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Point/Counterpoint

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# Refractory Knee Osteoarthritis: Adipose-Derived Stromal Cells Versus Bone Marrow Aspiration Concentrate

## CASE SCENARIO

A 56-year-old woman presents to the clinic with a long history of right knee pain. The pain began insidiously 4 years prior and she reports a slow progression in pain and decrease in her function. She has been treated with oral analgesics and anti-inflammatories. In addition, she is currently enrolled in her third round of physical therapy. Last year she had an intra-articular corticosteroid injection, which gave her about 6 weeks of relief. Following this, she underwent a series of 3 hyaluronic acid injections (SupartzFX) that she completed 3 months ago. She reports that this injection did not provide her with significant relief. The patient reports primarily knee pain over the medial joint line. Her alignment is normal and she does not report any swelling, buckling, or locking of her knee. The pain is worse when going up and down stairs, but she does not report any falls. Radiographs and magnetic resonance imaging (MRI) of the right knee reveal moderate to severe tibiofemoral osteoarthritis (Kellen Lawrence grade 3) with mild medial meniscus fraying. There is no discrete meniscus tear, and the anterior and posterior cruciate, and medial and lateral collateral, ligaments are intact.

She was reading information on the role of "stem cells" injected into the knee that could regenerate and repair her degeneration. Drs Gerald Malanga and Samuel Dona will argue for adipose-derived stromal cells (ADSCs). Drs Joanne Borg-Stein and Michael Auriemma will argue for bone marrow aspiration concentrate (BMAC).

## Drs Malanga and Dona Respond

This case scenario of a young woman with a history of knee osteoarthritis (OA) is typical and commonly seen in primary care, physiatric, and orthopedic offices around the world. Many patients continue to suffer with pain after completing the various available nonoperative interventions that comprise the traditional treatment algorithm of degenerative knee OA, including oral medications, physical therapy, bracing, corticosteroids, and hyaluronic acid injections. The long-term efficacy of these therapies is poor [1], often resulting in many years of progressive pain and loss of function for those who decline or are not deemed appropriate candidates for surgery. London et al define this period as the "osteoarthritis treatment gap" [2]. This is defined as the "time from unsuccessful exhaustion of conservative measures to surgical intervention." In addition to compromising physical capabilities and negatively impacting quality of life, London et al has noted the economic consequences of patients who fall into this treatment gap of knee OA management. More than 27 million middle-aged and older adults in the United States share this situation today [3]. The prevalence of knee OA is projected to increase with rising obesity rates and the continued aging of our population. There are approximately 700,000 TKAs performed annually at this time, and the fastest-rising incidence is occurring between 40 and 50 years of age [4]. Among countless others, this patient is now faced with limited choices in the management of her knee pain. It is therefore important that nonoperative specialists develop and trial innovative treatment methods to successfully bridge this treatment gap to maintain function and ease the financial burden of these patients.

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The potential for regenerative medicine to fill this role has gained considerable interest in recent literature and clinical practice. These treatments are often lumped into a category described by our patients and the media as "stem cell" therapy. The term *orthobiologic treatments* is perhaps a better designation and includes platelet-rich plasma, autologous bone-marrow concentrate (BMAC) and adipose-derived mesenchymal stem cell therapies. When applying the label "stem cells," there is relevant terminology that is frequently used improperly. Mesenchymal stem cells (MSCs) have been defined as multipotent adult stem cells that self-renew and have the ability to differentiate into various cell types, that is, muscle, bone, cartilage, etc [5]. These cells can be obtained from a patient and subsequently injected into a site of injury in the same patient (ie, autologous use). MSCs also reveal paracrine activity by releasing various growth factors and exhibit immunomodulatory capability [5].

