

Stem-cell therapy for musculoskeletal conditions

Clinical Expert

Paul A. Manner, MD

Professor, Department of Orthopaedics and Sports Medicine
University of Washington School of Medicine

WA - Health Technology Assessment

Applicant Name Paul Arthur Hans Manner, MD, FRCSC
Address [REDACTED]
[REDACTED]

1. Business Activities

(a) If you or a member of your household was **an officer or director of a business** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type

(b) If you or a member of your household **did business under an assumed business name** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type

2. Honorarium

If you **received an honorarium of more than \$100** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed

3. Sources of Income

(a) Identify **income source(s) that contributed 10% or more of the combined total gross household income** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type
1) UNIVERSITY OF WASHINGTON	ME	SALARY
2) SEATTLE CHILDREN'S HOSPITAL	SPOUSE	SALARY
3) CLINICAL ORTHOPAEDICS & RELATED RESEARCH	ME	STIPEND/ SALARY

WA - Health Technology Assessment

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

Yes No

If "yes", describe: [Click here to enter text.](#)

CLINICAL EXPERT

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

Yes No

If "yes", describe: [Click here to enter text.](#)

4. Business Shared With a Lobbyist

If you or a member of your household **shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist**, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared

Provide the information requested in items 5, 6, and 7 below only if:

(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.

(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than \$1,000

List each source (**not amounts**) of income over \$1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source

6. Business Investments of More Than \$1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than \$1,000, list the following:

Business Name	Business Address	Description of Business

7. Service Fee of More Than \$1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each *person for whom you performed a service for a fee of more than \$1,000* in the immediate preceding calendar year or the current year to date.

Name	Description of Service

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name [Click here to enter text.](#) Paul Mauer

Check One: Committee Member Subgroup Member Contractor

Signature [Redacted] Date 2/26/2020

CURRICULUM VITAE

Name: Paul A. Manner, MD, FRCSC
Professor

Office Address: Department of Orthopaedics and Sports Medicine
University of Washington School of Medicine
1959 Pacific Street NE
Box 356500
Seattle, WA 98195-6500

Office Phone: (206) 543-3690
Fax: (206) 685-3139

Work email: pmanner@uw.edu

Personal Data: United States Citizen

Education:

1986 B.Sc., Tufts University
Medford, MA (Biology)

For three years, I was enrolled in a five-year, double-degree (Bachelor of Music, Bachelor of Science) program at Tufts University and New England Conservatory of Music, in which I attended both schools simultaneously. In September 1985, I elected to withdraw from my studies as a clarinet performance major at NEC to concentrate on and complete my Tufts studies.

1991 M.D., McGill University Faculty of Medicine (Medicine)
Montreal, QC, Canada

Postgraduate Training:

Internship and Residencies:

1991 – 1992 Intern in General Surgery, St. Luke's/Roosevelt Hospital Center,
New York, NY
1992 – 1993 Resident in General Surgery, St. Luke's/Roosevelt Hospital Center,
New York, NY
1993 – 1996 Resident in Orthopaedic Surgery, McGill University, Montreal, QC

Fellowships:

- 1996 – 1997 Shriners Fellow, Orthopaedic Research, Joint Diseases Laboratory,
Shriners Hospital for Children, Montreal Unit
- 1997 – 1998 Fellowship - Adult Reconstruction and Joint Replacement, University of
Pittsburgh Medical Center, Pittsburgh, PA

Faculty Positions:

- 1996 – 1997 Shriners Fellow, Orthopaedic Research, Joint Diseases Laboratory,
Shriners Hospital for Children, Montreal Unit
- 1997 – 1998 Clinical Instructor, Department of Orthopaedic Surgery
University Of Pittsburgh Medical Center. Pittsburgh, PA
- 2001 – 2006 Assistant Professor of Orthopaedic Surgery,
The George Washington University, Washington, DC
- 2001 – 2006 Visiting Faculty/ Adjunct Investigator, Cartilage Biology and
Orthopaedics Branch, National Institute of Arthritis, Musculoskeletal and
Skin Diseases (NIAMS) National Institutes of Health, Bethesda, MD
- 2006 – 2010 Assistant Professor of Orthopaedics and Sports Medicine,
University of Washington, Seattle, WA
- 2010 – 2015 Associate Professor of Orthopaedics and Sports Medicine,
University of Washington, Seattle, WA
- 2015 Professor of Orthopaedics and Sports Medicine,
University of Washington, Seattle, WA

Hospital Positions:

- 1998 – 2000 Holy Cross Hospital, Silver Spring, MD
- 1998 – 2000 Washington Hospital Center, Washington, DC
- 2000 – 2001 Overlook Hospital, Summit, NJ
- 2000 – 2001 Rahway Hospital, Rahway, NJ
- 2001 – 2006 The George Washington University Hospital, Washington, DC
- 2006 – present University of Washington Medical Center, Seattle, WA

2006 – present Harborview Medical Center, Seattle, WA

2012 – present UW Northwest Hospital, Seattle, WA

Honors:

1997 Winner, Sherwood Davis & Geck Award for Excellence in Basic Science Research at McGill University

2002 – 2003 Resident Teaching Award
Department of Orthopaedic Surgery, The George Washington University
Washington, DC

2005 – 2006 Fellow, Leadership Fellows Program
American Academy of Orthopaedic Surgeons

2013 Achievement Award, American Academy of Orthopaedic Surgeons

2013 Election to the Association of Bone and Joint Surgeons

2013 America's Top Doctors; U.S. News & World Report

2013 UW Start-up Launch Celebration (Jointmetrixmedical.com)

2013 UW C4C (Center for Commercialization) Innovator Recognition Award

Board Certification:

1991 FLEX (New York State) National Board of Medical Examiners

1991 LMCC (Licensure of the Medical Council of Canada)

1994 Principles of Surgery Examination -
Royal College of Surgeons - Canada

1996 Specialty Examination in Orthopaedic Surgery -
Royal College of Physicians and Surgeons - Canada

1998 American Board of Orthopaedic Surgery
Part I Examination (written), July 14, 1998
Part II Examination (oral), July 10, 2000

2009 American Board of Orthopaedic Surgery: Maintenance of Certification

Current Licenses to Practice:

2006 Licensure in Washington State (MD 00045972)

Professional Organizations:

National and International:

- 1996 – present Fellow of the Royal College of Surgeons – Canada
- 1996 – present Canadian Orthopaedic Association
- 1998 – 2000 Candidate Member, American Academy of Orthopaedic Surgeons
- 2000 – present Fellow, American Academy of Orthopaedic Surgeons
- 2002 – present Orthopaedic Research Society
- 2012 – present Active Member, Association of Bone and Joint Surgeons
- 2013 – present Active Member, American Association of Hip and Knee Surgeons

Regional:

- 2000 – 2001 New Jersey Orthopaedic Society
- 2001 – 2006 Washington Orthopaedic Society
- 2006 – present Washington State Orthopaedic Association
- 2006 – 2011 Board Member, Arthritis Foundation
Pacific Northwest Chapter Seattle, WA

Teaching Responsibilities:

1. Local contributions

Medical School

- 2001 – 2006 “Introduction to Orthopaedics”
“Common Orthopaedic Problems”
“Examination of the Hip and Knee”
Medical Student Surgical Clinical Core Teaching Program
The George Washington University
- 2004 – 2006 “Introduction to Physical Examination of the Hip and Knee”
Medical Student Introduction to Clinical Medicine
The George Washington University
- 2008 – 2011 HuBio 553 Musculoskeletal System

University of Washington

Graduate Medical Education

- 2001 – 2006 Developed Adult Reconstruction and Arthroplasty Core Curriculum
GWU Orthopaedic Residency Program
- 2001 – 2006 Developed Basic Science Core Curriculum
GWU Orthopaedic Residency Program
- 2003 – 2006 Established research program for PGY-3 residents in Orthopaedic
Surgery at Cartilage Biology and Orthopaedics Branch
National Institute of Arthritis, Musculoskeletal and Skin Diseases,
NIH, Bethesda, MD
- 2002 – 2006 Orthopaedic Resident Selection Committee
The George Washington University
- 2006 – present Faculty Lecture Series
Department of Orthopaedics and Sports Medicine
University of Washington
- 2006 – present Shared responsibility for orthopaedic trauma and arthroplasty education
and clinical supervision at the University of Washington, Seattle, WA
- 2008 – present Orthopaedic Resident Selection Committee
Department of Orthopaedics and Sports Medicine
University of Washington
- 2008 - present Arthroscopy Boot Camp (Resident teaching)
Tracy, CA

Local Advisory and Supervisory Responsibilities

- 2001 – 2006 Responsible for clinical supervision and educational component of adult
reconstruction and arthroplasty for orthopaedic residency program
The George Washington University, Washington, DC
- 2002 – present Mentor for 2-3 medical students/year with interest in orthopaedics
Class of 2003: 2 students
Class of 2004: 3 students
Class of 2005: 2 students
Class of 2006: 2 students
Class of 2009: 2 students
Class of 2010: 1 student

Class of 2013: 1 student

- 2001 – 2006 Shared responsibility for orthopaedic trauma education and clinical supervision while at George Washington University, Washington, DC
- 2006 – present Shared responsibility for orthopaedic trauma and arthroplasty education and clinical supervision at the University of Washington, Seattle, WA
- 2007--present Faculty Research Adviser, University of Washington
Jason King, MD
Jason Wilcox, MD
Sean Amman, MD
Christopher Wolf, MD
Sid Baucom, MD
Dan Holtzman, MD
Ted Sousa, MD
Paige Mallette, MD
Sara Shippee, MD

Local Invited Teaching presentations (selected)

- 2002 Cartilage Biology and Orthopaedics Branch
NIAMS, NIH, Bethesda, MD
- 2002 Department of Rheumatology, The George Washington University,
Washington, DC
- 2004 Featured Speaker, Association of Surgical Technologists
Annual Meeting, Washington, DC
- 2004 Featured Speaker, Orthopaedic Surgery Department Grand Rounds
National Naval Medical Center, Bethesda, MD
- 2012 Faculty, UWEB21 Biomaterials Intensive Short Course,
University of Washington
"Orthopaedics and Biomaterials"
- 2012 Featured Speaker, Seattle Surgical Society
"Metal-on-Metal hips: a New Hope or the Dark Side?"
- 2012 University of Washington School of Pharmacy, Pharm 523: Survey of
Biomedical Regulatory Affairs

2014 - present Faculty, UWEB21 Biomaterials Intensive Short Course,
University of Washington
"Orthopaedics and Biomaterials – a Clinician's Perspective"

Continuing Medical Education

- 1997 Instructor, Revision Hip Surgery Course
American Academy of Orthopaedic Surgeons Orthopaedic Learning
Center, Rosemont, IL
- 1998 Instructor, Lower Limb Anatomy
University of Pittsburgh Medical School, Pittsburgh, PA
- 1998 Lecturer, Continuing Medical Education
Mid-Atlantic Permanente Medical Group, PC
Maryland and Washington, DC.
- 2006 Faculty, Western Sphere of Influence September Meeting
"Embarking on the 2-incision MIS Total Hip Replacement"
"Trabecular Metal in Total Knee Replacement"
"The Mysteriously Painful Total Hip Arthroplasty"
Las Vegas, NV
- 2006 "What's New in Hip Replacement"
Department of Geriatrics, Harborview Medical Center
University of Washington
- 2007 "What's New in Hip Replacement"
Arthritis Foundation Pacific Northwest Chapter
Rheumatology Conference, Seattle, WA
- 2007 Faculty, Western Sphere of Influence Spring Meeting
"Trabecular Metal for Hips and Knees"
"The Painful Total Knee - Assessment and Treatment"
"Hip Resurfacing in 2007 – Why Save the Neck?"
"The Mysteriously Painful THA"
Las Vegas, NV
- 2007 Faculty, Western Sphere of Influence September Meeting
"What's so great about big heads: Large Diameter Heads Should NOT be
Used Most of the Time in THA"
"Two-Incision Minimally Invasive total Hip Arthroplasty in 2008"

“Hip Resurfacing in 2007 – Why has it returned?”
Las Vegas, NV

2008 Faculty, The Hip and Pelvis in Function & Dysfunction: Biomechanical & Clinical Aspects of Hip & Pelvic Pain
“Recent Advances in Hip Replacement”
University of Washington, Seattle, WA

2009 Faculty, Idaho Orthopaedic Society Annual Meeting, Boise, Idaho
“MIS THA/TKA: Pearls and Pitfalls”
“Bearing Surfaces and Large Femoral heads”
“Unicompartmental and Patellofemoral Arthroplasty: A New Hope?”

2009 Faculty and Moderator, Modern Trends in Joint Replacement
“Diagnosis and Treatment of Infected Total Joint Arthroplasty”
“The AAOS Could Do a Lot Better!”
Indian Wells, CA

2010 Faculty and Moderator, Modern Trends in Joint Replacement
“New developments in Hard-Hard Bearings”
“Diagnosis and Treatment of Infected Total Joint Arthroplasty”
“The Middle Aged Arthritic Knee”
“Hip Impingement”
Indian Wells, CA

2011 Faculty and Moderator, Modern Trends in Joint Replacement
“Comparison of Surgical Approaches for Knee Arthroplasty”
“Modern Thinking in THA: Large heads or thick polys”
“Periprosthetic Joint Infection”
“PS versus CR - a question for the ages”
Indian Wells, CA

2012 Faculty and Moderator, Modern Trends in Joint Replacement
“Diagnosis and workup for revision TKA”
“Defect classification and preop planning for revision THA”
“DVT prophylaxis options in 2012”
Indian Wells, CA

2013 Faculty and Moderator, Modern Trends in Joint Replacement
“Nonoperative treatment options for the varus knee”
“Remote patient monitoring”
“Periprosthetic Joint Infection: Diagnosis”
Indian Wells, CA

- 2018 Grand Rounds Speaker
 “Osteoarthritis: When hips and knees get rusty”
 Northwest Hospital and Medical Center
 Seattle, WA
- 2019 Faculty, “Hip and Knee Surgery for the Non-surgeon”
 Wenatchee Valley Medical Conference
 Wenatchee, WA

2. Regional, National, And International Contributions

- 2001 – 2006 Developed Adult Reconstruction and Arthroplasty Core Curriculum
 GWU Orthopaedic Residency Program
- 2001 – 2006 Developed Basic Science Core Curriculum
 GWU Orthopaedic Residency Program
- 2003 – 2006 Established research program for PGY-3 residents in Orthopaedic
 Surgery at Cartilage Biology and Orthopaedics Branch
 National Institute of Arthritis, Musculoskeletal and Skin Diseases,
 NIH, Bethesda, MD
- 2002 – 2006 Orthopaedic Resident Selection Committee
 The George Washington University
- 2002 Lecturer, George Washington University Hospital Community Education
 Seminars - Replacing Worn Out Hips and Knees
 Washington, DC
- 2002 Advisor on HIPAA regulations with respect to orthopaedic implant
 company representatives to Kathleen Fyffe, Senior Advisor, Office of the
 National Coordinator for Health Information Technology, Department of
 Health and Human Services, Washington, DC
- 2003 “Basic Science of Cartilage – From the Machine Shop to the Greenhouse”
 Visiting Faculty, Harvard Arthroplasty Course
 Cambridge, MA
- 2003 “Two-incision Minimally Invasive Total Hip Arthroplasty”
 Arthroplasty Instructional Course
 Zimmer Institute; Warsaw, Indiana

- 2003 Lecturer, George Washington University Hospital Health Fair
Washington, DC
- 2004 – 2006 Lecturer, George Washington University Hospital Community,
Education Seminars – Minimally Invasive Knee Surgery, Minimally
Invasive Hip Surgery, Washington, DC
- 2004 “Two-incision Minimally Invasive Total Hip Arthroplasty”
Arthroplasty Instructional Course
PAWS (Practical Anatomy Workshop)
St. Louis, Missouri
- 2004 “Two-incision Minimally Invasive Total Hip Arthroplasty”
Arthroplasty Instructional Course
Johns Hopkins Bayview Medical Center, Baltimore, MD
- 2005 “Embarking on the *Zimmer MIS 2-Incision* Hip Procedure”
Emerging Technologies & Techniques in Minimally Invasive
Arthroplasty
Johns Hopkins Bayview Medical Center, Baltimore, MD
- 2005 National Orthopaedic Leadership Conference
American Academy of Orthopaedic Surgeons
Washington, DC
- 2006 National Orthopaedic Leadership Conference
American Academy of Orthopaedic Surgeons
Washington, DC
- 2006 “Computer-Assisted Total Knee Replacement”
Arthroplasty Instructional Course
Zimmer Institute, Warsaw, Indiana
- 2007 Moderator
6th Combined Meeting of the Orthopaedic Research Societies
Honolulu, HI
- 2007 Featured Speaker, Journey for a Cure
Arthritis Foundation Pacific Northwest Chapter
Seattle, WA

