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The Evidence for Orthopeadic Procedures: Lessons from Modern Clinical Trials

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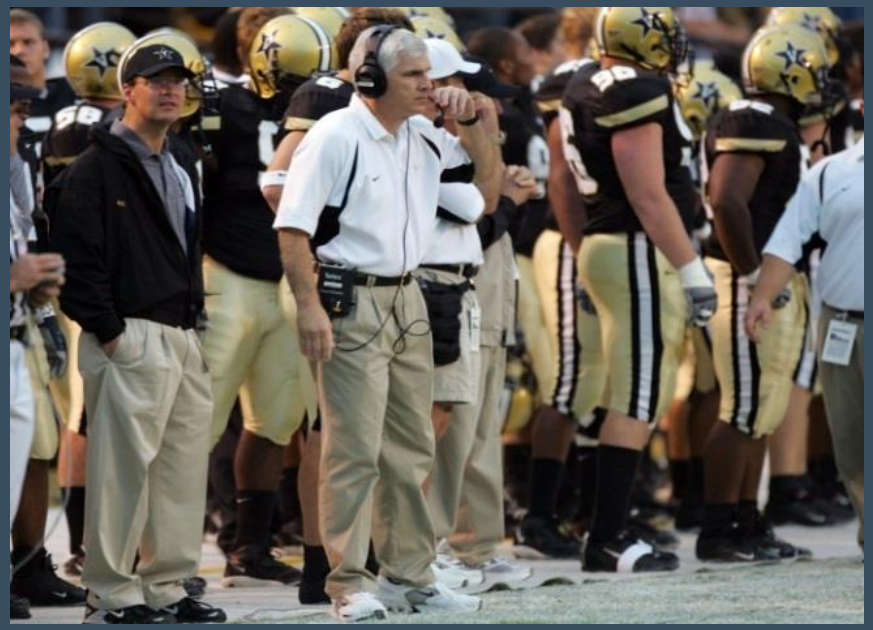
Disclosures Kurt P Spindler



- Current FUNDING
  - NIH R01 = MRI MOON (Li/Spindler co-PI)
  - NIH R01 = MeTeOR study (Katz – PI)
  - NIH R01 = BEAR-MOON (Spindler – PI)
  - NIH R56 = MOON (Spindler –PI)
  - DOD MTEC = MOTION-MOON (KPS co-I)
  - Research Grant: DJO Bracing BEAR-MOON
- Consultant: NFL, Novopeds
- Scientific Advisory Board: Novopeds
- Royalties: Oberd
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Two Fundamental Questions Clinical Decision Making: How Do We

1. Evaluate the evidence from clinical research studies to utilize practice ?
2. Apply which evidence (RCT vs Cohort) to an individual patient?
   a. Caveat why don't we use all the information available ?

GOAL of Clinical Research: Data Patients

1. First: Establish scientific **TRUTH** (statistics, epidemiology, study design)
2. Second: Is the "Truth" a **clinically meaningful difference (CMD)** or clinically relevant result (CRR)?
3. Finally: Is **COST** worth it to society vs. individual for this CMD or CRR?
   (E*xample: relatively same effect size but different costs of HA vs Corticosterod for Knee OA)*

Evidence-Based Medicine

- EBM Incorporates:
  - Clinician experiences
  - Patient preference
  - Best available “data”
- Medicine is both ART and Science
- Present Question: what is evidence for Orthopaedic Surgery
  - Focus Knee – my expertise and focus will take deeper dive

Hierarchy of Treatment Studies: Levels of Evidence

Systematic Review/Meta-analyses*

Randomized Controlled Trials (Level I)

Cohort Studies (Level II)

Case Control Studies (Level III)

Cross Sectional Surveys

Case Reports/Series (Level IV)

Expert Opinion (Level V)

Anecdotal

*Level I = RCTs, Level II include cohorts

JBJS Am introduced Orthopaedics over decade ago

Clinical QUESTION Determines Study Design

Research	Example	Preferred Study Design
Therapy	TKA vs Rehab Knee OA Autograft Choice ACLR	RCT Level 1 Cohort Level 2
Diagnosis	Labral tear	Cross-sectional survey
Screening	Role flexibility as injury risk	Cross-sectional survey
Prognosis	Which Pts benefit most and least AE?	Longitudinal cohort study
Risk Factor	Risk factors PTOA	Cohort or case control

Hypothesis Question Generating vs Testing

The control of major risk factors and sources of bias determine dichotomy

	*	* *	Other Designs	
Experimental	RCT	ITT Intention to tx		
Observational	Prospective Cohort	MV multivariable		
	↓			↓
Hypothesis Testing Clinical Practice Changing			**Hypothesis Generating Data for Hypothesis Testing**	

EBM use highest available evidence

Choose Appropriate Study Design for Clinically Relevant Question

1. Experimental (RCTs) if:
   a. Efficacy new technology
   b. Major shifts clinical practice
2. Observational (cohorts) if:
   a. "Natural experiments"
   b. Identify prognosis and predictors outcomes
   c. Post-market surveillance
   d. Shared decision-making
   e. Comparative effectiveness
3. Case-Controls if:
   a. Too few cases to do RCT or cohort

BEAR MOON RCT

Tissue Eng. Repair vs ACLR

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How Does an RCT vs Cohort Guide Decision Making

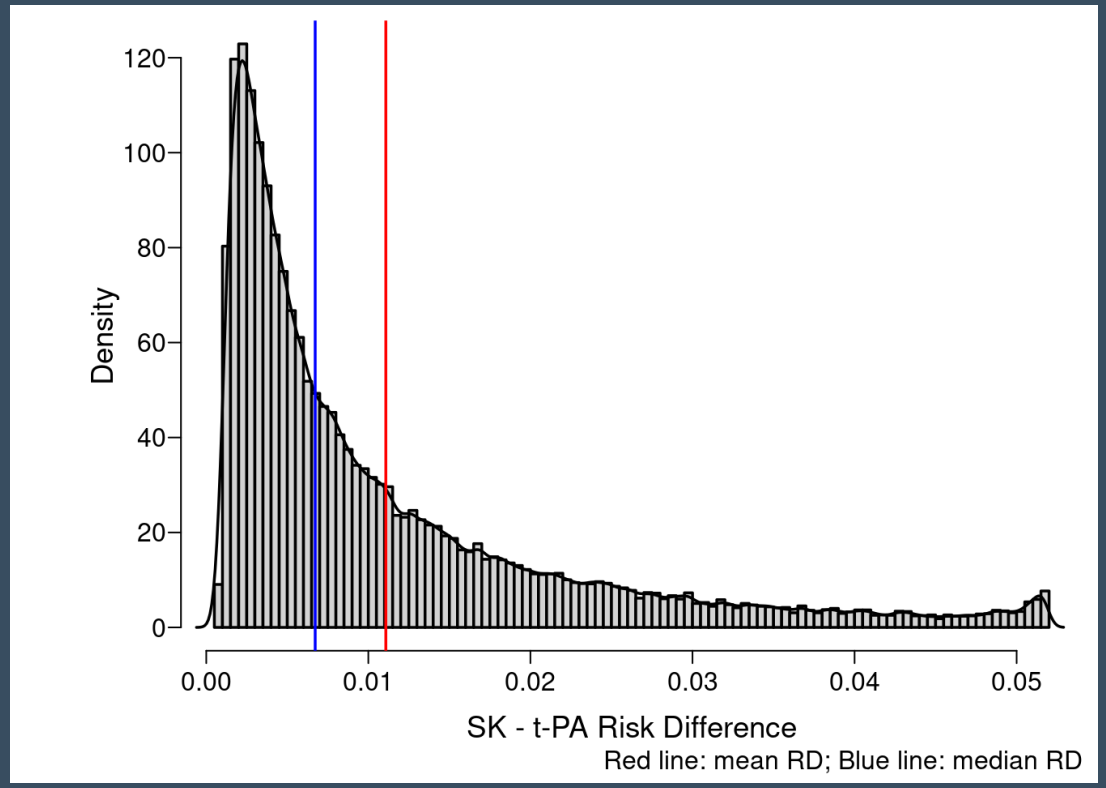
1. RCT compares the Mean Treatment effect vs "control"
   - In positive RCT on "average" experimental or new treatment is better than control
   - CONSORT criteria to evaluate quality
   - Trial does NOT tell WHO to apply treatment to?
     - Do all the experiment or new treat benefit or to same degree?
   - Solution LARGE medical trials of thousands of patients able risk stratify – See PATH publication. (Not option small Ortho RCT)
2. Cohort identifies risk factors for given outcome and a predictive calculation of outcomes at patient level
   - STROBE criteria

RCT: Application to an Individual Patient PATH Statements

1. Evidence is derived from groups while most medical decisions are made for individual patients
2. Reporting RCT results stratified by a risk model is encouraged when overall trial results are positive to better understand the distribution of effects across the trial population

3. **The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement**
David M. Kent, MD, MS; Jessica K. Paulus, ScD; David van Klaveren, PhD; Ralph D'Agostino, PhD; Steve Goodman, MD, MHS, PhD; Rodney Hayward, MD; John P.A. Ioannidis, MD, DSc; Bray Patrick-Lake, MFS; Sally Morton, PhD; Michael Pencina, PhD; Gowri Raman, MBBS, MS; Joseph S. Ross, MD, MHS; Harry P. Selker, MD, MSPH; Ravi Varadhan, PhD; Andrew Vickers, PhD; John B. Wong, MD; and Ewout W. Steyerberg, PhD
Ann Intern Med. 2020;172:35-45.

