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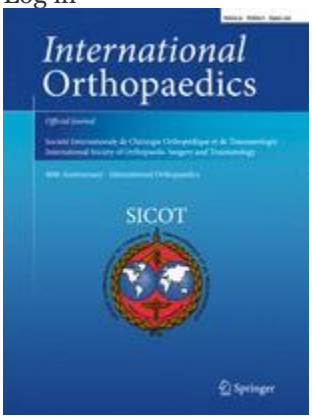

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A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions

- Authors
- Authors and affiliations
- Christopher J. Centeno Email author
  - Centenooffice@centenoschultz.com
  - Hasan Al-Sayegh :: https://www.linkedin.com/in/hasanalsayegh (Biostatistician at Boston Children's Hospita)
  - Michael D. Freeman [https://www.researchgate.net/profile/Michael_Freeman2]
  - Jay Smith :: https://www.mayoclinic.org/biographies/smith-jay-m-d/bio-20054086
  - https://connect.mayoclinic.org/2016/03/31/stem-cells-and-growth-factors-for-osteoarthritis-hope-or-hype/
  - William D. Murrell https://www.doximity.com/pub/william-murrell-md (MD)
  - Rostyslav Bubnov https://www.researchgate.net/profile/Rostyslav_Bubnov (MD Kiev, Ukraine Rostyslav does research in Radiology, Neurology and Gastroenterology)

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Abstract

Introduction

The purpose of the present investigation is to **report on detailed complications** among a much larger group of 2372 orthopaedic patients treated with stem cell injections who were followed in a treatment registry for up to nine years.

Methods [https://www.clinicalpainadvisor.com/aapm-2017-annual-meeting/degenerative-disc-disease-treatment-with-stem-cells/article/644401/]

All patients underwent an **MSC-based, percutaneous injection treatment** of an orthopaedic condition between **December 2005 and September 2014 at one of 18 clinical facilities. Treated** areas of the body included the knee, hip, ankle/foot, hand/wrist, elbow, shoulder, and spine. **The patients were followed prospectively via enrollment in a treatment registry.** Patients were followed prospectively at one, three, six and 12 months, and annually thereafter, using an electronic system, ClinCapture software.

Results

A total of 3012 procedures were performed on 2372 patients with follow-up period of 2.2 years. **A total of 325 adverse events were reported.** The majority were pain post-procedure (n = 93, 3.9 % of the study population) and pain due to progressive degenerative joint disease (n = 90, 3.8 % of the study population). Seven cases reported neoplasms, a lower rate than in the general population. The lowest rate of adverse events was observed among patients injected with BMC alone.

Conclusion

Lowest rate of adverse events was among those patients receiving BMC injections alone, but the higher rate of AEs for BMC plus adipose and cultured cells was readily explained by the nature of the therapy or the longer follow-up. There was no clinical evidence to suggest that treatment with MSCs of any type in this study increased the risk of neoplasm.

Keywords

Bone marrow concentrate Complications Mesenchymal stem cells Platelet rich plasma Registry Side effects

Electronic supplementary material

The online version of this article (doi: 10.1007/s00264-016-3162-y) contains supplementary material, which is available to authorized users.

A correction to this article is available online at https://doi.org/10.1007/s00264-017-3680-2.

Introduction

Autologous mesenchymal stem cells (MSCs) have been utilized to treat degenerative and post-traumatic orthopedic conditions for more than two decades [1]. Because MSCs can differentiate into bone, cartilage, muscle, tendon, and ligament tissue and

can use paracrine and other effects to elicit significant changes in injured tissues, their use for treating orthopaedic conditions holds significant promise [2, 3, 4, 5]. In a clinical setting MSCs are typically harvested from bone marrow, then isolated and either re-injected or implanted in the same surgical procedure or culture expanded and then used clinically.

The same surgical procedure use of bone marrow aspirate is known as bone marrow concentrate (BMC). This is a fraction of the whole marrow which is isolated via centrifugation and subsequently injected into joints and surrounding tissue [3]. BMC contains MSCs and other nucleated cells, including hematopoietic stem cells, endothelial progenitor cells, macrophages, and platelets [6]. MSCs can also be isolated from marrow aspirate and then expanded in culture as a means of increasing the MSC dose [7]. In contrast with therapy utilizing BMC in which the entire procedure is performed in the same procedure, *in vitro*culture-expansion of MSCs requires a one to two week period of preparation and incubation.

A number of studies published over an 18-year span have described the safe use of autologous bone marrow derived MSCs to treat orthopaedic conditions [1, 5, 8, 9, 10, 11, 12]. The results of these studies, bolstered by the results of *in vitro* and animal studies, indicate that bone marrow derived MSCs carry little to no risk of malignant transformation, and that they are likely safe for use in human orthopaedic applications [4, 7, 13, 14, 15]. However, no large scale investigations exist with long-term patient follow-up where all complications have been reported, adjudicated, and classified.

We have previously published the results of two treatment registry studies that followed reported complications among 227 (in 2010) and 339 (in 2011) orthopaedic patients treated with culture-expanded MSCs [9, 14]. The purpose of the present investigation is to report on detailed complications among a much larger group of 2372 orthopaedic patients treated with stem cell injections who were followed in a treatment registry for up to nine years. The patients in the present analysis fall into one of the following treatment groups: 1) those who were treated with BMC only; 2) those who were treated with BMC along with an adipose graft, and 3) those who were treated with culture-expanded MSCs.

Methods

Participants and settings

Subjects included in the present study are all patients who

1) underwent an MSC-based, percutaneous injection treatment of an orthopaedic condition between December 2005 and September 2014 at one of 18 clinical facilities located in the United States or Australia

2) and who had attained at least a three month follow-up period.

Treated conditions included:

1. those resulting from degenerative joint changes (*i.e.*, osteoarthritis, degenerative disc disease, degenerative disc disease)

2. as well as trauma (*e.g.*, anterior cruciate ligament injuries, rotator cuff tears, *etc.*). Treated areas of the body included the knee, hip, ankle/foot, hand/wrist, elbow, shoulder, and spine. Knee, hip, and shoulder patients constituted approximately 87 % of the population.

The patients were followed prospectively via enrollment in a treatment registry. Patients were grouped by type of MSC treatment (see below).

The choice of treatment type was left to the treating physician and while there were no exclusion criteria for MSC-treated patients to enter the registry, patients were naturally excluded from treatment if they were found not to be a candidate for the treatment by the attending physician.

Reasons for exclusion from treatment included:

1. [NO $$$],

2. conditions for which the only therapeutic alternative was deemed to be surgery

3. as well as medical conditions that **would make MSC therapy "difficult"**.

4. **Examples include: a) a completely torn and retracted tendon** or ligament, b) a severely osteoarthritic knee with deformity, c) severe spinal stenosis with neurologic compromise, and d) severe rheumatologic conditions like rheumatoid arthritis or systemic lupus erythematosus.

   Institutional **Review Board oversight for the registry protocol was provided by a U.S. Office of Human Research Protections registered organization (#IRB00002637).**

   Outcomes and efficacy of each procedure have been reported previously [2, 8, 13, 16]. Prior to each procedure, physicians discussed risks, benefits, and alternatives to the procedure. Each subject gave both oral and written informed consent for procedure. [BUT, did each subject "understand"?]

Baseline information collected in the registry included: primary diagnosis, patient demographics, medical history, and physical examination. Patients were followed prospectively at 1, 3, 6, and 12 months post treatment, and annually thereafter, using an electronic system, ClinCapture software (Clinovo Clinical Data Solutions, Sunnyvale,

California). Patients were sent automated e-mails that asked them to respond to a number of questions regarding outcomes, function, and general health. Three e-mails were sent once a week and if the patient failed to respond after three e-mails, the registry staff initiated two phone calls. If the patient failed to respond to these additional two queries, then the time point was considered lost to follow-up and the process began again at the next time point. Attending physicians participating in the registry were also encouraged to report any complications.

In addition to outcome information, patients were also asked the following two questions regarding possible treatment-related adverse events (AEs):

1. ***"Did you experience any complications you believe may be due to the procedure (i.e., infection, illness, etc.)? If yes, please explain;"***

2. **and *"Have you been diagnosed with any new illness since the procedure? If yes, please explain."*** The complications questions were intentionally broad in order to capture any change in the patient's health status that could possibly be related to the MSC procedure.

Treatment groups

The patients were grouped based on type of MSC treatment, as follows:

3. **SD** (same day aspiration, isolation, and re-injection procedure with BMC),

4. **AD** (same day aspiration, isolation, and re-injection procedure with BMC plus adipose graft),

5. and **CE** (culture expanded MSCs re-implanted weeks or months after bone marrow aspiration) (see Supplement 1). All physicians were trained to use the same protocol for bone marrow aspiration, adipose graft, and re-injection procedures.

Two weeks prior to the bone marrow harvest procedure, patients in all groups were restricted from using steroidal and non-steroidal anti-inflammatory drugs in order to avoid possible cytotoxic effects on MSCs [17].

All injections in this study were confirmed with ultrasound or fluoroscopic imaging to ensure accurate placement. **Two to five days prior to the administration of the MSCs to the treatment area, the patient's joint, ligament, or tendon was pre-injected with 12.5 % hypertonic dextrose to promote an inflammatory response and begin the process of tissue repair.**

The decision to use this protocol was based on promising earlier observations in animal models that this protocol aided tendon healing and improved function in knee osteoarthritis patients and confirmed more recently through stabilization of cartilage

volume on MRI in patients receiving only this treatment [18]. A detailed description of the procedures performed for the SD, AD, and CE groups are provided in our earlier publications [7, 9, 16].

Briefly, bone marrow harvest was completed via the collection of approximately 10–15 cc of bone marrow aspirate from the six to ten total sites from the bilateral posterior iliac crests.

For the BMC injections (SD and AD groups), the aspirate was centrifuged to separate the buffy coat, resulting in 1–3 ml of BMC generally containing 0.2-1.5 × 10^8 nucleated cells.

Platelet rich plasma (PRP) and platelet lysate (PL) was concurrently prepared and injected along with the BMC into the target region on the same day as the bone marrow aspiration.

In the AD group, an additional component of minimally processed lipo-aspirate which had been separated from the aqueous and oil components was co-injected along with the BMC (3–7 cc) and PRP and PL solution [7]. **All isolation techniques for PRP, PL, SD, AD, and CE were standardized using a standard operating procedure (SOP) protocol that has been described in previous publications [7, 9, 16].**

Specifically, "purpose-built kits" were not used, but all sites used the same off the shelf disposable lab supplies and the same or similar equipment such as centrifuges, pipettes, and microscopy. [HOW IS THIS KNOWN?] Staff at each site were trained in these SOP protocols. Based off the PLRA classification, the type of PRP produced is 1 cc of 14x/–/–/NO [19] **but baseline platelet counts were not obtained**. In the CE group, MSCs isolated from the bone marrow aspirate were expanded in an autologous based culture media for 12–16 days prior to injection into the joint space (1–3 cc in PL with dose ranges generally from 0.1-6 × 10^7 MSCs) or musculoskeletal structure (see Supplement 1 which elaborates on treatment differences between groups) [14]. Injectate volumes and dose were recorded, but not controlled and were determined by the treating physician. [Susan has saved Supplement ONE. Susan accessed – reference 14 ## https://www.ncbi.nlm.nih.gov/pubmed/19951252?dopt=Abstract]

Adverse events adjudication (AEs)

AEs accessed from the treatment registry were initially sorted into one of **20** categories:

1.Allergic bone,
2.cardiac,
3.endocrine,
4.gastrointestinal,
5.immune,
6.infection,

7.lab work,
8.neoplasm,
9.neurologic,
10.pain-post procedure,
11.pain due to progressive DJD, [Degenerative Joint Disease]
12.pain-other areas,
13.pain-other,
14.pulmonary,
15.renal,
16.rheumatological,
17.skin,
18.vascular,
19.and other. [**Only 19 categories cited.]**

[Adverse Events] AEs were further categorized by the attending physician as:
(1) **serious** adverse events (SAEs)
or non-SAEs (2) expected or unexpected,
and, as appropriate (3) related to the implantation procedure or related to stem cells (not mutually exclusive).

AEs related to the implantation procedure or the stem cells were further defined as "definite," "possible," "unlikely," or "not related."

SAEs were defined using guidelines developed by the United States Department of Health and Human Services [20].[Susan Update]

This is defined as "any untoward event that results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or requires intervention to prevent permanent impairment or damage." [The "definition" stated does NOT match any "exterior" citation source – when "Googled".]

All "possible" SAEs were tabulated by one author (CJC) and then provided to **five independent physician reviewers** who were blinded to any initial or subsequent adjudication by another reviewer. [Who are the "**five independent physician reviewers"? Please name.]** The tabulating author (CJC) also remained blinded as to the identity of the physician who performed any *specific independent adjudication*. [Why did these "independent" adjudicators "fail" to ask the questions – that (Susan) – merely a retired, software Technical Writer has found?]

The independent reviewers were unrelated to the treating physicians in the study. [Again, please name the "independent reviewers" – so, readers can determine – for themselves – their "relationship" if any.] Independent reviewers were recruited via an electronic discussion board for physicians if they:
(1) had experience in using platelet rich plasma or stem cells for orthopaedic conditions
(2) were a practicing physician in private or academic practice (Mishra, Feb 2009).

In order to estimate the AE incidence, a person-time metric was calculated based on the number of patients and the amount of time they were followed from the time of treatment. The follow-up period was calculated from the date of the procedure to the date of data access or study exit. [CAUTION: Do NOT use statistical jargon when reporting results of scientific study.]

Statistical analysis [Readers should also consult...]

The treatment groups were described by: age, body-mass index (BMI), follow-up time, gender, and the joint/area treated. Frequency, proportion, and the rate of AEs by category were reported for each treatment group. AE rates were compared between treatment groups using a chi-square test. Frequency, proportion, and rate were also reported for SAEs, expected AEs, procedure-related AEs, and stem cell-related AEs.

Categorical differences in proportions and rates between groups were analyzed using a chi-square test. *Post hoc* pair-wise comparisons between groups were made using chi-square or Fisher's exact test, as appropriate. [Who determined if "appropriate"?] AE incidence rates were calculated by dividing the frequency of a specific AE by the total person-year (PY) denominator, with the results reported per 100 PY. Logistic regression analysis for binary outcomes was used to quantify the risk of reporting an AE, SAE, and treatment-related AE by treatment group, and adjusted for potential predictive or confounding factors (i.e., length of follow-up, age, gender, and body area treated). All statistical analyses were performed using SAS software version 9.4 [21].

[page break added]

Results

There were 2372 patients in the registry who were treated with any one of the three autologous MSC protocols in the period between December 2005 and September 2014.

The follow-up period ranged from 1 month to 8.8 years, with 2.2 years mean follow-up time.

In the **SD group** 1590 patients were treated (1949 BMC injections),

247 patients were treated in the **AD group** (364 BMC injections with adipose graft),

and 535 patients were treated in the **CE group** (699 culture-expanded MSCs procedures).

The higher number of procedures than patients indicates both serial procedures that occurred at different times and/or bilateral or multiple joint procedures that occurred in the same treatment session.

The CE group was followed for an average of 4.4 years (3 months to 9 years), and the SD and AD groups were followed for an average of 1.1 (3 months-5 years) and 1.8 years (3 months to 4 years), respectively (see Fig. 1).

Other **baseline characteristics** are reported in Table 1.

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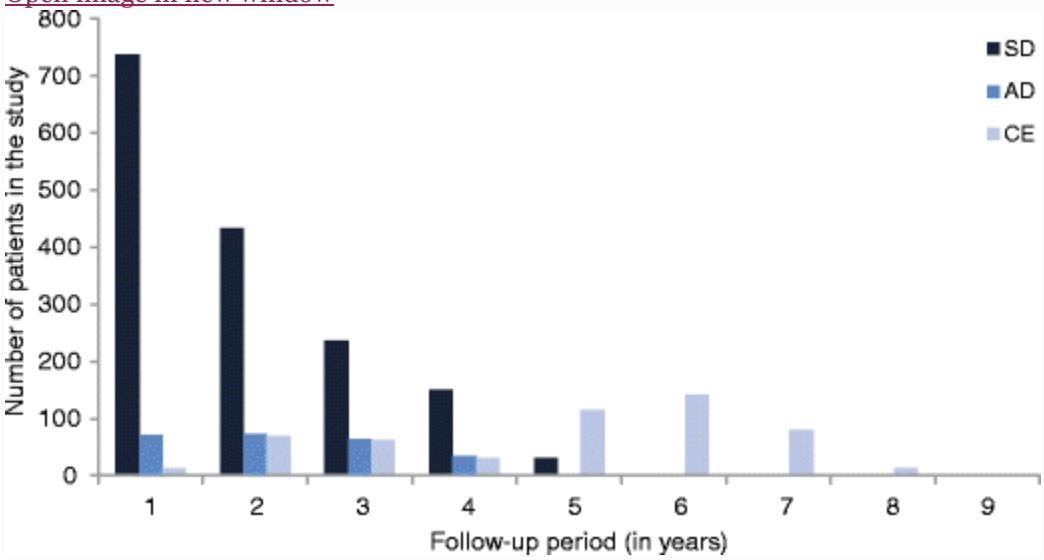

Fig. 1

Number of patients categorized by length of follow-up, in number of years

Table 1

Baseline characteristics and mean follow-up periods in years

	SD			AD			CE			Total	
	N	Mean	St. D.	N	Mean	St. D.	N	Mean	St. D.	N	Mea
Age	1589	55.6	14.2	246	60.0	10.9	535	53.4	13.2	2370	55.6
BMI	1447	26.5	4.8	226	27.1	4.2	347	26.5	4.5	2020	26.6
Follow-up time	1590	1.5	1.1	247	1.8	1.1	535	4.4	1.8	2372	2.2
	N	%		N	%		N	%		N	%
Gender											
Male	964	60.6		134	54.3		343	64.1		1441	60.8
Female	626	39.4		113	45.7		192	35.9		931	39.2
Joint/body area											
Knee	878	55.2		234	94.7		278	52.0		1390	58.6
Hip	366	23.0		6	2.4		124	23.2		496	20.9
Foot/ ankle	126	7.9		2	0.8		43	8.0		171	7.2
Spine	15	0.9		0	0		44	8.2		59	2.5
Shoulder	144	9.1		3	1.2		30	5.6		177	7.5
Hand/ elbow	52	3.3		2	0.8		13	2.4		67	2.8
General	9	0.6		0	0		3	0.6		12	0.5

Median age of the study population is 57 years (inter-quartile range = 48-65). Female proportion is 39.2 %, *SD* = same-day bone marrow concentrate; *AD* = bone marrow concentrate with adipose graft; *CE* = culture expanded stem cells *BMI* = body mass index, *St. D.* = standard deviation]

There were a total of 325 AEs reported by 287 patients (12.1 % of the study population), with 36 reported SAEs, representing 1.5 % of the study population and incidence of 0.7/100 PY (see Fig. 2 and Table 2). SAE incidences were significantly different between groups, with the CE group reporting the highest incidence at 1.1/100 PY, versus 0.9/100 PY in the AD group and 0.4/100 PY in the SD group (P = 0.006). There were 38 AEs that were deemed to be definitely related to the procedures (1.6 % of the total population) and ten AEs definitely related to stem cells (0.4 % of the total population). Incidences of procedure- and stem cell-related AEs were not significantly different between treatment groups.

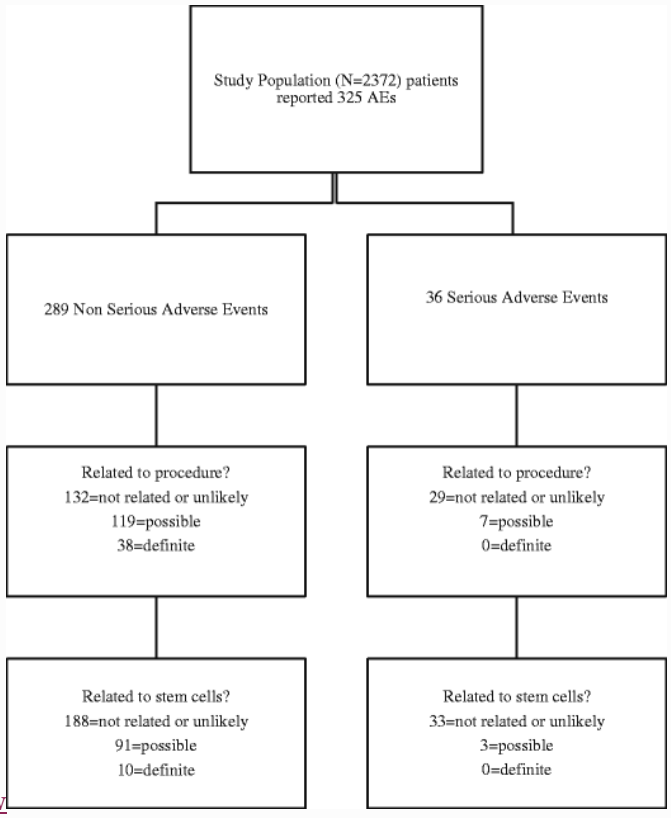

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Fig. 2

Flow chart demonstrating the distribution and number of serious adverse events, as they related to to procedure type or stem cells. AE = adverse event

Table 2

Frequency, proportion, and incidence (per 100 person-years) for serious adverse events, expected, procedure-related, stem cell-related adverse events (AE) and AE categories

	SD			AD			CE		
	N	%	Incidence	N	%	Incidence	N	%	Inci
SAE									
No	107	6.7	4.66	26	10.6	5.89	160	30.2	6.89
Yes	7	0.4	0.3	4	1.6	0.91	25	4.7	1.11
Expected									
No	98	6.2	4.22	28	11.4	6.34	160	30.2	6.89
Yes	16	1.0	0.77	2	0.8	0.45	21	4.0	0.9
Related to procedure									
Not related or unlikely	38	2.4	1.62	10	4.1	2.33	113	21.4	4.99
Possible	55	3.5	2.44	15	6.1	3.4	56	10.6	2.41
Definite	21	1.3	0.9	5	2.0	1.13	12	2.3	0.52
Related to stem cells									
Not related or unlikely	68	4.3	2.9	17	6.9	3.99	136	25.7	5.86
Possible	39	2.4	1.77	12	4.9	2.72	43	8.1	1.85
Definite	7	0.4	0.3	1	0.4	0.23	2	0.4	0.09
Category									
Allergic	6	0.4	0.26	0	0.0	0	5	0.9	0.22
Bone	0	0.0	0	0	0.0	0	1	0.2	0.04
Cardiac	3	0.2	0.13	3	1.2	0.68	2	0.4	0.09

	SD			AD			CE		
	N	%	Incidence	N	%	Incidence	N	%	Inci
Endocrine	0	0.0	0	0	0.0	0	4	0.8	0.17
Gastrointestinal	1	0.1	0.04	0	0.0	0	2	0.4	0.09
Immune	3	0.2	0.13	0	0.0	0	6	1.1	0.26
Infection	1	0.1	0.04	1	0.4	0.23	4	0.8	0.17
Lab work	2	0.1	0.09	0	0.0	0	5	0.9	0.22
Neoplasm	1	0.1	0.04	0	0.0	0	6	1.1	0.26
Neurologic	2	0.1	0.09	2	0.8	0.45	10	1.9	0.43
Other	11	0.7	0.47	2	0.8	0.45	14	2.6	0.6
Pain-other area	6	0.4	0.26	3	1.2	0.45	8	1.5	0.34
Pain-post procedure	37	2.3	1.58	11	4.5	2.49	45	8.5	1.94
Pain-DJD	30	1.9	1.28	6	2.4	1.36	54	10.2	2.33
Pulmonary	0	0.0	0	0	0.0	0	2	0.4	0.09
Renal	0	0.0	0	1	0.4	0.23	3	0.6	0.13
Rheumatological	1	0.1	0.04	0	0.0	0	0	0.0	0
Skin	2	0.1	0.09	0	0.0	0	5	0.9	0.22
Vascular	8	0.5	0.34	1	0.4	0.23	5	0.9	0.22
Total	114	7.2	4.87	30	12.2	6.79	181	34.2	7.79

SAE = serious adverse event

The majority of AEs were post-procedure pain or attributed to degenerative joint disease (DJD) for which the treatment was sought (Fig. 3). There were 93 reports of post-procedure pain (3.9 % of the study population), and 90 reports of pain due to DJD (3.8 % of the study population) (Table 2). There

were 27 AEs classified as “other” (i.e., that did not fit into any of the described categories) and “pain in other areas” was reported by 16 patients. This last category describes AEs where the patient reported pain in an area that was not treated (i.e., the knee was treated and the patient reported new onset shoulder pain). Frequencies of neurologic, vascular, and allergic AEs were 14 (0.6 %), 14 (0.6 %), and 11 (0.5 % of the study population), respectively (Table 2). Among SAEs the most frequent categories were neoplasm, neurologic, and vascular events (Table 3). There were seven neoplasm cases representing 0.3 % of the study population, with an incidence of 0.14/100 PY. The difference in neoplasm rates between groups was not statistically significant. Serious neurologic and vascular events were six and five cases, respectively, representing 0.25 % and 0.21 % of the total population.

