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Review article

# Concepts in regenerative medicine: Past, present, and future in articular cartilage treatment

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ABSTRACT

Regenerative medicine is emerging with great interest and hope from patients, industry, academia, and medical professionals. Cartilage regeneration, restoration, or repair is one of the prime targets that remains largely unsolved, and many believe that regenerative medicine can possibly deliver solutions that can be widely used to address the current gap(s) in treatment. In the United States, Europe, Australia, and India the regulation of regenerative based treatments has become a big debate. Although the rules and regulations remain unclear, clinicians that are interested should carry-on with the best available guidelines to ensure safety and compliance during delivery in clinical practice to avoid regulatory infraction. Many have made significant investment of time, resources, and facilities in recent years to provide new regenerative treatment options and advance medical care for patients. Instead of reinventing the wheel, it would be more efficient to adopt currently accepted standards and nomenclature borrowed from transplantation science, and cord blood storage industries. The purposes of this article are to provide some historical background to the field of regenerative medicine as it applies to cartilage, and how this field has developed. This will be followed by a separate discussion on regulatory oversight and input and how it has influenced access to care. Furthermore, we discuss current clinical techniques and progress, and ways to deliver these treatments to patients safely, effectively, and in a cost sensitive manner, concluding with an overview of some of the promising regenerative techniques specific to cartilage.

## 1. Introduction

Regenerative medicine is emerging with great interest and hope from patients, industry, academia, and medical professionals alike. The opportunity to cure un-curable or difficult to treat disorders and diseases captures and fuels momentum by most stakeholders to provide solutions for the today and the future. Cartilage regeneration, restoration, or repair is one of the prime targets that remains largely unsolved for which regenerative medicine can be a solution and address the current gap(s) in treatment.

The definition of regenerative medicine is the treatment of medical conditions that harnesses the human body's inherent ability to regenerate a tissue at the level of cellular or organ structure, that foster cellular communication, translation, organ system refurbishment, and result in overall organism well-being. Strategies of treatment include healing response, genetic influence/modification, external stimulus, cellular signaling, exogenous augmentation. Therefore, organ and tissue engineering will be excluded, however will include regeneration that may or may not include cellular transplantation.

Although it may not seem apparent, the underlying purpose of regenerative medicine may not be just for curing a disease, but for the perfection of human organism, and possibly physical immortality.[1] However, standing in the way of progress in the developed world are regulatory barriers that may or may not be appropriate for these treatments. The rapid expansion of the field has outpaced regulation and existing rules have provided little guidance for both clinicians and scientists on the best way to proceed. Unfortunately, organization in the required processes for determining who are good candidates for treatment, candidate

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evaluation and initiation, informed consent, sample collection and handling, cellular processing, standard operating procedures (SOPs), treatment administration, outcomes, reporting, and adverse events are still being established leaving the regulators in a precarious position of balancing the protection of patients between clinical progress.

The purposes of this article are to provide some historical background to the field of regenerative medicine as it applies to cartilage, and how this field has developed. This will be followed by a separate discussion on regulatory oversight and input and how it has influenced access to care. Furthermore, we discuss current clinical techniques and progress, and ways to deliver these treatments to patients safely, effectively, and in a cost sensitive manner, concluding with an overview of some of the promising regenerative techniques specific to cartilage.

