ePlasty

*Program Overview:*

# Consensus Panel Recommendations on the Use of Placental-Based Allografts in the Surgical Setting

# Program Overview:

## Educational Need

The long history associated with the use of placenta materials across medical disciplines contributes to advancing knowledge of the application of human placental-based products (PBAs) in the surgical setting. Challenges faced by surgeons in multiple areas of practice include educational gaps related to identifying patient candidates for PBA use with attention to comorbid conditions, determining surgical procedures best-suited for PBAs, understanding ways to properly integrate and optimize placental-based products, evaluating the costs of treatment, and a lack of published guidelines and algorithms. Surgeons can optimize healing, improve patient outcomes, and reduce the incidence and costs associated with complications by introducing the use of placental-based tissue allografts into surgical practice.

## Learning Objectives

- Examine up-to-date recommendations and algorithms, defined by expert opinion, to address treatment gaps related to the use of placental-based allografts in the surgical setting
- Determine the appropriate candidates for PBAs
- Determine which surgical procedures are appropriate for the use of PBAs
- Determine how to optimize their use
- Evaluate the economic impact and cost implications associated with the use of PBAs in the surgical setting

## Target Audience

This activity was designed for physicians and nurses involved in burns, tissue repair, vascular surgery, dermatologic surgery, surgical wound healing, and plastic and reconstructive surgery.

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# Consensus Panel Recommendations on the Use of Placental-Based Allografts in the Surgical Setting


## Abstract

The use of placental-based allografts (PBAs) to promote positive patient outcomes in the surgical setting is bolstered by years of evidence-based data involving PBAs in chronic wound treatment and specialty surgery applications such as ocular surgery. Even so, challenges faced by surgeons across surgical disciplines include educational gaps related to identifying patient candidates for PBA use with attention to comorbid conditions, determining surgical procedures best-suited for PBAs, understanding ways to properly integrate and optimize placental-based products, evaluating the costs of treatment, and a lack of published guidelines and algorithms. To address the educational gaps, a webinar presentation titled "Expert Consensus Panel Recommendations on Use of Placental-Based Allografts in the Surgical Setting" was released on July 23, 2021, by North American Center for Continuing Medical Education LLC, an HMP Global company, supported by an educational grant from MiMedx. This article reviews the webinar information presented by the 6-member program faculty consisting of surgeons practicing in general and colorectal, obstetrics and gynecology, reconstructive, foot and ankle, limb salvage, and vascular surgery. Key insights from this event and relevant literature review are presented in the discussions on the wound healing cascade, PBAs and their mechanism of action, product information, surgical setting applications, and cost-effectiveness.


Placental-derived human amnion/chorion tissue is rich in regulatory proteins with hundreds of tissue growth factors, inflammatory chemokines, inflammatory cytokines, proteases, and protease inhibitors, that contribute to the recruitment of stem cells and support essential physiological healing processes of inflammation, angiogenesis, and fibrosis involved with regenerative wound healing and tissue repair.[1] The value of regenerative medicine and amniotic products in wound healing, demonstrated in a growing body of literature including randomized controlled trials, carries over to the surgical setting as the use of placental-based allografts (PBAs) contribute to rebalancing the wound bed to facilitate the healing cascade.[2,3] While not every surgical patient or surgical procedure requires adjunctive interventions such as the use of PBAs, patients with comorbidities and other complicating factors that can impair healing may benefit from PBAs, which can help maintain balance of biomolecules and facilitate healing vs promoting tissue degradation.

Maintaining the biomolecular balance is evident in the 28:1 ratio of tissue inhibitors of metalloproteinases to matrix metalloproteases (MMPs) found in the composition of placental-based tissue products, specifically dehydrated human amnion/chorion membrane (dHACM), thereby encouraging a healthy wound environment.[3,4] The high ratio of MMP inhibitors to MMPs is essential in closing both acute and chronic wounds faster, whereas elevated levels and extended exposure to MMPs lead to extracellular matrix (ECM) degradation and impaired healing.[5]

Adjunctive use of placental-based tissue products in patients with substantial pre- and postsurgical wounds, complicated further by impaired healing due to comorbid conditions, can improve wound healing as the interrelated healing processes of inflammation, angiogenesis, vascular regeneration, ECM formation, and remodeling are promoted.[6] PBAs and related products do no harm and only benefit the healing of wounds in the surgical setting. However, establishing and maintaining a wound environment conducive to healing extends beyond simply applying PBA products and is partly based on the clinician's evaluation and subsequent integration of patient-, wound-, and procedural-specific factors.

