup> Some concerns still  
 44 exist regarding the heterogeneity of the implant; however,  
 45 the clinical correlation of this has yet to be determined.

46 Preliminary, short-term results indicate that DeNovo  
 47 NT is a safe, efficacious treatment option. However, further  
 48 studies need to be performed to define the indications for  
 49 use of DeNovo NT and to better understand expected  
 50 outcomes. Increased reporting of outcomes will improve  
 51 the likelihood of the procedure being accepted by insurance  
 52 carriers across the country. 77

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