## 2. History of regenerative medicine-cartilage

Although we may not recognize, regenerative medicine as far as addressing cartilage of synovial joints is concerned has dual origins. Non-operative treatment finds its foundations back to 1930s with a Philadelphia general surgeon' self treatment of a thumb injury with "proliferative" or sclerosing agents and later the treatment of painful hypermobile joints.[2] Shortly after, in 1940s surgical treatment to address osteoarthritis was described with the extensive debridement of osteoarthritic knee joints as described by Magnuson.[3] The procedure involved removal of synovium, loose cartilage, and osteophytes thus prompting a "healing response", and this procedure was used for many years until supplanted by formal arthroplasty. In 1950s again, on separate fronts regenerative promoting procedures were described. In America, Hackett (1956) thought that peripheral joints that became painful were a result of axial instability and referred neural input with loss of muscular and ligamentous control, and has laid the foundation for prolotherapy in the treatment of arthritic joints.[4] Almost simultaneously in the United Kingdom, Pridie expanding on the previous work of Magnuson, at the British Orthopaedic Association (1959) and presented a technique of closely spaced multiple drilling of knee arthritic articular cartilage defects to promote a regenerative response. Although complete clinical outcomes were not presented initially, Insall in 1974 for 60 patients, the procedure was successful in selected patients.[5,6] Microfracture is another healing response treatment, but was created to treat full-thickness cartilage injury in contrast to arthritis as Pridie drilling was intended. The initial technique was described in 1994,[7] however the clinical results from treatment were reported from 1981, by Steadman et al. much later with average 11-year follow-up demonstrating clear clinical utility.[8] Other investigators eventually reported their results which revealed smaller lesions located on the femoral condyles, and trochlea appeared to be the best to treat with this method. Large, multi-focal, and/or patellar lesions still presented a treatment dilemma. Around the same time, another method of cartilage repair called autologous chondrocyte implantation and the use of bone marrow derived cells to regenerate knee articular cartilage was published.[9,10] The first technique involved culture expansion of knee articular chondrocytes, re-implantation below a periosteal patch.[9] The second technique specifically used culture expanded bone marrow derived cells[11] (CE-BMDC) that demonstrated excellent short-term safety, and efficacy to autologous chondrocytes for focal cartilage lesions.[12] Concurrently, identification, characterization and mechanism of mesenchymal stem cell[13] was described by Caplan who coined the term "MSC." Many describe him as the "Father of Mesenchymal Stem Cell" and who reported that perivascular adluminal cell or pericyte surrounds all blood vessels, and that all pericytes are MSCs.[14] Later, cell augmented marrow stimulation procedures (microfracture and/or drilling) of both focal lesions as well as arthritis with concentrated bone marrow aspirate (BMAC), adipose-stromal vascular fraction (A-SVF), CE-BMDSC, culture expanded-adipose derived stem cells (CE-ADSC), peripheral blood stem cells (PBSC), and many other sources.[15,16] As the drive to improve continued, and patient desires for minimally invasive procedures, the age of Regenerative Injection Therapy (RIT) was born, largely by the advances of Linetsky who coined the term and is considered to be the originator of "Regenerative Injection Therapy or RIT".[17,18] Dr. Linetsky continued the initial work of prolotherapists (Gedney, Hackett, and Hemwall).[19,20] This progression consisted of injecting all sorts of agents that induce a biological response, including: dextrose, sodium bicarbonate/calcium gluconate, hyaluronic acid, platelet rich plasma (PRP), bone marrow aspirate concentrate (BMAC), nano or micronized fat, adipose-stromal vascular fraction (A-SVF), culture expanded meschymal stem cells (CE-MSCs) both allogenic as well as autologous from a multitude of sources are becoming more commonplace.[16] The aggregate number and quality of studies are steadily improving, it is no doubt that the application of the cells are safe[10,12,21,22] and efficacious.[16]

## 3. Regulatory implications facing cartilage regenerative medicine

In the United States, Europe, Australia, and India the regulation of regenerative based treatments has become a big debate.[23–28] Although the rules and regulations remain unclear, clinicians that are interested should carry-on with the best available guidelines to ensure safety and compliance during delivery in clinical practice to avoid regulatory infraction.[29] While ill-defined regulation encourages experimentation and novel clinical application, efficacy and patient safety concerns are a real concern.[30] Additionally, strict regulation strangles innovation and clinical implementation yet provides the proof of safety and efficacy, prior to routine use. However, put into perspective, in consideration of the bulk of regenerative medicine experimental and clinical work, that involves interspecies organ transplantation, genetic modification,[31,32] to ultimately create human bodies in bioreactors[1] (Fig. 1) in comparison at worse to the clinical use of culture expanded autologous cells stem cells with a long-term proven safety record is curious.

