NUsurface® Meniscus Implant

Docket No. FDA-2023-N-0008

Active Implants, LLC

April 20, 2023

NUsurface Meniscus Implant

Ryan Belaney, MSMBE

Active Implants, LLC.

Vice President: Clinical And Regulatory Affairs

Agenda

Introduction & Overview

Ryan Belaney, MS, Active Implants

Current Clinical Need, Study Design and Clinical Outcomes

Elliott Hershman, MD, Lenox Hill, New York, NY

Radiological Observations

Nogah Shabshin, MD, University of Pennsylvania, Philadelphia, PA

Benefits and Risks of the NUsurface Implant

Deryk Jones, MD, Ochsner Health, New Orleans, LA

NUsurface: Proposed Indication

The intended use of the NUsurface Meniscus Implant is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The indication for use is in patients with:

- --mild-to-moderate osteoarthritis,
- --mild or greater knee pain, and
- --cartilage present on the load bearing articular surfaces.

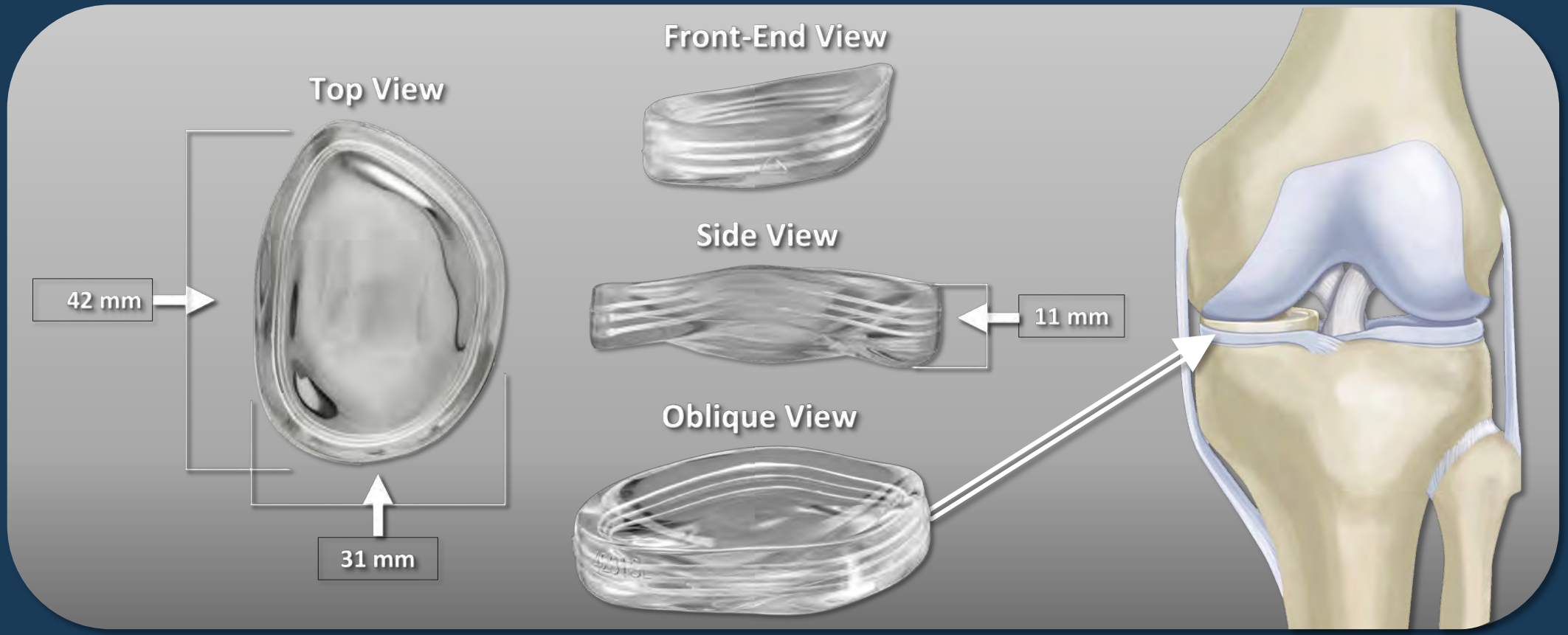
Each element needs confirmation from patient history, physical examination, radiographic imaging, and/or visual observation.

<u>Added Contraindications & Warnings</u>

- Patients with extrusion of the medial meniscus 5mm or greater are contraindicated for the device.
- Warning: Patients in which the height of the tibial spine is below 11mm are at greater risk of device related adverse events.

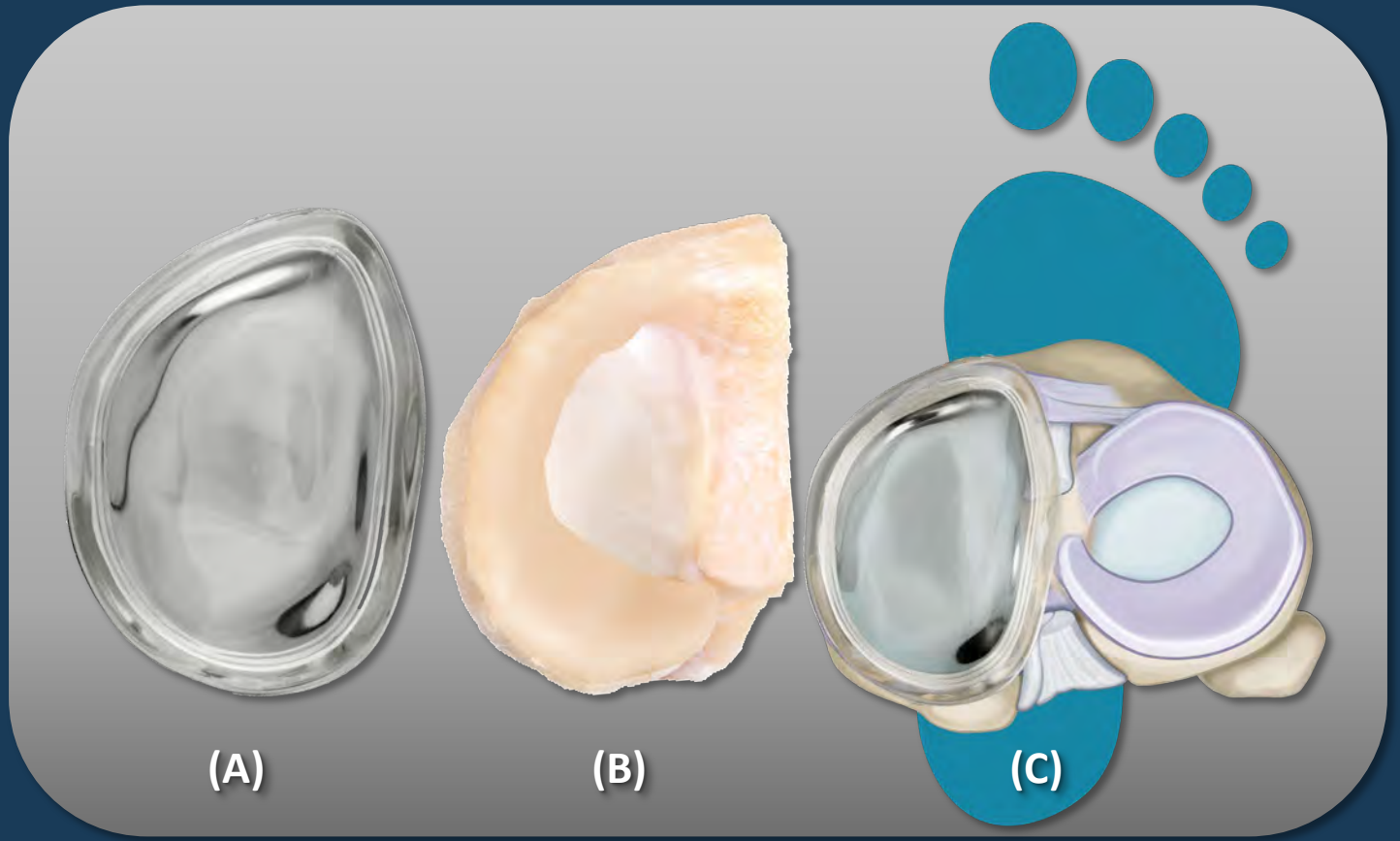
The NUsurface Implant
Made from Two Medical-Grade Polymers

- Bionate® polycarbonate-urethane (PCU)
- Dyneema Purity® fibers of Ultra-High Molecular Weight Polyethylene (UHMWPE) embedded around the periphery



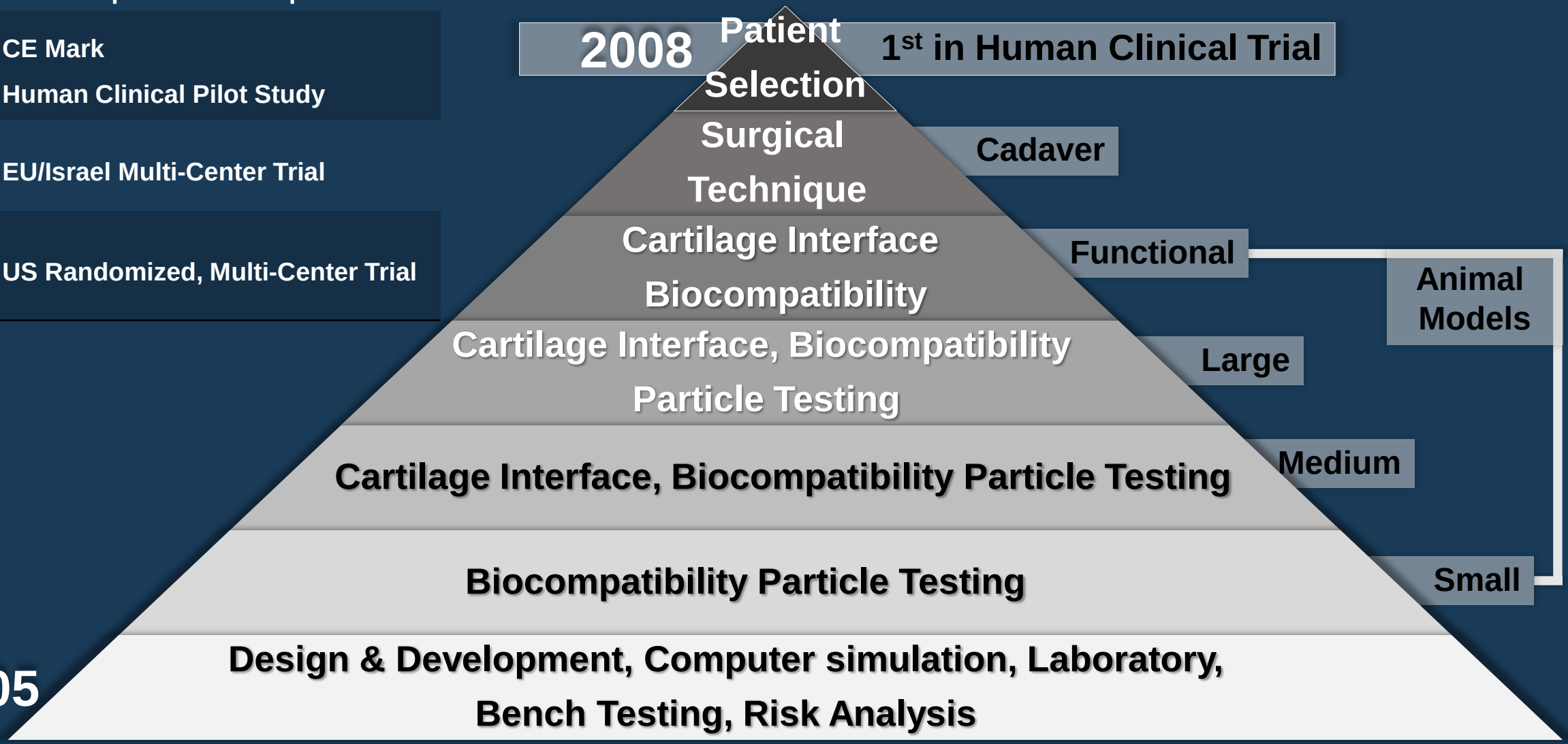
The NUsurface Implant
Designed to Replicate Function of Normal Meniscus

- Seven sizes were available during the MERCURY TRIAL for the left and right knees.
- Photograph of a NUsurface Implant (A), next to a natural meniscus prepared for transplant (B), and illustrated view from the top of the right knee, showing the orientation of the NUsurface (C).

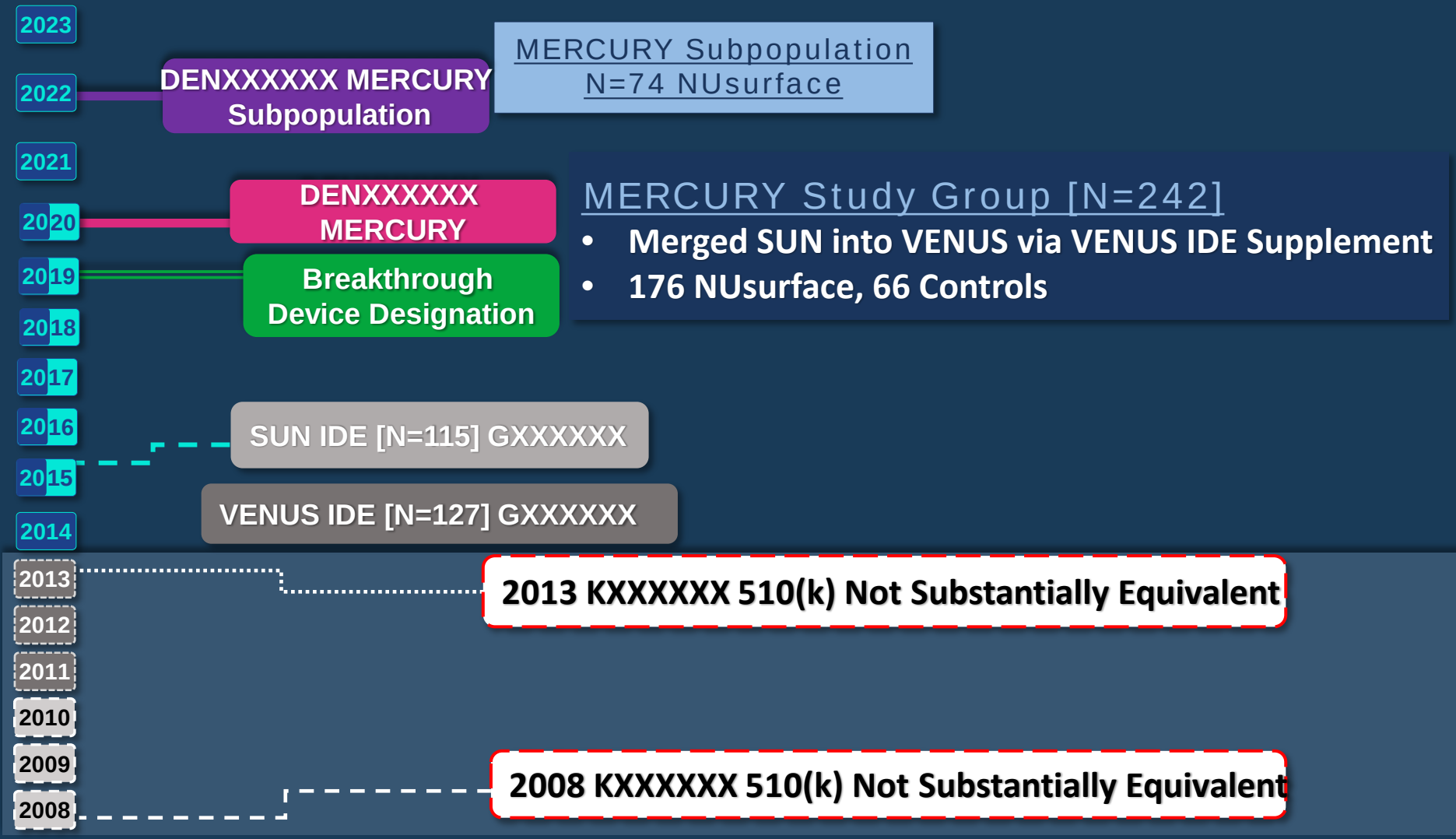


Milestones Along the Path to Validation:

2007	Sheep Model Demonstrates Proof of Concept for Chondroprotection
2008	CE Mark Human Clinical Pilot Study
2011	EU/Israel Multi-Center Trial
2012	US Randomized, Multi-Center Trial

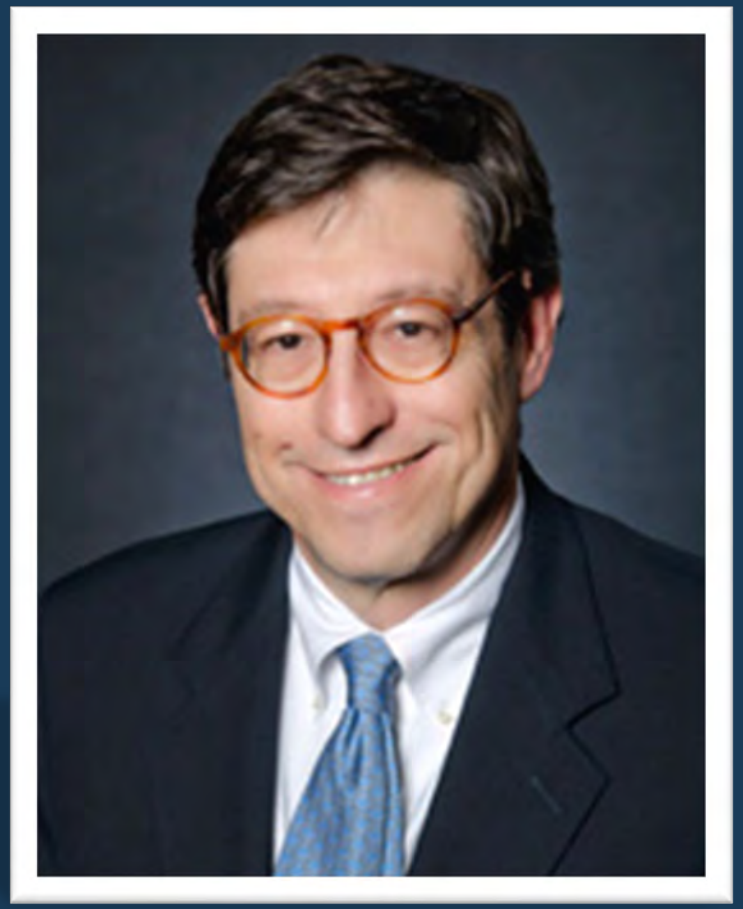


NUsurface Regulatory History



Elliott Hershman, MD

Orthopedic Surgeon, NUsurface Clinical Trial Investigator



Background, Development and Clinical Trial Outcomes of the NUsurface Implant

Knee Pain is a Leading Source of Physical Disability & Impaired Quality of Life in US

U.S. Annual Incidence	
Knee Injury	17.6M
Medications, PT, Bracing, Rehab, Weight-loss	15M
Injections	5M
Surgery	2.5M

- Most Common Reason for Orthopedic Surgery

cdc.gov/arthritis/data_statistics, Hunter 2019 Lancet, Bedard 2018 JBJS, Zhu 2022 JBJS, Deshpande 2016 Osteoarthritis, Gage 2012 Acad Emerg Med, Cisternas 2016 Arthritis Care Res

Majority of Patients are Managed Conservatively

- Non-Operative Therapies Usually Appropriate
- Use of Injection Therapies Increasing

15M Patients

Non-Operative:

- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

5M

Injections:

- Steroids
- HA

Cochrane in CORR 2022
Cochrane Library 2022
AAOS 2021
BASK 2019
ESSKA 2019
EFORT 2018
BMJ 2017
AHRQ 2017
OARSI 2014

There Are Many Types of Knee Preservation Options Surgical Treatment Begins w/ Most Conservative Approach

- Knee Preservation Treatment Options are Preferred
- Aim to Repair/Replace Diseased/Damaged Tissue Only
  - Remove Minimum
  - Maintain Maximum

15M Patients

Non-Operative:
- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

5M

Injection
- Steroids
- HA

< 100K

Knee Preservation:
- ACL Recon
- Cartilage Repair
- HTO
- Allograft

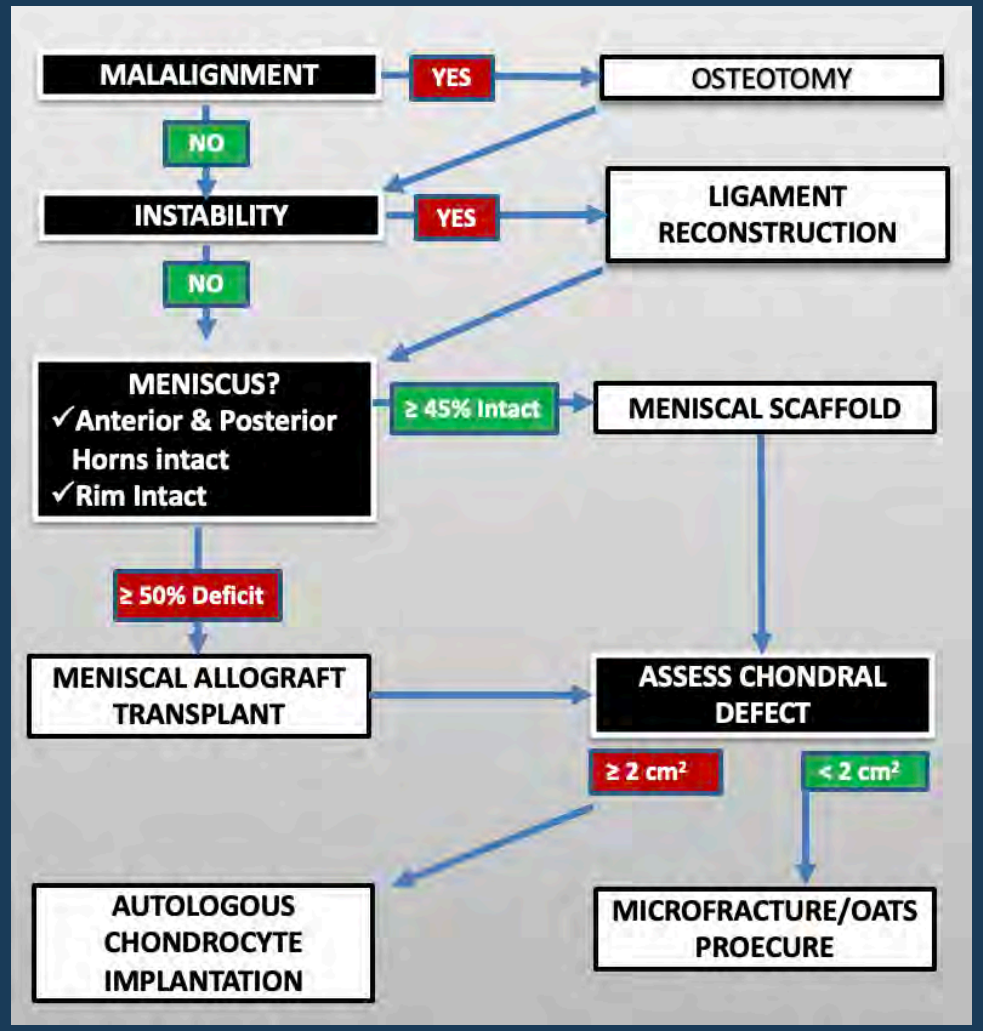


Fig. 45.2 Decision making algorithm for treatment of the meniscus-deficient knee, Bloch 2016 Springer

Meniscus Injuries are a Common Source of Knee Pain + #1 Reason for Knee Surgery

U.S. Annual Incidence	
Meniscal Injury	2.5M
Meniscectomy in the knee	1.1M
Medial Meniscectomy	750,000

- The Meniscus is Prone to Injury
- Has Poor Healing Potential

Hare 2017 Acta Orthop, Healthgrades.com/the-10-most-common-surgeries-in-the-u-s, 2010 Natl Health Stat Report: 1-15, 2017, Cullen 2009 Natl Health Stat, Report 2009; 20(11):1-25., Kim 2011 J Bone Jt Surg Am

Save The Meniscus! Unless You Can't:

>1 Million arthroscopic surgeries annually

Medial Meniscectomies = >70%

15M Patients

Non-Operative:
- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

5M

Injection
- Steroids
- HA

< 100K

Knee Preservation:
- ACL Recon
- Cartilage Repair
- HTO
- Allograft

1M

Arthroscopy:
- Repair
- Meniscectomy

> 750,000 medial Arthroscopic Partial Meniscectomies (APM)/Year

- ~ 450,000 on Patients >45
- Max Clinical Resonse Around 3-6-months
- Post-Meniscectomy pain afflicts ~15%-50%

Hare 2017 Acta Orthop.
Cullen 2009 Natl Health Stat Report 2009; 20(11):1-25.

The Meniscus is a Critical Structure in the Knee: Distributes load + Provides Chondroprotective Function

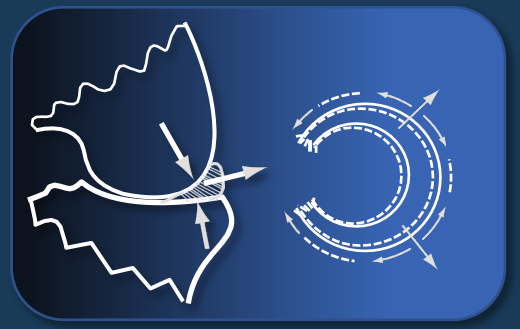
A Functioning Meniscus is Important for Maintaining:

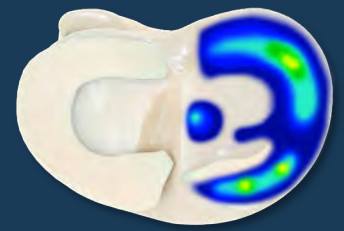
- Adjacent articular cartilage surface integrity and congruity,
- Bone integrity and density,
- Capsuloligamentous stability,
- Long leg alignment, and
- Lubrication/transportation of cells

Van Ginckel et al., 2010, Heikkinen et al., 2007; Huiskes, 2000; Vainionpaa et al., 2009, Krogsgaard, 2007; Schmitt, Fitzgerald, Reisman, & Rudolph, 2008, LaStayo et al., 2003, Horita et al., 2002; Kamibayashi & Muro, 2006, Maly et al., 2006

Normal Transmission of Bodyweight

Normal Load Distribution

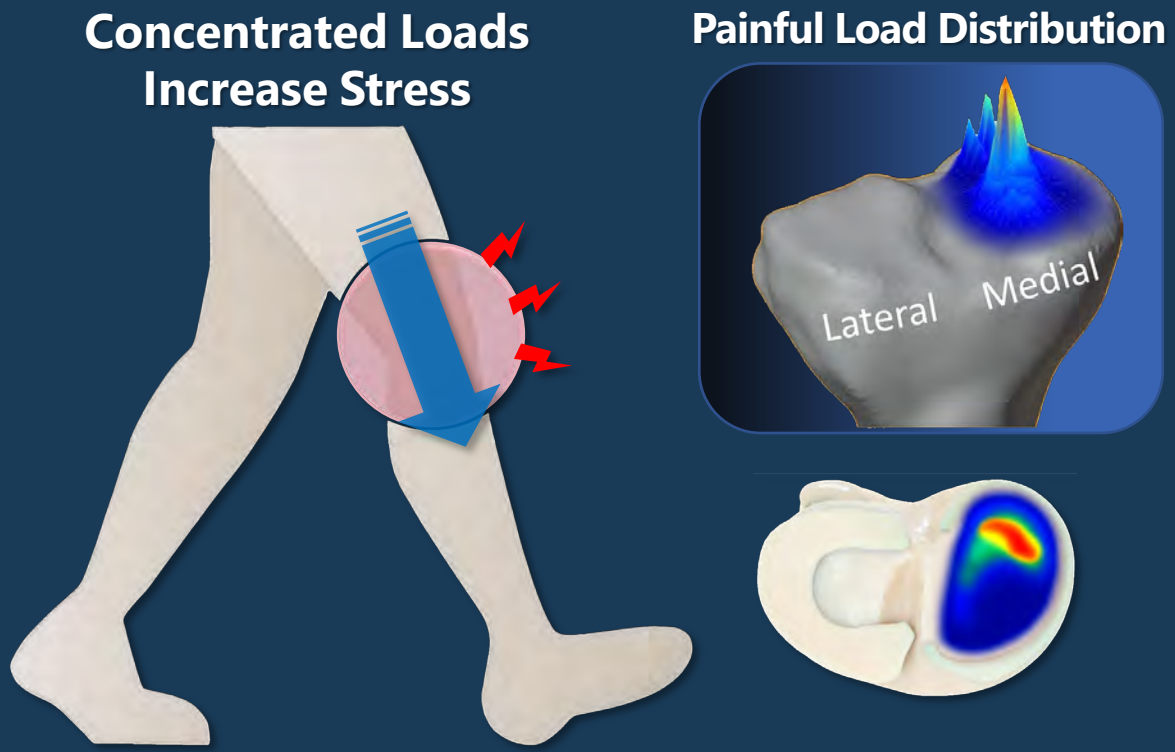




An Injured/Degenerative Meniscus Alters Normal Load Distribution – Concentrating Stress

Over-Loading leads to Dull, Aching Type of Pain Caused by:

- Increased pressure on articular cartilage and the underlying subchondral bone leading to:
  - Thinning Cartilage,
  - Loss of Joint Space,
  - Increasing Ligament Instability,
  - Altered joint alignment, and
  - Meniscus Extrusion



Drobnič *2019 Knee Surg Sports Traumatol Arthrosc, Hunter 2006 Arthritis Rheum, Wang 2022* Bone Joint Res, *Hunter 2006* Arthritis Rheum, Scanzello 2012 Bone, Cicuttini 2002 J Rheumatol, Liu-Bryan 2013 Curr Rheumatol Rep, van der Voet 2023 Semin Arthritis Rheum

These are the hallmarks of progressive osteoarthritis (OA)

What to Do for Middle-Aged Patients with Post-Meniscectomy Knee Pain?

A Real Unmet Need in Orthopedics Today:

15M Patients

Non-Operative:
- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

5M

Injection
- Steroids
- HA

< 100K

Knee Preservation:
- ACL Recon
- Cartilage Repair
- HTO
- Allograft

1M

Arthroscopy:
- Repair
- Meniscectomy

?