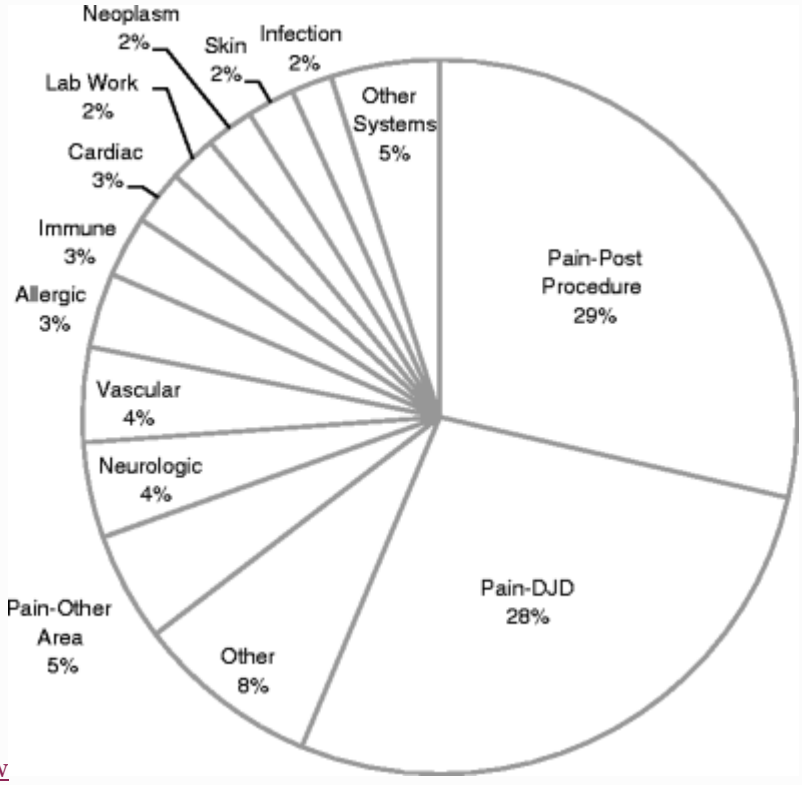

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Fig. 3

Proportions of adverse event (AE) subcategories versus the total number of AEs. “Other systems” include endocrine, renal, gastrointestinal, pulmonary, bone, and rheumatological, with <1 % each. DJD = degenerative joint disease

Table 3

Frequencies and proportions of serious adverse event categories

Category	Frequency	% of the total SAEs
Neoplasm	7	19.4
Neurologic	6	16.7
Vascular	5	13.9
Other	4	11.1

Category	Frequency	% of the total SAEs
Cardiac	2	5.5
Lab work	2	5.5
Skin	2	5.5
Endocrine	1	2.8
Gastrointestinal	1	2.8
Immune	1	2.8
Infection	1	2.8
Pain-post procedure	1	2.8
Pain-DJD	1	2.8
Renal	1	2.8
Rheumatological	1	2.8

SAE = serious adverse event, *DJD* = degenerative joint disease

Results of the SAE adjudication are reported in Table 4 and the Addendums. In Addendum 1, the adjudications of the six reviewers regarding the relatedness of the 36 SAEs are recorded. A majority opinion (as defined by >50 % agreement) was present in all but two SAEs (#15 and #30). Addendum 2 includes the results, by reviewer, of the relationship of the SAE to the procedure. In total, 19/36 (53 %) of the SAEs were considered as *not related* or *unlikely to be related* to the procedure. There were 13/36 cases or 36 % in which at least one reviewer indicated that the SAE was *possibly related*. Four of the 36 cases, or 11 %, of SAEs were adjudicated as *definitely related* to the procedure by a minority of reviewers (*i.e.*, one or two of the six reviewers). These four cases were categorized as neoplasm, pain post procedure, rheumatological, and other. Addendum 3 contains adjudication information from the reviewers regarding the relationship of the SAE to the stem cells or other biologic agent used. Fourteen of the 16 cases (39 %) of the SAEs were categorized as *not related* or *unlikely to be related*, while 16/22 (61 %) were adjudicated by one or more reviewer as *possibly related*. None of the SAEs were considered to be *likely* or *definitely related* to the stem cells or other biologic agent.

Table 4

Adjudication of serious adverse events

Reviewer	1		2		3		4		5		6	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(
Pre-existing condition												
No	27	(75)	22	(61.1)	20	(55.6)	21	(67.7)	30	(83.3)	24	(

Reviewer	1		2		3		4		5		6	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(
Yes	9	(25)	14	(38.9)	16	(44.4)	10	(32.3)	6	(16.7)	12	(
Relation to procedure												
Not related	10	(27.8)	19	(52.8)	27	(75)	23	(74.2)	22	(61.1)	25	(
Unlikely	19	(52.8)	5	(13.9)	4	(11.1)	1	(3.2)	12	(33.3)	4	(
Possible	7	(19.4)	8	(22.2)	5	(13.9)	4	(12.9)	2	(5.6)	6	(
Definite	0	(0)	4	(11.1)	0	(0)	3	(9.7)	0	(0)	1	(
Relation to stem cells												
Not related	8	(22.2)	20	(55.6)	21	(58.3)	10	(32.3)	21	(58.3)	17	(
Unlikely	25	(69.4)	4	(11.1)	14	(38.9)	13	(41.9)	11	(30.6)	6	(
Possible	3	(8.3)	10	(27.8)	1	(2.8)	8	(25.8)	3	(8.3)	13	(
Definite	0	(0)	2	(5.6)	0	(0)	0	(0)	1	(2.8)	0	(

Reviewer 1 = attending physician; Reviewer 2–6 = independent reviewers.

Logistic regression modeling revealed that patients in both the AD and CE groups were more likely to report an AE than in the SD group; ORs = 1.64 (95 % CI; 1.03, 2.61) and 1.68 (95 % CI; 1.11, 2.54), respectively (Table 5). Further analysis showed that, compared to the SD group, the increase in AE rate was largely attributable to post-procedure pain in the AD group, and pain due to DJD in the CE group (Figs. 4 and 5). A longer follow-up period, older age, and female gender increased the risk of reporting an AE. SAEs were more common in patients with a longer follow-up period and of older age [OR = 1.51 (95 % CI; 1.37, 1.67) and 1.03 (95 % CI; 1, 1.06), respectively]. Patients treated for spinal conditions were more likely to report any AE in comparison with patients undergoing knee procedures [OR = 2.17 (95 % CI; 1.13, 4.15)].

Table 5

Odds ratios and 95 % confidence interval (CI) of reporting adverse events, serious adverse events, and treatment-related adverse events for treatment types and potential confounding factors

	OR (95 % CI) of	OR (95 % CI) of	OR (95 % CI) of
Effect	**Any adverse event**	**Serious adverse events**	**Treatment-related adverse events**
Treatment type			
Group AD	1.64 (1.03-2.61) *	2.78 (0.8-9.66)	1.42 (0.83-2.44)
Group CE	1.68 (1.11-2.54) *	2.80 (0.88-8.94)	0.92 (0.55-1.56)
Group SD (eeference)	1	1	1
Follow-up (in years)	1.51 (1.37-1.67) *	1.6 (1.26-2.03) *	1.4 (1.24-1.58)*
Age (in years)	1.01 (1–1.02) *	1.03 (1–1.06) *	1 (0.99-1.01)
Gender			
Female	1.49 (1.13-1.96) *	1.95 (0.99-3.84)	1.26 (0.9-1.77)
Male (reference)	1	1	1
Joint/body area			
Foot/ankle	1.12 (0.65-1.9)	-	1 (0.53-1.91)
General	1.78 (0.3-10.36)	-	0.9 (0.1-7.85)
Hand/elbow	1.08 (0.46-2.56)	-	0.86 (0.3-2.45)
Hip	1.23 (0.87-1.73)	-	0.82 (0.52-1.3)
Shoulder	1.07 (0.6-1.88)	-	0.88 (0.43-1.81)
Spine	2.17 (1.13-4.15) *	-	2.46 (1.19-5.08)*
Knee (reference)	1	-	1

OR = odds ratio; *CI* = confidence interval; *AE* = adverse event; *SAE* = serious adverse events; treatment-related *AEs* = AEs definitely or possibly related to procedure or stem cells; *SD* = same-day bone marrow concentrate; *AD* = bone marrow concentrate with adipose graft; *CE* = culture expanded stem cells; * = statistically significant; Due to the

low SAE frequency per joint/body area category; the joint/body area variable was removed from the SAE logistic regression model.

Open image in new window

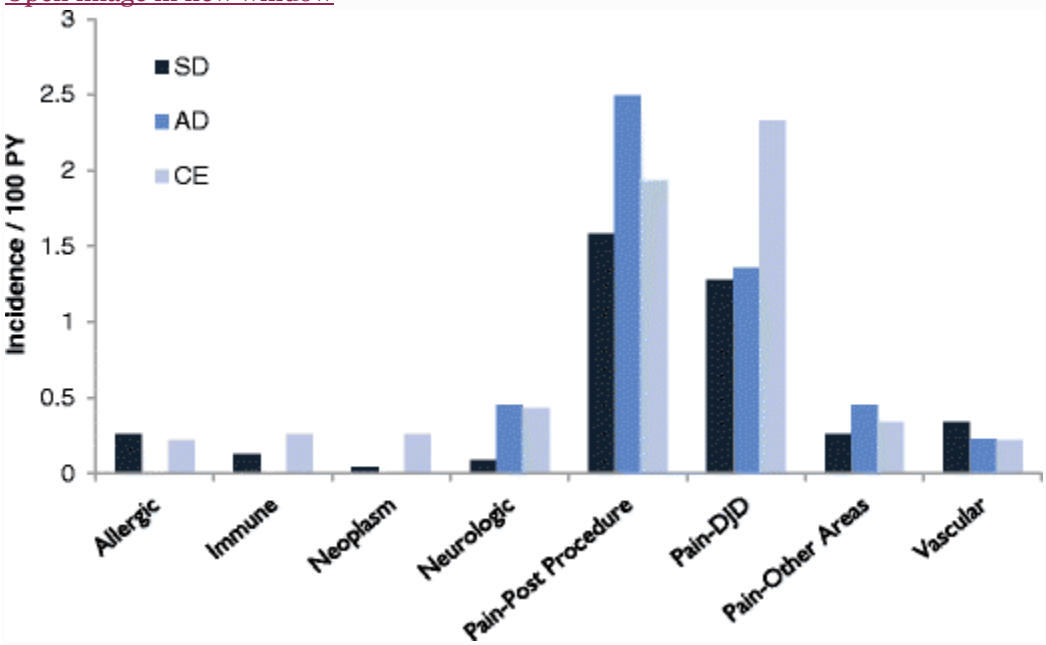

Fig. 4

Incidence of the most common adverse event categories, per 100 person-years (PY). SD = same-day bone marrow concentrate; AD = bone marrow concentrate with adipose graft; CE = culture expanded stem cells; DJD = degenerative joint disease

Open image in new window

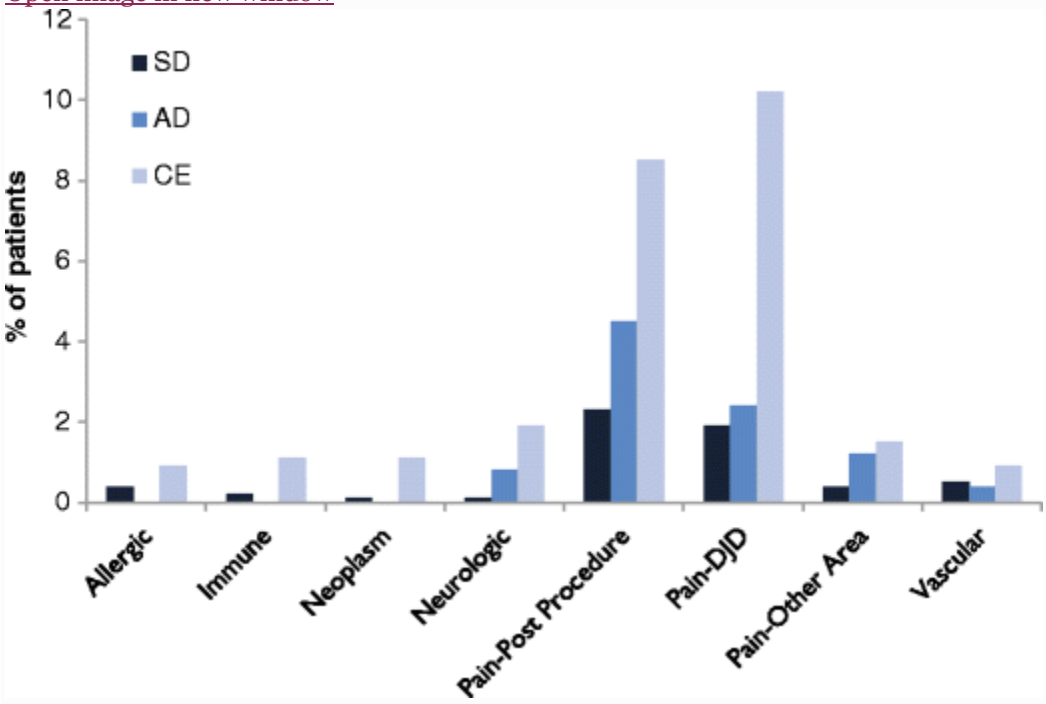

Fig. 5

Percentages of total patients reporting adverse events, for the most commonly reported categories. SD = same-day bone marrow concentrate; AD = bone marrow concentrate with adipose graft; CE = culture expanded stem cells; DJD = degenerative joint disease

Discussion

In the present study we generally observed low rates of reported AEs among patients treated with MSC procedures, and substantially lower rates of serious or treatment-related AEs. The finding that the majority of AEs were post-procedure pain or pain due to DJD that pre-existed the treatment was not surprising, and consistent with the progressive nature of the treated disorders.

While there have been several publications that have described the safety and efficacy of bone marrow derived stem cell therapies for orthopaedic applications [1, 7, 9, 10, 11, 12, 13, 15], to our knowledge the current investigation is the most comprehensive report of its kind, following the largest population for the longest time, and incorporating an analysis of the relative safety of several different approaches. Our findings are consistent with prior investigations demonstrating a favorable safety profile for the percutaneous use of BMC and MSC injections for the treatment of orthopaedic conditions of the peripheral and axial joints and surrounding tissues [7, 9, 13, 14]. The SAE rates observed in our study were substantially lower than those reported for more invasive orthopaedic surgical procedures [22]. As an example, the SAE rate for total knee arthroplasty among 260 patients at three months follow-up was 6 % [22]. In comparison, there were 13 *possibly* related SAEs in the present study among 2372 patients, approximately 0.55 %, and only four of these SAEs (0.17 %) were deemed *definitely* related to the procedure. While SAEs related to stem cell injections can and do occur, prior authors have indicated that the rate is not greater than that observed with other types of intra-articular injections, such as hyaluronic acid injections [23]. The findings in the present investigation reinforce this conclusion.

The differences observed in the AE rates between the treatment groups were not directly attributed to the treatment but rather to symptoms of progressive degenerative disease. Thus, the group that was tracked for the longest time (the culture expanded [CE] group) also had the highest incidence of AEs resulting from worsening of the treated condition over time. This observation is consistent with the natural history of painful degenerative joint disease [24, 25]. Further, the AEs reported in the first months of follow-up differ from those reported after several years of follow-up. For example, treatment-related AEs, including post-procedural pain, are more likely to be reported in the earliest few weeks after treatment; while unrelated or more serious AEs, such as neoplastic and cardiovascular events, are more likely to be reported after several years of follow-up (i.e., as patients age). The higher rate of AEs in the adipose graft (AD) BMC group versus the BMC only group (SD) was largely attributed to post-procedural pain. This difference may be explained by the pro-inflammatory effects of residual adipose oil in the injectate [26].

Of the seven reported cases of neoplasm among the registry patients, none occurred at the site of implantation despite all injections being confirmed with imaging guidance.

Given the number and age of the patients followed in the registry, and the amount of time that the patients were followed, some cases of cancer were expected. According to the National Cancer Institute, the annual incidence of cancer in the U.S. population in 2011 was 0.44 % (438 cases per 100,000 individuals), and 0.78 % in adults 50–64 years [27]. In contrast, we observed a lower annual cancer rate (0.14 %) among our registry participants. These findings are consistent with previous reports indicating no increased risk of tumor formation following BMC injections or treatment with culture-expanded MSCs [9, 11, 13, 15].

Older age and longer follow-up times increased the risk of reporting of both AEs and SAEs. These findings are explained both by the fact that morbidity increases with age [28], and that older patients are more likely to report adverse events after orthopaedic procedures [29]. A gender effect was also observed, in that women were more likely than men to report AEs. While the nature of the registry data makes it difficult to determine the reason for this disparity, previous authors have noted that women are more likely to report post-operative pain after arthroscopic procedures [30]. Patients who underwent treatment for degenerative joint and disc changes in the spine also had a higher rate of AE reporting, including AEs related to the treatment. Most of the reports in this group were of pain due to degenerative joint disease and post-procedural pain. While the explanation for this observation is not readily apparent; it could be due to the nature of the treated condition or it could be entirely due to differences in treatment efficacy. Further study would be required to provide more meaningful insight.

The results of the SAE adjudication by the attending physician and the panel of independent and blinded reviewers indicated good agreement on the categorization of pre-existing conditions, with majority agreement on 34 of 36 SAEs. One of the cases in which a minority of reviewers judged an SAE to be related concerned a neoplasm that a single reviewer opined was definitely related to the mechanics of the draw or re-implant injection procedure (the other five reviewers judged the relationship to be unlikely or not related). The SAE concerned a patient who was diagnosed with aggressive stomach cancer three weeks following a knee BMC injection, and who died from the disease at approximately two months following the injection. The protocol of the blinded adjudication process made impossible any follow up with the reviewer for an explanation as to why he or she believed that the stomach cancer, which likely pre-existed the procedure in nearly the same state as it was in three weeks following the procedure, was definitely related.

Another SAE, consisting of severe post-procedure swelling, was judged by two reviewers as definitely needle trauma related, and two reviewers judged the condition as definitely caused by the stem cells or other injectates. A rheumatologic condition was deemed to be definitely related to an injection by two reviewers. In that case, the patient presented with severe knee swelling after a pre-injection procedure with hypertonic dextrose. The joint was drained and found to be purulent, but gram stain and culture were negative. Ultimately synovial fluid crystalline structures were revealed and a diagnosis of gout was made. Because of the pre-injection complication the patient did not undergo the stem cell injection.

An SAE following treatment of a degenerated and painful intervertebral disc was judged to be to be definitely related to the trauma of the stem cell injection by two reviewers. In that case, at approximately eight months post-procedure, the patient sustained an acute disc herniation at the injected level. Three of the reviewers considered the SAE to be possibly related and one determined that it was unlikely to be related to the injection. It is certainly plausible that the needle trauma could have resulted in injury to the disk annulus, resulting in structural compromise and the latent herniation.

The strengths of the current study are its large patient population, the fact that data was collected from multiple centers, that SAEs were adjudicated by multiple independent and blinded reviewers, that AE/SAE rates of multiple treatment types are compared, and that unlike prior large studies all AEs were reported and classified. The main weaknesses of the current research are that it is based on data accessed from a treatment registry. Thus, there is no control group with which the frequency and type of observed illnesses could be compared. Further, the majority of AEs were patient reported. Despite the fact that repeated efforts were made to contact non-responders and all treating physicians were encouraged to report any possible complications while patients were under their care, it is possible that adverse events were under-reported to some degree.

Conclusion

To our knowledge, the present investigation is the first report to compare the clinical safety of different bone marrow derived stem cell therapies to treat orthopedic diseases and the first multi-site, large scale report of all AEs in stem cell treated orthopaedic patients. We found that the lowest rate of adverse events was among those patients receiving BMC injections alone, but the higher rate of AEs for BMC plus adipose and cultured cells was readily explained by the nature of the therapy or the longer follow-up. There was no clinical evidence to suggest that treatment with MSCs of any type in this study increased the risk of neoplasm. Although efficacy is best demonstrated with randomized controlled clinical trials, it is reasonable to conclude that the results of the present study add to the existing body of evidence showing the safety of MSC based therapies for orthopaedic conditions.

Notes

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Steve Gorin, M.D. and R. Amadeus Mason M.D. for acting as independent adjudicators for SAEs.

Supplementary material

264_2016_3162_MOESM1_ESM.docx (14 kb)

Supplement 1 (DOCX 14 kb)

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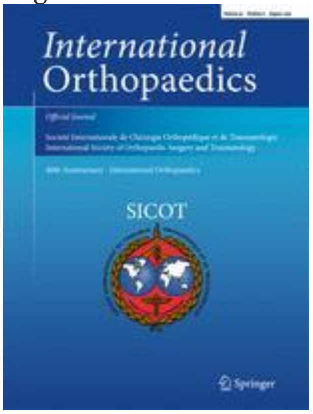

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A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions

- Authors
- Authors and affiliations
- Christopher J. CentenoEmail author
- Hasan Al-Sayegh
- Michael D. Freeman
- Jay Smith
- William D. Murrell
- Rostyslav Bubnov

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Original Paper

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Abstract

Introduction

The purpose of the present investigation is to report on detailed complications among a much larger group of 2372 orthopaedic patients treated with stem cell injections who were followed in a treatment registry for up to nine years.

Methods

All patients underwent an MSC-based, percutaneous injection treatment of an orthopaedic condition between December 2005 and September 2014 at one of 18 clinical facilities. Treated areas of the body included the knee, hip, ankle/foot, hand/wrist, elbow, shoulder, and spine. The patients were followed prospectively via enrollment in a treatment registry. Patients were followed prospectively at one, three, six and 12 months, and annually thereafter, using an electronic system, ClinCapture software.

Results

A total of 3012 procedures were performed on 2372 patients with follow-up period of 2.2 years. A total of 325 adverse events were reported. The majority were pain post-procedure (n = 93, 3.9 % of the study population) and pain due to progressive degenerative joint disease (n = 90, 3.8 % of the study population). Seven cases reported neoplasms, a lower rate than in the general population. The lowest rate of adverse events was observed among patients injected with BMC alone.

Conclusion

Lowest rate of adverse events was among those patients receiving BMC injections alone, but the higher rate of AEs for BMC plus adipose and cultured cells was readily explained by the nature of the therapy or the longer follow-up. There was no clinical evidence to suggest that treatment with MSCs of any type in this study increased the risk of neoplasm.

Keywords

Bone marrow concentrate Complications Mesenchymal stem cells Platelet rich plasma Registry Side effects

Electronic supplementary material

The online version of this article (doi: 10.1007/s00264-016-3162-y) contains supplementary material, which is available to authorized users.

A correction to this article is available online at https://doi.org/10.1007/s00264-017-3680-2.

Introduction

Autologous mesenchymal stem cells (MSCs) have been utilized to treat degenerative and post-traumatic orthopedic conditions for more than two decades [1]. Because MSCs can differentiate into bone, cartilage, muscle, tendon, and ligament tissue and can use paracrine and other effects to elicit significant changes in injured tissues, their use for treating orthopaedic conditions holds significant promise [2, 3, 4, 5]. In a clinical setting MSCs are typically harvested from bone marrow, then isolated and either re-injected or implanted in the same surgical procedure or culture expanded and then used clinically.

The same surgical procedure use of bone marrow aspirate is known as bone marrow concentrate (BMC). This is a fraction of the whole marrow which is isolated via centrifugation and subsequently injected into joints and surrounding tissue [3]. BMC contains MSCs and other nucleated cells, including hematopoietic stem cells, endothelial progenitor cells, macrophages, and platelets [6]. MSCs can also be isolated from marrow aspirate and then expanded in culture as a means of increasing the MSC dose [7]. In contrast with therapy utilizing BMC in which the entire procedure is performed in the same procedure, *in vitro*culture-expansion of MSCs requires a one to two week period of preparation and incubation.

A number of studies published over an 18-year span have described the safe use of autologous bone marrow derived MSCs to treat orthopaedic conditions [1, 5, 8, 9, 10, 11, 12]. The results of these studies, bolstered by the results of *in vitro* and animal studies, indicate that bone marrow derived MSCs carry little to no risk of malignant transformation, and that they are likely safe for use in human orthopaedic applications [4, 7, 13, 14, 15]. However, no large scale investigations exist with long-term patient follow-up where all complications have been reported, adjudicated, and classified.

