Smith & Nephew
REGENETEN

Kerrin Rennie Award Submission

smith&nephew

REGENETEN®

Bioinductive Implant

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Executive Summary

The REGENETEN BioInductive Implant is a highly porous, highly aligned, highly purified collagen scaffold that is disrupting the current treatment pathways for Rotator Cuff Disease.

The implant is both an Inductive and Conductive scaffold that rapidly induces the growth of new tendon like tissue.

Criteria 1
Innovation

REGENETEN™ Bioinductive Implant
First To Clinically Demonstrate Tendon Tissue Induction

Rotator Cuff Disease Progressions[1]

Rotator cuff inflammation and pain is caused by excessive micro-strains in the tendon
Excessive micro-strains lead to partial-thickness tears which often progress to full-thickness tears that require major surgical intervention

Hypothesis

Inducing a layer of new tendon-like tissue on the bursal side of the tendon will reduce the micro-strains in the tendon

- Reduced micro-strains will reduce inflammation and relieve pain
- Reduced micro-strains will slow or stop tear progression

Biological Augmentation – new tissue adds strength*[2]

In contrast, competitive approaches use implant to add strength to massive tears – mechanical augmentation only

Conduction vs. Induction

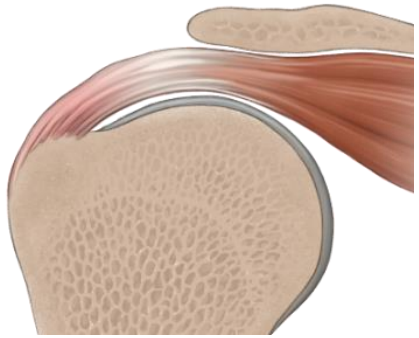
The REGENETEN Bioinductive Implant is also conductive

- A **conductive** implant "allows" a *general* biological response to occur[3]
- An **inductive** implant "causes" a *particular* biological response to occur[4]

*Based on Finite Elemement Modeling. **1**. Hodgson RJ, et al. *Brit J Radiology*. 2012;85(1016):1157-1172. **2**. Chen Q. Technical Report from the Material and Structural Testing Core. Mayo Clinic: Rochester, Minnesota; 2011. **3**. Balint R, et al. *Acta Biomateriala.* 2014;10:2341-2353. **4**. Sonarkar S, Purba R. *Int J Contemp Dent Med Rev*. 2015;2015:1-4. doi: 10.15713/ins.ijcdmr.47.

Current State RC Disease Treatment

Current State

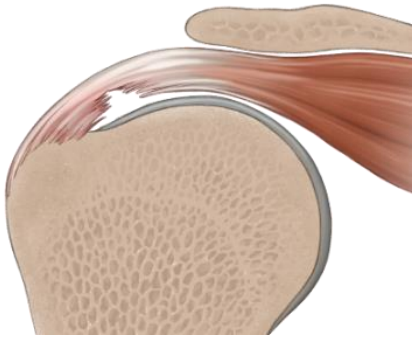


Severe Tendinosis/Low-Grade Partial-Thickness Tears (PTT) – Failed Conservative Treatment

- Chronic rotator cuff tendinosis has been identified as a primary cause of rotator cuff tears[1]
- ~44% have been reported to progress to full-thickness tears[7]

Subacromial Decompression (SAD):

Inconsistent results, limited long-term efficacy[2]

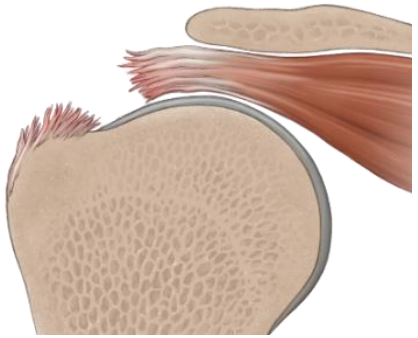


High-Grade Partial-Thickness Tears

- Up to 80% of PTTs increase in size within 2 years[3]
- ~10% have been reported to progress to full-thickness tears[4]

Take down/repair and trans-tendon approach:

Both have challenges and neither is an ideal treatment option[5]



Full-Thickness Tears (FTT)

- Small tears progress over time, eventually requiring surgical repair[6-8]
- Larger tears requiring repair tend to re-tear over **40%** of the time[9-11]

Repair:

High rate of revision/retear[11]

1. Hashimoto T, et al. *Clin Orthop Relat Res*. 2003;(415):111-20. **2**. Kartus J, et al. *Arthroscopy*. 2006;22(1):44-49. **3**. Yamanaka K, Matsumoto T. *Clin Orthop Relat Res.* 1994;(304):68-73. **4**. Keener JD, et al. *J Bone Joint Surg Am*. 2015;97(2):89-98.**5**. Internal knowledge, Smith & Nephew. **6**. Bokor DJ, et al. *MLTJ*. 2016;6(1):16-25. **7**. Schlegel TF, et al. *J Shoulder Elbow Surg.* 2018;27(2):242-251. **8**. Washburn R, et al. *Arthroscopy Techniques*. 2017:6(2);e297-e301. **9**. Bishop J, et al. *J Shoulder Elbow Surg*. 2006;15(3):290-299. **10**. Heuberer PR, et al. *Am J Sports Med*. 2017;45(6):1283-1288. **11**. Henry P, et al. *Arthroscopy*. 2015;31(12):2472-2480.

Our Hypothesis
The Problem

- While the biologic potential for healing may exist[1], several factors, such as subacromial impingement, may adversely affect this process
- Growing belief that the reason rotator cuffs do not heal on their own is a biomechanical issue – excessive stress and strain on the tendon inhibits the natural healing process*[2]

