

Injections of Bone Marrow Aspirate Concentrate
as Treatment for Discogenic Pain

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Abstract:

Low back pain (LBP) is one of the most common musculoskeletal pain complaints, affecting up to 84% of the U.S. adult population. In the United States, the highest rate of incidence is between the ages of 45 and 64 years. The causes for LBP are complex and of multiple origins, but one of the primary causes is mechanical low back pain that is discogenic in etiology. This can be secondary to either internal disc disruption (IDD) and/or degeneration of the intervertebral disc (IVD), also known as degenerative disc disease (DDD) [10,11].

Combined physical and medical therapies are successful in relieving pain in approximately 90% of cases of low back pain. However, the remaining 10% become chronic and generate a serious public health problem, known as chronic low-back pain (CLBP). CLBP decreases both the quality of life and the labor capacity of the patient. As specific diagnostic procedures for LBP have improved, discogenic pain has been identified as the primary cause of CLBP amongst adults. Within the classification of discogenic pain, the most common specific cause of pain – up to 42% of LBP complaints – is internal disc disruption (IDD), with other distinguishable causes including disc herniation, degenerative disc disease (DDD), and instability of the lumbar segment [10].

Effective treatment for discogenic LBP – and therefore for CLBP – would provide significant relief for individuals as well as for the overall health care system and the employers affected by the patients' condition. One promising treatment option involves the use of Mesenchymal Stem Cells (MSC), which may allow for regeneration of the disc itself. Treatment with MSCs via injections derived from autologous concentrated Bone Marrow Aspirate (cBMA) would capitalize on the regenerative potential of MSCs while reducing the risk of infection or rejection, both significant risks of treatment from a heterologous source.

This project analyzed data collected from 33 patients with confirmed discogenic LBP, who were treated with intradiscal injections of autologous concentrated Bone Marrow Aspirate. After initial treatment, patients were monitored through follow up visits and questionnaires (VAS, Oswestry, SF-36) to determine the efficacy of treatment. The areas of interest for this study were intentionally narrow. This study sought to identify specifically the patients' self-reported pain and functioning levels from 2 weeks post-treatment to 12 months

post-treatment. Those reports were gathered using the aforementioned instruments and synthesized to show overall trends and statistically significant changes in the patients' self-assessment. The patients were also asked to give an overall impression of whether or not their back pain had improved post treatment. While admittedly limited in authority compared to a double-blind, randomized, controlled trial, the information was gathered from the patients with the hopes of augmenting ongoing research related to innovative treatments for discogenic LBP and of identifying new areas for further, future research.

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Introduction:

Amongst the complaints of musculoskeletal pain in the adult population, one of the most common is low back pain (LBP). Affecting up to 84% of the adult population, LBP is a complex, multi-factorial problem. Recent studies show that the primary factor leading to LBP is discogenic pain. Discogenic pain includes pain caused by internal disc disruption, disc herniation, degenerative disc disease, spinal segment instability or any other disc-oriented pathological process [10]. Low back pain, and therefore discogenic pain, is a condition that can greatly affect the quality of a patient's life. Vertebral discs naturally degenerate as a person ages, and many individuals progress through the degeneration with little to no pain. Others, however, experience an escalation from mild pain to severe, chronic, even debilitating pain. When pain becomes chronic and especially when it is chronic *and* severe, the costs to the patient expand from compromised quality of life to expensive medical treatment and loss of productivity in (or removal from) the workforce [11].

The IVD is composed of the inner nucleus pulposus (NP) and the outer annulus fibrosus (AF). The AF is a fibrocartilaginous ring composed of concentric, dense lamellae of highly-oriented collagen type I fibers in which there are cells with the morphology and phenotype of fibroblasts. The NP is a less structured gelatinous extracellular matrix (ECM) that is rich in proteoglycans, mainly aggrecans and type II collagen. Negatively-charged sulfated glycosaminoglycans, embedded in the structure the aggrecans, attract and imbibe water. The resulting high level of hydration helps to maintain disc height and contributes to the load-bearing ability of the IVD. [5] Small chondrocyte-like cells are scattered within the NP and are responsible for synthesizing and maintaining the ECM. Degenerative disc disease (DDD) is an age-related chronic process (vs. cascade), characterized by a progressive reduction of proteoglycans and water content in the nucleus pulposus. This phenomenon leads to a characteristic reduction in the discs' ability to resist compressive forces, annular fissuring, and reduced disc height. On the other hand, the inner disc may suffer a fair amount of degeneration or trauma before the expected change in disc height is perceivable. A patient with a diagnosis of IDD, by definition, will not exhibit the peripheral structural differences in the discs nor the compression of nerves that are known causes of pain in a confirmed diagnosis of DDD [11].