We have previously published the results of two treatment registry studies that followed reported complications among 227 (in 2010) and 339 (in 2011) orthopaedic patients treated with culture-expanded MSCs [9, 14]. The purpose of the present investigation is to report on detailed complications among a much larger group of 2372 orthopaedic patients treated with stem cell injections who were followed in a treatment registry for up to nine years. The patients in the present analysis fall into one of the following treatment groups: 1) those who were treated with BMC only; 2) those who were treated with BMC along with an adipose graft, and 3) those who were treated with culture-expanded MSCs.

Methods

Participants and settings

Subjects included in the present study are all patients who underwent an MSC-based, percutaneous injection treatment of an orthopaedic condition between December 2005 and September 2014 at one of 18 clinical facilities located in the United States or

Australia and who had attained at least a three month follow-up period. Treated conditions included those resulting from degenerative joint changes (*i.e.*, osteoarthritis, degenerative disc disease, degenerative disc disease) as well as trauma (*e.g.*, anterior cruciate ligament injuries, rotator cuff tears, *etc.*). Treated areas of the body included the knee, hip, ankle/foot, hand/wrist, elbow, shoulder, and spine. Knee, hip, and shoulder patients constituted approximately 87 % of the population.

The patients were followed prospectively via enrollment in a treatment registry. Patients were grouped by type of MSC treatment (see below). The choice of treatment type was left to the treating physician and while there were no exclusion criteria for MSC-treated patients to enter the registry, patients were naturally excluded from treatment if they were found not to be a candidate for the treatment by the attending physician. Reasons for exclusion from treatment included conditions for which the only therapeutic alternative was deemed to be surgery as well as medical conditions that would make MSC therapy difficult. Examples include a completely torn and retracted tendon or ligament, a severely osteoarthritic knee with deformity, severe spinal stenosis with neurologic compromise, and severe rheumatologic conditions like rheumatoid arthritis or systemic lupus erythematosus. Institutional Review Board oversight for the registry protocol was provided by a U.S. Office of Human Research Protections registered organization (#IRB00002637). Outcomes and efficacy of each procedure have been reported previously [2, 8, 13, 16]. Prior to each procedure, physicians discussed risks, benefits, and alternatives to the procedure. Each subject gave both oral and written informed consent for procedure.

Baseline information collected in the registry included primary diagnosis, patient demographics, medical history, and physical examination. Patients were followed prospectively at 1, 3, 6, and 12 months post treatment, and annually thereafter, using an electronic system, ClinCapture software (Clinovo Clinical Data Solutions, Sunnyvale, California). Patients were sent automated e-mails that asked them to respond to a number of questions regarding outcomes, function, and general health. Three e-mails were sent once a week and if the patient failed to respond after three e-mails, the registry staff initiated two phone calls. If the patient failed to respond to these additional two queries, then the time point was considered lost to follow-up and the process began again at the next time point. Attending physicians participating in the registry were also encouraged to report any complications.

In addition to outcome information, patients were also asked the following two questions regarding possible treatment-related adverse events (AEs): *"Did you experience any complications you believe may be due to the procedure (i.e., infection, illness, etc.)? If yes, please explain;"* and *"Have you been diagnosed with any new illness since the procedure? If yes, please explain."* The complications questions were intentionally broad in order to capture any change in the patient's health status that could possibly be related to the MSC procedure.

Treatment groups

The patients were grouped based on type of MSC treatment, as follows: SD (same day aspiration, isolation, and re-injection procedure with BMC), AD (same day aspiration, isolation, and re-injection procedure with BMC plus adipose graft), and CE (culture expanded MSCs re-implanted weeks or months after bone marrow aspiration) (see Supplement 1). All physicians were trained to use the same protocol for bone marrow aspiration, adipose graft, and re-injection procedures.

Two weeks prior to the bone marrow harvest procedure, patients in all groups were restricted from using steroidal and non-steroidal anti-inflammatory drugs in order to avoid possible cytotoxic effects on MSCs [17]. All injections in this study were confirmed with ultrasound or fluoroscopic imaging to ensure accurate placement. Two to five days prior to the administration of the MSCs to the treatment area, the patient's joint, ligament, or tendon was pre-injected with 12.5 % hypertonic dextrose to promote an inflammatory response and begin the process of tissue repair. The decision to use this protocol was based on promising earlier observations in animal models that this protocol aided tendon healing and improved function in knee osteoarthritis patients and confirmed more recently through stabilization of cartilage volume on MRI in patients receiving only this treatment [18]. A detailed description of the procedures performed for the SD, AD, and CE groups are provided in our earlier publications [7, 9, 16]. Briefly, bone marrow harvest was completed via the collection of approximately 10–15 cc of bone marrow aspirate from the six to ten total sites from the bilateral posterior iliac crests. For the BMC injections (SD and AD groups), the aspirate was centrifuged to separate the buffy coat, resulting in 1–3 ml of BMC generally containing 0.2-1.5 × 10^8 nucleated cells. Platelet rich plasma (PRP) and platelet lysate (PL) was concurrently prepared and injected along with the BMC into the target region on the same day as the bone marrow aspiration. In the AD group, an additional component of minimally processed lipo-aspirate which had been separated from the aqueous and oil components was co-injected along with the BMC (3–7 cc) and PRP and PL solution [7]. All isolation techniques for PRP, PL, SD, AD, and CE were standardized using a standard operating procedure (SOP) protocol that has been described in previous publications [7, 9, 16]. Specifically, purpose built kits were not used, but all sites used the same off the shelf disposable lab supplies and the same or similar equipment such as centrifuges, pipettes, and microscopy. Staff at each site were trained in these SOP protocols. Based off the PLRA classification, the type of PRP produced is 1 cc of 14x/−/−/NO [19] but baseline platelet counts were not obtained. In the CE group, MSCs isolated from the bone marrow aspirate were expanded in an autologous based culture media for 12–16 days prior to injection into the joint space (1–3 cc in PL with dose ranges generally from 0.1-6 × 10^7 MSCs) or musculoskeletal structure (see Supplement 1 which elaborates on treatment differences between groups) [14]. Injectate volumes and dose were recorded, but not controlled and were determined by the treating physician.

Adverse events adjudication

AEs accessed from the treatment registry were initially sorted into one of 20 categories: allergic, bone, cardiac, endocrine, gastrointestinal, immune, infection, lab work, neoplasm, neurologic, pain-post procedure, pain due to progressive DJD, pain-other areas, pain-other, pulmonary, renal, rheumatological, skin, vascular, and other.

AEs were further categorized by the attending physician as: (1) serious adverse events (SAEs) or non-SAEs (2) expected or unexpected, and, as appropriate (3) related to the implantation procedure or related to stem cells (not mutually exclusive). AEs related to the implantation procedure or the stem cells were further defined as "definite," "possible," "unlikely," or "not related." SAEs were defined using guidelines developed by the United States Department of Health and Human Services [20]. This is defined as any untoward event that results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or requires intervention to prevent permanent impairment or damage. All "possible" SAEs were tabulated by one author (CJC) and then provided to five independent physician reviewers who were blinded to any initial or subsequent adjudication by another reviewer. The tabulating author (CJC) also remained blinded as to the identity of the physician who performed any specific independent adjudication. The independent reviewers were unrelated to the treating physicians in the study. Independent reviewers were recruited via an electronic discussion board for physicians if they: (1) had experience in using platelet rich plasma or stem cells for orthopaedic conditions (2) were a practicing physician in private or academic practice (Mishra, Feb 2009). In order to estimate the AE incidence, a person-time metric was calculated based on the number of patients and the amount of time they were followed from the time of treatment. The follow-up period was calculated from the date of the procedure to the date of data access or study exit.

Statistical analysis

The treatment groups were described by age, body-mass index (BMI), follow-up time, gender, and the joint/area treated. Frequency, proportion, and the rate of AEs by category were reported for each treatment group. AE rates were compared between treatment groups using a chi-square test. Frequency, proportion, and rate were also reported for SAEs, expected AEs, procedure-related AEs, and stem cell-related AEs. Categorical differences in proportions and rates between groups were analyzed using a chi-square test. *Post hoc* pair-wise comparisons between groups were made using chi-square or Fisher's exact test, as appropriate. AE incidence rates were calculated by dividing the frequency of a specific AE by the total person-year (PY) denominator, with the results reported per 100 PY. Logistic regression analysis for binary outcomes was used to quantify the risk of reporting an AE, SAE, and treatment-related AE by treatment group, and adjusted for potential predictive or confounding factors (i.e., length of follow-up, age, gender, and body area treated). All statistical analyses were performed using SAS software version 9.4 [21].

Results

There were 2372 patients in the registry who were treated with any one of the three autologous MSC protocols in the period between December 2005 and September 2014. The follow-up period ranged from 1 month to 8.8 years, with 2.2 years mean follow-up time. In the SD group 1590 patients were treated (1949 BMC injections), 247 patients were treated in the AD group (364 BMC injections with adipose graft), and 535 patients were treated in the CE group (699 culture-expanded MSCs procedures). The higher number of procedures than patients indicates both serial procedures that occurred at different times and/or bilateral or multiple joint procedures that occurred in the same treatment session. The CE group was followed for an average of 4.4 years (3 months to 9 years), and the SD and AD groups were followed for an average of 1.1 (3 months-5 years) and 1.8 years (3 months to 4 years), respectively (see Fig. 1). Other baseline characteristics are reported in Table 1.

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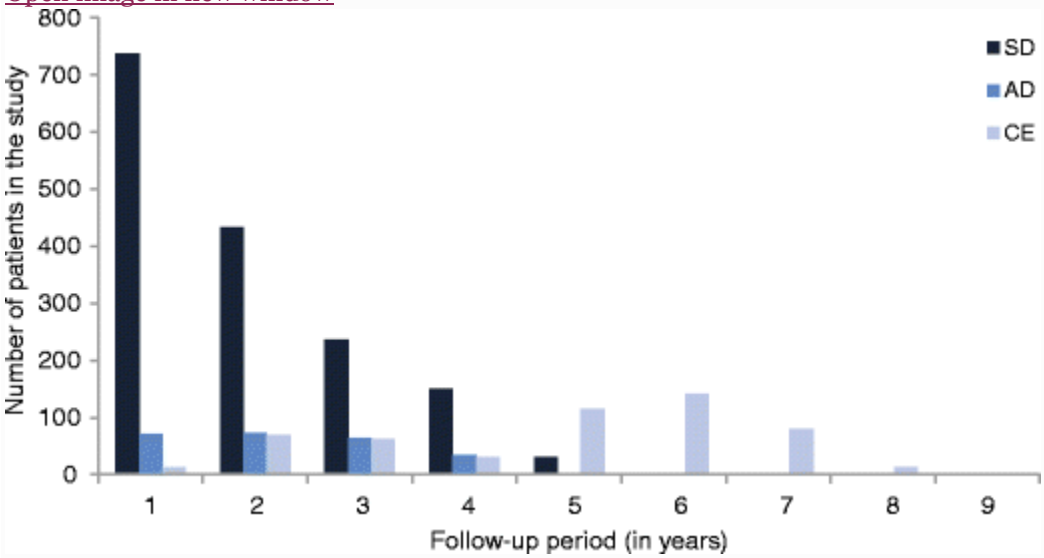

Fig. 1

Number of patients categorized by length of follow-up, in number of years

Table 1

Baseline characteristics and mean follow-up periods in years

	SD			AD			CE			Total	
	N	Mean	St. D.	N	Mean	St. D.	N	Mean	St. D.	N	M
Age	1589	55.6	14.2	246	60.0	10.9	535	53.4	13.2	2370	55
BMI	1447	26.5	4.8	226	27.1	4.2	347	26.5	4.5	2020	26
Follow-up time	1590	1.5	1.1	247	1.8	1.1	535	4.4	1.8	2372	2.
	N	%		N	%		N	%		N	%

	SD			AD			CE			Total	
	N	Mean	St. D.	N	Mean	St. D.	N	Mean	St. D.	N	M
Gender											
Male	964	60.6		134	54.3		343	64.1		1441	6
Female	626	39.4		113	45.7		192	35.9		931	3
Joint/body area											
Knee	878	55.2		234	94.7		278	52.0		1390	5
Hip	366	23.0		6	2.4		124	23.2		496	2
Foot/ ankle	126	7.9		2	0.8		43	8.0		171	7.
Spine	15	0.9		0	0		44	8.2		59	2.
Shoulder	144	9.1		3	1.2		30	5.6		177	7.
Hand/ elbow	52	3.3		2	0.8		13	2.4		67	2.
General	9	0.6		0	0		3	0.6		12	0.

Median age of the study population is 57 years (inter-quartile range = 48-65). Female proportion is 39.2 %, *SD* = same-day bone marrow concentrate; *AD* = bone marrow concentrate with adipose graft; *CE* = culture expanded stem cells *BMI* = body mass index, *St. D.* = standard deviation]

There were a total of 325 AEs reported by 287 patients (12.1 % of the study population), with 36 reported SAEs, representing 1.5 % of the study population and incidence of 0.7/100 PY (see Fig. 2 and Table 2). SAE incidences were significantly different between groups, with the CE group reporting the highest incidence at 1.1/100 PY, versus 0.9/100 PY in the AD group and 0.4/100 PY in the SD group (P = 0.006). There were 38 AEs that were deemed to be definitely related to the procedures (1.6 % of the total population) and ten AEs definitely related to stem cells (0.4 % of the total population). Incidences of procedure- and stem cell-related AEs were not significantly different between treatment groups.

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Fig. 2

Flow chart demonstrating the distribution and number of serious adverse events, as they related to to procedure type or stem cells. AE = adverse event

Table 2

Frequency, proportion, and incidence (per 100 person-years) for serious adverse events, expected, procedure-related, stem cell-related adverse events (AE) and AE categories

	SD			AD			CE		
	N	%	Incidence	N	%	Incidence	N	%	Inci
SAE									
No	107	6.7	4.66	26	10.6	5.89	160	30.2	6.89
Yes	7	0.4	0.3	4	1.6	0.91	25	4.7	1.11
Expected									
No	98	6.2	4.22	28	11.4	6.34	160	30.2	6.89
Yes	16	1.0	0.77	2	0.8	0.45	21	4.0	0.9
Related to procedure									
Not related or unlikely	38	2.4	1.62	10	4.1	2.33	113	21.4	4.99
Possible	55	3.5	2.44	15	6.1	3.4	56	10.6	2.41
Definite	21	1.3	0.9	5	2.0	1.13	12	2.3	0.52
Related to stem cells									
Not related or unlikely	68	4.3	2.9	17	6.9	3.99	136	25.7	5.86
Possible	39	2.4	1.77	12	4.9	2.72	43	8.1	1.85
Definite	7	0.4	0.3	1	0.4	0.23	2	0.4	0.09
Category									
Allergic	6	0.4	0.26	0	0.0	0	5	0.9	0.22
Bone	0	0.0	0	0	0.0	0	1	0.2	0.04
Cardiac	3	0.2	0.13	3	1.2	0.68	2	0.4	0.09
Endocrine	0	0.0	0	0	0.0	0	4	0.8	0.17

	SD			AD			CE		
	N	%	Incidence	N	%	Incidence	N	%	Inci
Gastrointestinal	1	0.1	0.04	0	0.0	0	2	0.4	0.09
Immune	3	0.2	0.13	0	0.0	0	6	1.1	0.26
Infection	1	0.1	0.04	1	0.4	0.23	4	0.8	0.17
Lab work	2	0.1	0.09	0	0.0	0	5	0.9	0.22
Neoplasm	1	0.1	0.04	0	0.0	0	6	1.1	0.26
Neurologic	2	0.1	0.09	2	0.8	0.45	10	1.9	0.43
Other	11	0.7	0.47	2	0.8	0.45	14	2.6	0.6
Pain-other area	6	0.4	0.26	3	1.2	0.45	8	1.5	0.34
Pain-post procedure	37	2.3	1.58	11	4.5	2.49	45	8.5	1.94
Pain-DJD	30	1.9	1.28	6	2.4	1.36	54	10.2	2.33
Pulmonary	0	0.0	0	0	0.0	0	2	0.4	0.09
Renal	0	0.0	0	1	0.4	0.23	3	0.6	0.13
Rheumatological	1	0.1	0.04	0	0.0	0	0	0.0	0
Skin	2	0.1	0.09	0	0.0	0	5	0.9	0.22
Vascular	8	0.5	0.34	1	0.4	0.23	5	0.9	0.22
Total	114	7.2	4.87	30	12.2	6.79	181	34.2	7.79

SAE = serious adverse event

The majority of AEs were post-procedure pain or attributed to degenerative joint disease (DJD) for which the treatment was sought (Fig. 3). There were 93 reports of post-procedure pain (3.9 % of the study population), and 90 reports of pain due to DJD (3.8 % of the study population) (Table 2). There were 27 AEs classified as “other” (i.e., that did not fit into any of the described categories) and “pain in other areas” was reported by 16 patients. This last category describes AEs where the patient reported

pain in an area that was not treated (i.e., the knee was treated and the patient reported new onset shoulder pain). Frequencies of neurologic, vascular, and allergic AEs were 14 (0.6 %), 14 (0.6 %), and 11 (0.5 % of the study population), respectively (Table 2). Among SAEs the most frequent categories were neoplasm, neurologic, and vascular events (Table 3). There were seven neoplasm cases representing 0.3 % of the study population, with an incidence of 0.14/100 PY. The difference in neoplasm rates between groups was not statistically significant. Serious neurologic and vascular events were six and five cases, respectively, representing 0.25 % and 0.21 % of the total population.

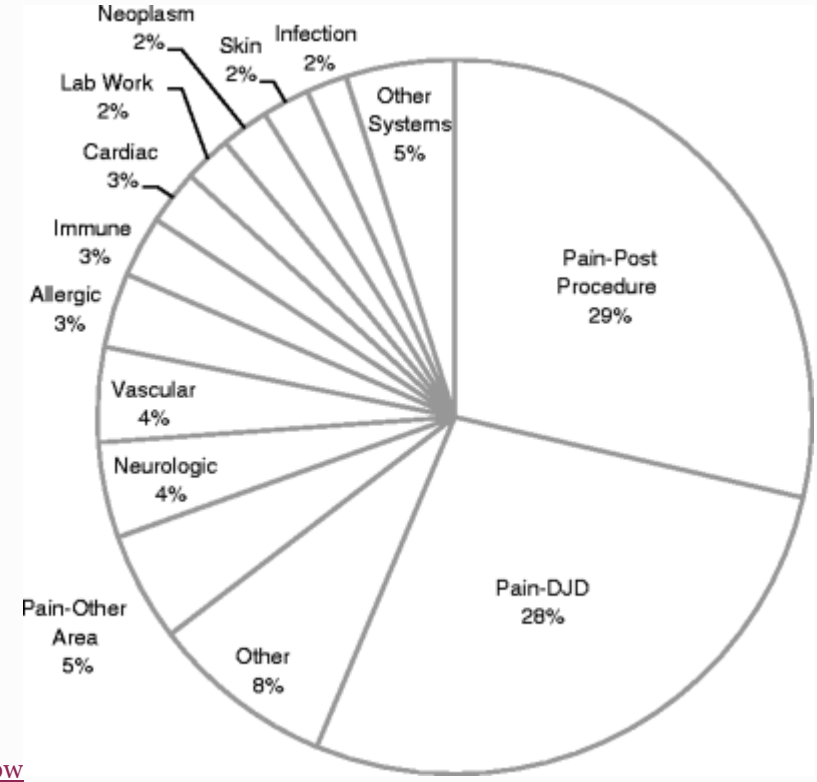

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Fig. 3

Proportions of adverse event (AE) subcategories versus the total number of AEs. “Other systems” include endocrine, renal, gastrointestinal, pulmonary, bone, and rheumatological, with <1 % each. DJD = degenerative joint disease

Table 3

Frequencies and proportions of serious adverse event categories

Category	Frequency	% of the total SAEs
Neoplasm	7	19.4
Neurologic	6	16.7
Vascular	5	13.9
Other	4	11.1
Cardiac	2	5.5

Category	Frequency	% of the total SAEs
Lab work	2	5.5
Skin	2	5.5
Endocrine	1	2.8
Gastrointestinal	1	2.8
Immune	1	2.8
Infection	1	2.8
Pain-post procedure	1	2.8
Pain-DJD	1	2.8
Renal	1	2.8
Rheumatological	1	2.8

SAE = serious adverse event, *DJD* = degenerative joint disease

Results of the SAE adjudication are reported in Table 4 and the Addendums. In Addendum 1, the adjudications of the six reviewers regarding the relatedness of the 36 SAEs are recorded. A majority opinion (as defined by >50 % agreement) was present in all but two SAEs (#15 and #30). Addendum 2 includes the results, by reviewer, of the relationship of the SAE to the procedure. In total, 19/36 (53 %) of the SAEs were considered as *not related* or *unlikely to be related* to the procedure. There were 13/36 cases or 36 % in which at least one reviewer indicated that the SAE was *possibly related*. Four of the 36 cases, or 11 %, of SAEs were adjudicated as *definitely related* to the procedure by a minority of reviewers (*i.e.*, one or two of the six reviewers). These four cases were categorized as neoplasm, pain post procedure, rheumatological, and other. Addendum 3 contains adjudication information from the reviewers regarding the relationship of the SAE to the stem cells or other biologic agent used. Fourteen of the 16 cases (39 %) of the SAEs were categorized as *not related* or *unlikely to be related*, while 16/22 (61 %) were adjudicated by one or more reviewer as *possibly related*. None of the SAEs were considered to be *likely* or *definitely related* to the stem cells or other biologic agent.

Table 4

Adjudication of serious adverse events

Reviewer	1		2		3		4		5		6	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(
Pre-existing condition												
No	27	(75)	22	(61.1)	20	(55.6)	21	(67.7)	30	(83.3)	24	(
Yes	9	(25)	14	(38.9)	16	(44.4)	10	(32.3)	6	(16.7)	12	(

Reviewer	1		2		3		4		5		6	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(
Relation to procedure												
Not related	10	(27.8)	19	(52.8)	27	(75)	23	(74.2)	22	(61.1)	25	(
Unlikely	19	(52.8)	5	(13.9)	4	(11.1)	1	(3.2)	12	(33.3)	4	(
Possible	7	(19.4)	8	(22.2)	5	(13.9)	4	(12.9)	2	(5.6)	6	(
Definite	0	(0)	4	(11.1)	0	(0)	3	(9.7)	0	(0)	1	(
Relation to stem cells												
Not related	8	(22.2)	20	(55.6)	21	(58.3)	10	(32.3)	21	(58.3)	17	(
Unlikely	25	(69.4)	4	(11.1)	14	(38.9)	13	(41.9)	11	(30.6)	6	(
Possible	3	(8.3)	10	(27.8)	1	(2.8)	8	(25.8)	3	(8.3)	13	(
Definite	0	(0)	2	(5.6)	0	(0)	0	(0)	1	(2.8)	0	(

Reviewer 1 = attending physician; Reviewer 2–6 = independent reviewers.

Logistic regression modeling revealed that patients in both the AD and CE groups were more likely to report an AE than in the SD group; ORs = 1.64 (95 % CI; 1.03, 2.61) and 1.68 (95 % CI; 1.11, 2.54), respectively (Table 5). Further analysis showed that, compared to the SD group, the increase in AE rate was largely attributable to post-procedure pain in the AD group, and pain due to DJD in the CE group (Figs. 4 and 5). A longer follow-up period, older age, and female gender increased the risk of reporting an AE. SAEs were more common in patients with a longer follow-up period and of older age [OR = 1.51 (95 % CI; 1.37, 1.67) and 1.03 (95 % CI; 1, 1.06), respectively]. Patients treated for spinal conditions were more likely to report any AE in comparison with patients undergoing knee procedures [OR = 2.17 (95 % CI; 1.13, 4.15)].

