Cement augmentation of suture anchors in the proximal humerus during rotator cuff repair improves pullout strength: a systematic review

Jeff S Kimball, Anirudh K Gowd, Brian R Waterman, Seth L Sherman, Jorge Chahla, Nirav H Amin, Joseph Liu

ABSTRACT

Importance Rotator cuff pathology is a growing concern in the ageing population. If cement augmentation of suture anchors improves pullout strength, its application can potentially be applied in cases of poor bone quality to prevent anchor failure.

Objective To evaluate the biomechanical benefits and fixation strength of cement-augmented versus non-augmented suture anchors in the proximal humerus during rotator cuff repair (RCR).

Evidence review A systematic review of PubMed, Embase and Cochrane Library was performed to identify all published articles reporting on biomechanical analysis of suture anchors in the shoulder in a cadaveric model. Inclusion criteria required fresh-frozen specimens, placement in the footprint of the proximal humerus, and comparative assessment of fixation constructs with or without polymethylmethacrylate (PMMA) or bioabsorbable composite cement augmentation. Biomechanical testing procedure, cement augmentation method and pullout force were assessed.

Findings After review of 105 abstracts, seven full manuscripts met inclusion criteria. Six of seven studies reported statistically significant differences in mean pullout force between augmented (three PMMAs, three composites, one PMMA vs composite) and non-augmented anchors. Of two studies evaluating cycles to failure, both found a significant increase in the augmented versus non-augmented anchors. Of two studies stratifying by anchor position, both investigations identified significant differences in mean pullout strength between augmented and non-augmented anchors at the postero-medial and antero-lateral anchor positions.

Conclusions and relevance Cement augmentation of suture anchors in cadaveric humeri for RCR improves pullout strength regardless of cement type used or anchor position. Cement augmentation may provide a viable option for future clinical application.

Level of evidence IV, systematic review.

INTRODUCTION

Both degenerative and traumatic shoulder pathology are a growing concern among the ageing population of the USA, with an increasing reported incidence of full-thickness rotator cuff tears ranging from 2.5% by age 65 to 50% for those 70 or older and 80% in those over 80 years old. Fatty infiltration, rotator cuff repair (RCR) in the elderly presents several important challenges due to increased medical comorbidities, impaired soft tissue healing, greater tuberosity remodelling, enthesopathy with cystic change and/or higher incidence of osteopenia.

Without bone mineral density and frequent subchondral bone cyst formation, concerns regarding fixation strength and RCR failure may persist. To this end, Tingart et al found a significant positive correlation between bone mineral density and suture anchor failure load in RCR. Benson et al reported an overall incidence of early anchor pullout of 2.4%, and this increased to 11% for tears greater than 3 cm in size. Anchor pullout is of particular interest in the elderly, as patients 60 years of age or older are approximately twofold to threefold more likely to experience large to massive rotator cuff tears. Given the high incidence of rotator cuff tears in the elderly and increased risk factors for anchor pullout, anchor fixation must be able to account for and mitigate against complications related to low bone mineral density.

To date, interventions to improve fixation in poor bone quality have relied mostly on optimised implant design. Iterative changes in suture anchor composition, width, length, thread pitch and depth have been evaluated, as well as design features seeking to obtain fixation at the cortical interface rather than the softer cancellous bone. Alternative techniques for fixation have also been...
explored, including the addition of so-called ‘buddy’ or ‘rescue’ anchor, impaction bone grafting and far lateral anchor placement. Conversely, numerous research studies have demonstrated the potential efficacy of cement augmentation in the hip and spine, where both polymethylmethacrylate (PMMA) and bioabsorbable composite cements (eg, tricalcium phosphate) serve as potential options to facilitate improved anchor fixation.

The purpose of this systematic review was to evaluate the biomechanical benefits and fixation strength of cement-augmented versus non-augmented suture anchors in the proximal humerus during RCR. We hypothesised that cement augmentation would significantly increase pullout force regardless of the type of cement used or the location of suture anchor placement.