For the purposes of this point/counterpoint, we will refer to adipose regenerative therapy as adipose-derived "stromal" cells (ADSCs) instead of adipose-derived "stem" cells. ADSCs are MSCs that have been isolated from homogenized adipose tissue located in the capillary and perivascular adventitia of large blood vessels within adipose tissue. Bone marrow—derived mesenchymal stem cells (BMSCs) are isolated from bone marrow aspirate (BMA) or bone marrow aspirate concentrate (BMAC) harvested from the trabeculae of marrow cavities. ADSCs and BMSCs are both felt to have a pericyte origin, with the same ability to express common cell surface markers, gene expression profiles, and differentiation potential [5]. Although ADSCs share common characteristics in morphology and phenotype with BMAC, recent literature has shown several distinct differences between these 2 alternative stem cell sources [6].

Compared with BMAC, studies have noted ADSCs are present in higher numbers per unit volume of tissue, more rapidly proliferate in culture, and are less susceptible to senescence secondary to culture expansion (see summary by Malanga and Ibrahim [5]). Furthermore, these studies revealed considerable variability in MSC concentration between ADSCs and BMAC. A gram of adipose tissue yields approximately 2 x 106 nucleated cells, with an estimated 5% being ADSCs, as compared to 1 mL of bone marrow aspirate yielding close to 6 x 106 cells, with roughly 0.01% of these representing true mesenchymal stem cells [6]. ADSCs may have a higher yield of cell counts between these MSC-based therapies, and therefore a potentially better strategy for knee OA.

Although ADSC therapies appear to be a beneficial treatment option for patients with knee OA, the Food and Drug Administration (FDA) continues to be concerned about the appropriate use of all stem cell therapies and especially those derived from adipose tissue. A recently published guideline [7] has stressed the importance of several areas for practitioners to be compliant in the use of these cells. Of first importance is the autologous use of ADSCs, which entails that all individuals undergoing therapy serve as both the donor and recipient, with strict regulation that includes same-day, nonexpanded use of harvested cells. Additionally, FDA criteria state that the use of adipose tissue must meet "minimal manipulation," which is defined as "processing of the human cells, tissues, and cellular and tissue-based product (HCT/P) that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." The FDA considers adipose tissue to be a structural tissue in this regard for application of the regulatory framework and processing should not alter the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. The FDA further specifies that the relevant characteristics of adipose tissue relate to its ability to provide cushioning and support because of its bulk and lipid storage capacity. The FDA expresses reservations that the manufacturer processes adipose tissue by removing the cells (such as after enzymatic digestion), leaving the decellularized extracellular matrix portion. This would generally be considered more than minimally manipulated because this processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. Likewise, the FDA states that the HCT/P must be meant for "homologous use," meaning that "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P must perform the same basic function or functions in the recipient as in the donor." Currently, there are FDA cleared devices for the harvesting, concentrating, and transferring of autologous adipose tissue for musculoskeletal applications. These devices incorporate "sizing and washing" technology that have been defined by the FDA to preserve the cell and tissue microarchitecture of the adipose tissue, eliminate residues of oil emulsion and blood, and provide a tissue that is minimally manipulated in accordance with the FDA guidelines.

A comprehensive review of the literature regarding the use of regenerative medicine options in knee OA historically reveals a greater amount of publications related to the study and clinical human application of BMAC. However, in the past 5 years there has been increasing evidence in research supporting the positive effects of ADSCs on improving knee joint pain and function. These studies have shown a positive effect on the progression of knee OA by reducing articular damage and cartilage degeneration [8-10]. Pagani et al performed an in vitro comparison study between BMAC and ADSCs in various inflammatory microenvironments to determine any differences in chondrogenesis [11]. Although both BMAC and ADSCs developed into mature micromasses, the ADSCs had increased matrix

composition and superior gene expression, which may suggest improved chondrogenic potential when subjected to an inflammatory environment, including inflamed synovium within an osteoarthritic knee.

