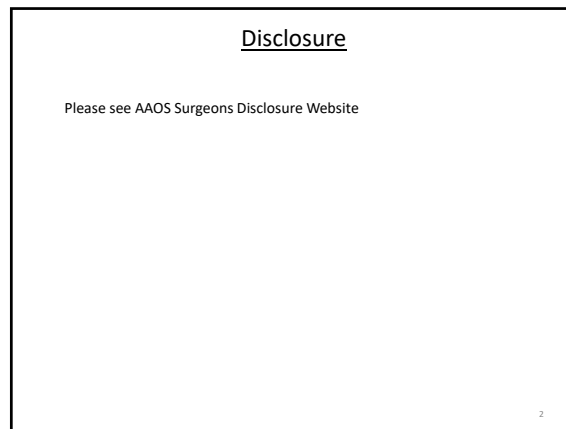
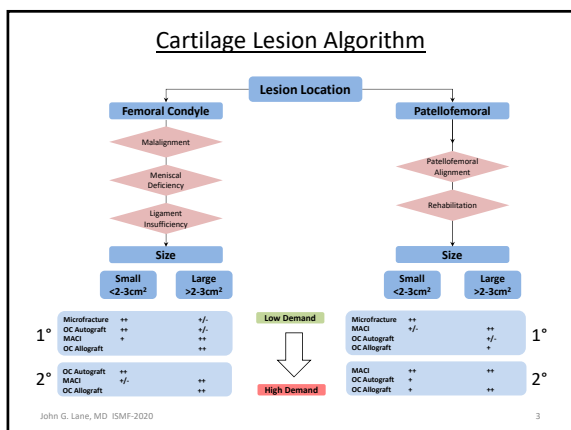


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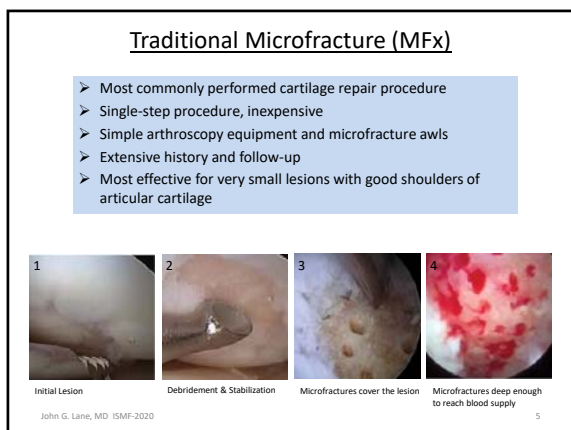
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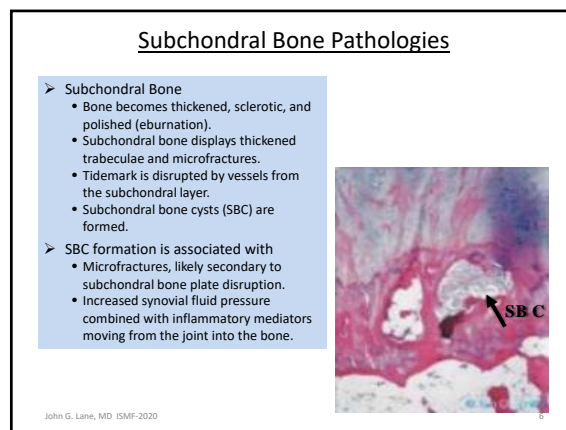
3

- ### Small Cartilage Lesion Options
1. Cartilage Lesion Algorithm
  2. Microfracture
    - a) Traditional
    - b) Microdrilling and Nanofractures
  3. Microfracture Plus
    - a) Biocartilage
    - b) Cartiform
    - c) ProChondrix
    - d) AMIC
  4. OATS (Osteo - Chondral Autograft Transfer)
  5. MACI (Cell Based Therapy)
  6. Allografts
    - a) DeNovo (Allograft)
    - b) OCA (Allograft)
  7. Reville (Autograft)
  8. Future Technologies
    1. Agii-C
    2. NeoCart
    3. BST CarGel
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### Improving MFX Bone Marrow Stimulation

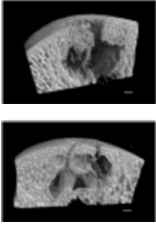
**MFX as we know it today**

- The super clot formation contains 0.02% MSC phenotype cells.
- The integrity of the subchondral bone surface is removed by 15%.
- Weakened trabecular bone structure can lead to subchondral bone pathology: upward migration of the subchondral bone plate and cyst formation.

