The Use of Biologics in NFL Athletes

An Expert Consensus of NFL Team Physicians

Iain R. Murray, FRCS, PhD, Timothy R. McAdams, MD, Kyle E. Hammond, MD, Fares S. Haddad, FRCS, MD(Res), Scott A. Rodeo, MD, and Geoffrey D. Abrams,* MD, on behalf of a Group of American Professional Football Physicians

Investigation performed at the Department of Orthopaedic Surgery, Stanford University, Stanford, California, USA

Background: There is a lack of published information outlining the use of biologics in National Football League (NFL) athletes and limited data to guide biologic treatment strategies.

Purpose: To develop a consensus on the use of biologics among NFL team physicians.

Study Design: Consensus statement.

Methods: A working group of 6 experts convened a consensus process involving NFL team physicians using validated Delphi methodology. Physicians from 32 NFL teams as well as NFL London were invited to take part. This iterative process was used to define statements on the use of biologics in NFL athletes. A recent scoping review exploring biologics in professional athletes was used to inform the first of 3 rounds of surveys, with statements considered under 7 headings: biologics in general, challenges of treating NFL athletes, terminology/nomenclature, autologous blood products, cell-based therapies, guidance for NFL team physicians, and biologic research in the NFL. In addition to rating agreement, experts were encouraged to propose further items or modifications. Predefined criteria were used to refine item lists after each survey. For a consensus within the final round, defined a priori, items were included in the final information set if a minimum of 75% of respondents agreed and fewer than 10% disagreed.

Results: Physicians from 26 NFL teams and NFL London responded to the initial invitation to participate in the Delphi process; 88.9% of participating team physicians completed the round 1 survey, with response rates of 87.5% in round 2 and 95.2% in round 3. After 3 rounds, 47 statements reached a consensus. A consensus was achieved that platelet-rich plasma has a positive impact on patellar tendinopathy and on symptoms in early osteoarthritis but not for other indications. NFL team physicians agreed that while cell therapies have the potential to improve symptoms, the misrepresentation of uncharacterized preparations as "stem cells" has contributed to the widespread use of unproven therapies.

Conclusion: This study established an expert consensus on 47 statements relating to the use of biologics in NFL athletes. In addition to providing clinical guidance for the use of biologics in NFL athletes, this study identified key areas for future focus including the development of athlete education materials.

Keywords: biologics; platelet-rich plasma; stromal cells; bone marrow aspirate concentrate; American football

Biologic treatments are increasingly used in the management of musculoskeletal injuries and degenerative conditions.[26] Athletes are particularly drawn to biologic therapies by the promise of an accelerated return to sport through minimally invasive techniques that harness the body's intrinsic healing responses.[20] While there are growing data evaluating biologic approaches in the management of a discrete number of sports injuries,[4,31] there remains considerable variation in outcomes, and current practices and indications remain ill-defined.[34]

Athletes in the National Football League (NFL) represent a unique group of patients, with distinct challenges relating to the athletic demands of full-time sport, discrete patterns of injury, and financial pressures on performance.[14,30] A growing number of NFL athletes have turned to biologic strategies, with media portrayals of these practices having the potential to influence the demand for biologic treatments in recreational athletes and the wider public.[20] In addition, a large number of unproven therapies are being marketed directly to athletes, with unsubstantiated claims of efficacy

The Orthopaedic Journal of Sports Medicine, 11(2), 23259671221143778
DOI: 10.1177/23259671221143778

and lack of information about risks, product manufacturing, and unrealistic expectations of outcomes.[27] While efforts have been made to evaluate biologic treatments in NFL athletes,[5] the considerable challenges of performing research on these players mean that there are currently few high-level studies to guide treatments.[20]

The purpose of this study was to establish an expert consensus among NFL team physicians on the use of biologics in NFL players using the Delphi method. We hypothesized that this research will establish agreement on specifics in treating NFL athletes, terminology, clinical use, and areas for further research in the area of biologics.

METHODS

This was an NFL Physicians Society–based study and was not sponsored by the NFL. A working group (I.R.M., T.R.M., K.E.H., F.S.H., S.A.R. and G.D.A.) facilitated the development of a consensus using the Delphi technique. The Delphi method is an iterative process in which a group of experts are led to achieve a consensus on a given topic.[23] A series of anonymized surveys are performed, with the result of each round collated and presented back to the group. Participants then reassess their responses after considering the group responses. The steps of collating and presenting data and the completion of surveys continue until a consensus is achieved. Details of the consensus are presented in Figure 1. Although the majority of Delphi studies have used between 15 and 20 respondents, team physicians representing all 32 NFL teams and NFL London were invited to increase representation in this broad field. Team physicians were orthopaedic surgeons from a range of backgrounds including academic and private institutions.

Identification of Items Relevant to the Use of Biologics in NFL Athletes

A scoping review exploring the use of biologics in professional and Olympic athletes was previously published by a subset of the authors and used to inform the first-round survey.[17,20] This scoping review was initially intended to chart studies specifically relating to American football but was expanded to include all sports because of the limited number of studies available. Draft statements for inclusion within first-round surveys were prepared by the working group. Statements were categorized into groups and refined to ensure there was no overlap. Online surveys were distributed to the wider group of NFL physicians to rate whether items should be included within the final consensus document with 5 possible responses on a Likert[15] scale: strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree. A free-text comments section was included to allow for suggestions of modifications or additional items. The survey was piloted by 4 experts (T.R.M., K.E.H., S.A.R. and G.D.A.) for face validity, understanding, and acceptability. After this, minor modifications were made.

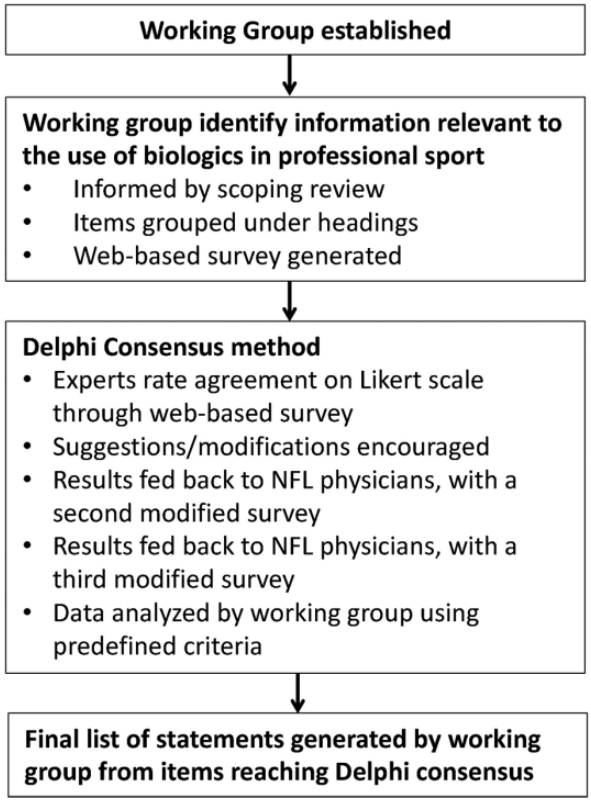

Figure 1. Flowchart showing the consensus process. NFL, National Football League.

Establishing a Consensus Through the Delphi Process

The Delphi method was used to establish a group consensus on the core list of statements generated by the working group. The wider group of NFL team physicians participated in 3 rounds of surveys between February and May

*Address correspondence to Geoffrey D. Abrams, MD, Department of Orthopaedic Surgery, Stanford University, 450 Broadway Street, Redwood City, 94063,CA, USA (email: geoffa@stanford.edu).

All authors are listed in the Authors section at the end of this article.

Final revision submitted May 22, 2022; accepted August 10, 2022.

One or more of the authors has declared the following potential conflict of interest or source of funding: I.R.M. has received consulting fees from Arthrex and Stryker. F.S.H. has received research support from Smith & Nephew and Stryker; consulting fees from Smith & Nephew and Stryker; and royalties from Corin, MatOrtho, Smith & Nephew, and Stryker. S.A.R. has received consulting fees from Teladoc and has stock/stock options in Ortho RTI. G.D.A. has received education payments from Evolution Surgical; has received consulting fees from Endonovo Therapeutics, RubiconMD, and Sideline Sports Doc; has received royalties from Orthofix Medical; has received other financial/material support from Arthrex and Stryker; and has stock/stock options in Cytonics, Sparta Biomedical, and Sparta Biopharma. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

Ethical approval was not sought for the present study.