~ 55 Years-old, in pain following knee surgery:
1. Good/Decent Cartilage
2. Degenerative Meniscus
   - No New Tear: Meniscectomy not Indicated
   - Tssue Too Damaged for Repair
3. Knee is Aligned: Not Ready for HTO

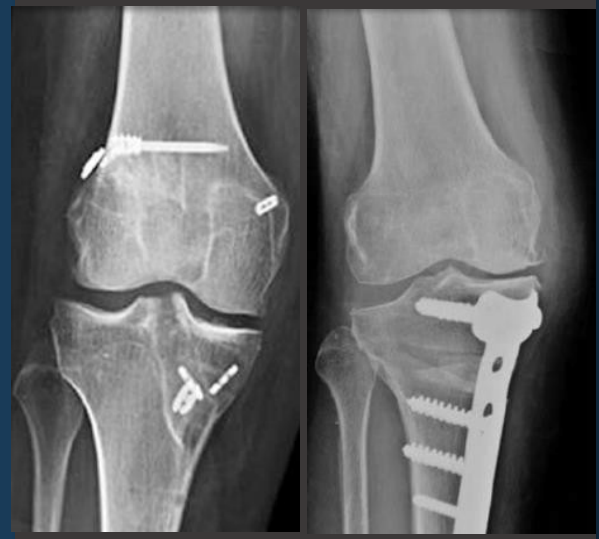
When Possible, Meniscus Transplantation +/- HTO Best Option to Replace a Dysfunctional Meniscus

Knee Preservation Option Considered Current Gold Standard

- MAT Provides the Best Long-Term Option for patients <50
- Can be Combined w/
  - Cartilate Repair for Focal Lesions
  - Alingment Correction w/ HTO
- Key meniscus structures maintained
  - Rim, Anterior/Posterior Root Attachments

Advanced Reconstructive Surgeries

- Meniscal Allograft Transplant
- High Tibial Osteotomy



Anderson 2021 J Am Acad Orthop Surg, Carter 2019 Arthroscopy, Zaffagnini 2019 Arthroscopy, *Getgood 2017* - Am J Sports Med, Gilat 2020 Arthroscopy, Smith 2018 Bone Joint J

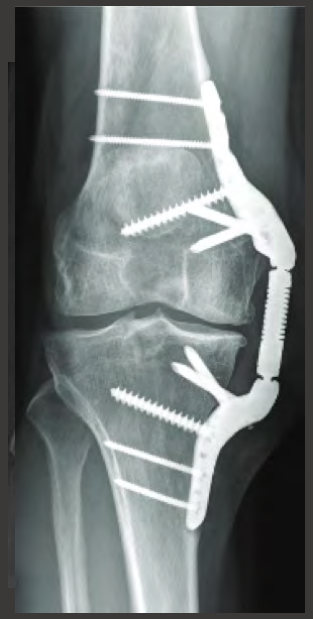
Joint Unloading W/ Internal Springs
A New Alternative to HTO

Medial Compartment Unloading

- Addresses Pain from Overloading Medial Compartment
- Indicated for >5° ~ <10° Varus Deformity

Joint Distraction/Unloading

Implantable Shock Absorber



Diduch 2023 Cartilage, Gomoll 2023 Knee Surg Sports Traumatol Arthrosc.

Lack of Effective Surgical Options Driving More Patients to Seek Knee Replacement

AAOS Projects increase of >600% in 20 Years

- Caseload would need to increase 2X per surgeon, or
- 10% Increase in # of Surgeons/Year X 5 years

Revision arthroplasty

Knee Arthroplasty

- Uni Compartmental Arthroplasty
- Total Joint Replacement

15M Patients

Non-Operative:

- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

5M

Injection

- Steroids
- HA

< 100K

Knee Preservation:

- ACL Recon
- Cartilage Repair
- HTO
- Allograft

1M

Arthroscopy:

- Repair
- Meniscectomy

Blue Cross Blue Shield Health IndexSM (2019), Lamplot 2018 J Bone Joint Surg Am., Singh 2019 J Rheumatol, AAOS Fact Sheet, March 2018, AAOS Fact Sheet, March 2023

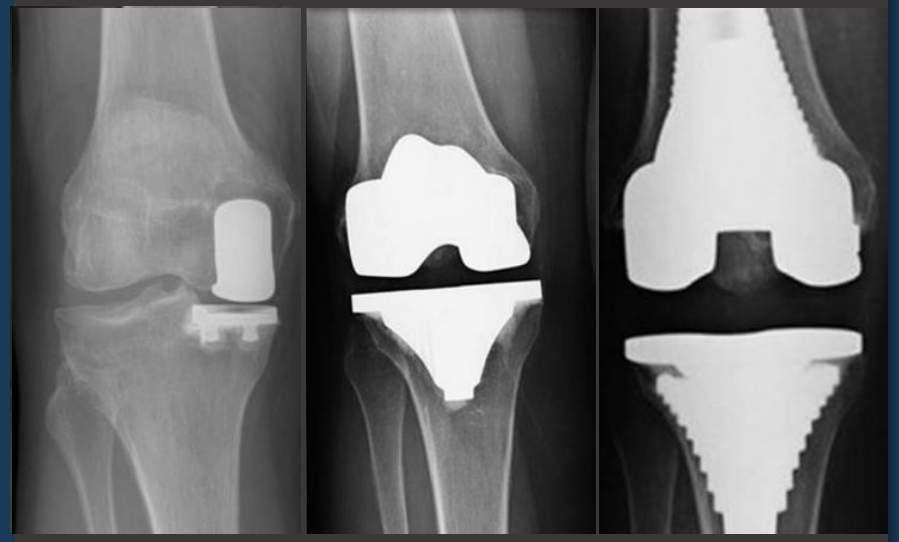
Knee Replacement Procedures Not Indicated for Many Middle-Aged Patients

- Patients Under 55 have worse TKA Outcomes than those over 75.
- End-stage therapy
  - Conversions/Revisions Increase Morbidity
- Patients with severe cartilage degeneration, advanced OA

Ayers 2023 AAOS P0121, Culliford 2012 Osteoarthritis Cartilage, Aujla 2017 J Arthroplasty,

Knee Replacement Surgeries

- Uni-Compartmental Arthroplasty
- Total Knee Arthroplasty
- Revision Total Knee Arthroplasty



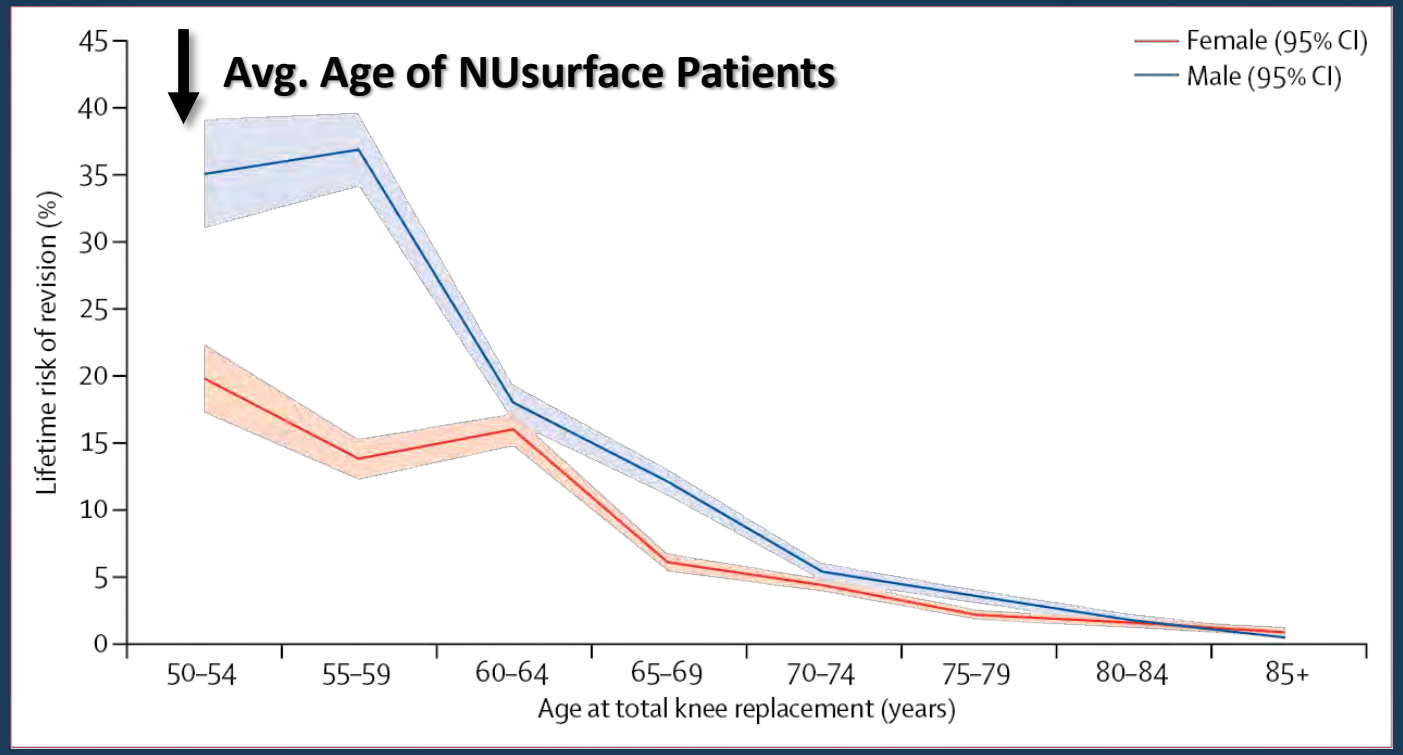
Risks of Early Knee Replacement
Lower Rates of Satisfaction + Higher Revision Rates

Middle-Age Patients Face:

- 1 in 3 Life-time Chance of Revision in 50-55 Year-olds
- 30%-40% Risk of TKA in 2nd Knee within 5-8 Yrs of Primary
- Delaying primary arthroplasty by 5 years could prevent 17% of TKA revisions.

Culliford, 2012 Osteoarthritis Cartilage, *Bayliss Lancet 2017; 389: 1424–30, J Bone Joint Surg Am. 2018;100(20):1750-1756, Acta Orthop. 2021;92(3):280-284.*

Lifetime Risk of Revision After Total Knee Replacement



Lifetime Risk of Revision TKR revision vs. Age at the time of Primary TKR (5-year bands) Stratified by Gender.

Lack of Effective Surgical Options Driving More Patients to Seek Knee Replacement

Revision arthroplasty

Knee Arthroplasty
- Uni Compartmental Arthroplasty
- Total Joint Replacement

Age 55 w/ ViableCartilage
1. Meniscus partly removed, no longer functioning
2. No new tear

1M

Arthroscopy:
- Repair
- Meniscectomy

< 100K

Knee Preservation:
- ACL Recon
- Cartilage Repair
- HTO
- Allograft

5M

Injection
- Steroids
- HA

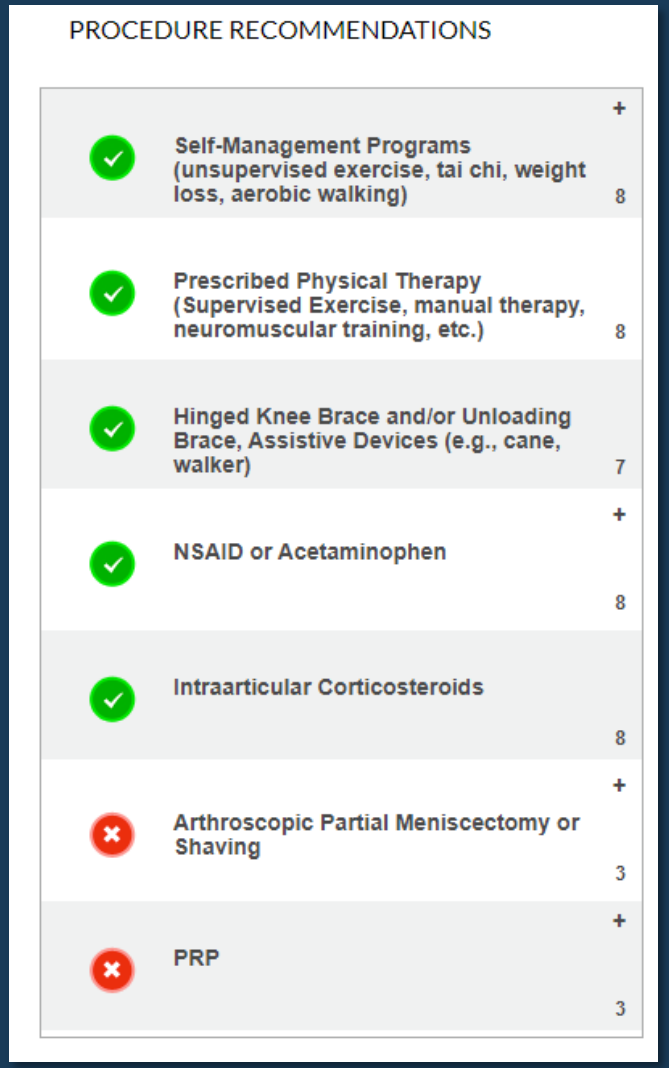
15M Patients

Non-Operative:
- Physical Rehab
- Weight Loss
- Activity Modification
- Medication
- Bracing

Current* AAOS Appropriate Use Criteria for the NUsuface Candidate

Appropriate Use Criteria for management of Osteoarthritis in the knee when:

- Function-limiting pain is constant with or without intense intermittent unpredictable episodes
- Arthritic involvement is predominantly in one weight bearing compartment
- Mild to severe joint space narrowing is present
- Mechanical symptoms are absent
- Young, middle-aged, or elderly patient



* Current as of 04/13/23 www.orthoguidelines.org

Clinical Care Pathway: 55-year-old patient, No Treatable Tear Medial Compartment Knee Pain, Early Signs of OA

Patient has undergone 1, or more, prior arthroscopies

Non-Operative Care

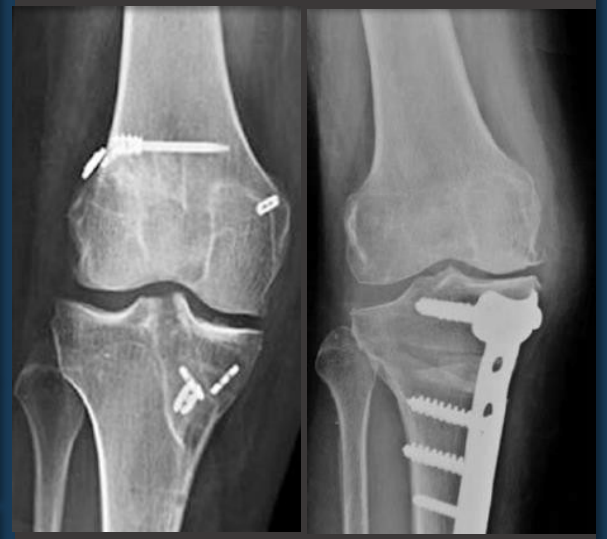
- Activity Modification
- Physical Rehab
- Weight Loss
- Medication
- Bracing
- Steroid Injections
- HA Injections

Arthroscopy

- Repeat Meniscectomy

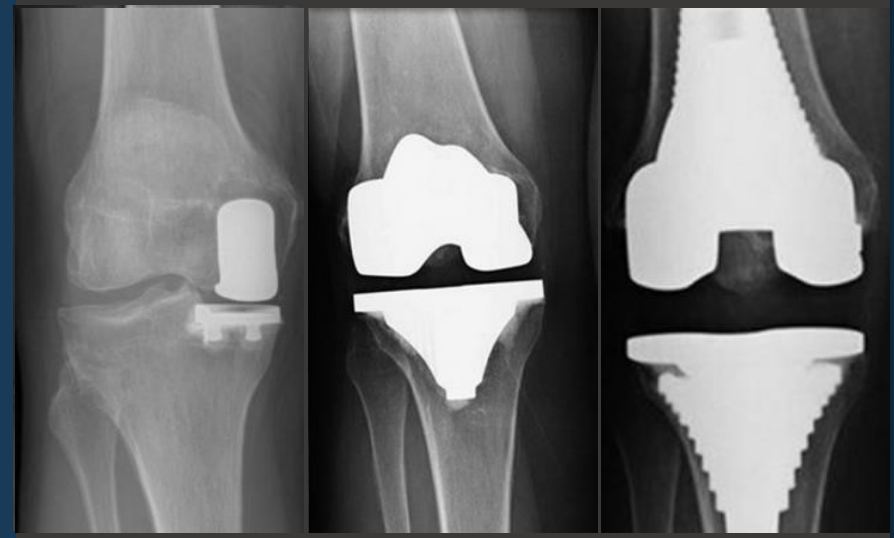
Advanced Reconstructive Surgeries

- Meniscal Allograft Transplant
- High Tibial Osteotomy



Knee Replacement Surgeries

- Uni-Compartmental Arthroplasty
- Total Knee Arthroplasty
- Revision Total Knee Arthroplasty



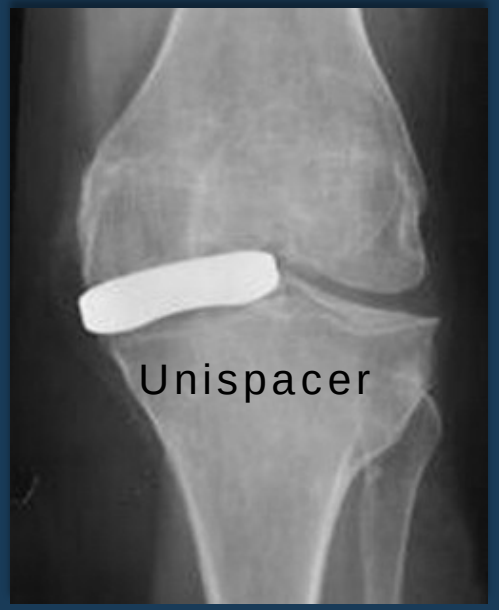
Implants to Replace the Meniscus Have Been Tried Previous Attempts Made from Metal

A Successful Meniscus Implant Must Be Tissue Friendly

- MacIntosh 1958 Vitallium
- Unispacer 2002 Cobalt-Chromium Molybdenum.
- iForma 2004 Cobalt-Chromium Molybdenum.
- OrthoGlide 2007 Cobalt-Chromium.

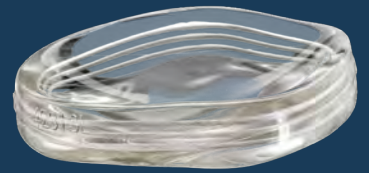
iForma

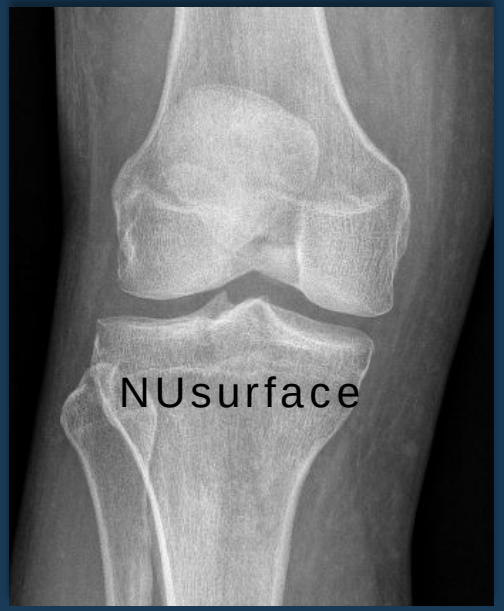
Unispacer



Emerson and Potter,1985; Scottetal.,1985; Springeretal.,2006; Amstutz etal.,1994; D'Arcy andDevas,1976; HallockandFell,2003; Sisto and Mitchell,2005; Bailie etal., 2008

The NUsurface Meniscus Implant is made from tissue-friendly materials

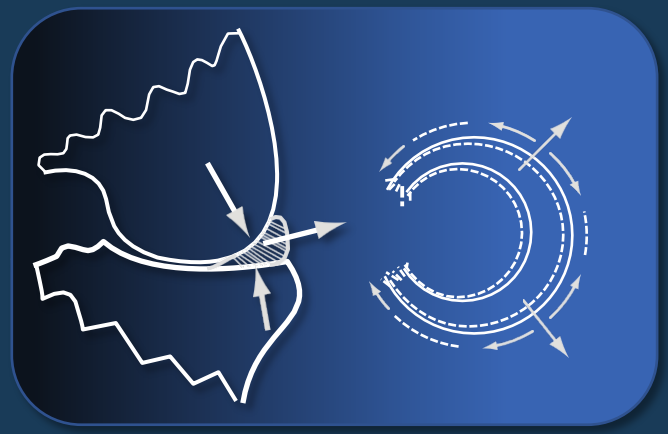




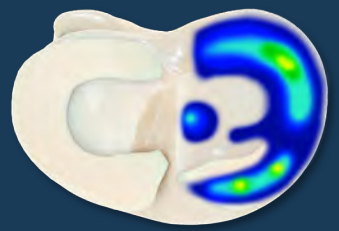
Majid 2017 Colloids Surf B Biointerfaces, Kanca 2018 J Mech Behav Biomed Mater, McCann 2008 Tribol Internat, McCann 2009 J Biomech. McCann 2009 Osteoarthritis Cartilage.

NUsurface Redistributes Load to Protect the Joint

The meniscus transmits load through the knee joint

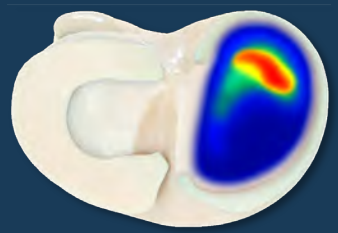


A healthy meniscus distributes pressure evenly

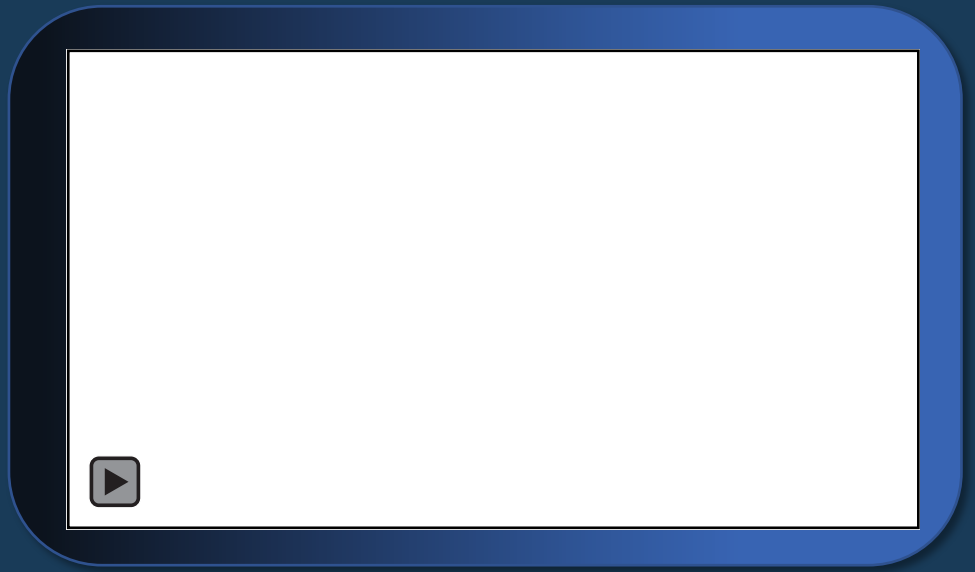


Following meniscectomy: Contact areas decrease & Contact stresses increase

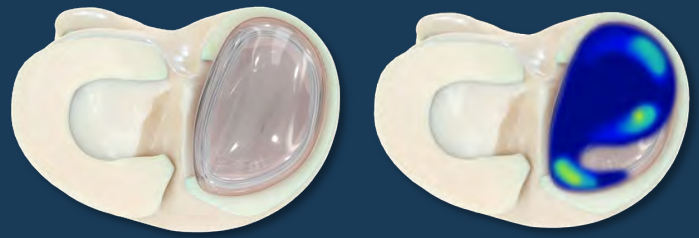
Concentrated stress can lead to joint overload and a ”toothache” type pain



The NUsurface mimics the natural meniscus, redistributing painful loads



NUsurface normalizes pressure distribution

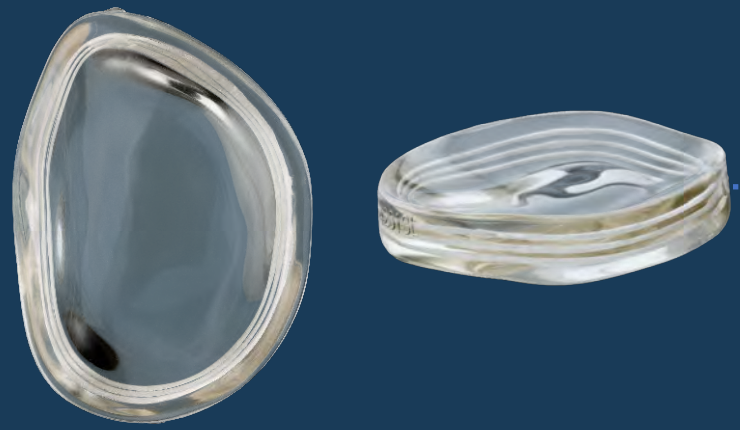


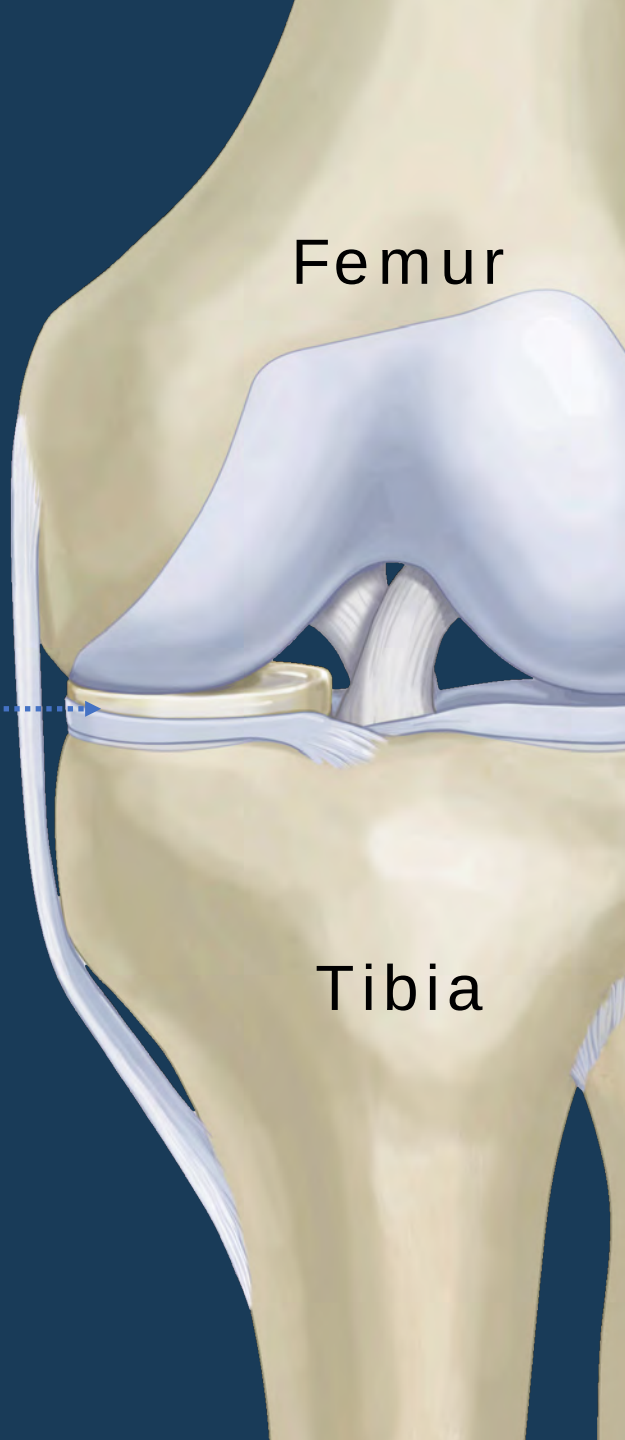
Bedi 2010 J Bone Joint Surg Am

The NUsurface Implant
Cartilage Friendly Pain Relief

The principles of the NUsurface Meniscus Implant are:

1. **Mimic the physical and mechanical properties of a normal meniscus,**
2. **More evenly distribute stress, and**
3. **Absorb some of the strain that would otherwise be transferred to the cartilage**
4. **In the absence of a normally functioning meniscus.**