Current treatment options for CLBP secondary to a discogenic etiology cover a broad spectrum from conservative medical measures to invasive surgical interventions. Conservative treatments begin with anti-inflammatory medications (NSAIDs, analgesics) and extend to physical therapy/exercise focusing on core stabilization, and finally to the use of a corrective brace. Minimally invasive procedures include epidural steroid injections, intradiscal thermal procedures (IDET), and radiofrequency ablation techniques [5]. Each of these techniques has been shown to provide patients with some degree of symptomatic relief. None of these techniques, however, have provided definitive, curative treatment, nor have they demonstrated consistent, high rates of success. When these treatments fail, more serious interventions are considered, including surgery. The most common surgical procedures involve insertion of metal prosthetics (artificial discs) or spinal fusions, with the intent of alleviating pain and restoring or preserving function [6]. However, the indication of surgery as treatment for discogenic LBP is controversial because of potential destructive side effects. Concerns arise over the alteration of the natural biomechanics of the spine. The disturbance of motion and other biomechanical processes consequences can actually accelerate the degenerative cascade at the operative vertebral level and in adjacent segments [4]. Despite the existence of multiple treatment options, curative efficacy is still low. In fact, the vast majority of current treatments target the clinical symptoms of LBP as opposed to the pathophysiology involved in the degenerative process. There is a clear need for effective, early intervention for discogenic LBP that would potentially slow down or reverse degeneration in the intervertebral disc.

Effective treatment for discogenic LBP and, therefore, for CLBP would provide physical and financial relief for individual patients and the overall healthcare system. As previously mentioned, LBP affects up to 84% of the adult population in the United States at some point in their lives. When that pain becomes debilitating, the burden is passed on to employers, insurance companies, and healthcare providers. Curative treatment of such a widespread condition would have dramatic effects on the landscape of health care on a national and even a global level. Biologics offer a new type of intervention that could lead to a paradigm shift in the treatment of discogenic LBP. One promising treatment option involves Platelet Rich Plasma (PRP), a natural concentration of platelets found in the body's blood supply. Platelets release

bio-reactive proteins, including multiple growth factors that have been revealed to play crucial roles in the healing process of injured tissue. While the exact mechanisms are still under investigation, it has been shown that growth factors in platelets support tissue regeneration and healing, even in the cartilaginous tissue of intervertebral discs [1-5]. PRP, usually containing 4-5 times the concentration of platelets compared to whole blood, can be introduced to stimulate a supra-physiologic concentration of growth factors, jumpstarting the healing process in injuries involving tendons or cartilage [12].

While the processes of regeneration and healing cannot be neatly separated, there are distinct elements at play. Healing depends on the transport of key factors and biochemical agents to an area of damaged tissue. Regeneration requires the presence of undifferentiated cells and an environment in which those cells can differentiate into cells of the same type as the surrounding tissue. The application of concentrated Mesenchymal Stem Cells (MSCs) to areas of injury and degeneration is showing promise in multiple arenas. It has been demonstrated that MSCs have the capability to differentiate into a range of connective tissue cells, including cartilage and ligament, which are the components of the discs. As these cells differentiate, they form a sort of structural matrix on which the regeneration and healing of tissue may occur. When PRP is placed in an injured structure in the presence of MSCs, the PRP builds upon that matrix and cells develop more rapidly into the local or native tissue [1-4]. Concentrated Bone Marrow Aspirate Concentrate (cBMA) is rich in platelets and growth factors while simultaneously serving as a source of MSCs. This combination of biochemical resources, along with cBMA's ability to be harvested and injected from the patient's own body, allows for a safer and simpler supply of PRP and MSCs. As an autologous source, cBMA has the potential to facilitate the regeneration of the disc while lowering the risks of infection or rejection inherent in the use of heterologous source material [1-5,8,9].