2021. Results were integrated and amended consensus statements prepared. In the second round, NFL team physicians were asked to review the anonymized results from round 1 and score all items within the second survey. As with round 1, a free-text comments section was included to allow for suggestions of modifications or additional items. Questionnaires were reanalyzed and the cycle repeated. The process was continued until a consensus was reached for all items as defined below or for a maximum of 3 rounds.

Data Analysis

In round 1 of the survey, items were categorized as "essential" and retained for round 2 if ≥70% of respondents agreed and <20% disagreed. Items not meeting these criteria were discarded or modified per responders' suggestions. In round 2, responses were analyzed with stricter cutoff criteria, retaining items if ≥70% of respondents agreed on their inclusion and <10% disagreed. Items retained after round 2 were considered in round 3. For a consensus, defined a priori, items were included in the final information set if ≥75% of respondents agreed and <10% disagreed. Agreement in 75% of participants is the most frequently specified determination of a consensus for Delphi studies.[9]

RESULTS

Identification of Relevant Items

The working group generated 78 items from group discussions and a review of existing related literature for consideration by the wider group of team physicians in the first-round survey. Items were categorized under 7 headings: biologics in general, challenges of treating NFL athletes, terminology/nomenclature, autologous blood products, cell-based therapies, guidance for NFL team physicians, and biologic research in the NFL.

Establishing a Consensus Through the Delphi Process

Team physicians from 26 NFL teams and the head physician for NFL London agreed to take part in the Delphi process. Of those who agreed to participate, 24 team physicians (88.9%) completed the first-round survey. All nonrespondents were excluded from participation in subsequent rounds. In round 2, 21 of 24 (87.5%) NFL physicians responded, with 20 of 21 (95.2%) of the remaining NFL physicians completing the third and final round. The results of each survey round are summarized in Table 1. The levels of agreement in rounds 1 to 3 are presented in Figures 2 to 4, respectively. Of 49 items, 47 (95.9%) included within the final survey achieved a consensus, with >75% of experts in agreement and <10% disagreeing (Figure 4 and Appendix Table A3). The levels of agreement for items at each round of the consensus process are summarized in Appendix Tables A1 through A3.

TABLE 1
Summary of Results at the Completion of Each Survey Round in the Delphi Process to Establish a Consensus on the Use of Biologics in National Football League Athletes

Delphi Round	Response Rate, %	Total Items Included in Survey	Items Reaching Consensus,[a] %	New Items or Modifications Suggested
1	88.9	78	56.0	22
2	87.5	73	79.4	2
3	95.2	49	95.9	0

[a]In round 1 of the survey, items were retained for round 2 if ≥70% of the respondents agreed on their inclusion and <20% disagreed. Statements not meeting these criteria were discarded or modified per the responders' suggestions. In round 2, the items were retained for round 3 if ≥70% of respondents agreed and <10% disagreed. In round 3, items were considered as reaching a consensus if ≥75% of the respondents agreed and <10% disagreed.

Consensus Findings

A total of 7 principal domains were identified within the consensus, with critical elements discussed below.

(A) Biologics in General. Biologics can be defined as therapies that seek to improve healing and relieve symptoms in musculoskeletal injuries or conditions by modulating the local biological environment. Biologic strategies include autologous blood products such as platelet-rich plasma (PRP), autologous and allogeneic cell therapies, and growth factors. Although there are only a limited number of studies specifically evaluating biologic therapies in NFL athletes,[17] all respondents (100.0%) agreed that biologic treatments have the potential to improve symptoms in athletes with sports injuries. However, the use of biologic treatments should be based on a known mechanistic target for each indication, with indiscriminate use having the potential to undermine the legitimate use of these therapies. NFL team physicians appreciated that the use of treatment modalities in NFL players can influence patterns of use in the wider population, further highlighting the importance of ensuring athletes are as well-informed as possible when making decisions about their treatment.

(B) Challenges of Treating NFL Athletes. The treatment of NFL athletes presents unique clinical challenges. Treatment decisions can be influenced by factors including time in the season and the specific treatment requests of players. Although most respondents indicated that treatment decisions may also be influenced by the contract status of players (66.7%) and the teams' standing/season performance, these items did not reach consensus agreement. All respondents (100.0%) agreed that treatment decisions in NFL athletes should be made using current best evidence and clinical experience.

(C) Nomenclature/Terminology. Despite the potential of biologic therapies, a major challenge to advancement in clinical practice and research has been the lack of clear nomenclature for describing these treatments.[2,6] Ambiguous terminology can lead to mistaken assumptions regarding the characteristics of preparations. As direct-to-consumer

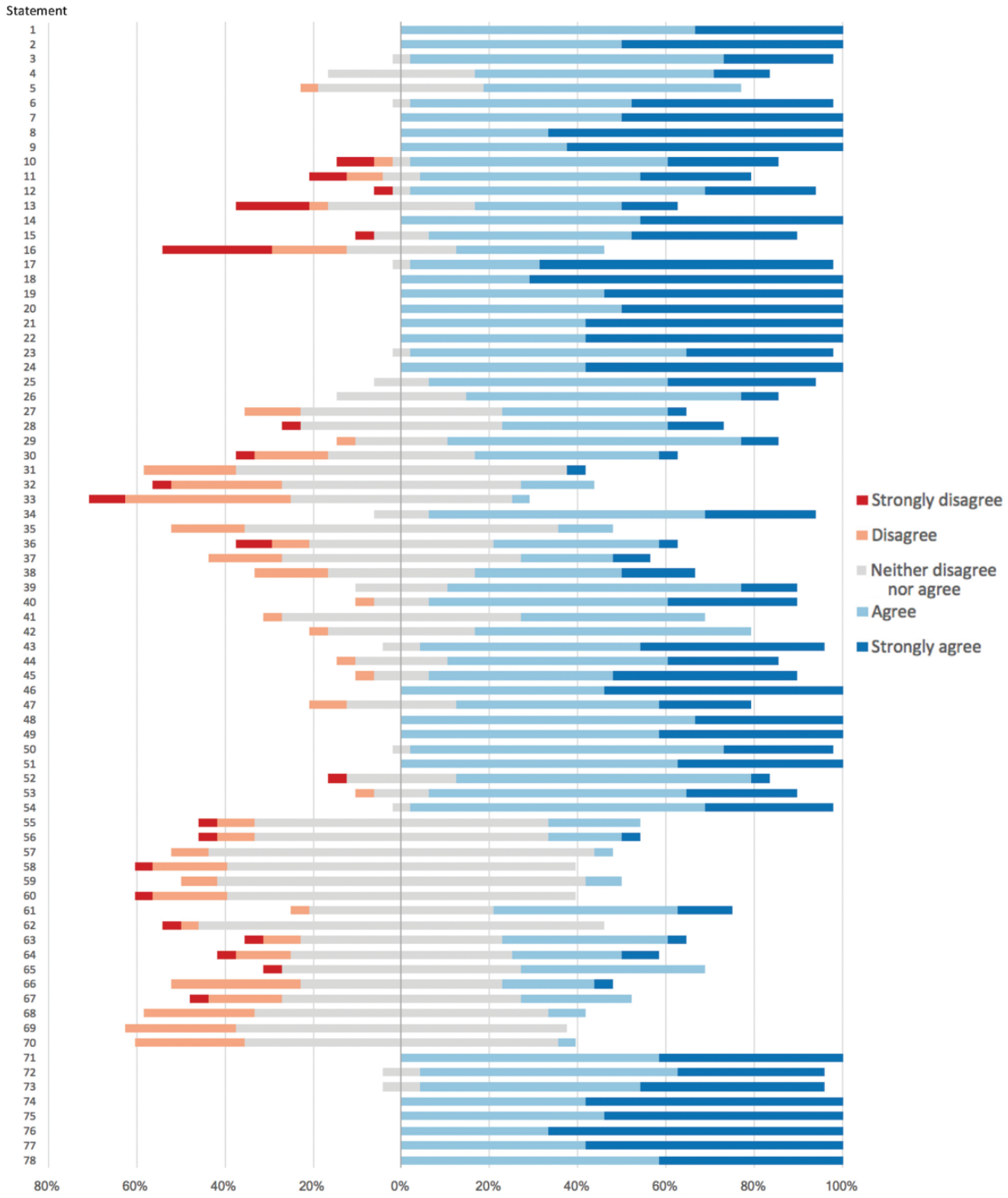

Figure 2. Levels of agreement for statements included within the first-round survey. Full statements and values are available in Appendix Table A1.