- 2008 Moderator
54th Annual Meeting, Orthopaedic Research Society
San Francisco, CA
- 2008 Featured Speaker, Journey for a Cure
Arthritis Foundation Pacific Northwest Chapter
Seattle, WA
- 2008-2011 Arthritis Foundation Community Lecture Series
Arthritis Foundation Pacific Northwest Chapter
Lynnwood, WA
- 2013 Faculty, International Consensus Meeting, International Consensus on
Periprosthetic Joint Infection
Philadelphia, PA
- 2014 Co-Chair, Musculoskeletal Infection: Where are we in 2014?
Research Symposium
Orthopaedic Research Society/American Academy of Orthopaedic
Surgeons
Rosemont, IL
- 2016 Faculty and Moderator
American Academy of Orthopaedic Surgeons Annual Meeting
Orlando, 2016
- 2017 Faculty and Moderator
American Academy of Orthopaedic Surgeons Annual Meeting
San Diego, CA, 2017
- 2018 Invited Faculty
6th Annual Combined Meeting of Chinese Hip Society/American
Association of Hip and Knee Surgeons
Guiyang, Guizhou. China
- 2018 Faculty and Moderator
American Academy of Orthopaedic Surgeons Annual Meeting
New Orleans, LA, 2018
- 2018 Faculty, International Consensus Meeting, International Consensus on
Periprosthetic Joint Infection
Philadelphia, PA

2019 Faculty and Moderator
American Academy of Orthopaedic Surgeons Annual Meeting
Las Vegas, NV, 2019

Editorial Board/Reviewer:

2004 – 2013 *Orthopedics* (Editorial Board)

2004 – 2014 *Tissue Engineering*

2006 – 2013 *Journal of Bone and Joint Surgery*

2005 – 2014 *Journal of Orthopaedic Research*

2007 Orthopaedic Research Society 53rd Annual Meeting Program

2007 Orthopaedic Research Society 6th Combined Meeting

2008 Orthopaedic Research Society 54th Annual Meeting Program

2009 – present Canada Foundation for Innovation/Fondation canadienne pour l'innovation - Expert Committee on Musculoskeletal Research

2012 – 2013 Editor, Hip Newsletter, *Journal of Bone and Joint Surgery*

2012 - 2014 Reviewer, *Clinical Orthopaedics and Related Research*

2014 - present Senior Editor, *Clinical Orthopaedics and Related Research*

2015-present AAOS Annual Meeting Central Program Committee

2019 Program Director (PD) of the Hip and Knee Grant program, Orthopaedic Research and Education Foundation

Special National Responsibilities

2005 – 2008 Committee for Professional Liability
American Academy of Orthopaedic Surgeons
Rosemont, IL

2008 – 2013 Research Development Committee
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2009 - 2017 Consultant, Orthopaedic and Rehabilitation Panel
Center for Devices and Radiological Health
Food and Drug Administration
Silver Spring, MD

- 2009 – 2013 Evidence Based Guideline: Osteoarthritis of the Knee Work Group
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2010 – 2013 Advocacy Committee
Orthopaedic Research Society
Rosemont, IL

- 2011 – 2012 Metal on Metal Technology Overview Workgroup
American Academy of Orthopaedic Surgeons
Rosemont, IL

On June 27, 2012, along with Young-Min Kwon (Harvard) and Markus Wimmer (Rush), I testified on behalf of the AAOS, AAHKS, ORS, and Hip Society at the FDA Panel meeting on Metal on Metal Bearings.

- 2012 – 2013 Voting Panel, *Appropriate Use Criteria for Optimizing the Management of Full-Thickness Rotator Cuff Tears*
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2014 – present Adult Reconstruction-Hip Program Committee
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2014 Writing Panel, *Appropriate Use Criteria for Management of Osteochondritis Dissecans of the Knee*
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2015 Writing panel, *Appropriate Use Criteria on the Surgical Management of Osteoarthritis of the Knee*
American Academy of Orthopaedic Surgeons
Rosemont, IL

- 2017 Voting panel, *Appropriate Use Criteria for Osteoarthritis of the Hip*
American Academy of Orthopaedic Surgeons
Rosemont, IL

2018 AAOS Representative
MEDCAC (Medicare Evidence Development & Coverage Advisory
Committee), Center for Medicare and Medicaid Services
Baltimore, MD

Special Local Responsibilities:

1998 – 2000 Clinical Leader, Arthroplasty Section, Centers of Excellence Strategy
Planning Group, Mid-Atlantic Permanente Medical Group, PC
Rockville, MD

2000 – 2001 Total Joint Replacement Sub-Committee, Orthopedic Service Line,
Atlantic Health System
Summit, NJ

2001 – 2006 Co-Director, The Total Joint Replacement Center
The George Washington University Medical Center
Washington, DC

2002 – 2006 Faculty Senate, The George Washington University, Washington, DC

2003 – 2006 Minimally Invasive Surgery Group
The George Washington University Medical Center
Washington, DC

2006 – 2011 Surgical Infections Committee, University of Washington Medical Center

2007 – 2011 Clinical Practice Committee, University of Washington Medical Center

2009 – 2011 Provider Satisfaction Committee, University of Washington Medical Center

2010 – 2012 Finance Committee, Department of Orthopaedics & Sports Medicine,
University of Washington Medical Center

2015-2016 NWH Hip and Knee Care Pathway Project
Northwest Hospital and Medical Center

2016 – present Faculty Senate, University of Washington

2016 – present Clinical Practice Innovator Program
University of Washington Medical Center

2018 – present Faculty Senate Adjudication Panel, University of Washington

2018 – present Orthopaedic Clinical Product Utilization Core Group, University of Washington

Research Funding:

A. Previously Funded Projects:

Cartilage Biology and Orthopaedics Branch of the National Institute of Arthritis Musculoskeletal and Skin Diseases, and Zimmer Holdings, **Manner PA**, \$145,000/annum support of resident education, George Washington University, 2002-2006. Principal Investigator.

(This provided salary support to all PGY-3 residents at George Washington University, who spent 6 months engaged in basic research in the Cartilage Biology and Orthopaedics Branch.)

Wallace H. Coulter Foundation, \$20,000 Seed Grant, **Manner PA**, University of Washington, August 2007-October 2007. Principal Investigator.

Wallace H. Coulter Foundation Translational Research Partnership, **Manner PA**, \$100,000, University of Washington, April 2008 – March 2009. Principal Investigator.

Wallace H. Coulter Foundation Translational Research Partnership, **Manner PA**, \$96,000, University of Washington, April 2009 – March 2010. Principal Investigator.

Wallace H. Coulter Foundation Translational Research Partnership: Remote Monitoring of Function after Total Knee Arthroplasty. Cavanagh PR, **Manner PA**, Hanson AM. \$100,000, University of Washington, July 2011 – June 2012. Co-PI.

Department of Defense (DOD) Congressionally Directed Medical Research Programs Peer Reviewed Orthopaedic Research Program (PRORP) Translational Research Award: Development of novel Point-of-Care treatment for articular cartilage injury. Use of a novel adipose-derived mesenchymal stem cell/biopolymer construct for acute and definitive osteochondral injury. Tuan R, Paek J, **Manner PA**. \$279,000, University of Washington, September 2010 – August 2013. Co- PI.

Wallace H. Coulter Foundation Translational Research Partnership: Remote Monitoring of Function after Total Knee Arthroplasty. Cavanagh PR, **Manner PA**, Hanson AM. \$100,000, University of Washington, October 2012 – September 2013. Co-PI.

Washington Research Foundation: Remote Monitoring of Function after Total Knee Arthroplasty. Cavanagh PR, **Manner PA**, Marver D, Odell R, Hanson AM. \$46,000, University of Washington, October 2012 - September 2013. Co-PI.

NICHD SBIR (Small Business Innovation Research) Program, Remote Monitoring During Rehabilitation. \$150,000, JointMetrixMedical. Odell R, Marver D, **Manner PA**, Hanson AM, Cavanagh PR. Co-PI.

B. Applications

NIAMS R-21 (Exploratory/Developmental Research Grant Award), Remote Monitoring of Function after Total Knee Arthroplasty. Cavanagh PR, **Manner PA**, Hanson AM. Amount TBA (as of 5/2011), University of Washington. Co-PI.

Telemedicine and Advanced Technology Research Center (TATRC), Department of Defense. Bone Repair with Sphere-templated (6S) Polymers. Ratner B, **Manner, PA**. \$200,000, University of Washington. Co-PI.

Washington State Life Sciences Discovery Fund: Remote Monitoring of Function after Total Knee Arthroplasty. Cavanagh PR, **Manner PA**, Marver D, Odell R, Hanson AM. \$250,000, University of Washington, January 2013 - December 2013. Co-PI.

University of Washington Royalty Research Fund. A new concept in the mechanism leading to osteoarthritis. Roudier M, **Manner PA**, Simkin P. \$39,562. Co-PI.

NIAMS R-21 (Exploratory/Developmental Research Grant Award), Bone Repair with Pro-Regenerative STEPP Scaffolds. \$200,000, University of Washington. Ratner B, **Manner, PA**. Co-PI.

C. Patents

Provisional Patent Applications # 61/681,015 (Filed 8/8/2012 and renewed 8/8/2013), 61/864,131 (Filed 8/9/2013), and 61/942,507 (Filed 2/20/2014). Systems and Methods for Assessment, Analysis, and Reporting of a Patient's Use of Post-Surgical or Post-Injured Joint.; Inventors: Peter Cavanagh, Paul Manner, Andrea Hanson, Alexandre Bykov.

E. Entrepreneurship

Chief Medical Officer, JointMetrix Medical. (<http://jointmetrixmedical.com>).

JointMetrix Medical was created to commercialize technology developed in the Department of Orthopaedics and Sports Medicine at the University of Washington. This remote monitoring technology was developed over the last decade in connection with NASA-sponsored research to measure astronauts' activity aboard the international space station.

Specialized for orthopedics, the technology allows continuous and accurate measurement of patients' joint motion and overall activity, and is designed enhance clinicians' ability to track and positively influence post-surgical outcomes.

In August 2014, 19% of JointMetrix Medical was acquired by Zimmer, a major orthopaedic implant company, for \$2 million. Zimmer has subsequently relinquished this share, and we are actively seeking other partners.

Bibliography:

A) Manuscripts in Refereed Journals:

1. **Manner P**, Rubash HE, Herndon J. Prospectus: Future Trends in Blood Transfusion in Orthopaedic Surgery. *Clinical Orthopaedics and Related Research*. 1998 Dec; 357:101-115.
2. Dahlberg L, Billingham RC, **Manner P**, Nelson F, Webb G, Ionescu M, Reiner A, Tanzer M, Zukor D, Chen J, Van Wart HE, Poole AR. Selective enhancement of collagenase-mediated cleavage of resident type II collagen in cultured osteoarthritic cartilage and arrest with a synthetic inhibitor that spares collagenase 1 (matrix metalloproteinase 1). *Arthritis Rheum*. 2000 Mar;43(3):673-82.
3. Tuli R, Seghatoleslami M, Tuli S, Wang M, Hozack W, **Manner P**, Danielson K, Tuan R. A simple, high-yield method for obtaining multipotential mesenchymal progenitor cells from trabecular bone. *Mol Biotechnol*. 2003 Jan;23(1):37-49.
4. Wang M, Tuli R, **Manner P**, Sharkey P, Hall D, Tuan R. Direct and indirect induction of apoptosis in human mesenchymal stem cells in response to titanium particles. *J Orthop Res*. 2003 21:697-707.
5. Tuli, R., Tuli, S., Nandi, S., Wang, M.L., Alexander, P.G., Smith, H.H., Hozack, W.J., **Manner, P.A.**, Danielson, K.G., and Tuan, R.S. Characterization of Multipotential Mesenchymal Progenitor Cells Derived from Human Trabecular Bone. *Stem Cells*. 2003 21:681-693.
6. Tuli R, Tuli S, Nandi S, Huang X, **Manner PA**, Hozack WJ, Danielson KG, Hall DJ, Tuan RS. Transforming Growth Factor- β -mediated Chondrogenesis of Human Mesenchymal Progenitor Cells Involves N-cadherin and Mitogen-activated Protein Kinase and Wnt Signaling Cross-talk. *J Biol Chem*. 2003 Oct 17;278(42):41227-41236.
7. Tuli R, Nandi S, Li WJ, Tuli S, Huang X, **Manner PA**, Laquerriere P, Noth U, Hall DJ, Tuan RS. Human mesenchymal progenitor cell-based tissue engineering of a single-unit osteochondral construct. *Tissue Eng*. 2004 Jul-Aug;10(7-8):1169-79.
8. Wang X, **Manner P**, Horner A, Shum L, Tuan RS, Nuckolls G. Regulation of MMP-13 expression by Runx2 and FGF2 in osteoarthritic cartilage. *Osteoarthritis Cartilage*. 2004 Dec;12(12):963-73.
9. Okafor CC, Haleem-Smith H, Laquerriere P, **Manner PA**, Tuan RS. Particulate endocytosis mediates biological responses of human mesenchymal stem cells to titanium wear debris. *J Orthop Res*. 2006 Jan 31; 24(3):461-473.

10. Levine MJ, West K, Michelson JD, **Manner PA**. Retrospective comparison of two-incision total hip arthroplasty with a standard direct lateral approach: a single surgeon's experience. *Seminars in Arthroplasty*. 2007 Dec 18(4):18-22.
11. McCarron J, Baumbusch C, Michelson JD, **Manner PA**. Economic evaluation of peri-operative admissions for direct lateral versus 2-incision minimally invasive total hip arthroplasty. *Seminars in Arthroplasty*. 2008 Jun 19(2):180-185.
12. Williams SL, Bachison C, Michelson JD, **Manner PA**. Component position in 2-incision minimally invasive total hip arthroplasty compared to standard total hip arthroplasty. *Journal of Arthroplasty*. 2008 Feb;23(2):197-202.
13. Birmingham P, Helm JM, **Manner PA**, Tuan RS, Simulated Joint Infection Assessment by Rapid Detection of Live Bacteria via Real-Time Reverse Transcription Polymerase Chain Reaction. *J Bone Joint Surg Am*. 2008 Mar;90(3):602-8.
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B) Other Publications

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33. **Manner PA.** Medicare Advantage – what will happen to arthroplasty? *pending publication*
34. **Manner PA.** Prosthetic Joint Infection: the Infectious Diseases Society update *pending publication*
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59. **Manner P.** AMPLIFY Group: Should We Use Apixaban for Venous Thromboembolism? *JBJS Orthop Highlights: Hip Surg*, 2013 Aug 6;3(8):e5
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62. **Manner P.** Is overcoverage overblown? *JBJS Orthop Highlights: Hip Surg*, 2013 Sep 4;3(9):e5

C. Videos

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2. *Minimally Invasive Total Hip Replacement*, UWTV, Seattle, WA, 2006.
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5. *Diagnosis and Treatment of Infected TJA.* OrthopaedicsOne, accessed at <http://www.orthopaedicsone.com>.
6. *Femoroacetabular impingement – Fact or fiction?* OrthopaedicsOne, accessed at <http://www.orthopaedicsone.com>.