**METHODS**

**Literature research**

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The review protocol was registered in February 2020 with the International Prospective Register of Systematic Reviews.

**Study selection and data abstraction**

A systematic search of PubMed/MEDLINE, Embase and Cochrane Library databases was conducted on 11 October 2020. No language or publication-date restrictions were applied. Studies were identified using search combinations of one word or phrase from each of the bracketed lists: ["humerus" or "shoulder" or "rotator cuff"] AND ["suture anchor"] AND ["bone cements" or "tricalcium phosphate" or "polymethylmethacrylate" or "PMMA" or "augmentation"]. Inclusion criteria included biomechanical studies evaluating pullout strength of cement-augmented suture anchors in a proximal humerus human cadaveric model using composite or non-absorbable bone cement.

In the screening stage, duplicates were removed, and all remaining studies were evaluated by title or abstract. Studies

---

**Figure 1**  Forest plot of pullout strength in newtons, augmented versus non-augmented, posteromedial versus anterolateral position, and PMMA versus composite cement. PMMA, polymethylmethacrylate; MPF, Mean Pullout Force.
were excluded in our screening phase if they did not report on suture anchor fixation, used cement or bioabsorbable composite but not a suture anchor in fixation, used a non-human cadaveric testing model, used a cadaveric model that did not test bone from the proximal humerus footprint, or if they did not include a biomechanical testing procedure.

All studies that were not excluded during the screening phase underwent a full-text review to assess for inclusion eligibility. All studies that were not excluded during the full-text review eligibility phase were included in the qualitative analysis demonstrated in figure 1. Data extraction was performed independently by two review authors. The references of the articles were also reviewed manually to identify any additional studies that met the inclusion criteria of which there were no further additions.

Risk-of-bias assessment
The quality of all included studies was independently evaluated by two authors using the Methodological Index for Non-randomised Studies (MINORS) tool25 (online supplemental appendix table 1).

RESULTS
In accordance with PRISMA guidelines, figure 2 summarises study selection for the current systematic review. Of the 46 identified articles, 9 underwent full manuscript review, and 7 publications met the inclusion criteria.26–32

The mean quality rating of all studies using the MINORS tool25 was 21.4 ± 0.53 (of a maximum of 24 points, 89.3%; range, 21–22 points) (online supplemental appendix table 2). Item 5 (unbiased assessment of study endpoint) and item 8 (prospective calculation of the study size) accounted for all point deductions due to lack of blinding and only three studies (Oshtory et al.,27 Gulecyuz et al.30 and Diaz et al.32) had conducted an a-priori power analysis.

The study demographics are described in table 1. Despite variations in testing protocols and cement augmentation procedures, there were numerous similarities between the seven included studies. All studies hypothesised that cement augmentation would increase pullout strength; two of seven studies also evaluated cycles to failure.26 27 Six of seven studies (see table 2) had results showing a significant increase in pullout strength with cement augmentation; only one study showed no significant difference between augmented and non-augmented anchors.30 The calculated effect size (d) also demonstrated a large effect in augmented anchors in five of six studies and a small effect in one. Five of seven studies assessed specimen bone density prior to biomechanical testing.26–28 30 31

The biomechanical testing protocols of each study are summarised in table 3. All studies used matched pairs of cadaveric specimens.26–32 Five of seven studies used an awl guide-hole26 28–31; one used a Jamshidi needle27; and one used a drill press.32 Six of seven studies inserted cement prior to anchor placement, the lone study to place the anchor and then the cement used a fenestrated HEALICOIL-type suture anchor.31 Of the seven studies, four used PMMA cement,26 28 30 31 while four used composite cement including tricalcium phosphate in

---

Figure 2  Preferred Reporting items for Systematic Reviews and Meta-Analysis flowchart.
three and calcium sulphate in one. Four of seven studies used metal screw-type suture anchors; two used a solid PEEK screw-type anchor and one used a fenestrated PEEK screw-type helical anchor. All studies allowed sufficient cement curing time based on manufacture recommendations, with four of seven allowing 10 min prior to biomechanical testing, and one not specifying time frame other than to state they allowed the cement to fully harden to touch. Finally, during biomechanical testing to failure, four of seven tested at deadman’s angle at approximately 90° from anchor insertion axis, and three of seven tested at 0°.