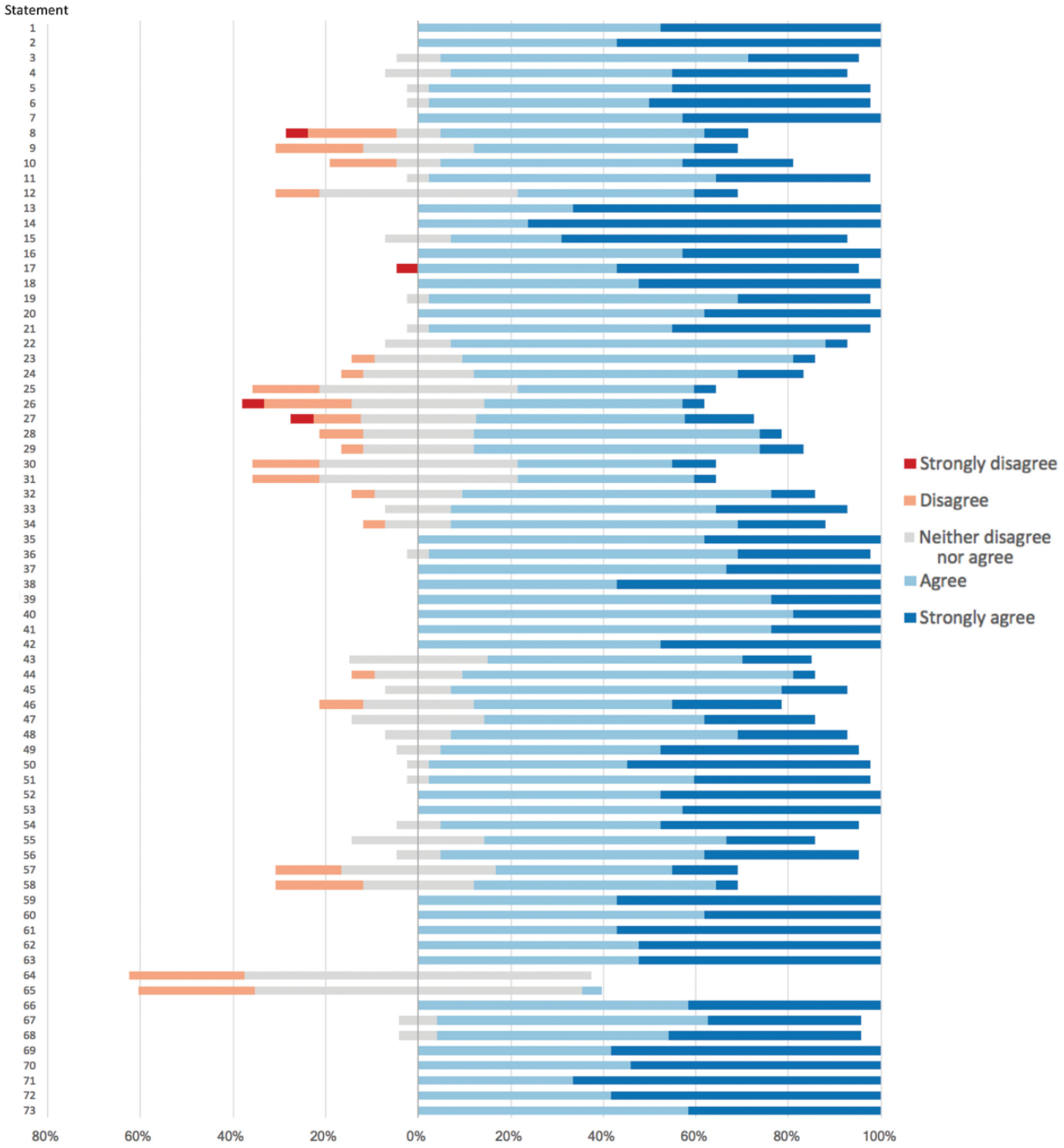

Figure 3. Levels of agreement for statements included within the second-round survey. Full statements and values are available in Appendix Table A2.

marketing is becoming more prominent, ambiguous terminology also makes it very challenging for athletes to understand the products they are considering, rendering them vulnerable to exploitation with misinformation.[8] Responding NFL team physicians agreed that biologic therapies should be described in a manner that is accurate and transparent (100.0% agreement) using terminology that best reflects the therapeutic components of the delivered therapy rather than a trade name (95.0%). All agreed that the introduction of novel terminology that does not accurately reflect

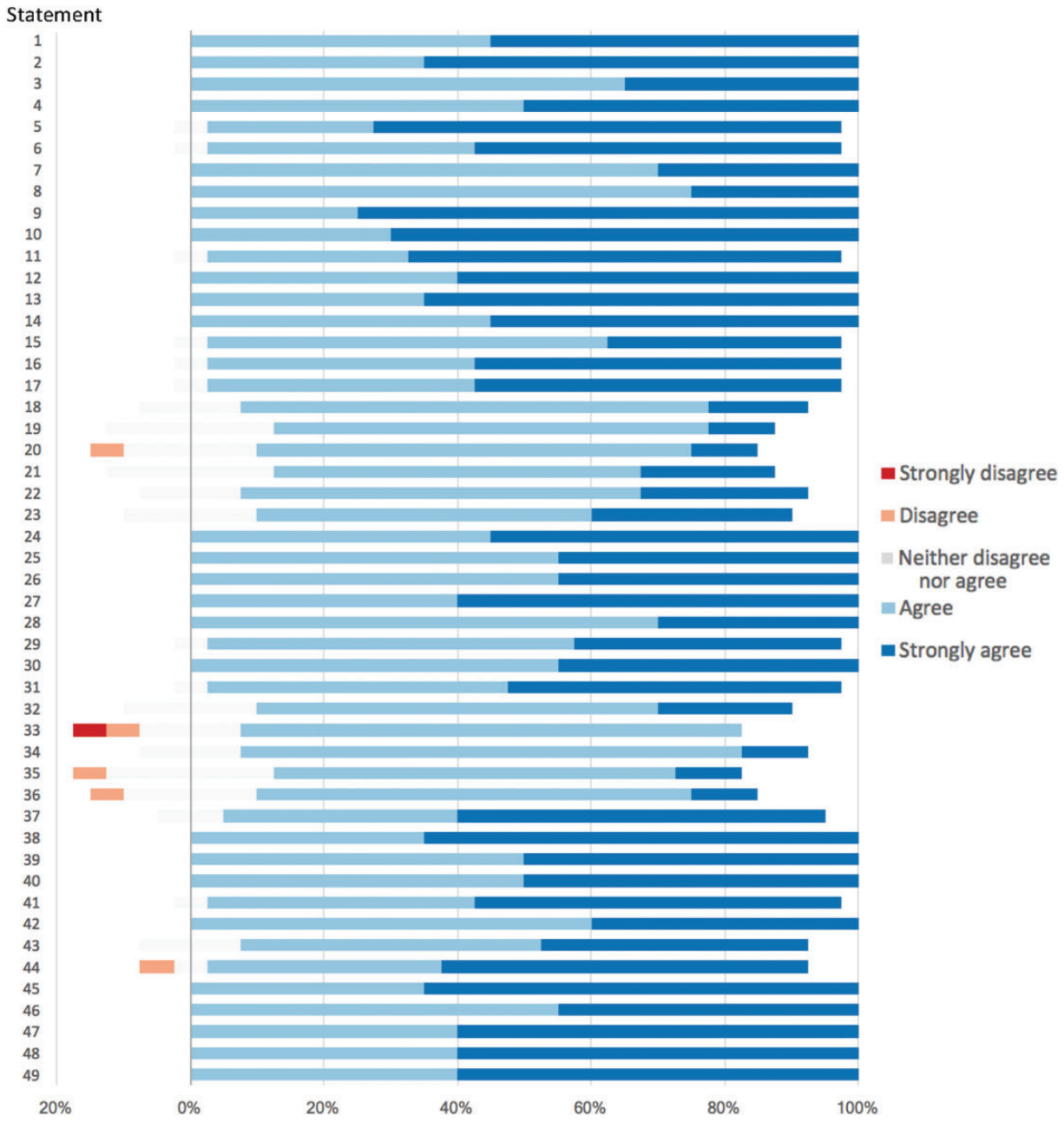

Figure 4. Levels of agreement for statements included within the third-round (final) survey. Full statements and values are available in Appendix Table A3.

the contents or proven therapeutic characteristics of biologic therapies may compound existing confusion relating to nomenclature.