**Possible Improvement**

Using smaller drill-holes with a diameter close to the physiological subchondral trabecular distance may

- result in better repair tissue
- improve subchondral plate and subarticular spongiosa restoration



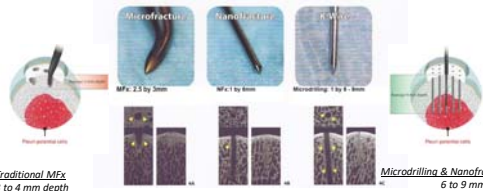
Micro-computed tomographic (microCT) 3D illustrations of subchondral bone cyst formation in the femoral condyle of sheep, 26 weeks following MFX, with persistent communications with the MFX hole.

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### Microdrilling and Nanofractures

- Microdrilling or Nanofracture: does it make a difference?
- Does drilling allow better access than MFX?
- Deeper channels - does it access more pluripotential cells?
- What effect does it have on the lacuna in the bone?



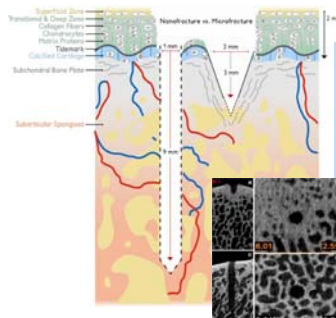
**Traditional MFX**  
3 to 4 mm depth  
Violation of the subchondral bone?

**Microdrilling & Nanofractures**  
6 to 9 mm depth  
More, Smaller, and Deeper Channels  
No bone compaction  
No heat necrosis

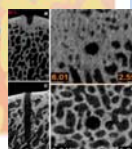
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### Nanofracture: Is it safer and more effective?



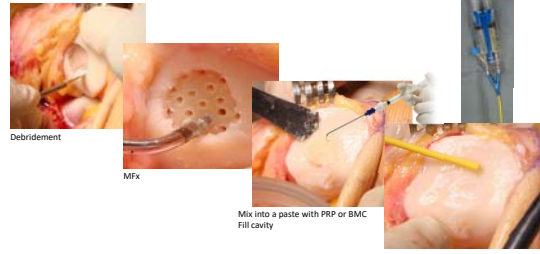
- MFX-induced fracturing and compaction of bone surrounding the holes 24hrs after creation (animal). This sealed off the holes from the subchondral marrow and caused osteonecrosis.
- In contrast, deeper drilling caused bone repair and remodeling over a greater region and restored the bone volume fraction.




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### Micronized Acellular Cartilage: BioCartilage



- The Goal is to provide an internal scaffold that will improve the quality of repair tissue after MFX





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### Micronized Acellular Cartilage: Features

- Dehydrated, micronized allogeneic cartilage
- Particle size 100-300 microns (For ease of use & increased surface area)
- Porous cartilage ECM scaffold - contains the ECM that is native to articular cartilage, such as type II collagen, PGs and additional cartilaginous GFs and peptides (TGF, FGF and BMP's)
  - Slow dry freeze & does not destroy peptides
  - Stem cells exposed to ECM will differentiate based upon factors with ECM





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### Allograft Surface Treatments





ProChondrix® and Cartiform® are wafer-thin allografts where the bony portion of the allograft is reduced. The discs are

- Laser etched or porated
- Contain hyaline cartilage with
  - ✓ Chondrocytes
  - ✓ Growth factors
  - ✓ Extracellular matrix proteins.

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### Cartiform: Cryo-Preserved Chondral Graft

A living biospecific chondral scaffold in conjunction with autologous MSCs  
 Intended to augment MFx, to access Autologous MSCs  
 "Best of both Worlds" - Allogeneic living healthy chondrocytes and autologous MSC's

**Cartiform Technique**

**Graft Fixation**

- ✓ Anchors
- ✓ Imm- all suture

**Sutures**

- ✓ 5.0 or 6.0 vicryl
- ✓ Sew right through fenestration
- ✓ Fibrin glue- periphery only

**Goal:** Secure sufficiently to allow for early ROM

Biomechanically, holes allow a bit more moldability and better application of the cryoprotectant into the inner portions of the graft so all cells receive cryoprotection during the storage process.