Li et al, through the use of a modified O'Driscoll histologic assessment and quantitative real-time PCR, demonstrated that ADSC treatment had significantly better tissue preservation as compared to controls. This study marked one of the first to correlate the proliferation of ADSC in knee joints during the time frame of clinical improvement as well as demonstrating increased cartilage thickness [12]. A retrospective study by Koh et al showed an improvement in cartilage whole-organ MRI score (WORMs) as well as improved pain scores (WOMAC, Lysholm, and visual analog scale) after intra-articular ADSC, suggesting that both clinical and radiologic benefits are related to its use [8]. In addition, Koh et al found in a cohort of elderly patients there was improvement or maintained cartilage status in 87.5% (14/16) patients after intra-articular knee injections of ADSCs at the time of second look arthroscopy [9]. Concerns regarding the safety profile of adipose-derived therapies in humans were highlighted in a study by Jo et al, with primary outcomes being safety and reduction in pain [10]. This study concluded that this treatment was safe and that after administration of high-dose ADSC (1 x 108), WOMAC scores decreased at 6 months whereas cartilage quality improved without adverse events.

Although the results of BMAC have been positive in case series, the only randomized controlled study of BMAC was performed by Shapiro et al. They evaluated pain and functional scores after intra-articular knee injections in patients with bilateral knee OA. In this study, one knee received BMAC mixed with platelet-poor plasma and the contralateral knee received a saline placebo. There were significant improvements in pain scores at all follow-up times at 1 week, 3 months, and 6 months in both treatment arms with no significant difference noted between the saline-treated knees and BMAC. They concluded that improvements in pain were similar in intra-articular injections with both placebo and BMAC. This study further suggests that future research efforts are needed to establish the mechanisms of action, duration of efficacy, optimal frequency of treatments, and regenerative potential of BMAC [13].

Lipoaspiration is thought to be a safe and relatively benign procedure. The harvest of subcutaneous ADSCs is generally associated with better patient acceptance when compared to the perceived pain and post-procedural discomfort that patients anticipate with a bone marrow aspiration. Moreover, the harvest of subcutaneous adipose allows for a larger amount of potential injectate that is more desirable for multiple joint procedures (eg, bilateral knee OA) versus the limited amount that can be prepared after a BMAC harvest at the iliac crest.

As related to the anatomy of the knee joint, current evidence in the literature has documented that the infrapatellar fat pad (IPFP), also known as the Hoffa fat pad, may play a significant role in the development and progression of knee OA. Structurally, the IPFP is composed of adipose tissue analogous to subcutaneous fat and is thought to expand the distribution of the lubricant effect of the intra-articular joint fluid by enlarging the synovial surface while also serving to reduce loading impact by absorbing forces generated at the knee joint. Studies have also shown that the IPFP is joint tissue capable of modulating inflammatory and destructive responses in knee OA by regulating the secretion of proinflammatory cytokines and the production of cartilage matrix proteins [14]. These findings would support the argument that the application of adipose tissue in the treatment of knee OA is in fact "homologous use," as the IPFP may play a central role in the mediation of joint inflammation and maintaining knee joint homeostasis. In addition, the studies by Koh et al reinforce this stance, demonstrating that intra-articular injection of IPFP-derived ADSCs can provide assistance in the reduction of pain and significantly improve function in knee OA [8,15].

Despite promising results in preclinical studies and the clinical usage of MSCs for the management of refractory pain secondary to knee OA, there remains a need to standardize the delivery and timing of such specific therapies along with further investigation of their true mechanism of action in future research. Ultimately, we would strongly recommend adipose-derived stromal cell therapy to "bridge the treatment gap" of knee OA in this patient for the various reasons which we have previously outlined.

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## Drs Borg-Stein and Auriemma respond

In the clinical scenario presented, we are faced with a patient who is suffering significant morbidity in the form of pain and functional decline as a result of osteoarthritis of the knee. Unfortunately, she has not experienced any meaningful benefit from the typical offerings of conservative management, including physical therapy, oral analgesics and anti-inflammatories, intra-articular corticosteroid injections, or intra-articular hyaluronic acid injections. Although we could, and should, also emphasize the importance of optimizing body weight and exercise, it is likely that the patient in question has already experienced difficulty tolerating the necessary activity level as a result of symptom-burden. Regrettably, such a clinical scenario is undoubtedly one that many of us encounter on a regular basis. Further complicating the current scenario is the patient's relatively young age (56 years old), which makes surgical intervention in the form of total knee arthroplasty, or even unicompartmental arthroplasty (if amenable), less desirable based on the patient's anticipated life expectancy and therefore high likelihood of need for eventual revision surgery. In our estimation, this scenario presents a very reasonable situation for the implementation of orthobiologic therapy.