The practice of medicine requires physicians to constantly innovate and update to improve patient care. On the surface, the benefits of strict regulation providing patient safety and efficacy seem worthwhile however; due to the individual and personalized nature of these treatments, it is quite difficult to establish protocols and procedures for treatments with conclusive and generalizable evidence. Currently, within the United States, the Food and Drug Administration (FDA) utilizes an outdated and inappropriate pathway for the ability of clinicians to utilize stem cell therapies in humans that is more akin to approval processes for conventional pharmaceuticals (Fig. 2). To date there has not been any stem cell product widely available despite extensive clinical trials.[33] After defining case upheld in the Washington, D.C. US Court of Appeals in 2014,[34] the basic conclusion is that an individual's cells are drugs, and only cellular products that have made it through exhaustive clinical trials after investigational new drug application (IND) can be used, and only after a biologic license is granted. There appears to be great coordination between the FDA and the European Medicines Agency (EMA) and current outstanding draft guidance(s) under debate pertaining to 21 CFR 1271 for same day procedures in the USA include: homologous use, surgical exemption, use of adipose tissue, minimal manipulation; and EU Regulation 1394/2007 classification of advanced medicinal therapeutic products (ATMPs)-homologous use, minimal manipulation, and hospital exemption.[35–38] The basis for intervention has been

