Which New Cartilage Repair Options are Worth Considering for Our Patients?

Jack Farr, MD
Indianapolis, IN
OrthoIndy Center for Knee Preservation, Cartilage Regeneration and OrthoBiologics
Financial Disclosures
(AAOS disclosures up to date)

Royalties
• Arthrex

Consulting
• Arthrex
• JRF
• MedShape
• Moximed
• Norvartis
• Organogenesis
• Samumed

Books
• 2018 Farr & Gomoll Editors of Cartilage Restoration: Practical Clinical Applications
  (royalties donated)
Use of Product Brand Names is for Clarity Only
This is NOT an Endorsement or Product Promotion
What is Here Now?

- Autograft Osteochondral Plugs
- Fresh Osteochondral Allograft (multiple tissue banks)
- Marrow Stimulation and Augments
- Cell Therapy MACI/ACI
- Sterilized acellular OCA
- PJAC
- “OCA” with “minimal bone”
- Particulated Autograft Cartilage
Why Not More Options?
Significant Barriers to the Market

Human cells, tissues, and cellular and tissue-based products

HCT/P 351, which requires FDA monitored RCT for Biologic License if:

• Manipulation of Cells/Tissue
• Culturing
• Addition of Growth Factors
• Non-Homologous use
RCT for 351 products are time consuming/expensive

• Typical 200-300 subjects
• Enrollment difficult 2° equipoise; exclusion criteria (<%5 of presenting cartilage patients)
• 2 years from pilot to pivotal; 2 y enrollment; 2 y follow-up 1-2 y data analysis and submission: ROI concerns
• Expense range of $20 M- $100 M
Cancelled 2° ROI

DeNovo ET (Zimmer)
  allogeneic chondrocyte implant
  study cancelled in Phase 3 due to enrollment issues

CAIS (DePuy Mitek)
  particulated cartilage autograft
  study cancelled in Phase 3 due to enrollment issues

Chondrocelect (Tigenix)
  ACI variant with optimized culture conditions
  Company elected not to start study and close US cell culture facility after discussions with FDA on design
Current HCT/P 351 FDA approved Trials

- **Agili-C (Cartiheal)**
  Coral based acellular plug

- **Gelrin C (Regentis)**
  PEG/Fibrinogen hydrogel cured *in situ* with UV

- **Novocart 3D (Aesculap)**
  autologous chondrocyte implant in phase 3

- **Cartistem (Medipost)**
  allogeneic umbilical cord blood stem cells in phase 2

- **Adipose-derived stem cells (Stanford)**
  autologous single-step ADSC RCT against MFx

- **Hyalofast™ (Anika Therapeutics)**
  Nonwoven hyaluronic acid (HA) with BMAC

- **Neocart (Histogenics)**
  failed superiority in phase 3
Option “around” HCT/P 351 required RCT

- HCT/P 361 allows allograft tissue **use** which is not FDA regulated IF:
  
  Minimally Manipulated
  
  Homologous Tissue Use
  
  Not combined with other materials/drugs/GF
361 “Gray Areas”

FDA announced Nov 2017 there may be stricter definitions in Nov 2020

• Is mincing/particulating/micronizing minimally manipulative?
• Is separation of blood products manipulative?
• Is use of bone marrow aspirates and blood products homologous to the joint?
• Is fat homologous to the joint?
• Are placenta and amnion homologous to the joint?
Does FDA approval or 361 allowed use mean insurance will pay? NO

- CMS medical policies
- Private Payer individual insurance policies
- Based on Medical Policy on Medical Policies
  - Adequately powered RCT
  - 2 or more independent studies in the English peer-reviewed literature
  - Long-term outcomes
361 Products in Use (No RCT trials)

• Marrow stimulation augments, e.g., micronized cartilage
• PJAC
• Sterilized decellularized OCA
• Minimal bone cartilage disks
• Viable allograft cartilage strips/ECM
• Particulated autograft cartilage
How to add New Products into Your Practice
When there are no LOE 1 studies

• Evaluation of Novel Cartilage Treatment Options for Clinical Use, Farr and Sherman, SMAR 2018
• Develop a personal system to evaluate each novel product—as new is not always better.
One Approach to New Products