Only in the study by Gülçüyüz et al was the pull-out strength not statistically significant. They endeavoured to compare non-augmented anchors to both PMMA augmented and composite cement-augmented anchors. When comparing all three methods, their results were not statistically significant (p=0.1624). All other studies evaluated augmentation with a single cement type, and each reached statistical significance compared with non-augmented anchors.

In total, six of seven studies reported statistically significant differences in mean pullout force between augmented (three PMMAs, three composites, one PMMA vs composite) and non-augmented anchors. Of two studies evaluating cycles to failure, both found a significant increase in the augmented versus non-augmented anchors. Of two studies stratifying by anchor position, both investigations identified significant differences in mean pullout strength between augmented and non-augmented anchors at the posteromedial and anterolateral anchor positions. The mean pullout strength in each study is presented in table 4.

### DISCUSSION

The principal findings of this systematic review demonstrate a significant difference in pullout force to failure in six of seven studies included in this systematic review comparing cement-augmented versus non-augmented anchors in the proximal humerus for RCR. Cement composition or anchor position in the postero-medial or anterolateral location did not influence the pullout forces to failure. This is notable as previous studies have shown the posteromedial bone to have better quality than the anterolateral aspect. Cement augmentation effectively increased pullout strength in both locations despite the propensity for

### Table 1 General demographics, by study

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Type of study</th>
<th>Model type</th>
<th>Matched pairs humeri (n)</th>
<th>Cement</th>
<th>Suture anchor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giori et al</td>
<td>CORR</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>6</td>
<td>PMMA</td>
<td>5 mm Fastin RC, Mitek</td>
</tr>
<tr>
<td>Ostorthy et al</td>
<td>CORR</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>10</td>
<td>TCP (Callos)</td>
<td>5 mm Fastin RC, Mitek</td>
</tr>
<tr>
<td>Braunstein et al</td>
<td>CB</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>14</td>
<td>PMMA (Synthes)</td>
<td>5 mm Corkscrew FT 1, Arthrex</td>
</tr>
<tr>
<td>Postl et al</td>
<td>AOTS</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>12</td>
<td>TCP (Norian)</td>
<td>5 mm Corkscrew FT 1, Arthrex</td>
</tr>
<tr>
<td>Gülçüyüz et al</td>
<td>HSS</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>8</td>
<td>PMMA/gentamycin and CS (Cerament)</td>
<td>5.5 mm Plla Biocork screw FT, Arthrex</td>
</tr>
<tr>
<td>Aziz et al</td>
<td>CB</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>6</td>
<td>Kyphon HV-R (PMMA base)</td>
<td>Fenestrated HEALICOIL PEEK, Smith &amp; Nephew</td>
</tr>
<tr>
<td>Diaz et al</td>
<td>Arthroscopy</td>
<td>Biomechanical</td>
<td>Fresh frozen cadaver</td>
<td>8</td>
<td>TCP (Accufill, Zimmer Biomet)</td>
<td>5.5 mm PEEK Quatro X, Zimmer Biomet</td>
</tr>
</tbody>
</table>

AOTS, Archives of Orthopaedic and Trauma Surgery; Arthroscopy, The Journal of Arthroscopic and Related Surgery; CB, Clinical Biomechanics; CORR, Clinical Orthopaedics and Related Research; CS, calcium sulfate; HSS, The Musculoskeletal Journal of Hospital for Special Surgery; PMMA, polymethylmethacrylate; TCP, tricalcium phosphate.