Table 5

Odds ratios and 95 % confidence interval (CI) of reporting adverse events, serious adverse events, and treatment-related adverse events for treatment types and potential confounding factors

	OR (95 % CI) of	OR (95 % CI) of	OR (95 % CI) of
Effect	**Any adverse event**	**Serious adverse events**	**Treatment-related adverse events**
Treatment type			
Group AD	1.64 (1.03-2.61) *	2.78 (0.8-9.66)	1.42 (0.83-2.44)
Group CE	1.68 (1.11-2.54) *	2.80 (0.88-8.94)	0.92 (0.55-1.56)
Group SD (eeference)	1	1	1
Follow-up (in years)	1.51 (1.37-1.67) *	1.6 (1.26-2.03) *	1.4 (1.24-1.58)*
Age (in years)	1.01 (1–1.02) *	1.03 (1–1.06) *	1 (0.99-1.01)
Gender			
Female	1.49 (1.13-1.96) *	1.95 (0.99-3.84)	1.26 (0.9-1.77)
Male (reference)	1	1	1
Joint/body area			
Foot/ankle	1.12 (0.65-1.9)	-	1 (0.53-1.91)
General	1.78 (0.3-10.36)	-	0.9 (0.1-7.85)
Hand/elbow	1.08 (0.46-2.56)	-	0.86 (0.3-2.45)
Hip	1.23 (0.87-1.73)	-	0.82 (0.52-1.3)
Shoulder	1.07 (0.6-1.88)	-	0.88 (0.43-1.81)
Spine	2.17 (1.13-4.15) *	-	2.46 (1.19-5.08)*
Knee (reference)	1	-	1

OR = odds ratio; *CI* = confidence interval; *AE* = adverse event; *SAE* = serious adverse events; treatment-related *AEs* = AEs definitely or possibly related to procedure or stem cells; *SD* = same-day bone marrow concentrate; *AD* = bone marrow concentrate with adipose graft; *CE* = culture expanded stem cells; * = statistically significant; Due to the

low SAE frequency per joint/body area category; the joint/body area variable was removed from the SAE logistic regression model.

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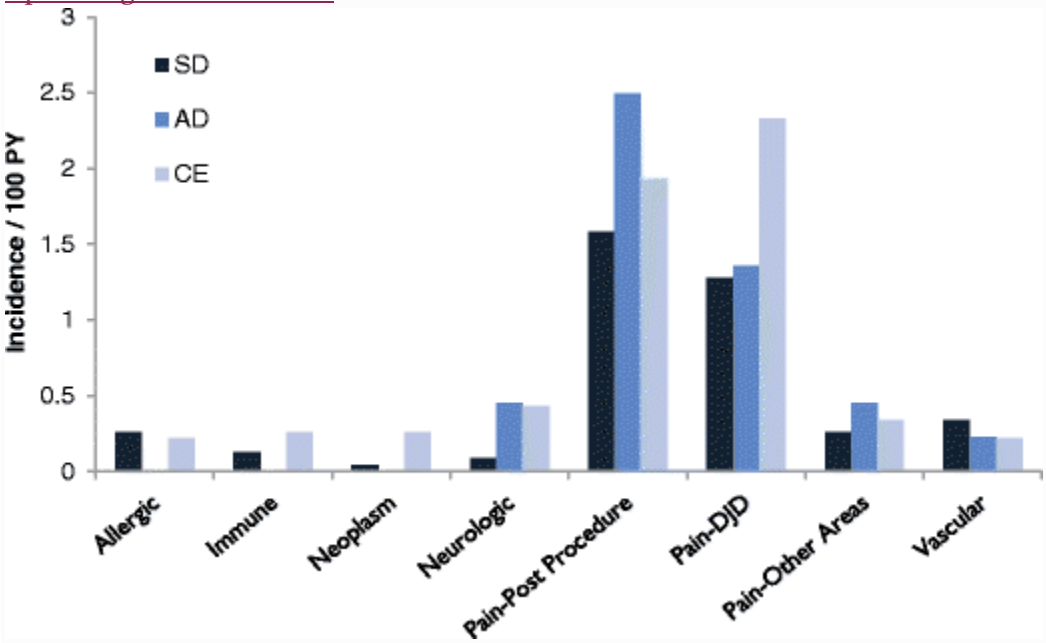

Fig. 4

Incidence of the most common adverse event categories, per 100 person-years (PY). SD = same-day bone marrow concentrate; AD = bone marrow concentrate with adipose graft; CE = culture expanded stem cells; DJD = degenerative joint disease

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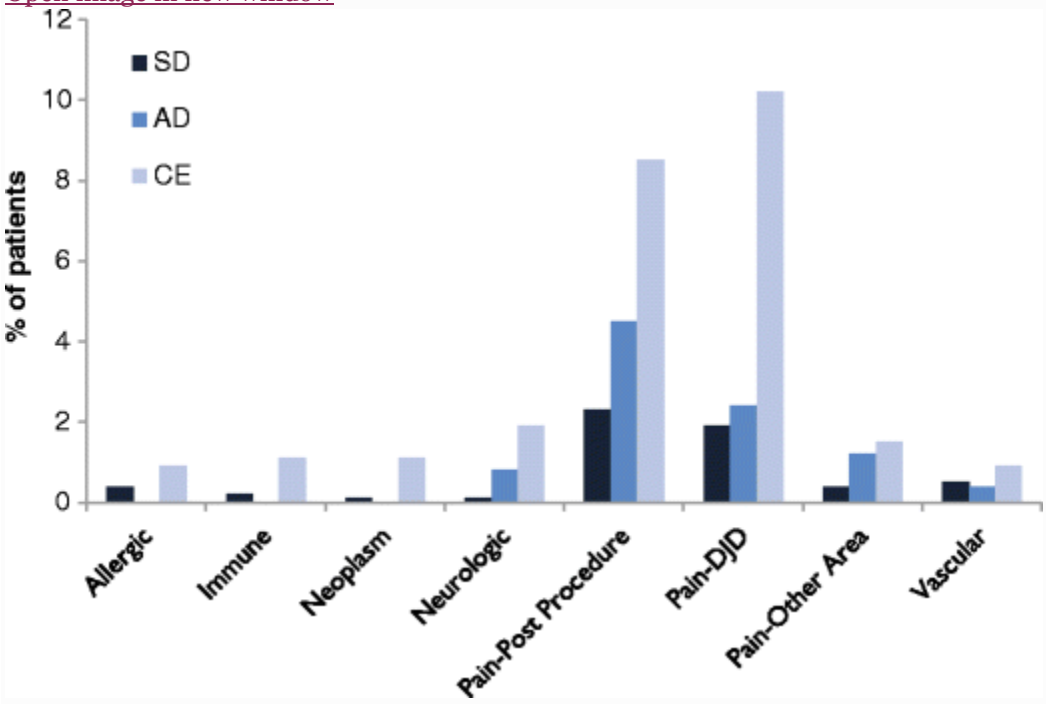

Fig. 5

Percentages of total patients reporting adverse events, for the most commonly reported categories. SD = same-day bone marrow concentrate; AD = bone marrow concentrate with adipose graft; CE = culture expanded stem cells; DJD = degenerative joint disease

Discussion

In the present study we generally observed low rates of reported AEs among patients treated with MSC procedures, and substantially lower rates of serious or treatment-related AEs. The finding that the majority of AEs were post-procedure pain or pain due to DJD that pre-existed the treatment was not surprising, and consistent with the progressive nature of the treated disorders.

While there have been several publications that have described the safety and efficacy of bone marrow derived stem cell therapies for orthopaedic applications [1, 7, 9, 10, 11, 12, 13, 15], to our knowledge the current investigation is the most comprehensive report of its kind, following the largest population for the longest time, and incorporating an analysis of the relative safety of several different approaches. Our findings are consistent with prior investigations demonstrating a favorable safety profile for the percutaneous use of BMC and MSC injections for the treatment of orthopaedic conditions of the peripheral and axial joints and surrounding tissues [7, 9, 13, 14]. The SAE rates observed in our study were substantially lower than those reported for more invasive orthopaedic surgical procedures [22]. As an example, the SAE rate for total knee arthroplasty among 260 patients at three months follow-up was 6 % [22]. In comparison, there were 13 *possibly* related SAEs in the present study among 2372 patients, approximately 0.55 %, and only four of these SAEs (0.17 %) were deemed *definitely* related to the procedure. While SAEs related to stem cell injections can and do occur, prior authors have indicated that the rate is not greater than that observed with other types of intra-articular injections, such as hyaluronic acid injections [23]. The findings in the present investigation reinforce this conclusion.

The differences observed in the AE rates between the treatment groups were not directly attributed to the treatment but rather to symptoms of progressive degenerative disease. Thus, the group that was tracked for the longest time (the culture expanded [CE] group) also had the highest incidence of AEs resulting from worsening of the treated condition over time. This observation is consistent with the natural history of painful degenerative joint disease [24, 25]. Further, the AEs reported in the first months of follow-up differ from those reported after several years of follow-up. For example, treatment-related AEs, including post-procedural pain, are more likely to be reported in the earliest few weeks after treatment; while unrelated or more serious AEs, such as neoplastic and cardiovascular events, are more likely to be reported after several years of follow-up (i.e., as patients age). The higher rate of AEs in the adipose graft (AD) BMC group versus the BMC only group (SD) was largely attributed to post-procedural pain. This difference may be explained by the pro-inflammatory effects of residual adipose oil in the injectate [26].

Of the seven reported cases of neoplasm among the registry patients, none occurred at the site of implantation despite all injections being confirmed with imaging guidance. Given the number and age of the patients followed in the registry, and the amount of

time that the patients were followed, some cases of cancer were expected. According to the National Cancer Institute, the annual incidence of cancer in the U.S. population in 2011 was 0.44 % (438 cases per 100,000 individuals), and 0.78 % in adults 50–64 years [27]. In contrast, we observed a lower annual cancer rate (0.14 %) among our registry participants. These findings are consistent with previous reports indicating no increased risk of tumor formation following BMC injections or treatment with culture-expanded MSCs [9, 11, 13, 15].

Older age and longer follow-up times increased the risk of reporting of both AEs and SAEs. These findings are explained both by the fact that morbidity increases with age [28], and that older patients are more likely to report adverse events after orthopaedic procedures [29]. A gender effect was also observed, in that women were more likely than men to report AEs. While the nature of the registry data makes it difficult to determine the reason for this disparity, previous authors have noted that women are more likely to report post-operative pain after arthroscopic procedures [30]. Patients who underwent treatment for degenerative joint and disc changes in the spine also had a higher rate of AE reporting, including AEs related to the treatment. Most of the reports in this group were of pain due to degenerative joint disease and post-procedural pain. While the explanation for this observation is not readily apparent; it could be due to the nature of the treated condition or it could be entirely due to differences in treatment efficacy. Further study would be required to provide more meaningful insight.

The results of the SAE adjudication by the attending physician and the panel of independent and blinded reviewers indicated good agreement on the categorization of pre-existing conditions, with majority agreement on 34 of 36 SAEs. One of the cases in which a minority of reviewers judged an SAE to be related concerned a neoplasm that a single reviewer opined was definitely related to the mechanics of the draw or re-implant injection procedure (the other five reviewers judged the relationship to be unlikely or not related). The SAE concerned a patient who was diagnosed with aggressive stomach cancer three weeks following a knee BMC injection, and who died from the disease at approximately two months following the injection. The protocol of the blinded adjudication process made impossible any follow up with the reviewer for an explanation as to why he or she believed that the stomach cancer, which likely pre-existed the procedure in nearly the same state as it was in three weeks following the procedure, was definitely related.

Another SAE, consisting of severe post-procedure swelling, was judged by two reviewers as definitely needle trauma related, and two reviewers judged the condition as definitely caused by the stem cells or other injectates. A rheumatologic condition was deemed to be definitely related to an injection by two reviewers. In that case, the patient presented with severe knee swelling after a pre-injection procedure with hypertonic dextrose. The joint was drained and found to be purulent, but gram stain and culture were negative. Ultimately synovial fluid crystalline structures were revealed and a diagnosis of gout was made. Because of the pre-injection complication the patient did not undergo the stem cell injection.

An SAE following treatment of a degenerated and painful intervertebral disc was judged to be to be definitely related to the trauma of the stem cell injection by two reviewers. In that case, at approximately eight months post-procedure, the patient sustained an acute disc herniation at the injected level. Three of the reviewers considered the SAE to be possibly related and one determined that it was unlikely to be related to the injection. It is certainly plausible that the needle trauma could have resulted in injury to the disk annulus, resulting in structural compromise and the latent herniation.

The strengths of the current study are its large patient population, the fact that data was collected from multiple centers, that SAEs were adjudicated by multiple independent and blinded reviewers, that AE/SAE rates of multiple treatment types are compared, and that unlike prior large studies all AEs were reported and classified. The main weaknesses of the current research are that it is based on data accessed from a treatment registry. Thus, there is no control group with which the frequency and type of observed illnesses could be compared. Further, the majority of AEs were patient reported. Despite the fact that repeated efforts were made to contact non-responders and all treating physicians were encouraged to report any possible complications while patients were under their care, it is possible that adverse events were under-reported to some degree.

Conclusion

To our knowledge, the present investigation is the first report to compare the clinical safety of different bone marrow derived stem cell therapies to treat orthopedic diseases and the first multi-site, large scale report of all AEs in stem cell treated orthopaedic patients. We found that the lowest rate of adverse events was among those patients receiving BMC injections alone, but the higher rate of AEs for BMC plus adipose and cultured cells was readily explained by the nature of the therapy or the longer follow-up. There was no clinical evidence to suggest that treatment with MSCs of any type in this study increased the risk of neoplasm. Although efficacy is best demonstrated with randomized controlled clinical trials, it is reasonable to conclude that the results of the present study add to the existing body of evidence showing the safety of MSC based therapies for orthopaedic conditions.

Notes

Acknowledgments

Steve Gorin, M.D. and R. Amadeus Mason M.D. for acting as independent adjudicators for SAEs.

Supplementary material

264_2016_3162_MOESM1_ESM.docx (14 kb)

Supplement 1 (DOCX 14 kb)

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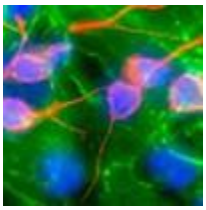

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Review of Centeno MSC safety paper: without controls, conclusions muted

April 11, 2016 admin Uncategorized 22

The number of people around the world being injected with stem cells every day has never been higher and the heterogeneous group of medical providers doing these procedures is also at or near its highest level ever.

The cells used are also highly variable as are the procedures themselves, but most of these cells fall under the umbrella of mesenchymal stromal/stem cells (MSC). The field needs to learn more about these MSC procedures in terms of safety and efficacy. Preliminary, relatively small and most often open label studies have been generally encouraging on safety, but not very definitive. For these reasons, whenever I hear about a new study published by a stem cell business, I am interested to read it and see what it teaches us.

A new published study from Dr. Christopher Centeno reports findings from a number of affiliated clinics that use MSCs for orthopedic procedures.

It is good to see stem cell clinics collecting and publishing their data so that is a plus. I commend them for that. The number of adverse events and in particular stem cell-related, severe adverse events was seemingly relatively very low amongst the population studied, but there's a catch.

Table 3 Frequencies and proportions of serious adverse event categories

Category	Frequency	% of the total SAEs
Neoplasm	7	19.4
Neurologic	6	16.7
Vascular	5	13.9
Other	4	11.1
Cardiac	2	5.5
Lab work	2	5.5
Skin	2	5.5
Endocrine	1	2.8
Gastrointestinal	1	2.8
Immune	1	2.8
Infection	1	2.8
Pain-post procedure	1	2.8
Pain-DJD	1	2.8
Renal	1	2.8
Rheumatological	1	2.8

SAE = serious adverse event, *DJD* = degenerative joint disease

Table 3, Centeno, et al., 2016

The overriding problem with this study is that there are no matched controls, leaving the reader unclear as to relative risk of the stem cell procedures. The data from this paper's population of stem cell transplant patients who received various kinds of MSCs for a variety of orthopedic conditions is only compared to data from other previous studies reporting rates of adverse events in other populations of patients getting standard of care treatment or to general patient populations.

This lack of controls is unfortunate, but not surprising. For-profit stem cell clinics are in the business after all of making money and most patients are not going to be interested in paying money to the clinics only to have a chance to be a control not getting the stem cells.

Further, clinics in general have not shown interest over the years to themselves pay the additional costs associated with having control subjects. But it could be done. For instance, a clinic could do a study at cost (no profit margin built in) and offer participants the chance to be research subjects at a relatively low cost. Another idea, and this may sound outlandish given where the stem cell arena is today but is perfectly logical and reasonable, is that clinics could even pay patients a small sum to be clinical trial subjects in a controlled study.

Overall, the lack of controls in the current paper greatly limit what we can learn from it. Of the adverse events reported in this new MSC paper some sound concerning such as cancer (termed "neoplasms"; see Table 3 above) in the paper, but again without controls there is no way to be certain if these tumors were stem cell-related. The authors do not believe they were. I can say, "most likely they are right", but scientifically there's no way to be sure at this point. It is possible a matched control population would have gotten even more tumors or conversely no tumors at all.

While this study had longer follow up than some past ones, the follow up here still was only around one and a half years on average and it is reasonable to imagine that some adverse treatment-related events could arise much later.

Another concern with the paper is that reading the methods seems to suggest that aspects of the protocols used to administer stem cells to patients varied considerably even within the three individual treatment groups (same day marrow MSCs, marrow and lipid aspirate combo, and culture expanded MSCs). For instance, the number of cells and the amount of co-injected platelet lysate had sizable

ranges. **An interesting side note** to this is that this variability reflects a challenge facing the stem cell clinic industry of every clinic even amongst affiliates doing things somewhat differently.

Update: I also meant to say that I think this paper was largely well written and where appropriate included caveats, limitations, etc.

Finally, I'm not clear on the strength of the methods for assessment of adverse events and assignment of potential adverse events to be related to treatment. Online recruitment of assessors may not be the most reliable approach.

Overall, I'd say this paper is just a bit encouraging on autologous MSC safety for orthopedic use in the short term. It is also a step in the right direction in terms of the more data the better from for-profit stem cell businesses, but without controls it is hard to say much more. For those who say that this kind of study is worthless, consider the hypothetical scenario that the same patients had been given these therapies exactly as reported, but none of this was published. How could that be a better situation than having a publication of the data even without controls? As long as we as a community soberly evaluate such publications, I see how they serve a role.

Finally, I propose a friendly challenge to those doing these experimental stem cell therapies to devote some funds to controlled studies and to do much longer follow up. This would also be a reassuring sign of good faith that the clinics have long term patient best interest as a top priority.

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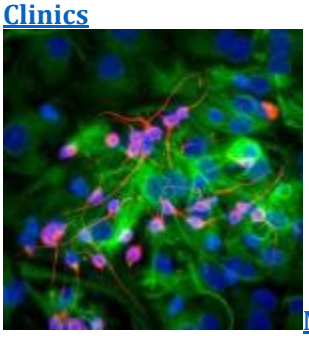
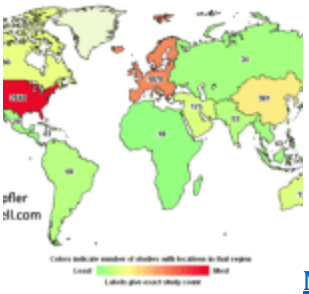
-  **My take on the much-touted 'SafeCell' paper on adult stem cell safety: encouraging, but some important reservations**

- 
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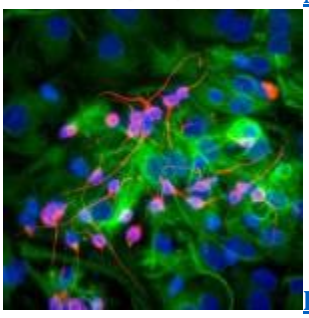
- 
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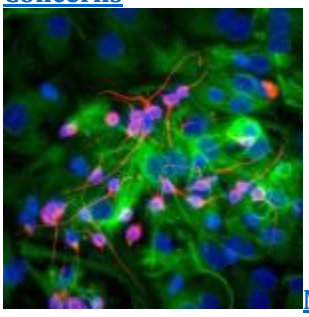
- 
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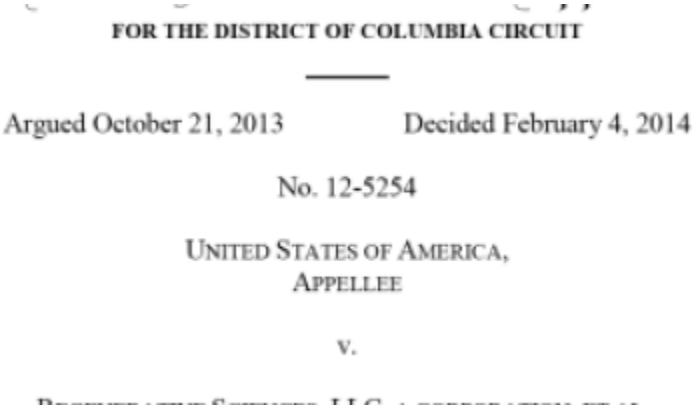
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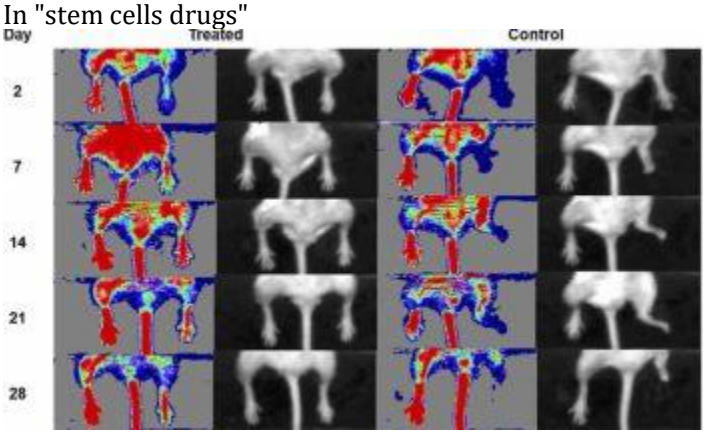

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- CHRISTOPHER CENTENO

PREVIOUS

Alliance for Regenerative Medicine (ARM) Opposes REGROW Act, Risks to Patients Cited

NEXT

Do for-profit stem cell studies have inherent potential biases?

22 COMMENTS

1. 

Jeff Muggles

APRIL 11, 2016 AT 1:27 PM

8

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Rate This

Nice review. To be fair, there are for-profit clinics that simply don't bother reporting anything and here we have one where the reporting is pretty well balanced and constructively critical of it's own limitations. Obviously barely any of the subjects would have been in the same cohort in a real clinical trial due to diverse backgrounds, pretreatments, and so on. But in addition to true controlled studies, there is value in such a wild mix of patients, as one may observe adverse events at n=1, that you don't otherwise see, and these can then be followed up more rigorously.

REPLY

- 

  admin

  APRIL 11, 2016 AT 1:28 PM

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  Rate This

  Thanks, Muggles.

  REPLY

2. 

   Doug Oliver

   APRIL 11, 2016 AT 1:31 PM

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   Rate This

   Dr. Centeno's study seems refreshingly hopeful and rounded when it comes to a true meta-analysis of actual clinical practice.

   I've wondered, though, why it is that our amazing research interests in this country are not taking full advantage of the ample safety (with animal study and controls) and efficacy research already established internationally? And why no mention of the international 7-8 year longevity studies establishing efficacy of MSC's. Especially for orthopedic uses.

The clinics seem to feel confident in their approaches for legitimate reasons. The factor making them "most likely" okay to let continue their practice.

We should embrace the seeming successes of this arm of treatment. Engage it further with our regulatory system, and allow our regulatory system to adapt to the unique situation the U.S. stem cell research community finds itself in.

REPLY

3. 

Dan Kaufman

APRIL 11, 2016 AT 2:46 PM

3

1

Rate This

It seems the main conclusion is, "well, at least they tried." That seems very "adequate."

The real question for those MSC therapies is do the benefits outweigh the risks? There seems to be relatively little downside. I agree the number of neoplasms is probably not significantly different than the general population. However, as you state, no way to know.

However, there is no way to determine clinical efficacy without appropriate controls. Sure, patients probably feel better after getting injected and paying some fee. How much of this is placebo affect and maybe non-specific inflammation, that could lead to angiogenesis and repair?

Getting a good, double-blind trial with sham injections is the only way to determine efficacy. Private clinics like this won't do it, and seems academic groups not too interested, unless you know of some "real" trials going on in this area.

REPLY

4. 

Chris Centeno, M.D.

APRIL 11, 2016 AT 4:17 PM

8

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Rate This

All, we have 3 RCTs ongoing, and have published more registry based efficacy data in orthopedics than anyone at this point (none of which can rule out a placebo effect). RCTs are great, but they will never have the statistical power nor duration to pick up rare events (like the neoplasms discussed above). This is why drug approvals rely on post-marketing surveillance, which is less intensive than what we did on these 2,372 patients. In conclusion, very large controlled trials where side effects can be compared to placebo is needed in addition to this type of work. Having said that, many problems with approved drugs are picked up after the approval using a comparison of reported events to those that happen randomly in the general population.

REPLY

- **admin**

  APRIL 11, 2016 AT 5:03 PM

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  Rate This

  @Chris,
  Thanks for the comment. Do you have a sense of which of the three treatments that were compared that you think is the safest/best?

  I'm also curious if you'd be comfortable weighing in on the REGROW Act and the Bipartisan Council report that both advocate for significant FDA changes including in some cases not requiring Phase III, conditional approval, delayed requirement for BLA, etc.