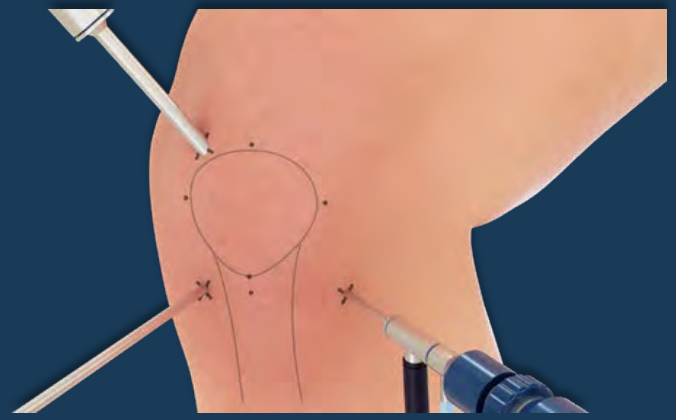


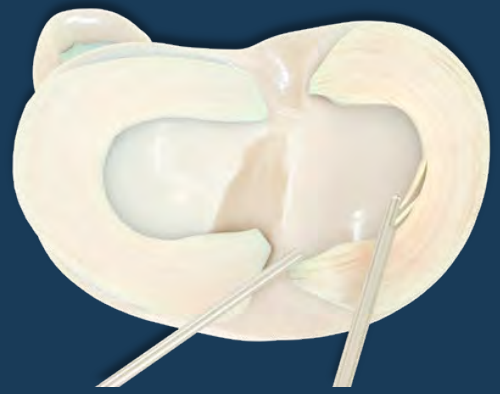


The NUsurace Surgical Technique

1

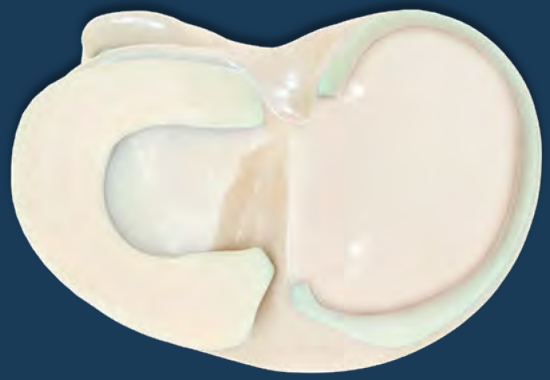
Prepare the Joint Arthroscopically





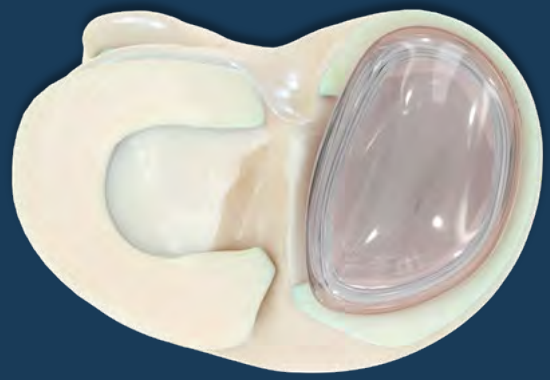
2

Confirm Preparation



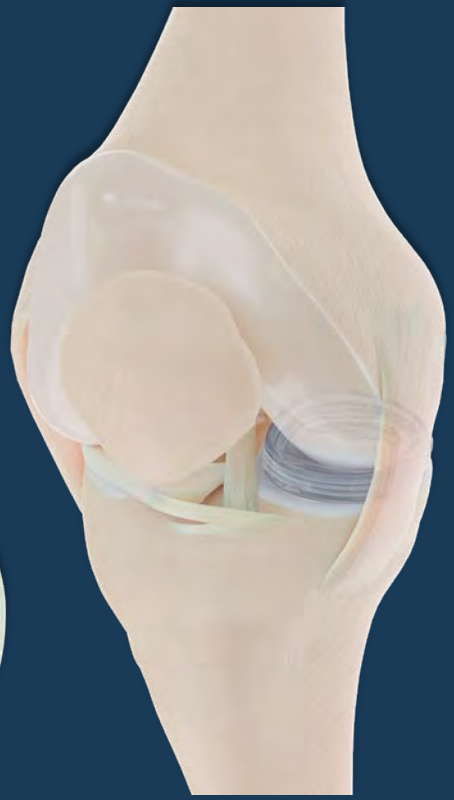
2

NUsurface® Implantation



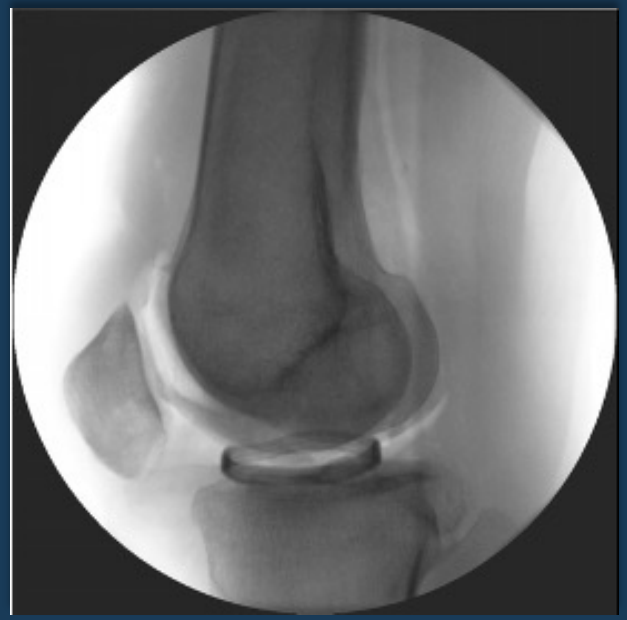
3

NUsurface® Final Position

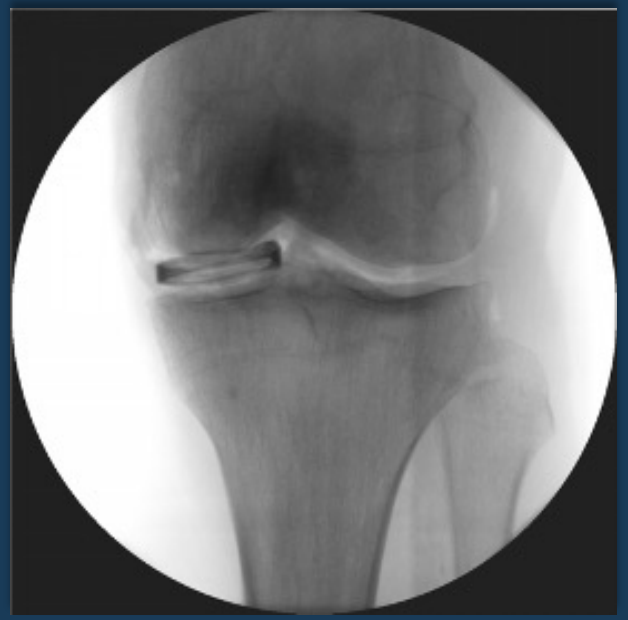


The Figures Below Depict Correct Sizing and Placement of the NUsurface Meniscus Implant for a Typical Patient

Sagittal View

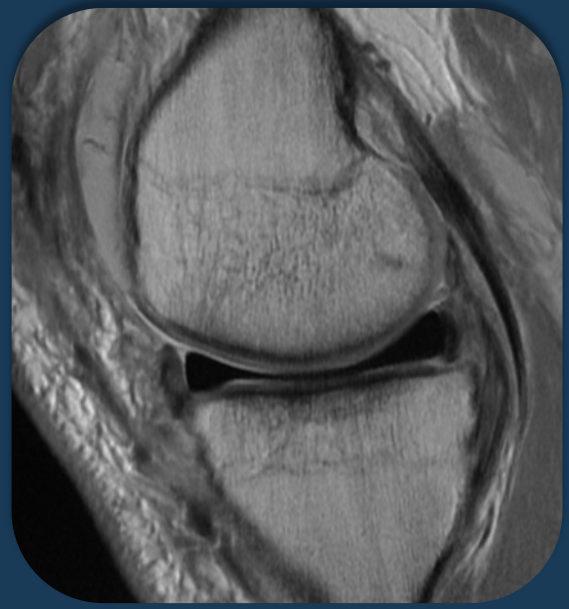


Coronal View

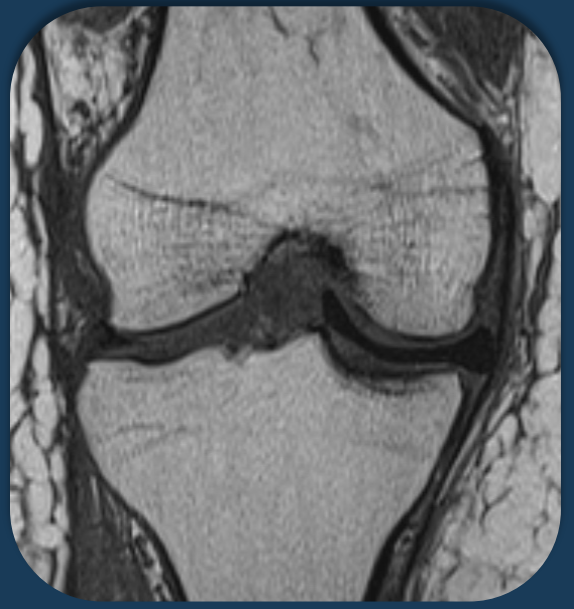


The NUsurface Trial implant is radiolucent. Correct placement and proper movement of the Trial through range of motion is confirmed by intraoperative fluoroscopy

Sagittal View



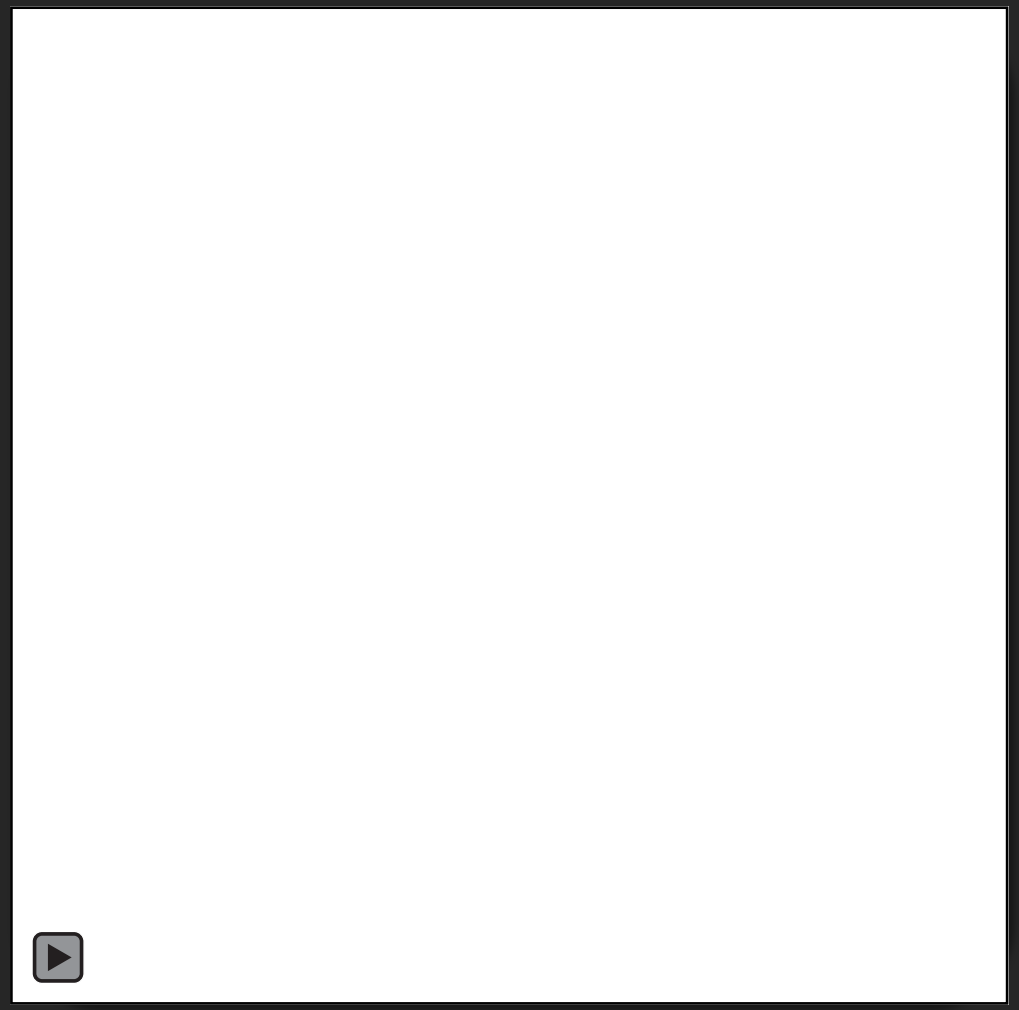
Coronal View



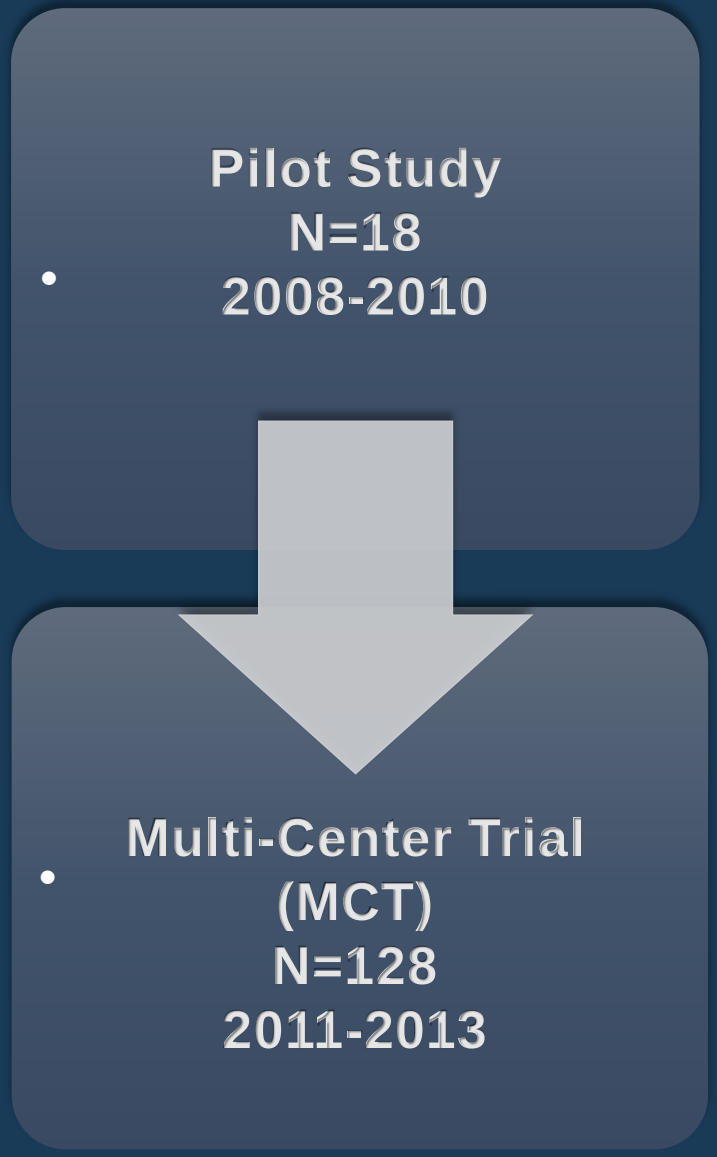
The NUsurface implant is radiolucent on X-ray. Postoperative evaluation should be performed using MRI.

Intraoperative Fluoroscopy

Sagittal view of the radiopaque NUsurface Trial implant under live fluoroscopy



Europe and Israel Clinical History



US Clinical Trials: VENUS & SUN

2014 ”VENUS” - Randomized Controlled Study [GXXXXXX]

- NUsurface Implant (N=61) vs. Non-Operative Therapy (N=66)

2015 “SUN” -Single Arm Study [GXXXXXX]

- NUsurface Implant (N=115) - No Concurrent Control

VENUS and SUN, Two Studies, 30 Surgeons, 22 Sites

VENUS Study: Randomized, 61 NUsurface® Patients, 66 Control Patients, 10 sites

Richard Alfred, MD (Albany, NY)
Maxwell Alley, MD (Albany, NY)
Jack Farr, MD (Indianapolis, IN)
William Garrett, MD (Raleigh, NC)
Thomas Giel, MD (Memphis, TN)
Andreas Gomoll, MD (New York, NY)
Elliott Hershman, MD (New York, NY)
Randall Holcomb, MD (Memphis, TN)
Christopher Kaeding, MD (Columbus, OH)
Christian Lattermann, MD (Boston, MA)
Brian McKeon, MD (Boston, MA)
Claude Moorman, MD (Raleigh, NC)
Allison Toth, MD (Raleigh, NC)
Kenneth Zaslav, MD (Richmond, VA)

SUN Study: Single Arm, 115 NUsurface® Patients, 13 sites

Larry Bankston, MD (Baton Rouge, LA)
Joseph Berman, MD (Dallas, TX)
Thomas Carter, MD (Phoenix, AZ)
Andrew Cooper, MD (Salt Lake City, UT)
Robert Easton, MD (Baton Rouge, LA)
Richard Edelson, MD (Portland, OR)
Rachel Frank, MD (Denver, CO)
Wayne Gersoff, MD (Denver, CO)
Jonathan Greenleaf, MD (Portland, OR)
Scott Hacker, MD (San Diego, CA)
Deryk Jones, MD (New Orleans, LA)
Peter Kurzweil, MD (Long Beach, CA)
Eric McCarty, MD (Boulder, CO)
William Montgomery, MD (San Francisco, CA)
Armando Vidal, MD (Vail, CO)
Noah Weiss, MD (Sonoma, CA)

VENUS and SUN Trials: Same Inclusion/Exclusion Criteria

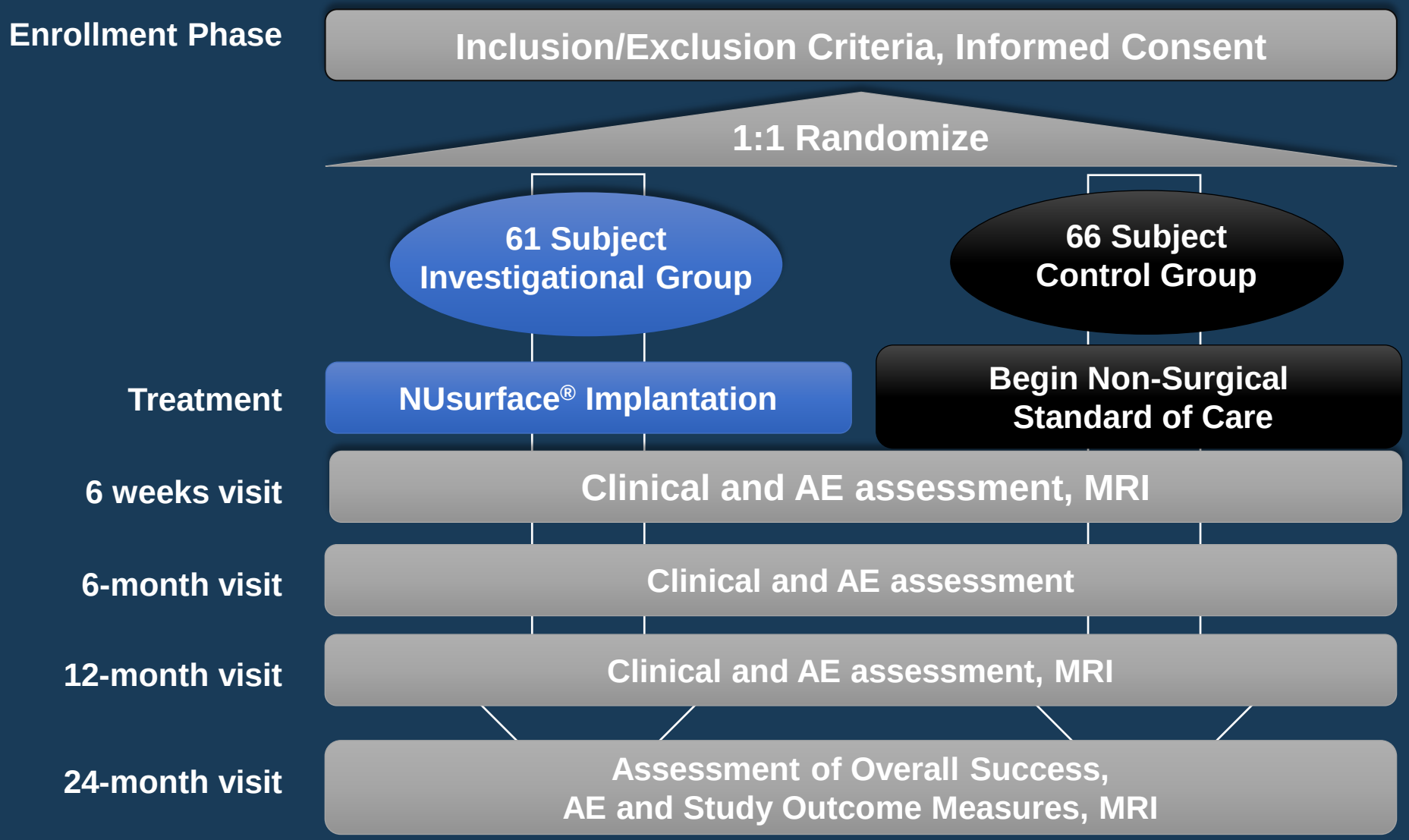
Inclusion criteria

- have a previous medial meniscectomy as confirmed by diagnostic MRI and subject history at least 6 months prior to the start of study treatment,
- have a pain score of 75 or less on the KOOS (Knee injury Osteoarthritis Outcome Score) pain scale, with 100 being normal,
- have ≥ 2 mm intact meniscal rim and is capable of receiving a NUsurface device, if used,
- have a subject age between age 30 and 75 at the time of the start of study treatment,
- enter subjects willing and able to follow the study protocol
- have subjects willing to receive, if used, non-surgical care therapy
- be able to read and understand English

Exclusion criteria

- have evidence of a Grade IV (Outerbridge) articular cartilage loss on the medial tibial plateau or femoral condyle that could contact the NUsurface® implant (e.g., a focal lesion >0.5 cm^2),
- have a varus/valgus knee deformity > 5 degrees,
- have a knee laxity level of more than II (ICRS), secondary to previous injury of the anterior cruciate ligament (ACL), and/or posterior cruciate ligament (PCL) and/or lateral collateral ligament (LCL) and/or medial collateral ligament (MCL),
- have patellar compartment pain and/or patellar articular cartilage damage greater than Grade II,
- have an ACL reconstruction performed less than 9 months before implanting the NUsurface® implant,
- be excessively obese (BMI > 32.5)

VENUS Study: RCT Study design



VENUS STUDY: Definition of Success

Non-Surgical Control Overall Success =
KOOS Success + No Automatic Study Failure

- **+20 pt KOOS Pain**
  +
- **+20 pt KOOS Overall**

No Knee Surgery

NUsurface® Overall Success =
KOOS Success + MRI Success + No Automatic Study Failures

- **+20 pt KOOS Pain**
  +
- **+20 pt KOOS Overall**

- **No Dislocated Implants**
- **No Implants Fractured**

No Implant Removal, Replacement, or Repositioning

VENUS and SUN: Data Quality

- Multiple Sites Enrolled
- Balanced Baseline between NU and Control
- Balanced Baseline Cartilage Condition
- High follow-up of >95% the expected follow-up at each timepoint
- 100% Monitored Data
- Active Implants and 4 Sites audited by FDA with no major observations.

VENUS Study Outcomes

- 24-Month Study results: NUsurface Superior to Controls at p=0.029
- Also Superior at 6, 12-month Follow-up
- Automatic Study Failures not statistically different compared to Controls at 6, 12, and 24 months
- KOOS Overall Responder Rate: 81% met MCID including 7 exchanges

SUN Study

Study Rationale

- To gather safety and probable clinical benefit data to support a future De Novo regulatory petition in the U.S. and/or provide additional clinical data of the safety and effectiveness of the NUsurface Meniscus Implant.

Primary Endpoint

- 90% of patients at one year without a device malfunction
- No single device related adverse event in more than 10% of subjects

SUN Merged into VENUS = MERCURY

- October 2017: Sponsor met with the review team to discuss data availability and timing
  - FDA suggested pooling SUN and VENUS and said 24-month data would be required for a de novo
- 2017 – 2019: Worked with FDA to merge SUN into VENUS
- March 2019: VENUS IDE Supplement GXXXXXX/SXXX approved with the revised VENUS Statistical Analysis Plan (SAP)
  - Proposed propensity analysis to adjust the combined studies before any 24-month data was unblinded.
  - The combined study was named MERCURY.
- MERCURY = 242 Subjects 176 NUsurface vs 66 Non-surgical Control
  - VENUS primary and secondary endpoints were adopted for the MERCURY Trial

MERCURY STUDY: NUsurface and Controls not Different at Baseline

Average Patient:

50 yrs. Old Male	2+ knee arthroscopies	Using oral/injections	Grade 2-3 cartilage damage

Baseline Demographic Characteristics:

Measure	NUsurface n= 176	Control n= 66	p
Age - yr	49.78 ±10.06	49.82 ±10.27	0.9814
Body Mass Index (BMI)	27.04 ±3.13	26.83 ±3.64	0.6558
Male Gender - n (%)	130 (73.9%)	48 (72.7%)	0.8709
Left Index Knee - n (%)	89 (50.6%)	31 (47.0%)	0.6662
Median (range) months since last meniscectomy	81.34 ±89.68	67.02 ±76.81	0.2519
One Previous Partial Meniscectomy - n(%)	123 (69.9%)	46 (69.7%)	1.0000
Two or More Previous Partial Meniscectomies - n(%)	53 (30.1%)	20 (30.3%)	1.0000

MERCURY: NUsurface Met the Primary Endpoint Overall study success (p=0.013)

Primary Endpoint Calculations

Propensity Adjustment	Success Rates	p value
Unadjusted	Control = 12/52 = 23.1% NUsurface = 77/172 = 44.8%	p = 0.006
Adjusted According to GXXXXXX/SXXX Statistical Analysis Plan (Per Protocol)	Control = 12/52 → 23.6% NUsurface= 77/172 → 44.3%	p = 0.010
Adjusted Using Dichotomized Propensity Score to Account for Prior Physical Therapy and Cartilage Surgery	Control = 12/52 → 23.3% NUsurface = 77/172 →43.1%	p = 0.013

Secondary Endpoint Calculations

Hierarchical Rank Order	Endpoint Description in the Statistical Analysis Plan	P-Value
1	Overall Success at 24-Months	0.013
2	24-Month VAS vs Baseline	0.002
3	24-Month MRI vs Baseline of Cartilage Condition In Medial Compartment	<0.001
4	24-Month IKDC SKEF Score vs Baseline	<0.001
5	24-Month QALY Score vs Baseline (using EQ-5D)	0.028
6	24-Month KOOS Pain	<0.001
7	24-Month KOOS Overall	0.003
8	12-Month KOOS Pain	<0.001
9	12-Month KOOS Pain vs Baseline	0.001
10	12-Month VAS vs Baseline	<0.001

Hierarchical Rank Order	Endpoint Description in the Statistical Analysis Plan	P-Value
11	12-Month KOOS Overall vs Baseline	<0.001
12	12-Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau	N/A*
13	12-Month IKDC SKEF Score vs Baseline	<0.001
14	12-Month QALY Score vs Baseline (using EQ-5D)	0.012
15	24-Month Return to Work	N/A*
16	6-Month KOOS Pain	<0.001
17	6-Month VAS vs Baseline	<0.001
18	6-Month IKDC SKEF Score vs Baseline	<0.001
19	6-Month KOOS Overall	<0.001
20	6-Month QALY Score vs Baseline (using EQ-5D)	0.028

Total Population Adverse Event Risks

Five Types of AEs Occurred at a Statistically Different Rate Than Controls

- **Four were device specific:**
  - **Damage, Dislocation, Dislocation and Damage, and Noise.**
  - **These events resulted in device related second surgeries in Table 1**
- **The fifth, Effusion, is related to having a surgical procedure and was transient, as shown in Table 2.**

Table 1: Device Related Secondary Surgeries	NUsurface Arm
Device Repositioning from Dislocation or Rotation	4/175 = 2.3%
Permanently Removed Device	18/175 = 10.3%
Device Exchanges	36/175 = 20.6%

Table 1: Device Related Secondary Surgeries

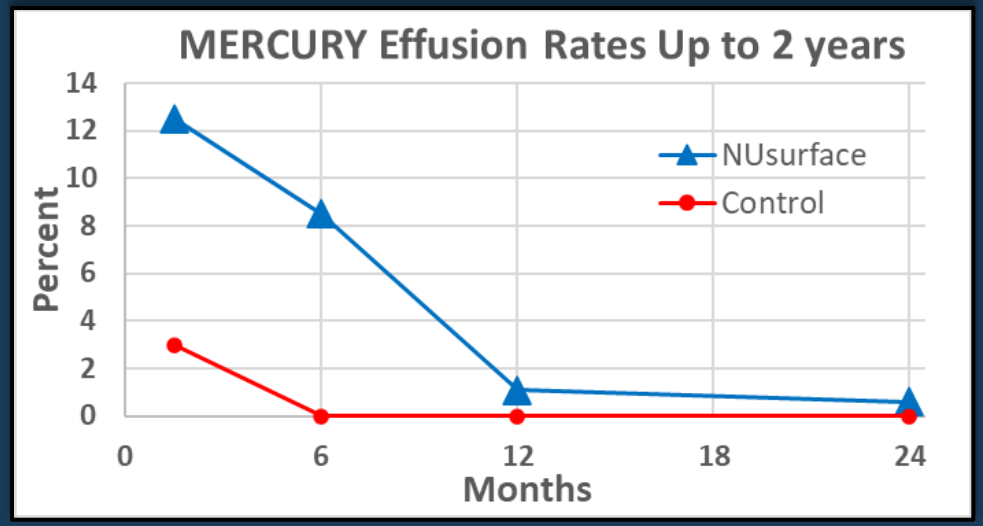


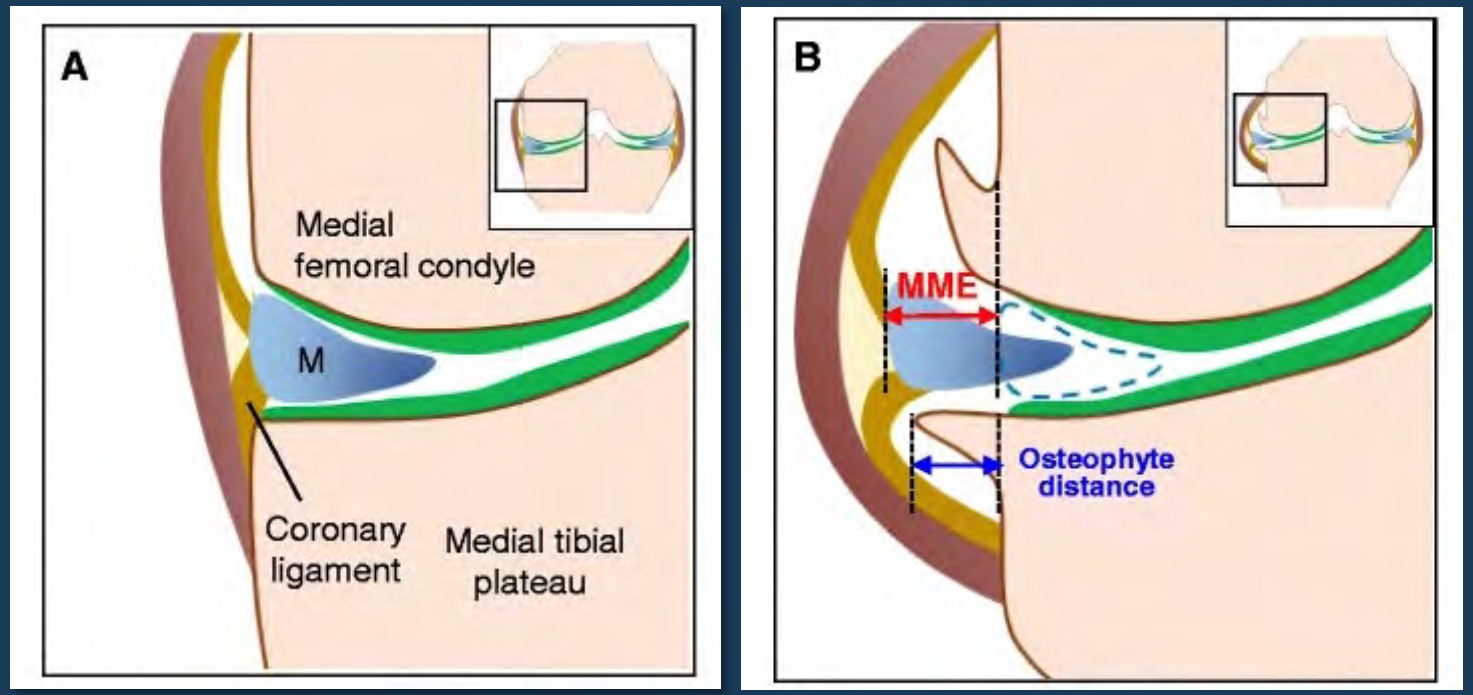
Table 2. Effusion Rates

Identifying the Subpopulation

- FDA denied the de novo submission in 2021 citing safety concerns because of the rate of revision surgeries.
- Patients with >1 previous meniscectomy had worse outcomes than patients with only 1 previous meniscectomy in MERCURY
- Meniscus extrusion is correlated with degenerative changes in the meniscus and cartilage
- The degree of meniscal extrusion identified a subpopulation with reduced rates of surgical failure, and an improved benefit-risk profile when compared to the total study population.

