The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective

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Abstract

The use of stem-cell therapies for the treatment of various musculoskeletal conditions, especially knee osteoarthritis (OA), is rapidly expanding, despite only low-level evidence to support its use. Centers offering these therapies are often marketing and charging patients out-of-pocket costs for such services. Therefore, the purpose of this study was to determine the current marketed: (1) prices and (2) clinical efficacy of stem-cell therapies for knee OA. This was a prospective cross-sectional study which queried 317 U.S. centers that offered direct-to-consumer stem-cell therapies for musculoskeletal conditions. A total of 273 of 317 centers were successfully contacted via phone or e-mail, using a simulated 57-year-old male patient with knee OA. Scripted questions were asked by the simulated patient to determine the marketed prices and clinical efficacy. Centers generally reported the proportion of patients who had "good results" or "symptomatic improvement." The mean price of a unilateral (same-day) stem-cell knee injection was $5,156 with a standard deviation of $2,446 (95% confidence interval [CI]: $4,550–5,762, $n = 65$). The mean proportion of claimed clinical efficacy was 82% with a standard deviation of 9.6% (95% CI: 79.0–85.5%, $n = 36$). Most American stem-cell centers offer therapies for knee OA. The cost of these therapies averages about $5,000 per injection, and centers claim that 80% of the patients had "good results" or "symptomatic improvement," denoting a gap between what is documented in the published literature and the marketing claims. These findings offer both patients and physicians insight into the current stem-cell market for knee OA. We hope that with this information, providers can more optimally make patients aware of discrepancies between what is being marketed versus the current evidence-based landscape of these therapies for knee OA.

Keywords
- knee
- osteoarthritis
- stem cells
- cell-based therapies

Over the past two decades, the use of stem-cell therapies for the treatment of various musculoskeletal and orthopaedic conditions, including knee osteoarthritis (OA), has been rapidly expanding in the United States.[1] Of the 351 U.S. businesses engaged in marketing of stem-cell therapies reported recently by Turner and Knoepfler in the August issue of *Cell Stem Cell*,[2] musculoskeletal conditions, including knee OA, were the most frequent conditions for which these therapies were marketed, with more than 300 of the 351 businesses providing treatment

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for such conditions. This is not surprising given the burden of musculoskeletal diseases, and considering that OA alone affects more than 27 million Americans and costs an estimated $89.1 billion dollars annually.[3,4]

However, despite the extensive marketing and use of cell-based therapies, most of the evidence surrounding usage is low quality.[5–7] Despite this, these therapies, often masked as "proven therapies," still require higher quality clinical studies to prove their efficacy (benefit–risk assessment), as well as to better understand their biological functions.[8,9] Therefore, the extensive development of facilities in the United States that offer cellular therapies presents a unique challenge.[8,10–12] Offering unproven or insufficiently proven cell therapies to patients as "treatments or therapies" for marked out-of-pocket costs without adequate clinical evidence places patients at risk both medically and financially. Therefore, it is imperative for physicians to answer basic questions about costs, clinical efficacy, and risks to patients and/or consumers.[13,14] Furthermore, while stem-cell therapies hold important promise for their regenerative potential, many such therapies still remain unapproved by the Food and Drug Administration (FDA).[15] In this sense, the rapid proliferation of stem-cell businesses presents a unique regulatory challenge due to the wide range of unregulated stem-cell interventions.[16] In particular, the direct-to-consumer marketing of these therapies calls into question the kind of regulation required to appropriately monitor the therapeutic benefits claimed by these "stem-cell" clinics.

Therefore, given the rapidly expanding use of stem-cell therapies for treatment of various musculoskeletal conditions including knee OA, it becomes important for physicians to not only understand the current available evidence but also to know what is being currently marketed to patients. This will aid providers in better answering questions and delineating discrepancies between clinical evidence and what is marketed. Therefore, the purpose of this study was to determine the current marketed: (1) prices and (2) clinical efficacy of stem-cell therapies for knee OA.

Methods

Centers that offered stem-cell therapies were identified by referring to the work by Turner and Knoepfler,[2] who used a rigorous internet keyword search to identify 351 U.S. centers that connect directly to consumers. Using the supplemental data from their work, we identified that 317 of 351 (90%) centers currently market treatment for musculoskeletal conditions.