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D. Abstracts:

Local

1. **Manner P**, Billingham RC, Ionescu M, Reiner A, Zukor D, Huk O, Poole AR. Use of an antibody, specific to the collagenase cleavage site in articular type II collagen, as a marker for osteoarthritis. *Winner, Sherwood Davis & Geck Award for Excellence in Basic Science Research at McGill University, May 1997.*
2. **Manner P**, Horner A, Wang X, Tuan R, Nuckolls G. The expression of Runx2/Cbfa1, a key regulator of chondrocyte hypertrophy in the growth plate, in osteoarthritic cartilage correlates with the severity of erosion. *Presented at the NIAMS retreat, Airlie, VA, June 2002.*
3. Hatakeyama Y, Horner A, **Manner P**, Tuan R, Nuckolls G, Shum L. Distinct Roles of BMP-4 and GDF-5 in the regulation of cartilage formation. *Presented at the NIAMS retreat, Airlie, VA, June 2002.*
4. Wang X, **Manner P**, Horner A, Shum L, Tuan R, Nuckolls G. Regulation of MMP-13 expression by FGF2 and RUNX2 in osteoarthritic cartilage. *Presented at the NIAMS retreat, Airlie, VA, June 2003.*
5. Hatakeyama Y, **Manner P**, Tuan RS, Shum L. BMP4 induces chondrogenic differentiation in adult human bone marrow derived mesenchymal stem cells. *Presented at the NIAMS retreat, Airlie, VA, June 2003.*
6. Tuli R, Li WJ, Tuli S, Huang X, **Manner P**, Laquerriere P, Hall DJ, Tuan RS. A tissue engineered osteochondral construct based on human mesenchymal stem cells: potential application for articular cartilage repair. *Presented at the NIAMS retreat, Airlie, VA, June 2003.*
7. McCarron JA, Alexander PA, Levine MJ, Melvin GM, **Manner PA**, Tuan RS. Rabbit animal model for articular cartilage and progression to osteoarthritis after impact injury. *Presented at the NIAMS retreat, Gettysburg, PA, June 2004.*

8. Murray PJ, Alexander PG, **Manner PA**, Tuan RS. Articular chondrocyte apoptosis following blunt impact in the New Zealand white rabbit knee. *Presented at the NIAMS IRP Retreat, Rockville, MD 2005.*
9. Long J, Alexander PG, Murray PJ, **Manner PA**, Tuan RS. Age-related differences in response of rabbit articular cartilage to blunt impact. *Presented at the NIAMS IRP Retreat, Rockville, MD 2005.*
10. Alexander PG, Li W-J, Lutton DM, Kaung G, **Manner PA**, Tuan RS. Development of a lapine model for the evaluation of tissue engineered constructs for the repair of articular cartilage. *Presented at the NIAMS IRP Retreat, Rockville, MD 2006*

National

11. Webb G, **Manner P**, Pidoux I, Poole AR. Type II collagen breakdown and lesion formation in osteoarthritis. *Presented at the Canadian Connective Tissue Society Annual Meeting London, ON, Canada, June 1998.*
12. Levine MJ, McCarron JA, Alexander PG, Melvin GM, Tuan RS, **Manner PA**. Cartilage degeneration after impact injury in a rabbit animal model. *Presented at the Western Orthopaedic Society Annual Meeting, San Francisco, 2004.*
13. Long J, Murray PJ, Alexander PG, **Manner PA**, Tuan RS. Age-related differential responses of rabbit articular cartilage to blunt impact. *Presented at the Ruth Jackson Orthopaedic Society Annual Meeting, San Antonio, TX 2005.*
14. Amann S, Cizik A, Leopold SS, **Manner PA**. Two-incision minimally invasive vs. standard total hip arthroplasty: Comparison of component position and hospital costs. *Presented at the Western Orthopaedic Society Annual Meeting, Honolulu, HI, 2011.*
15. Hanson AM, Lee EW, Jacques CM, **Manner PA**, Cavanagh PR. Assessing the real-world impact of clinical interventions and outcomes: The science of ambulatory assessment. *Presented at the Society for Ambulatory Assessment, Ann Arbor, MI 2011*

International

16. **Manner P**, Billingham RC, Ionescu M, Reiner A, Zukor D, Huk O, Poole AR. Use of an antibody, specific to the collagenase cleavage site in type II collagen, to study degeneration in human articular cartilage in osteoarthritis. *Presented at the 44th Orthopaedic Research Society Annual Meeting, New Orleans, March, 1998 – Finalist, New Investigator Recognition Award.*

17. **Manner P**, Billingham RC, Ionescu M, Reiner A, Zukor D, Huk O, Poole AR. Different patterns of collagenase cleavage of type II collagen in normal articular cartilage from individuals undergoing autopsy vs. organ transplant donors, and osteoarthritic cartilage. *Presented at the 44th Orthopaedic Research Society Annual Meeting, New Orleans, March, 1998.*
18. Webb GR, **Manner PA**, Pidoux I, Poole AR. Type II collagen and proteoglycan breakdown in early focal degenerative lesions in human articular cartilage in aging. *Presented at the 45th Orthopaedic Research Society Annual Meeting, Anaheim, CA, 1999.*
19. Tuli R, Tuli S, Seghatoleslami MR, Wang ML, Hozack WJ, **Manner PA**, Danielson KG, Tuan RS. Long term culture expansion, growth kinetics, and multilineage differentiation potential of mesenchymal progenitor cells derived from trabecular bone. *Presented at the 49th Orthopaedic Research Society Annual Meeting, New Orleans, 2003.*
20. Nuckolls, GH, Horner A, **Manner P**, Wang X, Shum L, Tuan RS. Increased expression of CBFA1/Runx2 in osteoarthritic cartilage correlates with MMP-13 expression. *Presented at the 49th Orthopaedic Research Society Annual Meeting, New Orleans, 2003.*
21. Wang ML, Tuli R, **Manner PA**, Sharkey PF, Hall DJ, Tuan RS. Direct and indirect induction of apoptosis in human mesenchymal stem cells in response to titanium particles. *Presented at the 49th Orthopaedic Research Society Annual Meeting, New Orleans, 2003.*
22. Tuli R, Tuli S, Wang ML, Hozack WJ, **Manner PA**, Hall DJ, Tuan RS. TGF- β 1 induced chondrogenesis of mesenchymal progenitor cells from human trabecular bone is mediated through MAP kinase signaling. *Presented at the 49th Orthopaedic Research Society Annual Meeting, New Orleans, 2003.*
23. Wang X, **Manner P**, Horner A, Shum L, Tuan R, Nuckolls G. FGF2 and RUNX2 synergistically up-regulate MMP-13 expression in articular chondrocytes. *Presented at the 50th Orthopaedic Research Society Annual Meeting, San Francisco, 2004.*
24. Tuli, R., Nandi, S., Li, W.J., Tuli, S., Huang, X., **Manner, P.A.**, Noth, U., Hall, D.J., and Tuan, R.S. Tissue engineering of a single-unit osteochondral construct using human mesenchymal progenitor cells. *Presented at the 50th Orthopaedic Research Society Annual Meeting, San Francisco, 2004.*
25. Okafor C, Smith H, Lacqueriere P, **Manner P**, Tuan RS. Endocytosis of titanium particles mediates biological responses of human mesenchymal stem cells to

- titanium wear debris. *Presented at the 50th Orthopaedic Research Society Annual Meeting, San Francisco, 2004.*
26. McCarron JA, Levine MJ, Alexander PG, Melvin GM, **Manner PA**, Tuan RS. Rabbit animal model for osteoarthritis and articular cartilage changes after impact injury. *Presented at the 5th Combined Meeting of the Orthopaedic Research Societies of Canada, USA, Japan, and Europe, Banff, Alberta, 2004.*
 27. Wang X, Nuckolls GH, **Manner PA**, Tuan RS. FGF-2 and IL-1 β exhibit similar effects on gene expression in articular chondrocytes. *Presented at the 51st Orthopaedic Research Society Annual Meeting, Washington, DC, 2005.*
 28. McCarron JA, Alexander PG, Levine MJ, Melvin GM, **Manner PA**, Tuan RS. Analysis of supraphysiologic impact injury to articular cartilage using an in vivo rabbit model for osteoarthritis. *Presented at the 51st Orthopaedic Research Society Annual Meeting, Washington, DC, 2005.*
 29. Alexander PG, Murray PJ, Long J, **Manner PA**, Tuan RS. Cell Death in a rabbit model for post-traumatic cartilage degeneration and osteoarthritis. *Presented at the OsteoArthritis Research Society International 10th World Congress, Boston, MA, 2005.*
 30. Wang X, **Manner PA**, Tuan RS. Histone deacetylase inhibitors antagonized FGF-2 effects on chondrocyte proliferation and MMP expression. *Presented at the 52nd Orthopaedic Research Society Annual Meeting, Chicago, IL 2006.*
 31. Levine MJ, West K, Michelson J, **Manner PA**. Comparison of minimally invasive two-incision total hip approach with the direct lateral approach. *Presented at the American Academy of Orthopaedic Surgeons Annual Meeting, San Diego, 2007.*
 32. Williams SL, Bachison C, Michelson J, **Manner PA**. Component position in two-incision minimally invasive total hip arthroplasty compared to standard total hip arthroplasty. *Presented at the American Academy of Orthopaedic Surgeons Annual Meeting, San Diego, 2007.*
 33. Birmingham P, Helm J, Tuan RS, **Manner PA**. Assessing joint infection by rapid detection of live bacteria via real time polymerase chain reaction. *Presented at the 53rd Orthopaedic Research Society Annual Meeting, San Diego, 2007.*
 34. Alexander P, Li WJ, Lutton D, Kaung G, **Manner PA**, Tuan RS. Repair of full thickness osteochondral defects using mesenchymal stem cell-seeded poly(L)-lactic acid nanofibrous scaffolds. *Presented at the 53rd Orthopaedic Research Society Annual Meeting, San Diego, 2007.*

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44. Amann S, Cizik A, Leopold SS, **Manner PA**. Two-Incision Minimally Invasive vs. Standard Total Hip Arthroplasty: Comparison of Component Position and

Hospital Costs. *Presented at the 75th Annual Meeting of the Western Orthopaedic Association, Honolulu, HI, 2011.*

45. Amann S, Cizik A, Leopold SS, **Manner PA**. Two-Incision Minimally Invasive vs. Standard Total Hip Arthroplasty: Comparison of Component Position and Hospital Costs. *Presented at the International Congress for Joint Reconstruction, San Diego, 2012.*
46. Cavanagh PR, Glauberman MD, **Manner PA**, Manner KT, Peterson EA, Maitland ME, Nguyen VD, Bykov AE. A System for Remote Monitoring and Activity Recognition after Knee Arthroplasty. *Presented at the 59th Annual Meeting of the Orthopaedic Research Society, San Antonio, TX 2013.*
47. Cavanagh PR, Glauberman MD, **Manner PA**, Manner KT, Peterson EA, Maitland ME, Nguyen VD, Bykov AE. A System for Remote Monitoring and Activity Recognition after Knee Arthroplasty. *Presented at the 65th Annual Meeting of The Association of Bone and Joint Surgeons, Istanbul, Turkey, 2013.*
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49. Roudier M, **Manner P**, Simkin P. Tidemark Duplication In Osteoarthritis: Evidence Of Incremental Progression? *Presented at the ACR/ARHP Annual Meeting, San Diego, 2013.*
50. **Manner P**. Can Academic Orthopaedics be Cost Effective in a Community Setting? *Presented at the 66th Annual Meeting of The Association of Bone and Joint Surgeons, New York, 2014.*
51. Roudier M, **Manner P**, Simkin P. Histological Evidence of Sequential Failed Osteochondral Repair: An Etiology for OA? *Submitted for presentation at ACR/ARHP Annual Meeting, Boston, MA, 2014.*
52. Cavanagh P, Fournier M, **Manner P**. Remote Patient Monitoring in Total Knee Arthroplasty. *Presented at the 27th Annual Congress, International Society for Technology in Arthroplasty, Kyoto, Japan, 2014.*
53. **Manner P**, Archdeacon M, Parvizi J. Scientific Exhibit: Musculoskeletal Infection (AAOS Research Development Committee). *Presented at the Annual Meeting of the American Academy of Orthopaedic Surgeons, Las Vegas, Nevada, 2015.*

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55. Gottardi R, Piroso A, Alexander PG, **Manner PA**, Puppi D, Chiellini F, Tuan RS. An in vitro Chondro-Osteo-Vascular Triphasic Model of the Osteochondral Complex for Studying Osteochondral Biology and for Drug Screening. *Presented at the 62nd Annual Meeting of the Orthopaedic Research Society, Orlando, FL, March 2015.*
56. Gottardi R, Conoscenti G, Alexander PG, **Manner PA**, La Carrubba V, Brucato V, Tuan RS. A PLLA Scaffold with Continuous Gradient Pore Size for Osteochondral Regeneration Validated in a Microphysiological Tissue System Bioreactor. *Presented at the 62nd Annual Meeting of the Orthopaedic Research Society, Orlando, FL, March 2015.*
57. Gottardi R, Lin H, D'Urso G, Iannetti GL, Zunino P, Lozito TP, Alexander PG, **Manner PA**, Sefton EA, Woodruff TK, Tuan RS. Validation of an Osteochondral Microphysiological System Applied to Study the Protective Role of Sex Hormones. *Presented at the 62nd Annual Meeting of the Orthopaedic Research Society, Orlando, FL, March 2015.*
58. Gottardi R, Hwang MP, Simson M, **Manner PA**, Tan J, Alexander PG, Tuan RS, Little SR. Autologous Stem Cell Recruitment for Articular Cartilage Regeneration. *Presented at the 13th US-Japan Symposium on Drug Delivery Systems, Maui, HI, December 2015.*
59. Gottardi R, Bianconi PA, **Manner PA**, Alexander PG, Tuan RS, Little SR. Prevention of Cartilage Calcification by Controlled Release of Dorsomorphin, *Presented at the 13th US-Japan Symposium on Drug Delivery Systems, Maui, HI, December 2015.*
60. Gottardi R, Lin H, Iannetti L, D'Urso G, Zunino P, Lozito T, Alexander P, **Manner P**, Sefton E, Woodruff T, Tuan R. Validation Of An Osteochondral Bioreactor Applied To Study The Protective Role Of Sex Hormones. *Presented at the Biomedical Engineering Society Annual Meeting, Minneapolis, October 2016.*
61. Gottardi R, Piroso A, Alexander P, **Manner P**, Puppi D, Chiellini F, Tuan R. An In Vitro Chondro-Osteo-Vascular Triphasic Model Of The Osteochondral Complex. *Presented at the Biomedical Engineering Society Annual Meeting, Minneapolis, October 2016.*
62. Gottardi R, Conoscenti G, Alexander P, **Manner P**, La Carrubba V, Brucato V, Tuan R. A Continuous Pore Size Gradient PLLA Scaffold For Osteochondral Regeneration. *Presented at the Biomedical Engineering Society Annual Meeting, Minneapolis, October 2016.*

63. Shippee-Wallace S, **Manner P**. Budget Impact Analysis for Total Joint Arthroplasty in Patients with Hemophilia. *Presented at the 69th Annual Meeting of The Association of Bone and Joint Surgeons, Austin, 2017.*



Agency medical director comments

Stem cell therapy for musculoskeletal conditions

Jason Fodeman MD, MBA
Associate Medical Director
Department of Labor and Industries
June 12, 2020



Stem cell therapy

- The safety and efficacy of stem cells from peripheral blood or bone marrow for hematopoietic reconstitution in conditions such as Leukemia and Lymphoma has been well established
- This is **NOT** what we will be talking about today

Washington State Health Care Authority



https://bjso.org/reader.php?id=103185&rsuite_id=1261189&native=1&source=The_Journal_of_Bone_and_Joint_Surgery/98/18/1509/fulltext&topics=bs#figures

Washington State Health Care Authority

Stem cell therapy

- A 2016 report found that nationally 351 businesses were advertising stem cell therapy treatments at 570 clinics across the country
 - Some clinics specialize while others take a broader approach offering stem cell therapy for up to over 30 diseases and injuries
 - Commonly marketed conditions include
 - Degenerative disorders
 - Neurological conditions
 - Spinal cord injuries
 - Pulmonary disease
 - Heart issues
 - Urological pathology
 - Cosmetic use
- Orthopedic disorders and pain were the two most commonly marketed conditions

Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry. *Cell Stem Cell*. 2016;19(2):154-157.



Why review stem cells?

- Stem cells are being targeted to a large, broad range of disorders
- High prevalence of these conditions
- Controversy and uncertainty
- Aggressive marketing and promotion
- Patients may be vulnerable to direct marketing



Agency Medical Directors' Concerns Level

Safety = **High**
Efficacy = **High**
Cost = **High**

6



FDA

- In the March 2017 *NEJM*:
 “Outside a few well-established indications, the assertion that stem cells are intrinsically able to sense the environment into which they are introduced and address whatever functions require replacement or repair is not based on scientific evidence.”
- In November 2017, the FDA released two comprehensive policy documents to provide additional clarity to industry and lay out its current thinking
- In light of this new guidance, the FDA has given lower risk products 36 months of enforcement discretion
- The FDA has incorporated new concepts and tools to help small investigators and firms
- The FDA is encouraging investigators to engage early on in the process with the agency

Marks PW, Witten CM, Califf RM. Clarifying stem-cell therapy's benefits and risks. N. Engl. J. Med. 376, 1007–1009 (2016).
 Marks P, Gottlieb S: Balancing safety and innovation for cell-based regenerative medicine. N Engl J Med 2018;378:954-959.



FDA

- The FDA has a tiered, risk-based regulatory framework for human cells, tissues, and cellular and tissue based products (HCT/Ps) determined by whether it meets the criteria of 21 CFR 1271.10

	Meets criteria	Doesn't meet criteria
Criteria	Minimally manipulated AND Homologous use	More than minimally manipulated i.e. (not minimally manipulated) OR Non-homologous use
Applicable regulations	Section 361 of the Public Health Service Act (PHS) 21 CFR Part 1271	Section 351 and 361 PHS Act FD + C Act 21 CFR Part 1271 Other applicable regulations
Premarket review?	Does not need pre-market review	Requires pre-market review
Requirements	Subject to the safe tissue regulations to prevent introduction, transmission, and spread of infection Registration and listing with FDA are required prior to marketing	Can only be used in clinical trials under Investigational New Drug (IND) application Required to submit biologics license application before marketing

Marks P, Gottlieb S: Balancing safety and innovation for cell-based regenerative medicine. N Engl J Med 2018;378:954-959

FDA, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use," November 2017, at <https://www.fda.gov/media/124138/download>



Key Questions

1. What is the evidence of the short- and long-term efficacy of autologous or allogenic stem cell therapy?
2. What is the evidence regarding short- and long-term harms and complications of autologous or allogenic stem cell therapy?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
4. What is the cost-effectiveness of autologous or allogenic stem cell therapy?