The purpose of this study was to retrospectively evaluate the clinical outcomes in a population of patients with chronic low back pain, confirmed to be discogenic in etiology, after they were treated with intradiscal injections of autologous cBMA. All patients were followed routinely and were assessed by several scoring systems. While the sample population was small, the analysis provided meaningful insight into the efficacy of the treatment overall and

into the efficacy of the treatment based on different pre-treatment scenarios. These insights will contribute to the continued development of the treatment as an option for patients with CLBP and other types of degenerative joint pain.

Research Methods and Materials:

Methods and Procedures:

The patient population will be derived from patients of Dr. Wolff who have received the aforementioned cBMA injection treatment for discogenic LBP. That treatment proceeded according to the following process:

Concentrated Bone Marrow Aspirate (cBMA)

- Patient was placed on procedure table in prone position and prepped and draped in a sterile fashion, per standard protocol.
- All participants were kept comfortable and administered conscious sedation (versed and fentanyl) as needed, under the direct supervision of the physician.
- The Posterior Superior Iliac Spine (PSIS) was identified under fluoroscopic guidance.
- Skin, superficial tissue, and periosteum was anesthetized with 2% Lidocaine using a 27 and/or 25 gauge needle under fluoroscopic guidance.
- BMA was completed using a standard BMA Kit (MAR01 by Arteriocyte).
- An 11 gauge Jamshidi bone aspiration needle was advanced under fluoroscopic guidance through the previously anesthetized tissue until contact was made with the periosteum. The needle was advanced through the cortex.
- 54 cc of BMA were drawn and combined with 8cc of ACD.
- Bandage and pressure was applied to the BMA site under sterile conditions.
- BMA was filtered and then processed per standardized protocol by the Magellan Platelet Separator System down to 3-6 cc of cBMA
 - All injection volumes were individually determined by utilizing information from prior provocation discography

After the cBMA was prepared and analyzed, disc entry proceeded as follows:

Disc Entry

- Participants were placed on the procedure table in prone position and prepped and draped in a sterile fashion per standard protocol.
- All participants were kept comfortable and administered conscious sedation (versed and fentanyl) as needed under the direct supervision of the physician. Local anesthetic was used in the soft tissue during needle placement to the annulus.
- Using fluoroscopy, the target disc was identified counting from T12 and marked.
- Fluoroscopic guidance (C-Arm) was utilized to safely guide needle entry into the disc during all procedures.
- Using a standard, two-needle technique and a right or left extrapedicular approach, a 22 gauge needle was placed into the nucleus of the disc. Proper placement was confirmed in two planes (AP and Lateral) and pictures of final placement were documented.
- cBMA was then injected.
- All needles were removed carefully.
- Bandage and pressure were applied to the injection site under sterile conditions.

Follow-up with the patients occurred through office visits, written questionnaires, and telephone communication. In order to determine the efficacy of treatment, patients were asked to complete the following assessments:

- Oswestry Low Back Pain Disability Questionnaire
- Short Form (SF) 36 Health Survey
- Visual Analog Scale

The patients' responses to the assessments were scored according to appropriate guidelines and the gathered data was examined in light of the aforementioned areas of interest.

This study, admittedly, did not have the gravity of a double-blind, randomized control trial. The sample size was small (33 patients in the treatment group), and the patients were aware of the treatment they received. However, as an initial survey of the treatment and its efficacy as perceived and experienced by the patient, this study was intended to serve as part of the growing foundation of support for procedures of this kind as innovative therapeutic measures for discogenic pain.

Results:

Thirty three patients with CLBP underwent the aforementioned procedure. Baseline data was collected prior to the procedure. Follow-up information was collected at post-procedure periods of 2 weeks, 6 weeks, 12 weeks, 6 months, and 12 months. Of the 33 initial patients, 31, 32, 29 and 23 provided follow-up information at each of those respective intervals. Three patients have not yet reached the 12 month post-procedure point, and others were lost to follow-up. When asked whether they had experienced overall improvement in their CLBP, 29 of the 33 patients reported at least some improvement. Four patients reported no change or worsening pain. More specifically, the patients were asked at each of the aforementioned follow-up intervals to assign a percentage by which their pain had improved or worsened. The responses to that question are in Table 1. Of note, at the 2 week interval, 69.7% of patients said they had experienced no noticeable change in their level of pain, while 18.2% said that their pain had worsened and 12.1% said that their pain level had improved. At 12 weeks, the number of patients who said they noticed no change had decreased to 56.2%. Those reporting that their pain had worsened had decreased to 6.2%, and the number of patients reporting improvement in their level of pain had increased to 37.5%. By 12 months post-procedure, the percentage of patients reporting no change had fallen to 43.5%. The percentage of patients saying their pain had worsened was 13.2% and the percentage of patients reporting a noticeable improvement in their pain level had risen to 43.4% from 12.1% at the 2 week interval. 30.4% of patients responding at the 12 month interval reported at least a 50% improvement in their level of pain, with 43.4% of patients reporting statistically significant improvement in their pain level a year after the procedure.