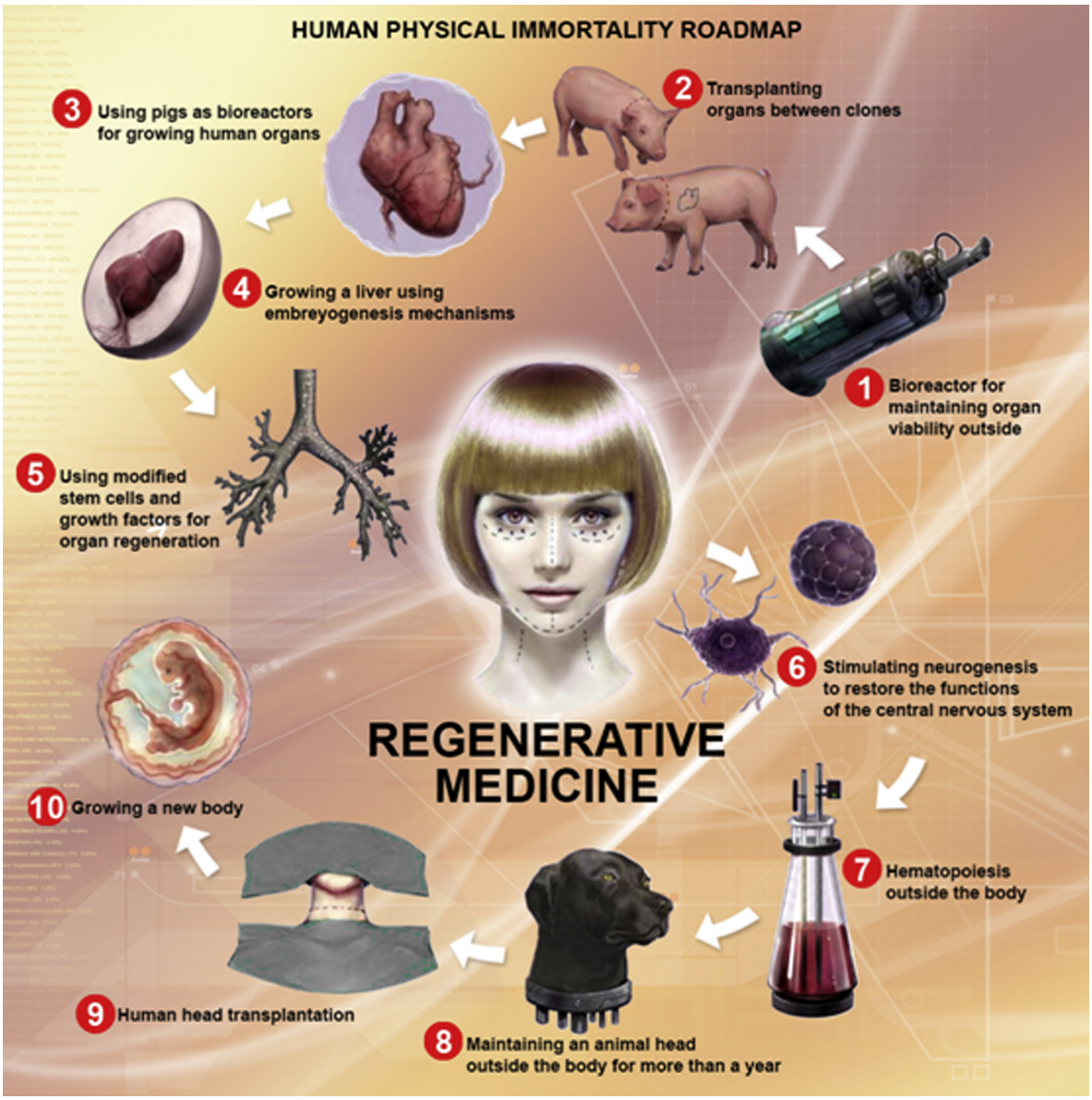


**Fig. 1.** Pathway for human physical immortality harnessing regenerative medicine.

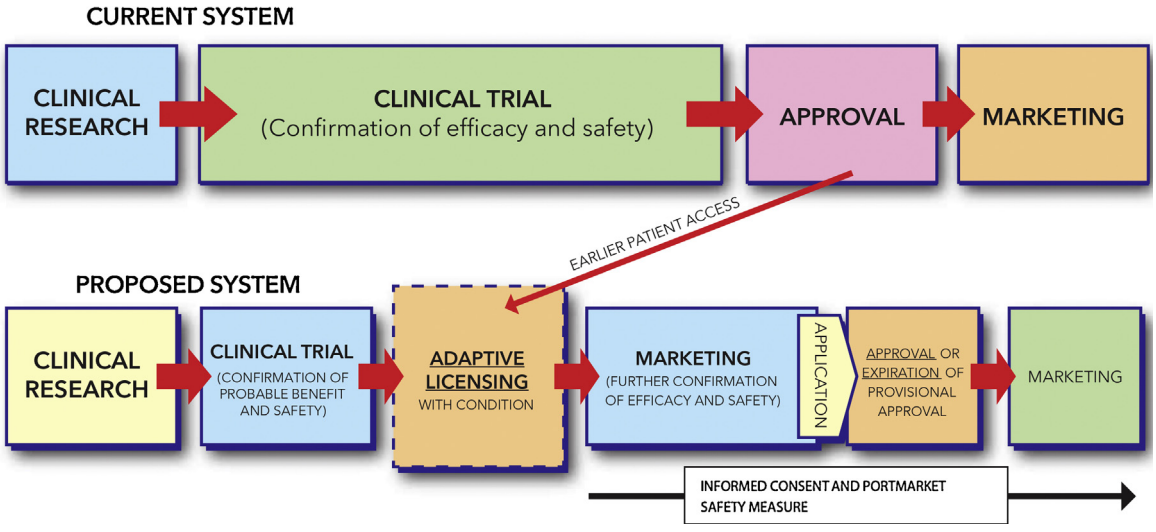


**Fig. 2.** Current and proposed systems of pharmaceutical drug and regenerative medicine therapeutic approval pathway.

the interpretation of stem cell therapies as high-risk biologic treatments despite data to the contrary.[10,12,21,22,39] Although an increasing number of warning letters to multiple clinics have been sent by the FDA, there are still numerous facilities that are operational and offering a full range of treatments to include administration of culture expanded cells, SVF delivered by intraarticular, intravenous, epidural, intra-discal, as well intrathecal transplantations. The US-FDA divides biologic therapies into low-risk and high-risk therapies by determining if the product has undergone minimal manipulation and autologous use (Fig. 3).[40] Additionally, the product is assessed for tissue combined with another product and whether the cells perform the same function transplanted that it does in the original harvest site. If a biologic does not meet these criteria, then the FDA requires that a treatment proceed through a developmental process outlined/observed by the FDA, which is similar to the process for a pharmaceutical validation as previously mentioned. The pathway involves pre-clinical animal trials and phases of clinical study before availability in clinical practice (Fig. 2) Following legislative inquiry, the FDA has softened its position after United States House of Representatives (HR) 4767 and Senate 2689, the Reliable and Effective Growth for Regenerative Health Options that Improve Wellness Act (REGROW) was proposed, that appears to adopt a more progressive pathway in the approval process for biological products that are not exempted from the regulations. However, upon closer look, it does not appear that the legislation will enable clinical practitioners the ability to bring forward personalized biological medical treatment, even if evidence indicates low risk as the costs to navigate the pathway remain prohibitively expensive. Even with this legislation, a significant hurdle remains for stem cell technologies in the United States while some countries follow FDA with restrictive regulatory mechanisms. In South Korea, and Japan the governments have taken a proactive stance on stem cell therapy regulation. While Japan's pharmaceutical drug pathway closely resembles the United States, they recently have labeled stem cell technologies as "regenerative medicine products," setting them apart from pharmaceuticals. A proposed approval system for these products allows for early-observed commercialization with further approval contingent upon studies confirming efficacy and safety (Fig. 2).