Evidence report

- There are currently not established guidelines or standard protocols to
 - Isolate stem cells
 - Concentrate and process them
 - Number to inject



Evidence report

- 14 RCTs total
 - 12 knee OA
 - 1 lumbar DJD
 - 1 Achilles tendinopathy



Evidence report

- Overall the quality of evidence was poor
- RCTs predominantly had a moderately high risk of bias
- Majority of studies for knee OA
- In general, studies did not abide by proposed standards for reporting of clinical stem cell studies



Evidence report--efficacy/effectiveness

- Heterogeneity
 - Patient populations
 - Stem cell sources and preparations
 - Use of adjunctive biological components
 - Pre and post injection therapies
- Small sample sizes
- Variable reporting of co-interventions and post-treatment rehabilitation protocols that could impact outcomes
- Follow up rarely exceeded a year limiting the ability to assess long term-impact of stem cells on pain and function
- Need for subsequent interventions usually not assessed



Evidence report-safety

- Overall the quality of evidence was poor
- Adverse events were poorly specified and poorly reported
- Small sample sizes in the majority of studies are likely too small to identify anything but common side effects
- Most studies had follow up of less than one year likely preventing the ability to evaluate long term risks of stem cells such as of neoplasm or other long term consequences



Serious infections and other serious AEs

- MMWR published a case series
 - 12 cases of serious infections from clinics in FL, TX and AZ in patients after they received injections with stem cells
 - Injection sites: knee, shoulder, cervical and lumbar spine
 - Local infections including osteomyelitis, septic arthritis, and epidural abscess
 - 8/12 became bacteremic
 - All 12 patients were hospitalized
 - E coli, Proteus, Enterococcus, Enterobacter, Citrobacter
 - “this investigation highlights the serious potential risks to patients of stem cell therapies administered for unapproved and unproven uses other than hematopoietic or immunologic reconstitution”
 - MMWR Dec 21, 2018; 67: 1397-99



Serious infections and other serious AEs

- 12/9/2019 FDA public safety alert on stem cell and exosome products
 - Serious AEs among multiple patients treated in Nebraska with exosome products
<https://www.fda.gov/safety/medical-product-safety-information/public-safety-alert-due-marketing-unapproved-stem-cell-and-exosome-products>
- According to the FDA, other potential safety concerns of stem cells include
 - The cells moving from the injection site and changing into unintended cell types and/or multiplying
 - The cells not working as expected
 - Tumor growth
- With the current use of stem cells, the FDA warns that AEs are likely more common than recognized given there is no reporting requirement of AEs when these interventions are performed outside of clinical trials

FDA, “FDA Warns About Stem Cell Therapies,” at <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>
Marks PW, Witten CM, Califf RM. Clarifying stem-cell therapy’s benefits and risks. N. Engl. J. Med. 376, 1007–1009 (2016).



US Food and Drug Administration: Safety concerns for unproven stem cell treatments

- 9/3/19 warning from the FDA:
- “the U.S. Food and Drug Administration is concerned that some patients seeking cures and remedies are vulnerable to stem cell treatments that are illegal and potentially harmful. And the FDA is increasing its oversight and enforcement to protect people from dishonest and unscrupulous stem cell clinics, while continuing to encourage innovation so that the medical industry can properly harness the potential of stem cell products.”
- The FDA advises patients to be sure that if they are considering stem cells, the stem cells are either:
 - FDA-approved, or;
 - In a study under an Investigational New Drug Application (IND)

FDA, “FDA Warns About Stem Cell Therapies,” at <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>



Key Question 3: Differential efficacy, effectiveness, or harms

- No evidence identified



Key Question 4: Cost-effectiveness

- No evidence identified

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Stem cell therapy costs

- In the United States, treatment protocols vary based on the clinic and the treating provider.
 - A one-time stem cell intervention utilizing blood drawn from that patient can cost \$1,500.
 - However, protocols involving stem cells from bone marrow or adipose tissue can cost as much as \$15,000 – \$30,000.
- Researchers contacted 273/317 US centers offering direct- to-consumer stem cell therapies for musculoskeletal conditions
- Using a simulated 57 year old male with knee OA the authors found
 - Mean price of a unilateral stem cell knee injection \$5156+/- \$2446
 - Prices ranged from \$1,150 to \$12,000

Cade Hildreth, "Cost Of Stem Cell Therapy And Why It's So Expensive," October 27, 2019, at <https://bioinformant.com/cost-of-stem-cell-therapy/#the>

Piuzzi et al. The Stem cell market for the treatment of knee osteoarthritis: A patient perspective J Knee Surg 2018; 31: 551-56



National Coverage Determination (NCD)

- CMS does not have a coverage determination for stem cell therapy for musculoskeletal conditions



Selected payers' coverage policy

Payer	Policy	Year
Aetna	Aetna considers the use of mesenchymal stem cell therapy (e.g., AlloStem, Osteocel, Osteocel Plus, Ovation, Regenexx, and Trinity Evolution), progenitor cells, and bone marrow aspirate experimental and investigational for all orthopedic applications, with the exception of bone cysts (unicameral/simple), for which Aetna considers bone marrow injections to be medically necessary to treatment.	2019
Anthem	Anthem considers mesenchymal stem cell therapy investigational and not medically necessary for the treatment of joint and ligament disorders caused by injury or degeneration as well as autoimmune, inflammatory and degenerative diseases.	2019
Premera Blue Cross	Premera Blue Cross considers mesenchymal stem cell therapy to be investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.	2019
Wellmark	Mesenchymal stem cell therapy from bone marrow, adipose tissue, peripheral blood or synovial tissue alone or in combination with platelet-derived products (e.g. platelet-rich plasma, lysate) is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.	2019

Quoted from Evidence Report



AMDG recommendations

- Stem cell therapy for treating musculoskeletal conditions is **not a covered benefit**



Questions?

Order of scheduled presentations:

Stem-cell therapy for musculoskeletal conditions

Name	
1	
2	
3	
4	
5	
6	

No requests to provide public comment on this technology review were received.

Stem Cell Therapy for Musculoskeletal Conditions

Presentation to
**Washington State Health Care Authority
Health Technology Clinical Committee**

Erika D. Brodt, BS
June 12, 2020

Report prepared by:
Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Mark Junge, BS
Shelby Kantner, BA



Background: Musculoskeletal Disease Burden



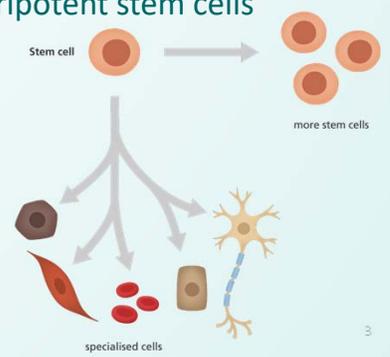
- In 2015...
 - 124 million Americans >18 years old reported having a musculoskeletal medical condition
 - 38 in 1000 adults in the work force reported they were unable to work at all due to a musculoskeletal condition
 - An additional 21 in 1000 reported they could only do limited work
- Capacity for endogenous repair for many orthopedic conditions is limited
- Effective, safe, cost-effective management options needed
- Cell-based therapies (including stem-cell therapy [SCT]) have been an area of active research
- Clinics offering SCT have rapidly expanded



2

Background: Stem Cell Basics

- Stem cells are the basis of all tissues and organs
- 3 general properties (NIH): dividing and renewing themselves for long periods of time, *unspecialized*, and can give rise to specialized cell types
- General stem cell types: embryonic; **tissue-specific (adult or somatic stem cells)**; induced pluripotent stem cells (experimental, engineered from specialized cells)
- Stem cell sources may be autologous or allogenic



Stem cell → more stem cells
specialised cells



Background: Stem Cell Basics

	Cell potency	Cell source	Cell differentiation examples	Comments
High Potency ↓ ↓ ↓ Low	Totipotent Stem Cell	<ul style="list-style-type: none"> Zygote formed at egg fertilization 	<ul style="list-style-type: none"> All cell types (body and extraembryonic tissues) 	
	Pluripotent Cells: undifferentiated	<ul style="list-style-type: none"> Embryonic cells: (5d pre-implant embryo) 	<ul style="list-style-type: none"> All body cell types Mesoderm, Endoderm, Ectoderm 	Divide w/o differentiating in culture; cannot make extra-embryonic tissues.
	Multipotent Cells: differentiated into specialized cells; can develop into more than one cell type; variety of sources	<ul style="list-style-type: none"> Bone marrow Adipose tissue Blood, lymph Cord blood Heart tissue Neural tissue 	<ul style="list-style-type: none"> Blood cells (hematopoietic) Bone, cartilage, fat (non-hematopoietic) Bone, cartilage, fat, others (non-hematopoietic) Hematopoietic cells All blood cell types Coronary vessels, heart muscle, (non-hematopoietic) Neurons, glia (non-hematopoietic) 	Mesenchymal Stromal Cells, (Mesenchymal Stem Cells): † tissue-specific, adult, somatic <ul style="list-style-type: none"> ➤ <i>small fraction of cells contained in a sample;</i> ➤ can be cultured to increase number & give rise to various connective tissues (e.g. bone, cartilage, fat); ➤ unclear mechanism of differentiation in humans
	Unipotent Cells: differentiate to one cell lineage	<ul style="list-style-type: none"> Muscle cells Blood cells Epithelial cells 	<ul style="list-style-type: none"> Muscle cells Blood cells Skin cells, fibroblasts 	Not technically "stem" cells;

Background: FDA Regulation of Stem Cell Therapy

Center for Biologics Evaluation and Research (2017): Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

- The only FDA-approved stem cell-based products consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood; approval is limited to treatment of conditions of the hematopoietic system.
- Culture-expanded connective tissue cells, i.e. MSCs, BM-derived cells, adipose-derived cells and cartilage-derived cells for orthopedic applications are not FDA-approved. Use requires participation in prospective FDA-approved clinical trials.
- **Not considered HCT/Ps, FDA approval not required:** Minimally manipulated “stem cells” for autologous use and not combined with another article; e.g. bone marrow concentrate, adipose stromal or stromal vascular fraction, placental tissue fragments, platelet-rich plasma



5

Background

Proposed Benefits of SCT

- Theoretical potential to facilitate repair, regeneration of tissue
- May modulate immune and inflammatory responses and may support and stimulate cells to enhance repair processes
- For many orthopedic conditions, effective non-surgical treatment options are limited and not curative

Potential Harms/AEs of SCT

- **Factors contributing to risk:** processes to obtain, manipulate and reinsert stem cells, stem cell source, patient factors and medications
- **Safety concerns:** administration site reactions, infection, abnormal immune reactions, undesirable bone formation, migration of cells from placement sites and differentiation into inappropriate cell types or excessive multiplication and tumor growth
- Risks of SCT outside of approved indications unknown



6

Background: Comparator Treatments

- Conventional treatments for musculoskeletal conditions vary by etiology
- Conservative, non-operative management (e.g. PT, exercise, pharmacological management)
- Minimally invasive injections (e.g. corticosteroids, hyaluronic acid [HA], or other biologics [e.g. PRP]); also common but efficacy is uncertain
- Most not considered curative; may improve symptoms, facilitate innate healing
- Surgical options are a current standard for many, but may be limited depending on etiology and patient characteristics



7

Background: Guidelines

1 clinical guideline, ASIPP (2019) on biologic therapies for LBP found on ECRI Trust (formerly NGC)

- Lumbar disc MSC injections; indications not articulated, low quality of evidence including studies of non-FDA approved processes
- Focus on office set up, patient management
- FDA-recommended “minimal manipulation” and “homologous use” draft guidelines should be followed

ACSP (2016): MSC therapies for OA, tendinopathy, muscle injury;

- Investigational; limited evidence that non-expanded MSCs don't work
- Use must be part of rigorous trial or “individualized innovative therapy”
- Written consent to include costs, provider COI, statements that MSCs are experimental and long-term harms have not been determined



8

Background: Consensus Statements, Coverage Policies

Expert consensus and research statements:

- AAOS/NIH conference (2018): No clinical recommendations; Summarizes FDA guidance, provides recommendations for terminology, reporting standards, accountability, research
- ISSCR: Effects and effectiveness of cell therapies for OA in humans unproven, cannot be recommended at present time (2019); Research and clinical translation recommendations made (2016)

Coverage policies:

- No national coverage determination from CMS
- Aetna, Anthem, Premera Blue Cross, Wellmark: mesenchymal SCT considered investigational, not medically necessary for any orthopedic applications



9

Background: Stem Cell Therapy - Challenges

- Terminology is imprecise, inconsistent and has led to substantial confusion
 - “stem cell” and “mesenchymal stem cell” have been used very broadly, often inaccurately
 - “stem cell” has been broadly used to include minimally manipulated cell preparations as well as tissue-derived culture-expanded cells
 - Marketed “stem cell” therapies may not contain stem cells and/or concentration is unknown
- Cells meeting the International Society for Cell Therapy criteria must be cultured in the laboratory; **cultured cells are not currently FDA-approved**
- A 2018 AAOS/NIH consensus document recognizes that stem cells have unique properties not met by minimally manipulated mixed cell preparations and suggest that the term “cell therapy” be used for such products
- No established guidelines or standard protocols for how to isolate, concentrate, or process stem cells, or on the number to inject.
- Processes for procuring and expanding MSCs may be proprietary
- Preparation, processing, cell characteristics and concentrations, injectate composition, etc. are inconsistently and inadequately reported

10

Key Questions

1. What is the evidence of the short- and long-term **efficacy and effectiveness** of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo/sham?
2. What is the evidence regarding short- and long-term **harms and complications** of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
3. Is there evidence of **differential efficacy, effectiveness, or safety** of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
4. What is the evidence of **cost-effectiveness** of autologous or allogenic stem cell therapy compared with other treatment options?



11

PICO Scope: Inclusion Criteria

Component	Inclusion
Population	Adults with: Cartilage defects, osteoarthritis or related joint conditions, muscle, ligament, or tendon condition; pain due to degenerative disc disease, joint pain
Intervention	Autologous or allogenic stem cell therapy
Comparator	Common conventional non-operative treatment(s), surveillance, placebo/sham, surgery
Outcomes	Primary: Validated measures of function, pain; objectively measured medication use, return to activity, adverse events/harms; cost-effectiveness outcomes (e.g. ICER)
Study Design	Studies with least potential for bias (e.g. RCTs, prospective comparative studies); full economic analysis
Setting	Outpatient, office
Publication	Studies published in English in peer reviewed journals; publicly available FDA reports

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Individual Studies: Risk of Bias

Criteria
<ul style="list-style-type: none">• Random sequence generation (RCT)• Statement of allocation concealment (RCT)• Intent-to-treat analysis (RCT) <p>RCTs and observational studies*</p> <ul style="list-style-type: none">• Blind, independent assessment of outcomes/analysis• Complete follow-up of >80%• <10% difference in follow-up between groups• Controlling for possible confounding<ul style="list-style-type: none">• Multivariate analysis, matching (including propensity) <p><small>*case series are considered at high risk of bias</small></p>



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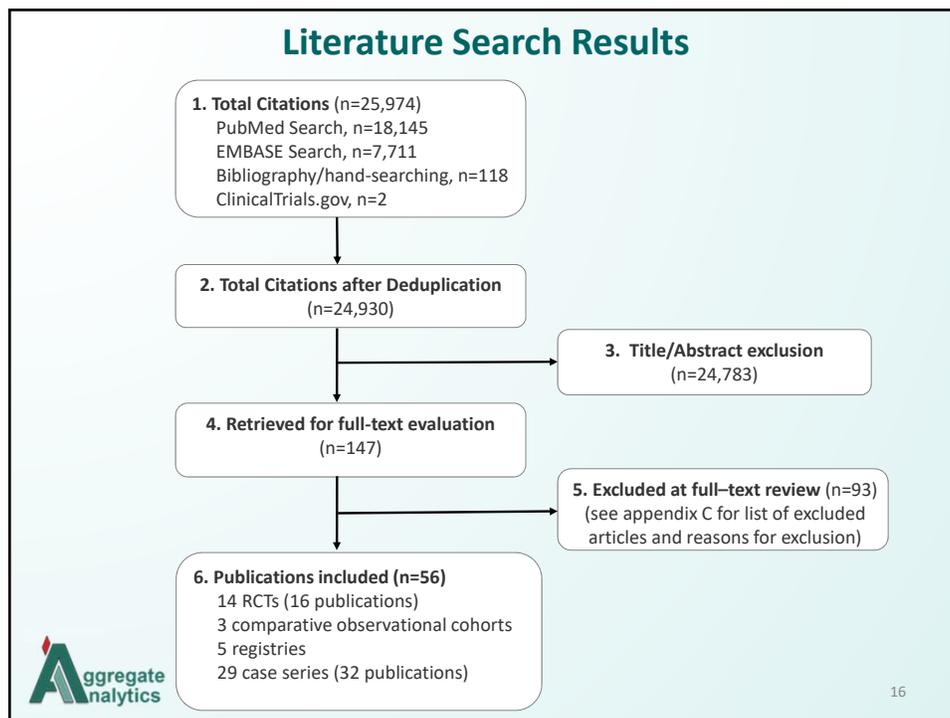
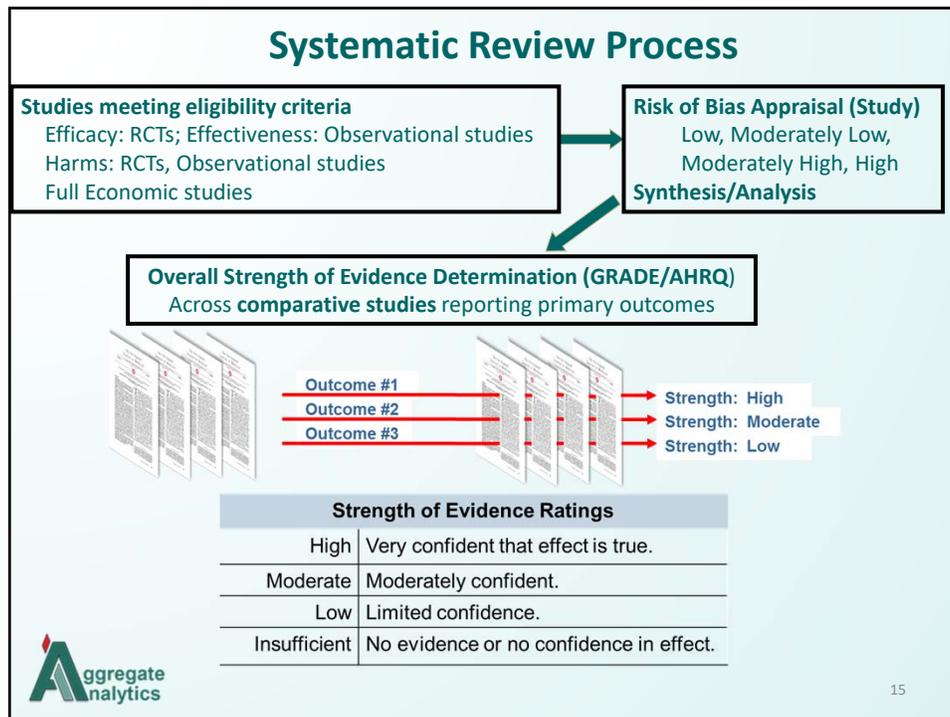
Strength of Evidence (SOE) Criteria – Appendices D, E

Overall body of evidence for primary outcomes:

- **Risk of bias (one criterion):** the extent to which majority of included studies protect against bias
- **Consistency:** degree to which estimates are similar in terms of range and variability.
- **Directness:** evidence directly related to patient health outcomes.
- **Precision:** level of certainty surrounding the effect estimates.
- **Publication/reporting bias:** selective reporting or publishing.