Table 1: Frequencies and (Proportions) of Change in Pain Level

	2 Week	6 Week	12 Week	6 Month	12 Month
Outcomes					
% Improvement Reported by Patient	# of patients (percentage of patients)				
<50%	1 (3.0)	5 (16.1)	3 (9.4)	1 (3.5)	3 (13.0)
>50%	3 (9.1)	5 (16.1)	9 (28.1)	5 (17.2)	7 (30.4)
No Change	23 (69.7)	18 (58.1)	18 (56.2)	22 (75.9)	10 (43.5)
Worse <50%	6 (18.2)	2 (6.5)	1 (3.1)	1 (3.5)	2 (8.7)
Worse >50%	0 (0)	1 (3.2)	1 (3.1)	0 (0)	1 (4.5)

In addition to being asked about their overall pain levels, the patients were also asked to complete three evaluative instruments: the Oswestry Low Back Pain Disability Questionnaire, the Short Form 36 Health Survey (SF-36), and a Visual Analog Scale (VAS). The SF-36 reflects the patients' feelings toward their overall health and functional level. Therefore, a higher score indicates a perceived improvement in the patient's condition. For the Oswestry and VAS, lower scores indicate improvement in the patients' perceived levels of pain and/or disability. Table 2 shows the means and standard deviations of the patients' responses to the three questionnaires at the same follow-up intervals as previously discussed. Included in the table is a denotation of statistically significant values as determined using Wilcoxon Sign Rank. Responses to each of the three questionnaires demonstrated statistically significant improvement at the six month interval. The responses to the VAS reported showed a 28.3% improvement in patient's pain level. Responses to the SF-36 showed an improvement of 34.7%, and responses to the Oswestry questionnaire showed an improvement of 43.8%. At the 12 month interval, each of the instruments demonstrated reported improvement in patients' condition over baseline. Figures 1, 2 and 3 represent results of the three questionnaires at each interval.

Table 2: Mean (SD) Outcomes

	Baseline	2 Week	6 Week	12 Week	6 Month	12 Month
Outcomes	Mean (SD)					
VAS	5.3 (2.1)	5.0 (2.3)	3.8 (2.1)	3.1 (2.4)**	3.8 (2.5)**	3.8 (2.9)*
SF-36	53.5 (14.6)	49.5 (17.5)*	60.3 (18.7)	72.1 (16.5)*	72.1 (19.7)**	64.1 (25.4)
OSWESTRY	36.8 (14.7)	38.5 (16.8)	26.6 (15.3)	22.1 (13.8)**	20.7 (14.8)**	24.0 (18.8)*

** Denotes P-Values < 0.05 using Wilcoxon Sign Rank after adjusting for multiple comparisons from baseline. * Denotes P-Values < 0.10 using Wilcoxon Sign Rank.

Figure 1: Mean Responses by Patients to the Oswestry Low Back Pain Disability Questionnaire. Downward trend represents increase in patients' perceived post-treatment levels of functionality over baseline.