Example RCT Heterogeneity



Gustilo RCT n=40,000

- This graph provides a much fuller picture than an OR or than the blue or red vertical lines (median and mean RD). Clinicians can readily see that most patients are lower risk and receive little absolute benefit form t-PA, while a minority of very high-risk patients can receive almost an absolute 0.05 risk reduction.
- The RCT regression analysis of the main trial result is more clinically interpretable, more consistent with individual patient decision making, and embraces rather than hides outcome heterogeneity in the RD distribution.
- Harrell, Frank PhD 2021

Orthopaedic RCT's

1. Limited in sample size ("fragility" of results too)
2. Limits any regression analysis to interpret to individual patient or control for heterogeneity
3. Proposed solution once RCT demonstrates overall or average efficacy vs control (justify intervention into clinical practice)
   - Utilize well designed cohorts (ideally prospective) with appropriate analysis for risk factors and bias to apply to a specific patient
4. What evidence to support efficacy Observational data vs RCT?

Observational Studies vs RCTs

1. NEJM Systematic Review Observational Studies vs RCTs in 2000
   - Benson: same 2 tx, outcome, inclusion ’85-’98 (no surgical trials)
     - *Little evidence that estimates of tx effects in observational studies after 1984 are either consistently larger than or qualitatively different from those obtained in RCTs.*
   - Concato: cohort or case-control ‘91-’95 (yes surgical trials)
     - *Results of well-designed observational studies do not systematically overestimate the magnitude of effects of tx as compared with those in RCTs on the same topic.*
2. Cochrane Systematic Review 2014: Our primary quantitative analysis, including 14 reviews, showed that the pooled ROR comparing effects from RCTs with effects from observational studies was 1.08 (95%confidence interval (CI) 0.96 to 1.22). Of 14 reviews included in this analysis, 11 (79%) found no significant difference between observational studies and RCTs. One review suggested observational studies had larger effects of interest, and two reviews suggested observational studies had smaller effects of interest.

Strength of Evidence Not Just Study Design But Specific to Question

- Example: Return Play Football MOON Cohort

  McCullough AJSM 2012 (LOE: 3)

  Prospectively identify football players tore ACL

  Then retrospectively asked the following questions:

1. Did you RTP in high school or college?

   recall bias?

2. How would you rate your performance?

   recall bias? How would measure prospectively?

3. What were reasons you did not RTP?

   recall bias? How quantify?

Focus on Knee: TKA, APM, ACLR

1. TKA annually US
    1. 800,000-1 million
2. APM (men and OA)
    1. 500,000-800,000
3. ACLR
    1. ~ 300,000

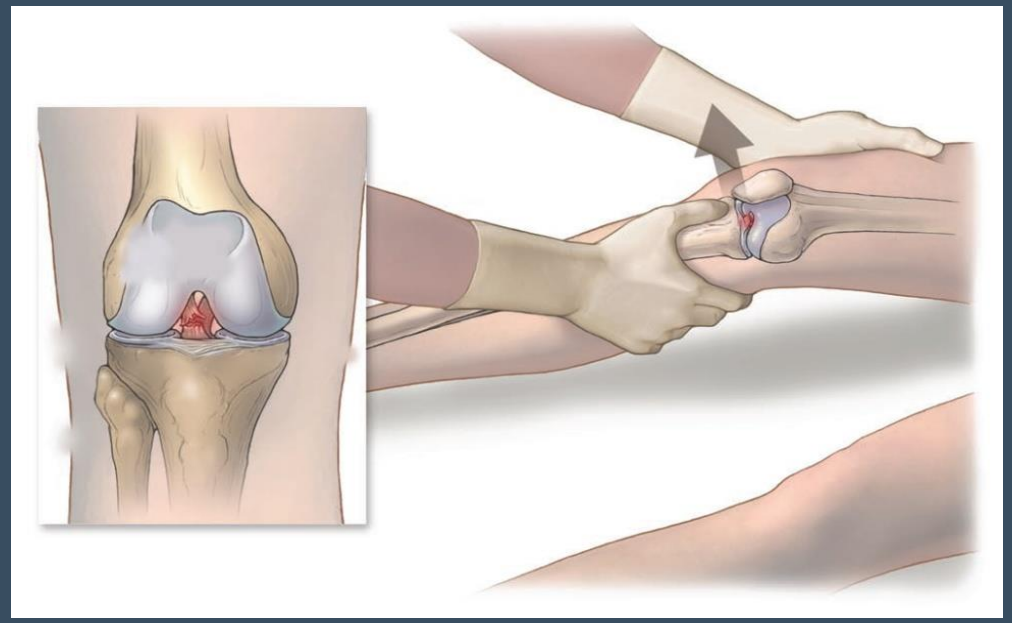
1. ~ 2 Million Procedures
2. Therefore at some point in your life you will see physician about a knee injury or pain

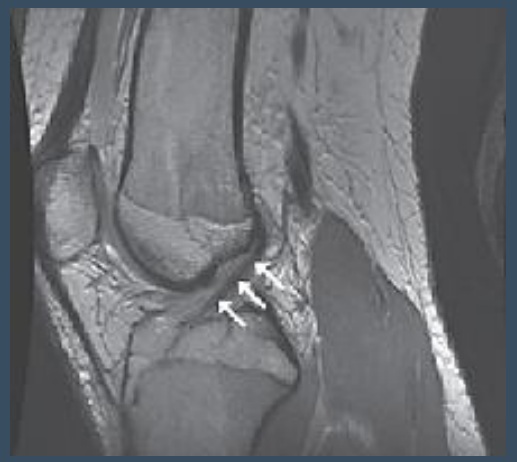
KP Spindler and RW Wright: Review ACL
N Engl J Med 359;20:2135-2142, Nov 13, 2008

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 359 NO. 20

ESTABLISHED IN 1812 NOVEMBER 13, 2008 WWW.NEJM.ORG





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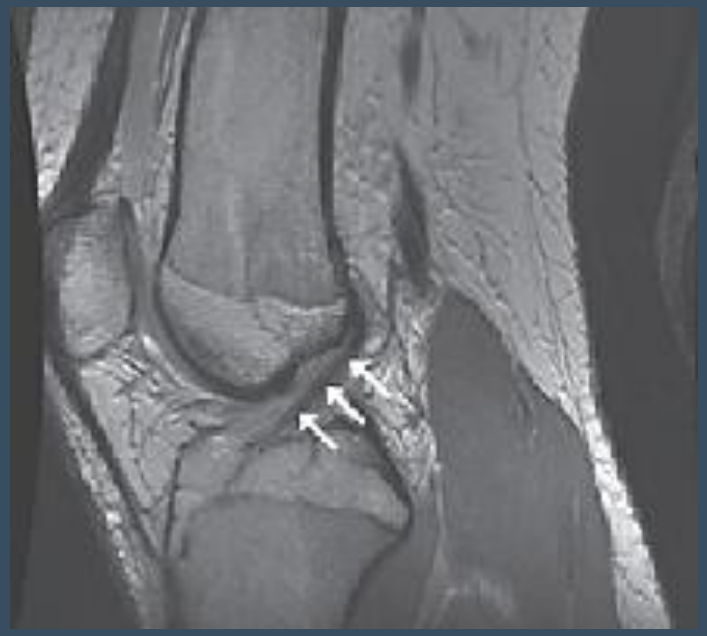
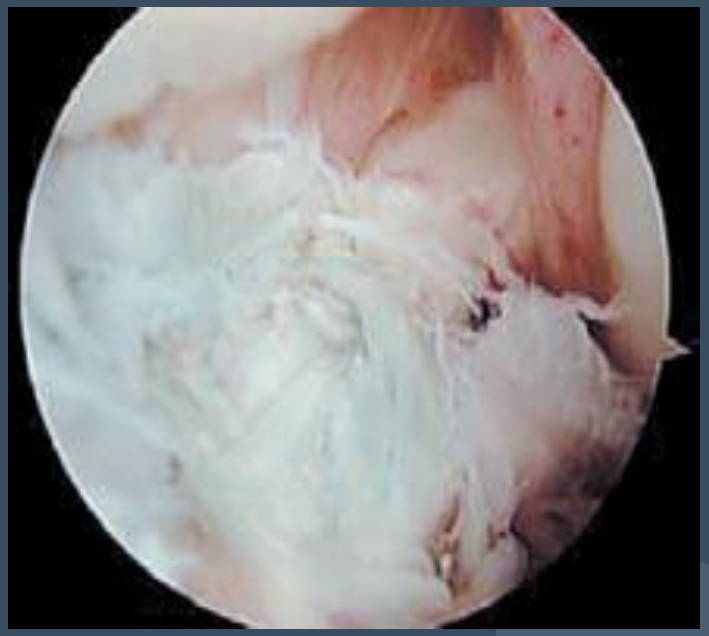
Anterior Cruciate Ligament (ACL)