### Table 2 Biomechanical testing results, by study

<table>
<thead>
<tr>
<th>Study</th>
<th>Anchors tested (n)</th>
<th>Pullout force in newtons and SD of anchors</th>
<th>P value</th>
<th>Effect size, Cohen (d)</th>
<th>Increase pullout force in augmented versus non-augmented anchors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giori et al</td>
<td>NA 8</td>
<td>NA 172 (56)</td>
<td>A 294 (139)</td>
<td>Stripped A 363 (166)</td>
<td>0.0212</td>
</tr>
<tr>
<td></td>
<td>Stripped A 8</td>
<td></td>
<td></td>
<td></td>
<td>0.0012</td>
</tr>
<tr>
<td>Ostorthy et al</td>
<td>NA 19</td>
<td>NA 203 (94)</td>
<td>A 261 (138)</td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>A 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braunstein et al</td>
<td>PM/NA 7</td>
<td>PM/NA 226 (56)</td>
<td>PM/NA 332 (101)</td>
<td>AL/NA 208 (72)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>PM/NA 7</td>
<td></td>
<td></td>
<td>AL/NA 331 (81)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>AL/NA 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postl et al</td>
<td>PM/NA 6</td>
<td>PM/NA 305 (89)</td>
<td>PM/NA 474 (101)</td>
<td>AL/NA 305 (100)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>PM/NA 6</td>
<td></td>
<td></td>
<td>AL/NA 533 (86)</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>AL/NA 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gülçüyüz et al</td>
<td>NA 8</td>
<td>NA 160 (41)</td>
<td>APMMA 206 (49)</td>
<td>ACS 207 (66)</td>
<td>0.1624 (comparing all three groups)</td>
</tr>
<tr>
<td></td>
<td>APMMA 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aziz et al</td>
<td>NA 6</td>
<td>NA 202 (125)</td>
<td>A 540 (184)</td>
<td>&lt;0.05</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>A 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaz et al</td>
<td>NA 8</td>
<td>NA 139 (110)</td>
<td>A 274 (102)</td>
<td></td>
<td>0.029</td>
</tr>
</tbody>
</table>

A, augmented; AL/IA, anterolateral/augmented; AL/NA, anterolateral/non-augmented; CS, calcium sulfate; NA, non-augmented; PM/IA, posteromedial/augmented; PMMA, polymethylmethacrylate; PM/NA, posteromedial/non-augmented.
variations in bone quality. These findings provide strong support to our hypothesis that cement augmentation would significantly increase pullout force regardless of the type of cement used or the location of suture anchor placement. Thus, cement augmentation may be a viable option for clinical application, particularly in patients with osteoporotic bone, cystic changes in the humeral head or in the case of intraoperative anchor pullout.

Early reports of RCR failure pointed to the suture–tendon interface as the primary mode of failure. More recently, Rizal and Mok suggested that as the strength of suture material has increased, the mode of failure has shifted towards the bone anchor interface. Development of broad suture tape may be one contributing component to this shift, in large part due to its broader contact area and force distribution. Leger et al evaluated biomechanical pull-through strength in bone of braided tape versus wire suture and showed that braided tape provided significantly higher pull-through load.

With optimisation of the suture–tendon interface, alternative factors affecting the strength at the anchor–bone interface must be considered, chiefly poor bone mineral density. Damaging the integrity of the greater tuberosity bone footprint by using multiple anchors in close proximity may be another factor.

Excessive anchor use may decrease the bone surface area for tendon-to-bone healing. Furthermore, the curved cortical edge of the proximal humerus can lead to incomplete anchor deployment, increasing the likelihood of failure. Increasing the strength of the anchor–bone interface then becomes a clinically useful focus to decrease RCR failure rates.