We've been having some debate on this blog about these with some in favor and some opposed to them. What do you think?
Paul

REPLY

5. 

Chris Centeno, M.D.

APRIL 11, 2016 AT 5:53 PM

2

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Rate This

On Regrow, I think if you're an early phase cell company pursuing FDA approval (as is one of the companies we licensed an intervertebral disc technology to), you love Regrow. If you're an existing cell therapy company past phase 1-2, you hate Regrow. As a provider, I'm pretty agnostic as the new pathway it creates is not one that most providers would be able to achieve. As an example, the company mentioned above has spent 600K in pre-IND alone and will likely spend 3-5 M to finish phase 1-2. Physicians don't have that kind of money. I also think the act will raise prices for patients into the stratosphere, as companies spending 5 M to play plus the cost of cGMP manufacturing of an autologous product will need to raise same day therapy prices from about 4-8K to 10-20K. In addition, the safety data generated by phase 1-2 is minimal compared to the paper we just published. On the other hand, autologous BMC and short-term cultured MSC therapies are likely pretty safe based on the existing literature, so safety is likely the least of the concerns. In addition, as a physician, if a patient is terminal or has a severe chronic disease, I'm not sure what we're protecting them from?

On the physician side, on the one hand the act doesn't change FDA's penchant to categorize everything as a drug. On the other, I'm no fan of the wild west of stem cells. Regrettably, the act also does nothing to try and rein in and control an out of control physician stem cell space, where doctors can take a weekend course and begin offering IV SVF treatments for every known human ailment. Or clean up the clinics (like the one you highlighted) that are offering "amniotic stem cells" which consists of a vial of dead tissue.

So on the one hand, it would help a technology that we licensed get to market, but do I think it will help physicians or patients, not so much…

REPLY

- 

  admin

  APRIL 12, 2016 AT 9:34 AM

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  Rate This

  @Chris,
  Thanks for sharing your take on REGROW, which I find quite interesting. Why do you think those who crafted the Act and support it are doing this?

  REPLY

6. 

   Chris Centeno, M.D.

   APRIL 11, 2016 AT 5:53 PM

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   Rate This

   The BMC+Adipose Graft group had the highest short-term complication rates, but that was mostly slef-limited pain/swelling. The cultured group had an overall higher rate of AEs, but the problem is that the longer duration of the follow-up and the age (most patients were middle aged on entry and this group will have more disease events occur over longer periods as they entering into prime disease prone years (i.e heart disease, stroke, cancer, etc…).

REPLY

7. 

Brian Sanderson

APRIL 11, 2016 AT 6:25 PM

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Rate This

Paul, your friendly challenge was way out of date before you wrote it, see, for example:
http://www.regenexx.com/regenexx-clinical-research-studies/
OK, it's not, perhaps, a pure control in the sense that a lab-rat scientist might prefer because they offer the patient the option of a cross-over afterwards. In my opinion, what they do is the ONLY ethical thing to do.

The issue of treating diverse vs carefully selected patients is an interesting one. Especially so when you consider that in the real world a medical doctor isn't always confronted with conveniently selected patients.

REPLY

- 

  admin

  APRIL 12, 2016 AT 9:31 AM

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  Rate This

@Brian,
I see your point, but I think the challenge stands.
Paul

REPLY

8. 

stemcellfan

APRIL 11, 2016 AT 11:10 PM

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Rate This

@Dr. Centeno Dear Dr. Centeno,
thank you very much answering the questions above. Safety is one big issue, but the second one is efficacy. Where can I find efficacy rates? Do you already have done studies about this? see next comment …

REPLY

9. 

stemcellfan

APRIL 11, 2016 AT 11:10 PM

0

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Rate This

… @Dr. Centeno, part two
… For example:
How high are the efficacy rates for …
… repair of a damaged disc?
… the repair of a meniscal tear?
… the repair of a small cartilage defect?
… the repair of a big cartilage defect?
… the repair of an avascular necrosis?
Do you have data about this outcome, so please let us know.

Because as Dan Kaufman already said:
"The real question for those MSC therapies is do the benefits outweigh the risks?"
To answer this question anybody must know the efficacy rates.

REPLY

10. **Chris Centeno, M.D.**

APRIL 12, 2016 AT 5:11 AM

1

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Rate This

Brian, you've framed a big issue nicely. RCTs are great, we always need more of them. Having said that, they purposefully create an artificial world where strict inclusion and exclusion criteria filter out 80-90% of the real world patients a physician is confronted with day in and day out. Hence, data from an RCT usually doesn't generalize well to the usual mix of real patients. This is why registry data is often used to craft better RCTs, providing important clues as to what's working and not working.

REPLY

11. 

Chris Centeno, M.D.

APRIL 12, 2016 AT 7:51 AM

2

0

Rate This

All published efficacy studies are here: **http://www.regenexx.com/stem-cell-research/** There are a number of multi-site, prospective registry based studies. We have additional similar studies now being submitted on other areas such as spine (you'll find shoulder, knee, hip-also tendon/ligament) on the site. All patient registry data by site is here: **http://www.regenexx.com/regenexx-patient-outcome-data/** As discussed, 3 RCTs in the works, one done recruiting. Does this stuff work? We've seen it work in many patients, but unlike other clinics in this space, we recognize that it's up to us to prove that to the best of our ability.

REPLY

12. 

Chris Centeno, M.D.

APRIL 12, 2016 AT 9:49 AM

1

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Rate This

@admin, the FDA process is very long and expensive. Given that we have companies in this space that began their quest for approval in the late 90s (Osiris for example which was later bought by Mesoblast) and we're sitting in 2016 without a single approved US FDA indication for an MSC cell drug, can you blame the companies for wanting an easier pathway? At least for autologous products, countries like Japan have decided that it's time to spur innovation by allowing these procedures to be performed in an alternate framework. If you're a fan of more regulations and more studies, then REGROW is likely perceived as bad. If you're a patient, you want more options. I had thought REGROW might be a great thing for physicians, but as I said, it's really not.

Who is behind REGROW? There's a long list of orgs that have thrown their weight behind it. Am I personal fan? I have mixed emotions. It won't help physicians or clean up the crazy stem cell space and will increase prices for therapies. On the other hand it's at least some recognition that maybe the drug pathway was never the right place for these therapies to live.

BYW, there seems to be an issue with the comment box in Chrome, as when you leave a longer comment it gets rid of the post comment button! Works fine in IE, so I just switched browsers to leave the comment.

REPLY

13. **Richie**

APRIL 12, 2016 AT 9:55 AM

0

0

Rate This

@Dr. Centeno part 1
I have personal experiences with PRP-therapy. My brother was suffering from avascular necrosis at his joint for 7 years. No other conservative therapy helped him. Then he received a PRP-treatment (6 times once a week in combination with a shock wave therapy) and he was healed within 6 weeks. It was very amazing. Of course this result is just n= 1, and so I would like to know, how is your success rate for the treating of avascular necrosis?
We discussed this case/theme here already several times in this forum, most comments were sceptic, but nobody was able to tell more about a efficacy results/outcome results which were backed by data. … part 2 next comment

REPLY

14. 

Richie

APRIL 12, 2016 AT 9:55 AM

1

0

Rate This

@Dr. Centeno part 2
… On your homepage I can only find data concerning other diseases, but not for avascular necrosis.
I think you have the data and could give us a valid answer. So I would like to ask you to give us some more information about the outcome rate/healing rate for avascular necrosis by PRP-therapy.
Thank you in advance

REPLY

15. 

Chris Centeno, M.D.

APRIL 12, 2016 AT 10:09 AM

2

0

Rate This

There is data showing efficacy of BMC in AVN via Herigou going back to the 90s-
see **http://www.ncbi.nlm.nih.gov/pubmed/?term=hernigou+osteonecrosis** . Not much data on PRP, but I have no problem believing it may work. We have treated about 100 cases with BMC over the

last 8-9 years via trocar into the bone lesion guided by fluoro-works well in ARCO grades 1-2, less in 3/4. Here's a nice case with MRI evidence: **http://www.regenexx.com/hip-avn-surgery-alternative/**

REPLY

16. **Chris Centeno, M.D.**

APRIL 12, 2016 AT 10:13 AM

2

0

Rate This

AVN is a good example of the physician innovation pathway, as Hernigou has linked outcomes to CFU content in bone marrow concentrate. This is a disease where an RCT against placebo is tough, as the placebo group in just 3-6 months could rapidly progress into a hip replacement. Hence, we have a long history of many published studies that are large case series. Given that there is a 80% chance of predictable collapse in the bone, any lowering of that rate is a high confidence that the effects are not placebo. Before/after MRIs showing rapid resolution after an injection is also interesting data, as spontaneous resolution is uncommon.

REPLY

17. **Richie**

APRIL 12, 2016 AT 12:42 PM

0

0

Rate This

@Dr. Centeno
So I guess BMC would be your first choice to treat AVN, not PRP?
After his AVN was healed, my brother has left cyst in his deep talus role (far away from the cartilage), is there any chance to heal this cyst, too?

REPLY

18. **Chris Centeno, M.D.**

APRIL 12, 2016 AT 2:58 PM

1

0

Rate This

Richie, out of respect for Paul's blog, best to take this to a private conversation about what could be best. My e-mail is **centenooffice@centenoschultz.com**.

REPLY

Leave a Reply

https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=9&bc=ACAAAAAAAgAAAA%3D%3D&

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Decision Memo for Autologous Stem Cell Transplantation for AL Amyloidosis (CAG-00050N)

Need a PDF?

AL Amyloidosis :: https://www.mayoclinic.org/diseases-conditions/amyloidosis/symptoms-causes/syc-20353178

HCFA conducted a thorough review of the request submitted by the Boston Medical Center and has concluded that a sufficient body of evidence does not exist to justify a national coverage decision in favor of AuSCT for patients with AL amyloidosis.

A substantial portion of the submitted materials did not meet the criteria for consideration described above.

Analysis of these studies identifies important biases that were not addressed.

Small sample sizes and discriminatory enrollment of patients introduces selection bias, which can lead to skewed results.

Furthermore, none of these studies compare HDCT and AuSCT to either a control group or other treatment modalities.

It is difficult to determine the effectiveness of a treatment unless it is compared to current standards of care.

Safety is another concern that was identified.

The wide range in treatment-related mortality (0, 12%, and 43%) leads to the conclusion that proper patient selection may be an issue.

Moreover, there is little indication that AuSCT has become the standard of care in treating AL amyloidosis. The utilization of this procedure in the

United States appears to be highly localized to specialized medical centers.
https://www.ncbi.nlm.nih.gov/pubmed/18158962

It is apparent by the evidence that much of the research conducted on this topic is relatively preliminary, perhaps no more than five years old. Leading researchers in the field differ on the safety and efficacy of the procedure. Kyle 1999, states that "confirmation of the favorable results obtained from AuSCT for primary AL is necessary... Consequently, a cohort of patients with primary AL who are eligible for transplant must be randomized to receive the best available chemotherapy regimen or AuSCT". The author also identifies a need for long-term follow-up studies before conclusive determinations on safety and efficacy can be made.
We note that none of the three cited studies involved any patients over 63. This procedure may in fact carry greater risk with advanced age; age has been suggested as a prognostic factor. In addition, the studies cited above were limited to AL amyloidosis. AuSCT in senile, familial, and slower forms of the disease has *not* been considered in this review. Since there is no evidence relating to the safety and efficacy of AuSCT for treatment of non-primary amyloidosis, or for treatment of any type of amyloidosis in patients over age 63, we believe it is appropriate to issue a national coverage policy that would exclude coverage of AuSCT for these situations. Further, the evidence on AuSCT for AL amyloidosis in younger patients (less than 64) is insufficient to change current Medicare coverage policy. Medicare beneficiaries, at this time, are best served if HCFA maintains its policy of contractor discretion in these situations.
HCFA is willing to reconsider this coverage determination if new evidence becomes available. If this issue is revisited, HCFA would especially be interested in seeing prospective randomized clinical trials that compare AuSCT to standard chemotherapy with larger, more diverse sample sizes that address the Medicare population.

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To:	File: Autologous Stem Cell Transplantation for AL Amyloidosis CAG-00050N
From:	Hugh F. Hill III, MD, JD Acting Director, Coverage and Analysis Group Svati B. Patel

Health Insurance Specialist, Coverage and Analysis Group

Joyce F. Eng, MS, MT(ASCP)
Health Insurance Specialist, Coverage and Analysis Group

Subject: National Coverage Policy Request

Date: January 14, 2000

This memorandum serves four purposes: (1) describes the etiology of primary (AL) amyloidosis and treatments currently available; (2) outlines current coverage policy for autologous stem cell transplantation (AuSCT); (3) analyzes relevant clinical literature; and (4) delineates reasons for limiting Medicare's current policy of contractor discretion.

Description and Background of AL Amyloidosis

AL amyloidosis is a hematological disorder, associated with plasma cell dyscrasias, in which extra-cellular insoluble protein (amyloid) fibrils accumulate in various tissues and organs throughout the body. These amyloid fibrils, formed by monoclonal populations of plasma cells in the bone marrow, consist of abnormal variable portions of immunoglobulin (Ig) light chain proteins (M proteins). Except for those within the central nervous system, amyloid fibrils can affect any major organ in the body. The most common organs affected are the kidney, heart, liver, and autonomic or peripheral nerves.

AL amyloidosis is a rare disease; only 1200 to 3200 new cases are reported each year in the United States.[1] It is similar in many ways to multiple myeloma, another plasma cell dyscrasia. In multiple myeloma, plasma cells proliferate and accumulate in the patient's bone marrow, replacing healthy tissue, and produce M-proteins. Two thirds of patients with AL amyloidosis are male and less then 5% of patients are under 40 years of age.[2] Both the etiology of AL amyloidosis and the mechanism of amyloid deposition remain poorly understood.

The clinical course of AL amyloidosis is usually associated with rapid disease progression, involvement of multiple organ systems, and short survival periods. Extensive organ system impairment, secondary to amyloid deposits, often results in death. Due to the rapid progression of AL amyloidosis, median survival from diagnosis is between one to two years, depending on which organ systems are affected. Patients with cardiac amyloid involvement have an even poorer prognosis with a median survival of less than six months, thus accounting for almost one half of deaths from AL amyloidosis.[3] Due to its similarities to multiple myeloma, treatment of AL amyloidosis has largely been focused around oral chemotherapy regimens. Patients are treated with standard doses of drugs such as melphalan, prednisone, and/or colchicine. Research suggests that multiple drug regimens can produce better response rates then single drug regimens.[4] However, response rates to standard chemotherapy are quite low. For example, many patients do not live long enough to receive enough cycles of melphalan to actually benefit from treatment.

On September 17, 1999, the Health Care Financing Administration (HCFA) received a formal request from the Boston Medical Center for the coverage of AuSCT in the treatment of AL amyloidosis. Evidence is cautiously emerging that suggests a clinical benefit of using AuSCT (described below) in conjunction with high-dose chemotherapy (HDCT) regimens to slow the progression of the disease in patients. Therefore, HCFA must evaluate whether enough substantive scientific evidence has accumulated to justify a national coverage decision.

Description and Current Coverage Policy for Stem Cell Transplantation

Stem cell transplantation is defined as a process in which stem cells, immature cells from which all blood cells develop, are harvested from either a patient's or donor's bone marrow or peripheral blood for intravenous

infusion. The stem cells are treated with drugs to eradicate existing cancer cells and then frozen until transplanted into a recipient.[5] The transplant can be used to effect hematopoietic reconstitution following severely high doses of chemotherapy and/or radiotherapy. There are two main types of bone marrow transplantation: allogeneic and autologous. Allogeneic stem cell transplantation is a procedure in which stem cells or bone marrow is obtained from a healthy donor. AuSCT restores stem cells using the patient's own previously harvested cells.

The *Coverage Issues Manual* (*CIM*) addresses Medicare's coverage policy for stem cell transplantation in §35-30.1. National coverage determinations for allogeneic stem cell transplantation have been made for treatment of the following conditions, after careful review and conclusion that such treatments are both reasonable and necessary:

- leukemia
- leukemia in remission
- aplastic anemia
- severe combined immunodeficiency disease
- Wiskott-Aldrich syndrome.

Medicare does not cover allogeneic stem cell transplantation for the treatment of multiple myeloma.

National coverage determinations for AuSCT have been made for treatment of the following conditions, after careful review and conclusion that such treatments are both reasonable and necessary:

- acute leukemia in remission with a high probability of relapse and having no human leukocyte antigens (HLA)-matched donor
- resistant non-Hodgkin's lymphomas or presenting with poor prognostic features following an initial response
- recurrent or refractory neuroblastoma,
- advanced Hodgkin's disease upon failing conventional therapy and having no HLA-matched donor

Medicare does not cover AuSCT for the treatment of the following conditions:

- acute leukemia not in remission
- chronic granulocytic leukemia
- solid tumors (other than neuroblastoma)
- multiple myeloma

In the absence of specific written coverage policies on other conditions in which stem cell transplantation may be used, Medicare contractors have the authority to develop local medical review policies (LMRPs). In developing local policies, assisted by their Contractor Advisory Committees (CAC), contractors must determine that the service is reasonable and necessary. LMRPs may vary from one state to another and may include instructions limiting the service and/or identifying clinical indications for its use.

Analysis of Clinical Evidence

The analysis established in this memorandum is limited to AuSCT for the treatment of AL amyloidosis. A coverage determination for allogeneic stem cell transplantation was not requested.

In its deliberation on this formal request, HCFA considered twenty-three distinct pieces of scientific material. In order to focus analysis on literature that only presents *direct* evidence on AuSCT on patients with AL amyloidosis, the following were excluded:

- Individual case studies
- Abstracts
- Overview article providing only background information on AL amyloidosis
- Clinical evidence that does not focus on AuSCT

This memorandum will review the following three studies that were not subject to exclusion:

- In Comenzo *et al.* 1996, five AL amyloidosis patients (median age of 41, range 18-61) were treated with dose-intensive intravenous (IV) melphalan followed by AuSCT. At 13 months, all five patients demonstrated either improvements in amyloid-related organ dysfunction and performance status or showed disease stability. After 12 months, plasma cell dyscrasias could not be detected in three patients. It was concluded that AuSCT could be conducted safely with dramatic improvements in outcome on patients with AL amyloidosis.
- In Comenzo *et al*. 1998 (a continuance of the previous study), 25 patients (median age 48, range 29-60) with proven AL amyloidosis were enrolled in a phase-II clinical study to receive dose-intensive IV melphalan followed by AuSCT. At 24 months, 68% of the patients were alive. Of this group, 87% of patients with two or less major organ systems involved had survived compared to only 40% of patients with greater than two involved systems. Furthermore, only 38% of patients with predominant cardiac involvement had survived compared to 82% of patients without cardiac involvement. At three months post transplant, 62% of surviving patients had achieved complete response of their clonal plasma cell disorder. Three patients (12%) died within 100 days of transplantation. The authors suggests that patients with predominant cardiac involvement, particularly those with more than 2 involved organ systems, are high-risk candidates for AuSCT.
- In Moreau *et al*. 1998, 21 patients (median age 48, range 36-62) with confirmed AL amyloidosis underwent AuSCT with high-dose melphalan. Patients with secondary, familial, senile, localized amyloidosis or overt symptomatic multiple myeloma were not included in this study. Authors noted that the number of patients who could not proceed to AuSCT was unknown. There were 9 toxicity-related deaths observed within the first month (a treatment mortality rate of 43%). At 14 months, 10 of the 12 surviving patients (83%) experienced response to treatment with improved organ function (representing 47% of all patients). Actuarial 4-year event free survival was 29.9% for the entire study. The number of clinical manifestations is identified as a possible prognostic factor.

All three studies contain extremely small sample sizes. In addition, there is almost no description on how patients were enrolled into the study. No comparisons are made to either a control group or alternative mode of treatment in any of the three studies. Because of these design issues, it is difficult to assess the significance of the results produced by the three studies. Serious safety concerns are also raised by Moreau *et al* because of the high toxicity rate associated with AuSCT. Furthermore, the authors' lack of specified exclusion criteria and the inability to account for AuSCT-intolerant patients points to potential selection bias within the data.
For a complete review of all scientific material submitted by the Boston Medical Center and HCFA, please refer to the literature review and bibliography attached to this memorandum.

Coverage Decision

HCFA conducted a thorough review of the request submitted by the Boston Medical Center and has concluded that a sufficient body of evidence does not exist to justify a national coverage decision in favor of AuSCT for patients with AL amyloidosis. A substantial portion of the submitted materials did not meet the criteria for consideration described above. Analysis of these studies identifies important biases that were not addressed. Small sample sizes and discriminatory enrollment of patients introduces selection bias, which can lead to skewed results. Furthermore, none of these studies compare HDCT and AuSCT to either a control group or other treatment modalities. It is difficult to determine the effectiveness of a treatment unless it is compared to current standards of care. Safety is another concern that was identified. The wide range in treatment-related mortality (0, 12%, and 43%) leads to the conclusion that proper patient selection may be an issue.

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HCFA is willing to reconsider this coverage determination if new evidence becomes available. If this issue is revisited, HCFA would especially be interested in seeing prospective randomized clinical trials that compare AuSCT to standard chemotherapy with larger, more diverse sample sizes that address the Medicare population.

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[1] Falk R, Comenzo R, et al.

[2] Hussein M.

[3] Hussein M

[4] Skinner M, Anderson J, et al.

[5] National Cancer Institute/PDQ Glossary found at cancer.med.upenn.edu/pdq_html/glossary/psct.html

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Articles Submitted by: Boston University

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Moreau P, Milpied N, Faucal P de, Petit T, Herbouiller P, Bataille R, Harousseau JL. Correspondence: high-dose melphalan and autologous bone marrow transplantation for systemic AL amyloidosis with cardiac involvement. Blood 1996; 87:3063.

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Skinner M. Amyloidosis. Current Therapy in Allergy, Immunology, and Rheumatology 1996; 235-240.

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Literature Review - ATTACHMENT B

hhhhhhhhhhhhhhhhhhhh

https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Autologous-Platelet-rich-Plasma-PRP.html

https://search.cms.gov/search?utf8=%C3%A2%C5%93%E2%80%9C&affiliate=cms-new&dc=&query=autologous+&commit=Search

SEARCHed "autologous"

- Partnership for PatientsAutologous Platelet-rich Plasma (PRP) - Centers for ...

www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Autologous-Platelet-rich-Plasma-PRP.html

CMS covers **autologous** platelet-rich plasma **(PRP**) only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when all ...

Autologous Platelet-rich Plasma (PRP) - Centers for ...

www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Autologous-Platelet-rich-Plasma-PRP.html

CMS covers **autologous** platelet-rich plasma **(PRP**) only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when all ...

[PDF] Autologous Cellular Immunotherapy Treatment of Metastatic ...

www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM7431.pdf

Related CR Transmittal #: R2380CP and R140NCD . Implementation Date: August 8, 2011 : **Autologous** Cellular Immunotherapy Treatment of Metastatic ...

National Coverage Determination (NCD) for Blood-Derived ...

www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCAId=260&NcaName=Autologous+Blood-Derived+Products+for+Chronic+Non-Healing+Wounds&ExpandComments=y&CommentPeriod=0&NCDId=217&ncdver=4&lcd_id=7060&lcd_version=77&show=all&bc=gABAAAAAIEAAAA%3D%3D&

07/2004 - Determined that **autologous** blood-derived products for chronic non-healing cutaneous wounds, both platelet-derived growth factor in a ...

[PDF] HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM-CELL SUPPORT ...

www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id3TA.pdf

high-dose chemotherapy with **autologous** stem-cell support for treatment of multiple myeloma in older patients april 2000 jerome seidenfeld, ph.d.

Decision Memo for Autologous **Cellular Immunotherapy ...**

www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NcaName=Autologous%20Cellular%20Immunotherapy%20Treatment%20of%20Metastatic%20Prostate%20Cancer&bc=ACAAAAAAIAAA&NCAId=247&

Use this page to view details for the decision Memo for **Autologous** Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N).

Autologous Platelet-rich Plasma **- Centers for Medicare ...**

www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Autologous-Platelet-rich-Plasma.html

CMS covers **autologous** platelet-rich plasma (PRP) only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when all ...

Draft ICD-10-CM/PCS MS-DRGv28 Definitions Manual

www.cms.gov/icd10manual/fullcode_cms/P0185.html

0SR907Z: Replacement of Right Hip Joint with **Autologous** Tissue Substitute, Open Approach: 0SR90J5: Replacement of Right Hip Joint with Synthetic ...

Decision Memo for Stem Cell Transplantation (Multiple ...

www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=280

Use this page to view details for the decision Memo for Stem Cell Transplantation **(Multiple Myeloma, Myelofibrosis,** and Sickle Cell Disease) ...