Misrepresentation of uncharacterized cell preparations as stem cells has contributed to the increasing clinical use of unproven cellular therapies.[18] The term "stem cell" specifically refers to native cells that retain the ability to divide asymmetrically. This results in self-renewal where one daughter cell retains its "stemness," with the other daughter cell capable of generating a population of progenitor cells that can further differentiate and form new tissue. Human tissues contain significantly more mature cells than progenitor cells and vastly more progenitor cells than stem cells. Fewer than 1 in 20,000 cells in bone marrow may meet the criteria for a connective tissue progenitor, with even fewer meeting the cellular, molecular, or functional criteria for stem cells.[21] In normal conditions, progenitors capable of differentiating into connective tissues are not present in blood. As such, most so-called stem cell preparations being marketed directly to patients in the United States include very few cells that meet the definition of a stem cell. NFL team physicians were in total agreement

(100.0%) that to be described as stem cell preparations, cells must meet strict criteria, including the demonstrated ability to undergo asymmetric division, self-renewal, and multilineage differentiation.[24]

(D) Autologous Blood Products Including PRP. PRP represents a broad spectrum of preparations containing variable levels of platelets, leukocytes, red blood cells, cytokines, and growth factors.[8] The bioavailability of growth factors delivered as PRP depends on individual patient characteristics, the platelet concentration, levels of leukocytes and red blood cells, and the method of activation, among other variables.[22] PRP preparations are generally safe with low adverse event profiles. Further information is required to define the specific type of PRP that will be most effective for a specific condition or injury.[28] Indiscriminate use of the same type of PRP for widely different injuries and conditions has contributed to unpredictable and variable outcomes. Based on their experience and available data, NFL physicians agreed that leukocyte-rich PRP (LR-PRP) is associated with increased postprocedure discomfort over leukocyte-poor PRP (LP-PRP) (85.0%). While NFL team physicians reached a consensus that PRP has a positive impact on patellar tendinopathy (round 3; 75.0%) and knee osteoarthritis (OA) (round 3; 75.0%), the levels of agreement for a positive impact of PRP on Achilles tendinopathy (round 1; 50.0%), hamstring muscle injuries (45.8%), acromioclavicular joint injuries (round 1; 4.2%), adductor muscle injuries (round 1; 16.7%), ankle syndesmotic injuries (round 1; 12.5%), and meniscal tears (41.7%) did not reach sufficient agreement to be considered a consensus. There was agreement that LR-PRP should be used preferentially over LP-PRP for chronic tendinitis of the patellar tendon (75.0%), while LP-PRP was most appropriate for treating symptoms of knee OA. The clear majority of responding NFL physicians agreed that the best available evidence suggests that PRP preparations may be symptom modifying, and there are little data to suggest that they are structure modifying.

(E) Cell-Based Therapies. The use of cell therapies to treat musculoskeletal injuries has received increasing publicity in print and social media, leading many athletes to pursue these treatments. There has been an increase in the use of uncharacterized cellular therapies, and misrepresentation of uncharacterized cell preparations as stem cells has contributed to the widespread clinical use of unproven cellular therapies.[13] Less stringent regulations mean that certain practices such as the culture expansion of stem cells are permitted in certain foreign countries, leading patients to consider travel overseas ("medical tourism").[18] The risk of travel overseas is that the standards of medical processing and manufacturing in other countries are unknown and often not as rigorous as protocols in the United States. The best available evidence indicates that any therapeutic effect of mesenchymal stromal cells/connective tissue progenitors occurs through paracrine effects rather than differentiation and engraftment.[7] While NFL physicians agreed that some very limited data exist to suggest that cells derived from bone marrow and fat tissue may improve symptoms from OA of the knee (75.0% agreement), at present, there was insufficient evidence to support the routine use of placental/amniotic injections to treat musculoskeletal injuries in NFL athletes. Furthermore, there was no robust evidence to support the use of intravenous infusions of cell therapies for musculoskeletal applications.

(F) Guidance for NFL Team Physicians. NFL team physicians reached a consensus that biologics should be delivered under the direction of sports medicine physicians or orthopaedic surgeons (90.0% agreement) with expertise in these treatments. There was also agreement on the need to educate players and agents to discourage the widespread/indiscriminate use of these treatments and to educate athletes of the dangers of medical tourism. It was agreed that further resources for NFL athlete education relating to biologics would be of value, as currently available information online can be confusing, can be challenging to navigate, and frequently contains misinformation.[25] In the process of shared decision-making, the lack of strong evidence for existing biologic therapies should be communicated to NFL athletes, and treating physicians should, where possible, document all parameters of the biologic preparation delivered that may critically influence outcomes. To monitor use, facilitate the early recognition of adverse effects, and ultimately evaluate outcomes, team physicians agreed that a centralized database on the use of biologics in NFL athletes would be of value.

(G) Biologic Research in the NFL. It was recognized by all respondents that further research is required to better characterize different biologic preparations and to match the most appropriate preparations and indications. To facilitate this, standards that define the criteria used to characterize cell preparations are required, and methods for classifying therapies that accurately reflect biologic activity, are reliable, and are reproducible must be developed.

DISCUSSION

The most important finding was the consensus among NFL team physicians that biologics have the potential to improve healing and improve symptoms after an injury in NFL athletes but that, at present, there are limited data to guide treatment decisions. As such, treatment decisions must be based on best currently available evidence and clinical experience. Educational materials that accurately convey current levels of evidence for biologic treatments may facilitate shared decision-making. A further conclusion was the value of a database of biologic use that may provide real-time data on emerging patterns of outcomes in this specific patient population and aid the detection of adverse effects.

While NFL team physicians reached agreement that PRP has a positive impact on patellar tendinopathy and early knee OA, lower levels of agreement were reached on the value of PRP on Achilles tendinopathy (50.0%), hamstring injuries (45.8%), acromioclavicular joint injuries (4.2%), adductor injuries (16.7%), sports hernia/core muscle injuries (4.2%), ankle syndesmotic injuries (12.5%), and healing of meniscal tears (41.7%). This wide range of opinion on the value of PRP for specific applications highlights

the need for ongoing research, particularly studies with level 1 evidence. However, given the low adverse-event profile of PRP, it is still used in these settings based on shared decision-making between athletes and physicians on a case-by-case basis. Efforts should continue to be made to ensure athletes are aware of up-to-date evidence to facilitate this process and to ensure that athletes, their medical care providers, and their agents have reasonable expectations of outcomes. A challenge will be addressing the potential misconception by the wider public that the use of a treatment by an NFL player is testament to its clinical efficacy.

It should be noted that the statements reaching a consensus among NFL physicians do not always equate with more recent best scientific evidence. For example, NFL physicians agreed that LP-PRP was most appropriate for treating symptoms of knee OA. A recent meta-analysis has reported that the leukocyte concentration of PRP does not play a significant role in patient-reported outcome measures for knee OA.[1] Furthermore, there are now limited data from one direct comparison[33] and a meta-analysis performed as part of the most recent American Academy of Orthopaedic Surgeons clinical practice guidelines[3] that support greater benefit with LR-PRP at 9 and 12 months over LP-PRP for knee OA. NFL physicians also agreed that LP-PRP was most appropriate for treating chronic tendinitis of the patellar tendon. While a number of studies have supported the use of LR-PRP in this setting,[10] a recent prospective randomized controlled trial reported no superiority of LR-PRP or LP-PRP over saline in managing chronic patellar tendinitis.[29] Ongoing uncertainty regarding the most appropriate formulations of PRP highlights the need for further well-designed studies. Ongoing challenges to this research include heterogeneity in the stages and phenotypes of each disease and in orthobiologic preparations.[19] Moving forward, sound clinical evidence will also benefit from reduced heterogeneity in relation to the manufacture, potency, and delivery of products. As always in medicine, one solution does not fit all, and the stratification of patients with OA will contribute to our ability to develop more targeted interventions.