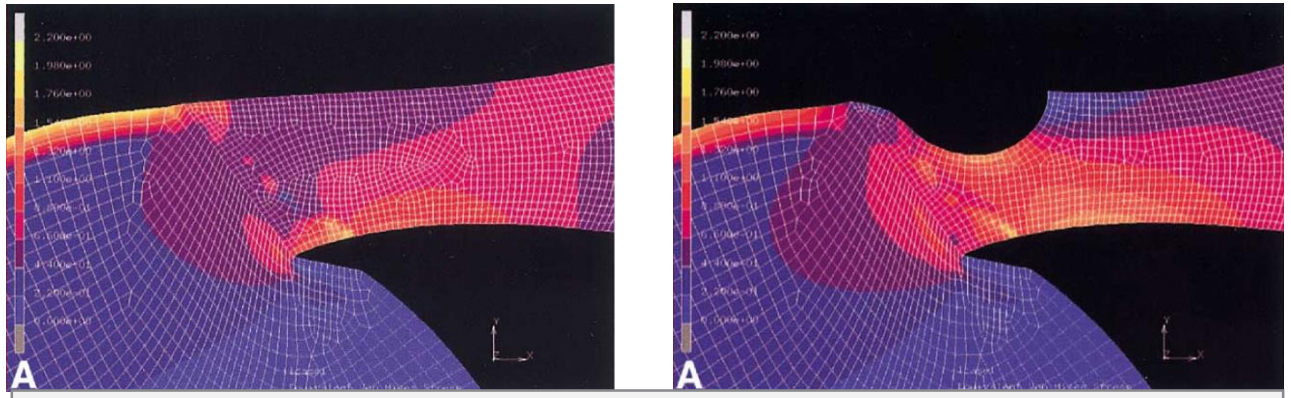
Injured Tendon

↓

Increased stress and strain on tendon

↓

Impaired Healing



Stress distribution in the supraspinatus tendon with partial-thickness tears: An analysis using two-dimensional finite element model[2]

* Based on Finite Element Modeling.

1. Schlegel TF, et al. *J Shoulder Elbow Surg.* 2018;27(2):242-251. **2**. Sano H, et al. *J Shoulder Elbow Surg*. 2006;15(1):100-105.

Our Hypothesis
The Solution:

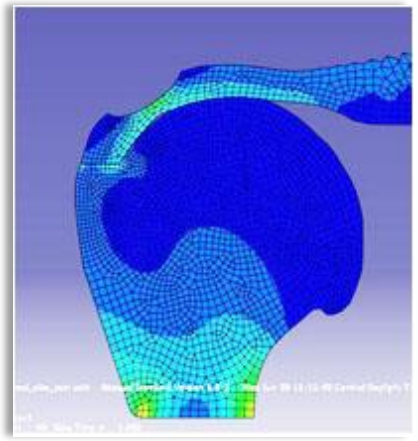
Hypothesis:[1]

The induction of a layer of new tendinous tissue on the bursal side of the supraspinatus tendon could reduce micro-strains within the tendon and could:

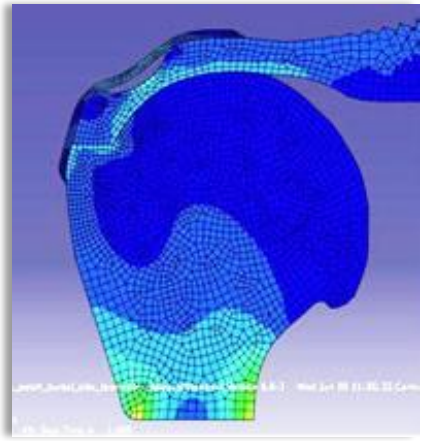
-**Provide an optimized, mechanical environment for tendon healing**

-**Inhibit, or arrest, tear propagation**

Baseline

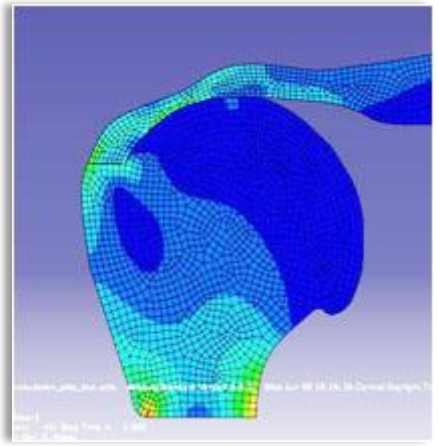


With 2mm of Induced Tissue

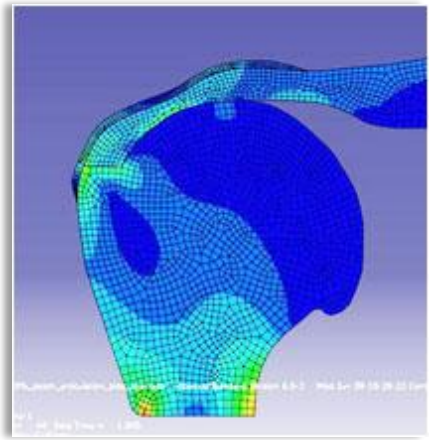


Bursal Surface Tear[1]
47% reduction in peak strain[2]

Baseline



With 2mm of Induced Tissue



Articular Surface Tear[1]
40% reduction in peak strain[2]

1.Images/data on file, Smith & Nephew. **2**. Chen Q. Technical Report from the Material and Structural Testing Core. Mayo Clinic: Rochester, Minnesota; 2011.

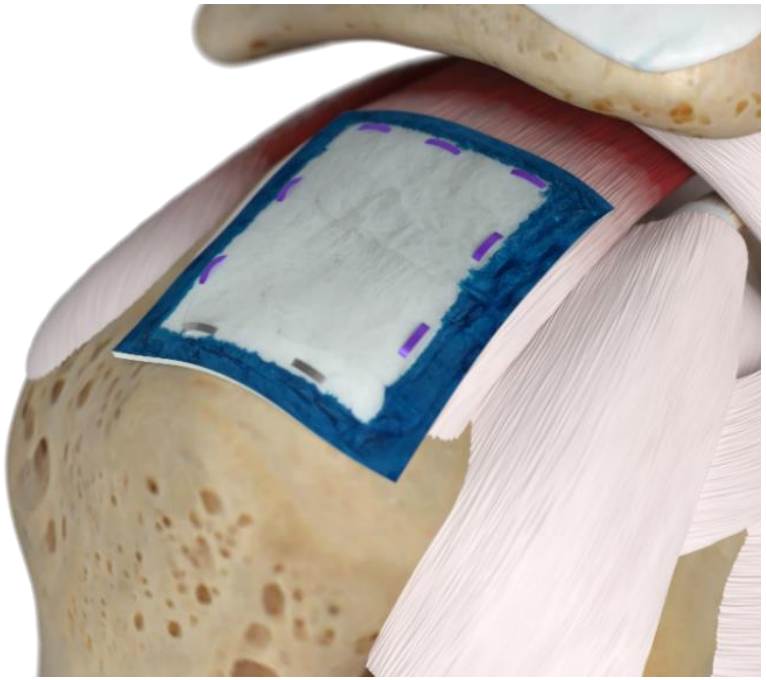
REGENETEN™ Bioinductive Implant
What is it?