National Coverage Determination (NCD) for **Heart ...**

www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCAId=126&NcaName=Autologous+Stem+Cell+Transplantation+(AuSCT)+for+Amyloidosis&ExpandComments=n&CommentPeriod=0&NCDId=112&ncdver=2&bc=ACAAAAAAEEAAAA%3D%3D&

Use this page to view details for national coverage determination **(ncd)** for heart transplants (260.9).

National Coverage Determination (NCD) for Diabetes ...

www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCAId=126&NcaName=Autologous+Stem+Cell+Transplantation+(AuSCT)+for+Amyloidosis&ExpandComments=y&CommentPeriod=0&CALId=103&CalName=Prothrombin+Time+and+Partial+Thromboplastin+Time+(Revision+of+ICD-9-CM+Codes+for+Swelling+of+Limb)&NCDId=251&ncdver=1&CoverageSelection=National&list_type=ncd&bc=gAAAABAAEEAAAA%3D%3D&

Use this page to view details for national coverage determination (ncd) for diabetes outpatient self-management training (40.1).

[PDF] Cytomedix cytomediX, Inc.

www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id208.pdf

Cytomedix **. cytomediX,** Inc. ... coverage detemlination for **autologous**, platelet-derived wound healing formulas intended to treat patients with ...

[PDF] **ICD-**10: Clinical Concepts for Cardiology
www.cms.gov/Medicare/Coding/ICD10/Downloads/ICD10ClinicalConceptsCardiology1.pdf

ICD-10 Clinical Concepts for Cardiology is a feature of . Road to 10, ... I25.710 Atherosclerosis of **autologous** vein coronary artery bypass graft(s) ...

Draft ICD-10-CM/PCS MS-DRGv28 Definitions Manual
www.cms.gov/icd10manual/fullcode_cms/P0119.html

Bypass Coronary Artery, One Site to Aorta with **Autologous** Venous Tissue, Percutaneous Endoscopic Approach: 02104A3: Bypass Coronary Artery, ...

[PDF] 2008 HCPCS REQUEST LIST **- Centers for Medicare and ...**
www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/2008RequestList.pdf

2008 HCPCS REQUEST LIST ... Indium In-111 **autologous** labeled white blood cells. Suggested language: "Indium In-111 **autologous** labeled white blood ...

ICD-10-CM/PCS MS-DRGv33 Definitions Manual
www.cms.gov/ICD10Manual/version33-fullcode-cms/fullcode_cms/P1058.html

0RG4371: Fusion of Cervicothoracic Vertebral Joint with **Autologous** Tissue Substitute, Posterior Approach, Posterior Column, Percutaneous Approach

National Coverage Determination (NCD) for **Blood ...**
www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=154

Use this page to view details for national coverage determination **(ncd)** for blood transfusions (110.7).

Draft ICD-10-CM/PCS MS-DRGv28 Definitions Manual
www.cms.gov/icd10manual/fullcode_cms/P0126.html

Supplement Thoracic Aorta with **Autologous** Tissue Substitute, Percutaneous Endoscopic Approach: 02UW48Z: Supplement Thoracic Aorta with Zooplastic ...

National Coverage Determination (NCD) for Autologous **...**
www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCAId=262&NcaName=Ocular+Photodynamic+Therapy+(OPT)+with+Verteporfin+for+Macular+Degeneration&ExpandComments=y&CommentPeriod=0&NCDId=344&ncdver=1&bc=AiAAAAAAEEAAAA%3D%3D&

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[PDF] **CMS Manual System**
www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R2254CP.pdf

of **autologous** cellular immunotherapy treatment - sipuleucel-T; PROVENGE, improves health outcomes for Medicare beneficiaries with asymptomatic or ...

ICD-10-CM/PCS MS-DRGv33 Definitions Manual
www.cms.gov/ICD10Manual/version33-fullcode-cms/fullcode_cms/P0122.html

Removal of **Autologous** Tissue Substitute from Great Vessel, Percutaneous Endoscopic Approach: 02PY48Z: Removal of Zooplastic Tissue from Great Vessel ...

medical claims Regenexx
https://www.regenexx.com/introducing-regenexx-sd-plus-procedure/

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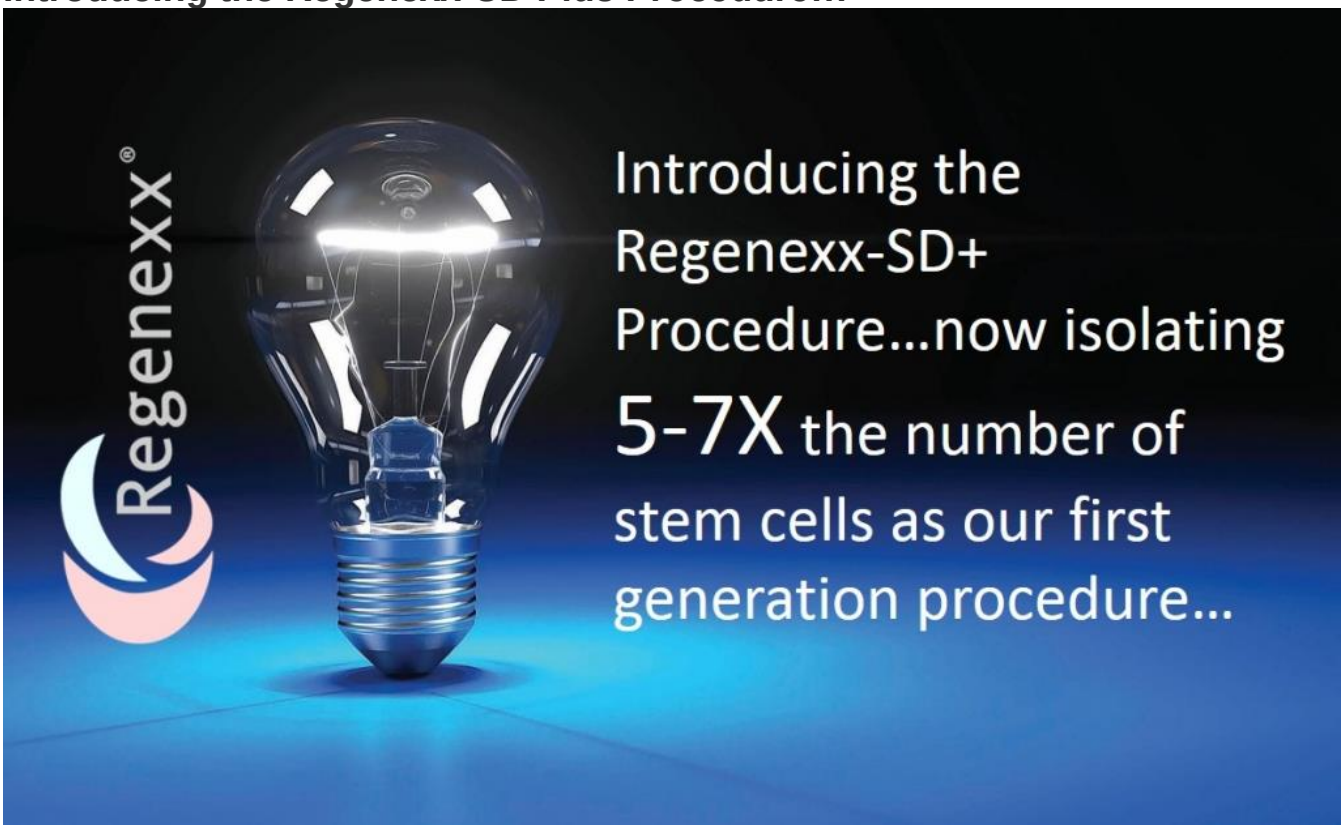
Introducing the Regenexx-SD Plus Procedure…

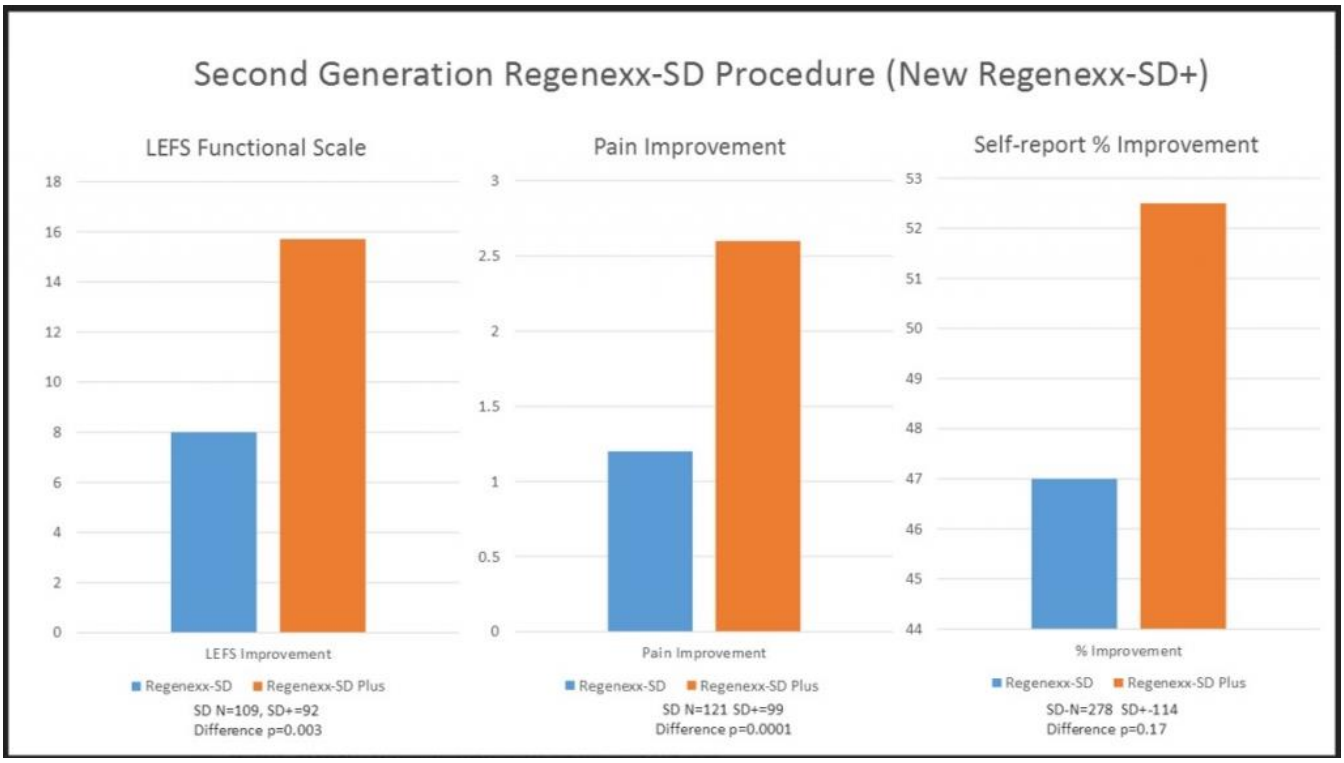


As many of you know, we spend heavily on innovation. It's a little humorous sometimes to see small clinics claim they're doing innovative stem cell work (or what we're doing) by simply taking a weekend course somewhere and using old technology. In contrast, we have a PhD led lab research team and a physician/bio stats led clinical research team to constantly update what we can offer. Last year we started various projects to determine if we could come up with a way of processing bone marrow that nobody had ever used. If so, could we double or even triple the number of stem cells extracted? We didn't triple the number of stem cells being extracted, we bumped it up 500%+ over what we could do before. Thus Regenexx-SD Plus (SD+) was born.

So where was the bar set with Regenexx-SD? Using that procedure we could extract about 3-4X stem cells per cc over what the average automated bedside centrifuge could muster. These little machines are used

by 98% of the physicians using bone marrow stem cells. All the physician really knows is where to place the sample in the machine and how to push the “ON” button. Because of this and the fact that these machines have to be one size fits all to process very different bone marrow samples from very different patients, it wasn’t hard to beat these little devices. However, could we do better? Our research team investigated many different ways to process marrow. After discarding many, we finally discovered one that was pretty revolutionary. However, while extracting more stem cells is something just about everyone would agree is a net positive, if it doesn’t make a clinical difference, who cares?

Below is clinical data for knee arthritis patients from before and after making the switch to the new Regenexx-SD+ procedure. As you can see, there are dramatic, statistically significant changes in the LEFS functional scale (knee function) and pain relief with the new SD+ process when we compare many treated patients (average follow-up is 5 months). So not only are we getting more stem cells, we’re getting better results. All Regenexx network providers are offering SD+ and all have been trained in the procedure. Is there an extra cost for this more advanced processing? No, everything will remain the same. So if you do the math, per stem cell you’re receiving, Regenexx is best value out there!



The upshot? SD+ is a second generation same day stem cell procedure and we're already working on the third. We're on our third generation platelet lysate (a mix of growth factors isolated from platelets) and working on our fourth. We're on our second generation SCP (Super Concentrated Platelets) and working on our third. This is how we roll. This is also something you'll never see from small mom and pop clinics offering discount stem cell procedures who are using older technology. Why spend huge amounts of money on million dollar research labs and innovation? Because Regenexx isn't run by guys running spreadsheets in Wall street, but physicians. We personally benefit (as does every Regenexx doc) when we innovate because our patients benefit. Most people struggle to think outside the box, at Regenexx, we say, "What box?" There's Regenexx and then there's everything else….

FILED UNDER:

- KNEE
- KNEE PROCEDURE OUTCOMES
- LATEST NEWS
- REGENEXX-SD

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Next: We Should Never Be Proud … »

By Chris Centeno on August 28, 2014

Chris Centeno, M.D. is a specialist in regenerative medicine and the new field of Interventional Orthopedics. Centeno pioneered orthopedic stem cell procedures in 2005 and is responsible for a large amount of the published research on stem cell use for orthopedic applications. Centeno regularly lectures on regenerative medicine and has spoken twice at the Vatican Stem Cell Conference, as well as the NFL Combine.

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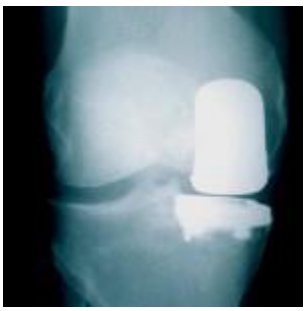
- 

  Regenexx-SD Knee Stem Cell Testimonial

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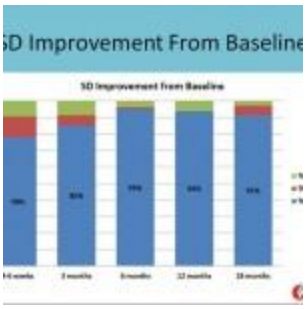
  Knee Stem Cell Procedure Research: Should You Get a Second Regenexx-SD Procedure?

- 

  [More Regenexx-SD Knee Stem Cell Data]

- 

  [Continued Knee Pain after Knee Replacement?]

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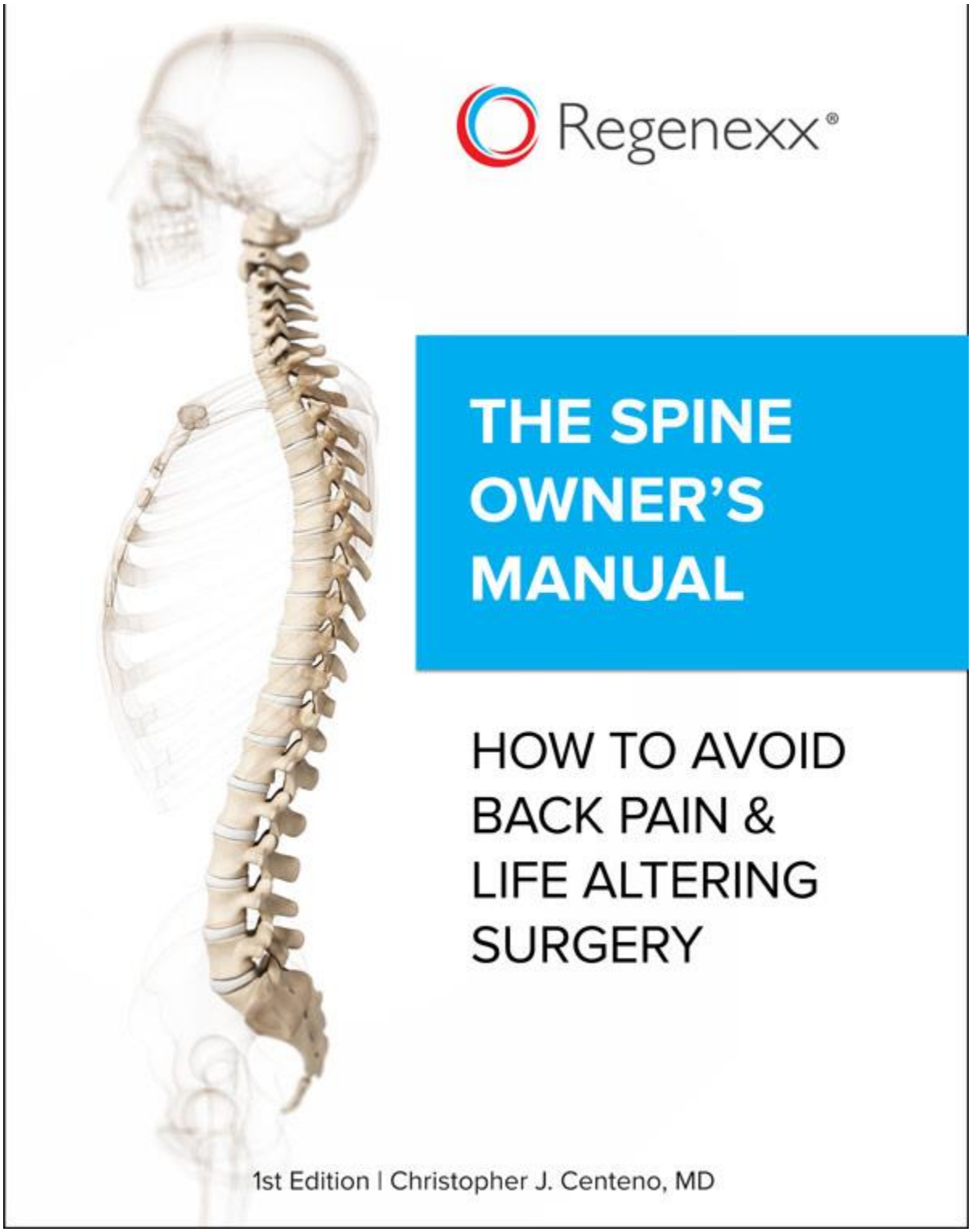

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Effective January 1, 2016

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This notice applies to all information collected or submitted on the Regenexx website. On some of our site's pages, you can make requests, register to receive materials, or provide contact and personal information for follow-up by Regenexx. The types of personal information collected at these pages are:

Name
Address
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Phone number
Information relating to a physical problem or condition you are experiencing.After the initial submission of basic information, we may ask to collect more specific medical information from you via a secure form.

The Way We Use Information:

We do not share this information with outside parties. We use information collected in two ways.

1) When patients submit a Regenexx Procedure Candidate Form, we use the information provided to follow up with the candidate and determine whether they meet our criteria for the Regenexx Family of Procedures. By completing the Regenexx Procedure Candidate Form, you are giving us permission to contact you with more information. If the initial evaluation determines that you are a good candidate, you may be asked to fill out a secure online form. The information collected on this form is

confidential and is used by a doctor for a more in-depth review of your condition prior to a phone interview with you. All information is strictly confidential to Regenerative Sciences.

2) We provide two ways to opt-in to receive our monthly newsletter an occasional update on news or events that may be of interest, such as new procedures or informational webinars or books.

1. When completing the Regenexx Procedure Candidate Form, the final step before submitting the form asks whether you would like to subscribe to our Regenexx Newsletter for occasional procedure news updates. If you prefer not to receive these updates, please select the radio button titled – No, thanks.
2. Our site provides an area in our sidebar that is an opt-in form for the Regenexx Newsletter. It is titled: Sign Up for Our eNewsletter. By entering your email and clicking the submit button, you are opting to receive occasional news from us.

We limit our news and event related mailings to a maximum of two per month. However, during the process of determining whether you are a Regenexx Procedure Candidate, you may receive additional emails from individuals within Regenerative Sciences while evaluating your specific condition. These communications are considered to be separate from opt-in mailings.

If you receive a mailing from us that is related to your acceptance of joining our mailing list, you will see an option to unsubscribe from that list and discontinue receiving these occasional news, procedure and event related mailings.

If you receive an email without an option to opt-out of the mailing, you are receiving that mailing as part of a personal communication with Regenerative Sciences.

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Please provide the requested details below. After submitting the form, you will receive an email detailing the next steps.

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☐ You can send text messages to the number above

Proceed to Step 2

Step 1 - Provide your contact information

Step 2 - Provide a few details about the condition for which you are considering treatment
Step 1 of 2

[after completing the contact information]

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Step 2 - Information About Your Condition

Please select your primary problem area:

Knee - General Knee - Meniscus Knee - OA Hip - General Hip - OA Shoulder - General
Shoulder - Rotator Cuff Spine - General Spine - DDD Hand / Wrist / Finger Foot / Ankle / Toe
Elbow Other

Date of Birth: MM/DD/YYYY

An MRI is typically required as part of the evaluation process and will help guide the planning of your actual treatment if you choose to proceed.

I understand that an MRI is required for most treatments (click the checkbox) *

Insurance may cover office visits, consultations, diagnostic testing, examinations and bracing. However, insurance does not currently cover Regenexx Procedures at this time.

I understand Regenexx Procedures are not covered by insurance (click the checkbox) *

Do you live within driving distance of a Regenexx Network Provider?

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Yes No Unsure

Upon submitting this form, you will be assigned a personal Regenexx Representative. Would you like them to call you to answer any questions you have?

Yes - Please Call Me No - Email Only for Now

If Yes, When is Typically the Best Time to Reach You?

7:00am - 9:00am MT 9:00am - 11:00am MT 11:00am - 1:00pm MT 1:00pm - 4:00pm MT

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Step 1 - Provide your contact information

Step 2 - Provide a few details about the condition for which you are considering treatment

Step 2 of 2

Supraspinatus Tendon tear - diagnosis via MRI technology AND Keith Bidwell M.D, and radiologist - Ohio. Documents and images are presented on my personal web site.

Dr. Centeno, I am NOT your enemy. I merely want to confirm the "medical claims" - that you make are true; AND, that your product, drug, device is safe. I was a student of human Genetics - at UWGB (in the 1970s) - and, my company helped to create the textbooks you cite. - Susan

Patient performs YOGA poses every day - as detailed on personal web site. P is retired, happy, married - an, "Obama Girl" ; and, her biological daughter is the Deputy Chief of Staff - at the USA-FBI.