With respect to cell therapies, a key finding was concern among NFL physicians that misrepresentation of preparations as stem cells has contributed to a misunderstanding of how these therapies may exert an effect and unrealistic expectations among athletes. It is therefore essential that athletes understand the nature of cell therapy treatments that they receive, the current deficiencies in evidence, and the potential adverse effects. A key challenge will be protecting players from misinformation.

The Delphi method used here offers several advantages over group-based methods.[11] Anonymity of responses reduces the effects of dominant participants.[11] Online methods are as reliable as face-to-face panels,[32] improving rather than jeopardizing the quality of results. The high response rate across all 3 survey rounds of the Delphi process demonstrates engagement with the process by NFL physicians.

Limitations

This study has some limitations. While Delphi panel methodology facilitates a more scientific approach to a consensus than popular nominal group techniques,[12] it does not avoid the potential risk of bias in the selection of participants. It is possible that individual biases relating to the involvement with industry may have influenced certain responses. Although as few as 10 experts is considered adequate for content validation,[16] a larger group was chosen to encourage representation from all 32 NFL teams. The potential influence of any single participant was reduced by including more experts than most published Delphi studies and by setting the threshold levels of agreement for a consensus high. Efforts to establish whether these standards are practical and generalizable to other professional sports may be merited.

CONCLUSION

This study has established an expert consensus on 47 statements relating to the use of biologics in NFL athletes. Effort should continue to educate athletes, team medical staff, agents, and other stakeholders on the best available evidence for the efficacy and potential adverse events of biologic therapies to facilitate informed decision-making.

AUTHORS

Members of the Group of American Professional Football Team Physicians: Larry Bankston, MD (New Orleans Saints); Asheesh Bedi, MD (Detroit Lions); Martin Boublik, MD (Denver Broncos); Mark Bowen, MD (Chicago Bears); James P. Bradley, MD (Pittsburgh Steelers); Dan E. Cooper, MD (Dallas Cowboys); Charles Craythorne, MD (Tampa Bay Buccaneers); Leigh-Ann Curl, MD (Baltimore Ravens); Neal ElAttrache, MD (Los Angeles Rams); David S. Gazzaniga, MD (Los Angeles Chargers); Fares S. Haddad, BSc, MD(Res) (NFL London); Kyle E. Hammond, MD (Atlanta Falcons); Kevin Kaplan, MD (Jacksonville Jaguars); Elias Edward Khalfayan, MD (Seattle Seahawks); Christopher Larson, MD (Minnesota Vikings); Timothy R. McAdams, MD (San Francisco 49ers); Matthew Pepe, MD (Philadelphia Eagles); Mark D. Price, MD, PhD (New England Patriots); Scott A. Rodeo, MD (New York Giants); J. Paul Schroeppel, MD (Kansas City Chiefs); John Uribe, MD (Miami Dolphins); James Voos, MD (Cleveland Browns); Gary Waslewski, MD (Arizona Cardinals); and Robin West, MD (Washington Commanders).

REFERENCES

1. Abbas A, Du JT, Dhotar HS. The effect of leukocyte concentration on platelet-rich plasma injections for knee osteoarthritis: a network meta-analysis. *J Bone Joint Surg Am*. 2022;104(6):559-570.
2. Abrams GD, Murray IR. Editorial commentary: please don't call it a mesenchymal stem cell. *Arthroscopy*. 2020;36(8):2134-2136.
3. American Academy of Orthopaedic Surgeons. Management of osteoarthritis of the knee (nonarthroplasty) evidence-based clinical

practice guideline. Published 2021. Accessed January 29, 2022. https://www.aaos.org/oak3cpg
4. Belk JW, Kraeutler MJ, Houck DA, et al. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2021;49(1):249-260.
5. Bradley JP, Lawyer TJ, Ruef S, Towers JD, Arner JW. Platelet-rich plasma shortens return to play in National Football League players with acute hamstring injuries. *Orthop J Sports Med*. 2020;8(4):2325967120911731.
6. Caplan AI. Mesenchymal stem cells: time to change the name! *Stem Cells Transl Med*. 2017;6(6):1445-1451.
7. Caplan AI, Correa D. The MSC: an injury drugstore. *Cell Stem Cell*. 2011;9(1):11-15.
8. Chahla J, Cinque ME, Piuzzi NS, et al. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am*. 2017;99(20):1769-1779.
9. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. 2014;67(4):401-409.
10. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med*. 2014;42(3):610-618.
11. Greenhalgh T, Wong G, Jagosh J, et al. Protocol—the RAMESES II study: developing guidance and reporting standards for realist evaluation. *BMJ Open*. 2015;5(8):e008567.
12. Hohmann E, Brand JC, Rossi MJ, Lubowitz JH. Expert opinion is necessary: Delphi panel methodology facilitates a scientific approach to consensus. *Arthroscopy*. 2018;34(2):349-351.
13. Kingery MT, Schoof L, Strauss EJ, Bosco JA, Halbrecht J. Online direct-to-consumer advertising of stem cell therapy for musculoskeletal injury and disease: misinformation and violation of ethical and legal advertising parameters. *J Bone Joint Surg Am*. 2020;102(1):2-9.
14. Kluczynski MA, Kelly WH, Lashomb WM, Bisson LJ. A systematic review of the orthopaedic literature involving National Football League players. *Orthop J Sports Med*. 2019;7(8):2325967119864356.
15. Likert R. A technique for the measurement of attitudes. *Arch Psychol*. 1932;140:1-55.
16. Lynn MR. Determination and quantification of content validity. *Nurs Res*. 1986;35(6):382-385.
17. Makaram NS, Murray IR, Rodeo SA, et al. The use of biologics in professional and Olympic sport: a scoping review protocol. *Bone Joint Open*. 2020;1(11):715-719.
18. Murray IR, Chahla J, Frank RM, et al. Rogue stem cell clinics. *Bone Joint J*. 2020;102-B(2):148-154.
19. Murray IR, Geeslin AG, Goudie EB, Petrigliano F, LaPrade RF. Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. *J Bone Joint Surg Am*. 2017;99(10):809-819.
20. Murray IR, Makaram NS, Rodeo SA, et al. Biologics in professional and Olympic sport: a scoping review. *Bone Joint J*. 2021;103-B(7):1189-1196.
21. Muschler GF, Nakamoto C, Griffith LG. Engineering principles of clinical cell-based tissue engineering. *J Bone Joint Surg Am*. 2004;86(7):1541-1558.
22. Mussano F, Genova T, Munaron L, et al. Cytokine, chemokine, and growth factor profile of platelet-rich plasma. *Platelets*. 2016;27(5):467-471.
23. Niederberger M, Spranger J. Delphi technique in health sciences: a map. *Front Public Health*. 2020;8:457.
24. Piuzzi NS, Dominici M, Long M, et al. Proceedings of the signature series symposium "Cellular Therapies for Orthopaedics and Musculoskeletal Disease Proven and Unproven Therapies: Promise, Facts and Fantasy," International Society for Cellular Therapies, Montreal, Canada, May 2, 2018. *Cytotherapy*. 2018;20(11):1381-1400.
25. Piuzzi NS, Ng M, Chughtai M, et al. The stem-cell market for the treatment of knee osteoarthritis: a patient perspective. *J Knee Surg*. 2018;31(6):551-556.
26. Rodeo SA. Moving toward responsible use of biologics in sports medicine. *Am J Sports Med*. 2018;46(8):1797-1799.
27. Rodeo SA, Bedi A. 2019-2020 NFL and NFL Physician Society orthobiologics consensus statement. *Sports Health*. 2020;12(1):58-60.
28. Rossi LA, Murray IR, Chu CR, et al. Classification systems for platelet-rich plasma. *Bone Joint J*. 2019;101-B(8):891-896.
29. Scott A, LaPrade RF, Harmon KG, et al. Platelet-rich plasma for patellar tendinopathy: a randomized controlled trial of leukocyte-rich PRP or leukocyte-poor PRP versus saline. *Am J Sports Med*. 2019;47(7):1654-1661.
30. Sheth SB, Anandayuvaraj D, Patel SS, Sheth BR. Orthopaedic and brain injuries over last 10 seasons in the National Football League (NFL): number and effect on missed playing time. *BMJ Open Sport Exerc Med*. 2020;6(1):e000684.
31. Tang S, Wang X, Wu P, et al. Platelet-rich plasma vs autologous blood vs corticosteroid injections in the treatment of lateral epicondylitis: a systematic review, pairwise and network meta-analysis of randomized controlled trials. *PM R*. 2020;12(4):397-409.
32. Washington DL, Bernstein SJ, Kahan JP, et al. Reliability of clinical guideline development using mail-only versus in-person expert panels. *Med Care*. 2003;41(12):1374-1381.
33. Yaradilmis YU, Demirkale I, Safa Tagral A, et al. Comparison of two platelet rich plasma formulations with viscosupplementation in treatment of moderate grade gonarthrosis: a prospective randomized controlled study. *J Orthop*. 2020;20:240-246.
34. Zlotnicki JP, Geeslin AG, Murray IR, et al. Biologic Treatments for Sports Injuries II Think Tank: current concepts, future research, and barriers to advancement. Part 3: articular cartilage. *Orthop J Sports Med*. 2016;4(4):2325967116642433.

