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
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:

<table>
<thead>
<tr>
<th>Title</th>
<th>Business Name &amp; Address</th>
<th>Business Type</th>
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<tbody>
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</tbody>
</table>

(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:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Business Type</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Received From</th>
<th>Organization Address</th>
<th>Service Performed</th>
</tr>
</thead>
<tbody>
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</table>

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.

<table>
<thead>
<tr>
<th>Source Name &amp; Address</th>
<th>Received By</th>
<th>Source Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVERSITY OF WASHINGTON ME</td>
<td>Salary</td>
<td></td>
</tr>
<tr>
<td>Seattle Children's Hospital Spouse</td>
<td>Salary</td>
<td></td>
</tr>
<tr>
<td>CLINICAL ORTHOPAEDICS ME &amp; RESEARCH</td>
<td>Salary</td>
<td></td>
</tr>
</tbody>
</table>
(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

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(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.

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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.)

<table>
<thead>
<tr>
<th>Lobbyist Name</th>
<th>Business Name</th>
<th>Type Business Shared</th>
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</thead>
<tbody>
<tr>
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</table>

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:

<table>
<thead>
<tr>
<th>Income Source</th>
<th>Description of Income Source</th>
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</table>
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:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Description of Business</th>
</tr>
</thead>
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</table>

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.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description of Service</th>
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</table>

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

Check One: [ ] Committee Member [ ] Subgroup Member [ ] Contractor

Signature

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.)


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.


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:


24. Tsai TL, Manner PA, Li WJ. Regulation of Mesenchymal Stem Cell Chondrogenesis by Glucose through Protein Kinase C/Transforming Growth Factor Signaling. Osteoarthritis and Cartilage. 2013 21(2):368-76.


**B) Other Publications**


28. **Manner PA.** Revision for dislocation - reducing the risk *pending publication*


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*

35. **Manner PA.** Should we look again at MIS? *pending publication*


39. **Manner PA.** Treating the juvenile – the role of arthroplasty. *JBJS Orthop Highlights:*

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P. A. Manner, MD FRCS(C)
Page 25
4/1/2019
40. **Manner PA.** Selected posters from the Orthopaedic Research Society *JBJS Orthop Highlights: Hip Surg*, 2013 Mar 6;3(3):e4


43. **Manner PA.** Butt out: why smoking is bad for joints *JBJS Orthop Highlights: Hip Surg*, 2013 Apr 6;3(4):e1


55. **Manner P.** Variations: Why Does the Cost of Care Differ from Place to Place? *JBJS Orthop Highlights: Hip Surg*, 2013 Jul 6;3(7):e1


61. **Manner P.** What do patients do in the years after arthroplasty? *JBJS Orthop Highlights: Hip Surg*, 2013 Sep 4;3(9):e2


**C. Videos**

1. *Joint Replacement Video CME Course*, Network for Continuing Medical Education, Secaucus, NJ, 2005


D. Abstracts:

**Local**

1. Manner P, Billinghurst 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.*


National


International


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.*


Order of scheduled presentations:

Stem-cell therapy for musculoskeletal conditions

<table>
<thead>
<tr>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

No requests to provide public comment on this technology review were received.
Stem cell therapy for musculoskeletal conditions

- 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.
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.

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
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:

---

**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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Meets criteria</th>
<th>Doesn’t meet criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally manipulated AND Homologous use</td>
<td>More than minimally manipulated i.e. (not minimally manipulated) OR Non-homologous use</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicable regulations</th>
<th>Section 361 of the Public Health Service Act (PHS) 21 CFR Part 1271</th>
<th>Section 351 and 361 PHS Act FD + C Act 21 CFR Part 1271 Other applicable regulations</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Premarket review?</th>
<th>Does not need pre-market review</th>
<th>Requires pre-market review</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Subject to the safe tissue regulations to prevent introduction, transmission, and spread of infection</th>
<th>Can only be used in clinical trials under Investigational New Drug (IND) application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration and listing with FDA are required prior to marketing</td>
<td>Required to submit biologics license application before marketing</td>
<td></td>
</tr>
</tbody>
</table>

---


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

- 12/9/2019 FDA public safety alert on stem cell and exosome products
  - Serious AEs among multiple patients treated in Nebraska with 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

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)


Key Question 3: Differential efficacy, effectiveness, or harms

- No evidence identified
Key Question 4: Cost-effectiveness

- No evidence identified

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


National Coverage Determination (NCD)

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

Selected payers’ coverage policy

<table>
<thead>
<tr>
<th>Payer</th>
<th>Policy</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetna</td>
<td>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.</td>
<td>2019</td>
</tr>
<tr>
<td>Anthem</td>
<td>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.</td>
<td>2019</td>
</tr>
<tr>
<td>Premera Blue Cross</td>
<td>Premera Blue Cross considers mesenchymal stem cell therapy to be investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.</td>
<td>2019</td>
</tr>
<tr>
<td>Wellmark</td>
<td>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.</td>
<td>2019</td>
</tr>
</tbody>
</table>

Quoted from Evidence Report
AMDG recommendations

- Stem cell therapy for treating musculoskeletal conditions is not a covered benefit
Stem Cell Therapy for Musculoskeletal Conditions

Presentation to Washington State Health Care Authority Health Technology Clinical Committee

Erika D. Brodt, BS
March 20, 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
**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