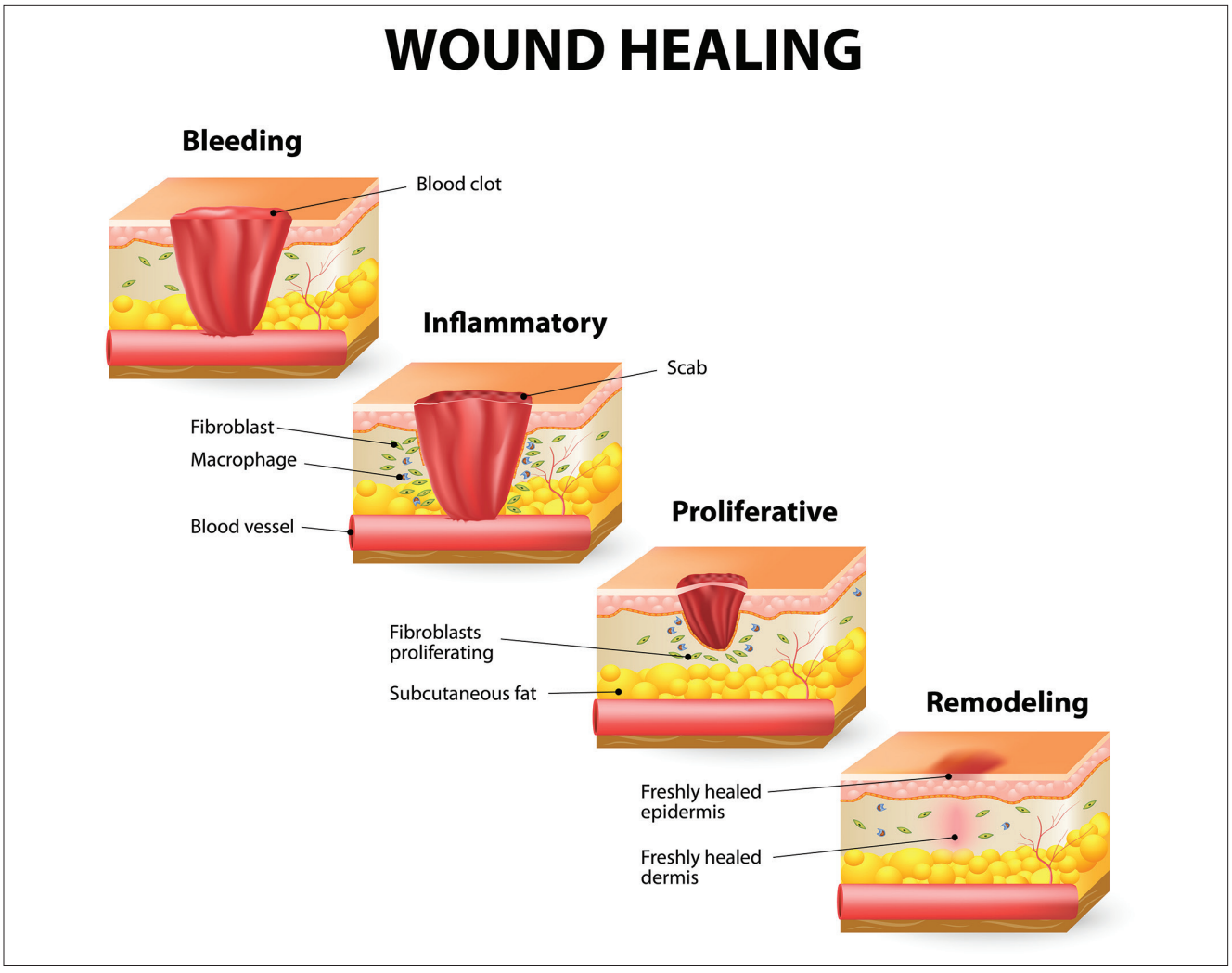


Figure 1. Healing of Normal Wounds

*Source: shutterstock/Designua*

## METHODS

"Expert Consensus Panel Recommendations on Use of Placental-Based Allografts in the Surgical Setting" was released on July 23, 2021, provided by North American Center for Continuing Medical Education, LLC, an HMP Global Company, and supported by an educational grant from MiMedx.