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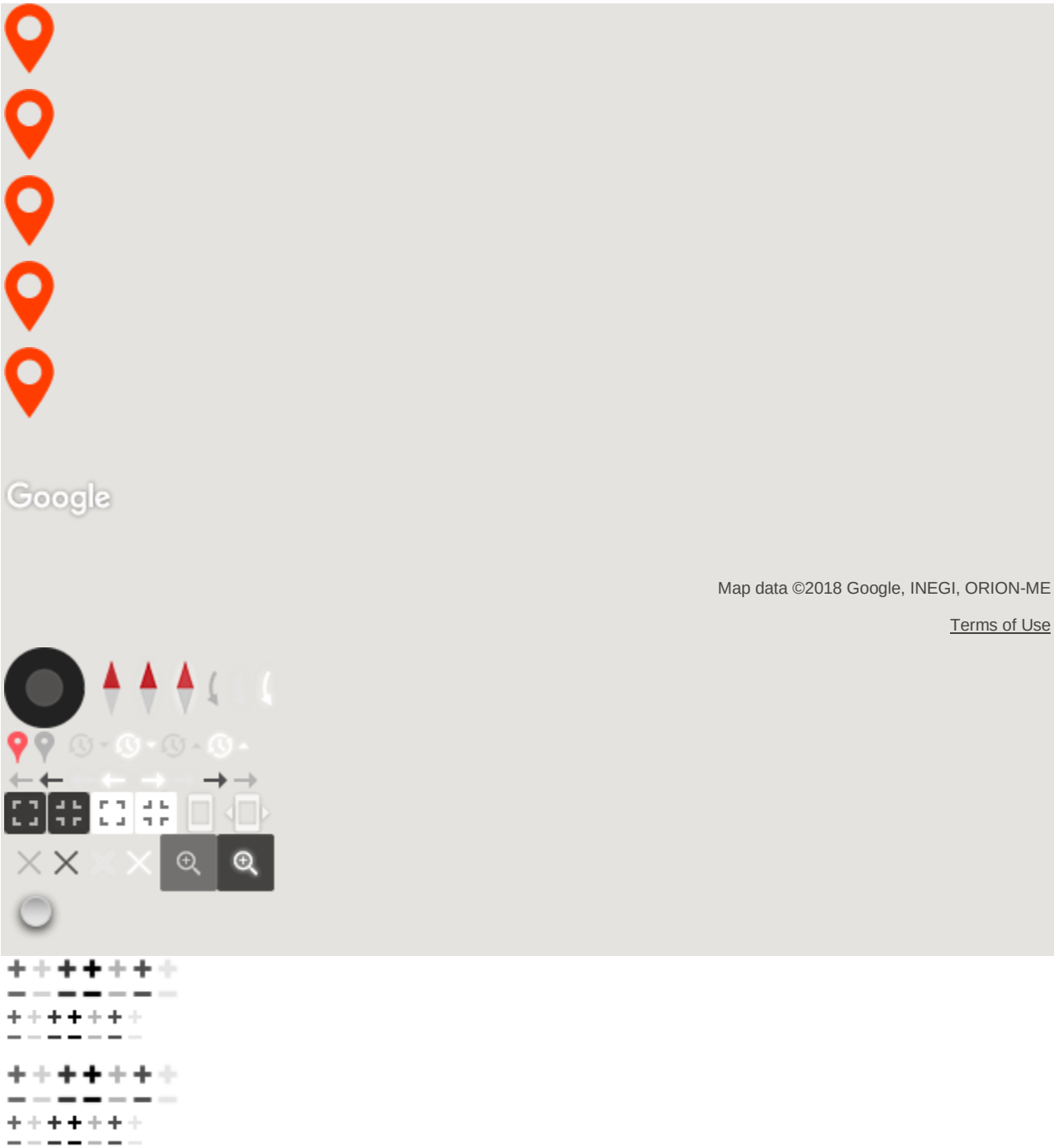
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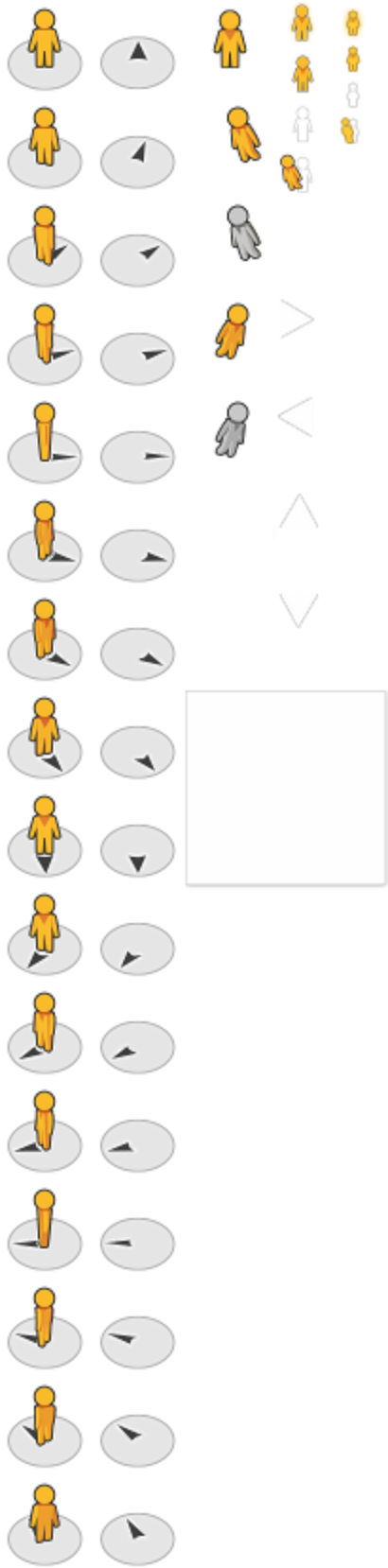

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- Rejuv Medical - Savage, MNAreas Treated: Ankle/Foot, Hip, Knee, Shoulder, Spine
- Rejuv Medical Clinic - Waite Park, MNAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- Restore PDX -- Beaverton, ORAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine

- Southern California Orthopedic Institute - Thousand Oaks, CAAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder
- Southern California Orthopedic Institute - Van Nuys, CAAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- StemCell ARTS - Chevy Chase, MDAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- StemCell ARTS - McLean, VAAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- Texas Interventional Orthopedics and Regenerative MedicineAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- TotalCare Health & Wellness Medical - Lafayette, LAAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- Vermont Regenerative Medicine - Winooski, VTAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine
- Wasatch Pain Solutions - South Jordan, UTAreas Treated: Ankle/Foot, Elbow/Wrist/Hand, Hip, Knee, Shoulder, Spine

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Regenexx - Where Orthopedic Stem Cell Injections Were Invented.

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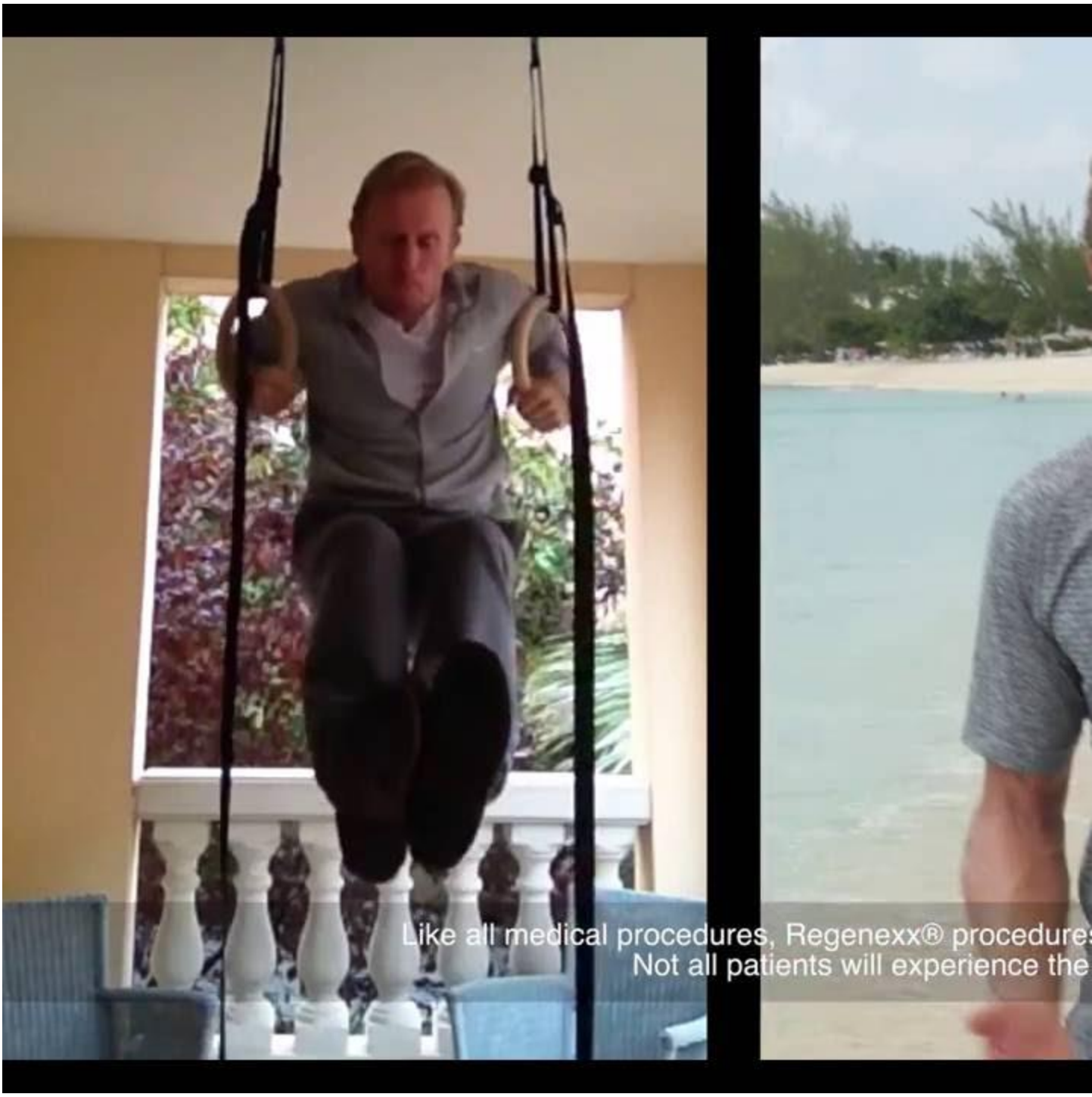
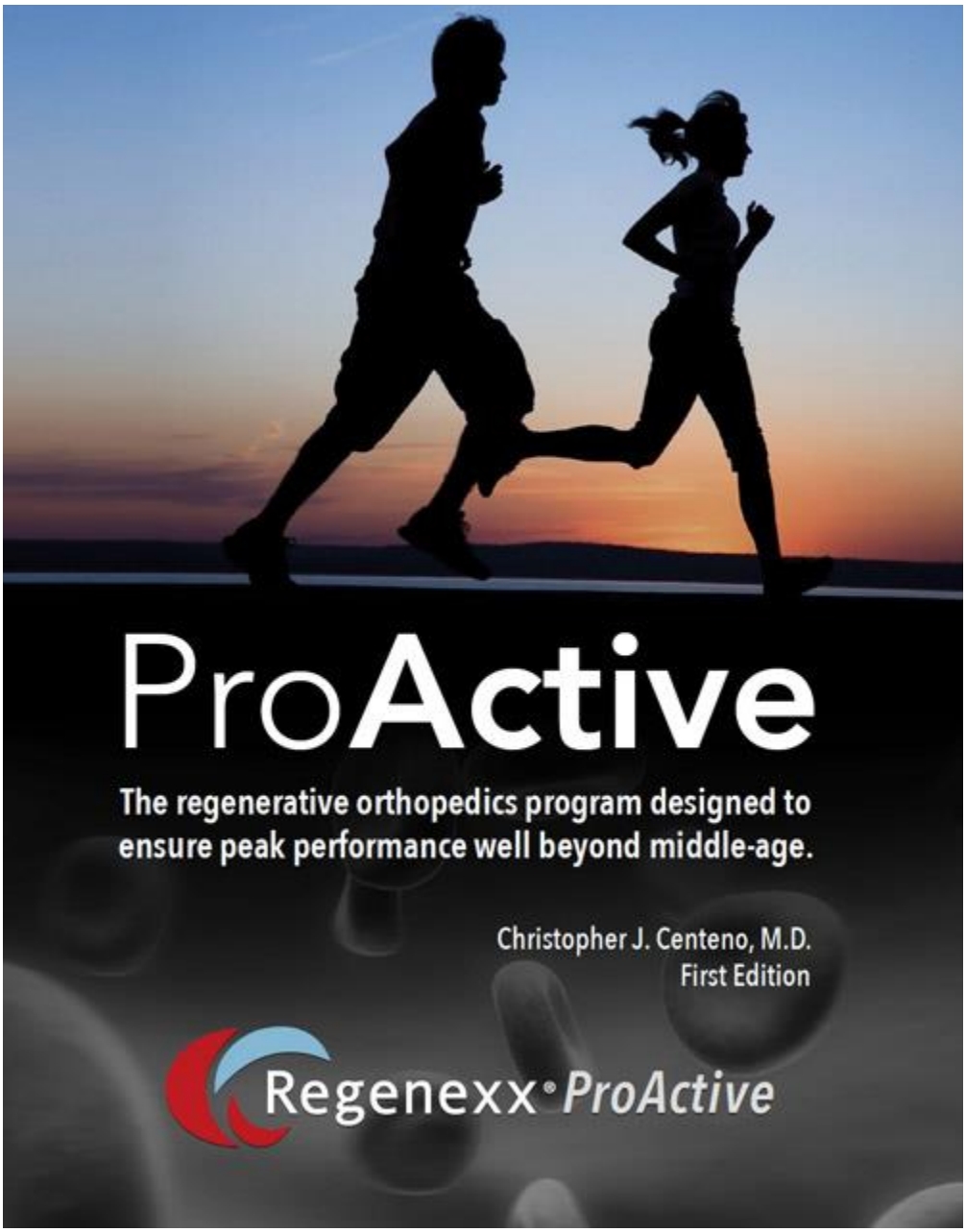
Regenexx® ProActive is for active individuals who want to stay at the top of their game & maintain peak health through their middle-age & senior years.

The ProActive program is designed for active individuals seeking to maintain joint and spine health, as well as treat & prevent the nagging injuries & pain that inevitably come along as an active adult, weekend warrior, or competitive athlete.



Regenexx Stem Cell Procedures Help Tony Maintain Peak Fitness in His 60's



Regenexx ProActive

As we grow older, our body begins to send us warning messages. When these messages are ignored, small musculoskeletal problems can spiral out of control and leave us sidelined from doing the activities we love. And left untreated, these issues may lead to more chronic conditions and may permanently reset what we consider to be our normal level of fitness, performance or activity. This is why some people in their 70's can run a marathon, while others in their 50's can barely walk a mile.

The Regenexx ProActive program provides practical advice on understanding these warning signs and taking action to maintain peak performance through middle-age and beyond. ProActive explains how the use of biologic treatments, such as stem cells and

blood platelet procedures, can help return joints and the spine to a healthy state before things go awry, ensuring that small problems don't go from bad to worse.
Written by Dr. Chris Centeno, ProActive includes hyperlinks to more detailed information and related research that supports the Regenexx ProActive program's approach to maintaining health, fitness and well-being throughout our middle and later years of life.

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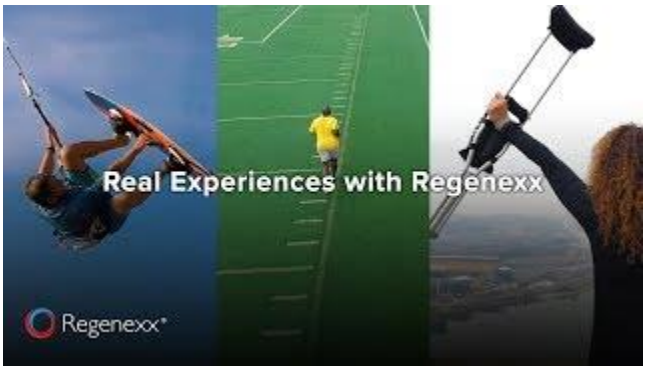
- 

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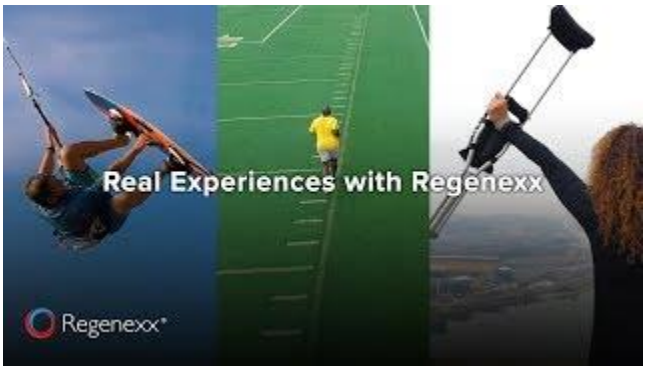
- 

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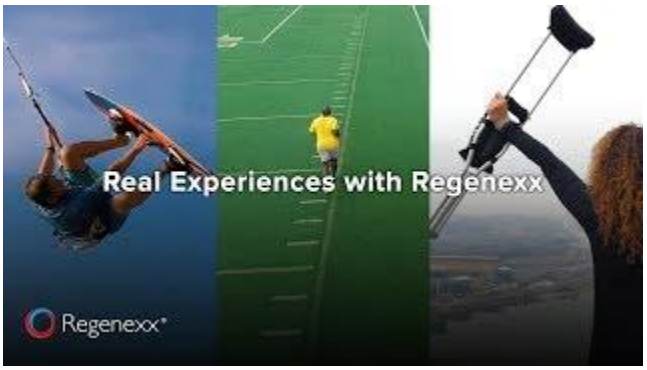
- 

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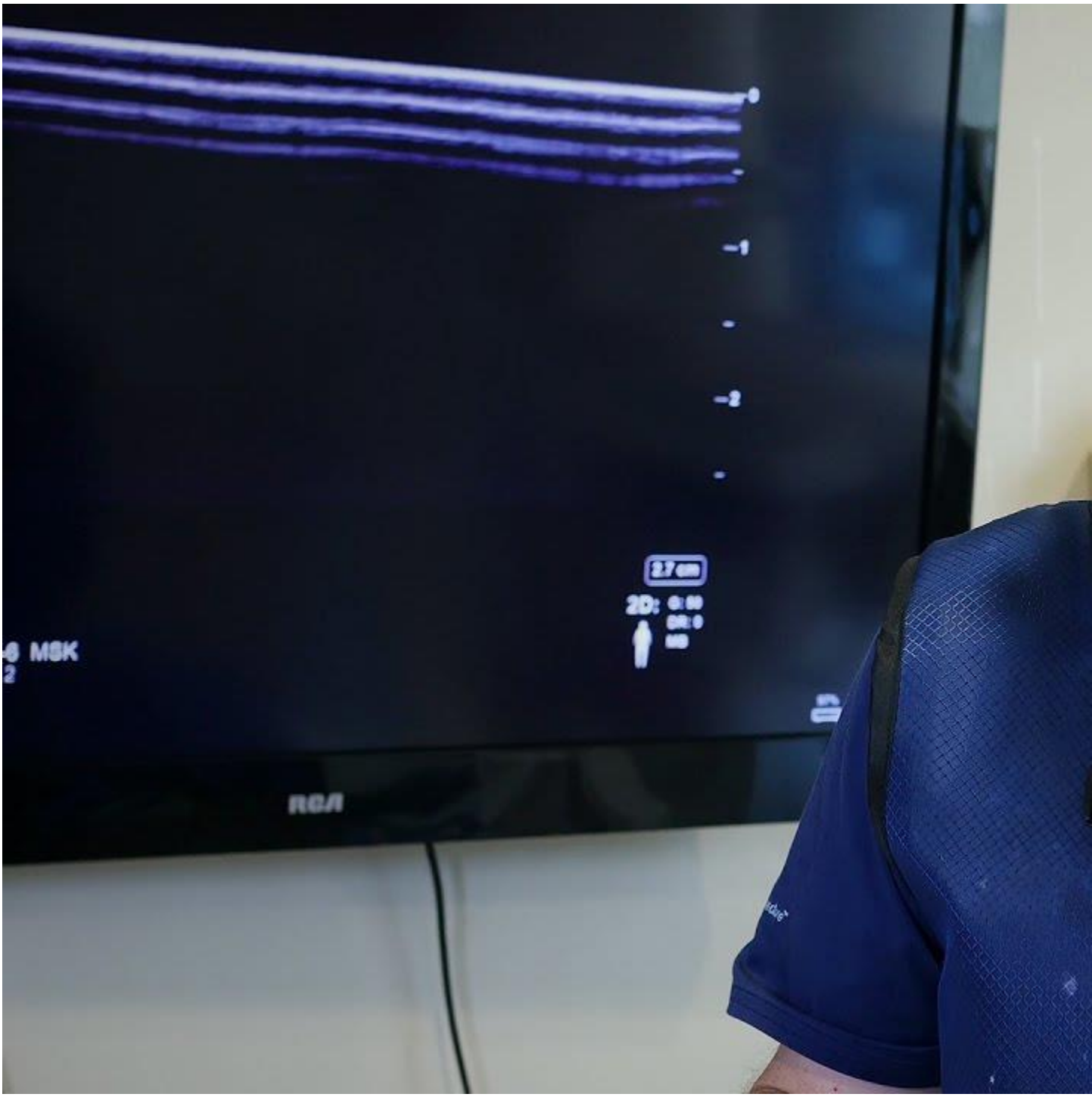
Regenexx® Stem Cell Procedures for Shoulder Arthritis, Rotator Cuff Tears & Other Shoulder Conditions.

The Regenexx® family of non-surgical stem-cell & blood platelet procedures are next generation regenerative injection treatments for those who are suffering from shoulder pain due to arthritis, rotator cuff and shoulder labrum tears, overuse injuries, and other degenerative conditions. Regenexx is also a viable alternative for those considering shoulder replacement surgery.

If you have encountered a rotator cuff tear, or experience pain related to shoulder arthritis, tendonitis, tendenosis, or bursitis, you may be a good candidate for a Regenexx Procedure. Shoulder surgery is particularly difficult due to the complexity of the joint. Post surgical recovery can be painful, requiring a lengthy rehab period to restore strength and mobility to the shoulder. As an alternative to shoulder surgery, Regenexx Procedures may help alleviate shoulder pain and restore joint damage with a non-invasive injection procedure. Patients typically experience little or no down time from the procedure.

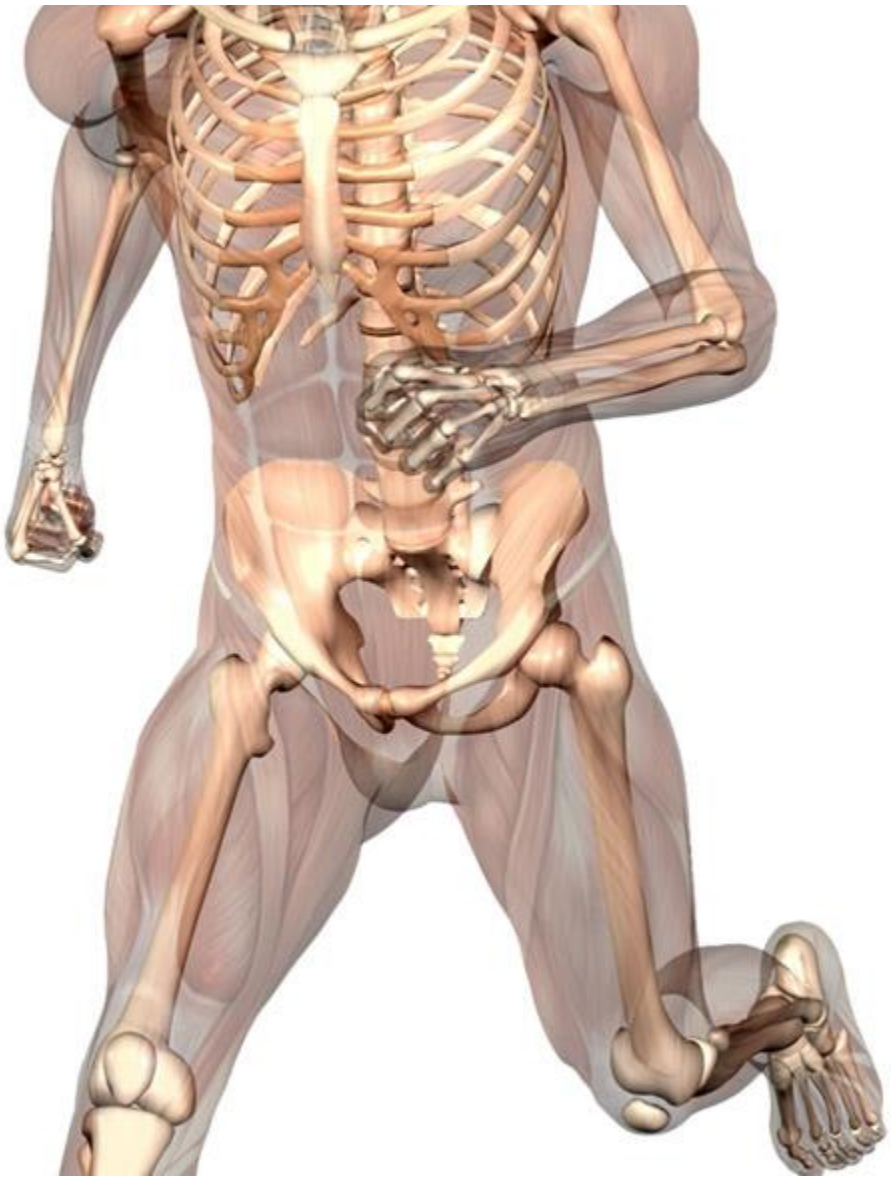
Patient Outcome Data & Commonly Treated Shoulder Conditions

Regenexx Shoulder Procedure Overview



Dr. John R. Schultz demonstrates the Regenexx shoulder procedure.