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### ProChondrix: Fresh Osteochondral Graft

**ProChondrix** is a cellular 3D fresh osteochondral allograft that provides

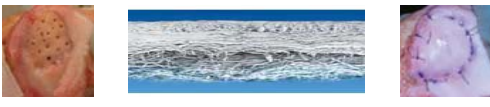
- Live functional cells and other biological components for repair and regeneration of damaged cartilage tissues.
- Internal scaffold promotes MSC migration.
- Induces chondrogenesis by signaling the host cells to differentiate into chondrocytes.
- Fresh graft for up to 28 days

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### AMIC: Autologous Matrix-Induced Chondrogenesis

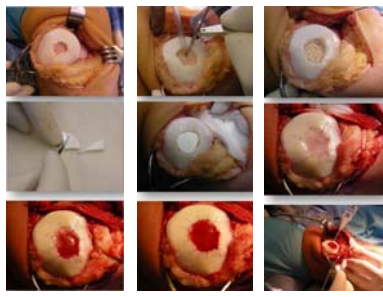


- Single Staged Procedure
- Type I/III Collagen Membrane Stabilizes MSC Clots
- AMIC Plus adds PRP to Augment
- Europe CE mark vs. US would need a BLA for a knee indication
- Case Series (Gill 2010 and Kusano 2012)
  - Increase quantity
  - Quality of tissue?
  - Effects on bone integration?

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### AMIC Combines MFx and Collagen Membrane



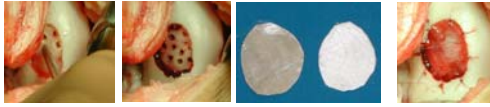
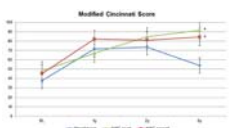
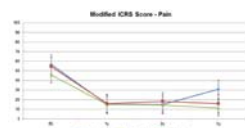
- Provides mechanical stability of the clot and is stimulus for chondrogenic differentiation.

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### A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years

Martin Valz<sup>1</sup>, Jens Schamberger<sup>2</sup>, Hubert Frick<sup>1</sup>, Joachim Grifka<sup>2</sup>, Sven Anders<sup>2</sup>

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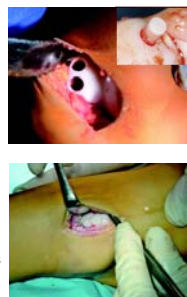
### OATS (Osteo - Chondral Autograft Transfer)

**Good to excellent clinical results\***

- 92% of patients with femoral condyles
- 87% of tibial resurfacings
- 74% of patellar and/or trochlear mosaicplasties
- 93% of talar procedures

**Disadvantages**

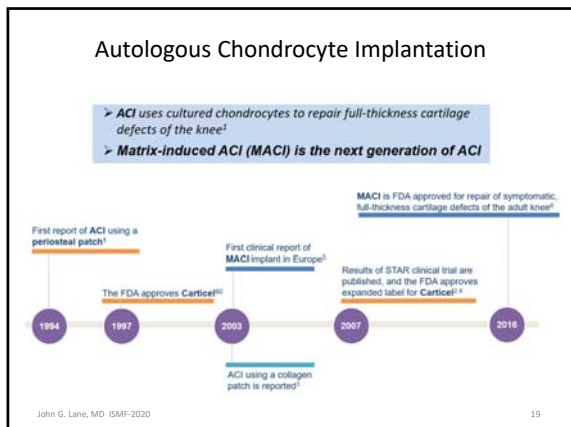
- Moderate and severe donor-site disturbances were present in 3% of patients
- Limited donor tissue availability in smaller joints



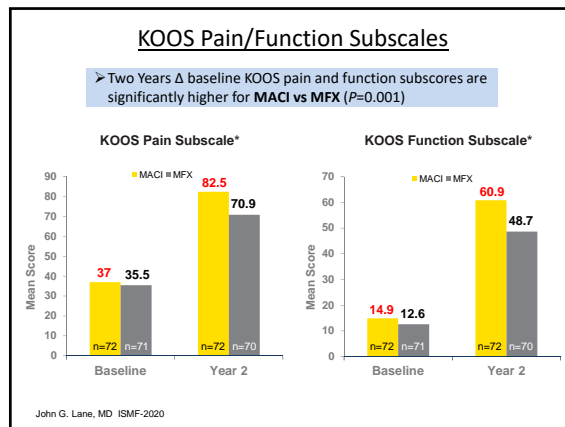
\*Hangody et. al. Autologous osteochondral grafting—technique and long-term results. Injury. 2008 Apr;39 Suppl 1:S32-9

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### MACI Implantation

MACI is implanted through mini-arthrotomy

- Defect is assessed and debrided**  
 All damaged and underlying cartilage must be removed, including the calcified cartilage layer, until vertical walls of healthy, stable cartilage surround the defect site. Hemostasis must be achieved prior to implantation using hemostatic agents.