## 4. Safe delivery of regenerative medicine programming

Many have made significant investment of time, resources, and facilities in recent years to provide new regenerative treatment options and advance medical care for patients. Instead of reinventing the wheel, it would be more efficient to adopt currently accepted standards and nomenclature borrowed from transplantation science, and cord blood storage industries.[41,42] In this section, a discussion of adaptable nomenclature and standards will be discussed in detail for application in musculoskeletal (MSK) regenerative medicine.

Although the terms used to describe much in MSK regenerative medicine are well established such as PRP, BMAC, stem cells, the consideration of the use of terms currently accepted by worldwide regulatory bodies may prove to be more prudent, as far as being recognized as acceptable treatment. It would be very easy to amend and supplant current descriptors, and substitute for them; HPC or hematopoetic progenitor cells, is a term that is recognized by most regulatory bodies worldwide, and have accepted labeling product codes created by the most frequently used labeling system, ISBT-128.[43] The ISBT 128 is a global standard for identification, labeling, and information transfer of medical products of human origin that includes cells, blood, tissues, milk, or organ products.[43]

HPC includes HPC-apheresis synonymous with PRP and or BMAC, HPC-cord blood, HPC-adipose tissue, and HPC-stromal vascular fraction (SVF). What is being done in MSK regenerative medicine is essentially cellular transplantation. HPC transplantation is allowed and approved for hematologic purposes and non-hematologic purposes, especially if they are autologous. Cellular transplantation has been carried out for many decades, and has been successful in many medical disciplines. If adopted by MSK practitioners, the pathways for use would be more accepted by regulatory bodies and third-party payers.

There are many organizations that have the ability to accredit both processing facilities, and treatment programs in the MSK regenerative medicine space. The American Association of Blood Banks (AABB) is one accrediting body for cellular based therapies, and established pathway is approved by the FDA. The cellular therapy accreditation process is highlighted by the following