A collagen implant derived from bovine Achilles tendon, with highly purified, highly porous, highly oriented design

Stimulates the body's natural healing response to support new tendon growth and disrupt disease progression[1,2]

Clinically proven to reliably induce new tendon-like tissue and promote tendon healing[1,2]

Gradually absorbs within six months, leaving a layer of new tendon-like tissue to biologically augment the existing tendon[3]



"[REGENETEN is the] first regenerative pathway to stimulate angiogenesis and be restorative, not reparative. If you believe in biology, this is a big step."[1-4]

- Felix "Buddy" Savoie III, MD, Tulane University School of Medicine, New Orleans, LA

1. Bokor DJ, et al. *MLTJ.* 2016;6(1):16-25. **2**. Schlegel TF, et al. *J Shoulder Elbow Surg.* 2018;27(2):242-251. **3**. Van Kampen C, et al. *MLTJ.* 2013;3(3):229-235. 4. Arnoczky SP, et al. *Arthroscopy.* 2017;33(2):278-283.

Criteria 2
Technical Excellence

REGENETEN™ Bioinductive Implant

Harnessing the Biology of the Body

A highly porous, precisely oriented reconstituted collagen implant made from thoroughly purified, bovine type I collagen

Stimulates the body's natural healing response to support new tendon growth and disrupt disease progression[1,2]

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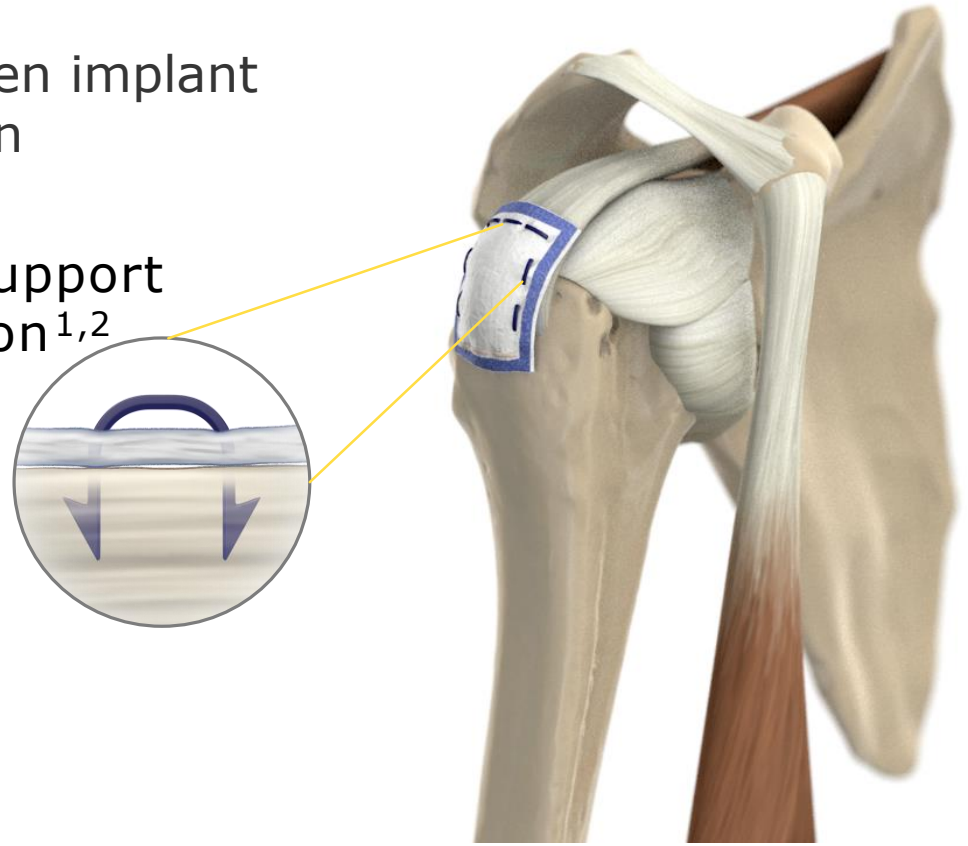


1. Bokor DJ, et al. MLTJ. 2016;6(1):16-25. 2. Schlegel TF, et al. J Shoulder Elbow Surg. 2018;27(2):242-251. 3. Van Kampen C, et al. MLTJ. 2013;3(3):229-235.

REGENETEN™ Bioinductive Implant

How does it work?

Injured Tendon

REGENETEN™ Induces New Tissue, Increasing Tendon Thickness[1-3]

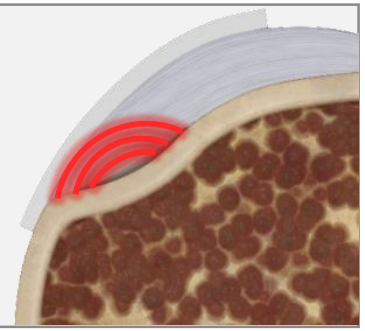
New Tissue Integrates with Native Tendon and Bone, Shares the Load, Decreasing Load on Native Tendon[1-4]

Stress and Strain Are Decreased*[4]

Favorable Biomechanics, Tendon heals[1-4]

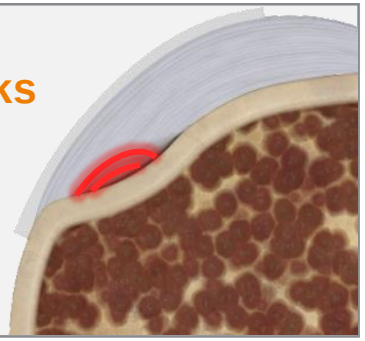
Implant placed over bursal surface of RCT

Proprietary implant design creates an environment conducive to healing[2]



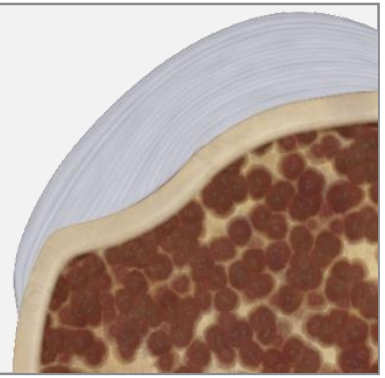
Implant induces new host tissue onto tendon by 12 weeks