This consensus panel presentation consisted of 6 experts from the surgical specialty areas of foot and ankle, obstetrics and gynecology, vascular, plastic and reconstruction, general and colorectal, and limb salvage. Key points from this event supported by relevant literature are included in this review article.

## RESULTS

***Overview of the Healing Cascade***

An orderly and orchestrated series of events occurs in response to tissue injury that triggers the wound-healing cascade. Complex processes that integrate specialized cells, cell mediators, and signaling processes lead to the four healing phases of hemostasis, inflammation, proliferation, and remodeling. Wound healing begins with hemostasis and the formation of clots through vasoconstriction, platelet aggregation, and coagulation. The inflammatory phase involves the secretion of immunomodulatory cytokines and chemokines that contribute to debridement, cleaning, and resurfacing the wound and preparing the tissue for proliferation and remodeling. The proliferative stage involves angiogenesis, granulation tissue, and re-epithelialization. The remodeling phase involves the deposition of ECM, further tissue remodeling, and wound contraction.[5,7]

As illustrated in **Figure 1**, the healing cascade in normal tissue is a fluid and balanced process as regulatory factors are up and down-regulated during different phases to promote healing.[7] When complications occur, sometimes resulting from comorbid disease states, impaired and delayed healing can result. Chronic wounds that fail

to progress as intended often remain in the inflammatory phase with extended exposure to proteases that disrupt the normal balance and flow of wound healing.[5,7] Adjunctive use of PBAs aids in rebalancing cellular mediators and moving the wound forward in the healing process.

## Placental-Based Allografts Mechanism of Action

Understanding the natural function of the amniotic membrane during pregnancy aids in understanding the mechanism of action (MoA) of PBAs. The amniotic membrane is composed of two primary and distinct layers. The amnion is the innermost layer found along the inner surface of the amniotic sac that surrounds and interfaces with the fetus. The chorion is the outermost layer that interfaces with maternal tissues.[8] The amniotic membrane has the structural integrity to accommodate and support the growth of the fetus through term.[9]

During pregnancy, the seminal fluid elicits a pro-inflammatory response in the ectocervix.[10] Cytokines and chemokines are released, and local recruitment of essential immune cells with a concomitant anti-inflammatory, immunosuppressive response in the endometrium occurs.[10] As the pregnancy progresses, a transition from pro-inflammatory to anti-inflammatory macrophages develops along with regulatory processes that support the immune system in promoting ECM formation and re-epithelialization.[11] The processes that involve the amnion/chorion membrane during pregnancy parallel the processes of wound healing.

PBAs promote angiogenesis with a confirmed presence of many pro-angiogenic growth factors and regulatory proteins, indicating that placental-based products support the wound healing cascade. Research has shown that avascular implants take on the vascular density and healed skin characteristics in about four weeks. Placental-based tissue products produce angiogenic cytokines and growth factors, enable neovascularization, promote local stem cell recruitment, and provide the necessary scaffolding for tissue regeneration.[9,12,13] The actions of placental-based tissue products, when used in wound healing, display similar properties as those that occur during pregnancy.

A further point of interest regarding surgical applications of placental-based tissue products, specifically dHACM. The dHACM semi-permeable membrane allows for greater efficiency in supporting the healing cascade as the ECM and the cells within the membrane are intact. The amnion/chorion membrane contains collagen, elastin, laminin, fibronectin, proteoglycans, and glycosaminoglycans within the intact cells. No acellular material is introduced into the wound area.