MERCURY Subpopulation: Meniscus Extrusion

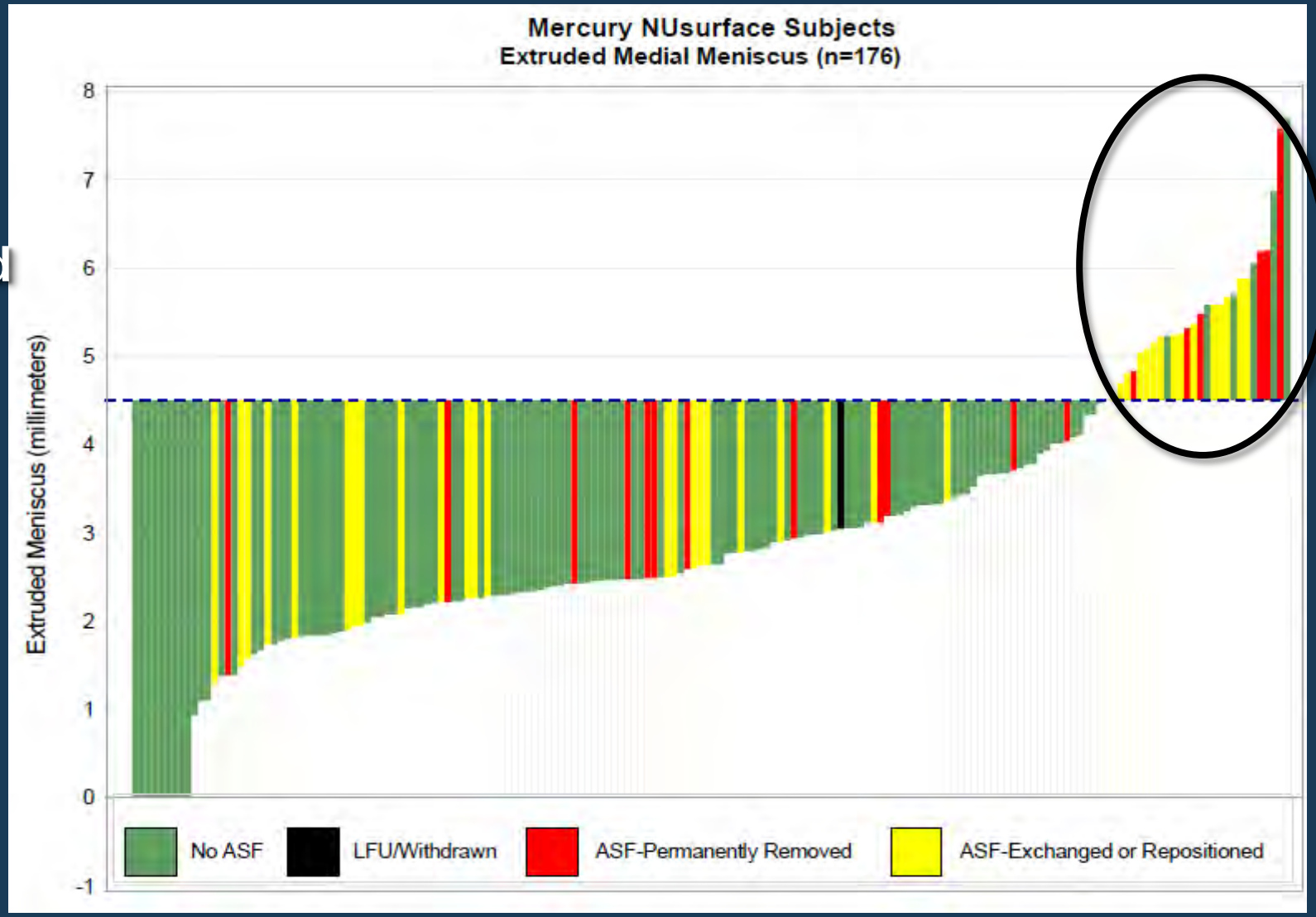
- Baseline meniscal extrusion indicates the quality of surrounding tissue
- Meniscal extrusion >3mm is associated with severe meniscus and cartilage degeneration and root tears, an indication of more advanced medial compartment osteoarthritis



Left knee showing a normal intact Medial Meniscus (A), and a Medial Meniscus Extrusion - MME (B). Taken from Shinnosuke et al., (2017)

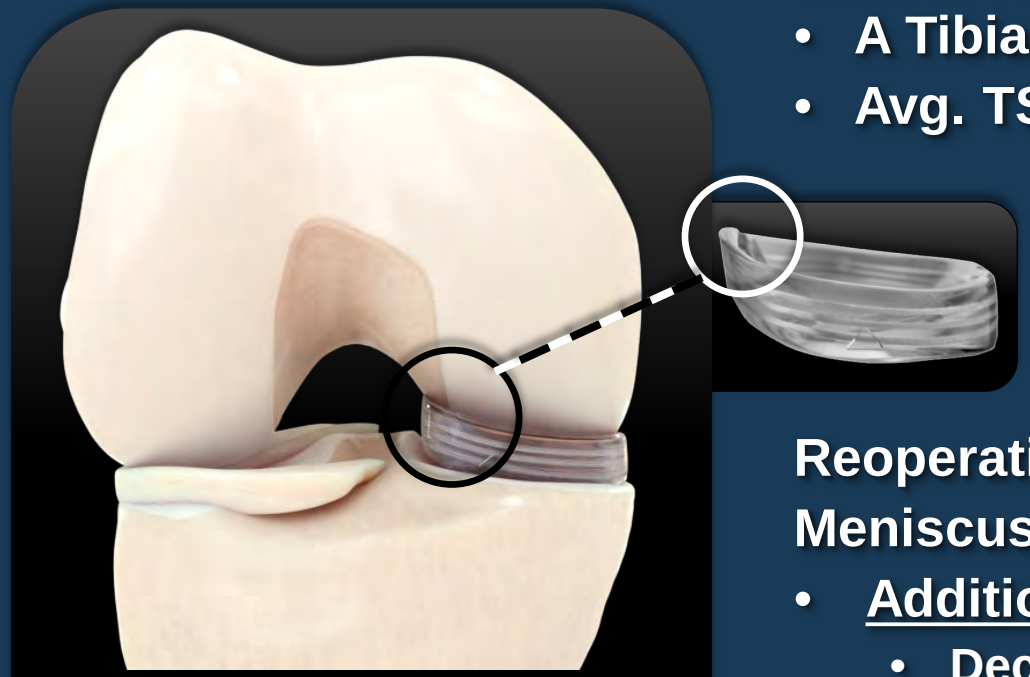
Meniscus Extrusion in the Subpopulation ≥5mm of Extrusion

- 28 NUsurface subjects had meniscus extrusion ≥5mm
- 78.6% of these subjects had device related second surgeries (circled).
- 23.6% of Subjects with extrusion <5mm has a device related second surgery.



MERCURY Subpopulation: Tibial Spine Height (TSH)

Non-Anchored Design Relies on Lateral Wall of the Tibial Spine for Stability



Lateral Bridge Design of the NUsurface

Lateral Wall of NUsurface Engages Lateral Wall of Tibial Spine

- A Tibial Spine that is Too Low Increases Instability
- Avg. TSH in the MERCURY Study Total Population = 11mm

Reoperations Significantly Reduced After Excluding Patients w/ Meniscus Extrusion >5mm, while

- <u>Additionally, Excluding Patients with TSH <11mm</u>:
  - Decreased Permanent Removals
    - From 8.3% to 6.9%.
  - Decreased Rate of Exchange
    - From 13.1% to 9.7%

MERCURY Subpopulation: Tibial Spine Height

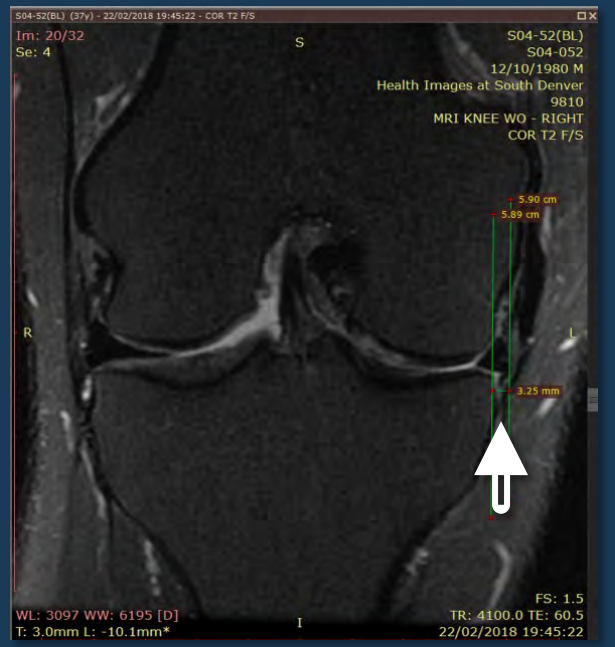
- Tibial spine height could have been as read as either 10mm or 11mm in 28 of 176 NUsurface subjects.
  - Including these 28 subjects would have increased the subpopulation from 74 to 102.
- Comparing the two subpopulations:
- Removal and Exchange rates are similar
- There was no difference in KOOS Overall improvement
- Precise measurement of TS height is not critical to identify a population with a better benefit risk profile.

MERCURY Trial Subpopulation Easy to Identify

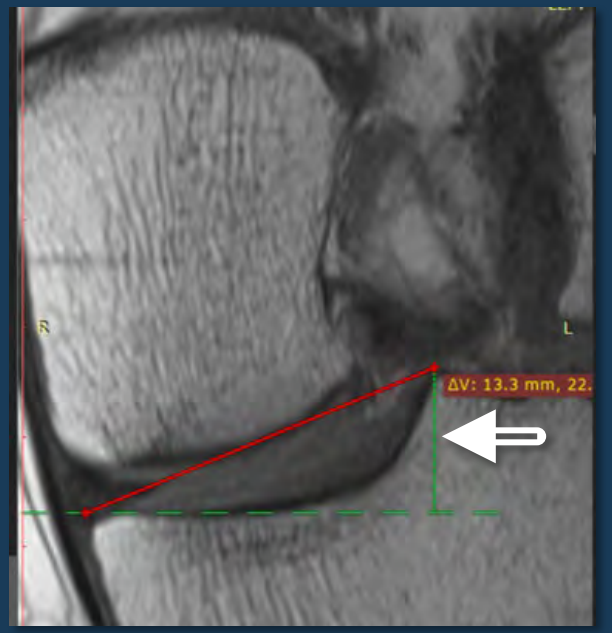
Two Pre-op MRI Measurements Identify Patients with Reduced Risk of Reoperations

Population Summary:			
Total Population:	242 Subjects	176 NUsurface	66 Control
Exclude:	Meniscus Extrusion (ME) Greater Than 5mm + Tibial Spine Height (THS) <11mm		
Subpopulation:	109 Subjects	74 NUsurface	35 Control

Representative MR-image of medial meniscus extrusion and measurement (3.25 mm)

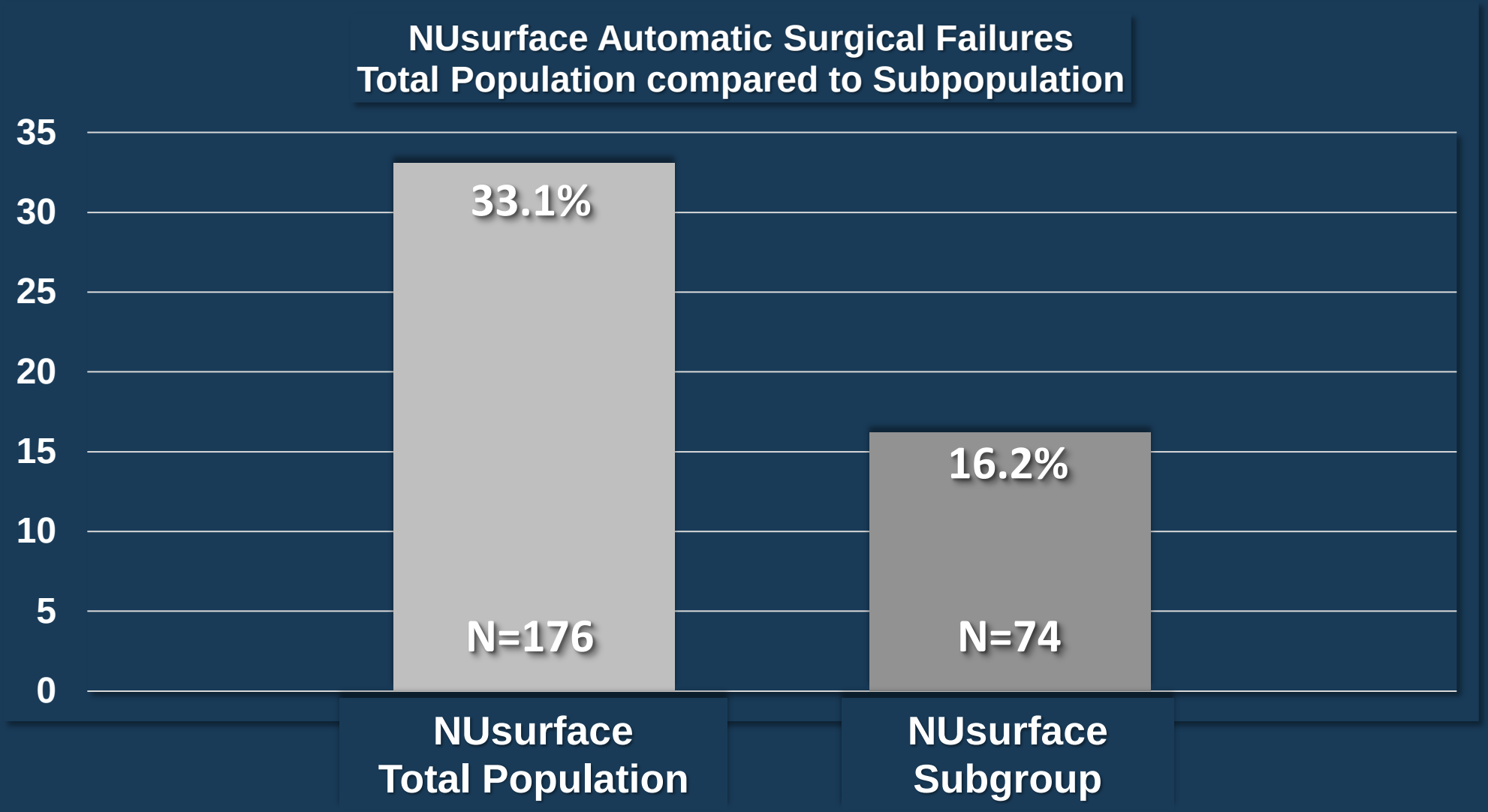


Medial Tibial Spine Proximal-Distal Height



Vertical leg of the right-angled triangle, 13.3 mm

NUsurface Subgroup reduced Surgical Failures by 50% from 33.1% to 16.2%



Confirmation of Subpopulation Methods

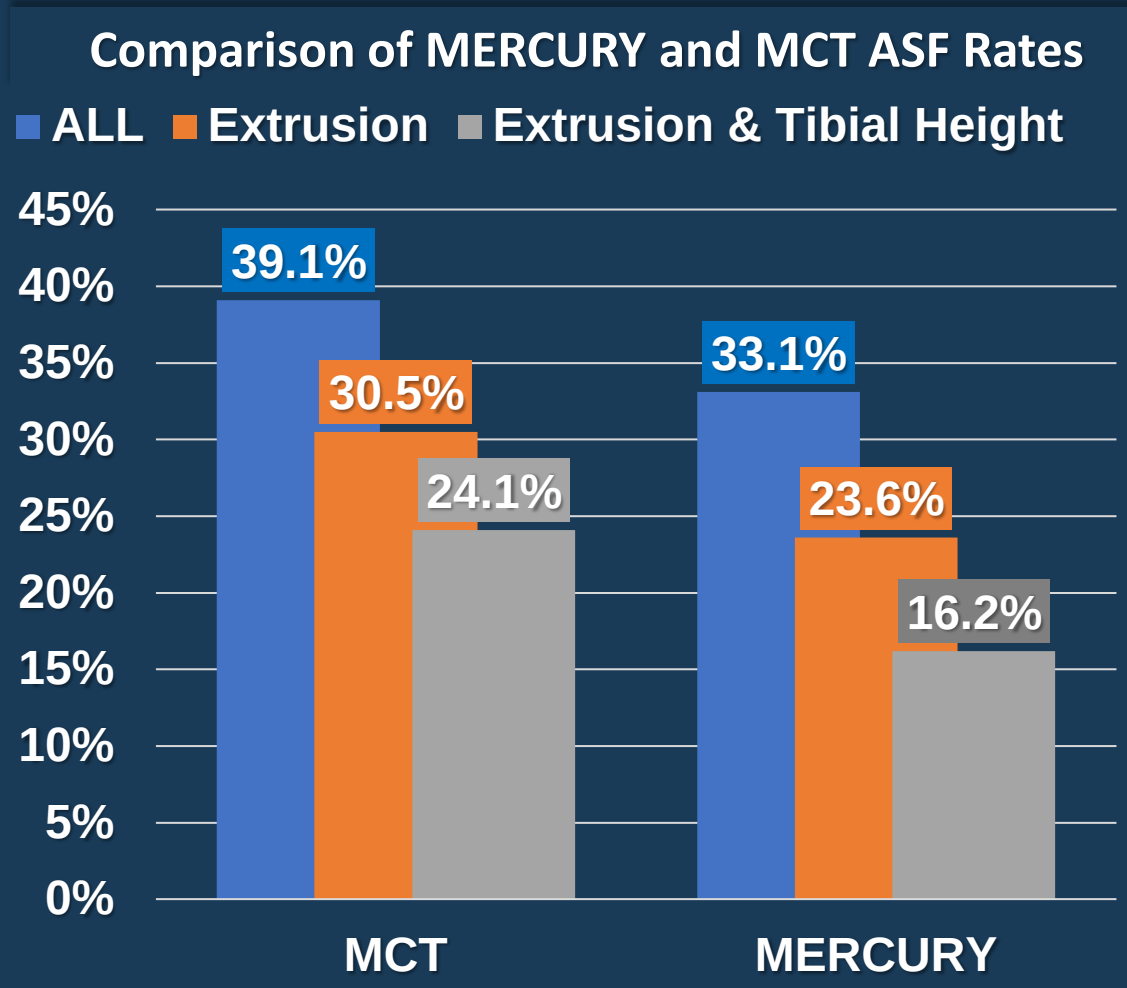
Multi Center Trial (MCT) Analysis Details:

- The radiographic criteria which defined the subpopulation were applied to data from the MCT study, a 24-month, single arm clinical trial of NUsurface in 128 subjects from the EU and Israel that began enrollment in 2011
- Inclusion/Exclusion criteria and PRO/MRI visit schedule were similar to MERCURY with average age and BMI matching MERCURY.
- All MRIs were radiographically screened according to the MERCURY subpopulation criteria.
- The MERCURY definition of Automatic Surgical Failure (ASF) was applied to MCT subjects.

Confirmation of Subpopulation Methods

Multi Center Trial (MCT) Analysis Details:

- NUsurface patients with <5mm of meniscus extrusion have a significantly decreased rate of device related second surgeries compared to subjects with 5mm or greater extrusion ($p<0.001$).
- MCT and MERCURY subjects with 5mm or greater meniscus extrusion had similar rates of secondary procedures; 77% and 79%.
- The average medial tibial spine height was 11mm in MCT and MERCURY subjects.
- 46% of subjects in the MCT study and 42% of subjects in the MERCURY study are included in the subpopulation, indicating comparability between the two studies.



NUsurface Subgroup Study Success

Overall Study Success of the MERCURY Trial:

- **Adjusted and Last Observation Carried Forward (LOCF) Total Population vs. Subpopulation**

Subpopulation Study Success Measurements			
Analysis	**NUsurface**	**Control**	**p-value**
Unadjusted 24 Month	51.4%	16.1%	**<0.001**
Adjusted 24 Month	48.1%	18.2%	**0.011**
LOCF 24 Month	48.1%	18.2%	**0.011**
LOCF 12-24 Month	48.7%	16.0%	**0.009**

All analysis methods improved superiority in the subpopulation

NUsurface Subgroup Superior in Secondary Endpoints

Superiority achieved in 3 prespecified secondary endpoints:

- Visual Analog Pain Scale (VAS)
- Medial Compartment Cartilage Condition
- International Knee Documentation Committee Subjective Knee Evaluation Form
- Secondary Endpoints superiority agree with Primary Endpoint, KOOS superiority.

Number	Hierarchical Rank Order	Calculated p Value
1	24 Month VAS vs Baseline	0.036
2	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006
3	24 Month IKDC SKEF Score vs Baseline	0.003

NUsurface Subgroup Secondary Endpoints

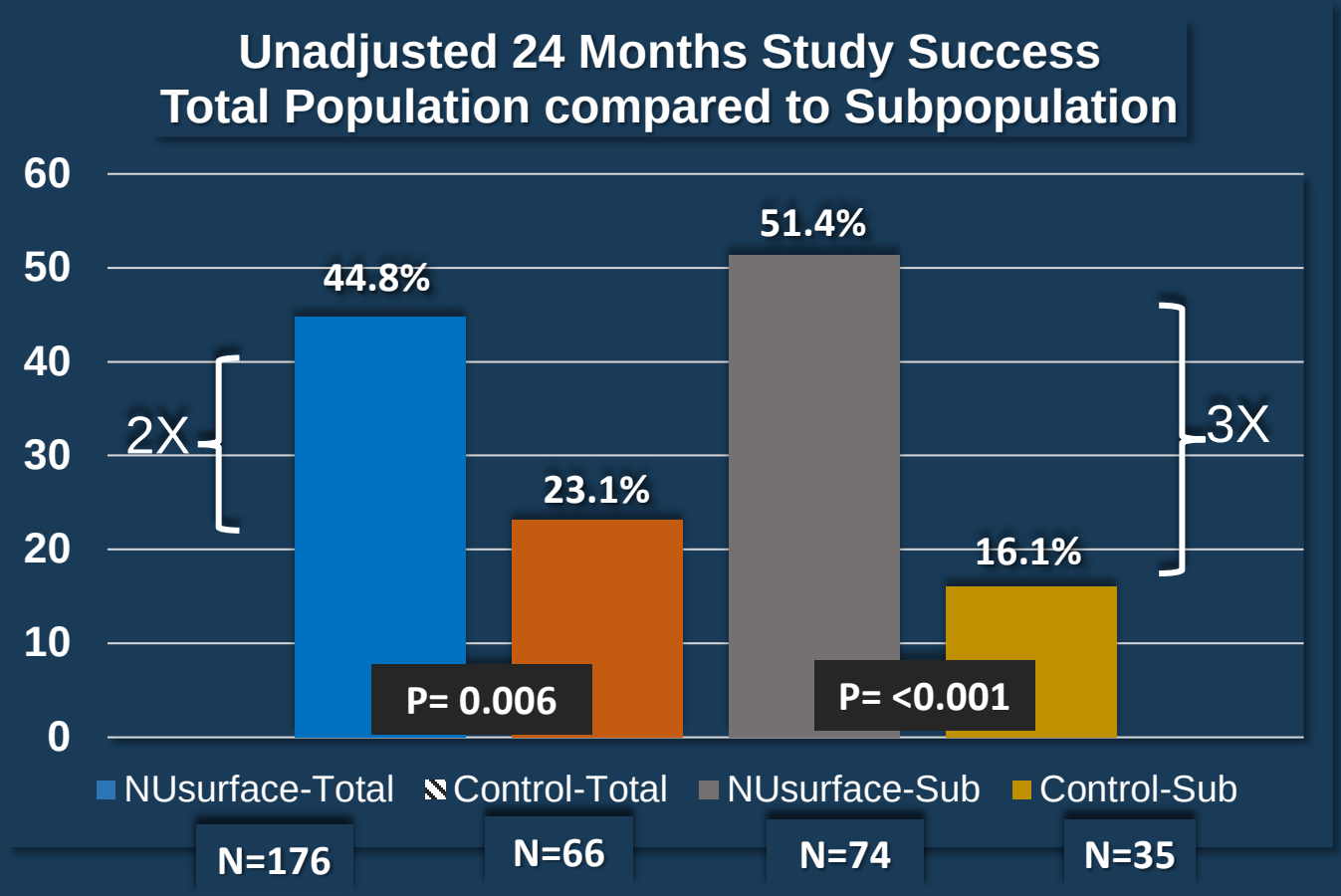
- Superiority in the first 3 prespecified secondary endpoints in green
- Additional secondary endpoints in orange had a p-value below 0.05.

Number	Hierarchical Rank Order	Calculated p Value
1	Overall Success at 24 Months	0.011
2	24 Month VAS vs Baseline	0.036
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006
4	24 Month IKDC SKEF Score vs Baseline	0.003
5	24 Month QALY Score (using EQ-5D)	0.810
6	24 Month KOOS Pain	0.101
7	24 Month KOOS Overall	0.273
8	12 Month KOOS Pain	0.107
9	12 Month KOOS Pain vs Baseline	0.019
10	12 Month VAS vs Baseline	0.002
11	12 Month KOOS Overall vs Baseline	0.004
12	12 Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau	-
13	12 Month IKDC SKEF Score vs Baseline	0.039
14	12 Month QALY Score (using EQ-5D)	0.850
15	24 Month Return to Work	-
16	6 Month KOOS Pain	0.054
17	6 Month VAS vs Baseline	<0.001
18	6 Month IKDC SKEF Score vs Baseline	0.003
19	6 Month KOOS Overall	0.034
20	6 Month QALY Score (using EQ-5D)	0.155

NUsurface Subgroup Has Improved Benefit/Risk Compared to Overall Population

Overall study superiority increased + superiority maintained in 10 secondary endpoints

- **Study Success vs controls increased from 2 times to over 3 times**
- **Superiority of 10 secondary endpoints at 24, 12, and 6 months**



Nogah Shabshin, MDMSK Radiologist
University of Pennsylvania

Radiological Evaluation of the NUsurface Implant

Disclosure statement

I am a consultant to Active Implants. I have been paid for my time and travel here today and have equity in the company but do not have any royalties or other interests contingent on the outcome of this meeting.