14



RESULTS



17

Overview of Evidence Base

Condition	Number of studies (number of publications)		
	KQ1	KQ2	Total
Knee OA	12 (14) 2	12 (14) 1 20 (21)	12 (14) 2 20 (21)
Degenerative Disc Disease	1 5 (7)	1 4 (6)	1 5 (7)
Tendinopathy	1 1	1	1 1
Partial Rotator Cuff Tear	1 1*	1	1 1
Hip OA	3†	1	3
Hip and/or Knee OA	1	1	1
Shoulder OA	2*†	None	2
ACL tear	1	1	1
Mixed Populations	N/A	5	5
Grand Total	14 (16) 3 12 (14)	14 (16) 2 32 (35)	14 (16) 3 34 (37)

 = RCT

 = Comparative cohort

 = Case series, single-arm registry

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KNEE OSTEOARTHRITIS (OA)

Autologous
Non-culture-expanded (5 RCTs, 1 NRCS)
Culture-expanded (5 RCTs)

Allogenic
Culture-expanded (2 RCTs)
Culture-expansion unknown (1 NRCS)

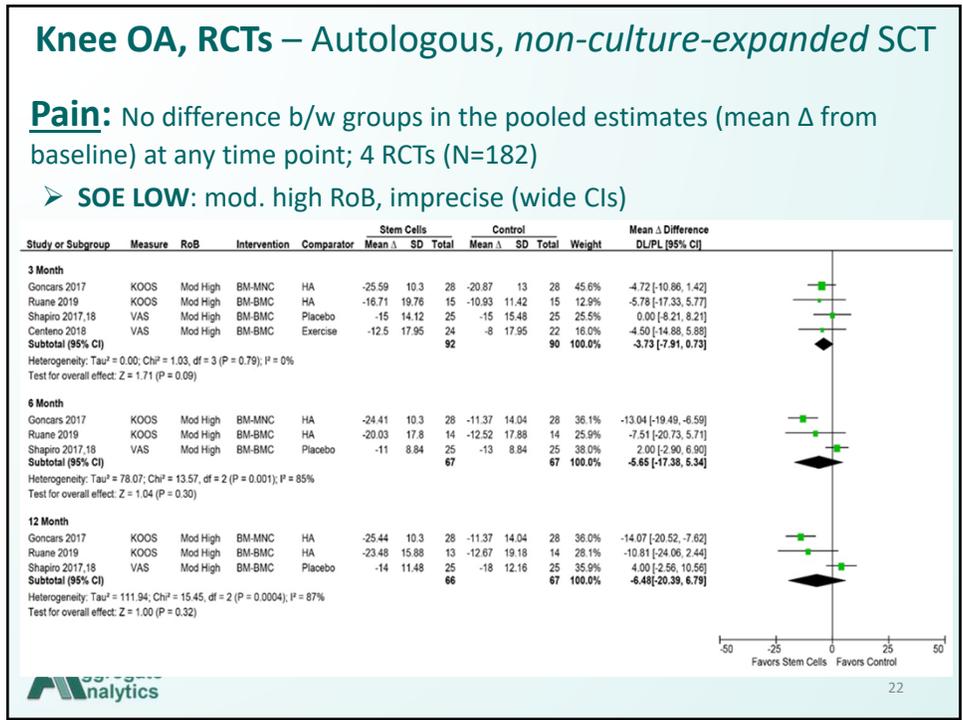
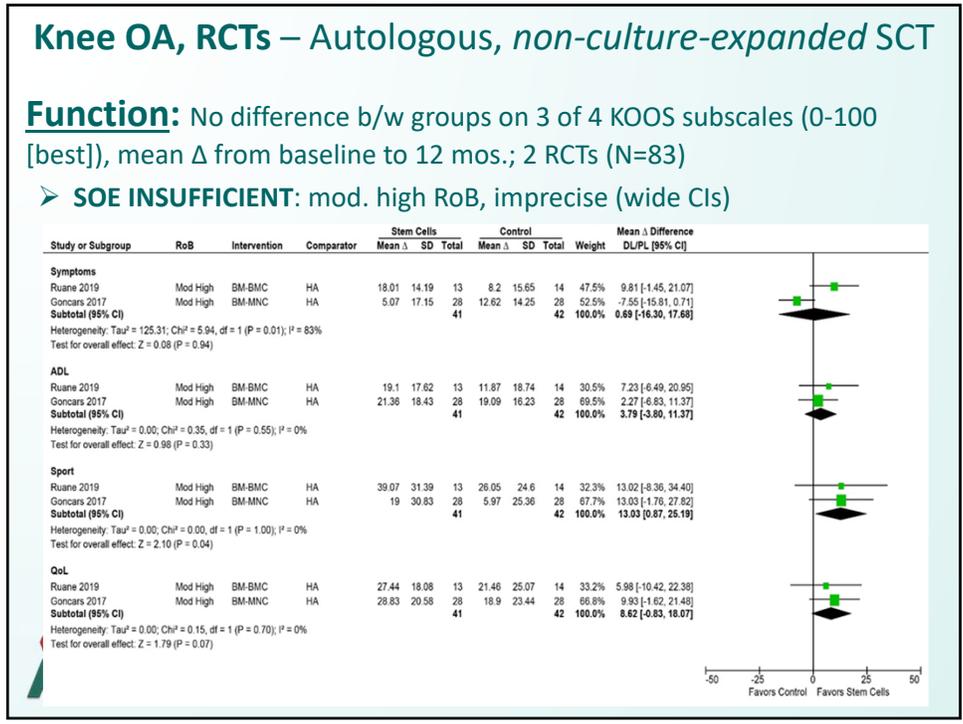


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Knee OA, RCTs – Patient, Procedure Characteristics, autologous, non-culture-expanded stem cells

	Shapiro 2017/2018 (N=50 knees in 25 patients)		Centeno 2018 (N=48)		Ruane 2019 (N=32)		Goncars 2017 (N=56)		Tucker 2019 (N=39)		
	BMC (n=25 knees)	Placebo (n=25 knees)	BMC (n=26)	Exercise (n=22)	BMC (n=17)	Gel-One® Hyaluronate (n=15)	BM-MNC (n=28)	HA (n=28)	Low-dose AD-SVF (n=13)	High-dose AD-SVF (n=13)	Placebo (n=13)
Males, %	28%		NR	NR	53%	67%	54%	36%	31%	54%	46%
Mean age, years	Median, 60		54	57	58	59	53	59	60.5	59.5	57.1
K-L OA grade	I: 8% II: 44% III: 48%	I: 8% II: 64% III: 28%	II: 42% III: 58%	II: 45% III: 55%	I: 29% II: 35% III: 35%	I: 13% II: 53% III: 33%	II: 32% III: 68%	II: 25% III: 75%	II: 31% III: 69%	II: 31% III: 69%	III: 69%
Co-morbidities	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Concomitant meds	Pain medication use discouraged		NR		No NSAIDs or oral steroids 2 wks. prior to tx		NSAID use ≤1 week during observation period		None allowed 7 days prior to any visit; oral steroids not allowed		
Patient blinded?	Yes		No		No		No		Yes		
Cell type(s) reported	BMC containing MSCs, platelets, HSCs, and red and white blood cells	NA	BMC containing MSCs, platelets, HSCs, and macrophages	NA	NR	NA	Mononuclear cells	NA	Nucleated SVF cells		NA
Stem cell count, mean ± SD (range)	Median total HSCs and MSC: 4,620,000 (174,000 to 130,200,000) and 34,400 (435 to 1,449,000)	NA	Total nucleated cell count: 622 ± 235 million	NA	NR	NA	Total mononuclear cells: 38.64 ± 33.7 x 10 ⁶ (8.3 x 10 ⁶ to 158.8 x 10 ⁶)	NA	15 x 10 ⁶ (12.5 x 10 ⁶ to 17.2 x 10 ⁶)	30 x 10 ⁶ (27.5 x 10 ⁶ to 32.5 x 10 ⁶)	NA
Other injectate	PPP	None	PRP and PL	NA	PRP	None	NaCl	None	None	None	NA
No. of injections	1	1	1	NA	1	1	1	3	1	1	1
Local anesthetic	NR		NR	NA	None	Vasocoolant spray	None		Lidocaine (dose NR)		
Imaging guidance	Ultrasound		Fluoroscopy w/ contrast	NA	Ultrasound		None		Ultrasound		
Post-treatment care	None; pain medication use discouraged		Weight-bearing w/ brace, activity modification, PT	NA	NR		Activity modification; short-term analgesic; maintained previous SYSODDA drug use		Crutches/non-weight bearing 2 wks; encouraged to bend and flex knee		





Knee OA, RCTs – Patient, Procedure Characteristics, autologous, culture-expanded stem cells

	Lamo-Espinosa 2018 (N=30)			Emadedin 2018 (N=47)		Lu 2019 (N=52)		Lee 2019 (N=24)		Freitag 2019 (N=30)		
	Low dose BM-MSCs (n=10)	High dose BM-MSCs (n=10)	HA (n=10)	BM-MSCs (n=19)	Placebo (n=24)	AD-SVF (haMPCs; Rejoin [®]) (n=26)	HA (n=26)	AD-MSCs (n=12)	Placebo (n=12)	AD-MSCs (x1) (n=10)	AD-MSCs (x2) (n=10)	Usual care (n=10)
Males, %	40%	80%	70%	63.2%	62.5%	12%	12%	25%	25%	70%	40%	50%
Mean age, years	65.9	57.8	60.3	51.7	54.7	55	60	62.2	63.2	54.6	54.7	51.6
K-L OA grade	II: 10% III: 20% IV: 70%	II: 30% III: 30% IV: 40%	II: 40% III: 20% IV: 40%	II: 10.5% III: 68.4% IV: 21.1%	II: 4.2% III: 83.3% IV: 12.5%	I: 4% II: 35% III: 62%	I: 8% II: 31% III: 62%	II: 50% III: 50% IV: 0%	II: 41.7% III: 50% IV: 8.3%	NR	NR	NR
Co-morbidities	NR			NR		NR		NR		NR		
Concomitant meds	NR			NR		NR		Acetaminophen ≤ 4,000 mg†		NR		
Patient blinded	Yes			Yes		Yes		Yes		No		
Total concentration of cells	10x10 ⁶	100x10 ⁶	NA	40x10 ⁶	NA	5x10 ⁷	NA	1x10 ¹⁰	NA	104 million ± 8	95 million ± 11 (#1); 103 million ± 8 (#2)	NA
Other injectate	1 HA injection	1 HA injection	None	saline + 2% human serum albumin		None		Saline (NaCl 9 mg/ml)		Sterile isotonic normal saline		NA
Local anesthetic	NR			NR		NR		NR		1% lidocaine (2 ml)		NA
No. of injections	1	1	1	1	1	2	4	1	1	1	2 (2nd @ 6 mos.)	0
Imaging guidance	None			Radiographic		NR		Ultrasound		Ultrasound		
Post-treatment care	NR			NR		Rest for 24 hours following each injection		No specific physical limitation was recommended		Analgesia PRN; crutches/non-weight bearing 4 wks.; ROM, exercise education		

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Knee OA, RCTs – Autologous, culture-expanded SCT

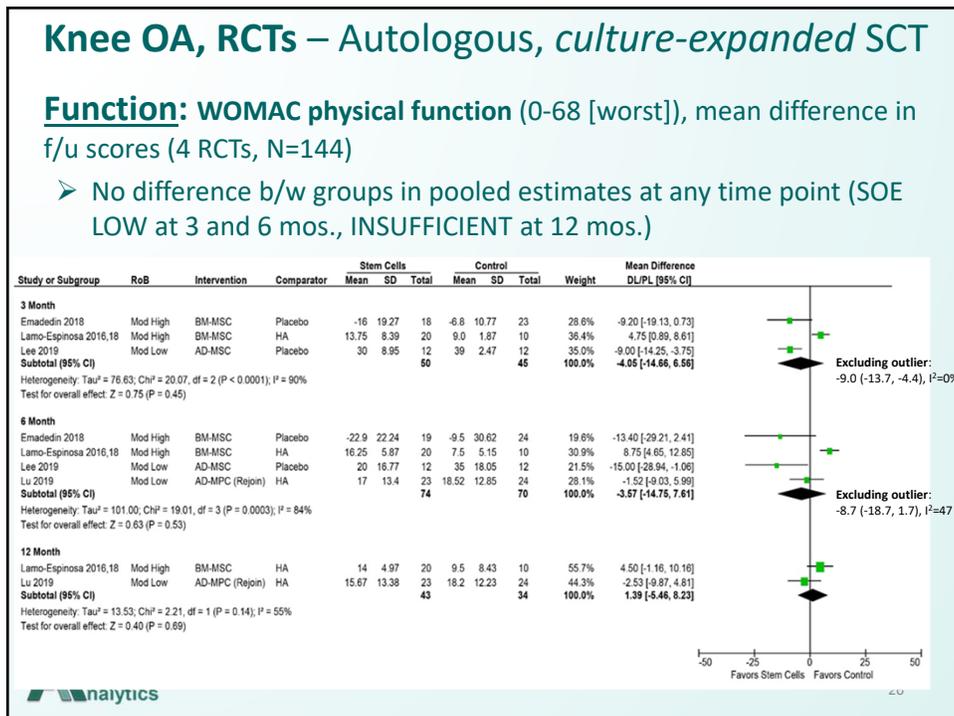
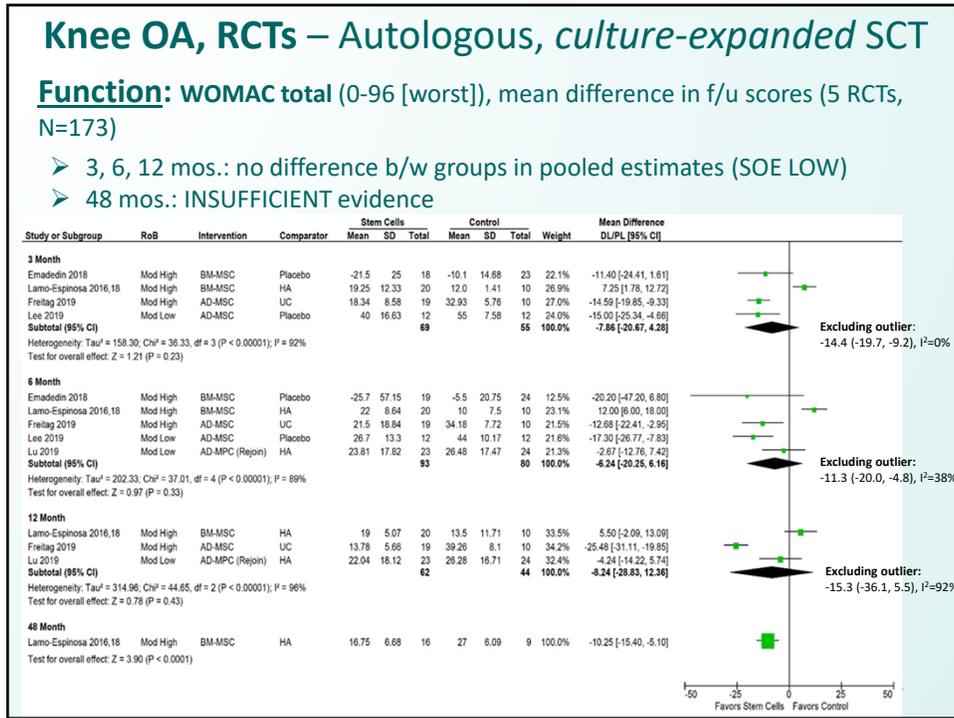
Function “Success”