APPENDIX

APPENDIX TABLE A1
Levels of Agreement for Items Included in the Round 1 Survey[a]

Round 1 Items	% Disagree	% Agree
A. Biologics in General		
1. Orthobiologics can be defined as therapies that seek to improve healing and relieve symptoms in musculoskeletal injuries or conditions by modulating the local biological environment	0.0	100.0
2. Orthobiologics include autologous blood products, autologous and allogeneic cell therapies, and growth factors	0.0	100.0
3. Orthobiologics have the potential to improve symptoms in athletes with sports injuries	0.0	95.8
4. Orthobiologics have the potential to improve function in athletes with sports injuries	0.0	66.7
5. Orthobiologics have the potential to increase tissue regeneration after sports injuries	4.2	58.3
6. The use of orthobiologic treatments should be based on a known mechanistic target for each indication	0.0	95.8
7. The use of treatment modalities in NFL players can influence patterns of use in the wider population	0.0	100.0
B. Challenges of Treating NFL Athletes		
8. The treatment of NFL athletes presents unique clinical challenges	0.0	100.0
Treatment decisions in NFL athletes can be influenced by		
9. *Time in season*	0.0	100.0
10. *Player's contract status*	12.5	83.3
11. *Team standing/season performance*	16.7	75.0
12. *Player's position*	4.2	91.7
13. *Injury status of teammates*	20.8	45.8
14. *Player's treatment requests*	0.0	100.0
15. *Agent's treatment requests*	4.2	83.3
16. *Coach/management's treatment requests*	41.7	33.3
17. Treatment decisions regarding the use of orthobiologics in NFL athletes should be based on current best evidence and clinical experience	0.0	95.8
C. Nomenclature/Terminology		
18. Orthobiologic therapies should be described in a manner that is accurate and transparent	0.0	100.0
19. Orthobiologic therapies should be described in a manner that best reflects the therapeutic component(s) of the delivered therapy rather than a trade name	0.0	100.0
20. The introduction of novel terminology that does not accurately reflect the contents or proven therapeutic characteristics of orthobiologic therapies may compound existing confusion relating to the nomenclature	0.0	100.0
D. Autologous Blood Products Including PRP		
21. PRP represents a broad spectrum of preparations containing variable levels of platelets, leukocytes, red blood cells, cytokines, and growth factors	0.0	100.0
22. The bioavailability of growth factors delivered as PRP depends on individual patient characteristics, the platelet concentration, levels of leukocytes and red blood cells, and the method of activation, among other variables	0.0	100.0
23. PRP preparations are generally safe, with low adverse event profiles	0.0	95.8
24. Further information is required to define the specific type of PRP that will be most effective for a specific condition or injury	0.0	100.0
25. Indiscriminate use of the same type of PRP for widely different injuries and conditions has contributed to unpredictable and variable outcomes	0.0	87.5
26. Leukocyte-rich PRP is associated with increased postprocedure discomfort over leukocyte-poor PRP	0.0	70.8
27. Leukocyte-rich PRP is associated with increased rehabilitation time over leukocyte-poor PRP	12.5	41.7
PRP has a positive impact on		
28. *Achilles tendinopathy*	4.2	50.0
29. *Patellar tendinopathy*	4.2	75.0
30. *Hamstring muscle injuries*	20.8	45.8
31. *Acromioclavicular joint injuries*	20.8	4.2
32. *Adductor muscle injuries*	29.2	16.7
33. *Sports hernia injuries*	45.8	4.2
34. *Knee OA/degenerative changes*	0.0	87.5
35. *Ankle syndesmotic injuries*	16.7	12.5
36. *Healing of meniscal repairs*	16.7	41.7
37. PRP does not assist with regeneration or improve healing of tendon/ligament repairs	16.7	29.2
38. PRP does not facilitate cartilage tissue regeneration or healing	16.7	50.0
39. Leukocyte-rich PRP should be used preferentially over leukocyte-poor PRP for chronic tendinitis of the patellar tendon in non-NFL athletic populations	0.0	79.2

(continued)

Appendix Table A1 (continued)

Round 1 Items	% Disagree	% Agree
40. Leukocyte-poor PRP should be used preferentially over leukocyte-rich PRP for symptoms of OA of the knee in non-NFL athletic populations	4.2	83.3
41. To minimize time away from sport during the season, it is acceptable to use leukocyte-poor preparations in the management of tendon and ligament injuries in NFL athletes	4.2	41.7
42. PRP can be preferentially used to treat injuries during a bye week to minimize game time loss	4.2	62.5
E. Cell-Based Therapies		
43. To be described as stem cell preparations, cells must meet strict criteria including the demonstrated ability to undergo self-renewal and to regenerate other types of cells and tissues	0.0	91.7
44. While stem cells can be isolated from tissues such as bone marrow and fat, the number of true stem cells is extremely small (approximately 1 in 10,000 cells)	4.2	75.0
45. Existing clinically available cell preparations in the United States include very few cells that meet the definition of a stem cell	4.2	83.3
46. The use of cell therapies for the treatment of numerous conditions has received increasing publicity in print and social media, leading many athletes to pursue these treatments	0.0	100.0
47. There is no high-quality evidence available to support the routine use of cell therapy for any musculoskeletal injuries	8.3	66.7
48. Less stringent regulations mean that certain practices such as the culture expansion of "stem cells" are permitted in certain foreign countries, leading patients to consider travel overseas ("medical tourism")	0.0	100.0
49. The risk of travel overseas is that the standards of medical processing and manufacturing in other countries are unknown and often not as rigorous as protocols in the United States	0.0	100.0
50. There has been an increase in the use of uncharacterized cellular therapies to treat musculoskeletal abnormalities	0.0	95.8
51. Misrepresentation of uncharacterized cell preparations as stem cells has contributed to the widespread clinical use of unproven cellular therapies	0.0	100.0
52. Some very limited data exist to suggest that cells derived from bone marrow and fat tissue may improve symptoms from OA of the knee	4.2	70.8
53. There is no evidence to support the use of intravenous infusions of stem cells to treat musculoskeletal disorders	4.2	83.3
54. Further research is required to determine the most appropriate BMAC formulation for any given indication	0.0	95.8
BMAC has a positive impact on		
55. *Achilles tendinopathy*	12.5	20.8
56. *Patellar tendinopathy*	12.5	20.8
57. *Hamstring muscle injuries*	8.3	4.2
58. *Acromioclavicular joint injuries*	20.8	0.0
59. *Adductor muscle injuries*	8.3	8.3
60. *Sports hernia injuries*	20.8	0.0
61. *Knee OA/degenerative changes*	4.2	54.2
62. *Ankle syndesmotic injuries*	8.3	0.0
63. *Healing of meniscal repairs*	12.5	41.7
64. *Healing of tendon/ligament repairs*	16.7	33.3
65. *Engraftment of osteochondral allografts*	4.2	41.7
66. BMAC does not facilitate cartilage tissue regeneration or healing	29.2	25.0
67. BMAC can be preferentially used to treat injuries during a bye week to minimize game time loss	20.8	25.0
68. Placental/amniotic cord blood–based cell products have a positive impact on degenerative knee conditions	25.0	8.3
69. Placental/amniotic cord blood–based cell products have a positive impact on muscle strain injuries	25.0	0.0
70. Placental/amniotic cord blood–based cell products have a positive impact on tendon/ligament injuries	25.0	4.2
F. Guidance for NFL Team Physicians		
71. The lack of strong evidence for existing orthobiologic therapies should be communicated to NFL athletes in shared decision-making	0.0	100.0
72. Treating physicians should document all parameters of the orthobiologic preparation delivered that may critically influence outcomes	0.0	91.7
73. A centralized database on the use of orthobiologics in NFL athletes would provide real-time data on emerging patterns of outcomes in this specific patient population and aid the detection of adverse effects	0.0	91.7
G. Biologic Research in the NFL		
74. Research is required to better characterize different orthobiologic preparations	0.0	100.0
75. Standards that define the criteria used to characterize cell preparations are required	0.0	100.0
76. Research is required to match the most appropriate orthobiologic preparations and indications	0.0	100.0
77. Further study is required to identify methods for the classification of orthobiologic therapies that accurately reflect biologic activity and that are reliable and reproducible	0.0	100.0
78. Minimum reporting standards of experimental variables that may influence outcomes of orthobiologic treatments should be used	0.0	100.0

[a]Items were considered for round 2 if they reached ≥70% agreement with <20% disagreement. BMAC, bone marrow aspirate concentrate; NFL, National Football League; OA, osteoarthritis; PRP, platelet-rich plasma.