Objectives of the MRI Study in MERCURY

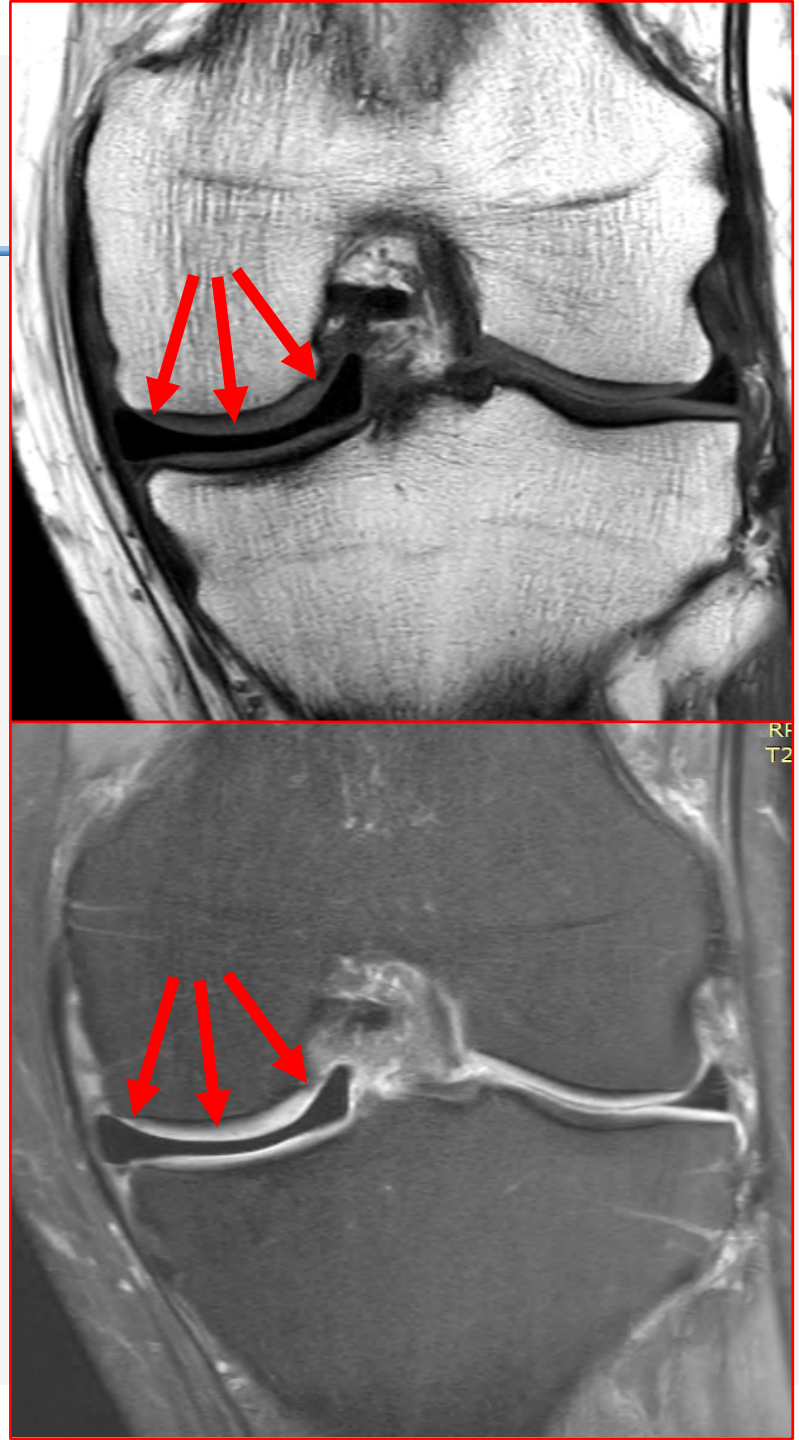
- To evaluate changes in the cartilage condition in NUsurface patients vs. Controls
- To assess the safety of the device

during the first 2 years of therapy

Role of MRI in MERCURY

- Pre-op candidate screening
- Non-invasive evaluation of cartilage and other joint structures during the study period
- MRI is better than arthroscopy for evaluation of the subchondral bone
- Evaluation of implant position and integrity

Chaudhari 2020 JMRI
Choi 2011 Magn Reson Imaging Clin N Am
Everhart 2019 JBJS
Gold 2009 AJR
Ochi 1994 Arthroscopy



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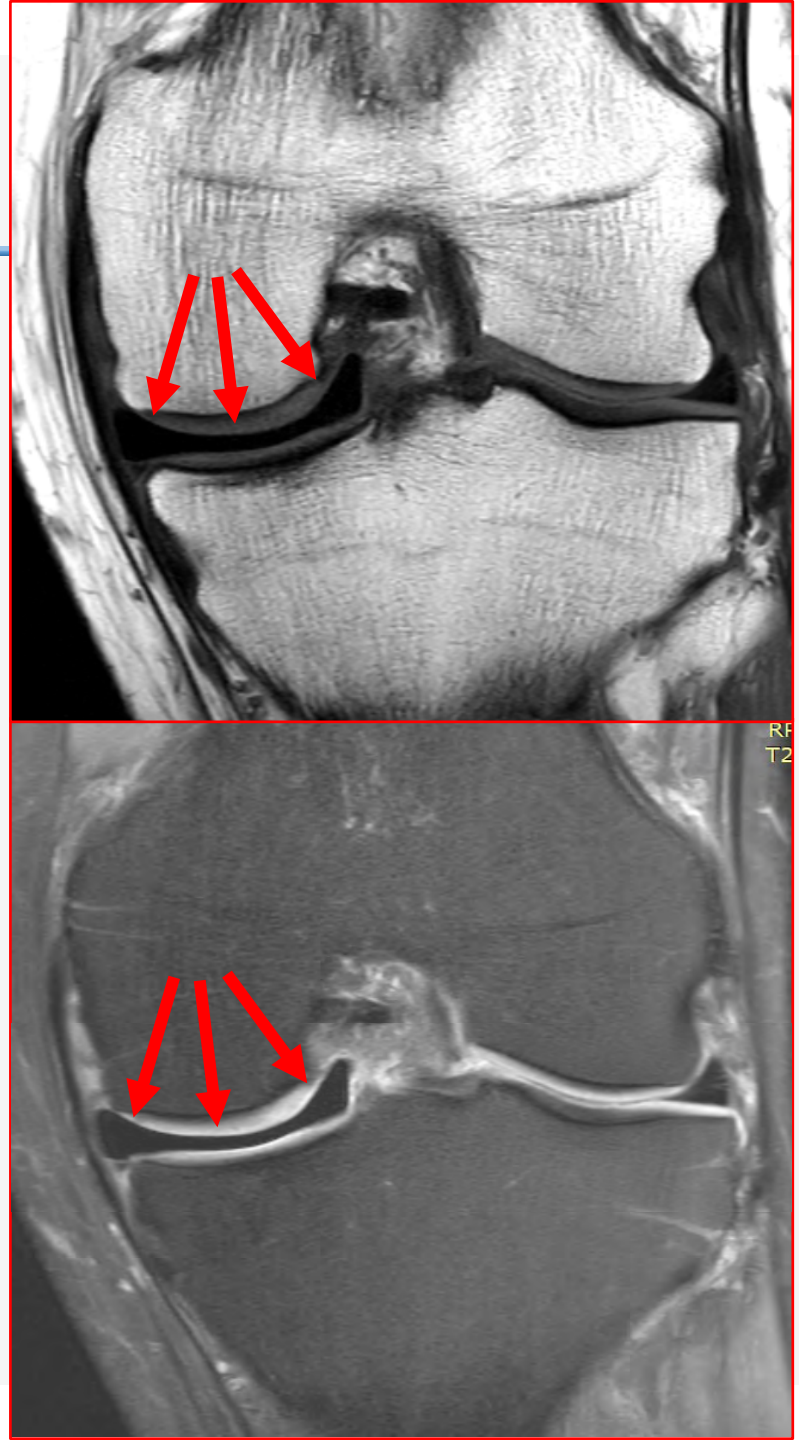
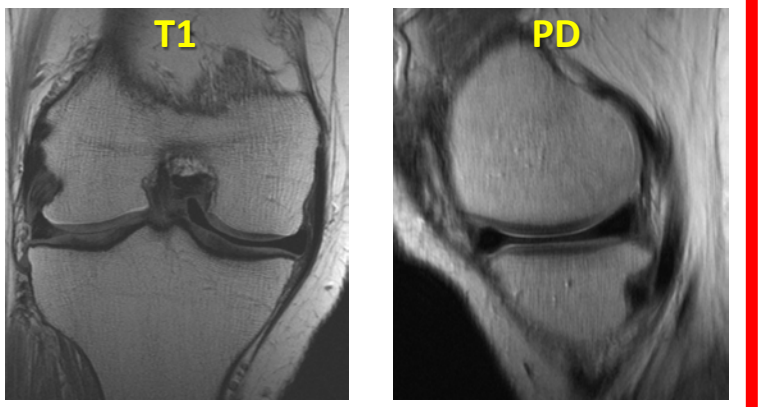
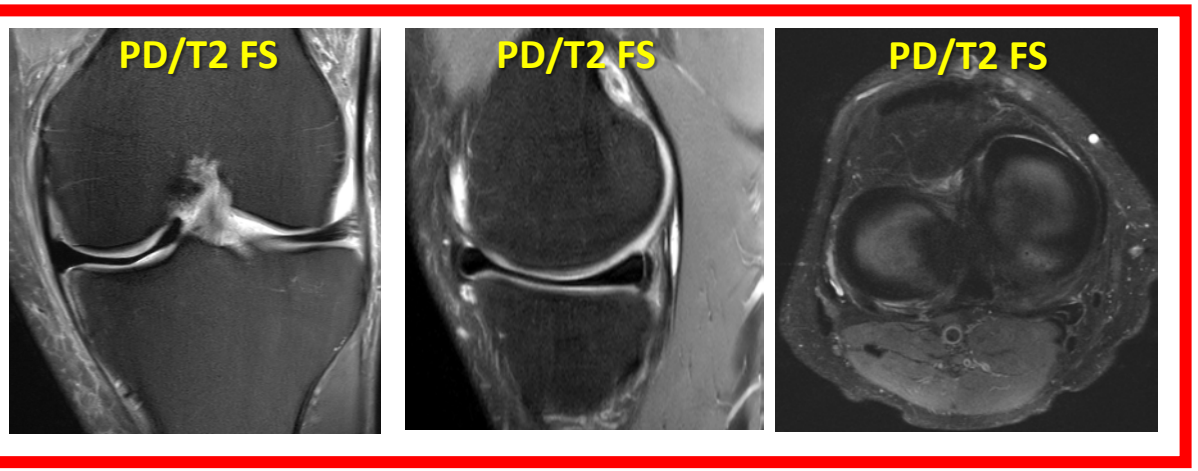


MRI Protocol Used in MERCURY

Anatomical



Pathological (Fluid sensitive)



Coronal Sagittal Axial

- Baseline, 1.5, 12, 24 months
- 1.5T or 3T
- ICRS cartilage protocol

Recht 2005 AJR
Kneeland 2007 JMRI
Brittberg 2003 JBJS

- Most commonly used knee protocol
- Easy to reproduce in all 21 sites over 24 months
- MRI Protocol was approved by FDA in 2013 (GXXXXXX)

Cartilage Condition

Cartilage Evaluation – Methodology Overview

MRI Evaluation	**2 Fellowship-trained US MSK Radiologists** • 3rd reader in case of disagreement • Blinded to each, patient IDs, surgeon and clinical information
Cartilage Assessment	**Full-thickness Cartilage Defects** in Implanted and Controls: • Medial compartment for secondary endpoint #2 • Lateral, Patellofemoral also assessed
Statistical Analysis	**2 Methods**: 1. % of patients with full-thickness defects at 24 months in each group 2. Progression of defects within each subject at 2 years

The Rationale Behind Evaluating Full-Thickness Cartilage Defects

Most reliable:

- Highest MR-arthroscopy correlation

Von Engelhardt 2010 BMC
Drape 1998 Radiology
Bredella 1999 AJR
Mori 1999 MRI
Flanigan 2013 J Orthop

- Excellent inter/intra observer agreement

Kohl 2015 J Orthop Surg
Von Engelhardt 2010 BMC

- Highest MR sensitivity

Von Engelhardt 2010 BMC
Von Engelhardt 2008 Orthopade
Bachmann 1999 ER
Kohl 2015 J Orthop Surg

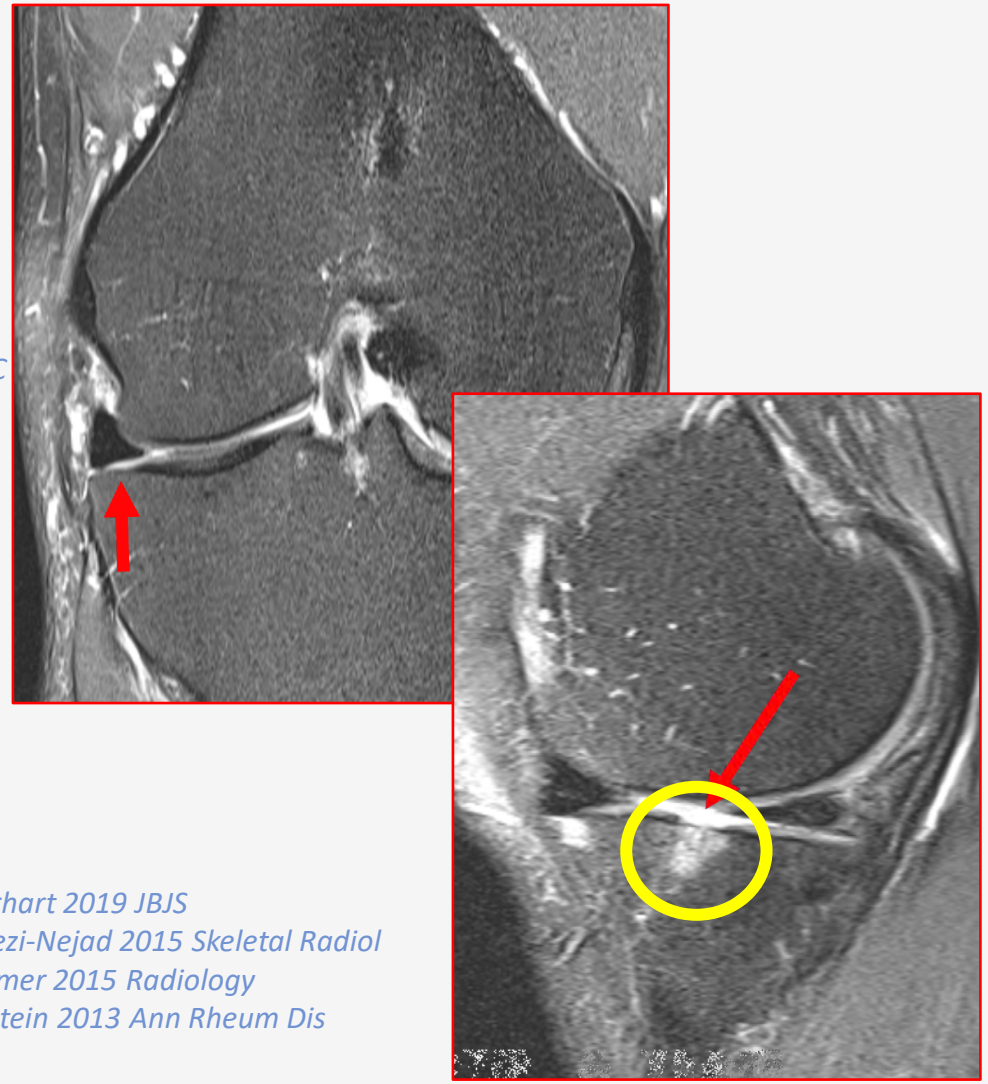
High clinical relevancy:

- Early indicator of future OA

Everhart 2019 JBJS
Hafezi-Nejad 2015 Skeletal Radiol
Roemer 2015 Radiology
Wluka 2005 Rheumatology (Oxford)

- Strong independent predictor of TKA within 5 years

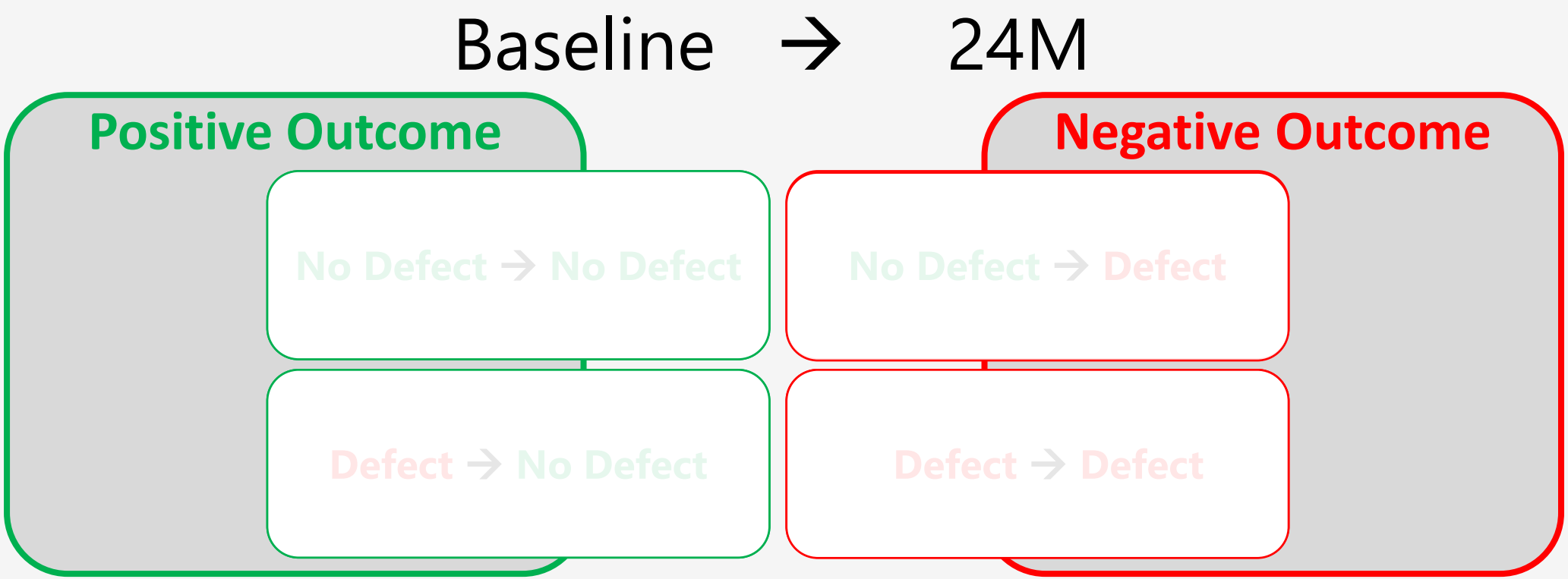
Everhart 2019 JBJS
Hafezi-Nejad 2015 Skeletal Radiol
Roemer 2015 Radiology
Eckstein 2013 Ann Rheum Dis



Comparison of full-thickness defects Between Groups

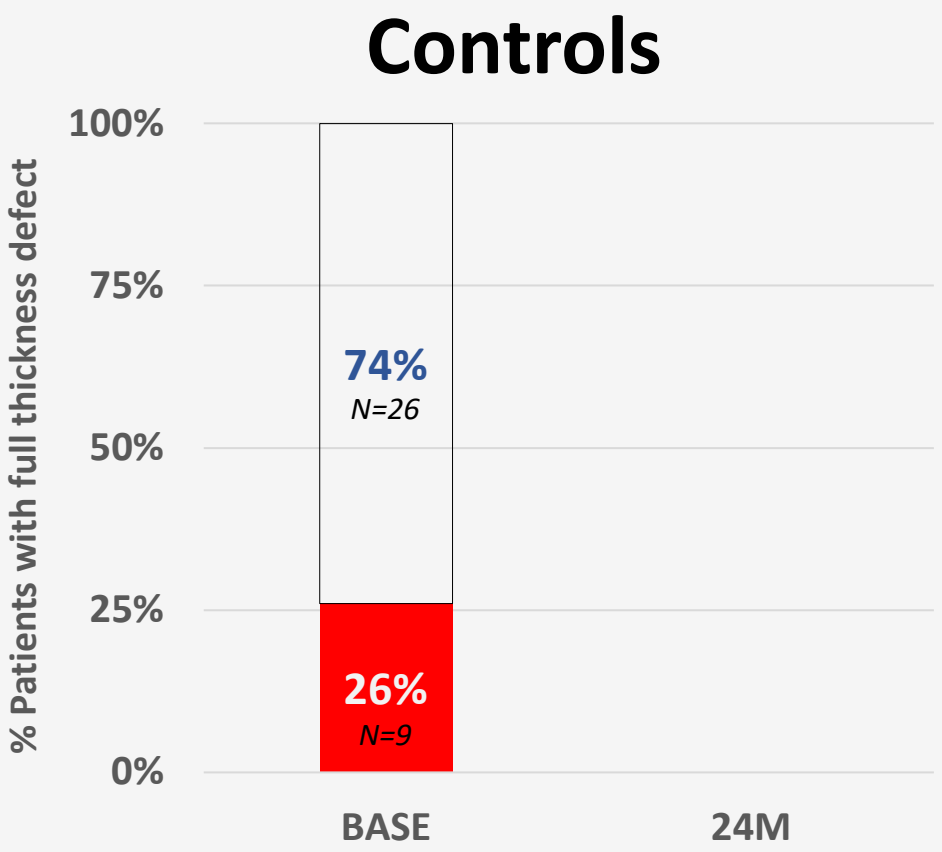
Method #1: Prevalence at 24 months

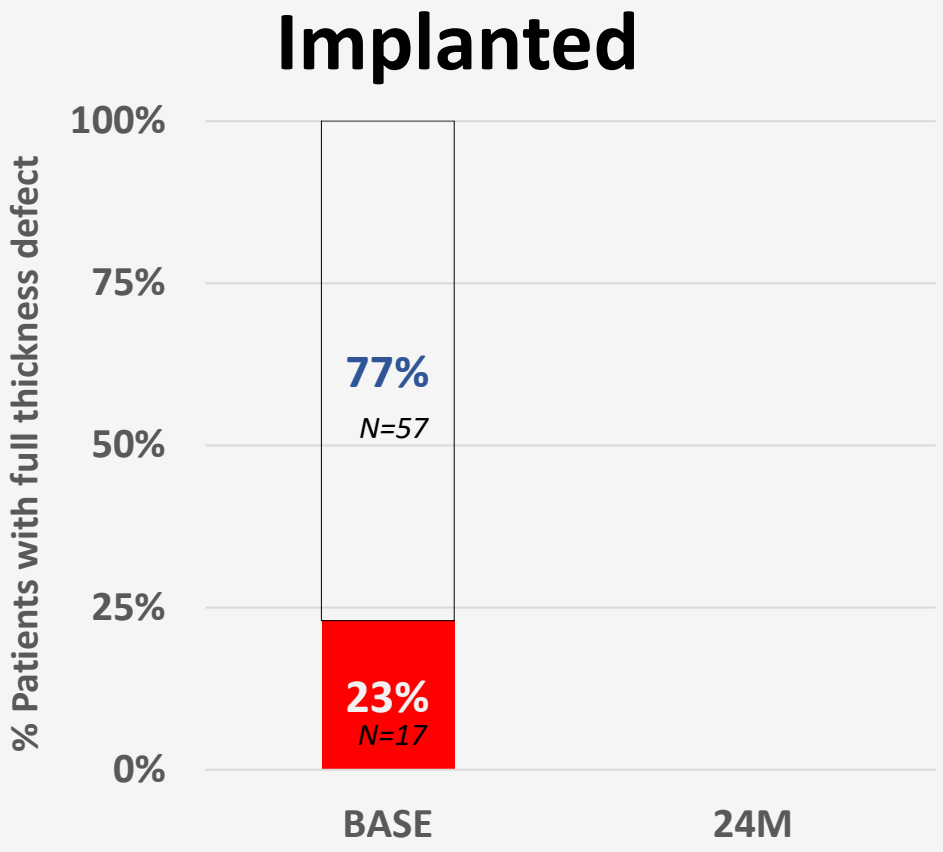
Method #2: Progression of defects in each subject at 2 years



Cartilage Condition

Prevalence of Full Thickness Cartilage Defects in the Medial Compartment (MFC & MTP)

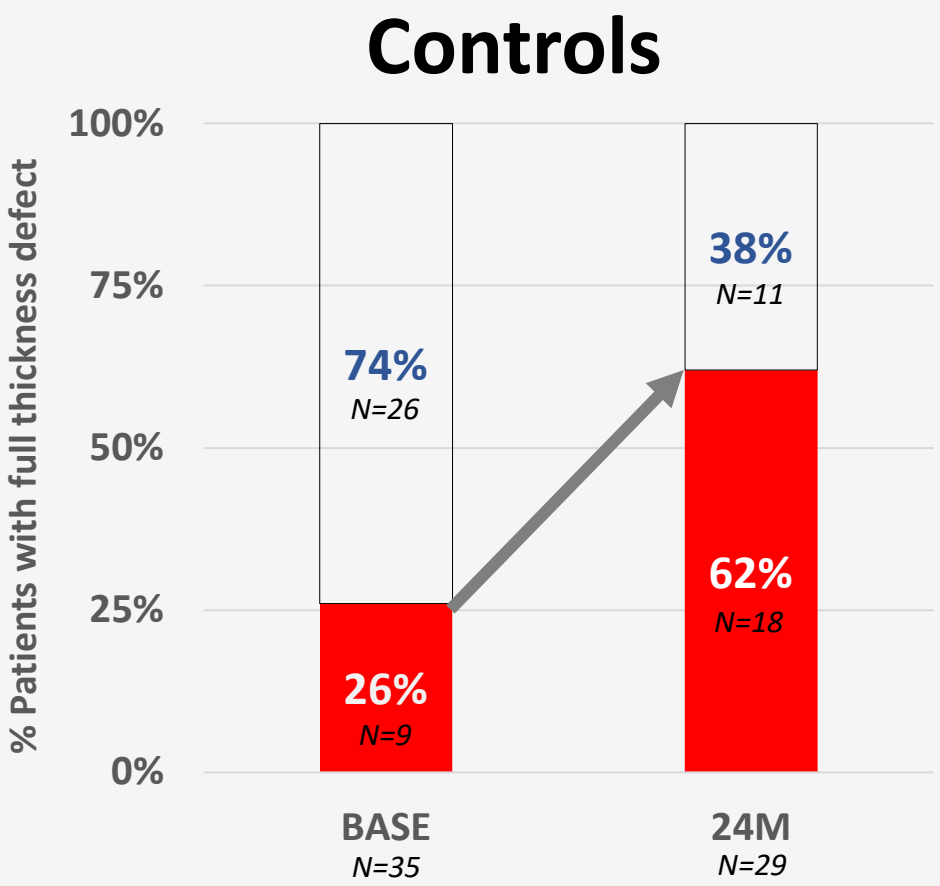


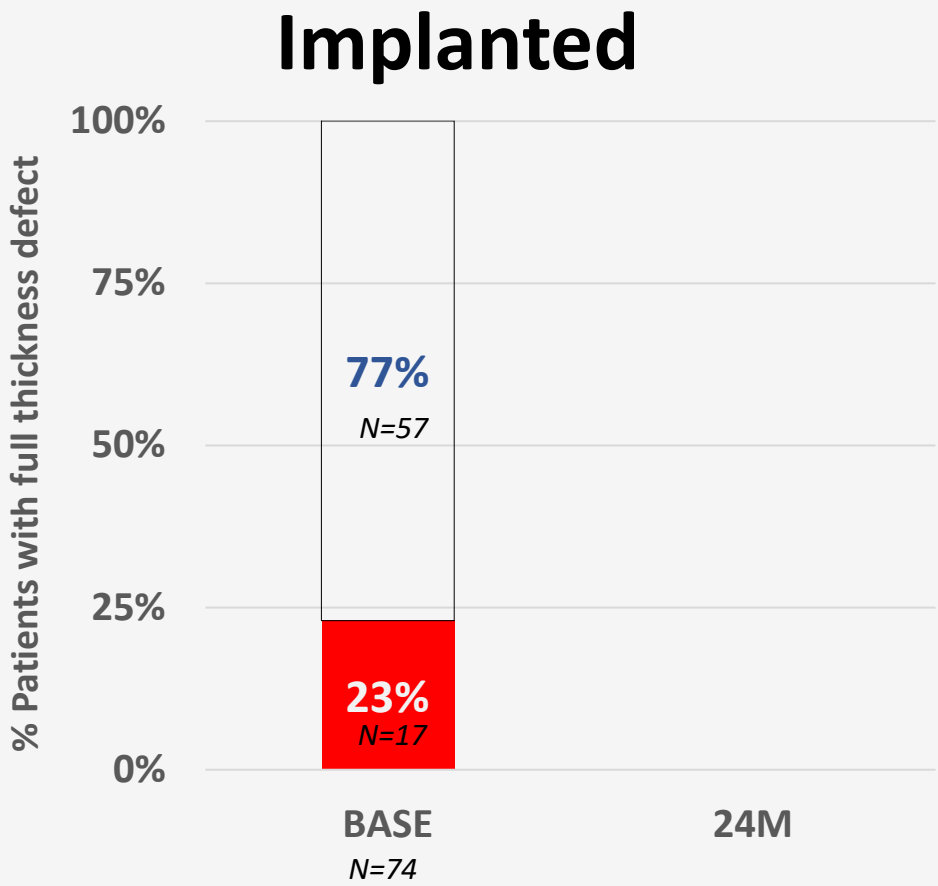


Control and Implanted patients are statistically the same at baseline

(p=0.8)

Prevalence of Full Thickness Cartilage Defects in the Medial Compartment (MFC & MTP)

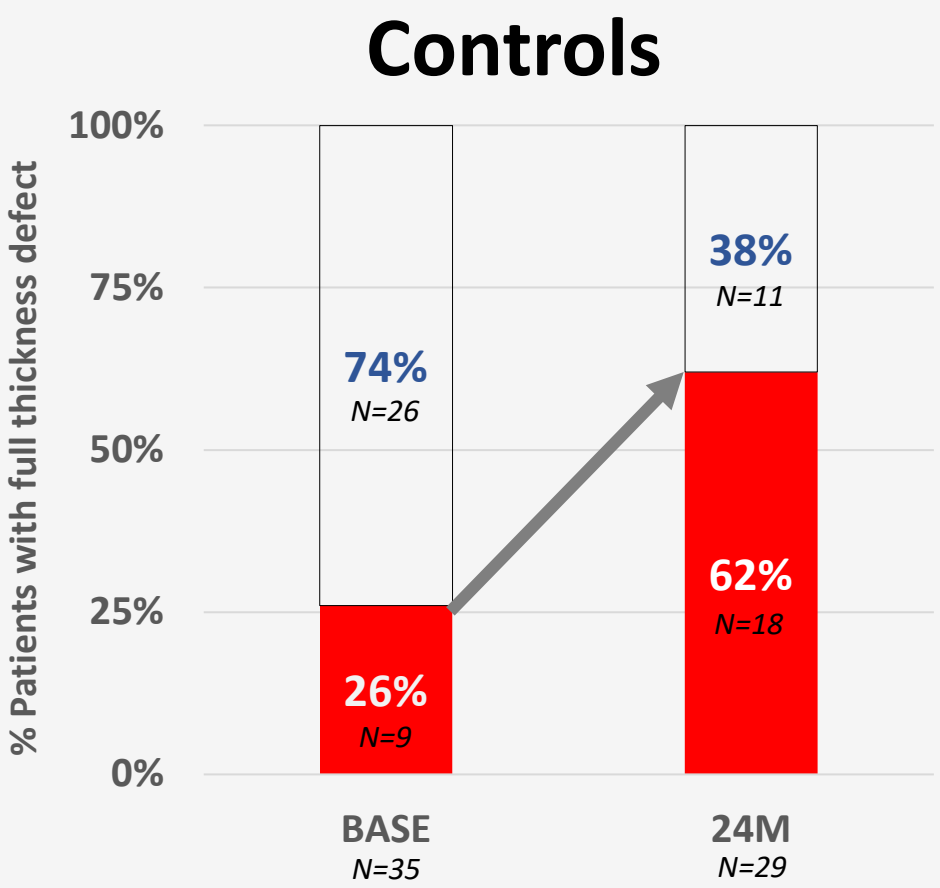


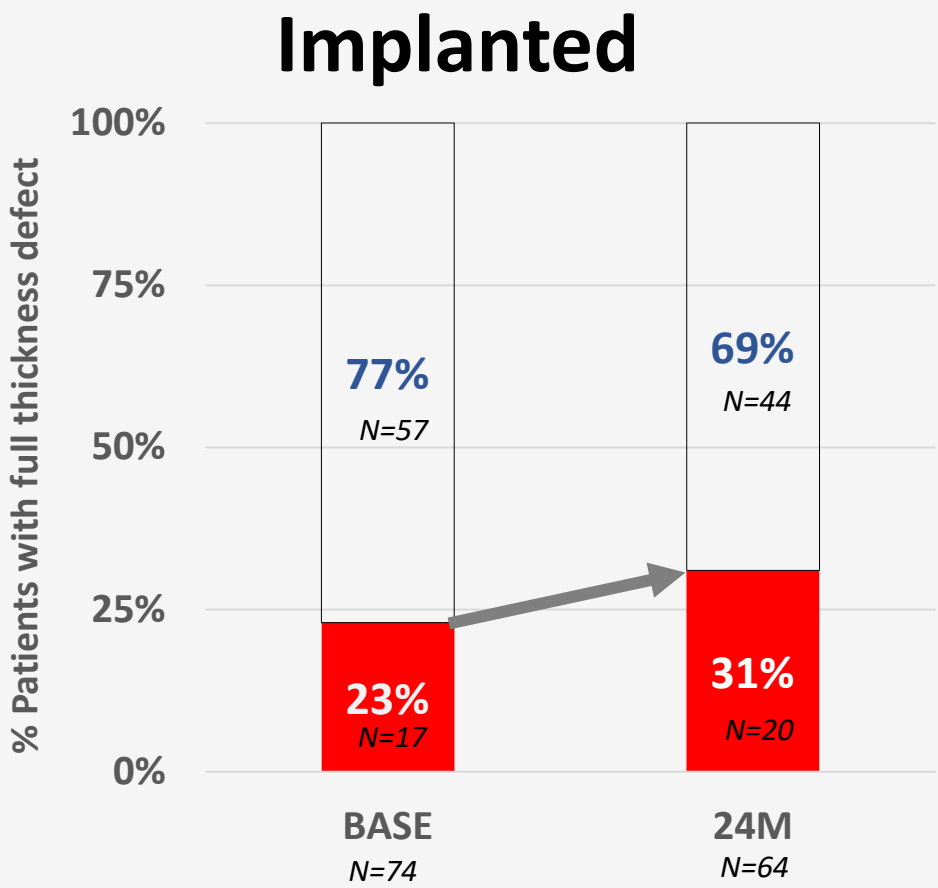


CONTROLS: DETERIORATED X2.5

(p=0.005)