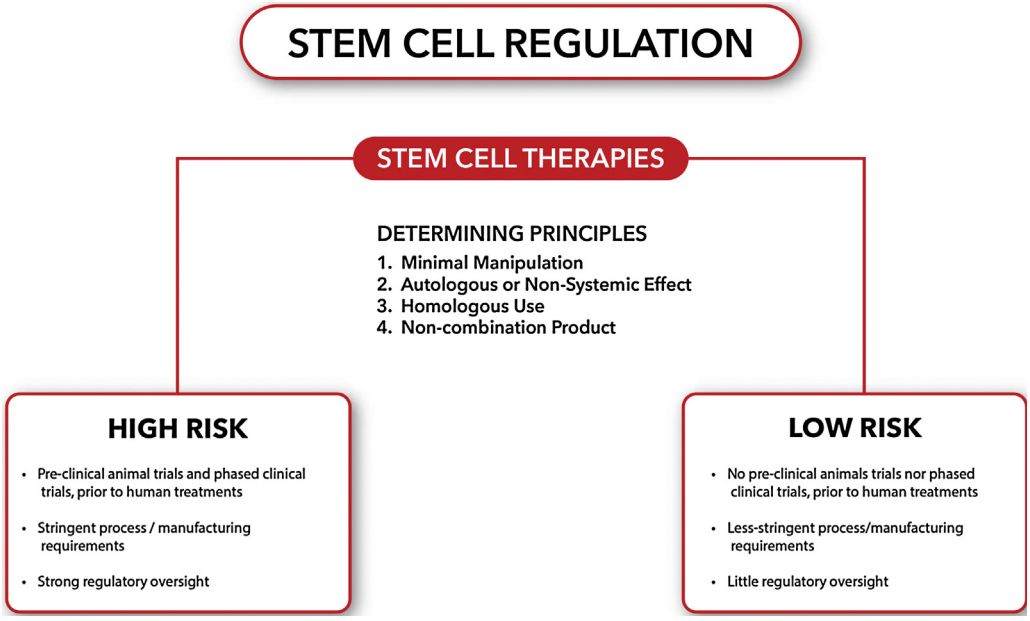


**Fig. 3.** Stem cell regulation risk designation.


**Fig. 4.** Accreditation of cellular therapies pathway.

documented steps: organization, equipment, resourcing, agreements, processing, records, deviations and non-conforming products, internal and external assessments, continual improvements, safety and facilities (Fig. 4).[43] Just like many other accreditation processes, many of the steps may appear to be redundant, and not salient to current practice focus, however the real benefit of the process is to encourage better documentation, easily reproducible processing, standardized patient treatment program entry, safety, and in the end, more consistent product. Improving consistency of products, will result in more reliable and uniform patient outcomes with less adverse events.[43]

Control documentation standardizes all policies and procedures pertaining to every aspect of the organization, personnel, processing, and treatment programming. When clear, concise, and updated documents are maintained and followed, the results are very consistent and reproducible products with minimal chances for errors in any phase of processing or treatment. If it is not clear at this point, documentation is the key underlying functional characteristic of successful regenerative medicine programming. More specific functional areas for program development are presented in Table 1.

Once a particular cellular therapy platform is chosen to pursue, the next step is to create and document the team. At a minimum it is recommended that roles of medical director, quality consultant or manager, scientist, and project coordinator be filled with unique individuals. It does not mean that these positions need to be full time, but just that they are uniquely filled. Optional personnel include a regulatory expert, attorney, and business manager. Support staff is routine, as in any clinical operation, however consideration of laboratory personnel may be a consideration based on the type of platform that is pursued. Once the team is assembled further documentations are required and consists of creating an organizational chart, employee files, document defining personnel roles, and initiating training programs for all personnel.

The minimum standards for patient assessment and entry into a cellular therapy treatment program are a four-part process. First, any candidate is assessed for eligibility. This includes review of current/previous treatments, current diagnosis, and past medical conditions. Next, patient screening is done and includes standard battery of validated infectious disease labs (Table 2), and testing for emerging diseases, even if autologous treatments are contemplated, and has to be done without exception to be compliant with regulations. From a medical prospective this highlights the candidates' general health, and protects both staff and patients from undesired adverse events. This is true even for simple same day procedures like HPC-apheresis (PRP), the laboratory investigations have to have been completed within the past 3 months to be compliant. Additionally the individual test kit used has to be approved by the designated regulatory body for the country, in many countries this requires FDA or CE designation.[44] Next, patient education is carried out to provide a complete understanding of the process to the patient.[43] The prospective patient has to be able demonstrate complete understanding of the entire treatment, and an opportunity to have questions answered at anytime, along with emergency contacts and facilities has to be documented. The final step includes informed consent, the most important piece of patient assessment and entry into a cellular therapy program. The consent has to highlight expected outcomes, along with realistic detailed risks and benefits and no false or unsubstantiated claims.[43]

A quality management system is instituted in all programs from their inception as it is the key process that ensures consistent, properly handled, and defined products. The system starts even before a sample is taken from a candidate. It defines the minimum facility requirements based on the type of cellular product that has been selected. The system provides control documents that describe the SOPs for each step of vessel labeling, sample collection, transportation, logging, processing, characterization, and patient administration.[43] A good control document is living,

**Table 1**
Basics for program development.

| Documentation | Team development | Team organization |
|---|---|---|
| Develop criteria for patient assessment | Develop criteria for patient entry into treatment program | Detailed consent |
| Define minimum facility requirements | Control documents | Outcomes monitoring |

**Table 2**
Testing requirements for patient assessment and entry into cellular therapy treatment program.

| Test | CLIA applicability |
|---|---|
| FDA-required testing for communicable diseases (HIV types 1 and 2, Hepatitis B, Helpatits C, *Treponema pallidum*, HTLV types I and II, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) | Yes |
| FDA-required testing for emerging infectious diseases | Yes |
| Purity and potency testing (TNC, CD34 and other cell phenotype assays, cell viability, CFU) | No |
| Outsource lab | Yes |

CLIA – the clinical laboratory improvement amendments regulate laboratory testing and clinical laboratories to be certified by their appropriate state or country regulatory body before they can accept human samples for diagnostic testing.