With the goal of obtaining information of what is being marketed directly to patients by these centers, we utilized a simulated 57-year-old male patient who claimed to suffer from moderate right knee OA (6/10 pain on a visual analog scale). This patient also stated that he had seen several orthopaedic providers, who had already offered him other nonoperative measures such as pain medications, corticosteroid and/or hyaluronic injections, braces, etc. He also stated that he had been told, by some providers, that he would need a knee replacement someday, and was seeking stem-cell treatment to help with his current knee problems. The contacted centers were consulted for information on same-day stem-cell injections, and specifically asked questions focusing on two main themes: (1) clinical efficacy ("How well do they work?" and "What effect do they have?") and (2) cost ("What is the cost of the therapy for one knee?").

Between October 28, 2016, and January 28, 2016, we successfully contacted 273 of 317 (86%) centers either electronically (e-mail) or by phone using relevant contact information provided on their Web sites. Overall, of the 273 centers contacted, 224 clinics (74%) were contacted electronically by an initial e-mail using a standardized template (►**Supplementary Fig. S1A** [online only]), and the remainder ($n = 49$) were contacted by phone call during business hours (between 9 am and 5 pm) using an initial standardized script (►**Supplementary Fig. S1B** [online only]). A total of 44 of 317 centers (14%) were unable to contact because they lacked up-to-date contact information, with either a nonfunctioning Web site, e-mail, and/or phone number, or went out of business or no longer offered these therapies (►**Fig. 1**). Out of 273 clinics contacted, 65 (24%) provided numerical information on the cost of a single stem-cell therapy injection for unilateral knee OA, and 36 clinics (13%) provided quantitative information on the success rate of their treatment, as measured by patient satisfaction (►**Fig. 1**). The remaining centers did not provide cost information (208/273, [76%]) or data on success rates (237/273, [87%]), stating that such information would be given during the first in-person consult or after examination.

Descriptive statistical analyses were performed to obtain mean, frequency, standard deviation, range, margin of error, and 95% confidence interval (CI). All analyses were performed using Microsoft Excel Spreadsheet (Microsoft Corporation, Redmond, WA). After aggregating and quantifying the marketed price and marketed clinical efficacy data, a correlation analysis was performed to determine whether a relationship existed between the cost of a single stem-cell injection for treatment of knee OA and the marketed clinical efficacy, as measured by patient satisfaction rate.

Results

Marketed Prices

Of the 65 centers that provided pricing information for a same-day stem-cell unilateral knee injection, the mean cost for each therapy was $5,156, with prices ranging from $1,150 to $12,000 (►**Table 1**). The standard deviation was $2,446, with a margin of error of $606 and a 95% CI of $4,550 to $5,762. Out of the 65 centers, 14 centers charged < $3,000, and 10 centers charged more than $8,000 per injection.

Marketed Clinical Efficacy

Of the 36 centers that provided information on clinical efficacy (►**Table 2**), the mean marketed clinical efficacy was 82.2% (range, 55–100%). The standard deviation was 9.6%, with a margin of error of 3.2% and a 95% CI of 79.0 to 85.5%. The distribution of the percentages reported by these clinics directly to consumers was aggregated, and shown as a