### Table: Stem Cell Basics

<table>
<thead>
<tr>
<th>Cell Potency</th>
<th>Cell Source</th>
<th>Cell Differentiation Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totipotent Stem Cell</td>
<td>Zygote formed at egg fertilization</td>
<td>All cell types (body and extraembryonic tissues)</td>
<td>3 examples: Mesoderm, Endoderm, Ectoderm</td>
</tr>
<tr>
<td>Pluripotent Cells:</td>
<td>Embryonic cells: (5d pre-implant embryo)</td>
<td>All body cell types</td>
<td>Divide w/o differentiating in culture; cannot make extra-embryonic tissues.</td>
</tr>
<tr>
<td>Multipotent Cells:</td>
<td>Bone marrow</td>
<td>Blood cells (hematopoietic)</td>
<td>Mesenchymal Stromal Cells; (Mesenchymal Stem Cells): + tissue-specific, adult, somatic</td>
</tr>
<tr>
<td>Differentiated into</td>
<td>Adipose tissue</td>
<td>Bone, cartilage, fat (non-hematopoietic)</td>
<td>small fraction of cells contained in a sample;</td>
</tr>
<tr>
<td>specialized cells; can develop into more than one cell type; variety of sources</td>
<td>Cord blood</td>
<td>Bone, cartilage, fat, others (non-hematopoietic)</td>
<td>can be cultured to increase number &amp; give rise to various connective tissues (e.g. bone, cartilage, fat);</td>
</tr>
<tr>
<td></td>
<td>Heart tissue</td>
<td>Hematopoietic cells</td>
<td>unclear mechanism of differentiation in humans</td>
</tr>
<tr>
<td></td>
<td>Neural tissue</td>
<td>All blood cell types</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary vessels, heart muscle, (non-hematopoietic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurons, glia (non-hematopoietic)</td>
<td></td>
</tr>
<tr>
<td>Unipotent Cells:</td>
<td>Muscle cells</td>
<td>Muscle cells</td>
<td>Mesenchymal Stromal Cells; (Mesenchymal Stem Cells): + tissue-specific, adult, somatic</td>
</tr>
<tr>
<td>Differentiate to one cell lineage</td>
<td>Blood cells</td>
<td>Blood cells</td>
<td>small fraction of cells contained in a sample;</td>
</tr>
<tr>
<td></td>
<td>Epithelial cells</td>
<td>Skin cells, fibroblasts</td>
<td>can be cultured to increase number &amp; give rise to various connective tissues (e.g. bone, cartilage, fat);</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unclear mechanism of differentiation in humans</td>
</tr>
</tbody>
</table>
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.

---

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
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

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
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

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
### 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?

### PICO Scope: Inclusion Criteria

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

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Random sequence generation (RCT)</td>
</tr>
<tr>
<td>• Statement of allocation concealment (RCT)</td>
</tr>
<tr>
<td>• Intent-to-treat analysis (RCT)</td>
</tr>
</tbody>
</table>

**RCTs and observational studies**
- • Blind, independent assessment of outcomes/analysis
- • Complete follow-up of >80%
- • <10% difference in follow-up between groups
- • Controlling for possible confounding
  - • Multivariate analysis, matching (including propensity)

*case series are considered at high risk of bias

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.
**Systematic Review Process**

Studies meeting eligibility criteria
- Efficacy: RCTs; Effectiveness: Observational studies
- Harms: RCTs, Observational studies
- Full Economic studies

Risk of Bias Appraisal (Study)
- Low, Moderately Low, Moderately High, High

Overall Strength of Evidence Determination (GRADE/AHRQ)
Across comparative studies reporting primary outcomes

**Strength of Evidence Ratings**
- High: Very confident that effect is true.
- Moderate: Moderately confident.
- Low: Limited confidence.
- Insufficient: No evidence or no confidence in effect.

**Literature Search Results**

1. Total Citations (n=25,974)
   - PubMed Search, n=18,145
   - EMBASE Search, n=7,711
   - Bibliography/hand-searching, n=118
   - ClinicalTrials.gov, n=2

2. Total Citations after Deduplication (n=24,930)

3. Title/Abstract exclusion (n=24,783)

4. Retrieved for full-text evaluation (n=147)

5. Excluded at full-text review (n=93)
   (see appendix C for list of excluded articles and reasons for exclusion)

6. Publications included (n=56)
   - 14 RCTs (16 publications)
   - 3 comparative observational cohorts
   - 5 registries
   - 29 case series (32 publications)
# RESULTS

## Overview of Evidence Base

<table>
<thead>
<tr>
<th>Condition</th>
<th>KOI</th>
<th>KOII</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee OA</td>
<td>12 (54)</td>
<td>2</td>
<td>12 (54)</td>
</tr>
<tr>
<td>Degenerative Disc Disease</td>
<td>1</td>
<td>3 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Tendinopathy</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial Rotator Cuff Tear</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hip OA</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hip and/or Knee OA</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shoulder OA</td>
<td>2</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>ACL tear</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mixed Populations</td>
<td>N/A</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- **= RCT**
- **= Comparative cohort**
- **= Case series, single-arm registry**
# 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)

---

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMM (n=25 knees)</td>
<td>BMM (n=25)</td>
<td>BMM (n=23)</td>
<td>BMM (n=28)</td>
<td>BMM (n=28)</td>
</tr>
<tr>
<td>Males, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Age, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>1.8%</td>
<td>84%</td>
<td>2.7%</td>
<td>5.3%</td>
</tr>
<tr>
<td>K. OA grade</td>
<td>1.8%</td>
<td>84%</td>
<td>2.7%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>1.8%</td>
<td>84%</td>
<td>2.7%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Concentrate may be requested</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
</tr>
<tr>
<td>Cell type(s) reported</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
<td>BMM containing MSCs, platelets, HSCs, and red and white blood cells</td>
</tr>
<tr>
<td>Stem cell count, mean ± SD (range)</td>
<td>Median nucleated cell count: 0.22 ± 235 million</td>
<td>Median nucleated cell count: 0.22 ± 235 million</td>
<td>Median nucleated cell count: 0.22 ± 235 million</td>
<td>Median nucleated cell count: 0.22 ± 235 million</td>
</tr>
<tr>
<td>Other injectate</td>
<td>PPP None</td>
<td>PPP None</td>
<td>PPP None</td>
<td>PPP None</td>
</tr>
<tr>
<td>No. of injections</td>
<td>1 1 1</td>
<td>1 1 1</td>
<td>1 1 1</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>NA None</td>
<td>NA None</td>
<td>NA None</td>
<td>NA None</td>
</tr>
<tr>
<td>Imaging guidance</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Post-treatment care</td>
<td>None; pain medication use discouraged</td>
<td>Ultrasound, fluoroscopy w/ contrast</td>
<td>Ultrasound, fluoroscopy w/ contrast</td>
<td>Ultrasound, fluoroscopy w/ contrast</td>
</tr>
</tbody>
</table>