How it Works



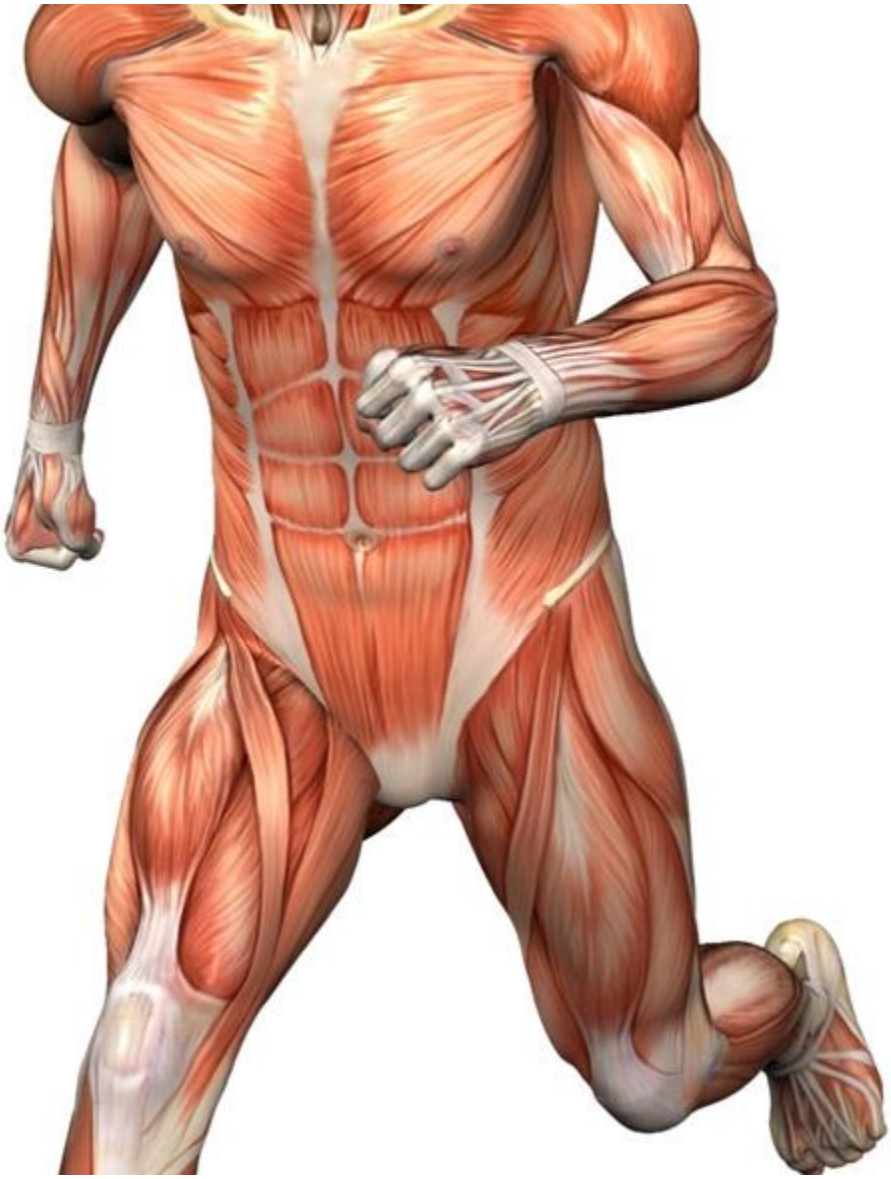
Stem Cell Treatments

Same Day Stem Cell Protocol (USA & International) & Cultured Stem Cell Procedure (Cayman Islands Only)

Adult stem cells are cells from your own body that can renew themselves and turn into other cells (differentiate). They live inside all of us in various tissues, poised to leap into action to repair damage as it occurs. As we age or have big injuries, we may not be able to recruit enough of these cells to the site to fully repair the area. Regenexx Stem Cell Procedures help overcome this problem by extracting stem cells from an area of high

volume, then concentrating the cells and reinjecting them into the damaged area to help the body heal naturally.
Our Patented Stem Cell Procedures can be used for a wide range of conditions and are the tool of choice for injuries, arthritis and other conditions that may be more significant than what may be treated with our Platelet Rich Plasma or Platelet Lysate Procedures.

Stem Cell Procedure Details



Blood Platelet Treatments

Super Concentrated Platelet Rich Plasma & Advanced Platelet Lysate Procedures (USA & International)

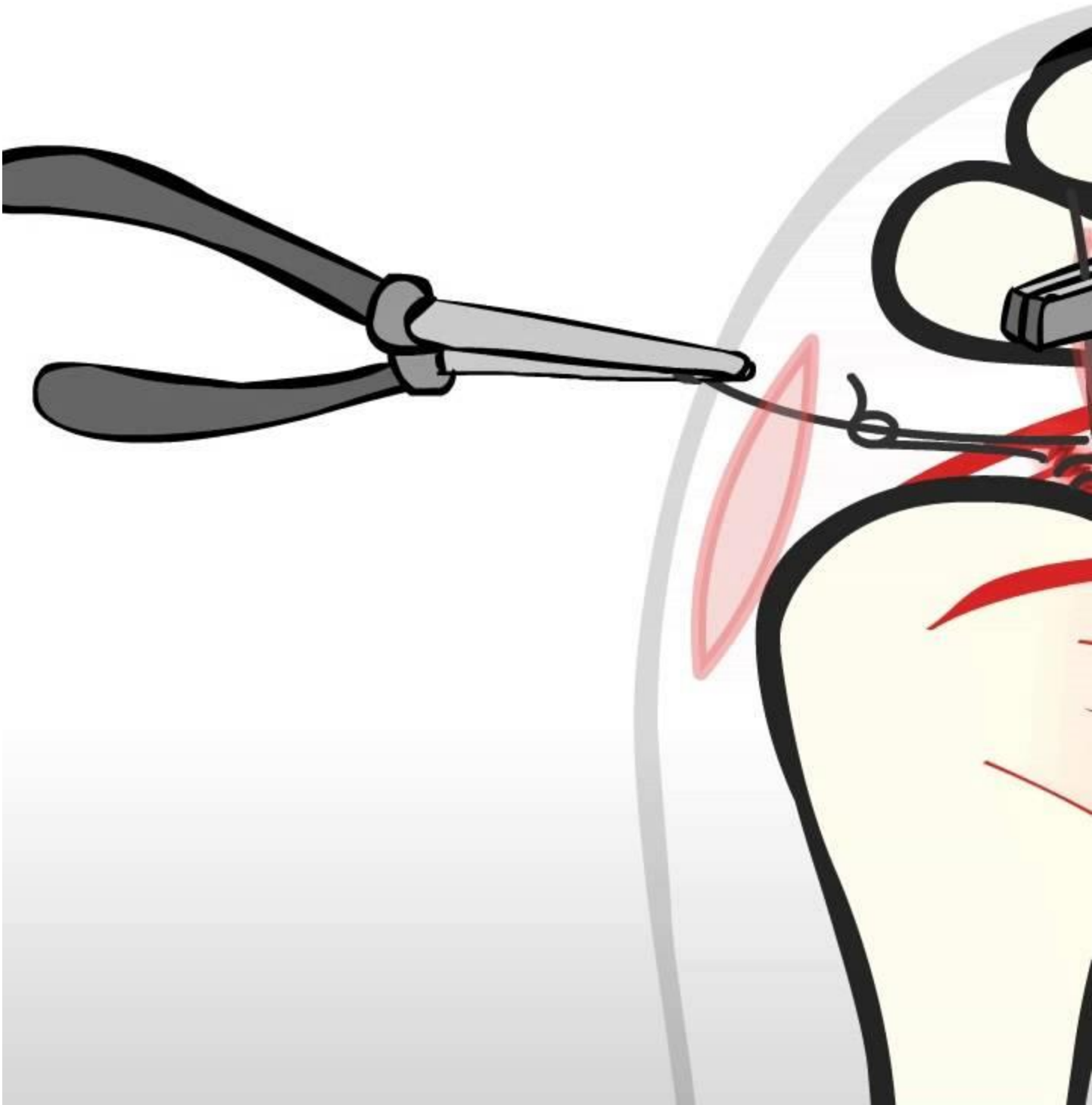
Platelet Rich Plasma (PRP) and Platelet Lysate Injection Treatments contain healing growth components from your own blood that increase your body's natural ability to repair

itself. The use of PRP to repair joint, tendon, ligament, and muscle injuries is becoming well known, thanks to exposure from professional athletes. Platelet injection treatments are effective because they have a stimulating effect on the stem cells within the targeted area, making those stem cells work harder to heal damaged tissues.
Our Advanced Platelet Procedures are more pure and concentrated than those created by the automated machines used at most regenerative medicine clinics. Platelet procedures are commonly used for soft tissue injuries, mild arthritis and spine conditions.

Platelet Procedure Details

Regenexx Procedures for Rotator Cuff Tears

The Regenexx Procedure for Rotator Cuff Tears is a patented same-day stem cell procedure. Through years of research and perfecting the use of stem cells and platelets to repair rotator cuff tears, Regenexx improves the rotator cuff's regenerative potential, rather than further damaging an area that has given way because of tissue weakness.
Using a precise, image-guided injection of your own stem cells and growth factors, we are able to get more of the body's natural "repairmen" directly into the tear. By mobilizing your body's own healing mechanisms and eliminating the trauma of surgery and atrophy caused by immobilization, Regenexx has produced good results in the treatment of partial rotator cuff tears and has even shown encouraging success with completely retracted tears.



The Best Possible Patient Outcomes

Continue to learn why we're the #1 orthopedic stem cell procedure

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Recent Regenexx Shoulder Articles & Patient Stories

Severe Shoulder Arthritis Stem Cell Update: I'm Blown Away

Chris Centeno Latest News Shoulder Shoulder and Rotator Cuff Procedure Outcomes

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What Others Are Saying About Regenexx*

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Regenexx Procedures at a Glance

Typical Condition Severity

$$$ Cultured Stem Cell Procedure (Cayman Islands Only)*

$$ Stem Cell Treatment Protocol (USA & Worldwide)

$ Platelet Rich Plasma & Platelet Lysate

Strains, muscle, ligament & tendon tears, overuse injuries, tendonitis & tendonosis, minor arthritis, joint maintenance, bulging or herniated discs, degenerative discs.

More severe muscle, ligament & tendon tears (including complete tears), joint arthritis, degenerative joint conditions, torn spinal discs, degenerative discs, avascular necrosis, bone conditions & non-union fractures.

Similar to USA Stem Cell Treatment, but stem cells are cultured to greater numbers.* Recommended for severe injuries, arthritis, advanced degenerative conditions, more severe spine conditions.

*Advanced culture expanded stem cell procedure-not approved by the USFDA and available only through licensed sites where culturing cells are the practice of medicine.

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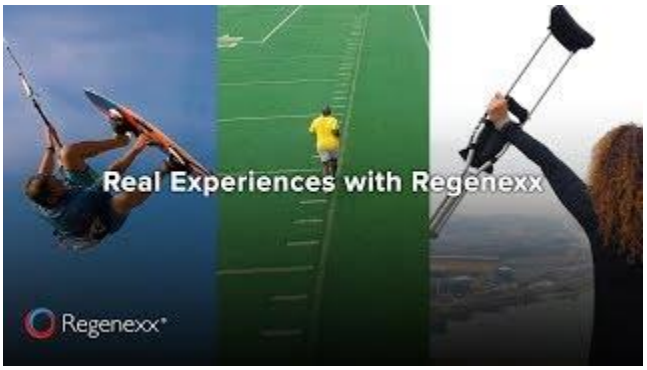
- 

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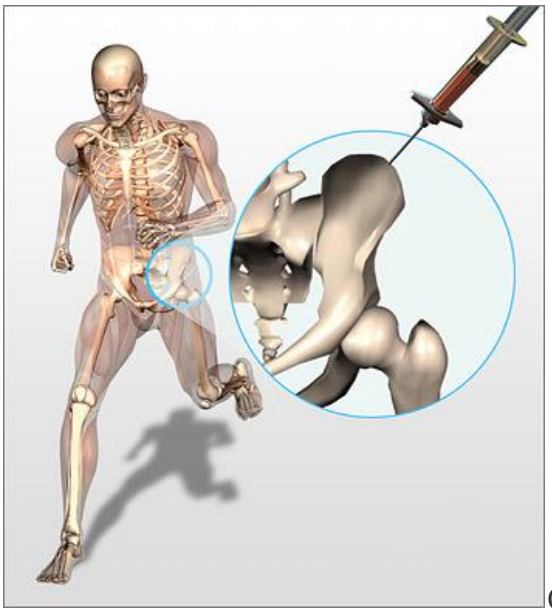
Regenexx® Patented Stem Cell Procedures

The World's Most Advanced Stem Cell Procedures for Orthopedic Conditions

At Regenexx, our #1 priority is to produce the best possible outcomes for our patients. And while our patented protocol is far more complex than you will find at other regenerative medicine clinics, we do not cut corners. Everything about your Regenexx experience is designed for results.

Stem cells live in all of us and they act as the repairmen of the body. However, as we age or get injuries, we sometimes can't get enough of these critical repair cells to the injured area. The Regenexx Procedures help solve this problem by greatly increasing your body's own natural repair cells and promote healing. This is accomplished by harvesting cells from areas known to be rich in mesenchymal stem cells and then concentrating those cells in a lab before precisely reinjecting them into the damaged area in need of repair.

The Regenexx® Patented Same Day Stem Cell Protocol (USA & International)



Our Same-Day Stem Cell Protocol is called a same-day procedure, because the stem cells are harvested and reinjected on the same day. However, for most patients the complete protocol is actually a series of injections that happen over the course of about a week, depending on your unique situation. These injections include a preinjection, the same-day stem cell extraction and reinjection procedure, followed by a post-injection of multiple proprietary platelet mixes a few days later.

On the day of your stem cell procedure, you will first have a blood draw from a vein in your arm. This will be processed in the lab along with your stem cell sample. When you are prepared for the first step of your stem cell procedure, your doctor will thoroughly numb the back of the hip and take a small bone marrow sample through a needle. The

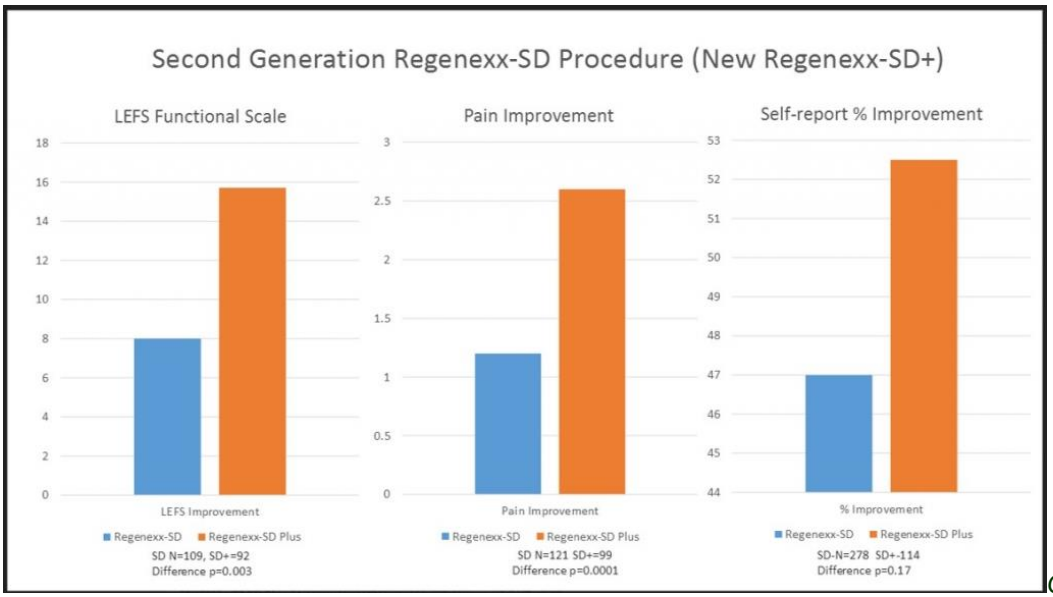
procedure we use is called a bone marrow aspirate. This is different than a bone marrow biopsy, which can be painful. The bone marrow aspiration process is often described by patients as being comfortable.

While your cells are being processed by a Regenexx Lab Technician, you will have some downtime to relax. A short period later, you will be ready for the second part of the procedure, where the doctor will reinject your stem cells and natural growth factors from your blood platelets using advanced imaging guidance into the area in need of repair (real time fluoroscopy or musculoskeletal ultrasound, using your MRI to plan the injection). This allows the doctor to pinpoint the exact location of the injection, as well as the dispersion of the cells into the tissues.

The goal is to deliver much greater numbers of stem cells to the injured area than your body can deliver on its own. Our same day procedure is available from our Regenexx Network Providers around the United States.

Regenexx Innovation and Why it Should Matter to You

Regenexx spends heavily on innovation and we have a PhD led lab research team and a physician/bio stats led clinical research team to constantly update what we can offer. A couple of years ago we started various projects to determine if we could come up with a way of processing bone marrow that nobody had ever used. Seeking to double or even triple the number of stem cells extracted in a bone marrow aspiration, we exceeded our own expectations and increased it 500%+ over what we could do before. Using our previous procedure, which was already superior to anything else, we could extract about 3-4 times the stem cells per cc over what the average automated centrifuge could do. This is important, because these little machines are used by 98% of the physicians performing bone marrow stem cell procedures. There is no real technical expertise required to use these machines. You just place the sample in the machine and push the “ON” button. Because of this and the fact that these machines are a one-size-fits-all solution to process very different bone marrow samples from very different patients, it wasn’t hard to outperform these devices. However, our research team investigated many different ways to process marrow. After discarding many, we finally discovered one that was pretty revolutionary. And while extracting more stem cells is a good thing, it doesn’t really make a difference if it doesn’t improve a patient’s procedure outcome.



Clinical data for knee arthritis patients from before and after making the switch to the newest generation of our patented same-day Regenexx procedure.

As you can see from this chart, there were dramatic, statistically significant changes in the LEFS functional scale (knee function) and pain relief with the new process when we compare many treated patients (average follow-up is 5 months). So not only are we getting more stem cells, but we're now getting better results over a procedure that was already superior to anything else being offered.

All Regenexx network providers are offering this procedure and all have been trained in the process. This is our second generation same day stem cell procedure and we're currently working on the third. We're on our third generation platelet lysate (a mix of growth factors isolated from platelets) and working on our fourth. We're on our second generation platelet rich plasma (Super Concentrated Platelets) and working on our third. This innovation is something you'll never see from small clinics offering stem cell procedures using inferior technology. At Regenexx, we're focusing 100% on orthopedic stem cell and platelet procedures that produce the best possible outcomes for our patients.

Why Regenexx is VERY Different

The Regenexx® Cultured Stem Cell Procedure (Cayman Islands Only*)

Regenexx®-C is a cultured stem cell procedure that is available only in the Cayman Islands. While our same-day stem cell protocol (described above) is the premier stem cell treatment available in the United States, some patients may benefit from the expanded numbers of cells that are delivered by a cultured stem cell procedure.

During part 1 of the Regenexx-C procedure, a patient's own bone marrow stem cells are extracted and harvested. Using a proprietary lab technique, the cell biologists at Regenexx Cayman then grow these cells in a state-of-the-art facility.

Typically, a patient's cells grow to 100-1,000 times more than what was initially harvested, and if there are extra stem cells, they can be preserved for future use.

The re-injection cycle normally takes place 4 – 6 weeks after your bone marrow aspiration (BMA). During this time, your cells are grown for approximately 10 days and then tested for quality assurance, including sterility testing and karyotype analysis to ensure there are no genetic abnormalities present in your stem cells. Once your cells have passed all safety and quality testing, you will be contacted with your results and invited to schedule the re-injection cycle.
During part 2 of the procedure, the cultured cells are thoroughly tested for quality assurance and re-injected, using guided imaging, to ensure the most precise placement of cells into the injured area.

More Details

[Disclaimer: The Regenexx same day procedures are performed in the United States. The Regenexx-C cultured stem cell procedure (herein referred to as “cultured”) is only offered through RegenexxCayman, which is an independently owned and operated medical services provider operating exclusively in the Cayman Islands and is not part of or affiliated with the Centeno-Schultz Clinic or any U.S. Regenexx Network provider. The Regenexx-C procedure licensed by RegenexxCayman is not approved by the U.S. FDA for use in the United States.]

The Best Possible Patient Outcomes

Continue to learn why we’re the #1 orthopedic stem cell procedure

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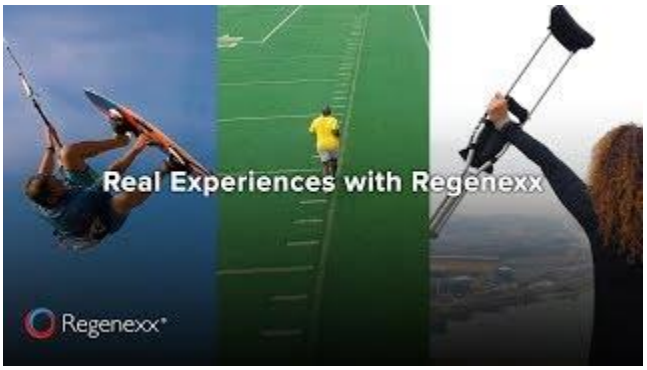
- 

Real Experiences with Regenexx

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What Everyone with a Non Union Fracture Needs to Know

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Regenexx Knee Stem Cell Treatment Helps Patient Return to the Game He Loves

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  Meet Lolly - A Regenexx Spine Procedure Success Story

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  How Stem Cells Saved the Soccer Ref

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- Knee Stem Cell Procedures
- Hip Stem Cell Procedures
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- Non-Union Fractures Treatment

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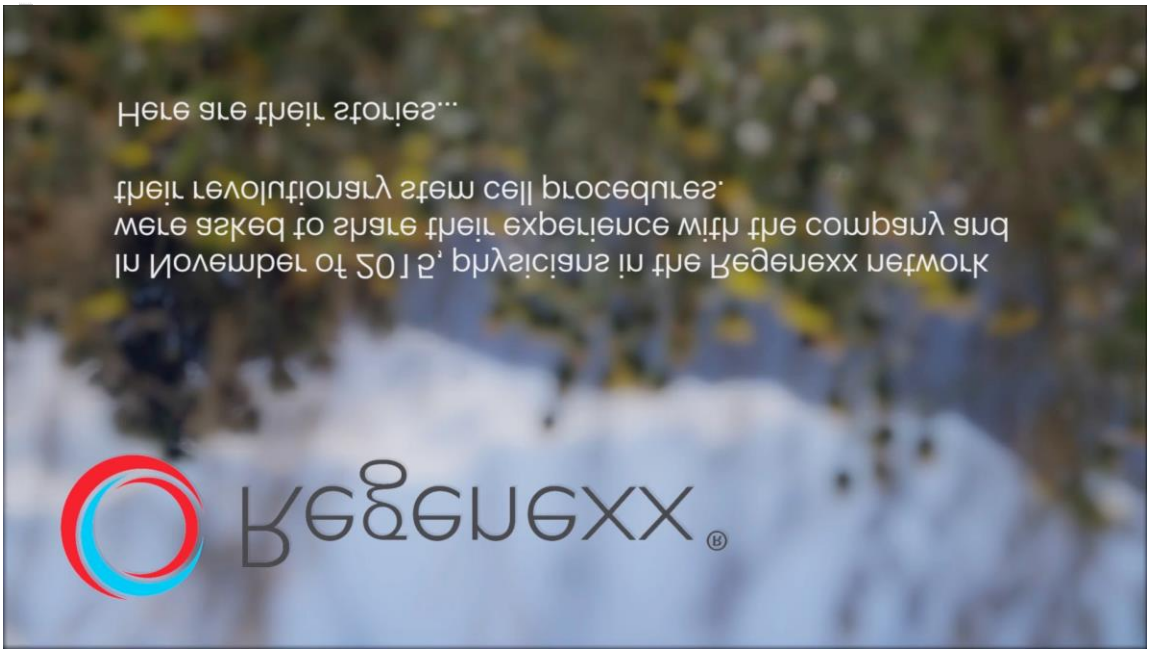
- 

Regenexx Network Physicians

Regenexx is not a product, but a family of medical procedures that define what we consider a new medical specialty-Interventional Orthopedics. Regenexx is also not an add-on to existing surgical procedures, but instead a new way of approaching orthopedic problems.

We are looking for a few well trained, board certified musculoskeletal medicine specialists to join our exclusive network. Joining the network involves extensive training and most providers who apply are not accepted due to lack of basic training in interventional orthopedics (fluoroscopy and MSK US guided injection based procedures). In addition, the ability to perform an in depth, complex musculoskeletal exam lasting more than 25-30 minutes of hands on time with the patient is required or must be learned. This includes the ability to quantify problems of stability, nerves, muscles, joints, and body symmetry.

Do you have the skills to join our growing team of providers? Fill out the form below to find out.

Regenexx® Physician Network Information

First Name * This is a required field

Last Name * This is a required field

Email *You have not given a correct e-mail address

Cell Phone

Physician Specialty * This is a required field

Country * Please select one

U.S. Physicians Only Please Enter Business Zip Code

Please enter the above code:

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CANDIDATE FORM

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How Regenerative Medicine & Interventional Orthopedics Will Change Everything

3rd Edition

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