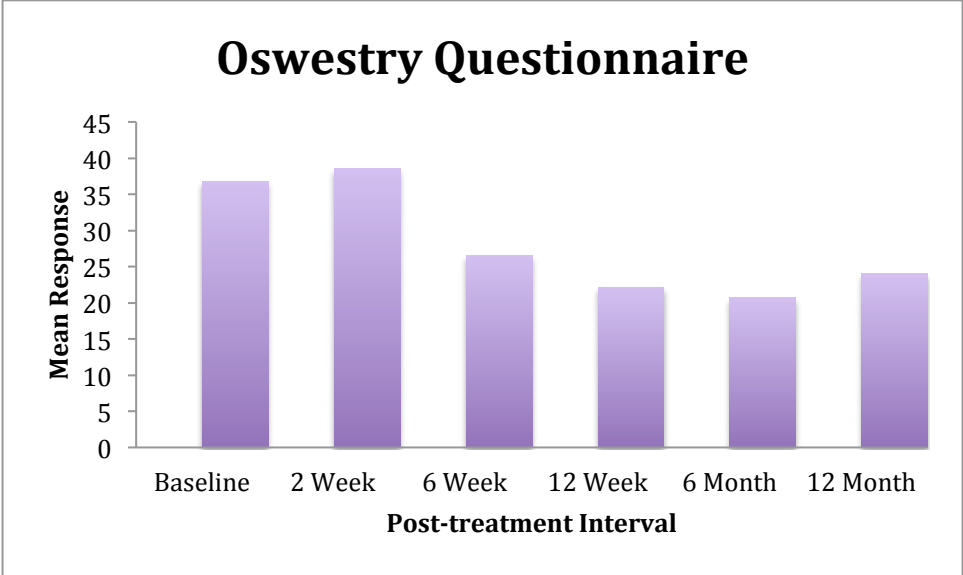


Figure 2: Mean Responses by Patients to the Short Form 36 Health Survey.

Upward trend represents a significant increase in patients' perception of their post-treatment health as compared to their baseline.

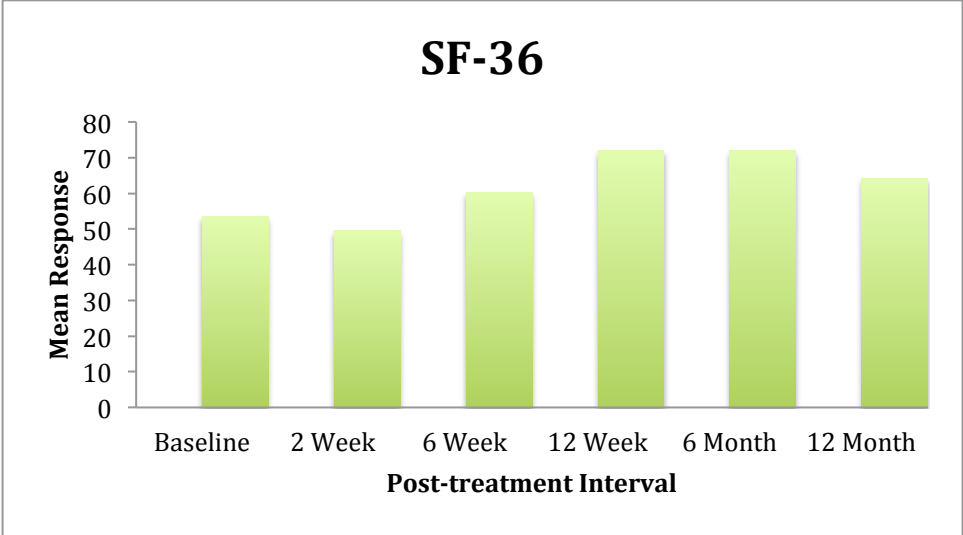
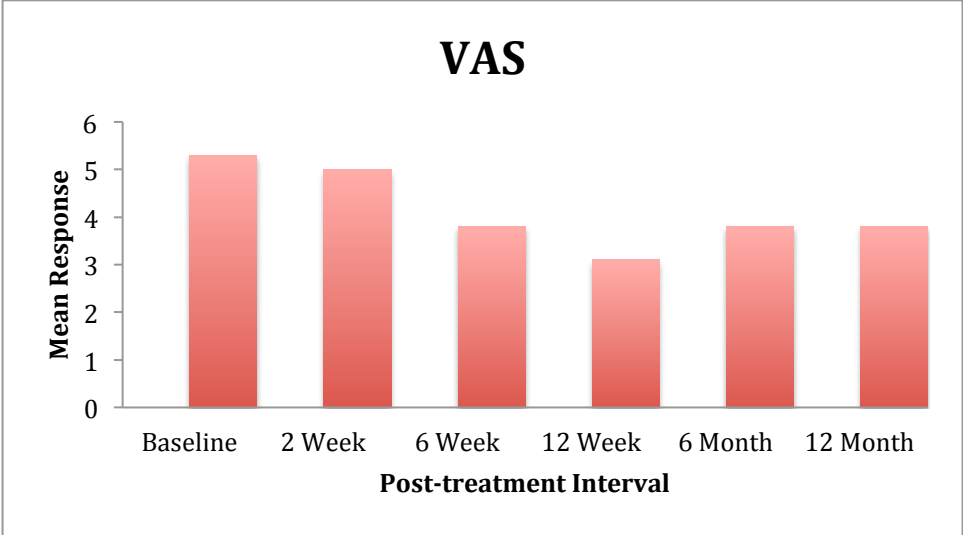