The reported studies were performed on open-air cadaveric specimens using similar cement augmentation techniques. Application of this technique using a dry scope approach is one option to control cement extravasation. A suture anchor cement augmentation technique that is compatible with the aqueous environment during arthroscopy would, however, offer the greatest clinical utility in contemporary RCR. The potential for extruded cement loose bodies in the intra-articular or subacromial spaces must also be considered as this could lead to painful mechanical symptoms or chondrolysis. Ensuring containment of cortical margins and carefully inspecting for extravasation of cement into the intra-articular and subacromial spaces are technically critical. Aziz et al designed their biomechanical testing around this arthroscopic compatible application. Notably, cement injection into the hollow helical anchor did not affect the sutures ability to slide. This may be anchor dependent, however; previous studies evaluating cement augmentation of transosseous fixation in the greater tuberosity also showed that the suture had good slide after the cement had cured. This suggests that cured cement does not limit the ability of suture to freely slide. Alternatively, a non-sliding knot technique can be employed. Each of the tested techniques offers a reasonable application of cement augmentation. Although loose bodies may result, direct visualisation of cement extrusion would be observable and arthroscopic technique would allow for removal.

Cement augmentation in an arthroscopic environment thus portends promise as a viable option and warrants further study in clinical application to confirm utility, to delineate the safety profile and to determine the most efficacious implementation protocol.

Use of bioabsorbable cements such as tricalcium phosphate may yield greater clinical benefits than PMMA. In contrast to PMMA, tricalcium phosphate has an isothermic curing process, limiting the risk to nearby neurovascular structures. Use of resorbable composite cement also offers the benefit of osteoinductive and osteoconductive properties replacing cement with native vascularised bone over time, increasing the potential for biological tendon to bone healing, and decreasing the morbidity and complexity of potential revision surgery with retained cement. Reoperation on the ipsilateral shoulder is not uncommon. Desmoineaux reported a 7% reoperation rate at 10 years for primary RCR. Frank et al reviewed 506 patients who had reverse and anatomical total shoulder arthroplasty; 144 (28%) had undergone prior surgery on the ipsilateral shoulder. If cement augmentation of suture anchors gain favour, using

---

Table 3: Biomechanical testing protocol, by study

<table>
<thead>
<tr>
<th>Study</th>
<th>Cement augmentation procedure</th>
<th>Cement cure time prior to testing</th>
<th>Angle of anchor pullout testing from anchor insertion axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giori et al⁵⁵</td>
<td>Awl guidehole, previously stripped or unstripped hole filled with liquid bone cement (PMMA), allowed to cure to doughy texture then anchor placed, with 1–2 cm of doughy cement extrusion removed</td>
<td>Not specified, ‘allowed to fully harden’</td>
<td>0°</td>
</tr>
<tr>
<td>Oshory et al⁵⁷</td>
<td>Guidehole made with jamshidi needle, bone cement (TCP) injected until back pressure, suture anchors then immediately placed</td>
<td>24 hours</td>
<td>0°</td>
</tr>
<tr>
<td>Braunstein et al⁵⁸</td>
<td>Awl guidehole, anchor placed into bone then removed, liquid bone cement (PMMA) injected into hole, anchor then immediately placed</td>
<td>10 min</td>
<td>–90° (deadman’s angle technique)</td>
</tr>
<tr>
<td>Postl et al⁵⁹</td>
<td>Awl guidehole, anchor screwed in then removed. 0.3 mL fibre reinforced liquid bone cement injected (TCP), Anchor reinserted.</td>
<td>36 hours</td>
<td>–90° (deadman’s angle technique)</td>
</tr>
<tr>
<td>Güleçyüz et al⁶⁰</td>
<td>Awl guidehole, liquid bone cement injected (PMMA or CS), anchor placed immediately, excessive cement removed</td>
<td>10 min</td>
<td>–90° (deadman’s angle technique)</td>
</tr>
<tr>
<td>Aziz et al⁶¹</td>
<td>Awl guidehole, fenestrated anchor placed, obturator inserted into cannula to place liquid bone cement (PMMA) into anchor which exited through fenestration in the anchor into bone; cement placement assessed under fluoroscopy</td>
<td>10 min</td>
<td>–90° (deadman’s angle technique)</td>
</tr>
<tr>
<td>Diaz et al⁶²</td>
<td>Drill press guidehole, 5 mL liquid bone cement injected (TCP) and allowed to cure for 10 min under direct heat, anchor placed after cement cured</td>
<td>10 min</td>
<td>0°</td>
</tr>
</tbody>
</table>

CS, calcium sulfate; PMMA, polymethylmethacrylate; TCP, tricalcium phosphate.