---

Centeno 2018:
- **Biologicals**: 25 knees
- **Procedure**: Ultrasound, fluoroscopy w/ contrast
- **Inclusion criteria**: Males, mean age 65, NR
- **Concomitant**: None
- **Grade**: NR
- **Cell type(s)**: BMM containing MSCs, platelets, HSCs, and red and white blood cells
- **Stem cell count**: Median nucleated cell count: 0.22 ± 235 million
- **Other injectate**: PPP
- **Local anesthetic**: NA
- **Imaging guidance**: Ultrasound
- **Post-treatment care**: None; pain medication use discouraged

Rume 2019:
- **Biologicals**: 23 patients
- **Procedure**: Ultrasound, fluoroscopy w/ contrast
- **Inclusion criteria**: Males, mean age 65, NR
- **Concomitant**: None
- **Grade**: NR
- **Cell type(s)**: BMM containing MSCs, platelets, HSCs, and red and white blood cells
- **Stem cell count**: Median nucleated cell count: 0.22 ± 235 million
- **Other injectate**: PPP
- **Local anesthetic**: NA
- **Imaging guidance**: Ultrasound
- **Post-treatment care**: None; pain medication use discouraged

Gozar 2017:
- **Biologicals**: 28 patients
- **Procedure**: Ultrasound, fluoroscopy w/ contrast
- **Inclusion criteria**: Males, mean age 65, NR
- **Concomitant**: None
- **Grade**: NR
- **Cell type(s)**: BMM containing MSCs, platelets, HSCs, and red and white blood cells
- **Stem cell count**: Median nucleated cell count: 0.22 ± 235 million
- **Other injectate**: PPP
- **Local anesthetic**: NA
- **Imaging guidance**: Ultrasound
- **Post-treatment care**: None; pain medication use discouraged

Tucker 2019:
- **Biologicals**: 28 patients
- **Procedure**: Ultrasound, fluoroscopy w/ contrast
- **Inclusion criteria**: Males, mean age 65, NR
- **Concomitant**: None
- **Grade**: NR
- **Cell type(s)**: BMM containing MSCs, platelets, HSCs, and red and white blood cells
- **Stem cell count**: Median nucleated cell count: 0.22 ± 235 million
- **Other injectate**: PPP
- **Local anesthetic**: NA
- **Imaging guidance**: Ultrasound
- **Post-treatment care**: None; pain medication use discouraged

---

*Note: The above table provides a summary of the characteristics of patients and procedures across different studies.*
## Knee OA, RCTs – Autologous, non-culture-expanded SCT

### Function:
No difference b/w groups on 3 of 4 KOOS subscales (0-100 [best]), mean Δ from baseline to 12 mos.; 2 RCTs (N=83)

> **SOE INSUFFICIENT:** mod. high RoB, imprecise (wide CIs)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Outcome</th>
<th>Level</th>
<th>Comparator</th>
<th>Stem Cells</th>
<th>Control</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Δ Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ruan 2019</td>
<td>Ind-High BM-MNC</td>
<td>HA</td>
<td>18.91</td>
<td>14.19</td>
<td>13</td>
<td>9.2</td>
<td>16.85</td>
<td>14</td>
<td>16.75</td>
<td>47.5%</td>
<td>-4.21 (13.64, 22.17)</td>
<td></td>
</tr>
<tr>
<td>Goncalves 2017</td>
<td>Ind-High BM-MNC</td>
<td>HA</td>
<td>6.91</td>
<td>17.19</td>
<td>28</td>
<td>12.62</td>
<td>14.26</td>
<td>28</td>
<td>13.17</td>
<td>52.0%</td>
<td>2.05 (0.71, 3.39)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 12.39, Q(df=6) = 13.64, <em>P</em> &lt; 0.05</td>
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<td><strong>Pain</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruan 2019</td>
<td>Ind-High BM-MNC</td>
<td>HA</td>
<td>19.17</td>
<td>17.02</td>
<td>13</td>
<td>11.87</td>
<td>16.64</td>
<td>14</td>
<td>17.05</td>
<td>30.0%</td>
<td>2.22 (0.48, 3.96)</td>
<td></td>
</tr>
<tr>
<td>Goncalves 2017</td>
<td>Ind-High BM-MNC</td>
<td>HA</td>
<td>21.36</td>
<td>16.43</td>
<td>28</td>
<td>10.69</td>
<td>16.23</td>
<td>28</td>
<td>11.27</td>
<td>36.0%</td>
<td>2.47 (0.02, 4.93)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 9.00, Q(df=6) = 18.52, <em>P</em> &lt; 0.05</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Pain:
No difference b/w groups in the pooled estimates (mean Δ from baseline) at any time point; 4 RCTs (N=182)