Prevalence of Full Thickness Cartilage Defects in the Medial Compartment (MFC & MTP)





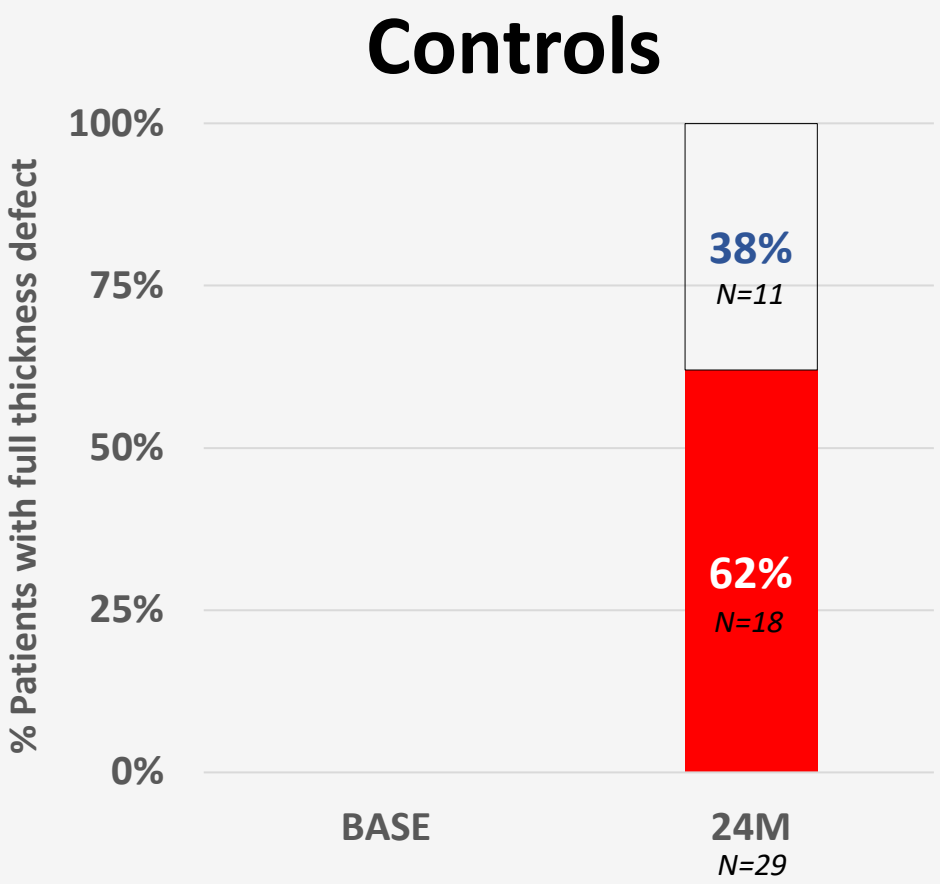
CONTROLS: DETERIORATED X2.5

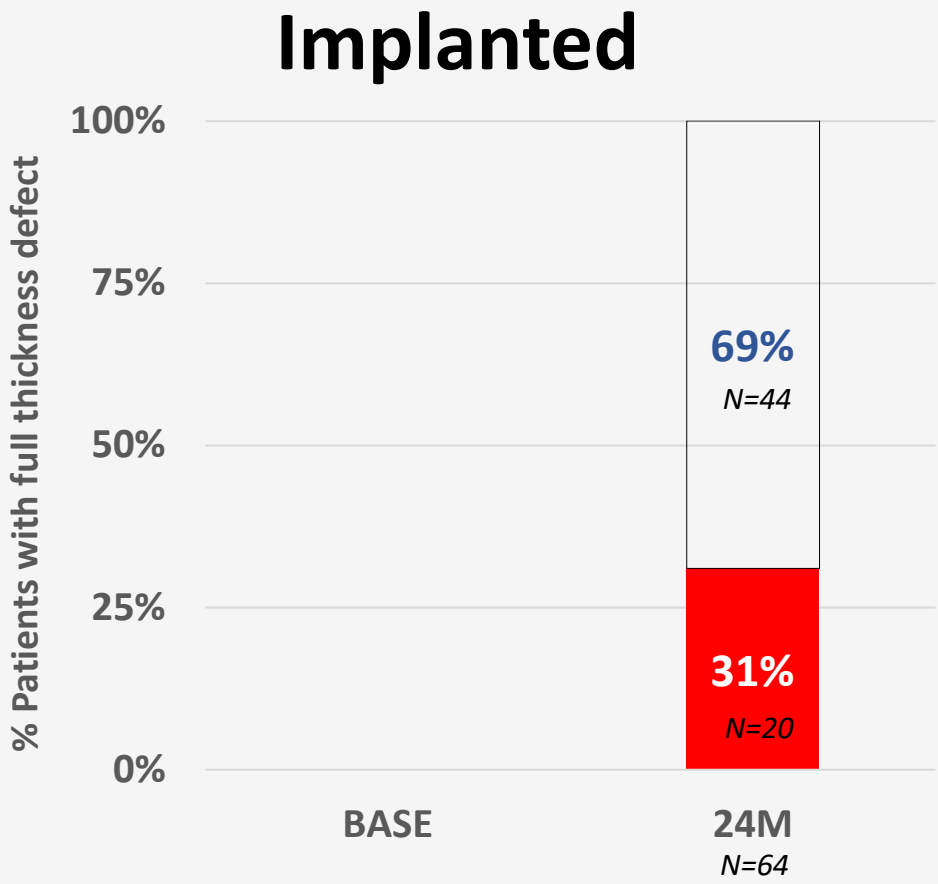
(p=0.005)

IMPLANTED: PRESERVED CARTILAGE

(p=0.336)

Prevalence of Full Thickness Cartilage Defects in the Medial Compartment (MFC & MTP)





IMPLANTED PATIENTS ARE STATISTICALLY SUPERIOR TO CONTROL AT 24M

(p=0.005)

Progression of Defects at 2 Years for Each Patient

No Defect → No Defect

No Defect → Defect

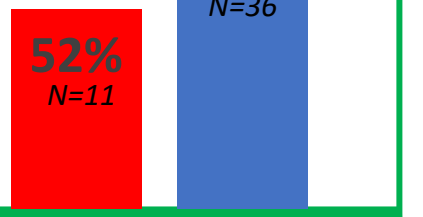
Defect → No Defect

Defect → Defect

Progression of Defects at 2 Years for Each Patient

No change

No Defect → No Defect



Better preservation in NUsurface Group

No Defect → Defect

100%

48%
N=10

25%
N=12

Defect → No Defect

0%

50%
N=8

Defect → Defect

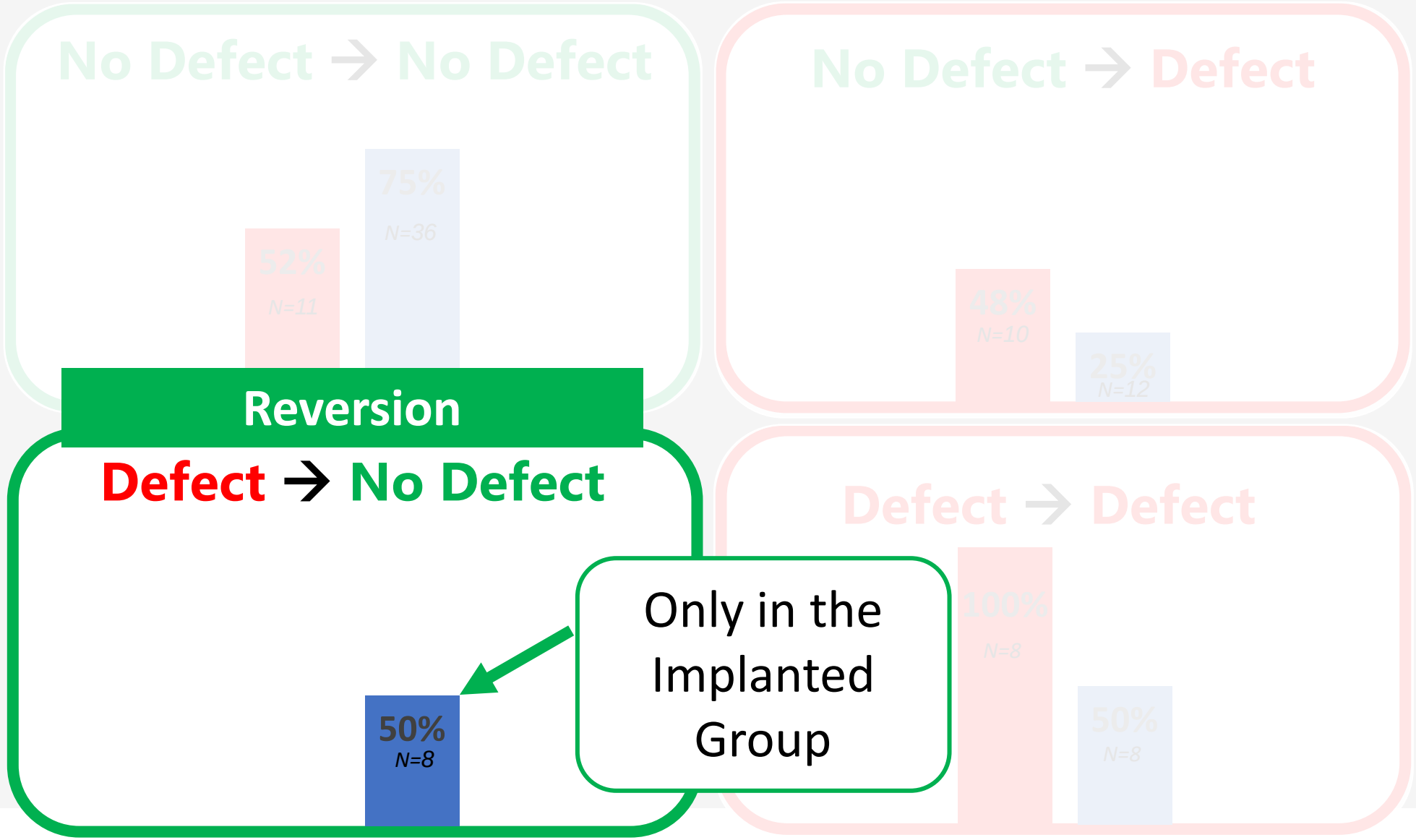
100%
N=8

50%
N=8

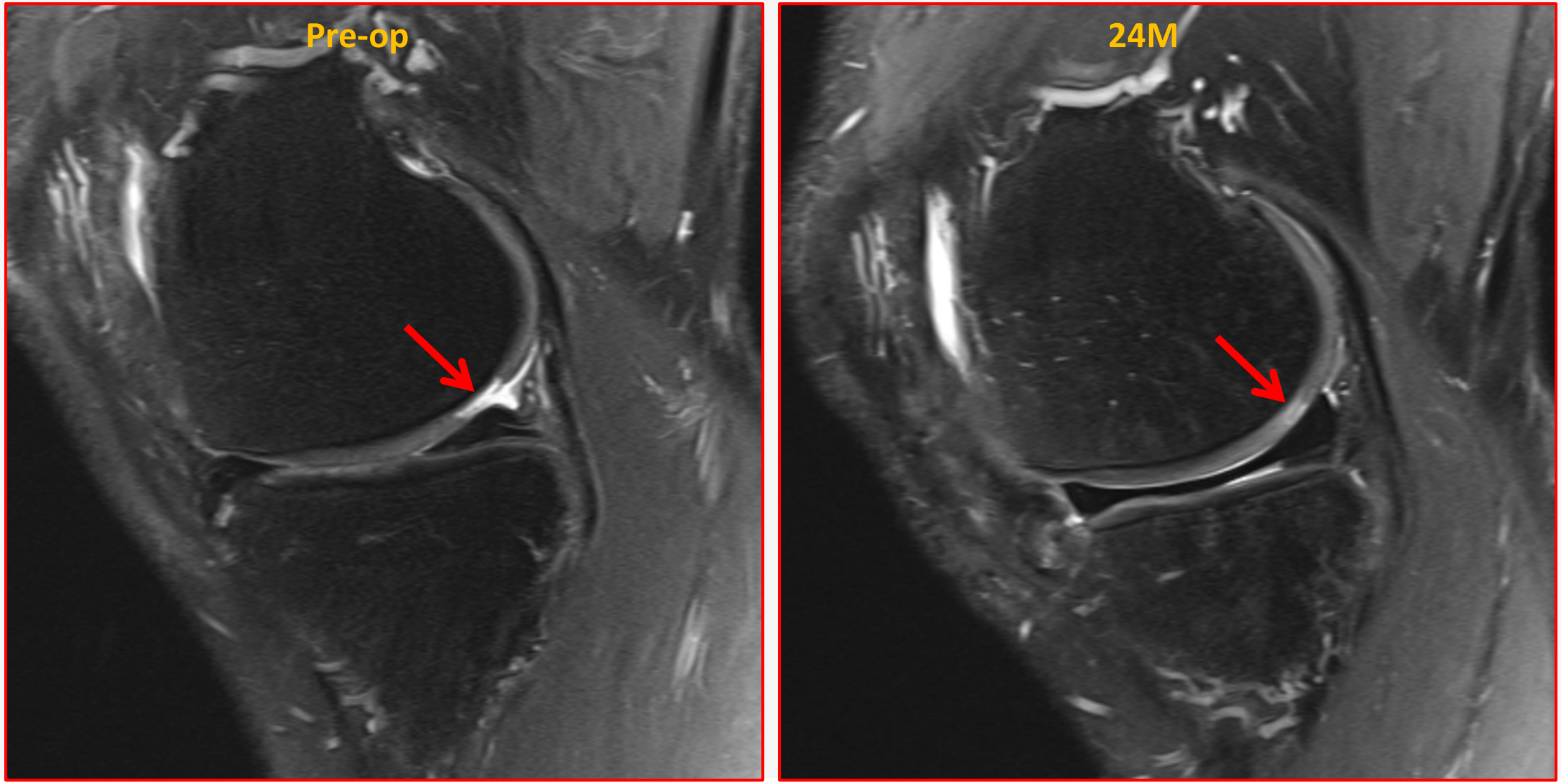
Implanted

Controls

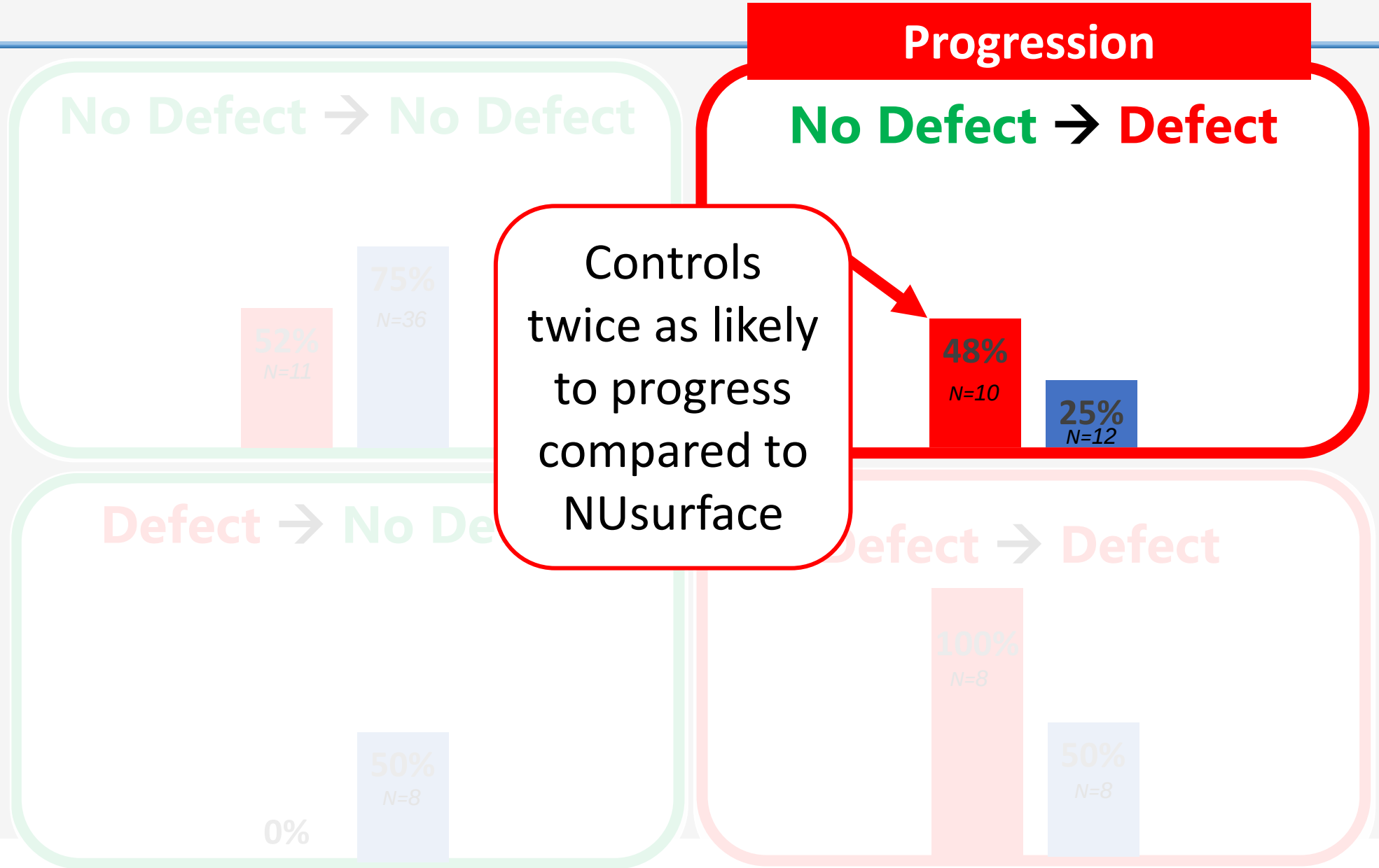
Progression of Defects at 2 Years for Each Patient



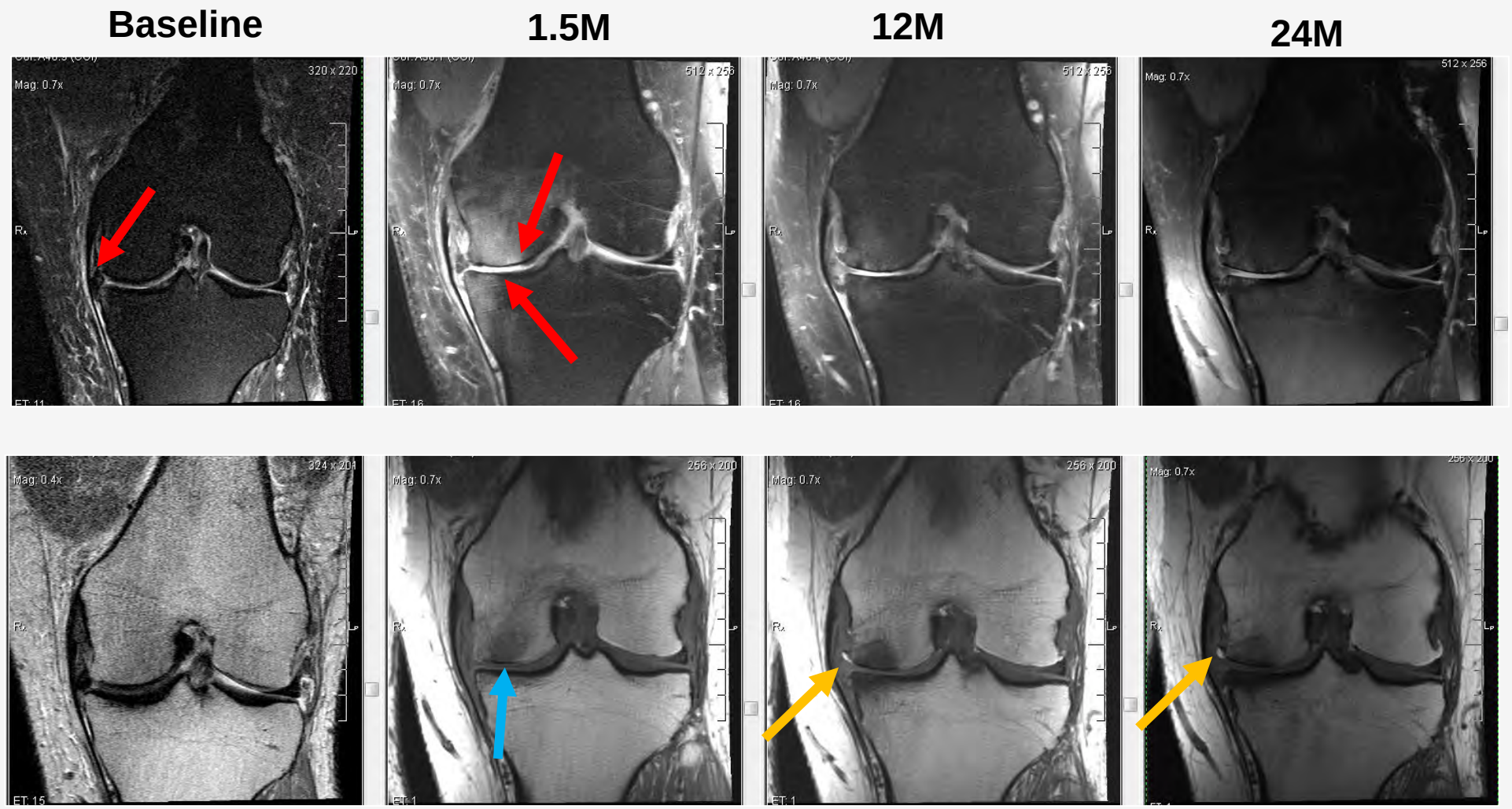
Example of an Improved NUsurface Patient



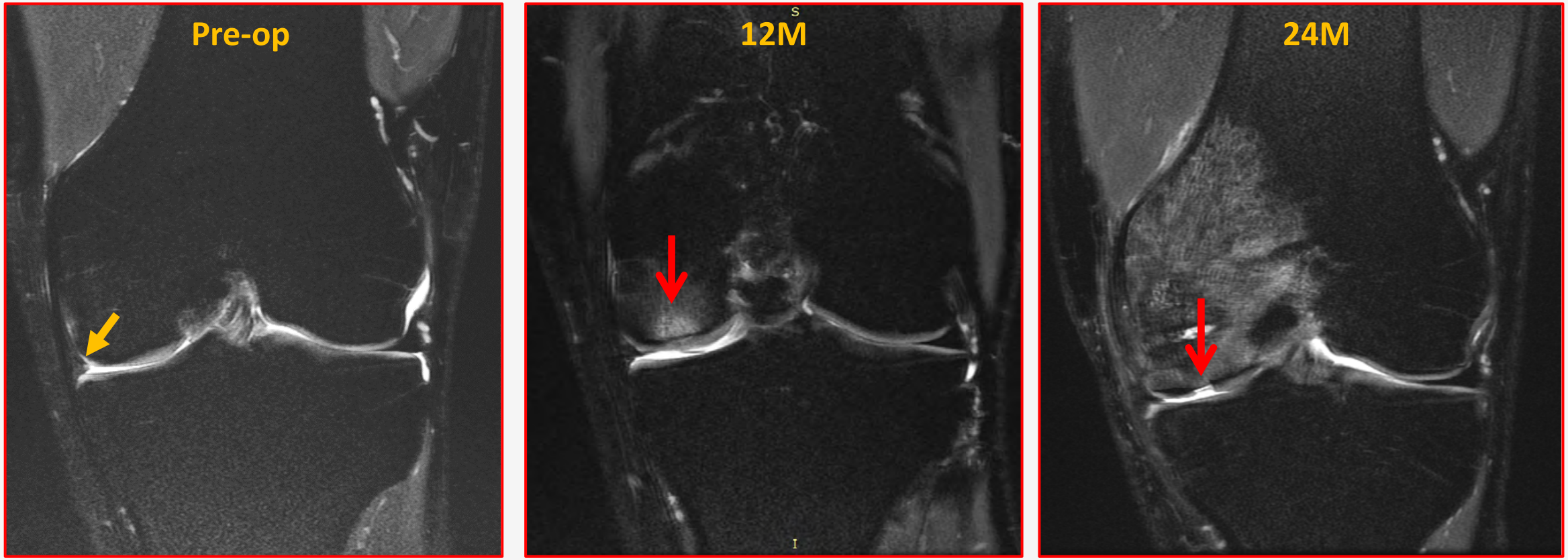
Progression of Defects at 2 Years for Each Patient



Rapidly Progressive OA Under Non-Operative Therapy

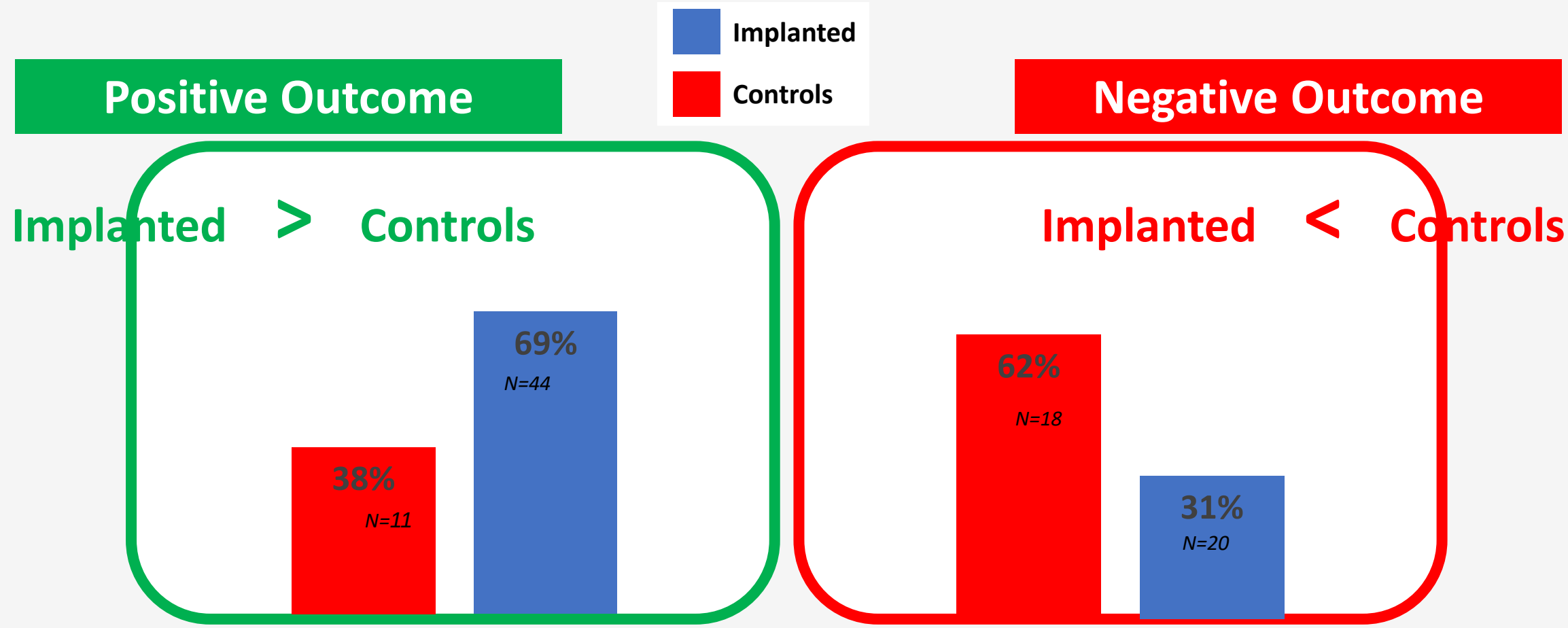


Degeneration in a Control Patient



Progression of Defects at 2 Years for Each Patient

Progression of defects at 2 years for each patient

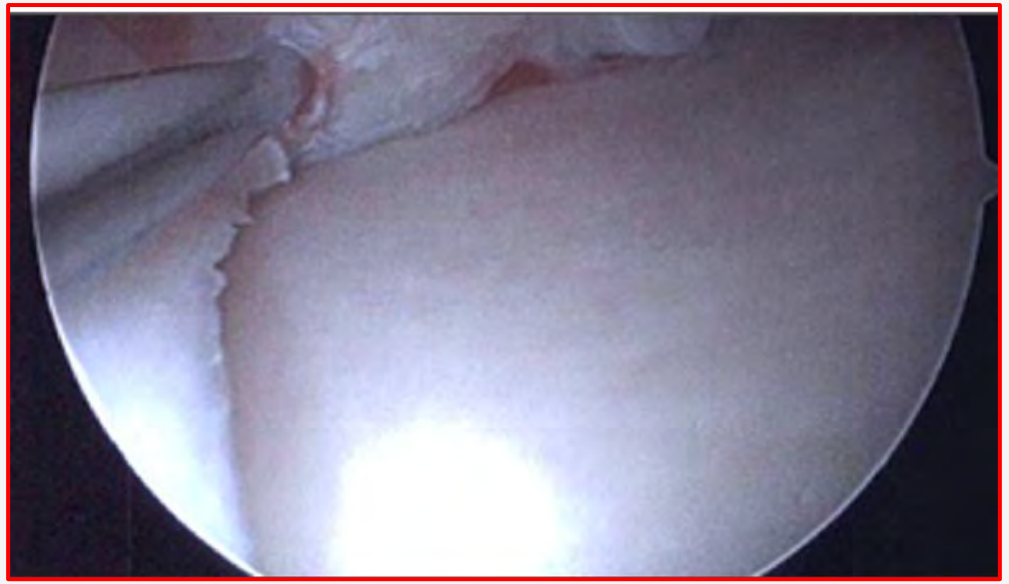


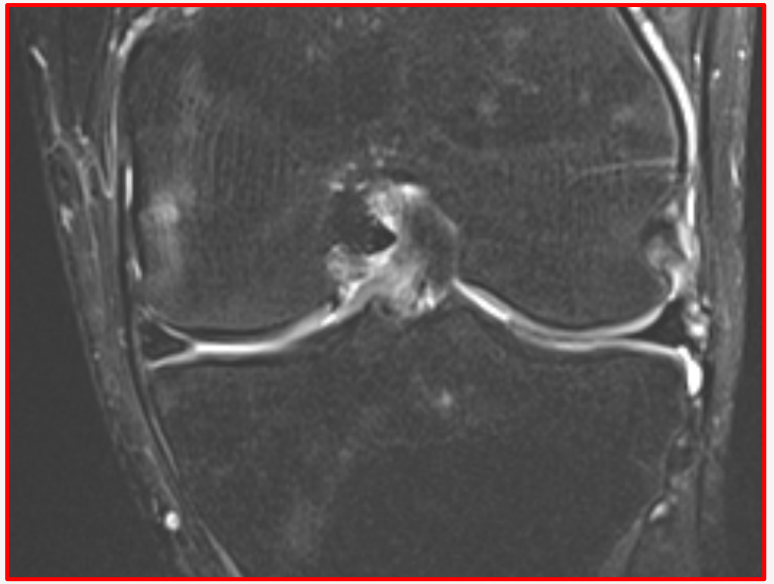
IMPLANTED PATIENTS ARE STATISTICALLY SUPERIOR TO CONTROL AT 24M

(p=0.005)