- Defined differently and at different timepoints across all 3 RCTs
 - 20%, 50%, 70% ↑ on WOMAC total at 6 and 12 mos.
 - MCID of 9.3 pts. and PASS (NOS) on WOMAC physical function at 3 and 6 mos.
 - MCID of 8 pts. on WOMAC total and KOOS Symptoms, ADL and Sport at 12 mos.
- Statistically significant differences favoring SCT seen at 12 mos. for:

Author	Outcome	SCT	Control	RR (95% CI)
Lu 2019 <i>AD-MPC vs. HA</i>	WOMAC total, 50% ↑	35% (9/26)	4% (1/26)	9.0 (1.2 to 66.1)
Freitag 2019 <i>AD-MSC vs. Conservative</i>	WOMAC total, MCID 8 pts	95% (18/19)	20% (2/10)	4.7 (1.4, 16.4)
	KOOS ADL, MCID 8 pts	84% (16/19)	30% (3/10)	2.8 (1.1, 7.4)
	KOOS Sport, MCID 8 pts	89% (17/19)	30% (3/10)	3.0 (1.1, 7.8)

SOE INSUFFICIENT: RCTs mod. high RoB; inconsistent results across trials and thresholds; imprecise (small N's, wide CIs)

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Knee OA, RCTs – Autologous, culture-expanded SCT

Pain “Success”

- Defined differently across 2 RCTs
- More AD-MSK vs. conservative care patients achieved success at 12 months in 1 RCT [Emadedin]:
 - **NRS pain (MCID 1 point):** 95% (18/19) vs. 40% (4/10); RR 2.4 (95% CI 1.1 to 5.1)
 - **KOOS pain (MCID 8 points):** 84% (16/19) vs. 10% (1/10); RR 8.4 (95% CI 1.3 to 54.6)
- No difference between BM-MSK vs. placebo at 3 and 6 months for **WOMAC pain (MCID 9.7 points and PASS)** in 1 RCT (N=43) [Freitag]

SOE INSUFFICIENT: both RCTs mod. high RoB; inconsistent results across trials and thresholds; imprecise (small N's, wide CIs)

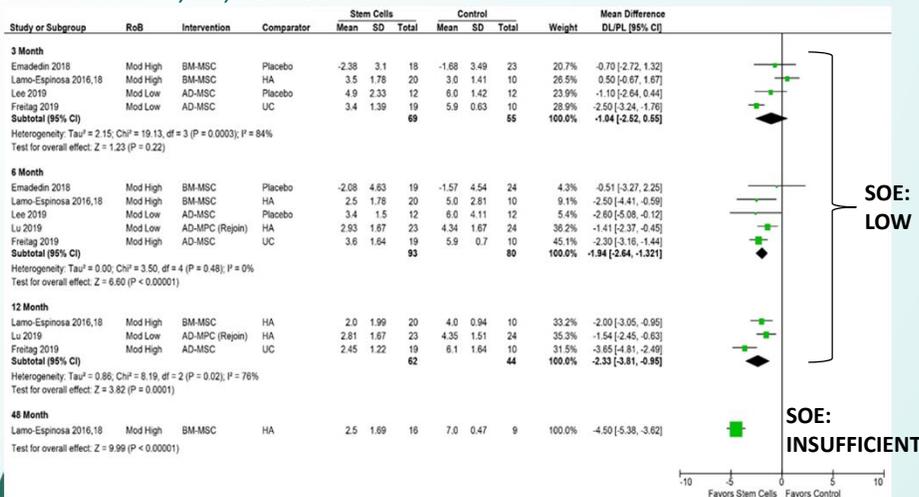


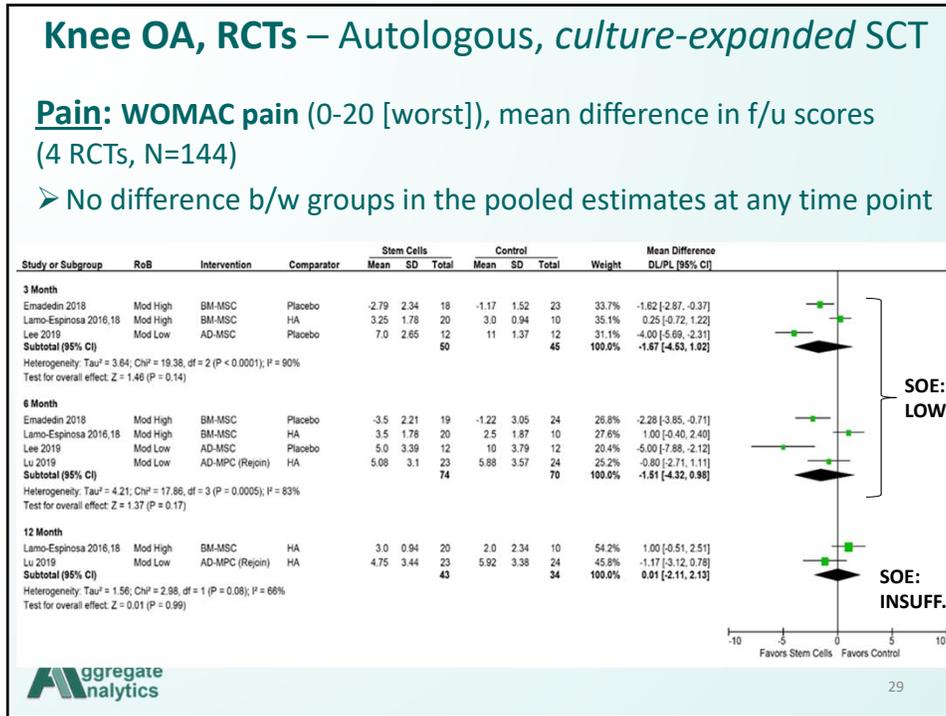
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Knee OA, RCTs – Autologous, culture-expanded SCT

Pain: VAS pain (0-10), mean difference in f/u scores (5 RCTs, N=173)

- No difference in pooled estimates at 3 mos.; less pain with SCT vs. controls at 6, 12, 48 mos.





Knee OA, RCTs – Patient, Procedure Characteristics, allogenic, culture-expanded stem cells

	Khalifeh Soltani 2019 (N=20)		Vega 2015 (N=30)	
	Placenta-derived MSCs (n=10)	Placebo (n=10)	BM- MSCs (n=15)	HA injection (Durolane®) (n=15)
Males, %	10%	10%	40%	33%
Mean age, years	57.5	55.8	57	57
K-L OA grade	II/III: 90% IV: 10%		II: 40% III: 40% IV: 20%	II: 47% III: 33% IV: 20%
Comorbidities	NR		NR	
Concomitant meds	NR		NR	
Patient blinded?	Yes		Yes	
Stem cell source (volume)	Donor placenta	NA	Bone marrow	NA
Cell type(s) reported	MSCs	NA	MSCs	NA
Stem cell count, mean ± SD (range)†	0.5-0.6x10 ⁸	NA	40x10 ⁶ cells/knee from a 5x10 ⁶ cell/mL suspension	NA
Local anesthetic used	NR	NR	No	NR
Other injectate (w/ stem cells)	None		None	
No. of injections	1		1	
Imaging guidance	NR		NR	
Post-treatment care	Immediate return to ADLs; heavy lifting and prolonged walking restricted for 1-wk.		NR	

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Knee OA, RCTs – Allogenic, culture-expanded SCT

Function: 1 RCT, N=30 (Vega 2015)

- Better function with BM-MSCs vs. HA; only the differences at 6 (both measures) and 12 (Lequesne) mos. statistically significant.

Outcome Measure (scale)	F/U	BM-MSC (n=15) mean ± SD	HA (n=15) mean ± SD	MD (95% CI)
WOMAC total (0-100 [worst])	Baseline	41 ± 11.6	45 ± 11.6	
	3 mos.	33 ± 19.4	41 ± 23.2	-8.0 (-24.0 to 8.0)
	6 mos.	28 ± 15.5	40 ± 15.5	-12.0 (-23.6 to -0.4)
	12 mos.	28 ± 19.4	41 ± 23.2	-13.0 (-29.0 to 3.0)
Lequesne (0-100 [worst])	Baseline	39 ± 15.5	45 ± 15.5	
	3 mos.	36 ± 15.5	40 ± 15.5	-4.0 (-15.6 to 7.6)
	6 mos.	25 ± 15.5	40 ± 15.5	-15.0 (-26.6 to -3.4)
	12 mos.	30 ± 11.6	42 ± 19.4	-12.0 (-23.9 to -0.1)

- SOE INSUFFICIENT: mod. high RoB, imprecise (small N, wide CIs)

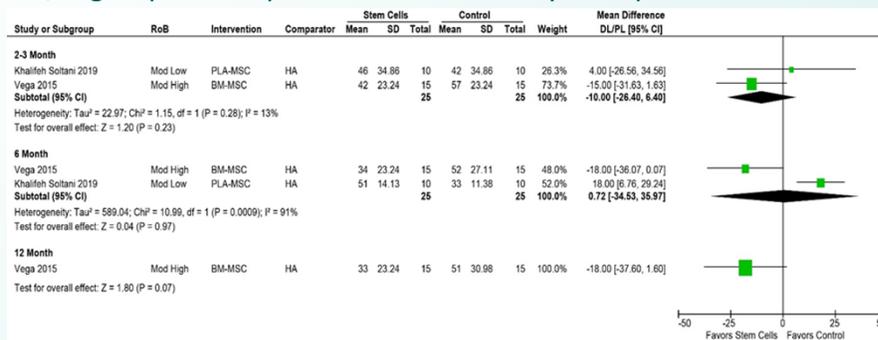


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Knee OA, RCTs – Allogenic, culture-expanded SCT

Pain: 2 RCTs, N=50

- VAS pain (0-10), mean difference in f/u scores: No difference b/w groups in the pooled estimate at any time point.



- WOMAC pain (0-20), 1 RCT, N=30 (Vega 2015): no difference b/w BM-MSC vs. HA at 3, 6, or 12 mos.



SOE INSUFFICIENT: mod. high RoB, imprecise (small N, wide CIs)

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Knee OA, SAFETY – Autologous, non-culture-expanded SCT

SOE: LOW		SCT	Control
Pain or swelling	3 RCTs	62% (16/26); 4% (1/26); “common”	NR
	1 RCT	4% (1/26)	0% (1/13)
Swelling	4 case series	17% (5/30) to 90% (69/75 knees) [3 series]; “common”	-----
	2 case series	41% (31/75 knees), 82% (57/70 patients)	-----
Pain and swelling	3 case series	“common” [2 series], “majority”	-----
	1 registry	4.3% (36/840 procedures); 63.2% of 57 total AEs	-----
Effusion	1 RCT	1 wk: 60% (15/25 knees)	24% (6/25 knees)
		6 mos.: 12% (3/25 knees)	8% (2/25 knees)
		12 mos.: 8% (2/25 knees)	4% (1/25 knees)
Effusion req. aspiration	1 RCT	4% (1/26)	NR



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Knee OA, SAFETY, cont. – Autologous, non-culture-expanded SCT

SOE: INSUFFICIENT		SCT	Control
All-cause mortality	2 RCTs	0% (0/43)	0% (0/28)
	1 registry	0.2% (2/840 procedures); 3.5% of 57 total AEs	-----
SAEs	4 RCTs	0% (0/94)	0% (0/75)
	3 case series	0% (0/115)	-----
	1 registry	0.4% (3/840 procedures); 5.3% of 57 total AEs	-----
Infection (non-serious)	1 RCT	8% (2/26)	0% (1/13)
	3 case series	0% (0/111)	-----
Neurologic; Neoplasm; Allergic Reaction; Cardiac; Bleed/Hematoma	1 registry	For each: 0.2% (2/840 procedures); 3.5% of 57 total AEs	-----
Def. injectate-related	1 registry	0.5% (4/840 procedures); 7.0% of 57 total AEs	-----
Poss. injectate-related		2.9% (24/840 procedures); 42.1% of 57 total AEs	-----
Def. procedure-related	1 registry	1.1% (9/840 procedures); 15.8% of 57 total AEs	-----
Poss. procedure-related		3.5% (29/840 procedures); 50.9% of 57 total AEs	-----



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Knee OA, SAFETY – Autologous, culture-expanded SCT

SOE: LOW		
Any treatment-related AE (non-serious, time-limited)	2 RCTs: SCT vs. placebo	100% (22/22) vs. 24% (6/25), RR 4.2 (2.1–8.4); 67% (8/12) vs. 8% (1/12); RR 8.0 (1.2–54.5)
	1 RCT: SCT vs. UC	1 injection: 80% (8/10) vs. NR 2 injections (baseline): 90% (9/10) vs. NR 2 injections (6 months): 100% (10/10) vs. NR
Joint pain; pain in injected joint	1 RCT: SCT vs. placebo	50% (6/12) vs. 0% (0/12), p=0.006
	1 RCT: SCT vs. HA	Low-dose SCT, 30% (3/10) vs. High-dose SCT, 60% (6/10) vs. HA, 10% (1/10); p=NS for all
	4 case series	Range, 23% (3/13) to 50% (25/50) [total N=90]



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Knee OA, SAFETY, cont. – Autologous, culture-expanded SCT

SOE: INSUFFICIENT		SCT	Control
All-cause mortality	1 RCT	0% (0/26)	0% (0/26)
SAEs	4 RCTs	0% (0/78)	2% (1/58) [w/ HA]
	3 case series	0% (0/115)	-----
“Severe” treatment-related AEs	1 RCT	10% (2/20) [pain, swelling impacting ADLs for 4 wks.]	NR [usual care]
Effusion	1 RCT	17% (2/12)	8% (1/12)
	2 case series	10% (1/10) to 25% (3/12)	-----
Infection, treatment-related	2 RCTs	2.1% (1/48) [w/ BM-MSCs]	1.9% (1/51) [w/ HA]
	1 case series	0% (0/20)	-----
Musculoskeletal and connective-tissue disorder, treatment-related	1 RCT	Any: 82% (18/22) Grade 3: 5% (1/22)	Any: 20% (5/25) Grade 3: 8% (2/25)
Joint swelling	2 case series	7% (1/15) [mild]; “most” pts.	-----



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Knee OA, SAFETY – Allogenic, *culture-expanded* SCT

➤ All Insufficient SOE

- No SAEs related to treatment, 1 small RCT (N=30), BM-MSCs vs. HA [Vega]
- Pain, effusion and/or swelling at injection site common, 2 small RCTs (N=50)
 - PL-MSCs vs. placebo: 40% (4/10) vs. 0% (0/10) [Khalifeh Soltani]
 - BM-MSCs vs. HA: 53% (8/15) vs. 60% (9/15) [Vega]



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DEGENERATIVE DISC DISEASE (DDD)

Autologous

Nonculture-expanded (3 case series)

Culture-expanded (2 case series)

Allogenic

Culture-expanded (1 RCT)



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DDD – Allogenic, *culture-expanded* SCs

1 small RCT (N=24) [Noreiga 2017]

- No difference between groups in function or pain at any time-point

F/U (mos.)	Function - ODI [0-100% (worst)] Mean ± SD			Pain - VAS [0-100 (worst)] Mean ± SD		
	BM-MSC (n=12)	Sham (n=12)	MD* (95% CI)	BM-MSC (n=12)	Sham (n=12)	MD* (95% CI)
Baseline	34 ± 23	24 ± 14	10 (-6.1, 26.1)	67 ± 26	62 ± 23	5 (-15.8, 25.8)
3 mos.	16 ± 20	25 ± 15	-9 (-23.9, 6.0)	43 ± 30	46 ± 27	-3 (-27.2, 21.2)
6 mos.	20 ± 24	30 ± 20	-10 (-28.7, 8.7)	40 ± 29	51 ± 29	-11 (-35.5, 13.5)
12 mos.	22 ± 24	34 ± 25	-12 (-32.7, 8.7)	47 ± 36	47 ± 28	0 (-27.3, 27.3)

sham = 1% mepivacaine into paravertebral musculature

- **SOE INSUFFICIENT:** mod. high RoB, imprecise (small N, wide CIs)



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TENDINOPATHY

Autologous, Nonculture-expanded

Achilles Tendinopathy (1 RCT)

Elbow Tendinopathy (1 case series)



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Tendinopathy – Autologous, *nonculture-expanded* SCs

1 small RCT (N=44) [Uselli 2018], Achilles Tendinopathy

- Improved function and pain with SVF vs. PRP based on AOFAS at 2 wks. and VAS pain at 2 wks., 1 mo. only (NS for all other results)

F/U (mos.)	FUNCTION (mean ± SD)				PAIN (mean ± SD)	
	VISA-A [0-100 (best)]		AOFAS [0-100 (best)]		VAS [0-10 (worst)]	
	SVF (n=21)	PRP (n=23)	SVF (n=21)	PRP (n=23)	SVF (n=21)	PRP (n=23)
Baseline	41.6 ± 13.6	46.5 ± 23.6	63.4 ± 20.1	63.2 ± 17.7	6.5 ± 1.6	6.3 ± 1.2
2 wks.	43 ± NR	43 ± NR	80 ± NR	67 ± NR	2.5 ± NR	4.4 ± NR
1 mo.	59 ± NR	47 ± NR	80 ± NR	72 ± NR	2.0 ± NR	3.8 ± NR
2 mos.	66 ± NR	59 ± NR	85 ± NR	79 ± NR	1.8 ± NR	2.5 ± NR
6 mos.	71 ± NR	71 ± NR	87 ± NR	87 ± NR	1.8 ± NR	1.8 ± NR