> **SOE LOW:** mod. high RoB, imprecise (wide CIs)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Measure</th>
<th>Level</th>
<th>Comparator</th>
<th>Stem Cells</th>
<th>Control</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Δ Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 Months</strong></td>
<td>KOOS</td>
<td>HA</td>
<td>MDC</td>
<td>25.99</td>
<td>10.3</td>
<td>20</td>
<td>20.67</td>
<td>13</td>
<td>29</td>
<td>45.9%</td>
<td>4.72 (10.68, 1.42)</td>
<td></td>
</tr>
<tr>
<td>Ruan 2019</td>
<td>KOOS</td>
<td>HA</td>
<td>MDC</td>
<td>-26.71</td>
<td>19.78</td>
<td>19</td>
<td>-10.93</td>
<td>11.42</td>
<td>19</td>
<td>12.9%</td>
<td>0.78 (0.77, 0.77)</td>
<td></td>
</tr>
<tr>
<td>Goncalves 2017,18</td>
<td>VAS</td>
<td>BM-BMC</td>
<td>PlanBio</td>
<td>-15</td>
<td>14.12</td>
<td>20</td>
<td>-15</td>
<td>15.46</td>
<td>24</td>
<td>25.5%</td>
<td>0.66 (0.15, 2.14)</td>
<td></td>
</tr>
<tr>
<td>Goncalves 2017,18</td>
<td>VAS</td>
<td>BM-BMC</td>
<td>Exercise</td>
<td>-12.5</td>
<td>17.95</td>
<td>24</td>
<td>8</td>
<td>17.85</td>
<td>22</td>
<td>16.0%</td>
<td>4.90 (4.88, 4.92)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 9.80, Q(df=6) = 13.64, <em>P</em> &lt; 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 6 Month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Measure</th>
<th>Level</th>
<th>Comparator</th>
<th>Stem Cells</th>
<th>Control</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Mean Δ</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Δ Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee OA, RCTs – Autologous, non-culture-expanded SCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Pain: No difference b/w groups in the pooled estimates (mean Δ from baseline) at any time point; 4 RCTs (N=182)

> **SOE LOW:** mod. high RoB, imprecise (wide CIs)
### Knee OA, RCTs – Patient, Procedure Characteristics, autologous, culture-expanded stem cells

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose BM-MSCs (n=10)</td>
<td>BM-MSCs (n=19)</td>
<td>Placebo (n=24)</td>
<td>AD-MSCs (n=12)</td>
<td>Usual care (n=10)</td>
</tr>
<tr>
<td>High dose BM-MSCs (n=10)</td>
<td>HA (n=10)</td>
<td></td>
<td>AD-MSCs (n=11)</td>
<td></td>
</tr>
<tr>
<td>Males, %</td>
<td>40%</td>
<td>63%</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>66.9</td>
<td>57.8</td>
<td>60.3</td>
<td>63.0</td>
</tr>
<tr>
<td>K/L OA grade</td>
<td>II: 10%; III: 20%; IV: 70%</td>
<td>II: 50%; III: 40%; IV: 10%</td>
<td>II: 10%; III: 40%; IV: 20%</td>
<td>II: 4.5%; III: 33%; IV: 2.5%</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Concomitant meds</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Anatomopathophy x 4,000 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient blinded</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Total concentration of cells</td>
<td>10⁶</td>
<td>10⁷</td>
<td>NA</td>
<td>5x10⁵</td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>1 HA injection</td>
<td>1 HA injection</td>
<td>None</td>
<td>Saline + 2% human serum albumin</td>
</tr>
<tr>
<td>No. of injection</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shaping guidance</td>
<td>None</td>
<td>Radiographic</td>
<td>Ultrasound</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Post-treatment care</td>
<td>NR</td>
<td>NR</td>
<td>Rest for 24 hours following each injection</td>
<td>No specific physical limitation was recommended</td>
</tr>
</tbody>
</table>

### 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:

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

**SOE INSUFFICIENT:** RCTs mod. high RoB; inconsistent results across trials and thresholds; imprecise (small N’s, wide CIs)
**Knee OA, RCTs – Autologous, culture-expanded SCT**

**Function: WOMAC total (0-96 [worst]), mean difference in f/u scores (5 RCTs, N=173)**

- 3, 6, 12 mos.: no difference b/w groups in pooled estimates (SOE LOW)
- 48 mos.: INSUFFICIENT evidence

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

**Function: WOMAC total (0-96 [worst]), mean difference in f/u scores (5 RCTs, N=173)**

- 3, 6, 12 mos.: no difference b/w groups in pooled estimates (SOE LOW)
- 48 mos.: INSUFFICIENT evidence

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

**Function: WOMAC physical function (0-68 [worst]), mean difference in f/u scores (4 RCTs, N=144)**

- No difference b/w groups in pooled estimates at any time point (SOE LOW at 3 and 6 mos., INSUFFICIENT at 12 mos.)
Knee OA, RCTs – Autologous, culture-expanded SCT

Pain “Success”

• Defined differently across 2 RCTs

• More AD-MSC vs. conservative care patients achieved success at 12 months in 1 RCT [Emadedin]:
  o NRS pain (MCID 1 point): 95% (18/19) vs. 40% (4/10); RR 2.4 (95% CI 1.1 to 5.1)
  o 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-MSC 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)

SOE: LOW

SOE: INSUFFICIENT

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 – Autologous, culture-expanded SCT

**Pain:** WOMAC pain (0-20 [worst]), mean difference in f/u scores (4 RCTs, N=144)

- No difference b/w groups in the pooled estimates at any time point

---

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Stem-Cells</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**Khalifeh Soltani 2019**

(N=20)

- Placeenta-derived MSCs (n=10)
- Placeo (n=10)

**Vega 2015**

(N=30)

- BM- MSCs (n=15)
- HA injection (Durolane®) (n=15)