APPENDIX TABLE A2
Levels of Agreement for Items Included in the Round 2 Survey[a]

Round 2 Items	% Disagree	% Agree
A. Biologics in General		
1. Orthobiologics can be defined as therapies that seek to improve healing and relieve symptoms in musculoskeletal injuries or conditions by modulating the local biological environment	0.0	100.0
2. Orthobiologics include autologous blood products, autologous and allogeneic cell therapies, and growth factors	0.0	100.0
3. Orthobiologics have the potential to improve symptoms in athletes with sports injuries	0.0	90.5
4. The use of orthobiologic treatments should be based on a known mechanistic target for each indication	0.0	85.7
5. The use of treatment modalities in NFL players can influence patterns of use in the wider population	0.0	95.2
B. Challenges of Treating NFL Athletes		
6. The treatment of NFL athletes presents unique clinical challenges	0.0	95.2
Treatment decisions in NFL athletes can be influenced by		
7. *Time in season*	0.0	100.0
8. *Player's contract status*	23.8	66.7
9. *Team standing/season performance*	19.1	57.1
10. *Player's position*	14.3	76.2
11. *Player's treatment requests*	0.0	95.2
12. *Agent's treatment requests*	9.5	47.6
13. Treatment decisions regarding the use of orthobiologics in NFL athletes should be based on current best evidence and clinical experience	0.0	100.0
C. Nomenclature/Terminology		
14. Orthobiologic therapies should be described in a manner that is accurate and transparent	0.0	100.0
15. Orthobiologic therapies should be described in a manner that best reflects the therapeutic component(s) of the delivered therapy rather than a trade name	0.0	85.7
16. The introduction of novel terminology that does not accurately reflect the contents or proven therapeutic characteristics of orthobiologic therapies may compound existing confusion relating to the nomenclature	0.0	100.0
D. Autologous Blood Products Including PRP		
17. PRP represents a broad spectrum of preparations containing variable levels of platelets, leukocytes, red blood cells, cytokines, and growth factors	4.8	95.2
18. The bioavailability of growth factors delivered as PRP depends on individual patient characteristics, the platelet concentration, levels of leukocytes and red blood cells, and the method of activation, among other variables	0.0	100.0
19. PRP preparations are generally safe, with low adverse event profiles	0.0	95.2
20. Further information is required to define the specific type of PRP that will be most effective for a specific condition or injury	0.0	100.0
21. Indiscriminate use of the same type of PRP for widely different injuries and conditions has contributed to unpredictable and variable outcomes	0.0	95.2
22. Leukocyte-rich PRP is associated with increased postprocedure discomfort over leukocyte-poor PRP	0.0	85.7
PRP has a positive impact on		
23. *Patellar tendinopathy*	4.8	76.2
24. *Knee OA/degenerative changes*	4.8	71.4
There is currently not sufficient evidence to support a positive impact of PRP on		
25. *Achilles tendinopathy*	14.3	42.9
26. *Hamstring muscle injuries*	23.8	47.6
27. *Acromioclavicular joint injuries*	15.0	60.0
28. *Adductor muscle injuries*	9.5	66.7
29. *Sports hernia injuries*	4.8	71.4
30. *Ankle syndesmotic injuries*	14.3	42.9
31. *Healing of meniscal repairs*	14.3	42.9
32. Leukocyte-rich PRP should be used preferentially over leukocyte-poor PRP for chronic tendinitis of the patellar tendon	4.8	76.2
33. Leukocyte-poor PRP should be used preferentially over leukocyte-rich PRP for symptoms of OA of the knee	0.0	85.7
34. The best available evidence suggests that PRP preparations may be "symptom modifying," and there are little data to suggest that they are "structure modifying"	4.8	81.0
E. Cell-Based Therapies		
35. To be described as "stem cell preparations," cells must meet strict criteria including the demonstrated ability to undergo self-renewal and to regenerate other types of cells and tissues	0.0	100.0
36. While stem cells can be isolated from tissues such as bone marrow and fat, the number of true stem cells is extremely small (approximately 1 in 10,000 cells)	0.0	95.2
37. Existing clinically available cell preparations in the United States include very few cells that meet the definition of a stem cell	0.0	100.0
38. The use of cell therapies for the treatment of numerous conditions has received increasing publicity in print and social media, leading many athletes to pursue these treatments	0.0	100.0

(continued)

Appendix Table A2 (continued)

Round 2 Items	% Disagree	% Agree
39. Less stringent regulations mean that certain practices such as the culture expansion of "stem cells" are permitted in certain foreign countries, leading patients to consider travel overseas ("medical tourism")	0.0	100.0
40. The risk of travel overseas is that the standards of medical processing and manufacturing in other countries are unknown and often not as rigorous as protocols in the United States	0.0	100.0
41. There has been an increase in the use of uncharacterized cellular therapies to treat musculoskeletal abnormalities	0.0	100.0
42. Misrepresentation of uncharacterized cell preparations as stem cells has contributed to the widespread clinical use of unproven cellular therapies	0.0	100.0
43. The best available evidence indicates that any therapeutic effect of mesenchymal stromal cells/connective tissue progenitors occurs through paracrine effects rather than differentiation and engraftment	0.0	66.7
44. Some very limited data exist to suggest that cells derived from bone marrow and fat tissue may improve symptoms from OA of the knee	4.8	76.2
45. There is no evidence to support the use of intravenous infusions of stem cells to treat musculoskeletal disorders	0.0	85.7
46. There is currently not sufficient evidence to support the routine use of bone marrow aspirate concentrate injections to treat musculoskeletal injuries in NFL athletes	9.5	66.7
47. There is currently not sufficient evidence to support the routine use of microfragmented adipose tissue injections to treat musculoskeletal injuries in NFL athletes	0.0	71.4
48. There is currently not sufficient evidence to support the routine use of placental/amniotic cord blood–based injections to treat musculoskeletal injuries in NFL athletes	0.0	85.7
F. Guidance for NFL Team Physicians		
49. Biologics should be delivered under the direction of sports medicine physicians or orthopaedic surgeons	0.0	90.5
50. There is a need to educate players and agents so as to discourage the widespread/indiscriminate use of these treatments	0.0	95.2
51. There is a need to educate players and agents of the dangers of medical tourism	0.0	95.2
52. Resources for NFL athlete education relating to biologics would be of value	0.0	100.0
53. The lack of strong evidence for existing orthobiologic therapies should be communicated to NFL athletes in shared decision-making	0.0	100.0
54. Treating physicians should document all parameters of the orthobiologic preparation delivered that may critically influence outcomes	0.0	90.5
55. When communicating with players and agents, the term stem cell should not be used to prevent misinterpretation of the likely actions of biologics	0.0	71.4
56. A centralized database on the use of orthobiologics in NFL athletes would provide real-time data on emerging patterns of outcomes in this specific patient population and aid the detection of adverse effects	0.0	90.5
57. Contributions to a centralized database on the use of orthobiologics in NFL athletes should be voluntary	14.3	52.4
58. A centralized database on the use of orthobiologics in NFL athletes should initially focus on documenting the range of biologic use in the NFL and reporting of adverse effects rather than seeking to establish efficacy	19.1	57.1
G. Biologic Research in the NFL		
59. Research is required to better characterize different orthobiologic preparations	0.0	100.0
60. Standards that define the criteria used to characterize cell preparations are required	0.0	100.0
61. Research is required to match the most appropriate orthobiologic preparations and indications	0.0	100.0
62. Further study is required to identify methods for the classification of orthobiologic therapies that accurately reflect biologic activity and that are reliable and reproducible	0.0	100.0
63. Minimum reporting standards of experimental variables that may influence outcomes of orthobiologic treatments should be used in clinical and preclinical studies	0.0	100.0
64. Placental/amniotic cord blood–based cell products have a positive impact on muscle strain injuries	25.0	0.0
65. Placental/amniotic cord blood–based cell products have a positive impact on tendon/ligament injuries	25.0	4.2
F. Guidance for NFL Team Physicians[b]		
66. The lack of strong evidence for existing orthobiologic therapies should be communicated to NFL athletes in shared decision-making	0.0	100.0
67. Treating physicians should document all parameters of the orthobiologic preparation delivered that may critically influence outcomes	0.0	91.7
68. A centralized database on the use of orthobiologics in NFL athletes would provide real-time data on emerging patterns of outcomes in this specific patient population and aid the detection of adverse effects	0.0	91.7
G. Biologic Research in the NFL[b]		
69. Research is required to better characterize different orthobiologic preparations	0.0	100.0
70. Standards that define the criteria used to characterize cell preparations are required	0.0	100.0
71. Research is required to match the most appropriate orthobiologic preparations and indications	0.0	100.0
72. Further study is required to identify methods for the classification of orthobiologic therapies that accurately reflect biologic activity and that are reliable and reproducible	0.0	100.0
73. Minimum reporting standards of experimental variables that may influence outcomes of orthobiologic treatments should be used	0.0	100.0