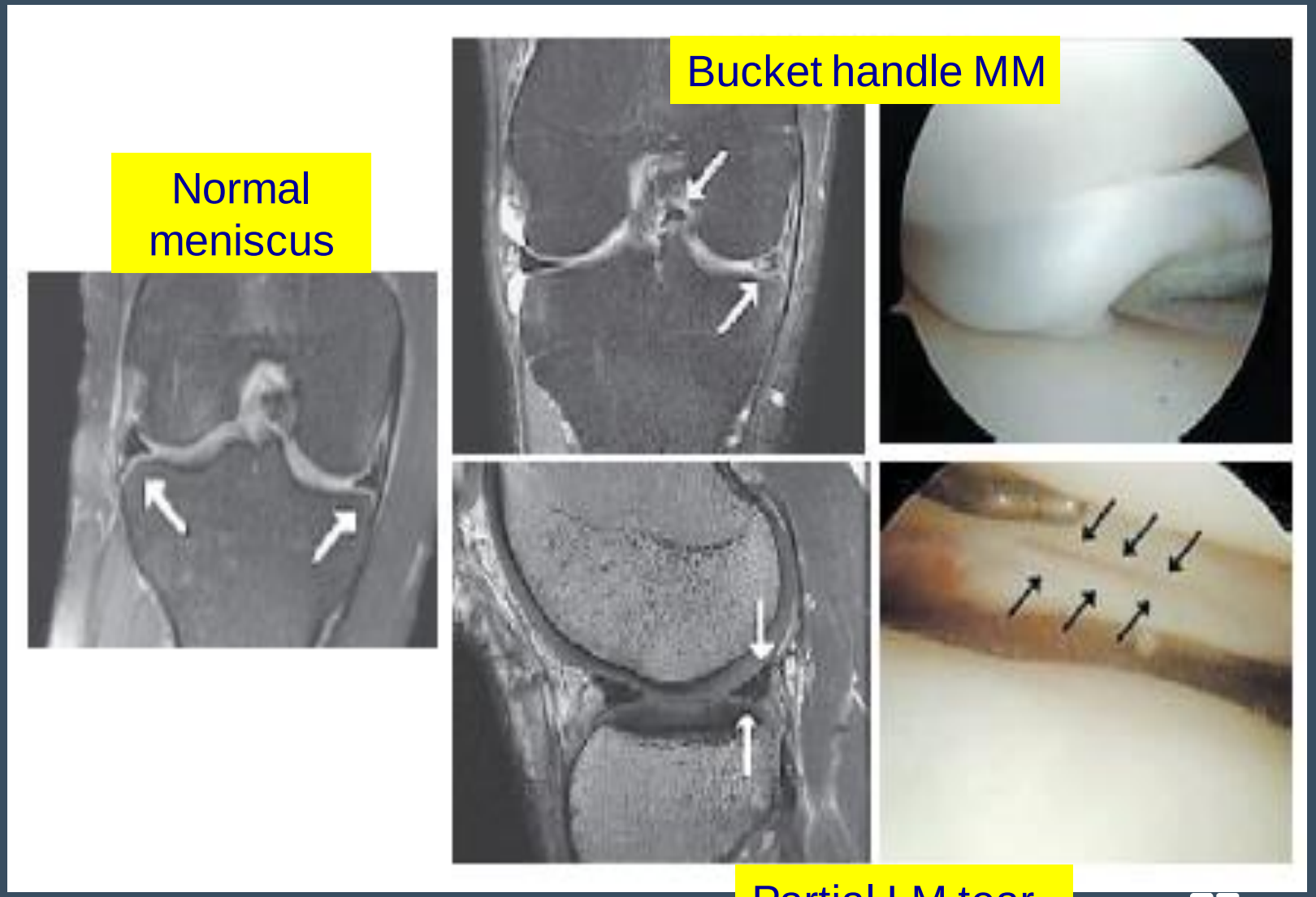
Normal ACL

ACL Tear



Scope ACL Tear

Medial and Lateral Meniscus



Spindler and Wright. *N Engl J Med* 359:20, 2135-2142, Nov 13, 2008

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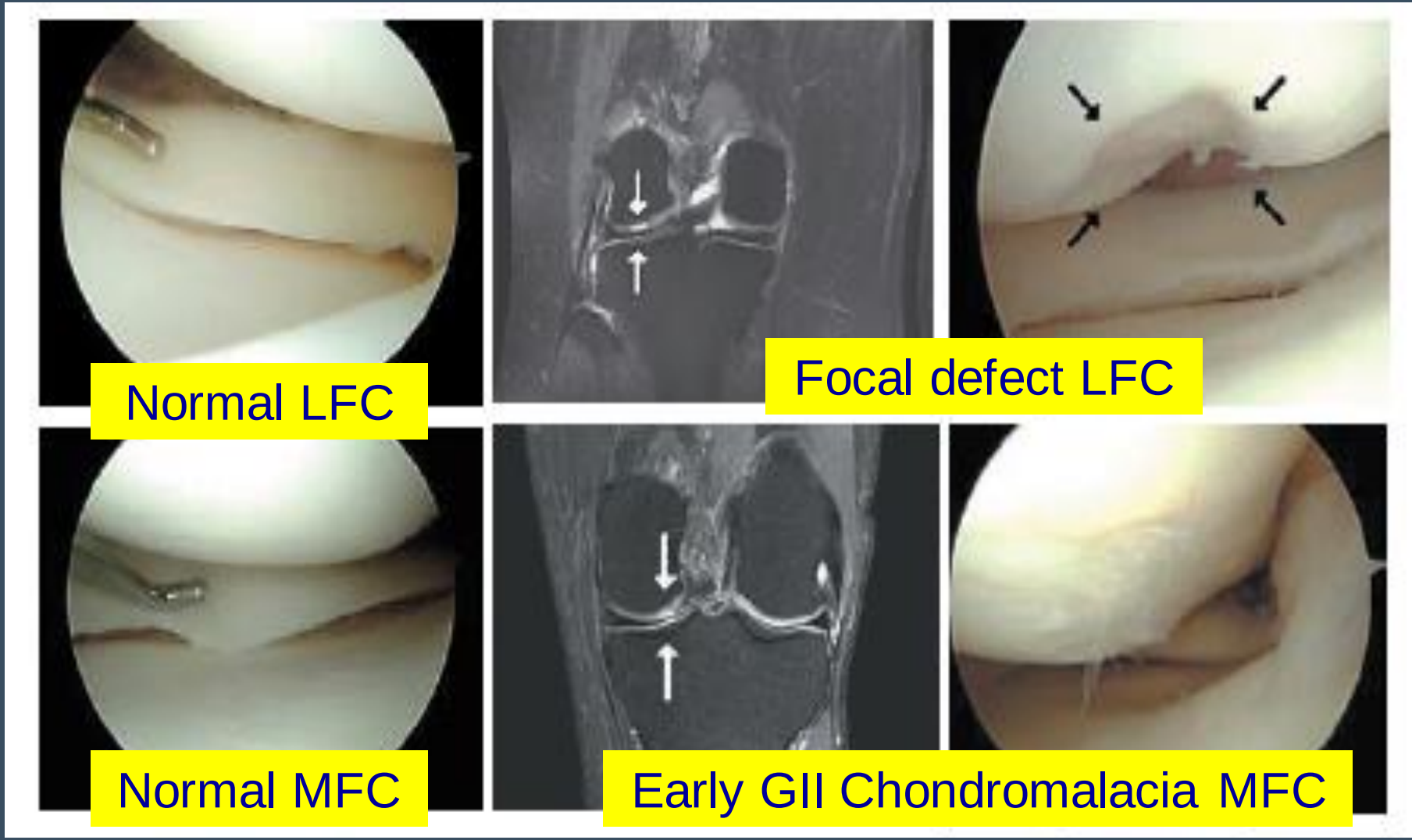
Articular Cartilage