- Males, %
  - Placeenta-derived MSCs: 10%
  - Placeo: 10%
  - BM- MSCs: 40%
  - HA injection: 33%

- Mean age, years
  - Placeenta-derived MSCs: 57.5
  - Placeo: 55.8
  - BM- MSCs: 57
  - HA injection: 57

- K-L OA grade
  - Placeenta-derived MSCs: II/III: 90%, IV: 10%
  - Placeo: II/III: 40%, IV: 20%
  - BM- MSCs: II: 40%, III: 40%, IV: 20%
  - HA injection: II: 47%, III: 33%, IV: 20%

- Comorbidities
  - Placeenta-derived MSCs: NR
  - Placeo: NR

- Concomitant meds
  - Placeenta-derived MSCs: NR
  - Placeo: NR

- Patient blinded?
  - Placeenta-derived MSCs: Yes
  - Placeo: Yes

- Stem cell source (volume)
  - Placeenta-derived MSCs: Donor placenta
  - Placeo: NA
  - BM- MSCs: Bone marrow
  - HA injection: NA

- Cell type(s) reported
  - Placeenta-derived MSCs: MSCs
  - Placeo: NA
  - BM- MSCs: MSCs
  - HA injection: NA

- Stem cell count, mean ± SD (range) *
  - Placeenta-derived MSCs: 0.5-0.6x10^6
  - Placeo: NA
  - BM- MSCs: 40x10^6 cells/knee from a 5x10^4 cell/mL suspension
  - HA injection: NA

- Local anesthetic used
  - Placeenta-derived MSCs: NR
  - Placeo: NR
  - BM- MSCs: NR
  - HA injection: NR

- Other injectate (w/ stem cells)
  - Placeenta-derived MSCs: None
  - Placeo: None
  - BM- MSCs: None
  - HA injection: None

- No. of injections
  - Placeenta-derived MSCs: 1
  - Placeo: 1

- Imaging guidance
  - Placeenta-derived MSCs: NR
  - Placeo: NR

- Post-treatment care
  - Placeenta-derived MSCs: Immediate return to ADLs; heavy lifting and prolonged walking restricted for 1-wk.
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.

<table>
<thead>
<tr>
<th>Outcome Measure (scale)</th>
<th>F/U</th>
<th>BM-MSC (n=15) mean ± SD</th>
<th>HA (n=15) mean ± SD</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC total (0-100 [worst])</td>
<td>Baseline</td>
<td>41 ± 11.6</td>
<td>45 ± 11.6</td>
<td>–8.0 (–24.0 to 8.0)</td>
</tr>
<tr>
<td></td>
<td>3 mos.</td>
<td>33 ± 19.4</td>
<td>41 ± 23.2</td>
<td>–12.0 (–23.6 to –0.4)</td>
</tr>
<tr>
<td></td>
<td>6 mos.</td>
<td>28 ± 15.5</td>
<td>40 ± 15.5</td>
<td>–13.0 (–29.0 to 3.0)</td>
</tr>
<tr>
<td></td>
<td>12 mos.</td>
<td>28 ± 19.4</td>
<td>41 ± 23.2</td>
<td>–10.0 (–24.0 to 4.0)</td>
</tr>
</tbody>
</table>

| Lequesne (0-100 [worst]) | Baseline | 39 ± 15.5 | 45 ± 15.5 | –4.0 (–15.6 to 7.6) |
|                          | 3 mos.   | 36 ± 15.5 | 40 ± 15.5 | –4.0 (–26.6 to –3.4) |
|                          | 6 mos.   | 25 ± 15.5 | 40 ± 15.5 | –15.0 (–29.0 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)

---

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.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RoB</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Mean</th>
<th>SD Total</th>
<th>Mean</th>
<th>SD Total</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Wk</td>
<td>Mod Low</td>
<td>BM-MSC</td>
<td>HA</td>
<td>40</td>
<td>43</td>
<td>40</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>BM-MSC</td>
<td>HA</td>
<td>62</td>
<td>67</td>
<td>62</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moderate (N=39)</td>
<td>T-score: Z = 1.09 (p = 0.29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.96 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-score: Z = 1.09 (p = 0.29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.96 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 4-Wk              | Mod Low | BM-MSC | HA | 34 | 32 | 34 | 32 | 0 | 6.0 | –6.0 (–14.6 to 2.6) |
|                   | High | BM-MSC | HA | 32 | 31 | 32 | 31 | 0 | 6.0 | –6.0 (–14.6 to 2.6) |
|                   | Moderate (N=39) | T-score: Z = 1.09 (p = 0.29) |
|                   | Test for overall effect: Z = 1.96 (P = 0.05) |

| 12-Wk             | Mod Low | BM-MSC | HA | 30 | 31 | 30 | 31 | 0 | 6.0 | –6.0 (–14.6 to 2.6) |
|                   | High | BM-MSC | HA | 30 | 31 | 30 | 31 | 0 | 6.0 | –6.0 (–14.6 to 2.6) |
|                   | Moderate (N=39) | T-score: Z = 1.09 (p = 0.29) |
|                   | Test for overall effect: Z = 1.96 (P = 0.05) |