Within 3 months, implant facilitates the formation of new tendon-like tissue[5]



New tissue integrates and remodels into the healed tendon

Strength comes from patient's own induced tissue, not the implant, which completely absorbs within 6 months[5]

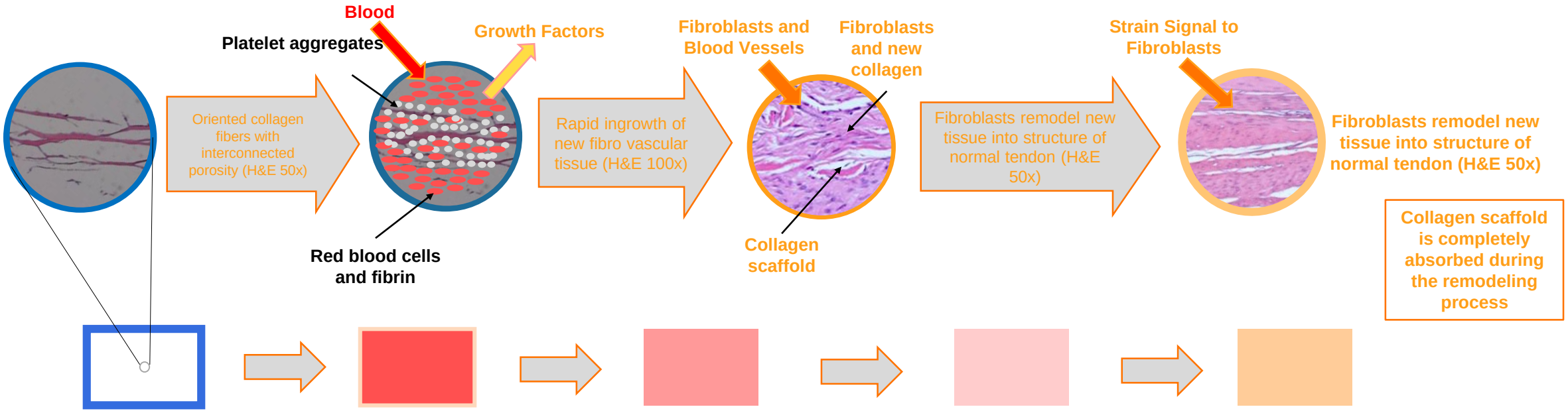


* Based on Finite Element Modeling. **1**. Bokor DJ, et al. *MLTJ.* 2015;5(3):144-150. **2**. Bokor DJ, et al. *MLTJ*. 2016;6(1):16-25. **3**. Schlegel TF, et al. *J Shoulder Elbow Surg.* 2018;27(2):242-251. **4**. Chen Q. Technical Report from the Material and Structural Testing Core. Mayo Clinic: Rochester, Minnesota; 2011. **5**. Arnoczky SP, et al. *Arthroscopy.* 2017;33(2):278-283.

REGENETEN™ Bioinductive Implant

How does REGENETEN stimulate healing using no growth factors?

By taking advantage of the body's normal healing process and orchestrating this process to produce new tendon tissue.



1. The reconstituted collagen scaffold is highly porous and highly purified, which avoids any adverse inflammatory response

2. Immediately after surgery the collagen scaffold becomes saturated with blood

3. The patient's own platelets undergo degranulation due to contact with the collagen scaffold, resulting in the release of growth factors that initiate the healing process

4. The growth factors released by the platelets attract the ingrowth of fibroblasts and blood vessels into the collagen scaffold

5. The fibroblasts produce new tissue and remodel the tissue according to the strain environment created by the collagen scaffold properties

1. Bokor DJ, et al. *MLTJ*. 2016;6(1):16-25. **2**. Schlegel TF, et al. *J Shoulder Elbow Surg.* 2018;27(2):242-251. **3**. Van Kampen C, et al. *MLTJ.* 2013;3(3):229-235. 4. Arnoczky SP, et al. *Arthroscopy.* 2017;33(2):278-283.

REGENETEN™ Bioinductive Implant

Harnessing the Biology of the Body

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3. New Tissue Integrates with Native Tendon and Bone, Shares the Load, Decreasing Load on Native Tendon[1-4]
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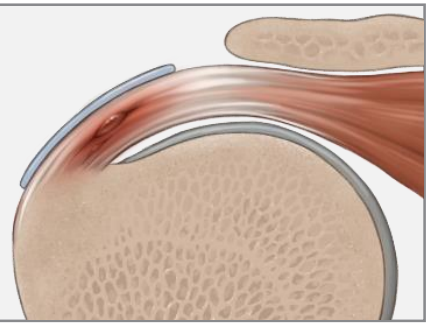

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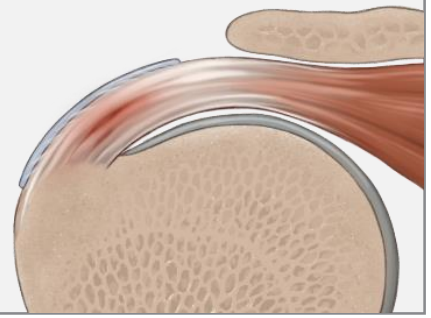

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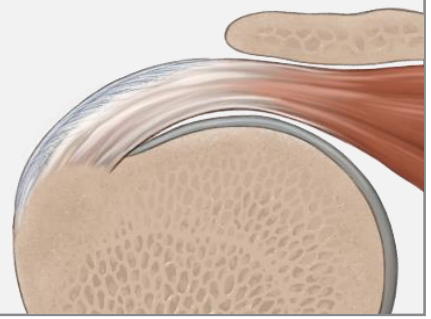

1. Bokor DJ, et al. MLTJ. 2015;5(3):144-150. 2. Bokor DJ, et al. MLTJ. 2016;6(1):16-25. 3. Schlegel TF, et al. J Shoulder Elbow Surg. 2018;27(2):242-251. 4. Chen Q. Technical Report from the Material and Structural Testing Core. Mayo Clinic: Rochester, Minnesota; 2011. 5. Arnoczky SP, et al. Arthroscopy. 2017;33(2):278-283.

Criteria 3

Significant contribution to improving patient outcomes by improving quality of life

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The REGENETEN BioInductive Implant has shown through published clinical data and a REBUILD registry to significantly improve patient outcomes post operatively from Rotator Cuff Repair Surgery.