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### MACI Implantation

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- Template is sized and shaped to match defect**  
 MACI implant is cut according to template.

MACI Surgical Manual, Cambridge, MA: Vericel Corporation, 2017.  
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### MACI Implantation

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- Template is sized and shaped to match defect**  
 MACI implant is cut according to template.
- Fibrin sealant is applied to empty defect**  
 MACI implant is placed on the defect, with the cells facing the bone bed. Fibrin is then added to the surrounding edge.
- Gentle pressure is applied until the MACI implant is secured**  
 After fibrin has set, knee is fully extended and flexed several times. Wound is closed in standard fashion.

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### DeNovo NT

#### Particulated Juvenile Articular Cartilage

- Fresh-stored articular cartilage**  
 Donors under 13 years old  
 Knee cartilage minced into 1 to 2 mm cubes

Surgical Steps

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### Why Juvenile Articular Cartilage?

Juvenile cartilage is more cellular and the cells have more robust matrix formation than adult chondrocytes (Fedder et al, 2004); Adkisson AJSM 2010 potential for cartilage restoration

Cellular senescence, the loss of the ability of cells to divide, has been noted as the major factor contributing to age-related changes in cartilage homeostasis, function, and response to injury. The underlying mechanisms of cellular senescence, while not fully understood, have been associated with telomere erosion, DNA damage, oxidative stress, and inflammation.

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### Two-Year Level IV Smaller Lesion Study: Results

Lesion Characteristics	23 patients 29 defects
Defect Size	2.7cm <sup>2</sup>
# of patients with 2 lesions	4
<b>Defect Location</b>	
Femoral Condyle	18
Tibiotra	11
<b>ICRS Grade</b>	
3A	2
3B	3
3C	16
3D	2
4A	6

**Clinical Outcomes: KOOS**

**MRI Outcomes: Fill rate persist for 2 years**

J. Farr, S. K. Tabet, E. Margerison, and B. J. Cole. "Clinical, Radiographic, and Histological Outcomes After Cartilage Repair With Particulated Juvenile Articular Cartilage: A 2-Year Prospective Study," Am. J. Sports Med., vol. 42, pp. 1417-1425, 2014. 26

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### Osteochondral Allografts

Hyaline cartilage is ideal for transplantation

- Avascular
- Metabolic needs met by diffusion from synovial fluid
- Aneural
- Immunoprivileged
- Viable chondrocytes survive hypothermic storage

Osseous structure features

- Underlying structural support
- Allows fixation to host
- Originally vascularized
- Cells do not survive hypothermic storage
- Scaffold for creeping substitution

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### Surgically Implanted Pre-shaped Plugs

➢ 10mm precut fresh-core OCA

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### Reveille™: Host Tissue Cartilage Processor

**BENEFITS/FEATURES:**

- Precision crafted blade and sieve design permits high speed cutting
- Designed to create convective movement of fluid during processing
- Easy to assemble; with detachable tissue reservoir
- Two minute processing time yields tissue particles with increased surface area suitable for grafting procedures
- Fluid environment protects tissue viability without the need for cell culture
- Easy to load and retrieve tissue
- High cell viability
- Produces tissue to fill defects up to 4cm<sup>2</sup>
  - Host tissue eliminates the potential of graft rejection
  - Off-the-shelf convenience
  - Increase in surface area allows greater chondrocyte exposure

**Crafted Blade for High Speed Cutting**

**Precision in Size Reduction and Separation Particle Size Approximately 800 to 1200 Microns**

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### Agili-C™ Cartiheel Coral Based Acellular Plug