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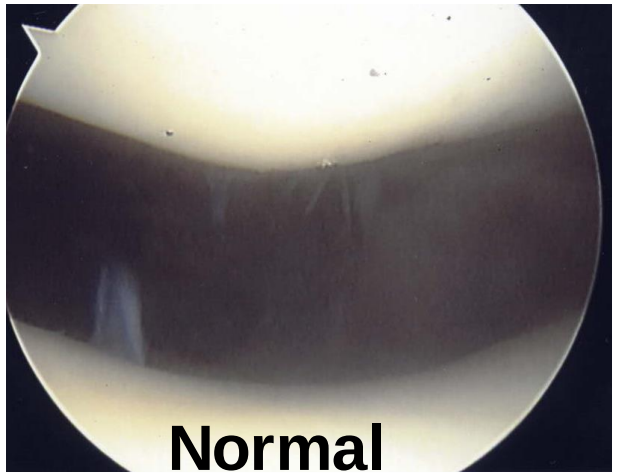
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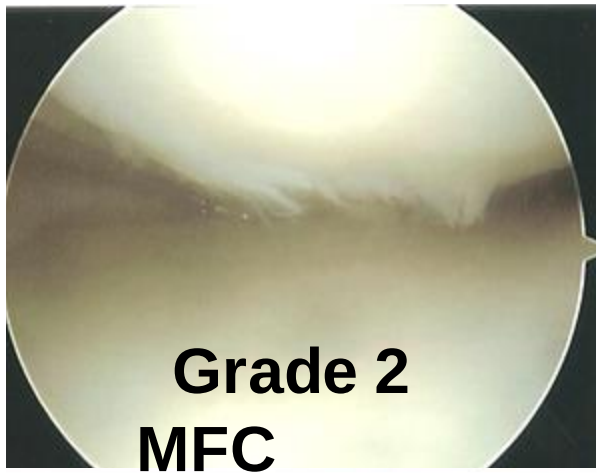
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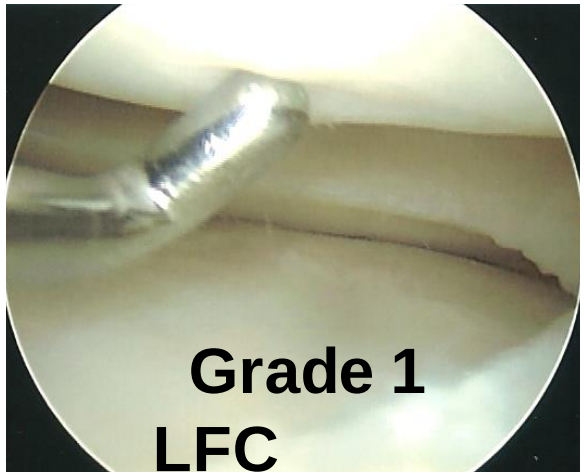
MFC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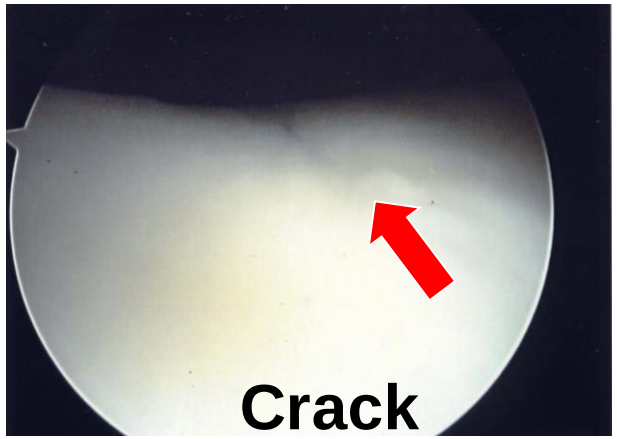
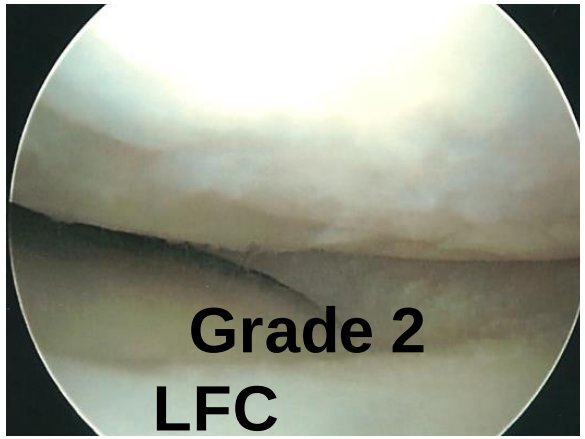
LFC


Crack


Grade 3/4
MFC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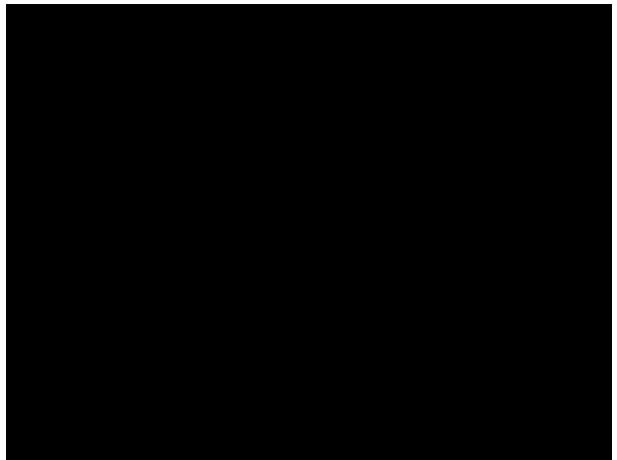

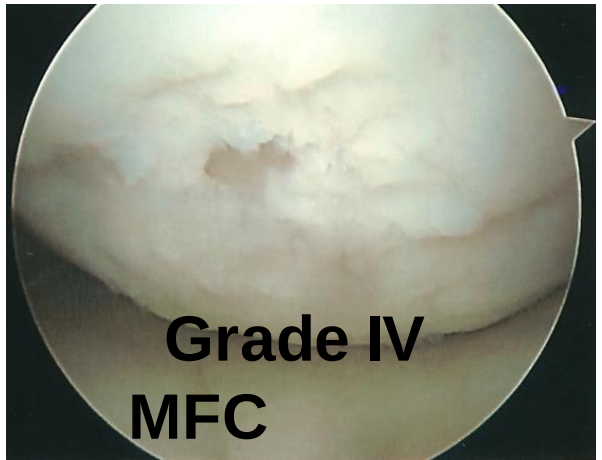
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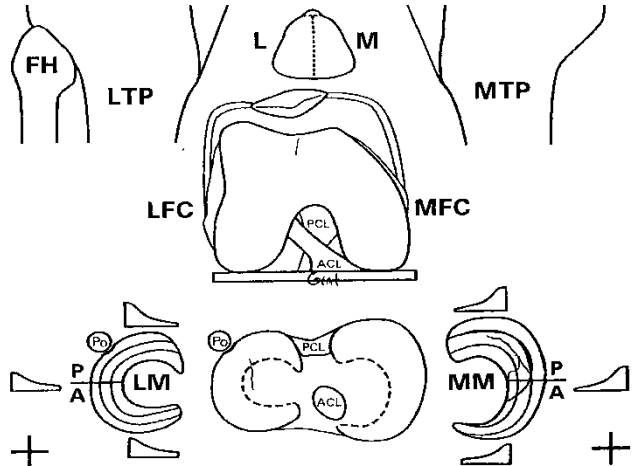
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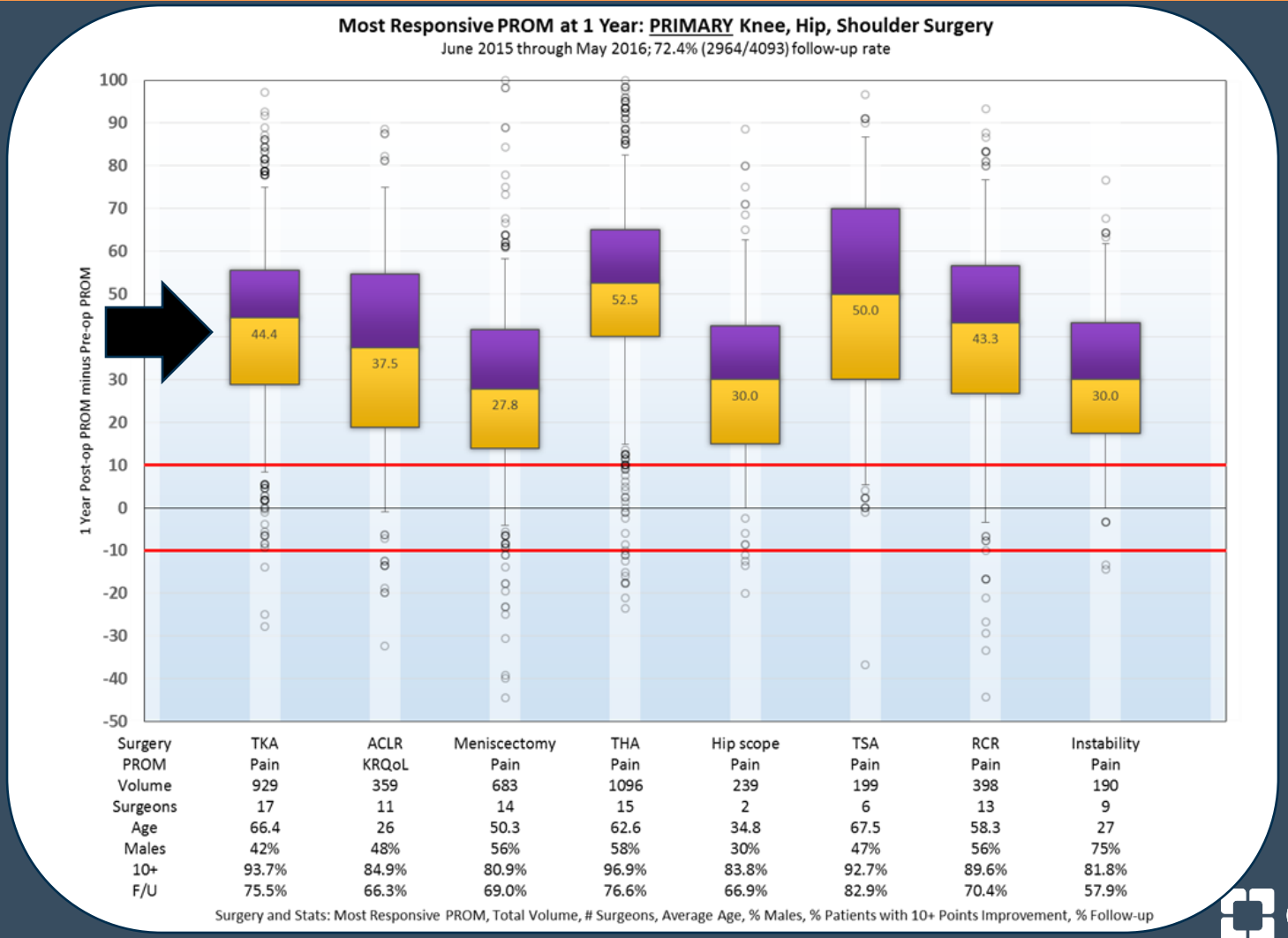
GOAL Apply EBM KNEE Injury or Pain to Individual Patient