The last 20 years have witnessed an explosion in research studies investigating potential orthobiologics, or "regenerative medicine," as well as clinical usage of such agents. A review of the literature can easily induce a head-spinning reaction based on the sheer number of potential treatments discussed. A few of the options include prolotherapy, platelet-rich plasma, BMSCs, BMAC, adipose-derived mesenchymal stem cells (AMSCs), adipose-derived stromal vascular fraction (SVF), and adipose-derived stromal cells (ADSCs). For the purpose of this point-counterpoint, we will consider only bone marrow—derived versus adipose-derived treatment. In particular, we will focus on autologous BMAC versus ADSCs, as these are the 2 treatments that are compliant with the minimal manipulation regulations put forth by the U.S. Food and Drug Administration (FDA) [1].

Before proceeding with any treatment, we would obviously begin by providing education. A physician's role as an educator is imperative when it comes to the consideration of orthobiologics. For the patient in this clinical scenario, education would commence by identifying the treatment options and emphasizing that any of the available orthobiologics, regardless of FDA compliance, are still considered experimental in nature. We would further emphasize that no orthobiologic in and of itself is a "magic bullet" but rather offers potential to ameliorate morbidity and possibly regenerate tissue. In order to decide between BMAC and ADSCs, we first must appreciate the difference between these treatments and other similar treatments.

Simply put, BMAC is a process whereby a bone marrow aspiration is performed, usually to the iliac crests, with the aspirated contents then concentrated via centrifugation. Concentration allows for the harvesting of final product, which contains mesenchymal stem cells, nucleated cells, platelets, growth factors, and cytokines. It should be noted that BMAC differs from BMSCs, a process in which stem cells are isolated, culture-expanded ex vivo, and then prepared for injection. In the United States, the FDA does not permit the latter for clinical use.

ADSCs are obtained through a newer technique that consists of first harvesting adipose tissue via lipoaspiration. The lipoaspirate is rinsed and then microfragmented through mechanical forces in a process intended to remove oil and blood while leaving behind vascular stroma with pericytes, mesenchymal stem cells, and other signaling cells. These cells are ultimately transplanted in the form of an adipose-derived tissue graft. This process differs from both AMSCs and SVF in that there is no culture-expansion of stem cells

nor is there enzymatic digestion to isolate the stem cells. It is important to note that differences exist between these varying techniques, and therefore caution should be exercised when attempting to draw conclusions from the available literature. For example, one should question whether the results of studies performed on SVF apply to that of ADSCs.

For the patient described in this clinical scenario, we support the use of BMAC over ADSCs. The case supporting BMAC over ADSCs is rooted in the basic tenet behind any medical intervention—that we first minimize risk and second maximize potential benefit. The evidence we provide will indicate that BMAC is the safer procedure, possesses demonstrable regenerative capacity (that is at least equivalent to ADSCs), and currently has significantly greater clinical evidence in terms of efficacy.

Admittedly, we perform procedures utilizing both BMAC and ADSCs. Both procedures consist of a product-harvesting phase followed by a product-injection phase. In our practice, we find that both the harvest and injection are well tolerated, with postprocedure harvest-site discomfort that typically resolves within 1-7 days and temporary pain and swelling at the respective injection site regardless of whether BMAC or ADSCs are used. Although this has been our personal experience, the available literature suggests that the harvesting techniques are not equivalent. When it comes to harvesting techniques, both bone marrow aspiration and lipoaspiration are considered minimally invasive procedures. Though many purport that liposuction is the gentler procedure, the available data do not support this position. A literature review indicates the reported overall complication rate following liposuction to be 8.6%, with a major complication rate of 0.7% [2,3]. Conversely, the adverse event rate following bone marrow aspiration is 0.0007% [4]. Published reports further indicate that 6.8% of patients undergoing liposuction develop chronic pain at the harvest site [5]. These reports support bone marrow aspiration over lipoaspiration as the safer, better-tolerated harvest procedure.