1. Read the pre-clinical literature; understand FDA regulatory pathway regarding loose or strict regulations for the particular products
2. Read the industry produced literature (“white papers” or sponsored case series) with a critical eye
3. Seek out the design surgeons to learn the “best results” possible and current indications
4. Seek out “earlier adapters” for their experience
5. Attend podium presentations and/or read about early clinical series in the literature
6. Conduct your own pilot historical controlled trial of approximately 10-20 patients—and wait.................
7. Evaluate your results and compare to historical control and other surgeons/literature
A cautionary tale: Decellularized OCA

- Applications similar to OCA
- 361 classification allowed clinical implementation without human trials: 2010 Equine trial then available for human implantation 2011

- High Failure Rate of a Decellularized Osteochondral Allograft for the Treatment of Cartilage Lesions, Farr et al, AJSM 2016
- Acute Delamination of Commercially Available Decellularized Osteochondral Allograft Plugs, Degen et al, Cartilage 2016
Farr et al Failures

Failure defined as structural damage of the graft diagnosed by:
Arthroscopy or MRI
And/or any reoperation resulting in removal of the allograft

- Twenty-three of the 32 knees (72%) were considered failures
- 14 of the 32 knees (43%) had further surgery
- Implant survivorship was 19.6% at 2 years
Old Adage is true:
Nothing Spoils Good Results Like Follow-Up
Current Options
Particulated Juvenile Allograft Cartilage

- Fresh stored articular cartilage
- Juvenile - donors < 13 years old
- Higher (>10x) chondrocyte density
- Minced into 1 mm cubes
- Increases surface area
- Facilitates chondrocyte outgrowth
Original Technique for PJAC

1. After completion of step 1-6, historically a sterile aluminum template mold is created from the defect. (Calculate the lesion area. One packet of PJAC covers approximately 2-2.5 cm²)

2. PJAC transport medium is removed from the transport packet except for a few drops

3. PJAC fragments are transferred into the mold in a monolayer with pieces close together, but not overlapping. With the mold on a sterile sponge, make several small holes in the mold base which allows the remaining transport medium to be wicked away

4. Add fibrin glue to a level just covering the PJAC and let fully cure (5-10 minutes)

5. Remove the glue/PJAC construct. Dry the defect base, apply fibrin glue to the base and immediately add the glue/PJAC construct adding/removing glue as needed to secure the construct at a slight below the vertical walls

6. After full curing assure the implant is stable through gentle range of motion
Original Surgical Technique
Most Commonly used Method for PJAC

1. Steps 1 and 2 as above, but place the PJAC fragments directly into the defect noting the scant amount of transport medium allows the fragments to adhere even on non-horizontal surfaces (move the limb/table angle to avoid fully vertical or higher angles). Fragments are monolayer and touching or near touching.

2. Wick excess transport medium from the margin with a sponge

3. Apply fibrin glue and wait until fully cured before checking with gentle range of motion
Most Commonly Used Method for PJAC

Once glued in position, both techniques appear the same.
Alternative Method for PJAC

Collagen patch in place over PJAC in:
- Monopolar lesion
- Bipolar lesion
Biopsy OC tissue was stained with H.E. staining. The top part of the healing tissue is fibrocartilage (b,d) and the bottom tissue is hyaline-like cartilage (c,e).
PJAC Pilot Knee Study
Histology of PJAC Graft at 2 yrs Post Op

Masson’s Trichrome: Good integration of repair tissue with underlying bone
Saf-O: High proteoglycan content
Col I: Minimal collagen I
Col II: High collagen II
PJAC
Long Term Observational Study in the Knee

• 15 Clinical centers, 197 lesions in 155 subjects (1/1/15)
  – 71@Preop, 100@12M, 58@18M, 73@24M, 60@36M, 36@48M, 17@60M

• Primary outcomes measures:
  – KOOS
  – Graft survival
  – Workdays lost pre- and post-op