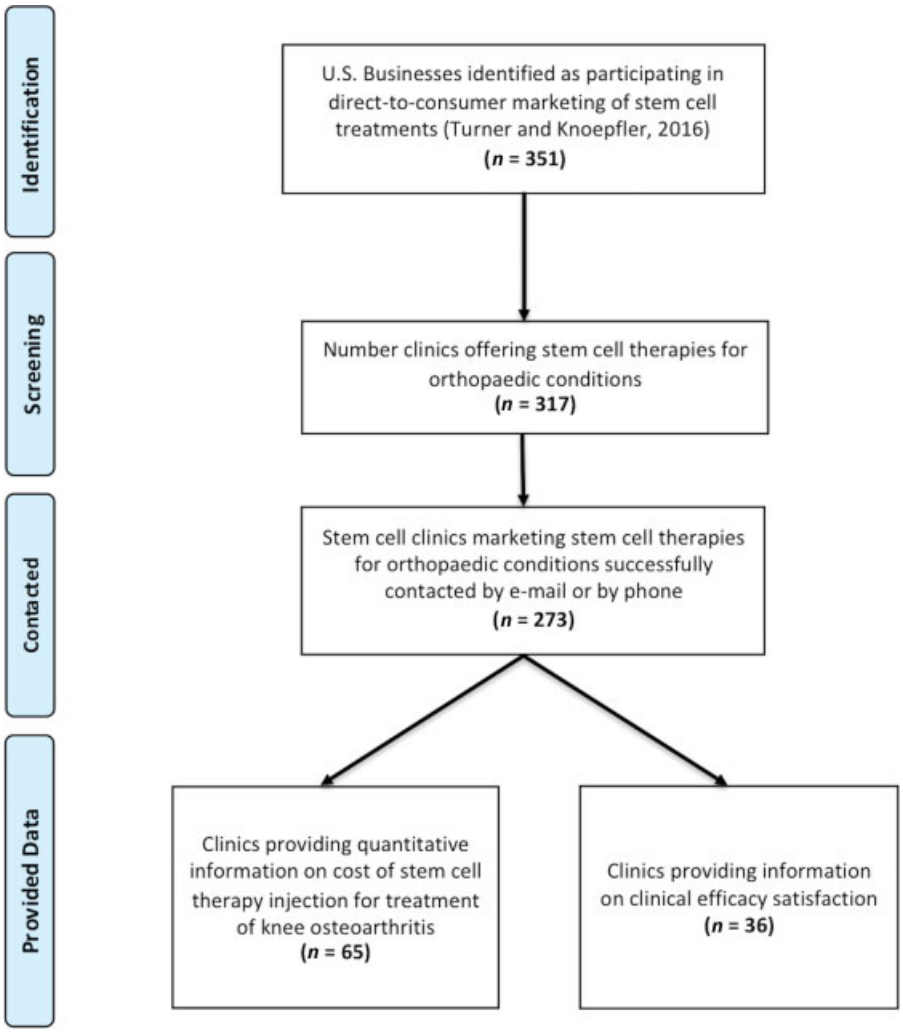

Fig. 1 Flow diagram presenting the systematic review process used in this study.

histogram (►**Fig. 2**). Out of the 36 clinics, 10 claimed "90 to 100% efficacy," 15 claimed "80 to 90% efficacy," 10 claimed "70 to 80% efficacy," and 1 claimed "55% or more clinical efficacy." We found no correlation between the treatment cost and the marketed clinical efficacy ($R^2 = 0.019$, $r = 0.14$).

Table 1 Pricing information of stem-cell therapies marketed to consumers for knee osteoarthritis in the United States

U.S. stem-cell clinics providing pricing information for knee injection ($n = 65$)	Statistics
Average cost	$5,156.43
Standard deviation	$2,445.61
Margin of error	$605.99
95% confidence interval	$4,550.44–$5,762.42
Price range (minimum–maximum)	($1,150.00–$12,000)

Discussion

The use of stem-cell therapies for the treatment of various musculoskeletal conditions, especially knee OA, is rapidly expanding, despite there being only low-level evidence to support its use. Centers offering these therapies are marketing and charging patients out-of-pocket costs for such services.[8–15]

Table 2 Patient satisfaction information of stem-cell therapies marketed to consumers for knee osteoarthritis in the United States

U.S. stem-cell clinics providing clinical efficacy information for stem-cell knee injection ($n = 36$)	Statistics
Average positive patient satisfaction	82.2%
Standard deviation	9.6%
Margin of error	3.2%
95% confidence interval	79.0–85.5%
Patient satisfaction range (minimum–maximum)	55.0–100.00%