Having provided evidence that BMAC is safer based on the harvest procedure, let us now consider whether it is likely to be more efficacious in the clinical scenario we are currently presented with. To make this determination, we believe it is necessary to consider both BMAC's and ADSCs' intrinsic regenerative capacity and the clinical support for both of these orthobiologics to date. Many believe that the regenerative capacity of orthobiologics is related to the MSC content. Although intuitively this may make sense, research provides conflicting results. In fact, a randomized, controlled, double-blind study indicated greater improvement on postinjection MRI of the knee following low-dose MSCs as compared to high-dose [6]. Thus, the presence of trophic factors, which are prevalent in BMAC, may be equally important as absolute MSC content in terms of regenerative capacity.

Despite these findings, if we still consider MSC content to be of maximal importance, then we posit that the regenerative potential of BMAC is at least equivalent to that of ADSCs, as both contain MSCs and in vitro studies have found that MSCs derived from both bone marrow and adipose are of similar quality [7]. There is additional evidence that both possess chondrogenic potential [8], further supporting their equivalency in terms of regenerative capacity and role in treating knee osteoarthritis. Though a common criticism of bone marrow—derived sources as opposed to adipose-derived is that the MSC count and chondrogenic potential tends to diminish with age, the critical age has not been well defined and is not as apparent in females [9]. Because our case involves a relatively young female, this is less likely to be a significant issue.

Although identifying regenerative capacity proves useful from an explanatory mechanistic standpoint, the demonstration of clinical utility is perhaps more important, particularly from a patient's perspective. It is in this area that the currently available literature is more supportive of BMAC than ADSCs for the treatment of knee pathology associated with osteoarthritis. To our knowledge, only 3 studies have been published examining the use of ADSCs in such scenarios. One of those 3 studies is a case report describing improved pain level, Knee Injury and Osteoarthritis Score (KOOS), and MRI signal/thickness of cartilage in the knee following the injection of ADSCs in a single patient with a medial meniscal tear [10]. The second study is a retrospective review that primarily assessed the safety of intra-articular injection of ADSCs into knees with diffuse degenerative chondral lesions [11]. Finally, the third study is a case series that was designed to primarily assess hyaline cartilage markers following intra-articular injection of ADSCs [12]. In summary, the available literature consists of a single case report and 2 additional studies that were both designed to evaluate factors other than clinical outcomes or efficacy.

As compared to ADSCs, BMAC has greater than 4 times as many studies published regarding its use in humans for the treatment of knee osteoarthritis and related pathology, such as chondral defects and meniscal tears. Admittedly, some of these studies have investigated the use of BMAC in isolation, whereas others have looked at BMAC in conjunction with other conservative and surgical treatments. Review articles from 2016 and 2017 both suggest that BMAC appears to be beneficial in the treatment of various knee pathologies [13,14]. As for individual studies, both Kim et al and Centeno et al have reported on the clinical efficacy of BMAC in the setting of knee osteoarthritis [15,16]. Kim et al performed a prospective case series of 45 patients. All patients were treated with an intra-articular BMAC injection combined with a nonmicrofragmented adipose graft to serve as a

scaffold for the BMAC. The 6-month follow-up data from this study indicated improvements in pain and functional scores, including the Lysholm Knee Questionnaire, International Knee Documentation Committee Score (IKDC), Short-Form 36 (SF-36), and KOOS [15]. The study from Centeno et al is a retrospective review of 681 patients who either underwent intra-articular injection with BMAC alone or in conjunction with a non-microfragmented adipose graft as a scaffold, with a total of 840 knees injected. Reported outcomes at 6-month follow-up suggested improvements in pain and function (as assessed via the Lower Extremity Functional Scale). Additional analysis indicated there was not a statistically significant difference in outcomes between the knees treated with and without the adipose graft, suggesting the addition of adipose did not affect outcome [16].