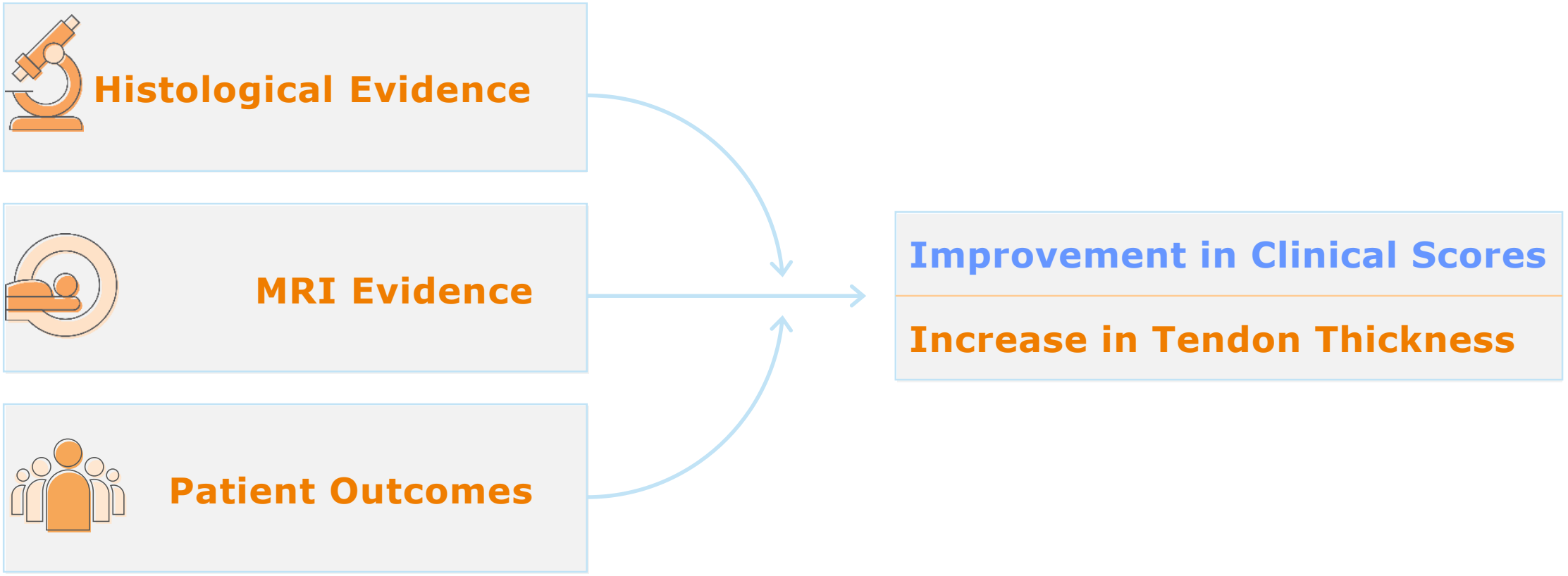
These outcomes have been based on previously proven clinical measurement systems as well as patient specific outcomes that have been deemed relevant to life post surgery.

See below the definitive data.

REGENETEN™ Bioinductive Implant:
Published Clinical Studies

Study Author(s)-Publishing Journal	Title	N	Key Results
Bokor DJ et al.[6] **Muscles Ligaments Tendons J.**, 2015 Sept	Evidence of healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a collagen implant: a 2-year MRI follow-up	**13**	• The implant induced significant ($p<0.0001$) new tissue formation in all patients by 3 months (mean increase in tendon thickness 2.2 ± 0.26 mm). • This tissue matured over time and became radiologically indistinguishable from the underlying tendon. • No tear progression was observed by MRI in any of the patients at 24 months. • Clinical scores improved significantly ($p<0.01$).
Bokor DJ et al.[14] **Muscles Ligaments Tendons J.**, 2015 Sept	Preliminary investigation of a biological augmentation of rotator cuff repairs using a collagen implant: A 2-year MRI follow-up	**9**	• There was a significant ($p < 0.01$) increase in mean tendon thickness in all subjects at 3 months when compared to published values • No re-tears were observed • Clinical scores improved significantly ($p<0.001$).
Arnoczky SP et al.[12] **Arthroscopy**, 2017 Feb	Histologic Evaluation of Biopsy Specimens Obtained After Rotator Cuff Repair Augmented with a Highly Porous Collagen Implant	**7**	• Biopsies of collagen implants retrieved from human rotator cuff repair subjects revealed cellular incorporation, tissue formation and maturation, implant resorption, and biocompatibility. • The histologic observations from these clinical biopsies support the biocompatibility of this implant and its ability to promote new connective tissue with the histological appearance of tendon over the surface of the native cuff tendon.
Schlegel T et al.[5] **J Shoulder Elbow Surg.**, 2018 Feb	Radiologic and clinical evaluation of a bioabsorbable, collagen implant to treat partial-thickness tears: a prospective multi-center study	**33**	• Mean tendon thickness increased significantly by 2.0 mm ($p<0.0001$). • Eight patients demonstrated MRI evidence of complete healing, 23 demonstrated considerable reduction in defect size, and 1 lesion remained stable. • Clinical scores improved significantly ($p<0.0001$) at one-year follow-up. • No serious adverse events related to the implant were reported.

REGENETEN™ Bioinductive Implant:
Consistent Excellence in Clinical Evidence and Patient Outcomes



REGENETEN™ Bioinductive Implant – The Evidence: f
Claims and Sources

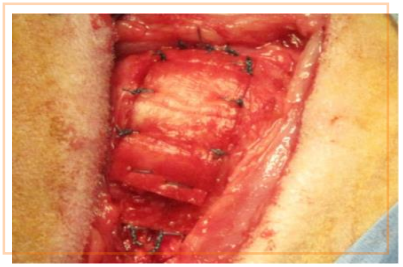
CLAIM	SOURCES*				
	1	2	3	4	5
- Reduces strain at tear site		✓			
- First bio-inductive implant to address tendon disease progression	✓	✓	✓	✓	
- Disruptive technology that prevents disease progression	✓	✓	✓	✓	
- Reverses disease progression in partial thickness tears/fill in defect (mri)	✓		✓	✓	
- Newly generated tendon-like tissue biologically augments host tissue	✓	✓	✓	✓	
- Clinically proven to induce healing response	✓	✓	✓	✓	
- Significantly improves clinical scores	✓			✓	✓
- Improves patient outcomes (sling time, return to work, pt sessions, etx)					✓
- Induces tendon-like tissue growth in all disease stages	✓		✓		
- No foreign body reaction	✓	✓	✓	✓	
- Resorbs within 3 to 6 months		✓	✓		
- Expands treatable patient population (diabetes, smoker)					✓

*Sources included in Appendix.