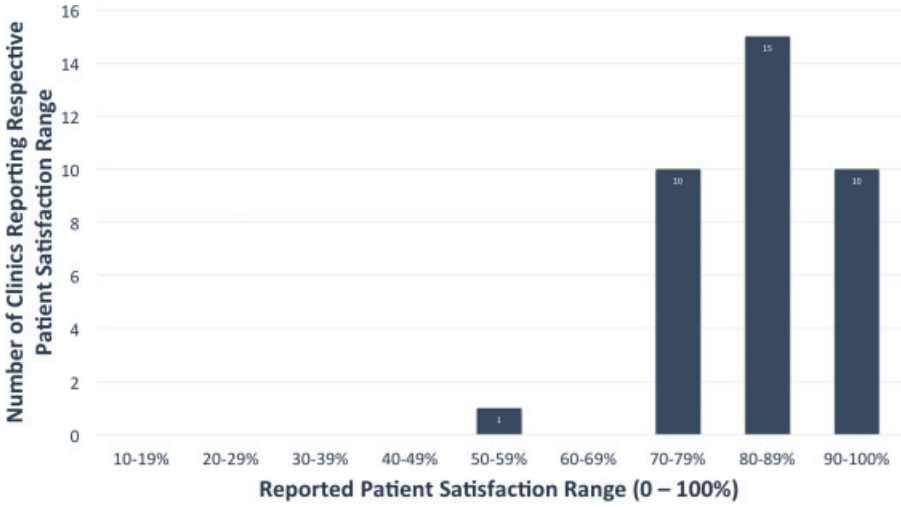

Fig. 2 Histogram of stem-cell treatment success rates reported by businesses to consumers.

Given this, it becomes essential for physicians to not only understand the current available evidence but also to be aware of what is being currently marketed to patients. This will aid providers for improved informing and delineating discrepancies between clinical evidence versus what is marketed. In the present study, the current marketed prices and clinical efficacy of stem-cell therapies for knee OA were analyzed. It was found that the cost of these therapies averages about $5,000 per knee, and that providing centers claim an average of 80% of patients having "good results" or "symptomatic improvement."

There were several limitations of this study. Most of the centers successfully contacted did not provide information over the phone or by e-mail, and recommended a face-to-face encounter, which limited the sample size. This may not allow for a comprehensive capture of pricing and marketing tactics. However, this does provide insight into how much information centers are willing to discuss with patients over e-mail and phone. It could be possible that more responsible centers do not provide this information until a proper examination and consultation regarding indications, benefits, risks, and expectations are done. Nevertheless, in attempting to contact all possible clinics, we have no reason to suspect that there was sampling bias. In addition, the low response rate encountered could potentially be attributed to an underlying intention of engaging the patient to physically go to the center. In addition, the scripted methods utilized in this study offered the providing centers an "open-ended" answer to questions regarding clinical efficacy. Therefore, we were unable to delineate exactly what knee-specific parameters (such as pain, range of motion, functional recovery), and their responses were referring to in terms of treatment success. Nevertheless, it offered insight into how these centers go about portraying and marketing clinical efficacy to their consumers. Finally, we did not query regarding the types or characteristics of stem cells offered, complications, approval status, and other relevant features. Despite these limitations, this study is the first to aggregate and to analyze data regarding stem-cell treatment marketed clinical efficacy and prices, and to provide insight into the patient perspective when considering associated costs and benefits for such treatments for the treatment of knee OA.

The median U.S. household income is $51,939/year, and with the average cost of a single knee stem-cell injection as $5,156.43 (►**Table 1**), we can agree that this is relatively high price tag (9.9% of mean annual income) when considering that this treatment is not covered by insurance and must be paid entirely out of pocket. Furthermore, the marketed price variation ranging from $1,500 to $12,000 indicates that a substantial amount of this cost is not attributable to fixed treatment expenses, but rather to the perceived cost of labor (►**Fig. 3**).

Our findings are in agreement with observations made by previous studies that many of the marketing claims about stem-cell interventions raise important ethical concerns due to the lack of supporting peer-reviewed evidence.[2] In a recent systematic review characterizing the use of intra-articular cellular therapy injections for OA and focal cartilage defects in the human knee, after screening 420 reports, only 6 studies had a level of evidence III or higher were found (4 Level II and 2 Level III).[5] Although the findings suggested some positive results with respect to clinical improvement, this was modest and a placebo effect could not be ruled out. Therefore, the gap between what is documented in the published literature and the marketing claims made by stem-cell centers suggests that patients are being exposed to substantial "hype (excitement)" and potential misrepresentation in the market place. Concerns about this unregulated territory have led to pleas to define clear methods and reporting requirements for the clinical evaluation of cell products within the appropriate regulatory environment.[1]

We believe that cellular-based therapies, and their commercial development, should still be considered at the proof-of-concept stage due to potential unknown risks, minimal supporting evidence, changing policies, and being a highly dynamic sector with multiple explored therapeutic approaches.[17] Most of the "same-day" stem-cell injection preparations offered are regulated under the 21 C.F.R. Part 1271 as a "361 exemption" (U.S. FDA—Human Cell and Tissue Products). To have a designation as a "361-exemption product," and therefore being subject to minimal oversight, it should be an autologous use, and it must