1. Why:
    1. My expertise as clinician-scientist
    2. View my Clinical practice application evidence
    3. Annually ~ 2 million procedures US: Huge COST
2. First Focus RCT Surgery vs PT/”sham”
3. Second application to population
4. Third approach the unique features of individual patient with there combination risk factors

Knee OA – Knee Arthroplasty (TKA)

- Skou NEJM 2015 Single Center RCT TKA vs PT
  - Primary Outcomes KOOS 4 at 1 year
  - Secondary Outcome Pain and SAE
- TKA significantly improved KOOS 4 by ITT
  - 32.5 vs 16
  - 26% PT crossed over to TKA
- TKA had more SAE 24 vs 6
- TKA improved baseline (49) pain by 35 vs 17 for PT

TKA Median 44 Points Improve Pain



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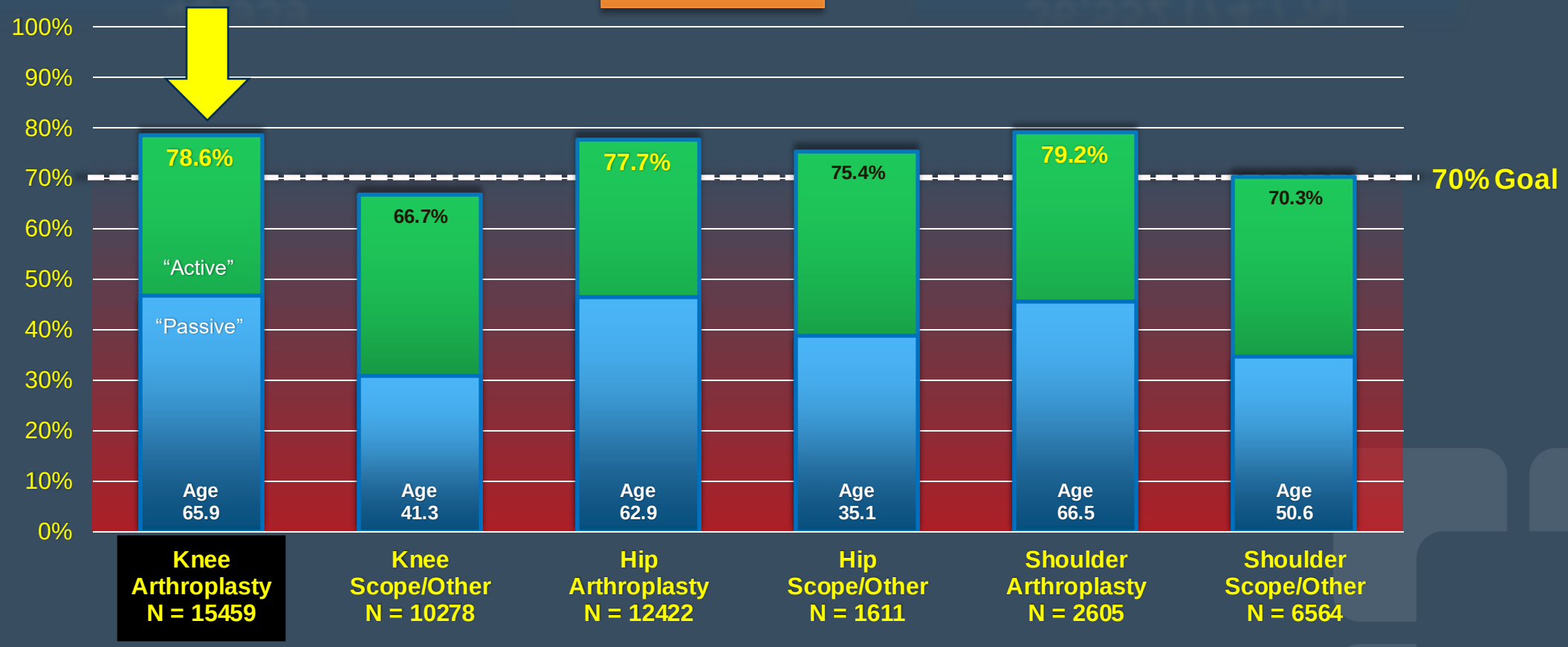
Percentage Follow-up OME: TKA = 79%

Complete Baseline Enrollment
48,939

Lost to follow-up
12,387 (25.3%)

1-Year Follow-Up
36,552 (74.7%)



Data range: Surgeries from February 18, 2015, to June 30, 2020
***Knee, hip, and shoulder** surgeries at 19 sites, 73 surgeons*

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Arthroscopic Debridement OA: NO Benefit

Moseley NEJM 2002

- Arthroscopic Single Center
  - RCT
  - Lavage vs Debridement
  - NO Benefit

Kirkley NEJM 2008

- Arthroscopic Multicenter
  - RCT
  - Lavage and debridement vs
  - Structured PT
  - NO Benefit

AAOS OrthoGuidelines

- Through rigorous evidenced based approach the AAOS has developed
  - CPG (Clinical Practice Guidelines)
  - Has received funding AHRQ
  - ALL approved AAOS Guidelines free PDF
  - http://www.AAOS.org/guidelines

Orthoguidelines OA

- Anesthesia and Analgesia in TJA (2021)
- Glenohumeral Joint OA (2020)
- Management of OA Hip (2023)
- OA of the Knee (2021)
- OA of the Knee Arthroplasty
- Periprosthetic Joint Infections (2019)
- Prevention of Implant Infection Dental Procedures (Updating)
- TXA (tranexamic) acid in TJA (2018)

My Evidenced Based Practice Knee OA

- Assume: Standing Bilat XR, History Pain
- Evaluate if PT or rehabilitation, Injections, etc
- Long-term safe strategy Exercise (start PT) and weight management ideally loss
- Use OTC Vol Gel and attempt Glucosamine
- Caveat: if moderate to large effusions must treat:
  - Preferred in Asp and Inj CS
  - Alternatively limited course NSAID
- If Fail then Injections CSI then HA then consider PRP