➢ Bi-phasic Implant for Osteochondral repair

➢ Composite Coral and Hyaluronic Acid

**Plug Construction**

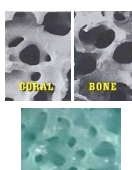
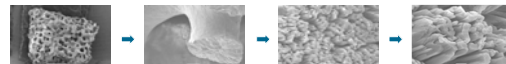
**Plug Installation**

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### Coralline Aragonite as a Scaffold

Aragonite ( $\text{CaCO}_3$ ) is derived from the coralline inorganic exoskeleton  
 Biocompatible & biodegradable  
 Interconnected porosity, facilitating vascularization  
 Similar to the human bone  
 Over 50 years of in vitro animal and human research





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### Mechanism of Cartilage Formation

Goat model



3 weeks post Op      6 weeks post Op      12 weeks post Op

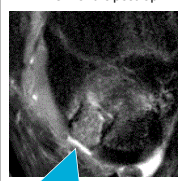
Cartilage flow from implant periphery towards the center is enhanced by cartilage formation from the drilled holes

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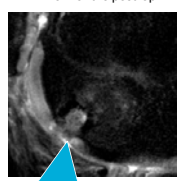
### Cartilage Formation and Bone Remodeling in Humans

MRI 3 months post-op



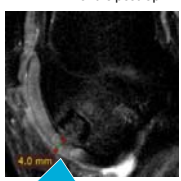
The implant is 2mm recessed

MRI 6 months post-op



Cartilage growth; bone remodeling on the periphery

MRI 12 months post-op



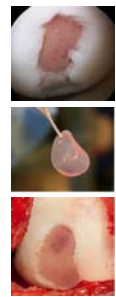
Full thickness cartilage regeneration; Complete subchondral bone remodeling

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### NeoCart

- Autologous chondrocytes are seeded in a bovine-derived three-dimensional type I collagen honeycomb matrix.
- The chondrocyte-embedded matrix is then cultured in a bioreactor, which creates an environment of variable hydrostatic pressure and low oxygen tension, to simulate intra-articular conditions.
- The resulting tissue has been shown to contain glycosaminoglycan and a favorable ratio of type I to type II collagen.
- The tissue is implanted into chondral defects with a sutureless technique utilizing a collagen polymer.




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### BST - CarGel


- Provides a biological scaffold: chitosan-glycerol phosphate-based scaffold
- Blood clot stabilized by the incorporation of a thrombogenic and adhesive polymer: Chitosan
- Physically stabilizes the wound repair environment
- Increases cell recruitment
- Prevents clot retraction



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### BST- CarGel: Surgical Technique



Chitosan-Glycerol Phosphate/Blood Mix

↓

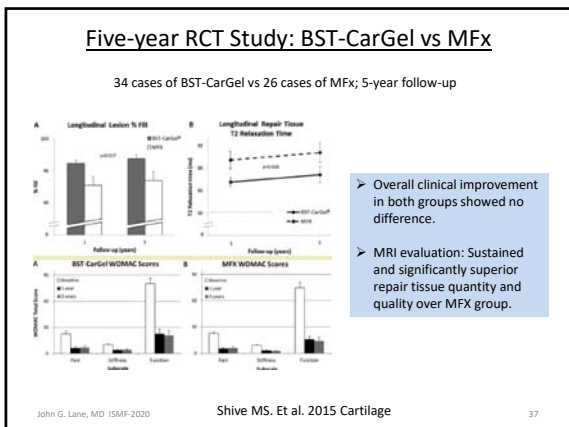
Arthroscopic → Microfracture → Microfracture Mix Implantation: 15 minutes

↓

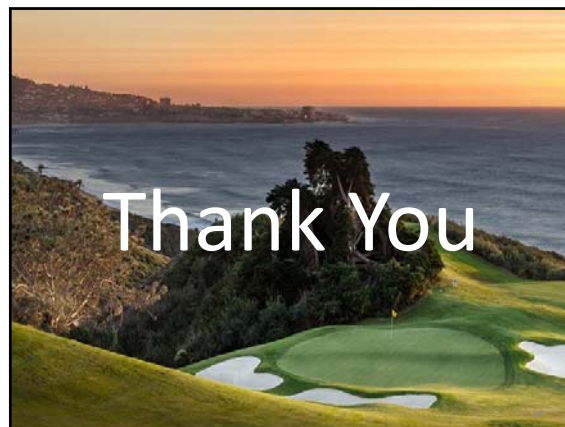
Stable Clot

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