## Human Amniotic Tissue Traits

Products made from placental-based tissues provide a ready-to-use adjunct that contains inherent cells and growth factors, provide a cellular matrix that serves as a natural scaffold for tissue growth and cellular proliferation, and improve the overall healing capacity for wound areas, including those relevant to the surgical setting.[14] Other beneficial traits associated with human placental-based tissue products include low immunogenicity, a source of stem cells, biocompatibility, ECM proteins, growth factors and cytokines, anti-inflammatory properties, antifibrotic effects, anti-microbial properties, reduced pain at the application site, low cost, and more.[14] The benefits of using amniotic membrane grafts continue beyond the initial product application. The extended benefits are partly due to the preservation of growth factors and the structure of the ECM following the initial application. Manufacturing procedures used in processing placental tissues to create usable products, such as dHACM and umbilical cord products, have resulted in many products determined to be identical to natural placental-based tissues. The stability characteristics of dHACM and umbilical products suggest that the integrity of the products is maintained for 5 years.[9,15]

**Table 1** contains basic information specific to the products mentioned by the consensus panel faculty. Products included were used by multiple panel members across surgical specialties and in multiple procedure settings. Product characteristics include product information provided by the manufacturer and comments made by the consensus panel faculty regarding their observations from hands-on applications in the surgical setting.

Additional products are available in the United States and globally, with some of those products presented in **Table 2**.[16,17]

## Placental-Based Allografts in Surgical Specialty Settings: Procedural Considerations and Case Examples

The integration of PBAs in clinical surgical practice settings facilitates a paradigm shift toward using biological and regenerative technologies, supplanting concerns of fibrosis with advancing clinical outcomes through regenerative, self-directed healing. Cells, signals, and scaffolds form the basis for PBAs and provide the machinery for their efficacy. In the comorbid patient, placental-based tissue products support the underlying structure with an ECM, stem cell recruitment actions, and the retention of signaling cascades. By employing a biological graft such as a PBA to augment the body's natural response, a certain degree of control can be regained to optimize patient outcomes. Natural biomaterials provide the supporting matrix or scaffolding to interface with host tissue and establish an environment conducive to cellular growth and wound healing. Human amniotic membrane products are biocompatible, have good cellular adhesion, are permeable, stable, flexible, resorbable, and contain growth factors and cytokines that promote tissue repair.[14]

The normal wound healing process may be hindered by factors such as hypertension, hyperlipidemia, poor glycemic control, renal insufficiency, or chronic tobacco use. Risk factors for developing complications include poor blood supply, wound degradation, dehiscence, gangrene, or a prior amputation. A practical approach to managing comorbid patients includes addressing modifiable risk factors. Examples include ensuring glycemic control, maintaining appropriate blood pressure and cholesterol levels, encouraging a healthy diet and non-smoking behaviors, employing wound care