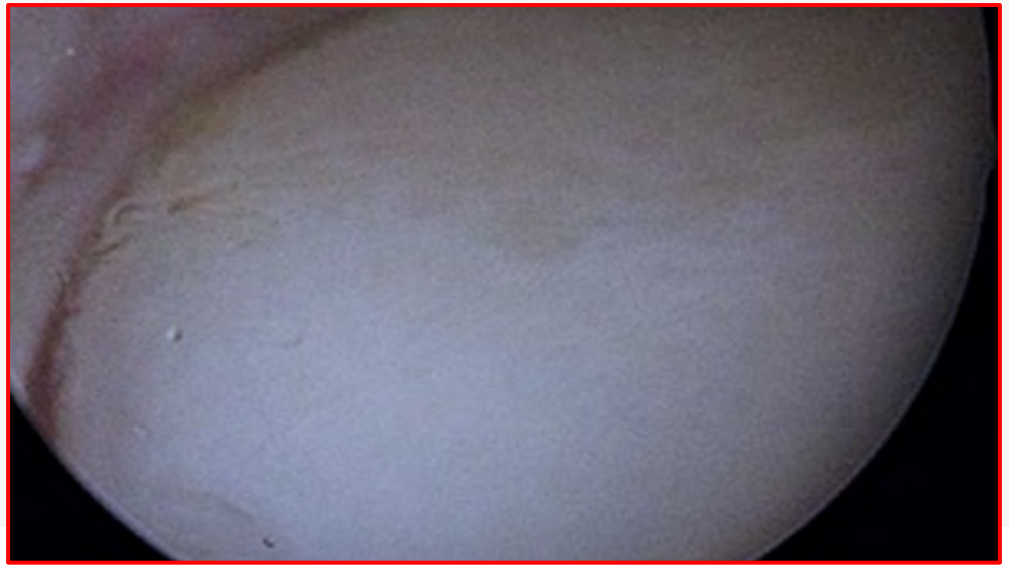
Cartilage Preservation at 53 Months After Implantation

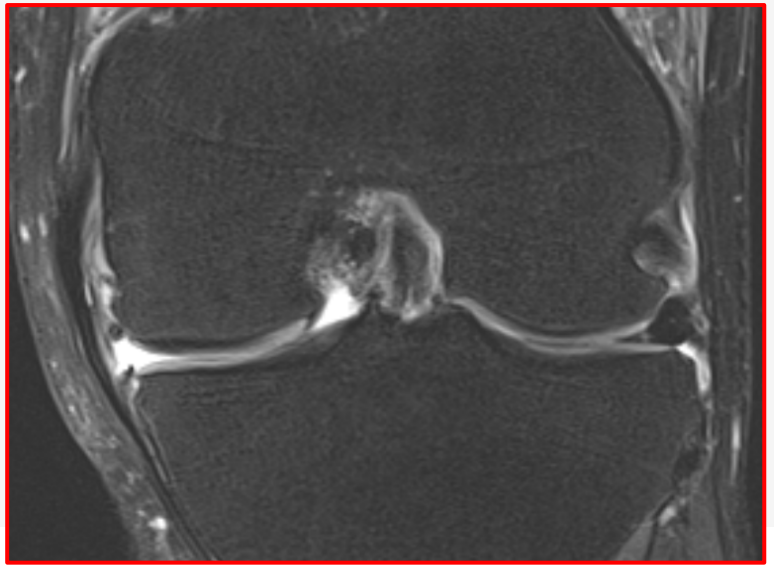
2015





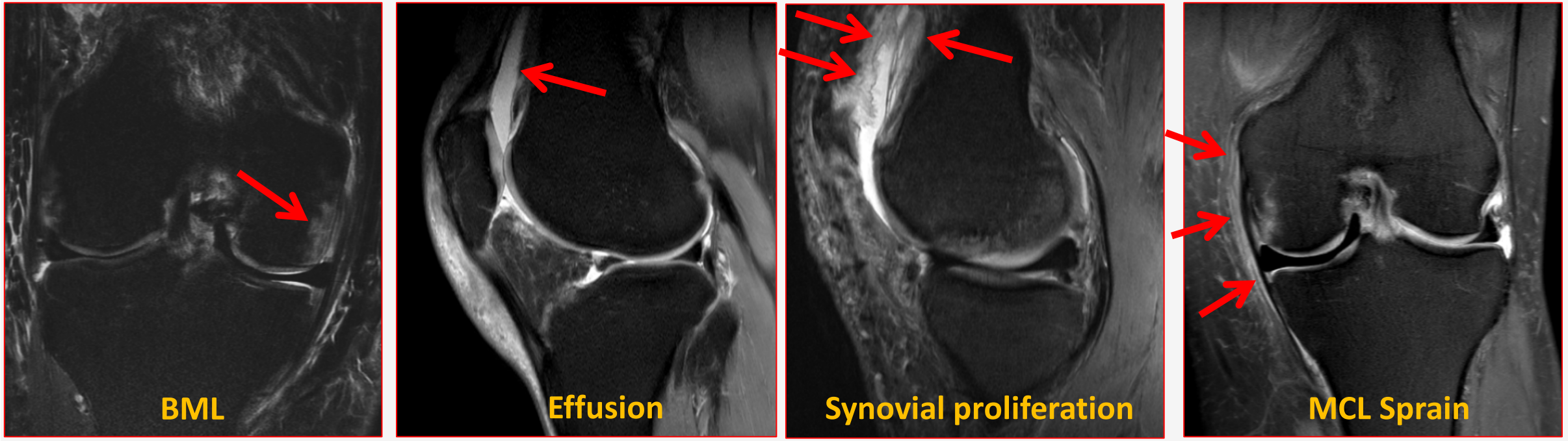
2020





Joint observations

MRI Evaluation



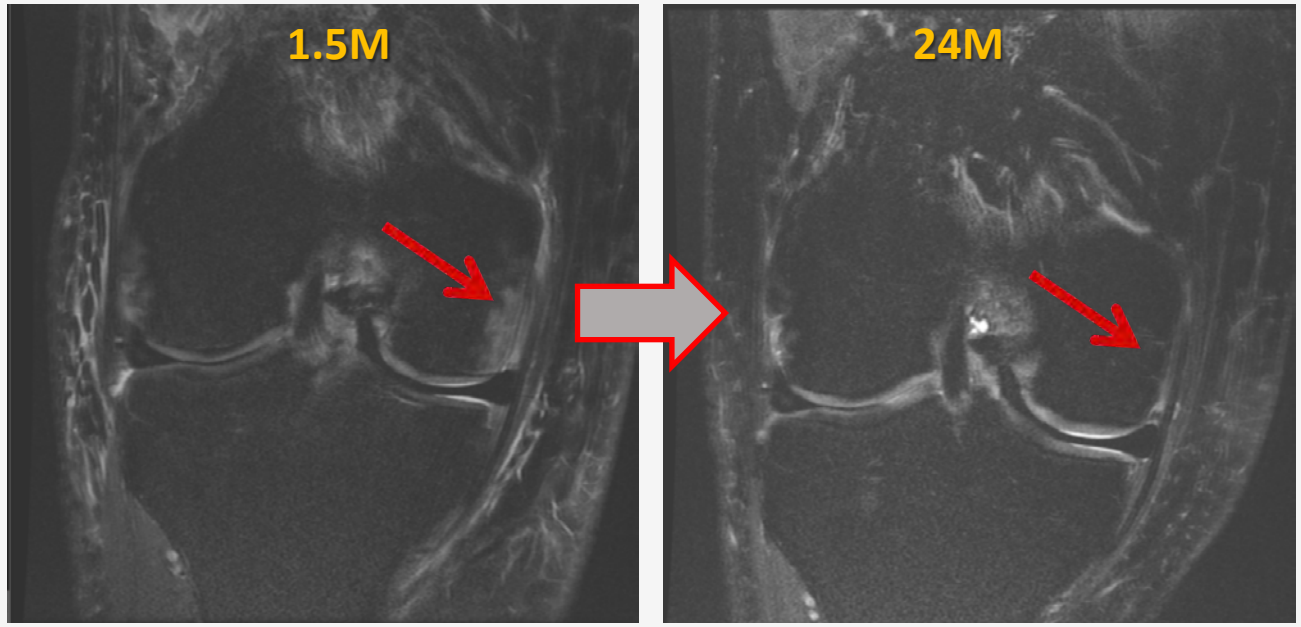
MR grading is based on scientific literature

Roemer 2009 Osteoarthr Cartil
Helms 2008 Musculoskeletal MRI
Østergaard 2009 Arthritis Rheum
Scanzello 2012 Bone

Transient Bone Marrow Lesions

Implanted vs. Controls:

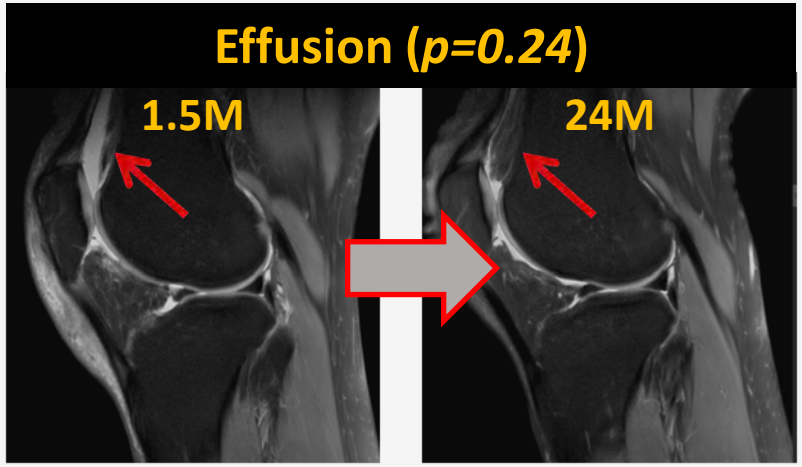
- Significant difference at 1.5 months
- No difference at 24 months (*p=0.72*)

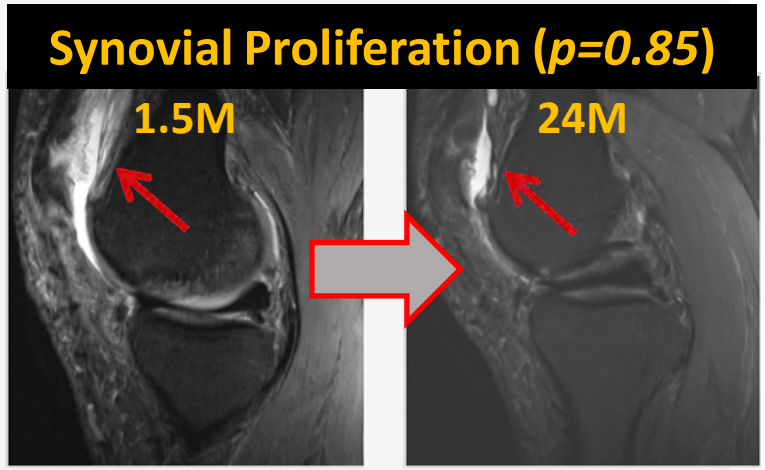


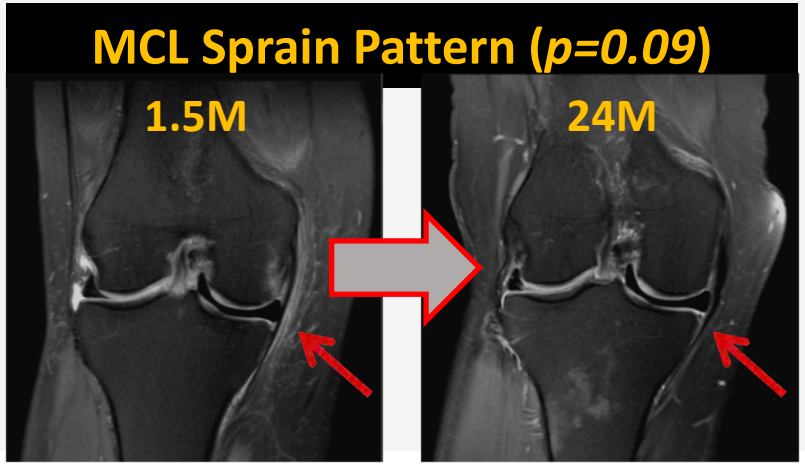
Other Observations

Implanted vs. Controls:

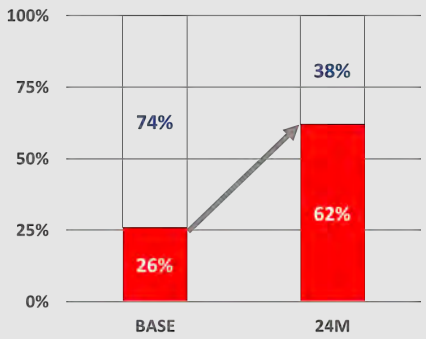
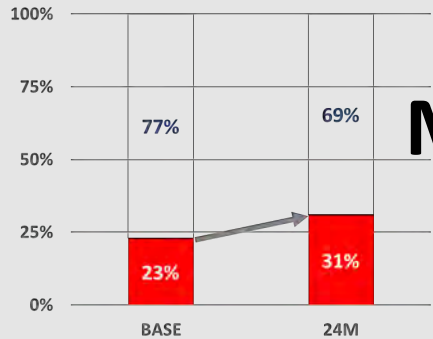
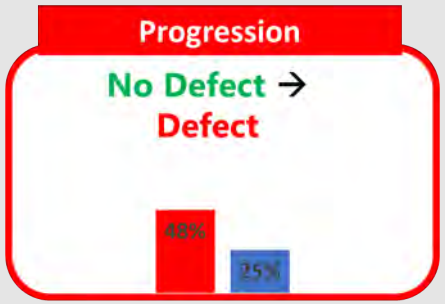
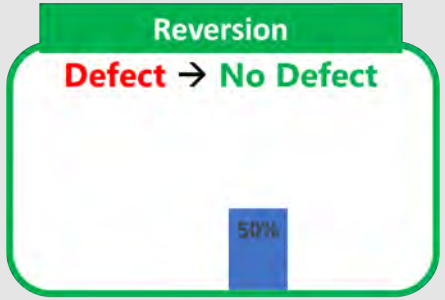
- Significant difference at 1.5M
- No difference at 24M







Main outcomes – Full-thickness Cartilage Defects

	Controls	Implanted
% Defects Baseline → 24M	 **Doubled** *(p=0.005)*	 **Maintained** *(p=0.336)*
% Defects at 24M	 **Half developed <u>new</u> defects = x2 more than Implanted**	 **Reversed (no defects) in 50% of patients with defects at baseline**

Discussion – Full-thickness Cartilage Defects

- Based on literature, full-thickness defect is:
  - An independent predictor for knee arthroplasty *Everhart 2019 JBJS; Hafezi-Nejad 2015 Skeletal Radiol; Roemer 2015 Radiology; Eckstein 2013 Ann Rheum Dis*
  - An indicator for OA progression *Houck 2018 Orthop J Sports Med; Everhart 2018 J Orthop Res*
  - Increases risk for further cartilage volume loss *Guermazi 2016 Arthritis Rheumatol; Cicuttini 2005 A & R*

Controls are at a significantly higher risk for knee arthroplasty in the upcoming years than implanted

The NUsurface implant may delay future knee arthroplasty

Discussion – Joint Safety Following Implantation

No significant differences between implanted and Controls at 24M:

- Effusion and synovial proliferation
- Bone marrow lesions
- MCL sprain pattern

MRI confirms the safety of the device in the knee joint

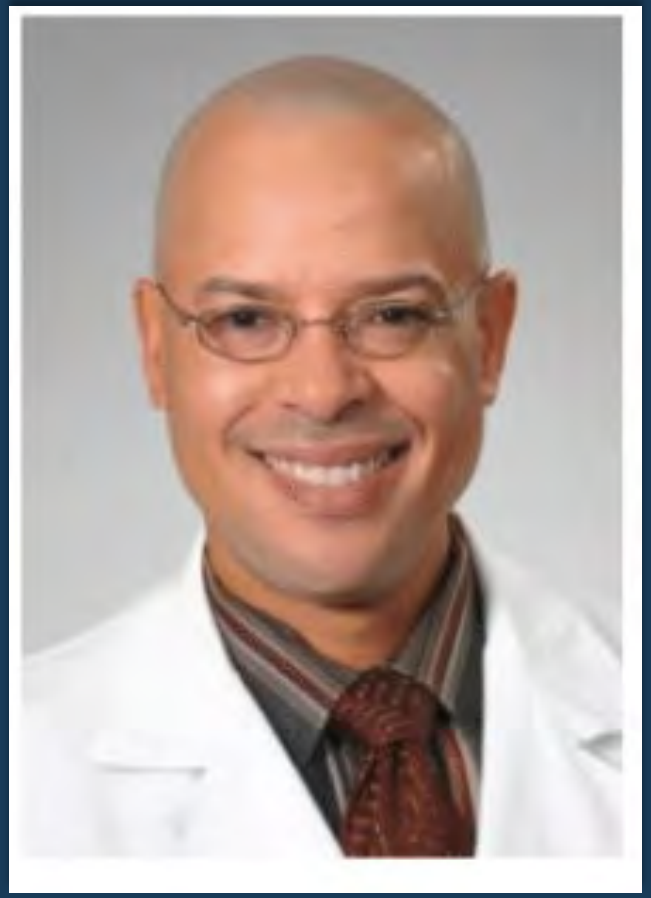
CONCLUSIONS

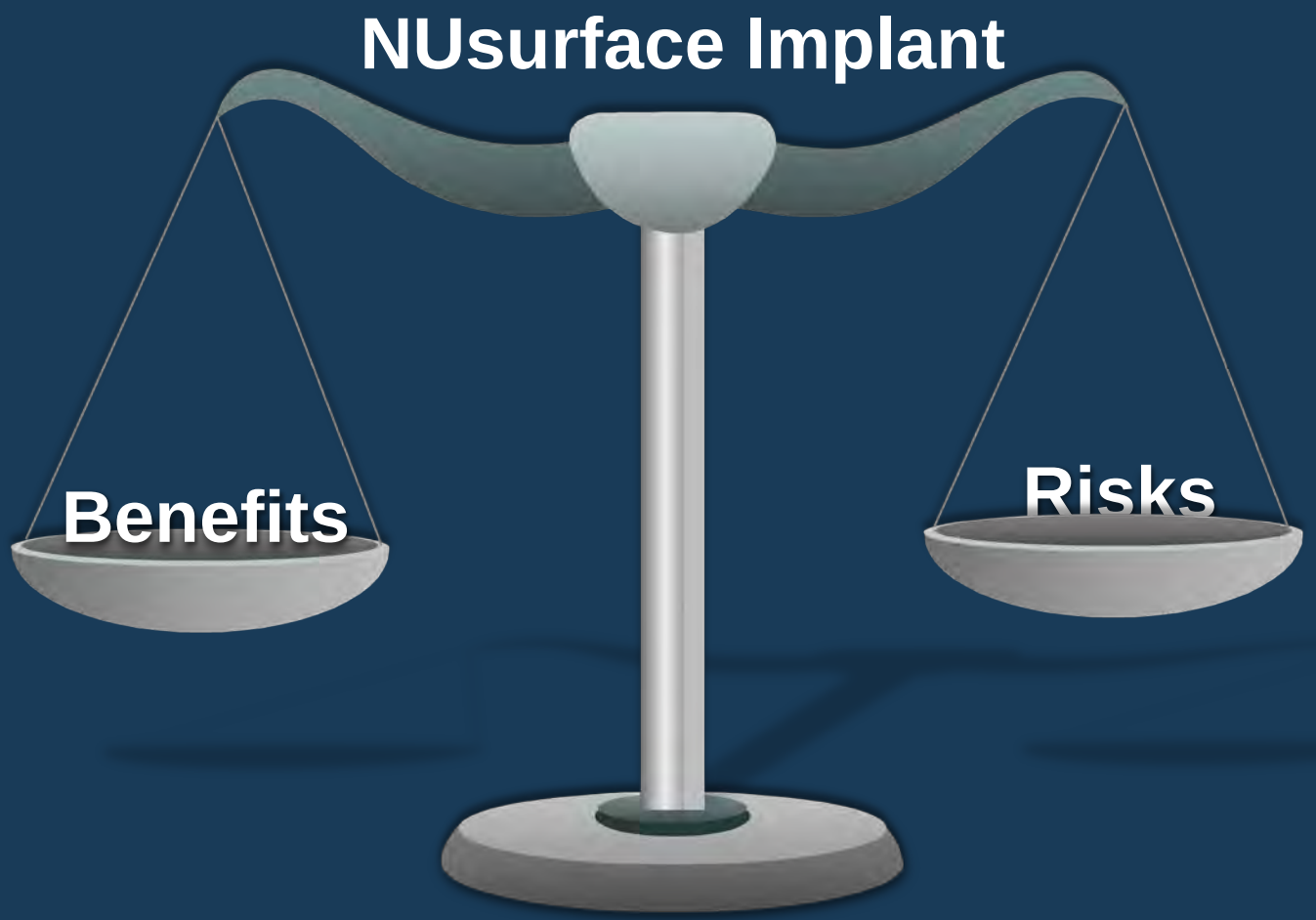
- NUsurface implanted patients are superior to non-operative standard of care in terms of cartilage condition after 2 years
- NUsurface is a safe device for the joint structures based on MRI evaluation

Thank You

Deryk Jones, MD

Orthopedic Surgeon, NUsurface Clinical Trial Investigator





MERCURY Control Data Provides Baseline for Comparing NUsurface Benefit/Risk

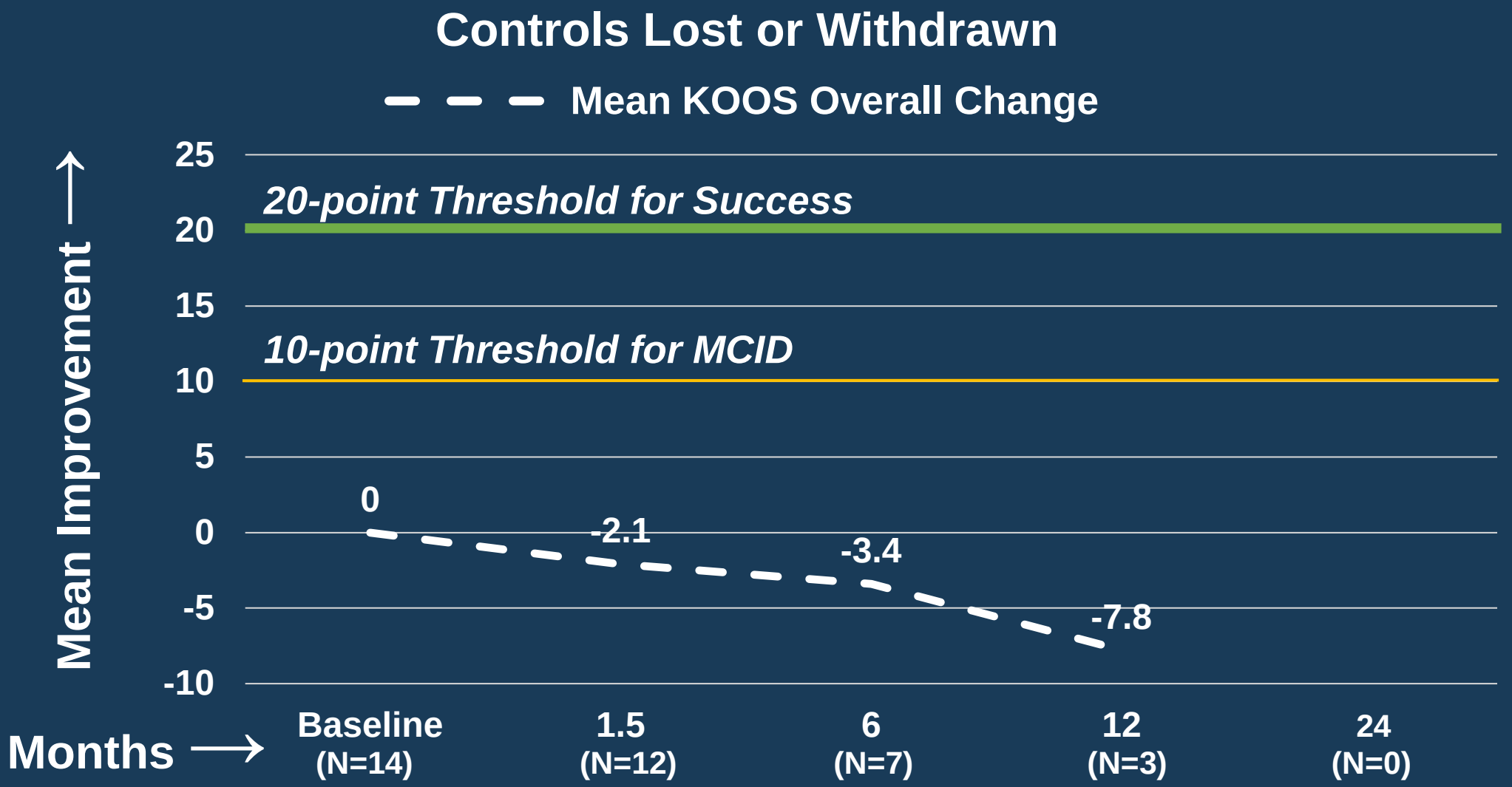
- Control Risk
- NUsurface Risk & Benefit
- Patient Preference

Non-Operative Care Probable Risk

66 Controls in MERCURY

- 52 made it to 24 months
  - 40 were overall study failures
    - 9 out of 40 were ASFs
- 14 withdrew or were lost to follow up
- Full thickness cartilage lesions doubled at 24-months

Lost to Follow-up Outcomes
VENUS Control Patients



Mean KOOS Improvement: VENUS Controls

Last Observation Carried Forward (LOCF) KOOS measurements reduced the mean Control KOOS Overall Score to 10

Mean Improvement	Total Population 24 Month	Total Population LOCF
KOOS Overall Scores	14.9 (N=46)	10.3 (N=64)

Literature Comparing Outcomes to VENUS Controls

Comparative literature in the FDA Summary

van der Graaff (2022):
- **Subjects did not have a previous meniscectomy**
- **Average age 36**
- **30% elite athletes**

Katz 2013:
- **Subjects did not have a previous meniscectomy**
- **Results at 12-months**

Sihvonen (2018):
- **Subjects did not have a previous meniscectomy**
- **Compared the outcomes of primary meniscectomy to Sham surgery**

No previous meniscectomy

Little data outside of MERCURY exist on the Control population

Nine Control Surgical Failures

- Surgical interventions include:
  - Arthroscopy (4)
  - HTO
  - MAT
  - Chondral Allograft
  - Compartment reconstruction
  - UNI

- Surgical Failure rate was 17.3%

- Average time to surgery was 7.2 Months

Incidence and severity no different than subpopulation

Literature of the NUsurface Population

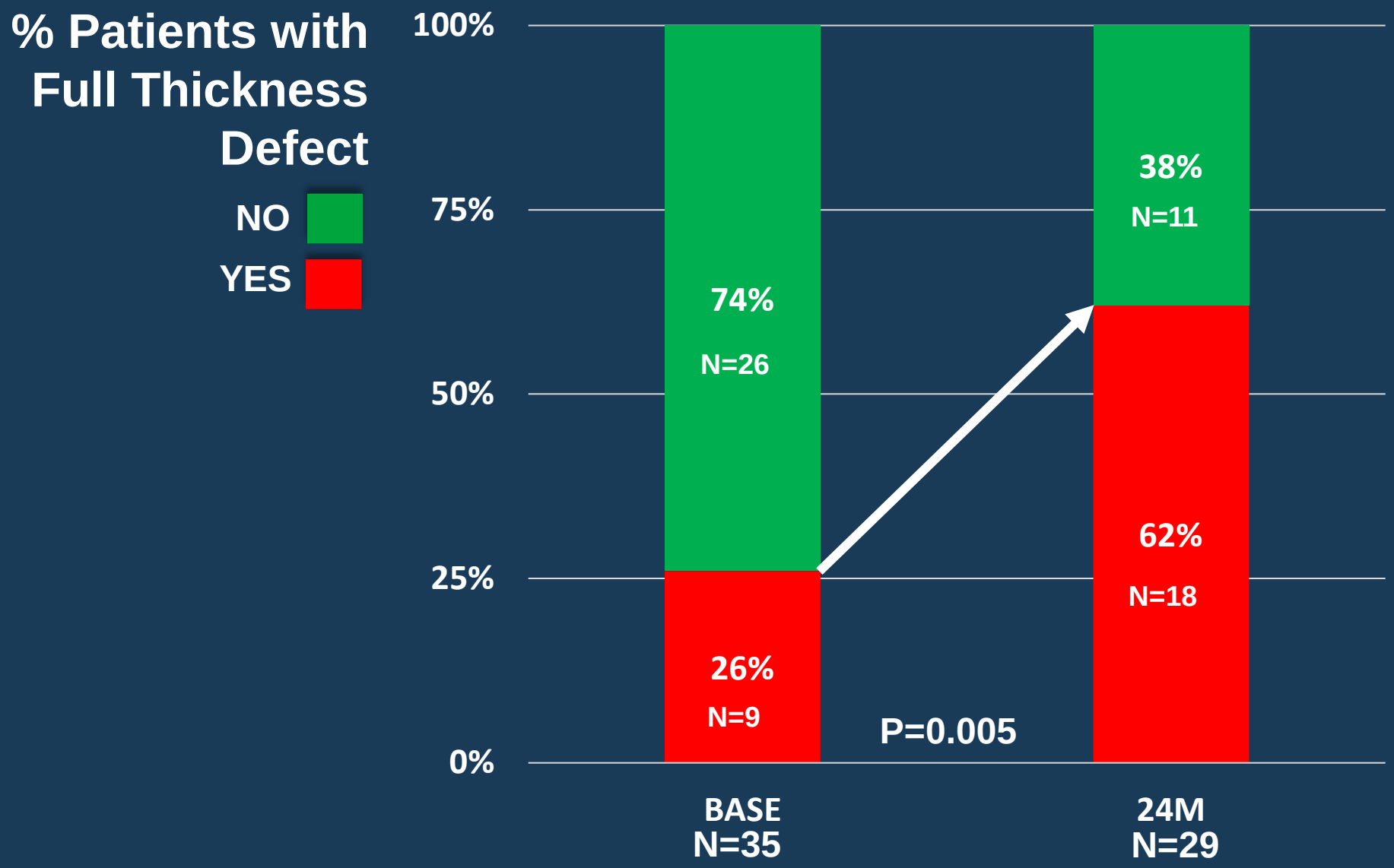
- Metanalysis of the rate of arthroplasty following arthroscopy
  - Twelve journal articles
  - 1,678 patients and 8 registries
  - Outcomes from 372,032 patients met the criteria for inclusion

- Annual TKA rate following arthroscopy
  - Total Population: 2.62%
  - Patients over 50: 3.89%
  - Mean duration between arthroscopy and TKA: 3.4 years

- Results confirmed in >800,000 patient analysis
- MERCURY underestimates the risk to controls
- Expected 2-year TKA rate >7%.