and it takes into account all possible eventualities, in short it takes away any guesswork. Specific to environment or facility is concerned, if closed systems or industry kits are used for example to prepare HPC-apheresis (PRP), then a normal treatment room where injections would be performed is sufficient. If it is desired to decrease cost to produce cellular products, this can be done, however regulations clearly stipulate the type of environment required is based on the risk associated with the production, manipulation, and handling of the product. Manual HPC-apheresis (PRP) can be produced at very low cost, however the facility has to be upgraded, and the processing should occur at a minimum in a Type II biological safety cabinet.[43] If further manipulations are desired such as culturing, cellular pre-treatment (hypoxic, $CO_2$ rich, low temperature) either an approved clean room, or self-contained biological unit is required. Once the sample is taken from the subject, it must be properly logged in and labeled in accordance with the ISBT rules, which will assign both patient data, as well as unique product information (Fig. 5) on a barcode. However; it does not stop here, characterization of the injectate is required. For platelets, kit manufacturers can give close estimates of the concentration of platelets produced after using their proprietary systems as a multiple of baseline platelet concentration. If a standard complete blood count is drawn at the same time as the sample collection for preparation, a good estimate of actual platelets administered can be documented.

$$\text{Platelet number} = \text{Baseline concentration(plts/ml)} \times \text{ml administered} \times (3-17 \times \text{baseline concentration}) \times (\text{depending on system used})$$

Alternatively, if budget allows, a hemocytometer can be used, and with dilution, an exact number of platelets can be calculated. At a minimum, for bone marrow aspirates, nucleated cells per high-powered field can be manually counted with a microscope. Cell count and differentials can be calculated along with cell viability. To calculate an approximate number of stem cells present in an aspirate, or concentrated aspirate the monocyte layer percentage is multiplied by the total cell count to obtain the aggregate mononuclear fraction, and about 5% of this layer are MSCs. The numerical range of MSCs for 60 cc of bone marrow aspirate concentrate is between 10,000 and 100,000 MSCs in a 10 cc injectate. Additional characterization can be done culturing samples and plating cells on growth media and counting colony forming units–fibroblast (CFU-F), and/or performing flow cytometry on samples to numerate, and qualify the cells present. The final element of the quality management system is the process of recording subject outcomes, non-conforming product deviations and reporting, and adverse effects.[43] Many would recommend the creation of a treatment registry, so that patient outcomes are more easily tracked, and all pertinent data maintained for ease of access, especially if external auditing of policies, procedures, and operations are done on an annual or biannual basis.

## 5. Cartilage repair in regenerative medicine

The study of regenerative medicine applications within the realms of cartilage repair and treatment of symptomatic cartilage degeneration is vast. Basic science in vitro, laboratory studies and in vivo animal studies have demonstrated great promise, however for the purposes of this discussion the focus will be on current and proposed applications in humans. The use of MSCs for cartilage repair has a relatively long track record of limited use, with a good safety record to support further use with.[10,12,21] Additional cartilage repair techniques involving stem cells are in the early


**Fig. 5.** (A) Entry portal for clean room sample login. (B) Manual logging of biological sample. (C) ISBT 128 product barcoding verification process. (D) Biological safety cabinet processing of regenerative samples.

**Table 3**
Summary of the use of stem cells to augment cartilage repair or regeneration not inclusive of tissue engineered products.[16]