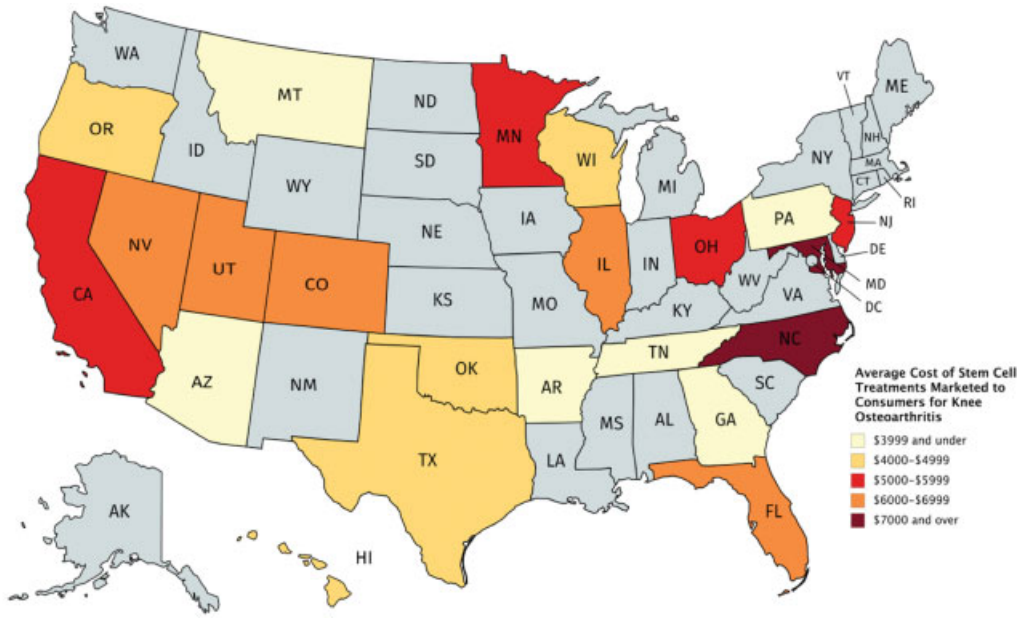

Fig. 3 Distribution of average cost of stem-cell therapies marketed to consumers for knee osteoarthritis in the United States.

meet each of the following four criteria: (1) minimally manipulated; (2) intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent; (3) not involving a combination cells or tissues with another article (e.g., drug); and (4) having a systemic effect or being dependent on the metabolic activity of living cells for its primary function. All these products are not subject to premarket review and approval requirements. Therefore, most of these therapies have avoided heavy regulation, although the FDA has issued warning letters.[18] Consequently, it is imperative to implement accurate characterization and reporting on cell-based therapies requires defining and standardizing cell sources, harvesting methods, processing, characterization, and quantification to really begin to define the clinical indications and clinical efficacy. The value and effective use of stem-cell therapy in orthopaedics remains unclear due to the dearth of well-designed clinical trials and a lack of standardization both in the preparation/formulations as well as the measurement of outcomes.[19] Until these data become available, patients and providers need to be aware of the stage of the development of this field. While some benefits have been reported, precise clinical indications have yet to be defined, and marketing claims should reflect this reality to patients.

Furthermore, establishing an appropriate sustainable pricing and reimbursement for cell-based regenerative therapy will become a greater challenge, and many interrogations on who should pay for these therapies or the mechanisms that regulate fair access to these innovative treatments have begun.[20,21] To date, the cost of these therapies is high, and is even sometimes higher than that of a total knee arthroplasty in the United States.[22]

Conclusion

Most American stem-cell centers offer therapies for knee OA. The cost of these therapies averages approximately $5,000 per knee, and centers claim that in excess of 80% of patients had "good results" or "symptomatic improvement." These findings offer both patients and physicians insight into the current stem-cell market for knee OA. We hope that with this information, providers can better educate patients of the discrepancies between what is being marketed versus the current evidence-based landscape of these therapies for knee OA.

Conflict of Interest
None.

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