Winter, A.R., (2017), Abram (2019)

Controls Doubled Full Thickness Cartilage Defects in the Medial Compartment at 24-Months



Patient Expectations in the Real World

- NUsurface subjects are surgical veterans
- Have exhausted current treatment options
- Understand the goal of knee preservation is to delay the degenerative process
- In the real-world, delaying arthroplasty, even if reoperation is necessary, is a successful outcome.
- A 40-year-old having an arthroplasty can expect 2 revision in their lifetime

NUsurface Subpopulation Risks

74 Total subjects

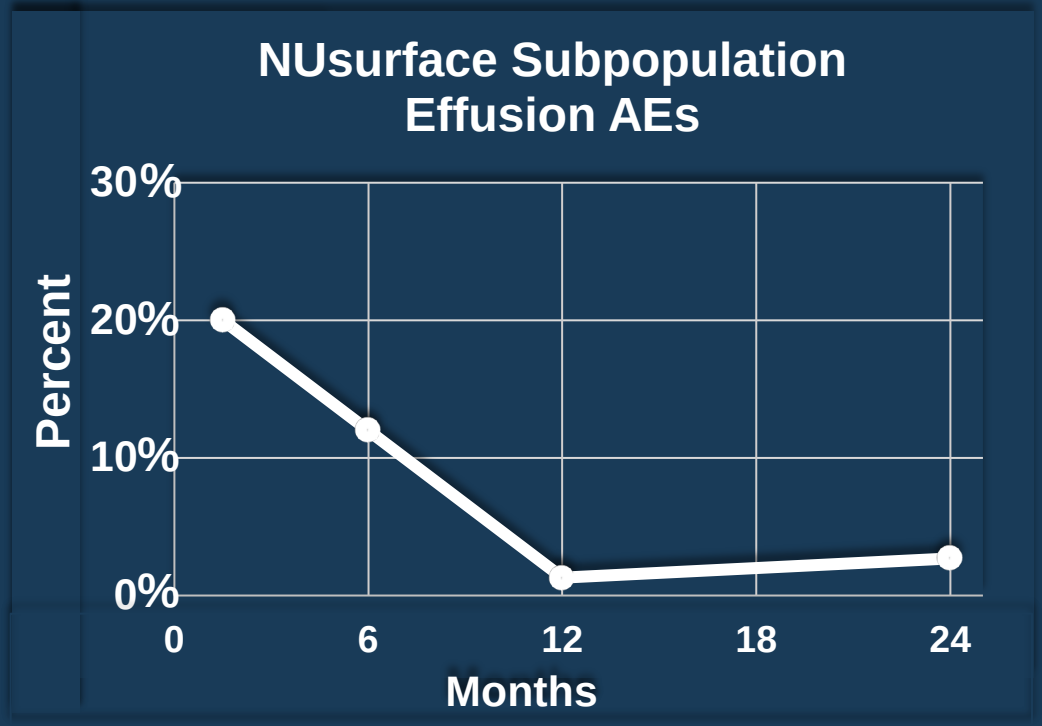
- Procedure Risk: Effusion
- 74 made it to 24 months
  - 35 Study Failure
    - 12 out of 35 were ASFs
  - 0 lost to follow-up

NUsurface Subpopulation Risks

Five types of AEs occurred at a statistically different rate than controls

- **Same AEs identified in the total population**
- **Four were device specific: Damage, Dislocation, Dislocation and Damage, and Noise. These events resulted in device related second surgeries in Table 1**
- **The fifth, effusion, is related to having a surgical procedure and shown in Table 2 to be transient.**

Table 1: Device Related Secondary Surgeries	NUsurface Arm
Device Repositioning from Dislocation or Rotation	1/74 = 1.4%
Permanently Removed Device	5/74 = 6.9%
Device Exchanges	6/74 = 8.3%



Exchange/Repositioning Surgeries

- 30 minute, in an outpatient setting, local anesthesia
- Subjects report symptom recovery at 2 weeks
- 83% (5/6) with exchange achieved 20-point KOOS Overall Improvement at 24-Month

Arthroplasty Risk of NUsurface

5 subjects permanently removed, 3 went on to arthroplasty

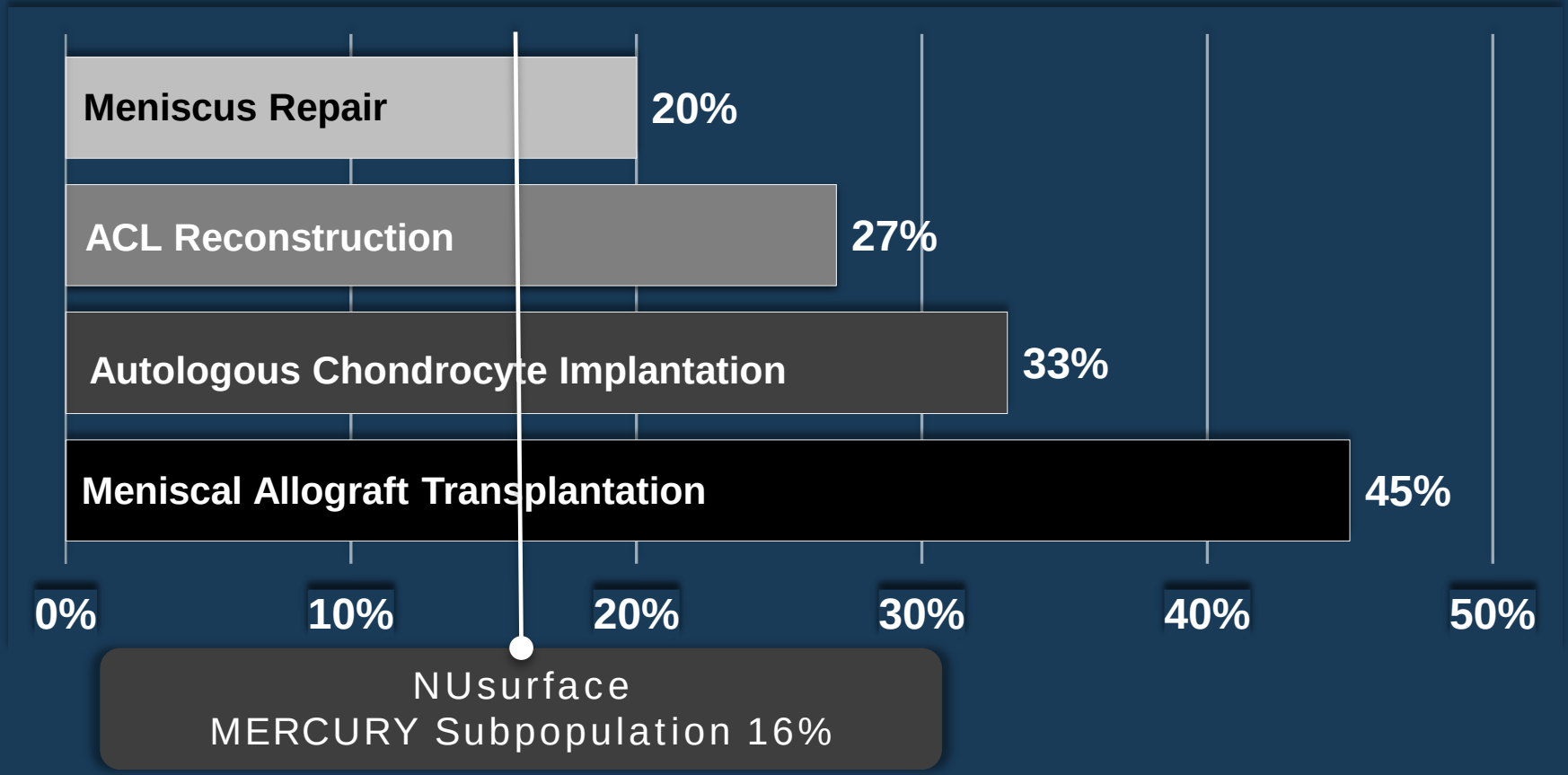
- Mean time to removal: 15 months
- Mean time to TKA: 22 months

Arthroplasty risk after NUsurface removal: Not statistically different than Controls (p=1.0)

- NUsurface rate 4.1%
- Control rate 2.9%

Knee Preservation Treatments Have Similar Reoperation Rates

All Knee Preservation Surgeries Have an Ambient Reoperation Rate

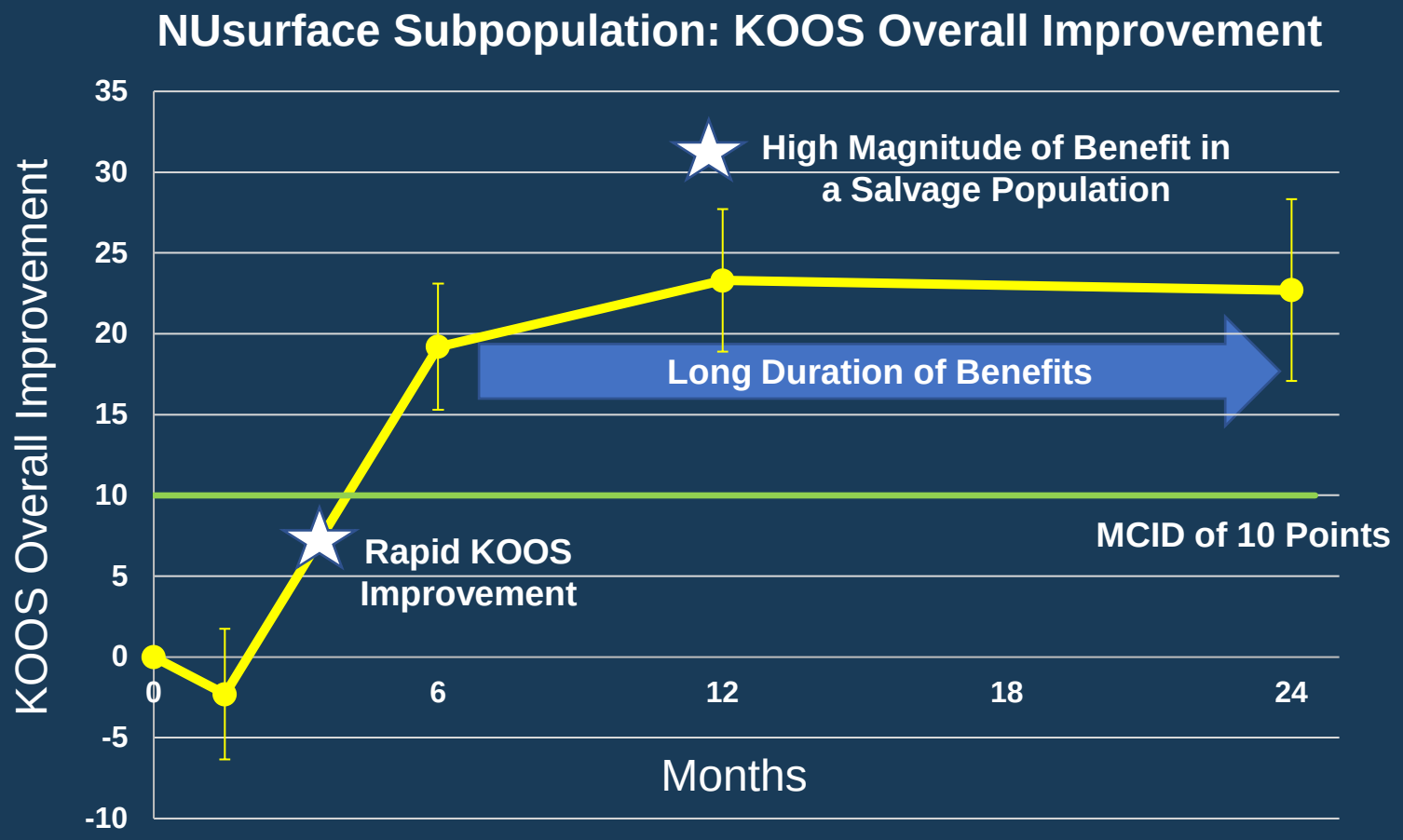


Primary Surgery	Citations
Meniscal Allograft Transplant	• [Familiari 2011] • [Stone 2010] • [McCormick 2014] • [Noyse 2004] • [Rue 2008] • [Van Arkel 1995] • [Saltzman 2016]
Autologous chondrocyte implantation	• [Harris, 2011] • [Minas 2009] • [Pascual-Garrido 2009]
ACL reconstruction	• [Kartus 1999] • [Nepple 2012]
Meniscal repair	• [Paxton 2011] • [Harris 2011]
Implantable Shock Absorber	• Diduch [2023]

- **MERCURY Subpopulation Permanent Removal Rate: 7%**
- **Misha® Implantable Shock Absorber: 14%**

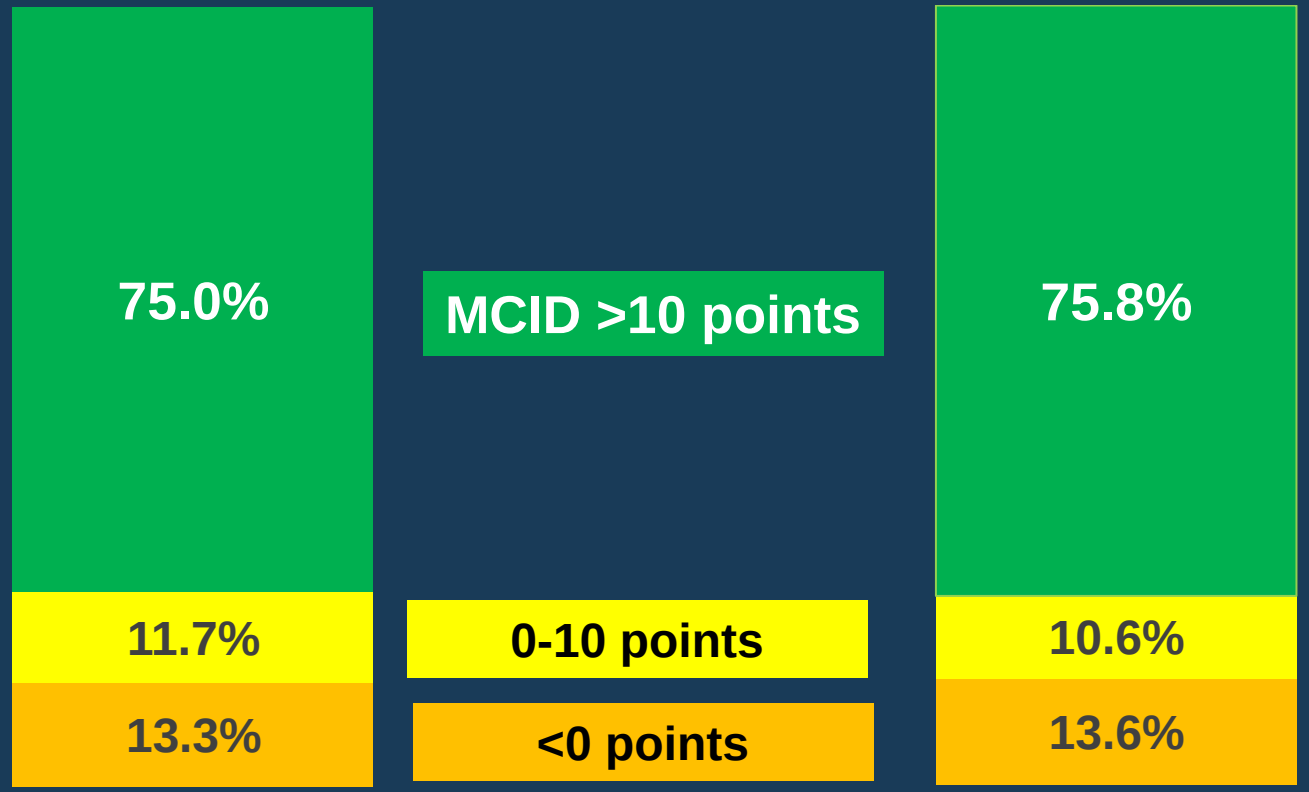
NUsurface Benefits as Early as 6 Months

- Rapid Improvement in KOOS Scores after surgery
- Magnitude of improvement over the MCID
- Duration of improvement from 6 to 24-months
- 24-Mo mean KOOS Overall: 22.7



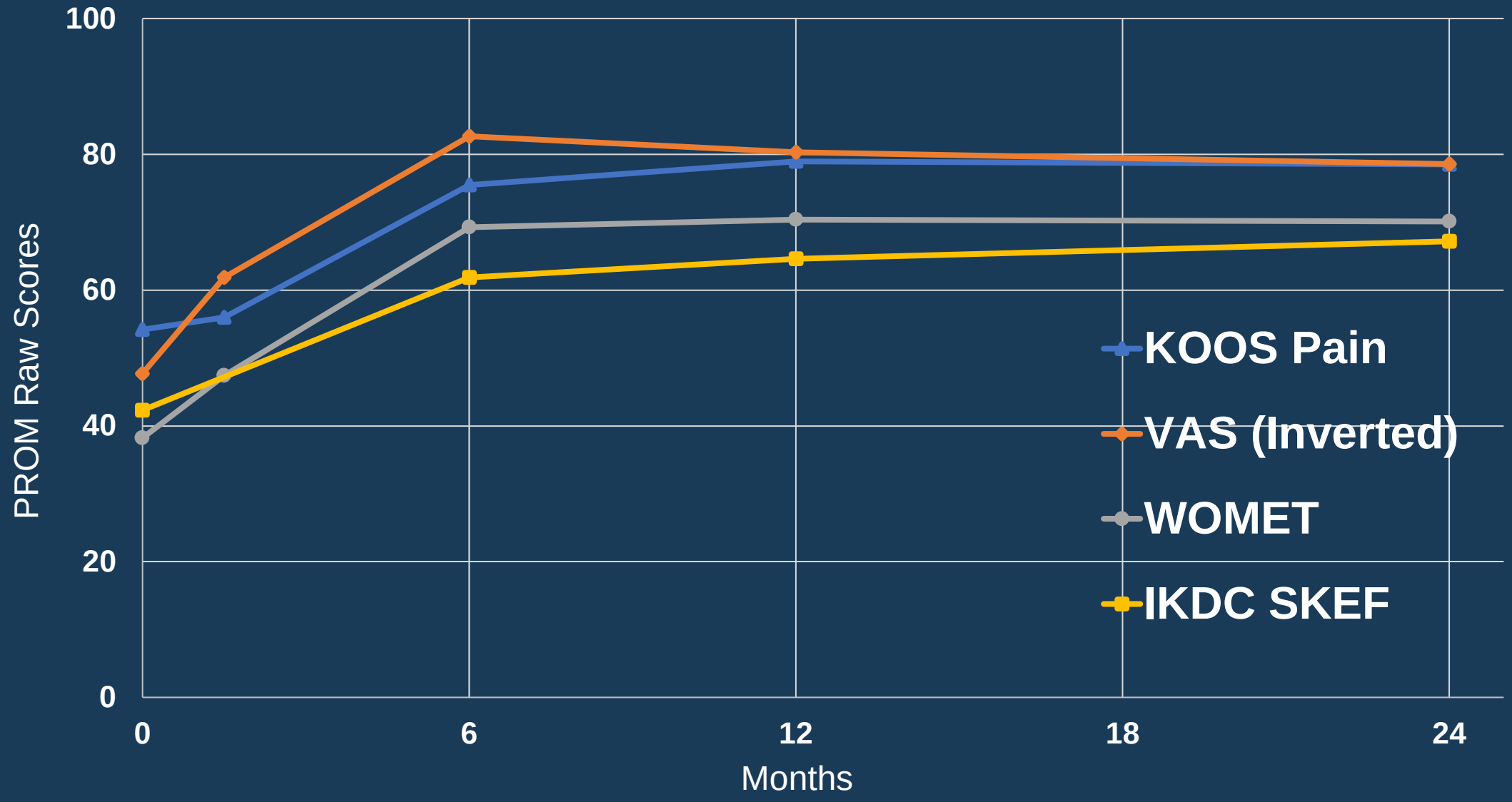
NUsurface 24-Month KOOS Overall Responder Rates High: No Difference with /or/ Without a Device Exchange Surgery

24-Month KOOS Overall Responder Rates (%)

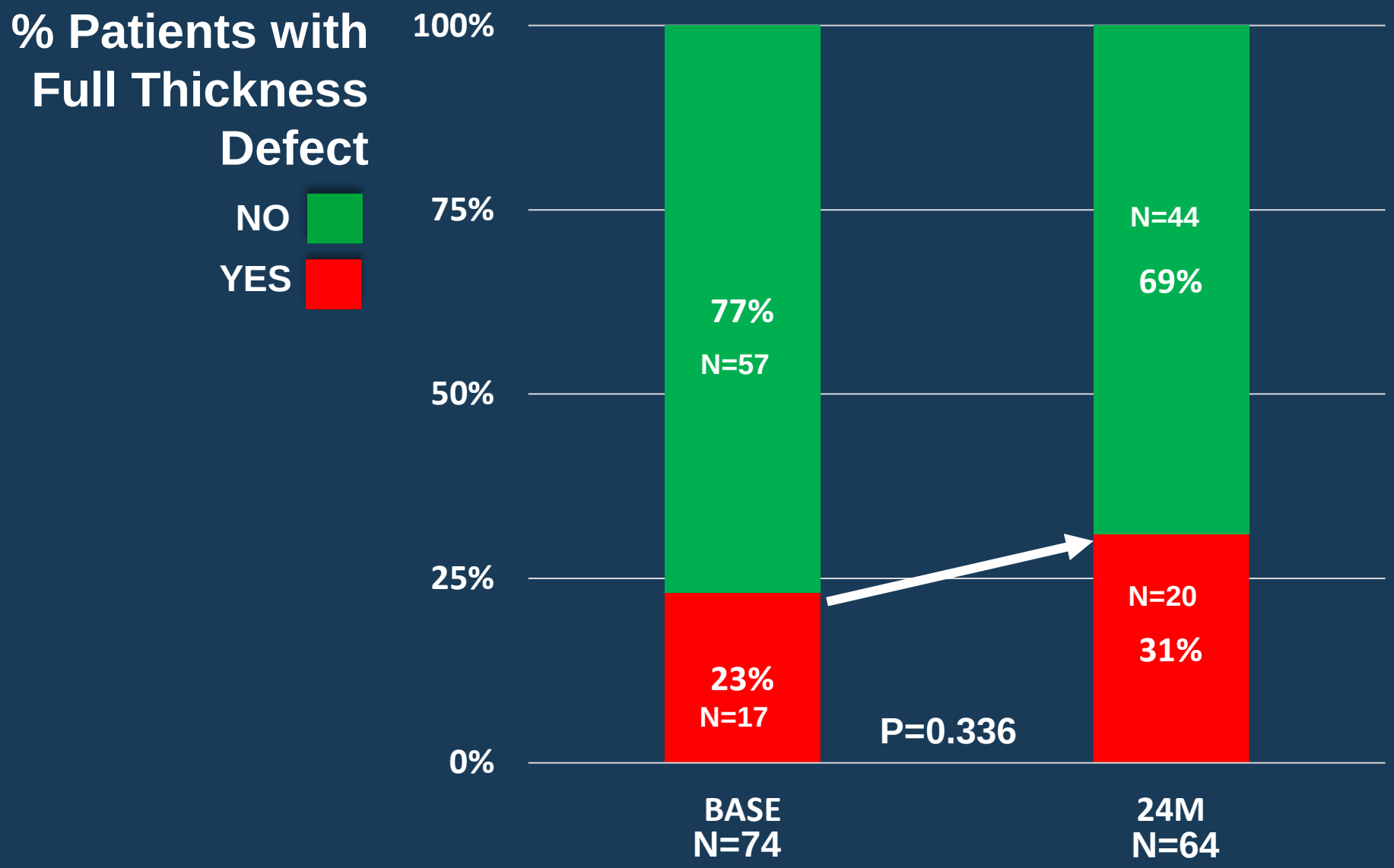


NUsurface Patient Reported Outcome Measures Agree

Improvement at 6 months and continuing until 24 months



NUsurface Maintained Full Thickness Cartilage Defects in the Medial Compartment at 24-Months



Summary of NUsurface Benefits

- KOOS improvements 6 months timepoints
- Responder rates over 75%
- Multiple, different PROMs agree on benefits
- Cartilage protection

Putting it All Together

- Risk of a surgical implant compared to non-operative therapy
- Subjects with no second surgeries = excellent clinical benefit
- Subjects with a second procedure:
  - Implant easy to replace
  - Clinical benefits comparable to first procedure
- Mitigating Risk
  - Warn of potential risk from high impact activities
  - Surgeon training

MERCURY PPI Information: Survey #7

207 Individuals Matched to the MERCURY Study Demographics Including Knee Pain.

- **Educated on the benefits and risks of NUsurface and non-operative therapy**
- **Asked if:**
  - **The rate of second surgery was acceptable**
  - **Potential benefits versus potential risks**
- **Results: 93% on average preferred NUsurface over Controls**

MERCURY PROs with Patient Perspective Information

7 Questions Interpret Emotional or Mental Health Aspect of Health-Related Quality of Life

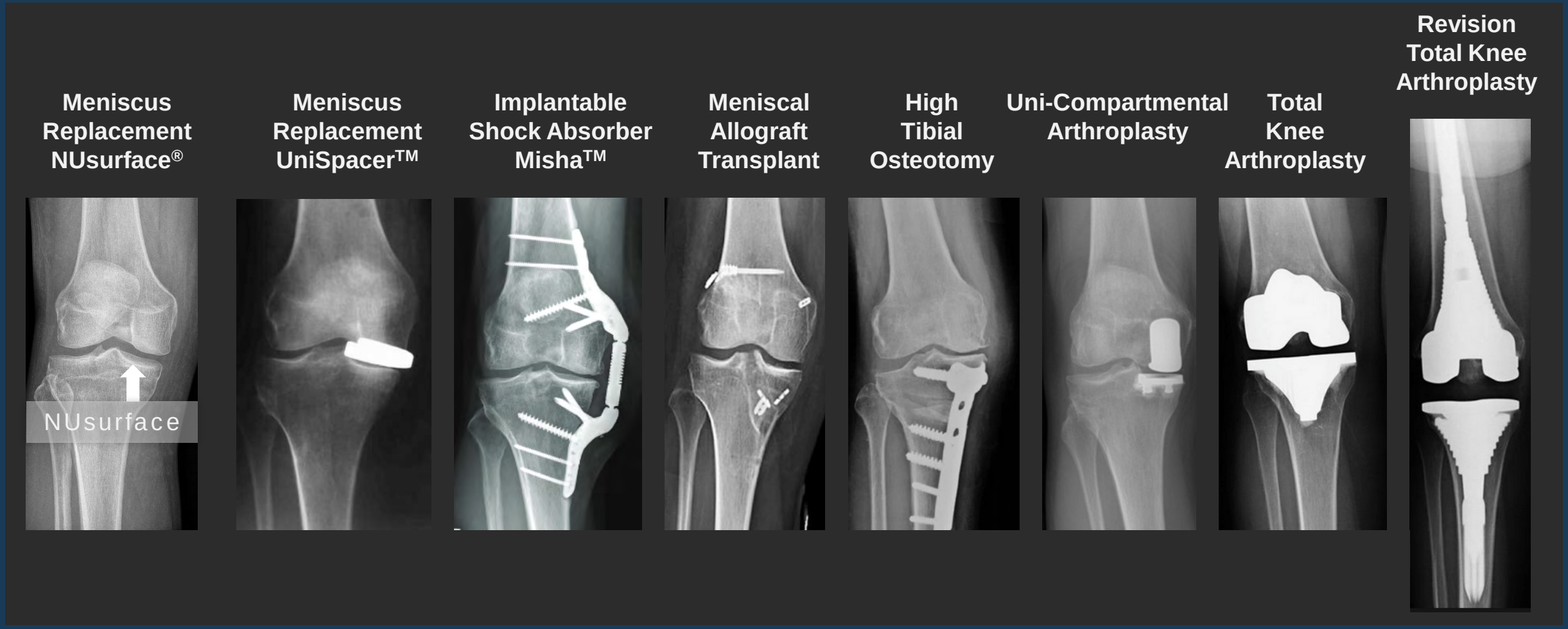
NUsurface vs. Control Results: → 24 Months Change

KOOS Quality of Life	Entire Study (N=242)	Subgroup (N=109)
6 Months	P = <0.001	P = <0.001
12 Months	P = <0.001	P = <0.002
24 Months	P = 0.001	P = 0.004
WOMET Emotion	**Entire Study (N=242)**	**Subgroup (N=109)**
6 Months	P = <0.001	P = <0.001
12 Months	P = 0.001	P = 0.017
24 Months	P = 0.003	P = 0.006

All p values in Favor of NUsurface

Patient Perspective Captured by NUsurface Patient Choice to Replace NUsurface vs. Knee Replacement

- The Ultimate Patient Preference



Benefit/Risk Decision

Indicated Patient: Salvage population that previously failed meniscus surgery

Benefits:

- Pain relief and function recovery superior over the standard of care at 24-months
- Pain relief beginning at 6-months
- 75% responder rate
- Preserves the cartilage, unique among current therapies
- Addresses a gap in the current continuum of care for patients in pain who have failed non-surgical care

Risks:

- Risk identified in the MERCURY Trial were no different than Controls
- Additional procedure to exchange a device
  - Easier and faster procedure for surgeon
  - Easier and faster recovery for patient
  - Same pain relief and function recovery as 1st implant
- Procedure preserves all future options, if needed