Figure 3: Mean Responses by Patients to the Visual Analog Scale.

Downward trend represents decrease in patients' perceived level of pain after treatment as opposed to baseline.



Discussion:

An effective, curative treatment for low back pain and chronic low back pain would mark a major watershed in the provision of health care in the U.S. The expense incurred due to the sheer number of patients who suffer from LBP and CLBP is shared between individual patients, the providers who care for them, the insurance companies that dictate care options, and the companies or employers affected by the relative ability or inability of these patients to perform their job responsibilities. While symptomatic management has continued to make minor strides in its effort to relieve patients' pain, physicians and other health care providers have remained unable to provide curative treatment to long-suffering patients. Therefore, the possibilities surrounding innovative, regenerative treatments warrant further investigation. The employment of cBMA, with its inherent supply of growth factors, platelets and Mesenchymal Stem Cells represents one such treatment.

The potential healing and regenerative properties of autologous MSCs have been sufficiently demonstrated in the literature. The harnessing of said properties and the targeting of them as an intervention for discogenic back pain represent promising possibilities for a major medical problem. As demonstrated in this study, injections of cBMA into vertebral discs in the lumbar section have led to statistically significant improvement in pain levels and functional status over a period of one year. 29 of the 33 patients (88%) who participated in this study stated that they had experienced a noticeable improvement in their pain and other symptoms after undergoing the cBMA injection. Furthermore, zero patients reported post-procedure infection, and there were no other complaints of complications from the procedure itself. Finer examination of the data indeed exposes lingering questions (Why do some patients experience worsening pain? How long will the effects of the treatment last? What other treatments or therapies have these patients utilized?), but the possibility of lasting relief at least begs the pursuit of further study.

Admittedly this study was subject to confounding variables including age, gender, and previous treatment modalities, among others. To truly advance the research in this field of treatment, a large, prospective randomized controlled trial would be ideal. This study certainly cannot claim to be sufficient proof of the efficacy of cBMA injections as treatment for

discogenic LBP and CLBP, but it certainly adds to the growing field of evidence in favor of the treatment and its potential. The use of biologics – in this case, cBMA with its included MSCs – represents a paradigm shift in the approach to the major medical problem of discogenic LBP. Further investigation into these possibilities is certainly warranted.

Future Directions:

Further investigation into the use of cBMA injections as treatment for LBP and CLBP is both warranted and exciting. Additional studies with greater controls and larger patient populations would galvanize the evidential support for the treatment as a potential curative option for patients. The authors of this study recommend a large scale, double-blind, randomized controlled trial investigating this treatment's potential for effectively curing low back pain and chronic low back pain.

Conclusions:

In a population of 33 patients dealing with low back pain or chronic low back pain, 29 reported that treatment with an injection of Bone Marrow Aspirate Concentrate into their lumbar disc led to a noticeable reduction in their pain level and/or an increase in their functional capacity. Twelve months after the treatment, more than 30% of patients responding reported an overall improvement in their pain by greater than 50%. As measured by the Oswestry Questionnaire, the SF-36 and a Visual Analog Scale, there was statistically significant ($p < 0.05$) improvement in the mean scores of each instrument at the 6-month post-treatment interval.

Overall there is an undeniable trend of improvement in patients' CLBP after treatment with BMAC injections. At the very least these findings provide adequate grounds for further investigation into BMAC injections as effective, curative treatment of one of the most widespread medical problems in the United States. Larger, more comprehensive studies have the potential to corroborate these findings and expand upon them. The movement away from mere symptomatic control for LBP and CLBP toward a definitive cure would quite literally be life-changing for millions of people in the U.S. alone.

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