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

#### SOE: LOW

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

---

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

#### SOE: INSUFFICIENT

<table>
<thead>
<tr>
<th>SOE</th>
<th>SCT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td><strong>2 RCTs</strong></td>
<td><strong>0% (0/43)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1 registry</strong></td>
<td><strong>0.2% (2/840 procedures); 3.5% of 57 total AEs</strong></td>
</tr>
<tr>
<td><strong>SAEs</strong></td>
<td><strong>4 RCTs</strong></td>
<td><strong>0% (0/94)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>3 case series</strong></td>
<td><strong>0% (0/115)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1 registry</strong></td>
<td><strong>0.4% (3/840 procedures); 5.3% of 57 total AEs</strong></td>
</tr>
<tr>
<td><strong>Infection (non-serious)</strong></td>
<td><strong>1 RCT</strong></td>
<td><strong>8% (2/26)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>3 case series</strong></td>
<td><strong>0% (0/111)</strong></td>
</tr>
<tr>
<td><strong>Neurologic; Neoplasm; Allergic Reaction; Cardiac; Bleed/Hematoma</strong></td>
<td><strong>1 registry</strong></td>
<td><strong>For each:</strong> 0.2% (2/840 procedures); 3.5% of 57 total AEs</td>
</tr>
<tr>
<td><strong>Def. injectate-related</strong></td>
<td><strong>1 registry</strong></td>
<td><strong>0.5% (4/840 procedures); 7.0% of 57 total AEs</strong></td>
</tr>
<tr>
<td><strong>Pos. injectate-related</strong></td>
<td><strong>1 registry</strong></td>
<td><strong>2.9% (24/840 procedures); 42.1% of 57 total AEs</strong></td>
</tr>
<tr>
<td><strong>Def. procedure-related</strong></td>
<td><strong>1 registry</strong></td>
<td><strong>1.1% (9/840 procedures); 15.8% of 57 total AEs</strong></td>
</tr>
<tr>
<td><strong>Pos. procedure-related</strong></td>
<td><strong>1 registry</strong></td>
<td><strong>3.5% (29/840 procedures); 50.9% of 57 total AEs</strong></td>
</tr>
</tbody>
</table>
**Knee OA, SAFETY – Autologous, culture-expanded SCT**

### SOE: LOW

<table>
<thead>
<tr>
<th>Any treatment-related AE (non-serious, time-limited)</th>
<th>2 RCTs: SCT vs. placebo</th>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RCT: SCT vs. UC</td>
<td>1 injection: 80% (8/10) vs. NR</td>
<td>2 injections (baseline): 90% (9/10) vs. NR 2 injections (6 months): 100% (10/10) vs. NR</td>
</tr>
<tr>
<td>Joint pain; pain in injected joint</td>
<td>1 RCT: SCT vs. placebo</td>
<td>50% (6/12) vs. 0% (0/12), p=0.006</td>
</tr>
<tr>
<td></td>
<td>1 RCT: SCT vs. HA</td>
<td>Low-dose SCT, 30% (3/10) vs. High-dose SCT, 60% (6/10) vs. HA, 10% (1/10); p=NS for all</td>
</tr>
<tr>
<td></td>
<td>4 case series</td>
<td>Range, 23% (3/13) to 50% (25/50) [total N=90]</td>
</tr>
</tbody>
</table>

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

#### SOE: INSUFFICIENT

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>1 RCT</th>
<th>0% (0/26)</th>
<th>0% (0/26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAEs</td>
<td>4 RCTs</td>
<td>0% (0/78)</td>
<td>2% (1/58) [w/ HA]</td>
</tr>
<tr>
<td></td>
<td>3 case series</td>
<td>0% (0/115)</td>
<td>-------</td>
</tr>
<tr>
<td>&quot;Severe&quot; treatment-related AEs</td>
<td>1 RCT</td>
<td>10% (2/20) [pain, swelling impacting ADLs for 4 wks.]</td>
<td>NR [usual care]</td>
</tr>
<tr>
<td>Effusion</td>
<td>1 RCT</td>
<td>17% (2/12)</td>
<td>8% (1/12)</td>
</tr>
<tr>
<td></td>
<td>2 case series</td>
<td>10% (1/10) to 25% (3/12)</td>
<td>-------</td>
</tr>
<tr>
<td>Infection, treatment-related</td>
<td>2 RCTs</td>
<td>2.1% (1/48) [w/ BM-MSCs]</td>
<td>1.9% (1/51) [w/ HA]</td>
</tr>
<tr>
<td></td>
<td>1 case series</td>
<td>0% (0/20)</td>
<td>-------</td>
</tr>
<tr>
<td>Musculoskeletal and connective-tissue disorder, treatment-related</td>
<td>1 RCT</td>
<td>Any: 82% (18/22) Grade 3: 5% (1/22)</td>
<td>Any: 20% (5/25) Grade 3: 8% (2/25)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>2 case series</td>
<td>7% (1/15) [mild]; “most” pts.</td>
<td>-------</td>
</tr>
</tbody>
</table>
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)
  o PL-MSCs vs. placebo: 40% (4/10) vs. 0% (0/10) [Khalifeh Soltani]
  o BM-MSCs vs. HA: 53% (8/15) vs. 60% (9/15) [Vega]

DEGENERATIVE DISC DISEASE (DDD)

Autologous
Nonculture-expanded (3 case series)
Culture-expanded (2 case series)

Allogenic
Culture-expanded (1 RCT)
DDD – Allogenic, culture-expanded SCs

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

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

<table>
<thead>
<tr>
<th>F/U (mos.)</th>
<th>Function - ODI [0-100% (worst)] Mean ± SD</th>
<th>Pain - VAS [0-100 (worst)] Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BM-MSC (n=12)</td>
<td>Sham (n=12)</td>
</tr>
<tr>
<td>Baseline</td>
<td>34 ± 23</td>
<td>24 ± 14</td>
</tr>
<tr>
<td>3 mos.</td>
<td>16 ± 20</td>
<td>25 ± 15</td>
</tr>
<tr>
<td>6 mos.</td>
<td>20 ± 24</td>
<td>30 ± 20</td>
</tr>
<tr>
<td>12 mos.</td>
<td>22 ± 24</td>
<td>34 ± 25</td>
</tr>
</tbody>
</table>

sham = 1% mepivacaine into paravertebral musculature

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

TENDINOPATHY

Autologous, Nonculture-expanded

- Achilles Tendinopathy (1 RCT)
- Elbow Tendinopathy (1 case series)
**Tendinopathy – Autologous, nonculture-expanded SCs**