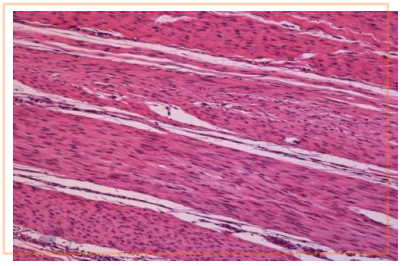
REGENETEN™ Bioinductive Implant – The Evidence:
Histological Evidence

Pre-Clinical Sheep Study[13]

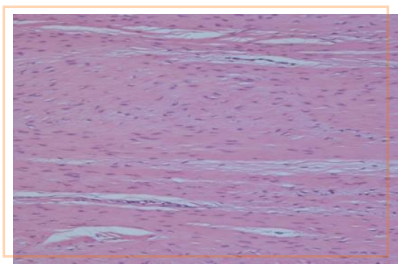
Baseline:
Implantation of Bioinductive Implant



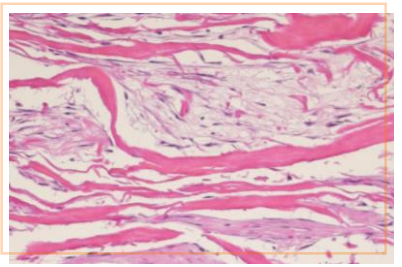
Month 3:
Increased collagen formation, maturation, and orientation



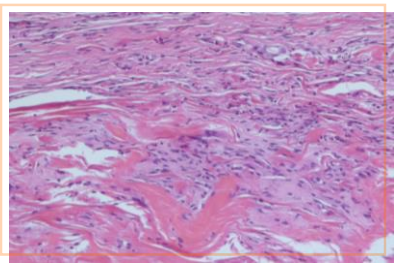
Month 6:
Dense, regularly-oriented newly-regenerated connective tissue; implant fully absorbed



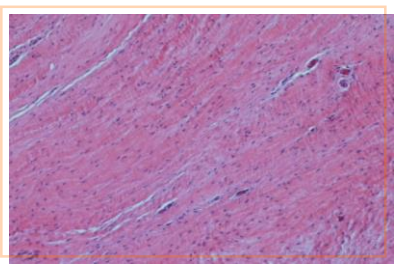
Human Biopsy Study[12]



Week 5:
Host cell ingrowth with early collagen production and alignment



Month 3:
Increased collagen formation, maturation, & orientation

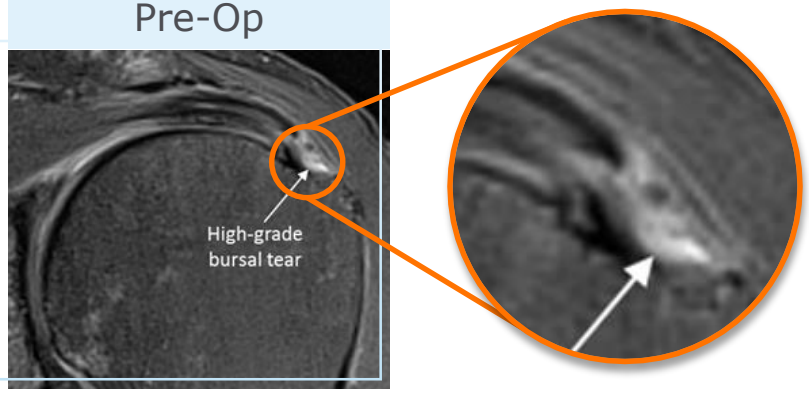


Month 6:
Dense, regularly-oriented newly-regenerated connective tissue; implant fully absorbed

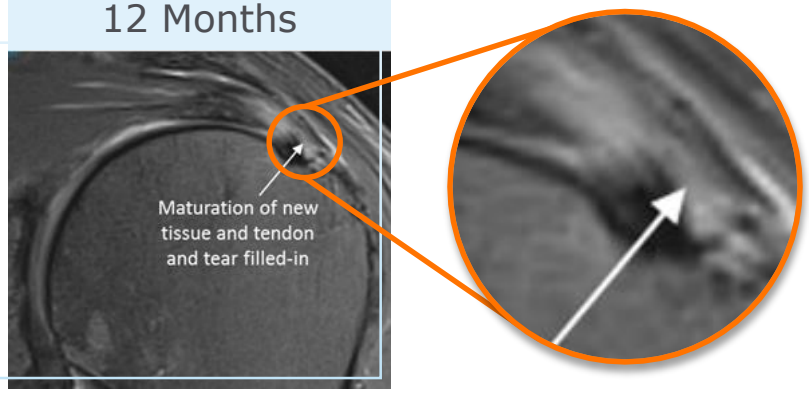
REGENETEN™ Bioinductive Implant – The Evidence: f
MRI Evidence

Partial Thickness Tear[6]

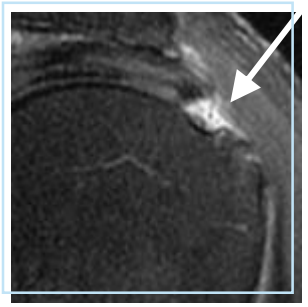
Pre-Op



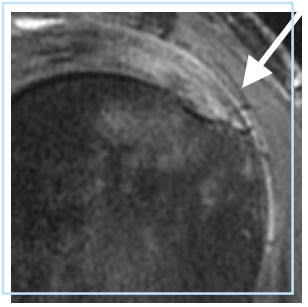
12 Months



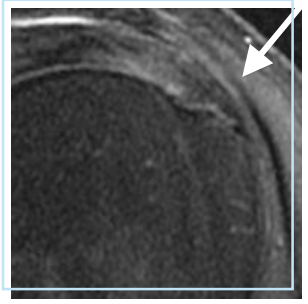
Full Thickness Tear[14]



Pre-Op:
8x12mm tear



Month 3:
Newly induced inhomogeneous tissue



Month 12:
Better tissue quality; still somewhat amorphous

REGENETEN™ Bioinductive Implant – The Evidence: f
Outcomes – US Partial Thickness Tear Study (Schlegel)[5]

Supports the fact that the radiological images correlate to improved patient outcomes (12 month data):

Radiological Evidence

- 24% of defects completely filled in
- 70% showed reduction in size
- Tendon increased an average of 5.2mm

Outcomes

- ASES combined scores improved from 57 to 89.1 (P<.0001)
- CMS scores improved from 57.1 to 81.4 (P<.0001)
- ZERO dissatisfied patients

Patient Outcomes Measures

Constant-Murley Score (CMS)

- Physical exam component = 65%
  - 40% ROM
  - 25% strength testing
- Patient-reported functional assessment = 35%
  - 15% pain
  - 20% function with activities of daily living (ADLs)

ASES Score

- Society of American Shoulder and Elbow Surgeons
- Surgeon-rated and patient-rated sections
- Score broken down into 50% pain and 50% function

Single Assessment Numerical Evaluation (SANE)

- "On a scale of 1-100, how would you rate…."