Bold indicates p value < 0.05

SOE INSUFFICIENT: mod. high RoB, imprecise (small N, no measure of variance)



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DDD, TENDINOPATHY – SAFETY

DDD

- No SAEs (treatment-related or otherwise) reported by any study
 - Autologous, non-culture-expanded (3 case series, N=51)
 - Autologous, culture-expanded (2 case series, N=20)
 - Allogenic, culture-expanded (1 RCT, N=24; MSC vs. Sham) [Noriega 2017]

TENDINOPATHY (all SCT autologous, non-culture-expanded)

- No AEs in 1 RCT (N=44, SVF vs. PRP; Achilles) [Uselli 2018], 1 case series (N=30, BMC; Elbow)
- Hematoma/discomfort at harvest site in 25% (5/21) of SVF patients the RCT



➤ **SOE INSUFFICIENT for all**

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OTHER CONDITIONS

Hip OA (1 registry, 2 case series)

Hip and/or Knee OA (1 case series)

Shoulder OA (1 registry, 1 case series)

ACL Tear (1 registry)

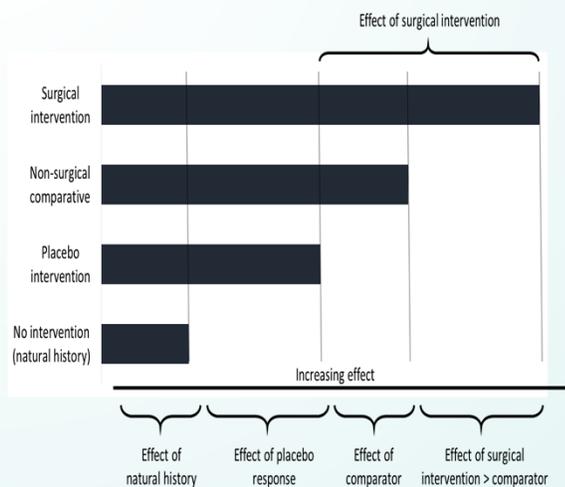
Rotator Cuff Tear (1 cohort, 1 registry)

Mixed Conditions (3 registries, 3 case series)



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Conceptual contribution of effects following an intervention



- Treatment response is more than the effect of a given treatment: culture, presentation and ceremony around the treatment and expectation of provider and patient impact outcome
- The placebo response heightens the significance of having a comparative group to evaluate treatment effectiveness; case series should rarely be interpreted as supporting treatment effectiveness



Dettori, JR, et. al. Global Spine Journal Vol. 9(6) 680-683

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Summary – Efficacy, Effectiveness

		Function Favors SOE				Pain Favors SOE			
		3 mos.	6 mos.	12 mos.	48 mos.	3 mos.	6 mos.	12 mos.	48 mos.
Knee OA	Autologous, nonculture-expanded	insufficient evidence	insufficient evidence	insufficient evidence	no evidence	⊖ LOW (4 RCTs)	⊖ LOW (3 RCTs)	⊖ LOW (3 RCTs)	no evidence
	Autologous, culture-expanded	"Success"				"Success"			
		insufficient evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence	no evidence
		WOMAC total				VAS			
		⊖ LOW (4 RCTs)	⊖ LOW (5 RCTs)	⊖ LOW (3 RCTs)	insufficient evidence	⊖ LOW (4 RCTs)	↑ (? MCID) LOW (5 RCTs)	↑ (? MCID) LOW (3 RCTs)	insufficient evidence
WOMAC physical, stiffness				WOMAC-pain					
	⊖ LOW (3 RCTs)	⊖ LOW (4 RCTs)	insufficient evidence	no evidence	⊖ LOW (3 RCTs)	⊖ LOW (4 RCTs)	insufficient evidence	no evidence	
	insufficient evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	insufficient evidence	no evidence	
DDD	Allogenic, culture-expanded	insufficient evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	insufficient evidence	no evidence
Tendinopathy	Autologous, nonculture-expanded	insufficient evidence	insufficient evidence	no evidence	no evidence	insufficient evidence	insufficient evidence	no evidence	no evidence


⊖ = no diff. b/w SCT vs. controls
↑ = SCT favored vs. controls
MCID = clinically significant
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Challenges to drawing conclusions regarding EFFICACY or EFFECTIVENESS

- Substantial heterogeneity in patient populations, stem cell sources and preparations
- Inadequate characterization of injectate cellular composition and stem cell concentration and characterization (particularly for autologous, minimally manipulated cell studies)
- Use of adjunctive biological components, pre/post injections; inadequate reporting of co-interventions (e.g. NSAID use) or post treatment rehabilitation
- Small sample sizes, no long-term follow-up; poor quality studies, potential publication bias


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Summary – Safety

		Safety SOE						
		All-cause mortality	SAEs	Neurologic, neoplasm, allergic reaction, cardiac, bleeding/hematoma	Pain and/or swelling at injection site, in joint	Effusion	Treatment, injectate, and/or procedure related AEs	Infection (non-serious)
Knee OA	Autologous, nonculture-expanded	insufficient evidence	insufficient evidence	insufficient evidence	4% to 82% LOW (3 RCTs, 8 CS)	4% to 8% LOW (2 RCTs)	insufficient evidence	insufficient evidence
	Autologous, culture-expanded	insufficient evidence	insufficient evidence	no evidence	23% to 60% LOW (2 RCTs, 4 CS)	insufficient evidence	67% to 100% LOW (3 RCTs)	insufficient evidence
	Allogenic, culture-expanded	no evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence	no evidence
DDD	Autologous, nonculture-expanded	no evidence	no evidence	no evidence	no evidence	no evidence	insufficient evidence	no evidence
Achilles Tendinopathy	Autologous, nonculture-expanded	no evidence	no evidence	no evidence	no evidence	no evidence	insufficient evidence	no evidence



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Challenges to drawing conclusions regarding SAFETY

- AEs variably defined and adjudicated; studies did not describe potential treatment-specific (i.e. injectate-related) AEs *a priori* leading to concerns regarding possible reporting bias
- No differentiation between AEs that could be due to the injection procedure, the injectate components (stem cell preparation and/or added components) or both
- Short follow-up (≤ 12 months) precludes evaluation of long-term consequences (e.g. neoplasia)
- Sample sizes were likely inadequate to detect all but extremely common events



Questions?



<https://www.docwirenews.com/docwire-pick/future-of-medicine-picks/top-potential-uses-of-stem-cells-in-medicine/>
<https://stemcellthailand.org/therapies/knee-injury-acl-mcl-pcl-surgery-alternative/>

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Appendix/Additional Slides



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Knee OA, RCTs – Autologous, *non-culture-expanded* SCT

Other Function: SOE INSUFFICIENT for all

- RCTs mod. high RoB, small sample sizes, imprecise (wide CIs)
- No difference b/w groups (BMC or BM-MNC vs. HA or Exercise) in mean Δ from baseline
 - **KOOS ADL, Sport, and Symptoms** subscales (1 RCT, N=30), 3 and 6 mos.
 - **KSS Function Score**, 3 mos. (1 RCT, N=46) or 12 mos. (1 RCT, N=56)
 - **KSS Knee Score**, 12 mos. (1 RCT, N=56)
- Greater improvement with BMC vs. Exercise/Usual Care versus in **KSS Knee scores** at 3 mos.: mean change 12 vs. 0.6 points, $p < 0.001$ (1 RCT, N=45)



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Knee OA, RCTs – Autologous, *non-culture-expanded* SCT

Secondary outcomes:

- **Quality of Life (2 RCTs):** no differences in mean change from baseline
 - BMC vs. HA (Ruane 2019): KOOS QoL, PROMIS scales at 3, 6, 12 mos.
 - BMC vs. Exercise (Centeno 2018): SF-12 PCS/MSD at 3 mos.
- **Secondary procedures (4 RCTs), F/U range 6-24 months:**

Author	
Centeno 2018	BMC vs. Exercise/UC (NR by tx arm) <ul style="list-style-type: none"> • TKA: n=3 (at 3, 6, 12 mos.) • Additional tx (e.g., HA injection): n=7 • PRP injections for recurrent knee pain: n=17 (19 procedures)
Tucker 2019	High dose vs. low dose SVF vs. placebo <ul style="list-style-type: none"> • TKA: 8% (1/13) vs. 0% (0/13) vs. 0% (0/13)
Ruane 2019	BMC vs. HA <ul style="list-style-type: none"> • Additional tx (NOS): 12% (2/17) vs. 7% (1/15)
Shapiro 2018	BMC vs. Placebo <ul style="list-style-type: none"> • None (surgery or additional injections); N=50 knees, 25 patients



52

Knee OA, Cohort – Autologous, *non-culture-expanded* SCT

1 small nonrandomized cohort: BM-MSC vs. acetaminophen [NO SOE]

- SCT superior to acetaminophen for all measures at all timepoints ($p < 0.001$ for all) (baseline scores similar when reported)

F/U	FUNCTION, mean \pm SD [0-100 (best)]						PAIN, mean \pm SD			
	WOMAC total		WOMAC physical		WOMAC stiffness		WOMAC pain [0-100 (best)]		VAS pain [0-10 (worst)]	
	SCT (n=26)	Control (n=25)	SCT (n=26)	Control (n=25)	SCT (n=26)	Control (n=25)	SCT (n=26)	Control (n=25)	SCT (n=26)	Control (n=25)
Baseline	62.6 \pm 18.6	69.9 \pm 17.9	NR	NR	NR	NR	NR	NR	5.3 \pm 2.2	4.3 \pm 2.4
1 mo.	88.6 \pm 17.1	69.9 \pm 14.9	87.6 \pm 17.6	73.3 \pm 16.2	88.9 \pm 20.3	67.6 \pm 23.6	88.7 \pm 17.2	70.4 \pm 17.4	1.6 \pm 2.0	4.2 \pm 2.7
6 mos.	91.7 \pm 9.5	73.0 \pm 15.0	91.5 \pm 9.8	72.3 \pm 14.8	92.3 \pm 11.2	70.0 \pm 21.7	92.3 \pm 9.4	68.8 \pm 18.4	0.9 \pm 1.3	4.6 \pm 2.4

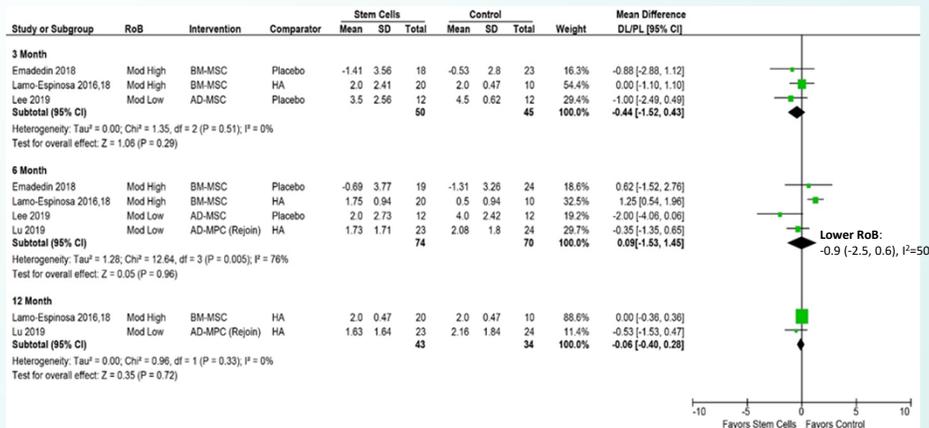


53

Knee OA, RCTs – Autologous, *culture-expanded* SCT

Function: WOMAC stiffness (0-8 [worst]), mean difference in f/u scores (4 RCTs, N=144)

- No difference b/w groups at any timepoint (SOE LOW at 3 and 6 mos., INSUFFICIENT at 12 mos.)



54

Knee OA, RCTs – Autologous, *culture-expanded* SCT

Function and Pain: KOOS subscales (0-100 [best]), mean difference in f/u scores [NO SOE]

- 2 RCTs (N=53) [Freitag, Lee], AD-MSCs vs. Placebo or Conservative
 - **3 mos.:**
 - Function: no difference b/w groups on any subscale
 - Pain: less pain with AD-MSC; pooled MD 17.4 (95% CI 7.6 to 21.3), $I^2=0\%$
 - **6 mos.:** pooled estimates favored SCT on all subscales:
 - ADL: MD 11.9 (95% CI 4.5 to 19.2), $I^2=0\%$
 - Sport: MD 21.5 (95% CI 8.7 to 34.2), $I^2=26\%$
 - Symptoms: MD 19.9 (95% CI 5.0 to 34.7), $I^2=77\%$
 - Pain: MD 14.4 (95% CI 7.6 to 21.3), $I^2=0\%$



55

Knee OA, RCTs – Autologous, *culture-expanded* SCT

Secondary outcomes:

- **KOOS QoL:** 2 RCTs (N=53); AD-MSCs vs. conservative care (Freitag 2019) or placebo (Lee 2019)
 - No difference at 3 mos. (pooled MD 9.4, 95% CI -8.4 to 27.3; $I^2=84\%$) but better QOL with AD-MSCs at 6 mos. (pooled MD 16.6, 95% CI 4.6 to 28.6; $I^2=56\%$) and 12 mos. in 1 RCT vs. conservative care (MD 25.2, 95% CI 1.63 to 34.0)
- **Secondary procedures** (2 RCTs)
 - **TKA:** BM-MSCs (+HA) [**5% (1/20)**] vs. HA alone [**10% (1/10)**], 1 RCT (Lamo-Espinosa 2016/2018); AD-MPCs [**4% (1/26)**] vs. HA [**0% (0/26)**], 1 RCT (Lu 2019)
 - **PRP injections:** BM-MSCs (+HA) [0% (0/20)] vs. HA alone [20% (2/10)]



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Knee OA, cohort – Allogenic, *culture-expanded* SCT

1 small nonrandomized cohort (high RoB): Amniotic fluid vs. Triamcinolone acetone [NO SOE]

- SCT superior to control for all measures at all timepoints (p<0.01 for all) (baseline scores similar)

F/U	FUNCTION				PAIN	
	Walking distance (m/min)		mHAQ [0-3 (best)]		VAS [0-100 (worst)]	
	SCT (n=26)	Control (n=26)	SCT (n=26)	Control (n=26)	SCT (n=26)	Control (n=26)
Baseline	39.8 ± 3.8	38.6 ± 4.8	2.4 ± 0.3	2.2 ± 2	57 ± 10.2	56 ± 11.3
3 mos.	58.6 ± 6.9	51 ± 4.8	2.1 ± 0.12	2.3 ± 0.2	17 ± 3.4	21 ± 6.5
6 mos.	61.4 ± 7.2	42.2 ± 4.8	1.8 ± 0.31	2.2 ± 0.4	12 ± 4.8	32 ± 4.8



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DDD – Autologous SCs

Nonculture-expanded (3 case series)

- **Function:** improvement in ODI with BM-MSCs at 3, 6, 12 mos. (1 case series) but no difference with AD-SVF at 2 and 6 mos. (1 case series)
- **Pain:** improvement in VAS/NRS with BM-MSCs at 3, 6, 12 mos. and AD-SVF at 2 and 6 mos. (2 case series); no pain relief with hematopoietic cells from BMA (1 case series)

Culture-expanded (2 case series)

- **Function and pain** improved at 3, 6, 12 months following BM-MSCs (1 case series) and AD-MSCs + HA (1 case series); standard deviations were large



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Other Conditions – Effectiveness and Safety

- All but one study non-comparative (all HIGH RoB) – SOE INSUFFICIENT for all
- **Autologous, non-culture-expanded (13 studies):**
 - 12 used BMC, 1 used AD-MSCs (\pm PRP, PL, fat graft); N range, 10 to 1837; PT was the comparator in the cohort, N=24
- **Autologous, culture-expanded BM-MSCs (2 studies);** 1 case series (hip OA, N=10); 1 registry (mixed conditions, N=535)
- **EFFECTIVENESS:** All reported improvement in function and pain with SCT
- **SAFETY:** no serious AEs; minor complications were not uncommon and included pain at injection site (2.3% to 26.3%), swelling at injection site (4.3% to 5.2%), and skin reactions (0% to 1%)



HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective¹ as expressed by the following standards²:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms³:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

¹ Based on Legislative mandate: See RCW 70.14.100(2).