1 small RCT (N=44) [Usuelli 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)

<table>
<thead>
<tr>
<th>F/U (mos.)</th>
<th>Function (mean ± SD)</th>
<th>Pain (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VISA-A [0-100 (best)]</td>
<td>AOFAS [0-100 (best)]</td>
</tr>
<tr>
<td>Baseline</td>
<td>41.6 ± 13.6</td>
<td>46.5 ± 23.6</td>
</tr>
<tr>
<td>2 wks.</td>
<td>43 ± NR</td>
<td>43 ± NR</td>
</tr>
<tr>
<td>1 mo.</td>
<td>59 ± NR</td>
<td>47 ± NR</td>
</tr>
<tr>
<td>2 mos.</td>
<td>66 ± NR</td>
<td>59 ± NR</td>
</tr>
<tr>
<td>6 mos.</td>
<td>71 ± NR</td>
<td>71 ± NR</td>
</tr>
</tbody>
</table>

Bold indicates p value < 0.05

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

---

**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) [Usuelli 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**
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)

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
### Summary – Efficacy, Effectiveness

<table>
<thead>
<tr>
<th>Function</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors</td>
<td>SOE</td>
</tr>
<tr>
<td>4 mos.</td>
<td>6 mos.</td>
</tr>
<tr>
<td>AUTLOGOUS, nonculture-expanded</td>
<td>insufficient evidence</td>
</tr>
<tr>
<td>AUTLOGOUS, culture-expanded</td>
<td>insufficient evidence</td>
</tr>
<tr>
<td>WOMAC total</td>
<td>Θ LOW (3 RCTs)</td>
</tr>
<tr>
<td>WOMAC physical, stiffness</td>
<td>Θ LOW (3 RCTs)</td>
</tr>
</tbody>
</table>

*Θ = no diff b/w SCT vs. controls  ↑ = SCT favored vs. controls  MCID = clinically significant*

### 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
Summary – Safety

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

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?


Appendix/Additional Slides
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)

---

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/MSC at 3 mos.

- Secondary procedures (4 RCTs), F/U range 6-24 months:

<table>
<thead>
<tr>
<th>Author</th>
<th>Description</th>
</tr>
</thead>
</table>
| Centeno 2018 | BMC vs. Exercise/UC (NR by tx arm)  
  • 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  
  • TKA: 8% (1/13) vs. 0% (0/13) vs. 0% (0/13) |
| Ruane 2019  | BMC vs. HA  
  • Additional tx (NOS): 12% (2/17) vs. 7% (1/15) |
| Shapiro 2018 | BMC vs. Placebo  
  • None (surgery or additional injections); N=50 knees, 25 patients |
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)

<table>
<thead>
<tr>
<th>Function, mean ± SD [0-100 (best)]</th>
<th>Pain, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F/U</strong></td>
<td><strong>SCT (n=26)</strong></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.6 ± 18.6</td>
</tr>
<tr>
<td>1 mo.</td>
<td>88.6 ± 17.1</td>
</tr>
<tr>
<td>6 mos.</td>
<td>91.7 ± 9.5</td>
</tr>
</tbody>
</table>

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.)
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), $I^2=0\%$

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

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

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

<table>
<thead>
<tr>
<th>F/U</th>
<th>Function</th>
<th></th>
<th>Function</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCT (n=26)</td>
<td>Control (n=26)</td>
<td>SCT (n=26)</td>
<td>Control (n=26)</td>
</tr>
<tr>
<td>Baseline</td>
<td>39.8 ± 3.8</td>
<td>38.6 ± 4.8</td>
<td>2.4 ± 0.3</td>
<td>2.2 ± 2</td>
</tr>
<tr>
<td>3 mos.</td>
<td>58.6 ± 6.9</td>
<td>51 ± 4.8</td>
<td>2.1 ± 0.12</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>6 mos.</td>
<td>61.4 ± 7.2</td>
<td>42.2 ± 4.8</td>
<td>1.8 ± 0.31</td>
<td>2.2 ± 0.4</td>
</tr>
</tbody>
</table>

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
Other Conditions – Effectiveness and Safety

• All but one study non-comparative (all HIGH RoB) – SOE INSUFFICIENT for all

• Autologous, non-culture-expanded (13 studies):
  o 12 used BMC, 1 used AD-MSCs (± 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-effective\(^1\) as expressed by the following standards\(^2\):

- 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 harms\(^3\):

- 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.

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\(^1\) 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](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](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 evidence 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.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

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4 Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](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)

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

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

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Efficacy / Effectiveness evidence</th>
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### Cost outcomes

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Cost evidence</th>
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</table>

### Special population / Considerations outcomes

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Special populations / Considerations evidence</th>
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### For safety:
Is there sufficient evidence that the technology is safe for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
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<tbody>
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### For efficacy/ effectiveness:
Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
</thead>
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</table>

### For cost outcomes/ cost-effectiveness:
Is there sufficient evidence that the technology is cost-effective for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
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</table>
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

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence Base</th>
<th>Recommendation/Consensus</th>
<th>Rating/Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Interventional Pain Physicians (ASIP) 2019</td>
<td>Lumbar Disc Injections of Mesenchymal Stem Cells: 1 RCT, 4 case series, 4 comparative cohorts, 1 single arm meta-analysis, 2 SRs</td>
<td>Informed Consent A consent form should be discussed with the patient and signed by both the provider and the patient. <strong>Office Set-up</strong> 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. <strong>Contraindications</strong> • 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 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. <strong>Pre-injection Management of Patient</strong> 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.</td>
<td>Level III</td>
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<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence Base</th>
<th>Recommendation/Consensus</th>
<th>Rating/Strength of Recommendation</th>
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</thead>
<tbody>
<tr>
<td>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.</td>
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</table>