Knee Arthroscopy Meniscus Tear with Mild to Moderate OA

- Katz NEJM 2015 Multicenter RCT APM vs PT
  - Primary Outcomes WOMAC pain at 6 mo
  - Secondary Outcome failure to achieve MCID WOMAC Function or crossover from PT to APM
- NO significant difference Pain improvement by ITT
  - APM (20.9) vs PT (18.5)
  - 30% PT crossed over to APM (note 6% in APM no surgery
- Adverse events same

Knee Arthroscopy Meniscus Tear with Mild to Moderate OA

- Secondary ITT definition failure as crossover to APM from PT or failure to achieve MCID WOMAC function (8 pt)
  - APM is more likely to succeed
- Economic Analysis: PT is more cost effective
- Incidence TKA at 5 years is less then 10% and lower in the PT group that didn't crossover
- Progression of OA changes occurred in the first 6 mo primarily in APM group. Then both groups progressed at similar rates

My Evidenced Based Practice Meniscus Tears and Mild to Moderate OA

- Majority patients should proceed to trial PT
- If fail PT (providing MRI doesn't show more extensive OA then XR) consider APM (in crossover 81% improved with APM)
- Caveat if only have 3 mo improve consider APM first
- FYI both Meniscus and OA are potential sources pain and APM only helps meniscus-- discussion

ACLR vs Rehabilitation

- Frobell NEJM 2010 multicenter RCT (2yr)
  - PT and Early ACLR vs
  - PT and delayed ACLR
- Frobell BMJ 2013 5 year follow-up
- Design
  - 62 early ACLR (1 no surg)
  - 59 PT and delayed surgery
- Primary Outcome KOOS ITT
- Crossovers

ACLR vs Rehabilitation

- By ITT no difference in KOOS scores
- However crossover to ACLR
  - 2 years = 39%
  - 5 years = 51%
  - Doesn't include the number of additional scopes
- Statistical interpretation is Early ACLR is not different then delayed ACLR.
- Caveat NOT Rehab is equal to ACLR. The degree of crossovers violate assumptions ITT
- Therefore customize approach to patient

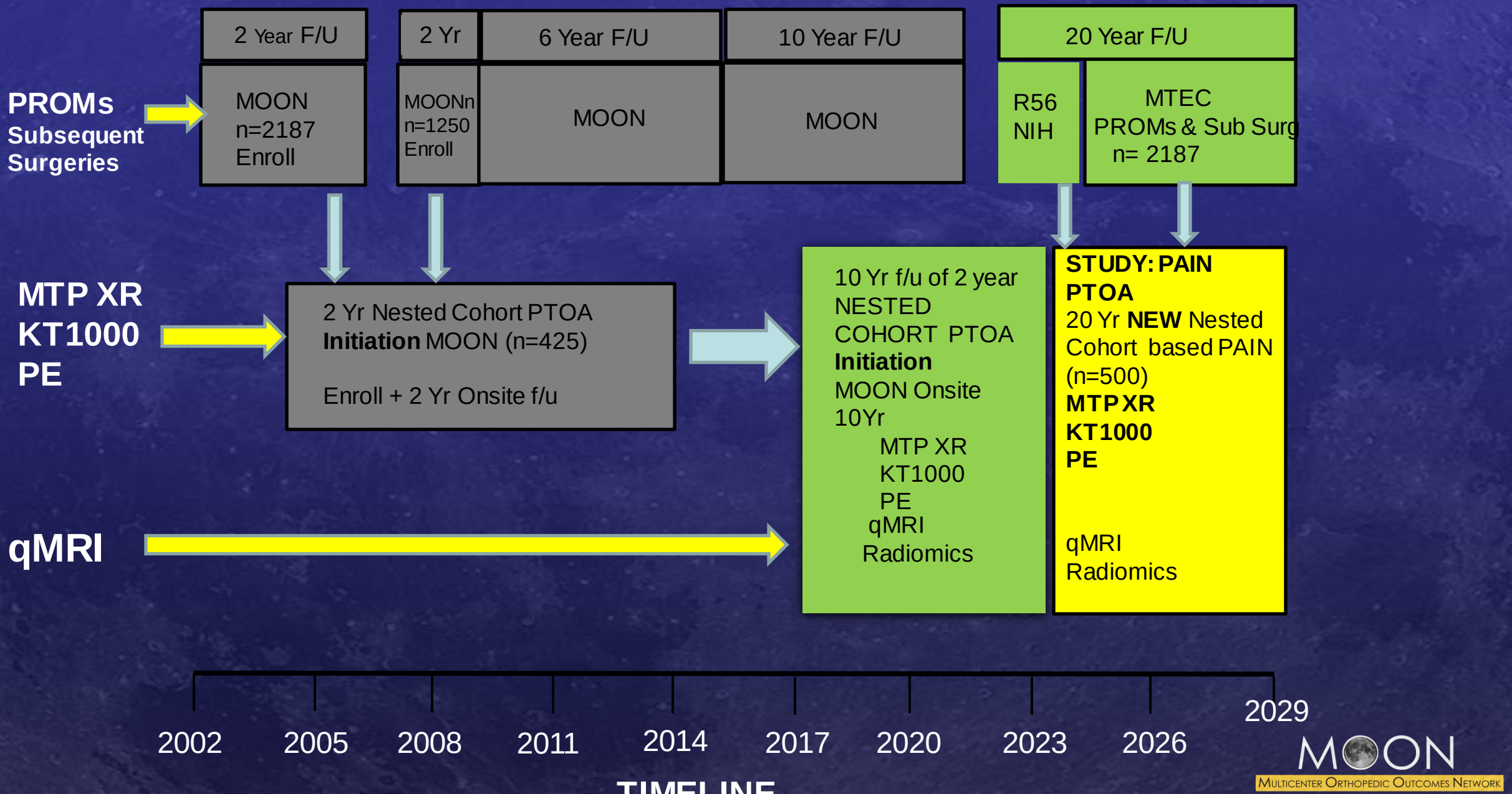
My Evidenced Based Practice ACL tears

- Clearly NOT everyone needs ACLR
- Rational for initial treatment:
  - If High School, College, Pro athlete rational ACLR ?
  - If recreational athlete
  - If not an athlete at all
- In general the more aggressive a patients wishes to cut in pivot the more likely they require ACLR

My Evidenced Based Practice ACL tears

- Outcomes ACLR MOON evidence and guidelines
  - ACLTear.info – Website patients built by MOON
- AAOS Guidelines on ACL tears
- Cleveland Clinic Care Path
  - Initial evaluation
  - Rehabilitation
  - Decision making ACLR and Graft choice
  - Postop Rehabilitation

MOON Timeline, Outcome Measures and Nested Cohort



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Entire MOON (PROMs) Cohort F/U

Enrollment Years	N	2 Years	6 Years	10 Years
2002-2003	1080	85%	86%	82%
2004-2005	1217	86%	84%	80%
2007-2008	1250	84%	80%	73%
Total	3547	85%	82%	78%

>90% f/u failure and additional surgery (via phone)