Pain Visual Analog Scale (VAS)

- Similar to the SANE, but uses visuals:

REBUILD Registry

REBUILD (Rotation MEdical BioindUctive ImpLant Database) is a prospective, non-randomized, multicenter registry designed to collect patient reported outcomes, including shoulder function, pain and quality of life after receiving the Bioinductive Implant.

Interim results of the first 200 patients presented by Dr. Louis McIntyre at the 2017 Arthroscopy Association of North America (AANA) Annual Meeting, showed:

+ Reduction in post-operative pain
+ Decreased narcotic use
+ Less sling time
+ Faster return to function
+ Improved overall shoulder rating

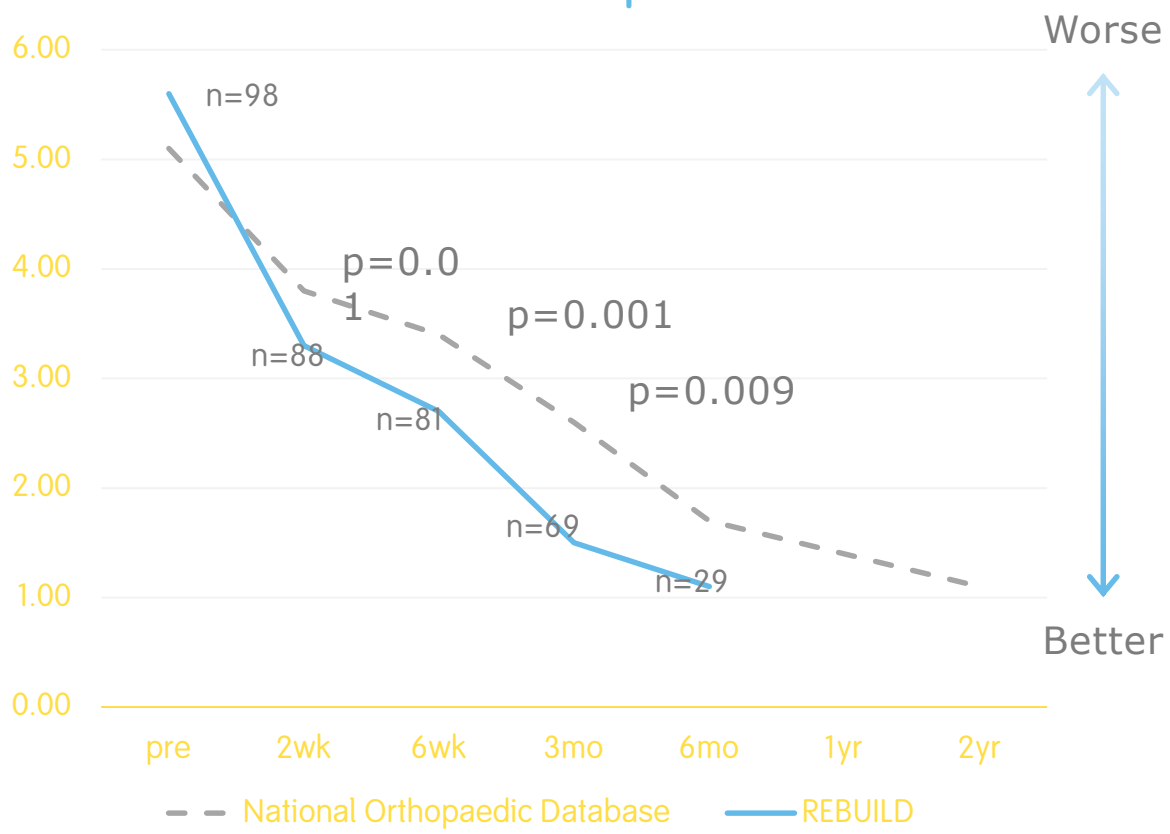
The study will follow up to **500** patients across 20 study centers