**Pre-injection management of biologic materials**
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.

**Intra-injection management**
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.

**Post-injection management**
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
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence Base</th>
<th>Recommendation/Consensus</th>
<th>Rating/Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International Society for Stem Cell Research (ISSCR)</strong></td>
<td>1 SR, 2 RCTs, 1 comparative cohort</td>
<td>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.</td>
<td>NR</td>
</tr>
<tr>
<td><em>Current State of Cell-based Therapies for Osteoarthritis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Australasian College of Sports Physicians (ACSP)</strong></td>
<td>Osteoarthritis</td>
<td>1. Mesenchymal stem cell (MSC) therapies are still under investigation.</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Guideline**

- **Evidence Base**
  - 1 SR, 2 RCTs, 1 comparative cohort

**Recommendation/Consensus**

- Significant subjective and objective report of improvement in pain and function and is based on the discretion of the clinic thereafter.

**Continued Therapy**

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.

**Antithrombotic Therapy**

Antithrombotic therapy should be halted (even temporarily)

**Adverse Reactions and Complications**

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.

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%).
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence Base</th>
<th>Recommendation/Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 ACSP—Position Statement: The Place of Mesenchymal Stem/Stromal Cell Therapies in Sport and Exercise Medicine</td>
<td>1 SR, 5 RCTs, 2 comparative cohorts, 21 case series</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Tendinopathy 1 SR, 4 case series</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Muscle Injury No evidence identified</td>
<td>4. There is currently insufficient evidence from high-quality clinical trials to recommend the clinical use of MSC therapies for joint or tendon regeneration.</td>
</tr>
<tr>
<td></td>
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<td>5. The ACSP encourages the establishment of research studies to determine the safety and efficacy of MSCs for the treatment of musculoskeletal conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical research trials must be registered with an appropriate clinical research trial registry.</td>
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<tr>
<td></td>
<td></td>
<td>• Any research trial must be subjected to peer review and receive human research ethics committee approval.</td>
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<td>• Any and all research findings will be shared within the scientific and medical community including adverse outcomes.</td>
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<tr>
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<td>6. The ACSP believes that any use of MSCs for musculoskeletal conditions must fit within either of the following pathways:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• As part of a rigorous clinical research trial.</td>
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<tr>
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<td>• As an individualized innovative therapy. It is expected that only small numbers of patients would go through this pathway.</td>
</tr>
<tr>
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<td>7. The use of MSCs must only be undertaken within the expectations of the relevant medical regulatory organizations.</td>
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<tr>
<td></td>
<td></td>
<td>8. Australasian College of Sports Physicians members must inform all patients receiving MSC therapy that:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• They are part of a research trial or are receiving innovative therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mesenchymal stem cells are experimental and have not yet been proven to be safe or effective for clinical use.</td>
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<td>• The long-term harms from the use of MSCs have not been determined.</td>
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<td>• Identifiable personal patient or participant information and treatment will be entered to a database and accessed by researchers.</td>
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<td>• They may be contacted at a later date for research purposes.</td>
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<td>• Ethical approval will be sought before accessing patient data.</td>
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<td>• Any conflicts of interest held by the researcher or clinician providing innovative therapy will be declared.</td>
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<td>• 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.</td>
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| Research and clinical translation                                         | Expert Consensus | **Sourcing Stem Cells**  
  • 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. | NR |
| International Society for Stem Cell Research (ISSCR)                     |               | **Manufacturing of Stem Cells**  
  • 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. | |
| 2016                                                                     |               | **Standards for Clinical Conduct**  
  • 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 | |
<p>| <em>Guidelines for Stem Cell Research and Clinical Translation</em>              |               |                                                                                                                                                                                                                                |                                   |</p>
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<td>than minor increase over minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit.</td>
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<td>• 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.</td>
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<td>• 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.</td>
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<td>• 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.</td>
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<td>• 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.</td>
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<td>Stem Cell-Based Medical Innovation</td>
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<td>• 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.</td>
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<td>Clinical Application of Stem Cells</td>
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<td>• 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.</td>
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<td>• 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.</td>
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<td>• Registries of specific patient populations can provide valuable data on safety and outcomes of stem cell-based interventions within defined populations but should</td>
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|                                                                           | 8 level I, 12 level II, 3 level III, 10 level IV studies, and 19 level V (expert opinion) publications | not substitute for stringent evaluation through clinical trials prior to introduction into standard care.  
• Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties associated with stem cell-based interventions.  
Access and Economics  
• 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.  
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.  
**Recommendations to improve accountability:**  
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.  
   • 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. | NR                                                                             |
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<td>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.</td>
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<td>Minimum Information for studies reporting Biologics (MIBO) check lists should be used to guide study design and reporting.</td>
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<td>Regarding MSC, ISCT standard can be used to indicate whether cells meet published standard</td>
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<td>3. Establish Registries for Postmarket Monitoring and Quality Assessments of Biologic Therapies.</td>
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<td>Recommendations to accelerate discovery, development and delivery of 21st Century cures</td>
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<td>4. Designate Osteoarthritis (OA) as a Serious Medical Condition.</td>
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<td>5. Clarify, by Disease State, a Consensus Approach for Biological Markers of Interest and Clinical Trial Design.</td>
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<td>6. Establish the Framework for a Multicenter Knee OA Clinical Trial Consortium.</td>
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<td>7. Explore Accelerated Pathways for FDA Approval of New Drug Applications for Biologics to Treat Musculoskeletal Conditions</td>
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<td>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.</td>
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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