² The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

³ The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence⁴ using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

⁴ Based on GRADE recommendation: <http://www.gradeworkinggroup.org/FAQ/index.htm>

3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
 - Direct outcome or surrogate measure
 - Short term or long term effect
 - Magnitude of effect
 - Impact on pain, functional restoration, quality of life
 - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
 - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
 - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
 - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

- 1) Does the committee have enough information to identify conditions or criteria?
 - Refer to evidence identification document and discussion.
 - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
 - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
- 2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
 - What are the known conditions/criteria and evidence state
 - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Serious treatment-related AE or serious AE		
Neurologic events or nerve damage		
Allergic reaction		
Fat embolism		
Sepsis, septic arthritis		
Infection		
Joint effusion (not expected with procedure may be due to materials injected)		
All-cause mortality		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Function (validated measures)		
Pain (validated measures)		
Objectively measured medication use		
Return to normal activities (sports, work, or activity)		
Time to recovery		
Quality of life		
Patient satisfaction		
Recurrence		
Secondary procedures (e.g., surgery)		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Race		
Gender		
Ethnicity		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

Not covered Covered unconditionally Covered under certain conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

- 1) Based on public comment was evidence overlooked in the process that should be considered?
- 2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines

[From page 39 of [final evidence report](#)]

- **Centers for Medicare and Medicaid Services (CMS) National Coverage Determination**

There is no national coverage determination.

Clinical Practice Guidelines

[From page 22 of [final evidence report](#)]

The ECRI Guideline Trust (based on the former National Guideline Clearing House), PubMed, Google, Google Scholar, professional orthopedic societies, references in other publications, and the websites of the International Society for Stem Cell Research, Regenexx®, and the International Society for Cell and Gene Therapy, were searched for evidence-based clinical guidelines related to the use of stem cells for treating musculoskeletal conditions. One evidence-based clinical guideline from the American Society of Interventional Pain Physicians addressing the use of stem cell therapy in patients with low back pain was identified via the ECRI Guidelines Trust. A position statement from the Australasian College of Sports Physicians concerning the place of mesenchymal stem/stromal cell therapies in sports and exercise medicine was also identified. The International Society for Stem Cell Research (ISSCR) provides recommendations regarding the use of stem cells for treating OA, but the strength of their recommendation was not assessed.

A consensus document on optimizing use of biological therapies in orthopedics that resulted from a 2018 AAOS conference was identified; it provides recommendations for improving accountability for reporting and clinical use of cell therapies and future research. The ISSCR guideline also provides recommendations for stem cell research and clinical translation. The identified documents are summarized in Table 1 below. It should be noted that evidence used to form these guidelines and consensus statements was not exclusively focused on stem cell therapy in the outpatient setting.

Table 1. Summary of Guidelines and Consensus Statements

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
<p>American Society of Interventional Pain Physicians (ASIPP)</p> <p>2019</p> <p><i>Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: ASIPP Guidelines</i></p>	<p><u>Lumbar Disc Injections of Mesenchymal Stem Cells</u></p> <p>1 RCT, 4 case series, 4 comparative cohorts, 1 single arm meta-analysis, 2 SRs</p>	<p><u>Informed Consent</u></p> <p>A consent form should be discussed with the patient and signed by both the provider and the patient.</p> <p><u>Office Set-up</u></p> <p>The environment in which a stem cell injection occurs must be a highly aseptic environment with comprehensive controls of both raw materials and handlers. The physicians performing the procedures need to be properly trained and comfortable in performing the interventional techniques. They must be ready and available to handle any resulting complications at all times and be available on-call for emergencies that may ensue from the procedure.</p> <p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Hematologic blood dyscrasias • Platelet dysfunction • Septicemia or fever • Cutaneous infections in the area to be injected • Anemia (hemoglobin less than 10 g/dl) • Malignancy, particularly with hematologic or bony involvement • Allergy to bovine products if bovine thrombus is to be used • Severe psychiatric impairment or unrealistic expectation <p>For an autologous therapy procedure, cell harvesting from the patient will be aimed at collecting healthy cells whenever this is possible. This is an especially important consideration for patients with inherited diseases.</p> <p><u>Pre-injection Management of Patient</u></p> <ol style="list-style-type: none"> 1. The patient candidacy requirements, as emphasized above, are met. Imaging modalities must also demonstrate the pathology, and can include MRI, computed tomography (CT) scan, ultrasound, or x ray as appropriate for viewing a specific pathology. 2. The patient should avoid the use of any corticosteroids two or three weeks before the procedure. Also, NSAIDs are avoided within one week of the procedure; any necessary anticoagulation precautions should be taken before the procedure as recommended by consensus guidelines from ASIPP and American Society of Regional Anesthesia and Pain Medicine. 	<p>Level III</p>

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		<p>3. Before and during the procedure, anti-anxiety medications and mild sedation may be required for certain patients. However, deep sedation should be avoided ensuring that the patients are arousable and alert at all times.</p> <p><u>Pre-injection management of biologic materials</u></p> <ol style="list-style-type: none"> 1. To be clinically effective, it is agreed that platelet concentration in an injectate should be at least 2.5 times greater than the baseline plasma concentration. 2. The biologics follow the FDA recommended “minimal manipulation” and “homologous use” draft guidelines in clinical practice. 3. Cell viability is comparable between fresh extraction, 24 hours, and 72 hours, though proliferation may be enhanced at 24 hours. It is recommended to use the cells within 24 hours of thawing from a frozen medium if so used. 4. The tri-lineage capabilities, differentiation, and viability of MSCs are not affected by the gauge of the needle used to extract them, although it has been found that a 19-gauge needle reduced the incidence of apoptosis. 5. A 2 mL syringe is recommended to avoid over inflation. The majority of available studies are also performed with this value. <p><u>Intra-injection management</u></p> <ol style="list-style-type: none"> 1. Cell material, patient, joint location and effected side should be verified before injection. 2. Materials should be injected under direct visualization with image guidance such as with ultrasound, fluoroscopic, CT, MRI or arthroscopic/endoscopic guidance. <p><u>Post-injection management</u></p> <ol style="list-style-type: none"> 1. Patients should be instructed to rest and partially immobilize the injected body part for a few days to 2 weeks. 2. The patient should avoid anti- inflammatory medications for at least a few weeks postoperatively, as the therapy is grounded in the benefit of the patient’s inflammatory cascade. The risks and benefits for Aspirin should be reviewed in conjunction with the patient and the clinician prescribing it. 3. Post-operative instructions should be verbally discussed with the patient and the person driving the patient home. Red flags and appropriate pain control measures should also be reviewed. A written copy of the instructions should be given to the patient or the patient’s driver prior to discharge. 4. Close follow-up should be scheduled every 2-4 weeks post-procedure. Follow-ups can extend to 1 or 2 times per year once there has been a demonstration of 	

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		<p>significant subjective and objective report of improvement in pain and function and is based on the discretion of the clinic thereafter.</p> <p><u>Continued Therapy</u> 1. Repeat injections may be required, depending on the patient’s response. 2. Frequent repeat imaging is not recommended unless there has been a change in patient symptoms or pathology. However, obtaining an x-ray to determine improvement in a joint space or as an indirect assessment of cartilage interval while treating osteoarthritis or obtaining an MRI scan to identify changes in soft tissue structures including articular cartilage, may be considered necessary.</p> <p><u>Antithrombotic Therapy</u> Antithrombotic therapy should be halted (even temporarily)</p> <p><u>Adverse Reactions and Complications</u> Risks may include, but are not limited to, infection, tissue rejection and changes in the characteristics of the cells in the product that may alter how they respond. Generalized rest and restraining from the use of NSAID medications are important to optimize therapy.</p> <p>A final concern for the use of biologic therapies is the induction of neoplasms from undifferentiated cells in high volume. A multicenter analysis of over 2,300 patients treated with MSCs (bone marrow and adipose included) for musculoskeletal conditions demonstrated that after nine years, only seven patients developed a neoplasm. This is lower than the rate of neoplasm development in the general population, MSC therapy is therefore not considered causative. The review also noted that the majority of postoperative complications were very few, but included pain post-procedure (3.9%), and pain due to continued degeneration of the joint (3.8%).</p>	
International Society for Stem Cell Research (ISSCR) 2019 <i>Current State of Cell-based Therapies for Osteoarthritis</i>	1 SR, 2 RCTs, 1 comparative cohort	The effects and effectiveness of cell therapies for the treatment of OA in humans remains unproven and as such cannot be recommended at the present time.	NR
Australasian College of Sports Physicians (ACSP)	<u>Osteoarthritis</u>	1. Mesenchymal stem cell (MSC) therapies are still under investigation.	NR

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
<p>2016</p> <p>ACSP—Position Statement: <i>The Place of Mesenchymal Stem/Stromal Cell Therapies in Sport and Exercise Medicine</i></p>	<p>1 SR, 5 RCTs, 2 comparative cohorts, 21 case series</p> <p><u>Tendinopathy</u> 1 SR, 4 case series</p> <p><u>Muscle Injury</u> No evidence identified</p>	<p>2. Research evidence to date suggests MSCs may be safe in the treatment of OA and tendinopathies so that it is reasonable to proceed to further robust clinical trials with rigorous long-term follow-up.</p> <p>3. There is limited evidence that suggests that non-expanded MSC therapies do not work. Further research is required to determine the safety and efficacy of expanded MSCs with and without biological scaffolds/growth factors.</p> <p>4. There is currently insufficient evidence from high-quality clinical trials to recommend the clinical use of MSC therapies for joint or tendon regeneration.</p> <p>5. The ACSP encourages the establishment of research studies to determine the safety and efficacy of MSCs for the treatment of musculoskeletal conditions.</p> <ul style="list-style-type: none"> • Clinical research trials must be registered with an appropriate clinical research trial registry. • Any research trial must be subjected to peer review and receive human research ethics committee approval. • Any and all research findings will be shared within the scientific and medical community including adverse outcomes. <p>6. The ACSP believes that any use of MSCs for musculoskeletal conditions must fit within either of the following pathways:</p> <ul style="list-style-type: none"> • As part of a rigorous clinical research trial. • As an individualized innovative therapy. It is expected that only small numbers of patients would go through this pathway. <p>7. The use of MSCs must only be undertaken within the expectations of the relevant medical regulatory organizations.</p> <p>8. Australasian College of Sports Physicians members must inform all patients receiving MSC therapy that:</p> <ul style="list-style-type: none"> • They are part of a research trial or are receiving innovative therapy. • Mesenchymal stem cells are experimental and have not yet been proven to be safe or effective for clinical use. • The long-term harms from the use of MSCs have not been determined. • Identifiable personal patient or participant information and treatment will be entered to a database and accessed by researchers. • They may be contacted at a later date for research purposes. • Ethical approval will be sought before accessing patient data. • Any conflicts of interest held by the researcher or clinician providing innovative therapy will be declared. • The full cost of the procedure, including a full breakdown will be provided to the patient. Costs involved in MSC interventions used within research will not be passed onto participants. 	

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		<ul style="list-style-type: none"> • Informed consent to the procedure will be obtained in writing. 	
Research and clinical translation			
<p>International Society for Stem Cell Research (ISSCR)</p> <p>2016</p> <p><i>Guidelines for Stem Cell Research and Clinical Translation</i></p>	Expert Consensus	<p><u>Sourcing Stem Cells</u></p> <ul style="list-style-type: none"> • In the case of donation of cells for allogeneic use, the donor should give written and legally valid informed consent that covers, where applicable, terms for potential research and therapeutic uses, return of incidental findings, potential for commercial application, and other issues. • Donors should be screened for infectious diseases and other risk factors, as is done for blood and solid organ donation, and for genetic diseases as appropriate. • Components of animal origin used in the culture or preservation of cells should be replaced with human or chemically defined components whenever possible. • Criteria for release of cells for use in humans must be designed to minimize risk from culture-acquired abnormalities. Final product as well as in-process testing may be necessary for product release and should be specified during the review process. • Funding bodies, industry, and regulators should work to establish public repositories and databases of clinically useful lines that contains adequate information to determine the lines' utility for a particular disease therapy. <p><u>Manufacturing of Stem Cells</u></p> <ul style="list-style-type: none"> • All reagents and processes should be subject to quality control systems and standard operating procedures to ensure the quality of the reagents and consistency of protocols used in manufacturing. For extensively manipulated stem cells intended for clinical application, GMP procedures should be followed. • The degree of oversight and review of cell processing and manufacturing protocols should be proportionate to the risk induced by manipulation of the cells, their source and intended use, the nature of the clinical trial, and the number of research subjects who will be exposed to them. <p><u>Standards for Clinical Conduct</u></p> <ul style="list-style-type: none"> • Risks should be identified and minimized, unknown risks acknowledged, and potential benefits to subjects and society estimated. Studies must anticipate a favorable balance of risks and benefits. • When testing interventions in human subjects that lack capacity to provide valid informed consent, risks from study procedures should be limited to no greater 	NR

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		<p>than minor increase over minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit.</p> <ul style="list-style-type: none"> • A stem cell-based intervention must aim at ultimately being clinically competitive with or superior to existing therapies or meet a unique therapeutic demand. Being clinically competitive necessitates having reasonable evidence that the nature of existing treatments poses some type of burden related to it that would likely be overcome should the stem cell-based intervention prove to be safe and effective. • Individuals who participate in clinical stem cell research should be recruited from populations that are in a position to benefit from the results of this research. Groups or individuals must not be excluded from the opportunity to participate in clinical stem cell research without rational justification. Unless scientifically inappropriate, trials should strive to include women as well as men and members of racial and/or ethnic minorities. • Clinical research should compare new stem cell-based interventions against the best therapeutic approaches that are currently or could be made reasonably available to the local population. • Where there are no proven effective treatments for a medical condition and stem cell-based interventions involve invasive delivery, it may be appropriate to test them against placebo or sham comparators, assuming early experience has demonstrated feasibility and safety of the particular intervention. <p><u>Stem Cell-Based Medical Innovation</u></p> <ul style="list-style-type: none"> • Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial and according to the highly restrictive provisions outlined in this section. <p><u>Clinical Application of Stem Cells</u></p> <ul style="list-style-type: none"> • The introduction of novel products into routine clinical use should be dependent on the demonstration of an acceptable balance of risk and clinical benefit appropriate to the medical condition and patient population for which new treatments are designed. • Developers, manufacturers, providers, and regulators of stem cell-based interventions should continue to systematically collect and report data on safety, efficacy, and utility after they enter clinical use. • Registries of specific patient populations can provide valuable data on safety and outcomes of stem cell-based interventions within defined populations but should 	

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		<p>not substitute for stringent evaluation through clinical trials prior to introduction into standard care.</p> <ul style="list-style-type: none"> • Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties associated with stem cell-based interventions. <p><u>Access and Economics</u></p> <ul style="list-style-type: none"> • Stem cell-based interventions should be developed with an eye towards delivering economic value to patients, payers, and healthcare systems. • Developers, funders, providers, and payers should work to ensure that cost of treatment does not prevent patients from accessing stem cell-based interventions for life-threatening or seriously debilitating medical conditions. 	
Consensus document on accountability and future direction			
<p>American Academy of Orthopaedic Surgeons (AAOS)</p> <p>2018</p> <p><i>Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference</i></p>	<p>8 level I, 12 level II, 3 level III, 10 level IV studies, and 19 level V (expert opinion) publications</p>	<p>A collaborative symposium was convened to create a consensus framework for improving, and accelerating clinical evaluation, use and optimization of biologic therapies for musculoskeletal conditions in response to public demand for such therapies and concerns regarding misinformation on unproven “biologic” treatments. Authors state that misrepresentation of uncharacterized and unproven minimally manipulated products as stem cells may erode public trust and compromise development of legitimate cell therapies.</p> <p>Recommendations to improve accountability:</p> <ol style="list-style-type: none"> 1. Define Terminology to Clearly Distinguish Uncharacterized Minimally Manipulated Autologous Cell Products from Rigorously Characterized, Culture-expanded and Purified Stem Cell and Progenitor Cell Populations. <ul style="list-style-type: none"> • The term “stem cell” has been overused to include minimally manipulated cell preparations in addition to tissue-derived, culture –expanded cell preparations. • “Cell therapy” should be used for minimally manipulated cell products and tissue-derived culture-expanded cells • The untested and uncharacterized nature of these treatments should be understood by providers, communicated within the profession and to patients and the public 2. Standardize Reporting Requirements. 	<p>NR</p>

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		<ul style="list-style-type: none"> • There is substantial variability in progenitor and MSC populations isolated from a donor and variability due to preparation, age, sex, source, harvest and processing; standards are needed for characterization of products. • Minimum Information for studies reporting Biologics (MIBO) check lists should be used to guide study design and reporting. • Regarding MSC, ISCT standard can be used to indicate whether cells meet published standard <p>3. Establish Registries for Postmarket Monitoring and Quality Assessments of Biologic Therapies.</p> <p>Recommendations to accelerate discovery, development and delivery of 21st Century cures</p> <p>4. Designate Osteoarthritis (OA) as a Serious Medical Condition.</p> <p>5. Clarify, by Disease State, a Consensus Approach for Biological Markers of Interest and Clinical Trial Design.</p> <p>6. Establish the Framework for a Multicenter Knee OA Clinical Trial Consortium.</p> <p>7. Explore Accelerated Pathways for FDA Approval of New Drug Applications for Biologics to Treat Musculoskeletal Conditions</p> <p>General Recommendation: Patient demand and clinical need along with the international experience support exploration of new pathways developed through the 21st Century Cures Act to accelerate clinical evaluation of the use of autogenous cell sources and culture-expanded cell-based therapies to treat musculoskeletal conditions.</p>	

CT = computed tomography; FDA = Food and Drug Administration; GMP = Good Manufacturing Procedures; MIBO = Minimum Information for studies reporting Biologics; MRI = magnetic resonance imaging; MSC = mesenchymal stem cell; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; RCT = randomized controlled trial; SR = systematic review