| Study | Year/Journal | # Patients | Result |
|---|---|---|---|
| Saw et al.[45] | 2013/Arthroscopy | 50 | Level 2-SCD followed by PBPC + HA (LMW) vs HA, 6 sequential week injections, 2 h CPM, PWB. Biopsies at 18 M sig ICRS-2 Scores, MRI 24 months significant difference in quality. No other measures different. *80% Biopsies in both group. |
| Nejadnik et al.[48] | 2010/AJSM | 72 | Level 3-ACI vs Culture-BMD-MSCs – Greater improvement over time in the BMD-MSC group (24 M), otherwise no difference. BMD-MSCs less cost, single surgery-open under periosteal flap. |
| Lee et al.[12] | 2012/AAMS | 70 | Level 3-Marrow stimulation + BMDSCs + HA had comparable results vs BMDSCs + periosteal patch, but less invasive, 24-month follow-up. |
| Wakitani et al.[10] | 2011, JTERM | 41 | Level 4-Safety and long term AE. CD. No tumors/infection 11.5 years. 31/41 (76%) F/U |
| Koh et al.[47] | 2016/Arthroscopy | 80 | Level 2-MFx + SVF vs MFx. Significant difference MOCART-24 M, KOOS-pain and sport, ICRS-2 mean score. Bx >40%. |
| Freitag et al.[46] | 2015/Personal communication | Ongoing | RCT Modified subchondral drilling with HA; with and without culture expanded adipose derived stem cells administered over time. Adaptation of the SAW trial. |
| Skowroński et al.[51 a] | 2012/Orthop Traumatol Rehabil | 52 | Level 3-PBSCs covered by collagen membrane. No adverse events, improvement in all clinical scores at 12 M. Outcomes poor in 2 patients at 1 year. At 72 M minor deterioration of condition in 2 additional patients. |
| Skowroński et al.[52 a] | 2013/Orthop Traumatol Rehabil | 46 | Level 3-BMC-21 vs PBSC-25, superior results in the PBSC group. Slight drop in clinical scores in both groups at 60 M. |
| Sekiya et al.[53 a] | 2015/Clin Orthop Relat Res | 10 | Level 3-48 M follow-up for use of SDCS surgically delivered that showed clinical improvement, good MRI findings, good histology in 3 out 4 biopsies. |

*Abbreviations*: SCD, subchondral drilling; PBPC, peripheral blood progenitor cell; HA, hyaluronic acid; LWM, low molecular weight; h, hour; CPM, continuous passive motion; PWB, partial weight bearing; M, month; ICRS, international cartilage repair society; MRI, magnetic resonance imaging; ACI, autologous chondrocyte implantation; BMD, MSCs-culture expanded bone marrow derived mesenchymal stem cells; SCs, stem cells; MFx, microfracture; SVF, stromal vascular fraction; CD, chondral defect; MOCART, magnetic resonance observation of cartilage repair tissue; Bx, biopsy; RCT, randomized controlled trial; PBSC, peripheral blood stem cells; BMC, bone marrow concentrate; SDCS, synovial derived cultured stem cells.
[a] Study source.

phases of clinical development. Modified arthroscopic subchondral drilling with multiple peripheral blood progenitor cell injections has histology supporting a high quality of repair tissue and Level II data suggesting superiority to subchondral drilling alone. This technique utilizes G-CSF mobilized hematopoietic progenitor cells harvested by apheresis and cryopreserved for repeat injections over long timeframe.[45] Further, randomized controlled study is underway. Another study underway using culture expanded adipose derived stem cells instead of peripheral blood progenitor cells utilizing the Saw surgical technique described above.[46] Another application of stromal vascular fraction (SVF) combined in a fibrin glue scaffold to augment microfracture, recently reported a comparative study to microfracture alone. The stem cell group illustrated superiority in certain KOOS subsets and MRI evaluation; similar structural repair tissue was seen upon histologic evaluation however overall statistical difference in favor of the SVF group.[47] A model involving cultured expanded bone marrow derived stem cells has also been developed and compared to first generation autologous chondrocyte implantation (ACI). The Singapore group first studied an open method with a periosteal patch for implantation with similarity to ACI upon study.[48] A second follow-up study compared a scaffold-less model involving arthroscopic microfracture and one postoperative injection demonstrated superiority to the open method.[12] Correction of mechanical malalignment, such as varus, with high tibial osteotomy has shown to be instrumental in combination with stem cell augmentation.[49,50] Table 3 outlines all the studies discussed above, and a few additional studies that have used stem cell related products without tissue engineering with at least 10 patients in the investigation.[16]

## 6. Conclusion

In conclusion, although regenerative medicine has established its importance in the field of medical science, gaps in the practice of this treatment are due to developmental delays of protocols and standards for the assessment and management of a disorder, processing of products, therapeutic administration, and clinical monitoring. Streamlining of concept to clinical solution can be done with more flexible regulation that allow for more accessibility for non-pharmaceutical clinical entities to continue to deliver more personalized and precise autologous medicinal products with limited approvals. This pathway can encourage higher-level studies and trials to provide additional on-going evaluation of the safety and efficacy of cellular therapy regenerative medicine treatments of articular cartilage before final approvals are granted.

## Conflicts of interest

The authors have none to declare.

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