In conclusion, we support the use of orthobiologics in the treatment of this 56-year-old woman with knee osteoarthritis for whom other conservative treatments have failed. We believe that BMAC is the safer, more reliable option because of its extensive track record of safety and efficacy. Though both treatments are considered FDA-compliant, they are still viewed as experimental procedures. Before initiating treatment, a thorough conversation with the patient is of utmost importance to discuss anticipated outcomes based on the currently available evidence. Although our personal experience suggests that both procedures are safe, the literature indicates that bone marrow aspiration is the safer harvesting technique. Further, there is a greater amount of evidence supporting the clinical efficacy of BMAC in treating knee osteoarthritis as compared to ADSC. Although the available literature is certainly subject to criticism regarding the quality of evidence and glaring paucity of randomized controlled trials, there is no debating which treatment has the longer established track record.

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## Drs Malanga and Dona rebut

We appreciate Drs Borg-Stein and Auriemma's response and agree with the evidence that both ADSCs and BMSC possess the chondrogenic potential to treat this patient. Although we have previously also used BMAC on similar patients, we respectfully disagree on several arguments posed by our colleagues against the use of ADSCs.

Regarding the use of innovative therapies, we contend to "first, do no harm." The premise that harvesting ADSCs potentially exposes the patient to adverse events is not supported by the literature presented. We intend to clearly define the harvest technique of ADSCs in orthopedic conditions as a fat aspiration. The

complication rates quoted in the studies by Kim et al and Kaotzanis et al are related to liposuction procedures that involved large volume aspirations under sedation. This is not applicable to the small volumes obtained under local anesthesia for use in musculoskeletal applications.

There is no substantial evidence to support the stance that BMAC is the safer procedure as recent studies have demonstrated excellent safety outcomes harvesting adipose tissue. In 2015, Michalek et al performed a multicenter case-control study including 1114 patients with knee and hip OA [1]. These patients were treated with autologous adipose SVF and followed for a mean of 17.2 months. The clinical effects were measured using modified KOOS/HOOS clinical scores before treatment, at 1 week, and 1, 3, and 6 months after treatment. At 12 months after treatment, there was 75% score improvement in 63% of all patients and 50% score improvement in 91% of all patients. There were no serious side effects or incidents of cancer reported.

The regenerative capacity of orthobiologics may be more importantly related to the inherent trophic factors and perhaps not the total MSC content. Conversely, the argument that BMSCs have greater efficacy and equivalent regenerative potential compared with ADSCs is not definitively supported by data in the literature. It is interesting to note that Vangsness et al showed using low-dose (not high-dose) allogenic (not autologous) MSCs actually led to an increased meniscal volume. However, the robust evidence that ADSCs are superior in MSC content [2], have a higher proliferative capacity, retain multipotency longer and have more potent immunomodulatory effects in vitro [3] validates that BMSCs are not of the same quality. Furthermore, we argue that the earlier onset of replicative senescence observed in BMSCs from the same donor [4] is indeed a significant age-related issue that limits the usefulness of these MSCs in older patients.

Although there are greater numbers of publications regarding the use of BMAC in humans, the studies presented include only 1 RCT using BMAC, which failed to demonstrate efficacy against saline controls [5]. Additionally, Kim et al used an adipose graft to serve as a scaffold for the BMAC [6]. Despite similar outcomes in the knees treated with and without the adipose graft, one cannot presume that BMAC has better efficacy from these results. The potential for future ADSC research to exceed BMAC is anticipated with recent trends. A 2017 prospective, non-randomized clinical trial by Hudetz et al [7] showed that the use of autologous microfragmented adipose in patients with knee OA had increased glycosaminoglycan content in hyaline cartilage on imaging as well as improved visual analog scale scores at rest and with motion.