[a]Items were considered for inclusion in round 3 if they reached ≥70% agreement with <10% disagreement. NFL, National Football League; OA, osteoarthritis; PRP, platelet-rich plasma.

[b]Experts were asked to rerank these items, which had reached a consensus in the previous round.

APPENDIX TABLE A3
Levels of Agreement for Items Included in the Round 3 Survey[a]

Round 3 Items	% Disagree	% Agree
A. Biologics in General		
1. Biologics can be defined as therapies that seek to improve healing and relieve symptoms in musculoskeletal injuries or conditions by modulating the local biological environment	0.0	100.0
2. Biologics include autologous blood products, autologous and allogeneic cell therapies, and growth factors	0.0	100.0
3. Biologics have the potential to improve symptoms in athletes with sports injuries	0.0	100.0
4. The use of biologic treatments should be based on a known mechanistic target for each indication	0.0	100.0
5. The use of treatment modalities in NFL players can influence patterns of use in the wider population	0.0	95.0
B. Challenges of Treating NFL Athletes		
6. The treatment of NFL athletes presents unique clinical challenges	0.0	95.0
7. Treatment decisions can be influenced by time in the season	0.0	100.0
8. Treatment decisions can be influenced by a player's treatment requests	0.0	100.0
9. Treatment decisions in NFL athletes should be based on current best evidence and clinical experience	0.0	100.0
C. Nomenclature/Terminology		
10. Therapies should be described in a manner that is accurate and transparent	0.0	100.0
11. Therapies should be described in a manner that best reflects the therapeutic component(s) of the delivered therapy	0.0	95.0
12. The introduction of novel terminology that does not accurately reflect the contents or proven therapeutic characteristics of biologic therapies may compound existing confusion relating to the nomenclature	0.0	100.0
D. Autologous Blood Products Including PRP		
13. PRP represents a broad spectrum of preparations containing variable levels of platelets, white blood cells, red blood cells, cytokines, and growth factors	0.0	100.0
14. The bioavailability of growth factors delivered as PRP depends on individual patient characteristics, the platelet concentration, levels of white blood cells and red blood cells, and the method of activation, among other variables	0.0	100.0
15. PRP preparations are generally safe, with low adverse event profiles	0.0	95.0
16. Further information is required to define the specific type of PRP that will be most effective for a specific condition or injury	0.0	95.0
17. Indiscriminate use of similar preparations for different conditions has contributed to unpredictable/variable outcomes	0.0	95.0
18. Leukocyte-rich PRP is associated with increased postprocedure discomfort over leukocyte-poor PRP	0.0	85.0
19. PRP has a positive impact on patellar tendinopathy	0.0	75.0
20. PRP has a positive impact on knee OA/degenerative changes	5.0	75.0
21. Leukocyte-rich PRP should be used preferentially over leukocyte-poor PRP for chronic tendinitis of the patellar tendon	0.0	75.0
22. Leukocyte-poor PRP should be used preferentially over leukocyte-rich PRP for symptoms of OA of the knee	0.0	85.0
23. Best available evidence suggests that PRP may be "symptom modifying," with little data to suggest that they are "structure modifying"	0.0	80.0
E. Cell-Based Therapies		
24. To be described as stem cell preparations, cells must meet strict criteria including the demonstrated ability to undergo self-renewal and to regenerate other types of cells and tissues	0.0	100.0
25. While cells can be isolated from tissues such as bone marrow and fat, the number of true stem cells is extremely small	0.0	100.0
26. Existing clinically available "stem cell preparations" in the United States include very few cells that meet the definition of a stem cell	0.0	100.0
27. Cell therapies have received increasing publicity in the media, leading many athletes to pursue these treatments	0.0	100.0
28. Less stringent regulations mean that certain practices such as the culture expansion of "stem cells" are permitted in certain foreign countries, leading patients to consider travel overseas ("medical tourism")	0.0	100.0
29. Standards of medical processing and manufacturing in other countries are unknown and often not as rigorous as the United States	0.0	95.0
30. There has been an increase in the use of uncharacterized cellular therapies to treat musculoskeletal abnormalities	0.0	100.0
31. Misrepresentation of uncharacterized preparations as stem cells has contributed to an increased use of unproven therapies	0.0	95.0
32. Best available evidence indicates that any therapeutic effect of mesenchymal stromal cells/connective tissue progenitors occurs through paracrine effects rather than differentiation and engraftment	0.0	80.0
33. Some limited data exist to suggest that cells from bone marrow and fat tissue may improve symptoms from knee OA[b]	10.0	75.0
34. There is no evidence to support the use of intravenous stem cell infusions to treat musculoskeletal disorders	0.0	85.0
35. There is insufficient evidence to support the routine use of microfragmented adipose tissue to treat injuries in NFL athletes[b]	5.0	70.0
36. There is insufficient evidence to support the routine use of placental/amniotic injections to treat injuries in NFL athletes	5.0	75.0

(continued)

Appendix Table A3 (continued)

Round 3 Items	% Disagree	% Agree
F. Guidance for NFL Team Physicians		
37. Biologics should be delivered under the direction of sports medicine physicians or orthopaedic surgeons	0.0	90.0
38. There is a need to educate players and agents to discourage the widespread/indiscriminate use of these treatments	0.0	100.0
39. There is a need to educate players and agents of the dangers of medical tourism	0.0	100.0
40. Resources for NFL athlete education relating to biologics would be of value	0.0	100.0
41. The lack of strong evidence for existing biologic therapies should be communicated to athletes in shared decision-making	0.0	95.0
42. Physicians should document all parameters of the biologic preparation delivered that may critically influence outcomes	0.0	100.0
43. The term stem cell should not be used to prevent misinterpretation of the likely actions of biologic therapies	0.0	85.0
44. A centralized database on the use of biologics in NFL athletes would provide real-time data on emerging patterns of outcomes in this specific patient population and aid the detection of adverse effects	5.0	90.0
G. Biologic Research in the NFL		
45. Research is required to better characterize different biologic preparations	0.0	100.0
46. Standards that define the criteria used to characterize cell preparations are required	0.0	100.0
47. Research is required to match the most appropriate biologic preparations and indications	0.0	100.0
48. Further study is required to identify methods for the classification of biologics that are reliable and reproducible and accurately reflect biologic activity	0.0	100.0
49. Minimum reporting standards of variables that may influence outcomes of biologic treatments should be used in clinical studies	0.0	100.0

[a]NFL, National Football League; OA, osteoarthritis; PRP, platelet-rich plasma.
[b]Items not reaching a consensus, defined as $\geq$75% agreement with $<$10% disagreement.