No exclusion of any patients over the age of 18

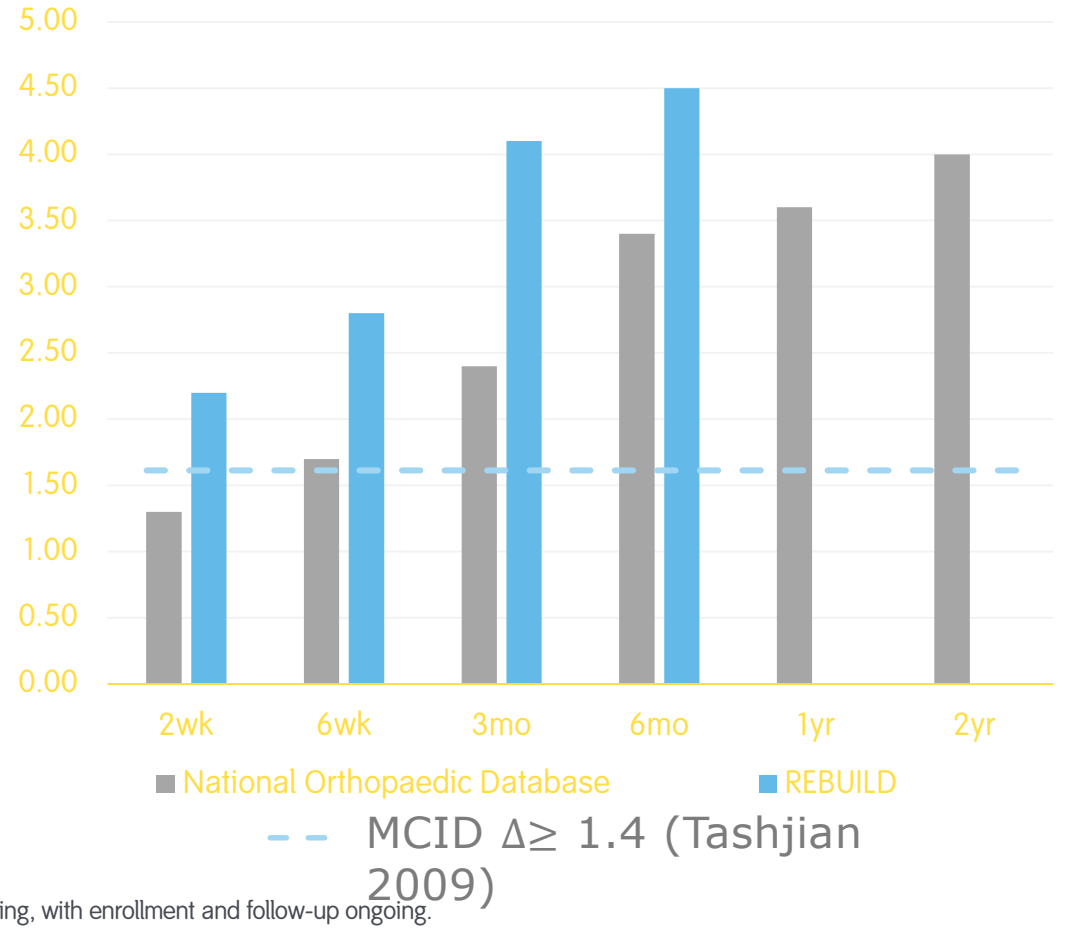
Patients	200
Age (years)	53.6 ± 10.0 (Range: 24.0 to 80.0)
History of Symptoms (months)	26.2 ± 52.0 (Range: 0 to 540.0)
Gender	
Male	58%
Female	42%
Type of Injury	
Acute	32%
Acute-on-Chronic	17%
Chronic	51%
Diabetes	
Yes	11%
No	89%
Smoker	
Yes	12%
No	88%
Worker's Comp	
Yes	10%
No	90%
Chronic Narcotic/Opioid Use	
Yes	11%
No	89%

REBUILD Registry:
Significant Reduction in Pain

Average VAS Pain (0-10): Partial-thickness/No Repair Cohort



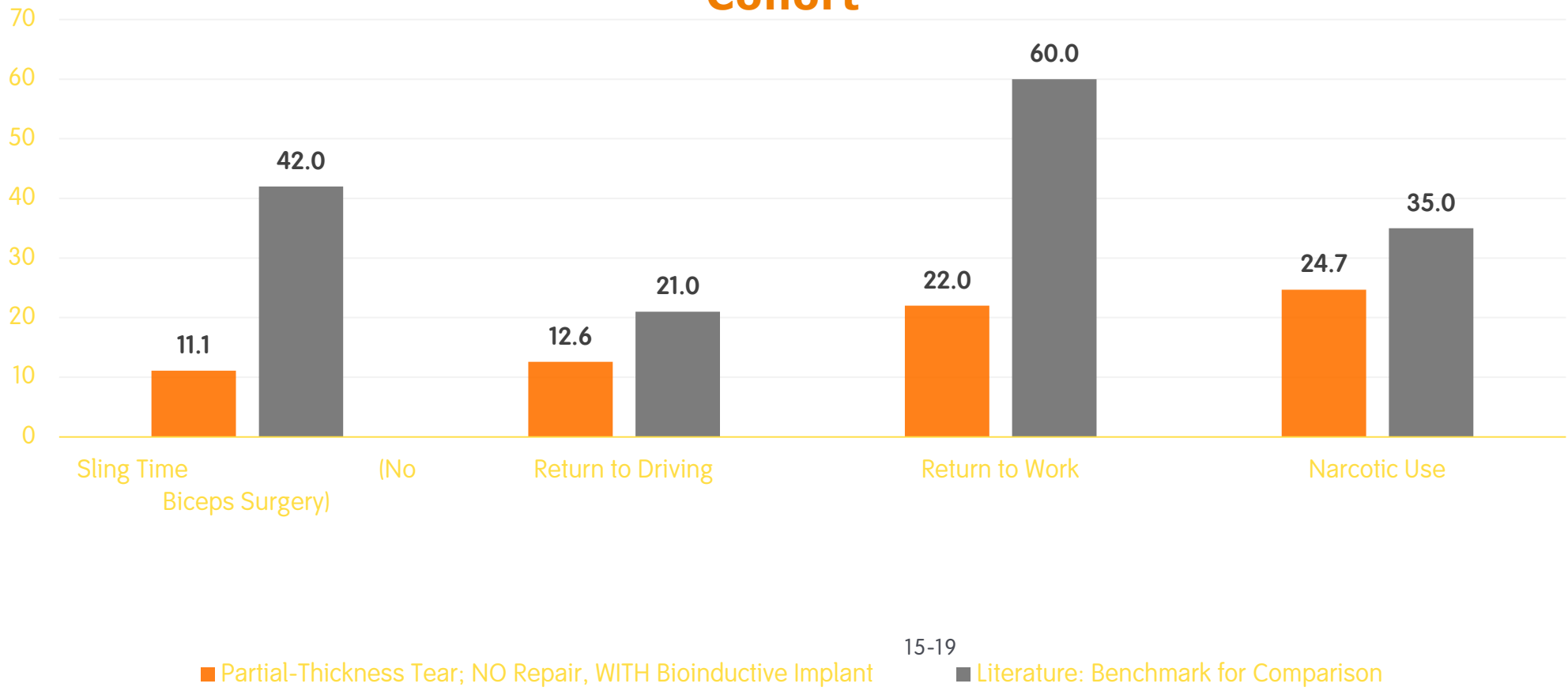
Change in Average VAS Pain from Pre-Surgery: Partial-thickness/No Repair Cohort



*Data shown represents partial-thickness/no takedown repair cohort. REBUILD Registry data on file as of 2017 AANA Meeting, with enrollment and follow-up ongoing.

REBUILD Registry:
Additional Patient Benefits

Benefits of Biological Augmentation in Partial-thickness/No Repair Cohort



*REBUILD Registry data on file as of 2017 AANA Meeting, with enrollment and follow-up ongoing.

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