• Demographics:
  – Mean age 32.8 +/- 9.1 (range 15-60)
  – BMI 28.0 +/- 5.4 (range 17.6-46.2)
  – 4.6 +/- 5.8 years from injury (range 0.0-25.2)
  – 1.4 +/- 2.8 years from most recent symptom onset (range 0.0–20.7)
PJAC
Long Term Observational Study in the Knee

• Total Lesion Size 3.5cm$^2$ per patient
  – Majority of lesions $\geq$ grade 3C
  – 25% of subjects have >1 lesion
  – 112 Femoral lesions (57%) mean 2.9cm$^2$
  – 83 Patella lesions (42%) mean 2.6cm$^2$
  – 2 Tibial lesions (1%) mean 1.8cm$^2$

• 86 subjects (55.5%) $\geq$1 Concomitant Surgery:
  – 53 (34% of total) patellar realignment
  – 22 (14% of total) meniscus
  – 7 (5% of total) ligament
PJAC

Long Term Observational Study in the Knee

• 77% of subjects ≥ 1 prior surgery on Index Knee (mean 1.7, range 1-8)
  – 227 surgeries in 119 subjects

• 59% of subjects ≥1 cartilage repair on index knee
  – 125 surgeries in 91 subjects
  – 44% Debridement
  – 15% Microfracture
  – 2% OC allograft, 2% ACI + periosteum
  – 18% other (fragment fixation, loose body removal…)
All post op times are statistically significant v baseline at p<0.05 except for Sports at 6M
PJAC Reoperations
Long Term Observational Study in the Knee

- 43 subjects (27% of total) had 55 reoperations:
  - 20 (13%) chondromalacia
  - 11 (7%) arthrofibrosis
  - 14 (10%) painful hardware
  - 6 (4%) DJD
  - 16 (10%) total revisions at mean of 20.3 months
PJAC Conclusions

- Not regulated by FDA
- Thousands of applications since 2007
- Outcomes appear similar to other cell therapies
- Attention to co-morbidities is essential
- No RCTs to date or planned
- Labeled as experimental/investigational by most insurance companies
Initial Literature

- Bonner et J Knee Surg 2010
  Single patellar lesion at 2 y improved from baseline
- Farr et al Cartilage 2011
  4 patients at 2 y post op improved from base line
- Tompkins Arthroscopy 2013
  15 knees in 13 patients 73% normal/nearly normal ICRS MRI
- Tompkins et al Operative Techniques in Sports Med 2013
  Technique review
- Farr et al AJSM 2014
  25 patients with minimum 2 y post op; majority improved
Additional Literature

Cartilage Regeneration in Full-Thickness Patellar Chondral Defects Treated with Particulated Juvenile Articular Allograft Cartilage: An MRI Analysis Grawe et al Cartilage. 2017


Use of chondral fragments for one stage cartilage repair: A systematic review Bonasia et al World J Orthop. 2015

Use of Particulated Juvenile Articular Cartilage Allograft for Osteochondral Lesions of the Wrist Hess et al Hand (N Y) 2017

Particulated articular cartilage for symptomatic chondral defects of the knee Riboh et al Curr Rev Musculoskelet Med. 2015


Allograft Cartilage Disks
Waiting on Large Case Series

• Minimal but Detectable Bone
• Flexible: ease of matching patellar median ridge and trochlear groove defects

Cartiform®
Osiris® & Arthrex®

Prochondrix®
AlloSource® & Stryker®
Comparison

**Cartiform®**
- “is a cryopreserved, viable OCA that contains factors that promote cartilage healing, including extracellular matrix, viable chondrocytes, and chondrogenic proteins. It is used in combination with microfracture of a lesion base as a single-stage procedure and features a porous structure that enhances flexibility of the graft, promotes the preservation of native chondrocytes, and facilitates mesenchymal stem cell migration to the Cartiform graft after marrow stimulation.”