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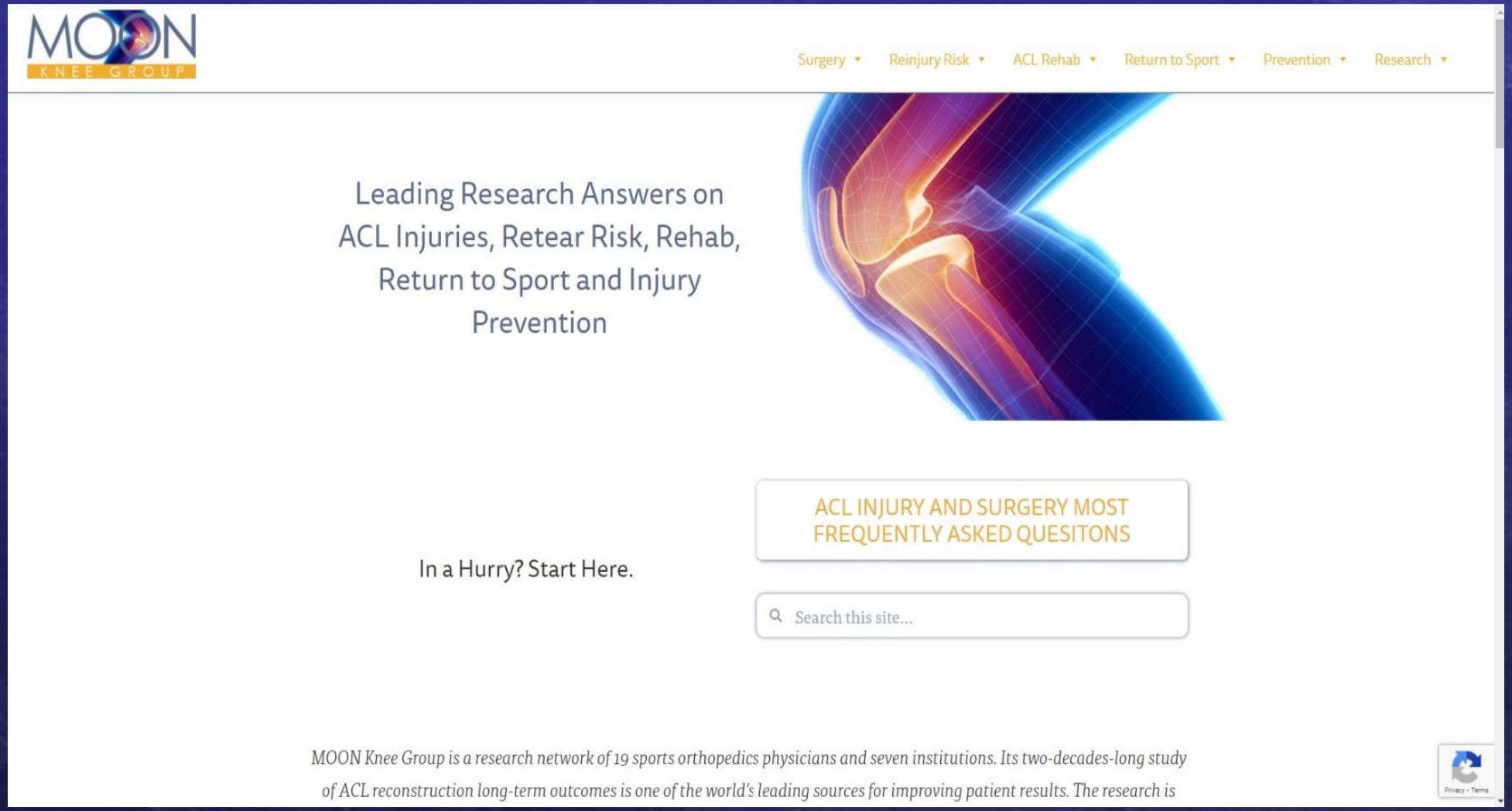
ACLtear.info



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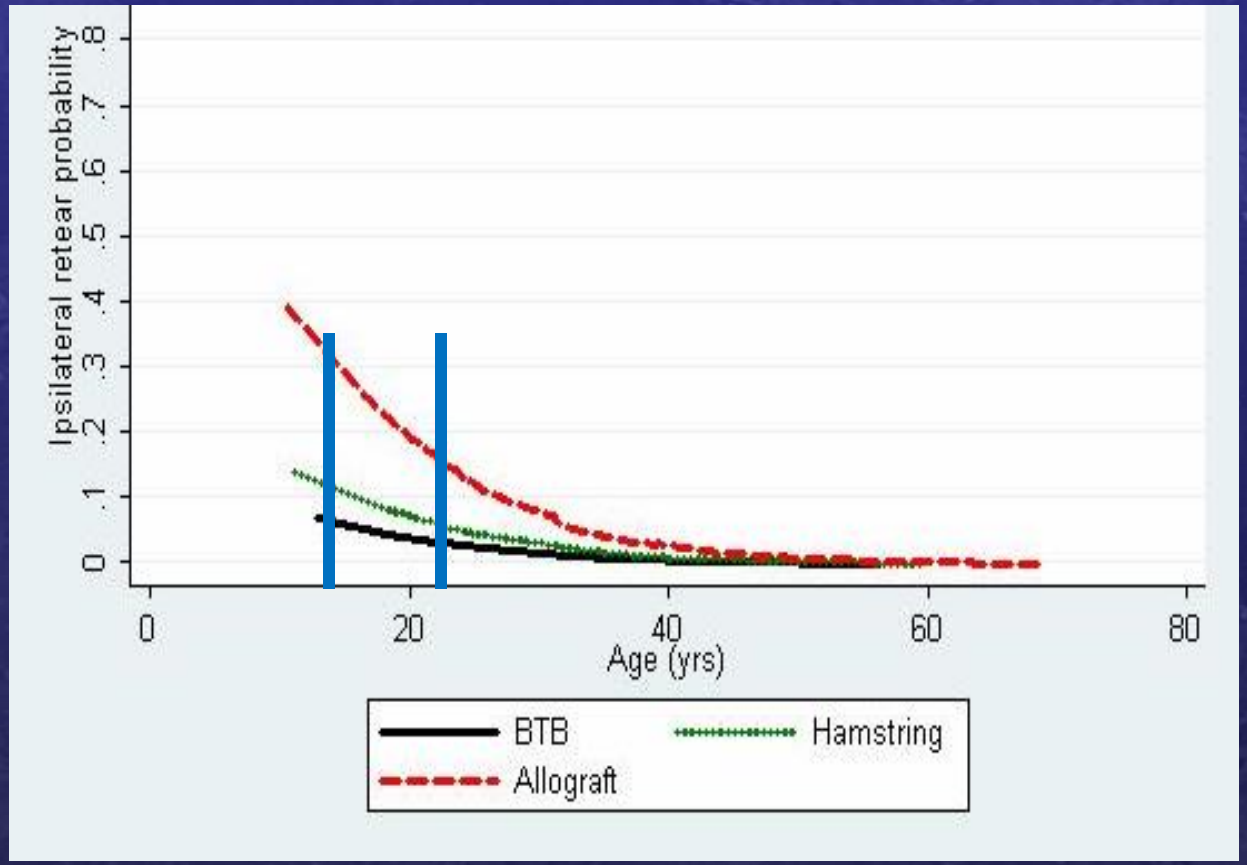
#3: Avoid Allografts in High School and College Athletes

- 2488 Primary ACLR
- 92.7% f/u @ 2 years
- AVOID failure by NOT using allografts in high school and college!
- Risk factors besides graft:

  Age **and** ***activity***



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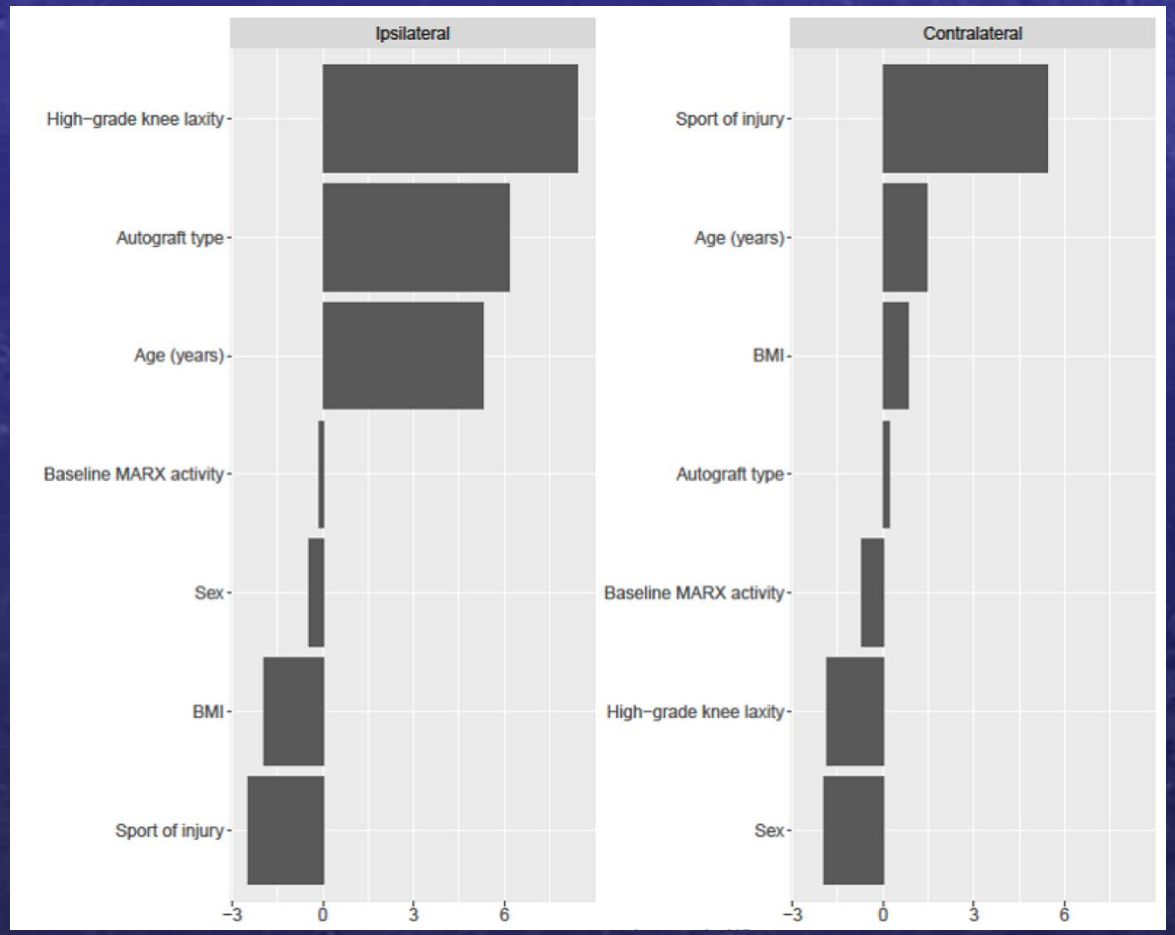
2 Best Autograft in HS and College Athlete