In closing, although Drs Borg-Stein and Auriemma provide a substantiated rationale for the use of BMAC, we feel that the optimal treatment strategy for this patient would be adipose-derived stromal therapy based on the sound arguments we have presented.

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## Drs Borg-Stein and Auriemma rebut

As stated in our initial response, we believe the purpose of this point-counterpoint is to debate the merits of BMAC versus ADSCs for the treatment of knee OA in this 56-year-old woman, with ADSCs specifically referring to a microfragmented adipose product. The purpose of framing the debate in this manner is to compare 2 treatments that both meet FDA compliance. In their position supporting ADSCs over BMAC, Drs Malanga and Dona highlight the differences between adipose-derived and bone marrow—derived stem cells, argue that ADSCs are FDA compliant, state that lipoaspiration is better accepted by patients than bone marrow aspiration, and review a randomized control study on BMAC for knee osteoarthritis. To these points, we provide the following response.

BMAC and ADSCs are more than their respective MSC components, with trophic factors and paracrine activity that may be equally or more important in determining regenerative potential. The importance of these additional factors seems to be supported by a study cited in our initial response [1]. That being said, when analyzing respective MSC content, there is evidence that MSCs from adipose sources proliferate more rapidly in culture, are less susceptible to senescence secondary to culture expansion, and yield a higher MSC concentration per unit volume of tissue [2]. We question, however, whether these culture-based findings translate to regenerative potential, as multiple studies have indicated bone marrow—derived stem cell products possess greater chondrogenic capacity than adipose-derived ones [3-5]. Additionally, the very source cited by our opponents in support of ADSCs over BMAC also states that "it should be noted that the in vitro differentiation potential of MSCs does not necessarily predict or correlate with their in vivo differentiation capacity.... If paracrine factors are implicated in the therapeutic effects of these MSCs, there would be little difference between the 2 cell types [2]."

Drs Malanga and Dona eloquently explain why ADSCs should be viewed as being compliant with the FDA's minimal manipulation and homologous use requirements. We do not argue this assertion, as long as we are specifically referring to ADSCs obtained via microfragmentation as opposed to being enzymatically digested or culture-expanded. Unfortunately, all the sources cited by our opponents utilized ADSCs that fall within this latter category [6-9]. In our opinion, these studies use a different product from what we are actually debating and thus are not applicable to the current point-counterpoint.

In terms of harvest technique safety, they contend that "the harvest of ADSCs is generally associated with better patient acceptance." They do not provide, however, any citations to support this claim. This is in stark contrast to the published evidence we provide that supports bone marrow aspiration as being safer than lipoaspiration [10-13]. On a further note regarding harvesting techniques, our opponents suggest that lipoaspiration "allows for a larger amount of injectate that is more desirable for multiple joint procedures." This is a point that we find completely irrelevant to the clinical scenario in question, as we are treating a patient with unilateral knee osteoarthritis.

Finally, they highlight the results of a trial that demonstrated equal improvement between BMAC and saline in the treatment of knee osteoarthritis [14]. In this study, a potential reason for there being no significant difference between knees may be that BMAC has the potential to exert an effect on both the treated knee and contralateral (untreated) knee. In fact, previous studies have indicated that the intra-articular injection of both anesthetics and corticosteroids can illicit responses in contralateral joints [15,16]. There are additional studies that indicate possible systemic effects from injected MSCs [17,18]. Thus, the possibility that BMAC induced a contralateral response cannot be excluded.

In conclusion, we stand by our assertion that BMAC is safer, possesses regenerative capacity that is at least as potent as ADSCs, and is supported by far greater relevant literature demonstrating its clinical efficacy, making it the preferred treatment for this patient.

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## Disclosure

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**Web Poll Question**
For the case described in this Point/Counterpoint, which treatment would you recommend?

a. Adipose-derived stromal cells (ADSCs).
b. Bone marrow aspiration concentrate (BMAC).

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