**ProChondrix®**
- “is a cellular, 3-dimensional fresh OCA with viable chondrocytes, extracellular matrix, and growth factors, is another off-the-shelf solution and may be used with microfracture to treat chondral or osteochondral lesions.
- Fibrin glue fixation is recommended, with or without additional fixation techniques. The shelf life for ProChondrix is 35 days when stored at 4°C”

Beer OJSM 2019
Case Example 2013

Caton-Deschamps: 1.0
TT-TG: 9mm
TT-PCL: 24mm
Standard “Cell Therapy” Lesion Prep
Use of Cryopreserved Allograft Cartilage
Follow-Up Imaging

6 mon MRI:

Implant expansion of thickness with good basilar integration, incomplete marginal integration; small joint effusion
Cartiform® Publications: Limited Case Series


2. Cigan et al Nutrient Channels Aid the Growth of Articular Surface-Sized Engineered Cartilage Constructs Tissue Eng 2016

3. Woodmass et al Viable Osteochondral Allograft for the Treatment of a Full-Thickness Cartilage Defect of the Patella Arthrosc Tech. 2017


5. Vangsness et al Implantation of a Novel Cryopreserved Viable Osteochondral Allograft for Articular Cartilage Repair in the Knee J Knee Surg. 2018

Viable allograft cartilage strips/ECM

• CartiMax® by MTF®/Conmed®
• “Cryopreserved, viable, cartilage fibers combined with cartilage allograft matrix to make a biologically-active scaffold with putty-like handling characteristics used to treat focal cartilage defects. This product offers the potential to facilitate cartilage healing and regeneration along with ease of use.”
• Prepare defect as per cell therapy; create the CartiMax® putty and fill defect; no scaffold necessary
Conmed® Literature Support of CartiMax®

1. Data on File, MTF Biologics.
Per Conmed®

“These grafts have been studied in a small number of patients and preliminary outcomes (up to 6 months) are very promising with early indications of decrease in pain and increase in IKDC [International Knee Documentation Committee] and KOOS [Knee Injury and Osteoarthritis Outcome Score] scores, no significant bone edema or graft delamination, and early observation of complete fill and excellent incorporation. We continue to collect data and plan to publish clinical results in the coming months.”
Particulated Autograft

- First Animal Study (Rabbit) in German literature, Albrecht 1983
KOOS change from baseline

KOOS pain

KOOS Symptoms/Stiffness

KOOS ADL

KOOS Func/ Sports & Recreation

KOOS Quality of Life

Cole, Farr et al AJSM 2012
CAIS cancelled for ROI concerns
Current Particulated Autograft Cartilage Options

• Manual Chipped cartilage pursued in Denmark
  Foldager Cartilage 2015 Clinical Case Series
  Christensen 2016 Mini Pig

• Mechanical particulated autograft: Reveille™ from Exactech 2017

• Capture of shaver harvested autograft: GraftNet® from Arthrex 2019
Exactech Reveille™ CP
Autograft Cartilage Processing System

Point-of-care cartilage autograft processor

Conveniently powered by surgical drill handset
Exactech Reveille™ CP
Autograft Cartilage Processing System

- Precision in size reduction and separation
- Rapid increase in surface area and chondrocyte exposure
Chondrocyte outgrowth in culture following particulation

Reveille CP ≈ 1.5x Hand minced
Chondrocyte viability maintained at >90%
Alternative Mincing in Gian Salzmann Lab:

Conclusion:
“The outgrowth potential, the viability after 28 days in culture, and the matrix deposition were not different between the mincing techniques and the tested biomaterials, yet device mincing is faster and results in significantly smaller cartilage particles."
GraftNet® Arthrex® Released 2019

- Collects arthroscopic shavings
- Bone and Cartilage reported viable
- May be used as with prior particulated autograft techniques

Lavender et al Autograft Cartilage Transfer Augmented With Bone Marrow Concentrate and Allograft Cartilage Extracellular Matrix  Arthroscopy Techniques January 2020

Mead et al A Technique Utilizing GraftNet to Fill Graft Donor Sites in Bone-Patellar-Bone Anterior Cruciate Ligament Reconstruction Arthroscopy Techniques December 2019
All these options need careful study
Conclusions

• Currently majority are 361 products, which are **allowed by FDA, not approved**;
• MACI only 351 product with **FDA approval**
• Thus, no RCT to base 361 product use in most cases
• Need to monitor one’s own cases with PROs, imaging and longer-term follow up
• Caveat Emptor
Thank You