Table 4: Mean Pullout strength in newtons, by study

<table>
<thead>
<tr>
<th>Study</th>
<th>A</th>
<th>NA</th>
<th>PM/A</th>
<th>PM/NA</th>
<th>AL/A</th>
<th>AL/NA</th>
<th>PMMA</th>
<th>Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giori et al⁵⁵</td>
<td>294</td>
<td>172</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>294</td>
<td>–</td>
</tr>
<tr>
<td>Oshory et al⁵⁷</td>
<td>261</td>
<td>203</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>261</td>
<td>–</td>
</tr>
<tr>
<td>Braunstein et al⁵⁸</td>
<td>332</td>
<td>217</td>
<td>332</td>
<td>226</td>
<td>331</td>
<td>208</td>
<td>332</td>
<td>–</td>
</tr>
<tr>
<td>Postl et al⁵⁹</td>
<td>501</td>
<td>305</td>
<td>474</td>
<td>305</td>
<td>533</td>
<td>305</td>
<td>–</td>
<td>501</td>
</tr>
<tr>
<td>Güleçyüz et al⁶⁰</td>
<td>207</td>
<td>160</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>206</td>
<td>207</td>
</tr>
<tr>
<td>Aziz et al⁶¹</td>
<td>540</td>
<td>202</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>540</td>
<td>–</td>
</tr>
<tr>
<td>Diaz et al⁶²</td>
<td>274</td>
<td>139</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>274</td>
</tr>
</tbody>
</table>

A, augmented; AL/A, anterolateral/augmented; AL/NA, anterolateral/non-augmented; NA, non-augmented; PM/A, posteromedial/augmented; PMMA, polymethylmethacrylate; PM/NA, posteromedial/non-augmented.
bioabsorbable composite cement could make these cases of ipsilateral shoulder reoperation less complex. The biomechanical data support the use of both composite cement and PMMA in this application.

Despite its merits, cement augmentation is not without potential drawbacks and may be cost prohibitive. With an incidence of anchor pullout of approximately 2.3%, a cost–benefit analysis would be useful; however, large-scale clinical trials would need to be performed to capture the true absolute risk reduction associated with cement augmentation and to determine which patients may gain the most benefit.

LIMITATIONS
Differences between studies including variations in biomechanical testing protocol, cement and suture anchor type used as well as angle of pull-out testing are limitations in this review; thus, quantitative pooling was not performed. Small sample sizes and testing performed on cadaveric specimens in a non-aqueous environment also limit the generalisation of results to clinical application in arthroscopic RCR. Also, specimen selection was limited in most studies to availability of fresh frozen cadavers. While most of the studies evaluated bone density to make results more comparable, this does not completely eliminate selection bias.

CONCLUSIONS
Cement augmentation of suture anchors in cadaveric humeri for RCR improves pullout strength regardless of cement type used or anchor position. Cement augmentation may provide a viable option for future clinical application.

Twitter Brian R Waterman @H2O_SportsMD

Contributors The primary and supervising authors performed review design and literature search. All contributing authors provided significant contribution to manuscript development, drafting and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests Other others maintain the following competing interests: JL: paid presenter; JC and SLS: board membership and paid consultant; BRW: board membership, paid consultant, presenter and royalty/stock option; BR: board membership, paid consultant and stock options.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any errors and/or omissions arising from translation and adaptation or otherwise.

ORCID ID
Jeff S Kimball http://orcid.org/0000-0001-9775-1270

REFERENCES