MOON Knee Group AJSM 2020
Marmura, H AJSM 2021

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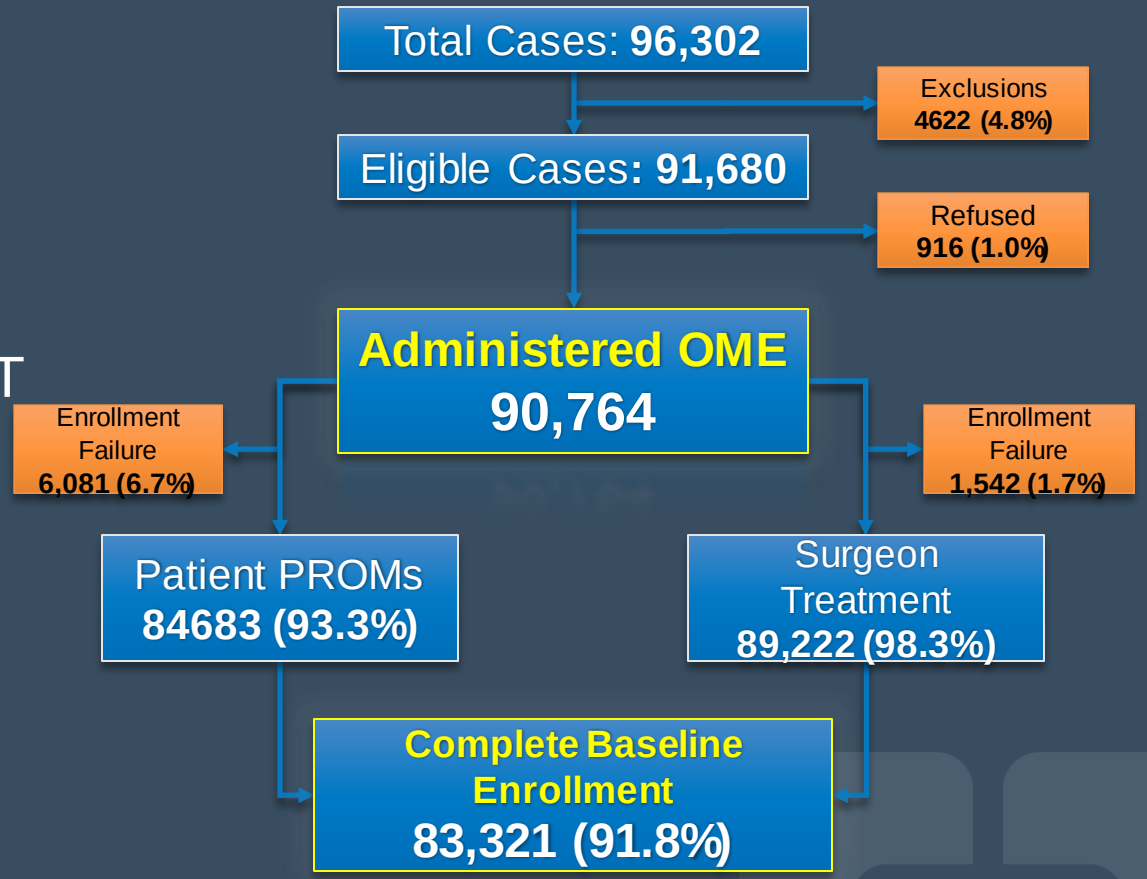
Summarize Orthopaedic Knee Procedures

- Question becomes when a surgical procedure should be performed based on the unique risk factors for each patient.
  - TKA after failed PT and endstage OA on XR
  - APM for meniscus tear after failure of PT
  - ACLR based on future sports activity
- No benefit to Arthroscopic debridement for OA

Cleveland Clinic Orthopaedics PROMs System Outcome Measurement Evaluation (OME) 2015-present

- COST EFFECTIVE
  - Electronic baseline data capture (iPad)
  - Integrated into workflow at point-of-care
  - No additional FTE for Baseline enrollment
  - Surgeon APR
  - NIH/funding: prospective cohort, nested RCT
- SCIENTIFICALLY VALID
  - IRB approved, standard of care & quality
  - >97% patient capture; 100% surgeon capture
- SCALABLE
  - Core OME (knee, hip, shoulder)
  - Extension OME (centers)
  - 16 CCF hospitals + ASC sites
  - Outcome Calculator OBERD product



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Knee, hip, and shoulder** surgeries at **19 sites, 82 surgeons

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OME Results One Year Follow-up (T1 F/U)

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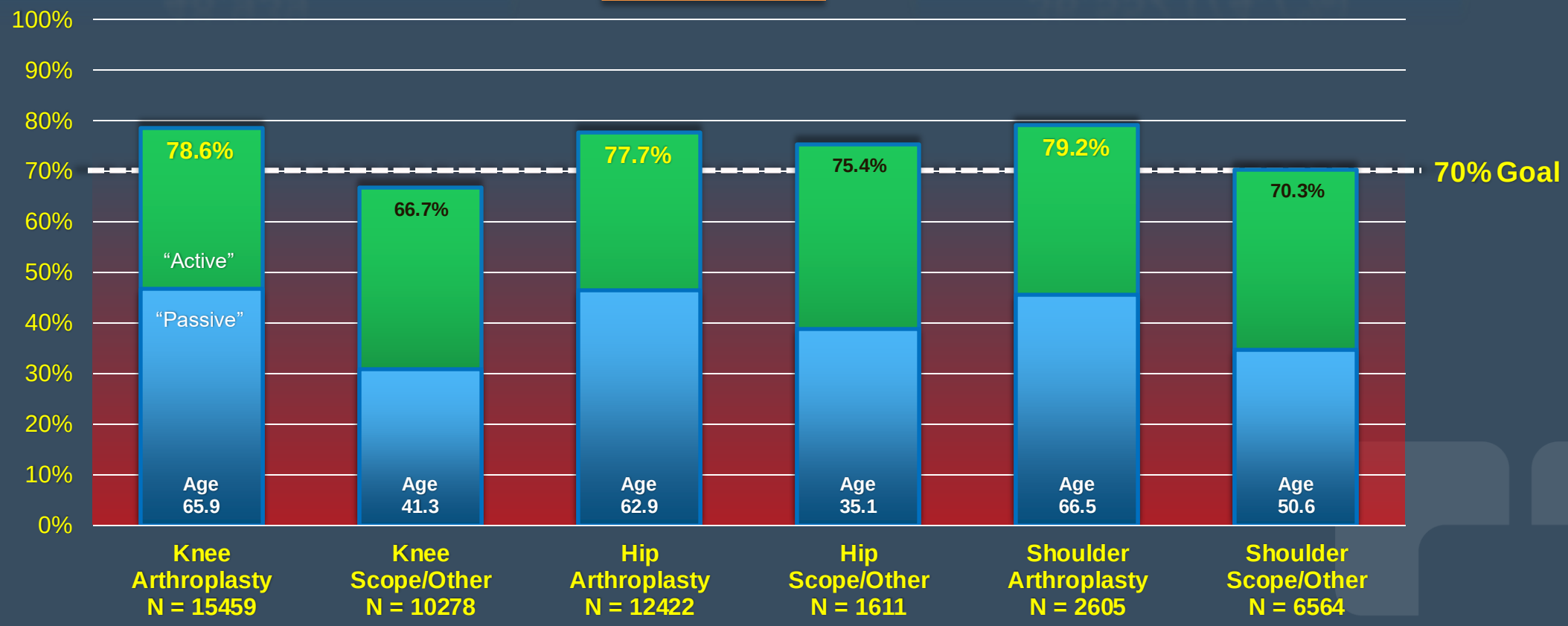

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Grant Funding and Gifts

- **OREF Clinical Research Grant**
- **NFL Charities**
- **Aircast**
- **Don Joy**
- **Smith and Nephew**

Vanderbilt Sports Medicine

Improving the lives of others through science, education, and clinical skill

U.S. Department of Health
and Human Services

Supported by the

National Institutes of Health

National Institute of Arthritis and
Musculoskeletal and Skin Diseases

MOON
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References

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- **RCT Surgery vs PT in the powerpoint**