| Table 1. Placental-Based Graft Types and Uses | | | |
|---|---|---|---|
| **Allograft** | **Graft Characteristics** | **Surgical Specialty** | **Procedure Application Examples** |
| Human amnion/ chorion membrane (AmnioFix®) | - A composite amniotic tissue membrane.<br>- Available in multiple sizes.<br>- Available in sheet, wrap, and particulate forms.<br>- Considered a highly adaptable product.<br>- Consists of dehydrated human amnion/chorion membrane.<br>- Can be applied directly over bone to encourage the development of granulation.<br>- Useful adjunct for eventual skin graft procedures. | Foot & Ankle | Peroneus Brevis Repair |
| | | | Lower Leg Mass Pigmented Fibroma |
| | | | Lipoma Attached to Tibia |
| | | | Tarsal Tunnel Release |
| | | Vascular | Large Lower Leg Wound with Anticipated Leg Amputation Avoided |
| | | | Right Femoral Aneurysm and Gangrene- Limb Amputation Reduced to Distal Foot Area |
| | | Colorectal | Anastomotic Leaks |
| | | | Fistula-in-Ano |
| Graft derived from human umbilical cord (AmnioCord®)<br><br>Dehydrated Human Umbilical Cord dHUC allograft (EpiFix®)<br><br>Graft derived from human umbilical cord (EpiCord®) | AmnioCord:<br>- Derived from human umbilical cord.<br>- In a thick graft form.<br>- Consists of an extracellular matrix of hyaluronic acid and collagen.<br>- Manufacturing procedures involve the process of SMR2T™ Technology.<br>- Provides a protective biocompatible environment that aids in the development of granulation tissue that supports the healing process.<br>- High in hyaluronic acid which reduces the incidence of scarring.<br>EpiFix:<br>- Made from dehydrated human amnion/chorion membrane.<br>- Available in sheet configurations in different sizes.<br>- Creates a semi-permeable protective barrier that protects the wound bed and aids in the development of granulation tissue.<br>- Manufacturing procedures involve the process of SMR2T™ Technology.<br>EpiCord:<br>- A thick graft conducive to suturing.<br>- Consists of an extracellular matrix of hyaluronic acid and collagen.<br>- Manufacturing procedures involve the process of SMR2T™ Technology.<br>- Useful in smaller and deeper wounds or surgical sites.<br>- A 2 cm x 3 cm piece expands to 12 $cm^2$.<br>- Conforms to uneven surfaces.<br>- Umbilical cord products are ideal for graft fixation when needed.<br>- Greater tensile strength provided by the product promotes healing.<br>- Holds stitches well.<br>- The additional thickness facilitates challenging wound closures.<br>- Can be used in deeper structures. | Foot & Ankle | Hallux Limitus<br>Valenti Procedure<br>Plantar Fibroma Resection<br>Tarsal Tunnel Release |
| | | Reconstructive | MOHS Reconstruction following Squamous Cell Carcinoma Excision |
| | | | Patellar Tendon Salvage following MRSA |
| | | | MOHS Reconstruction following Basal Cell Excision |
| | | | Lower Extremity Salvage with Anticipated Amputation Avoided |
| | | Colorectal | Anastomotic Leaks |
| | | | Complex Perineal Wounds |
| | | | Pilonidal Disease |
| | | | Fistula-in-Ano |
| A placental-based tissue matrix in a particulate configuration (AmnioFill®) | - Used to replace or supplement damaged or inadequate integumental tissue in challenging closures.<br>- Manufacturing procedures involve the process of SMR2T™ Technology.<br>- Can be made into a paste form. | Vascular | Large Lower Leg Wound with Anticipated Leg Amputation Avoided |

| Table 2. Additional Placental-Based Graft Types | | |
|---|---|---|
| **Graft** | **Description** | **Manufacturer** |
| Clarix® FLO | Umbilical cord and amniotic tissue | Amniox Medical |
| PX50® | Amnion membrane particulates and products that are cryopreserved | Human Regenerative Technologies |
| PalinGen® Flow/ Sport Flow | Amniotic tissue allografts | Amnio Technology |
| Allogen™ | Mixed allograft derived from amniotic fluid | ViVex |
| FloGraft® | Amniotic tissue allografts | Applied Biologics |
| NuCel® | Cryopreserved bioactive amniotic suspension allograft of amnion and amniotic fluid | NuTech |
| Affinity® | Fresh amniotic membrane | Organogenesis |
| AmnioFlex® | Cryopreserved amnion and amniotic fluid | SurgiLogix |
| Neox® | Cryopreserved human amniotic membrane and umbilical cord | Amniox Medical |
| XWrap™ Hydro Plus | Chorion-free human amnion allograft | Applied Biologics |
| *General information regarding examples of placental-based products not mentioned in the consensus panel discussion.*[16,17] | | |

measures that involve debriding necrotic or fibrinous exudate, and employing anti-infective measures. Wound care measures are essential in creating clinical situations that lead to positive patient outcomes. However, nonmodifiable risk factors may require aggressive management, including the use of PBAs, especially in difficult-to-treat patients such as those with exposed tendons, vessels, or bones.

Good granulation tissue provides a base for satisfactory application and acceptance of a split-thickness skin graft, or a full-thickness skin graft, as warranted. Exposed bone or tendon creates a challenging situation for applying skin substitutes that are not rejected by the host tissues. PBAs create an environment that establishes acceptance in such situations. Before proceeding with a challenging wound, such as exposed fibula or periosteum following ischemia, a thorough washout to cleanse the area of any retained foreign bodies, infection, or fibrinous exudates is necessary.

Successful patient outcomes have been demonstrated in a range of surgical settings. This review focuses on areas that include foot and ankle surgeries, obstetrics and gynecology, vascular, reconstructive, general and colorectal, and limb salvage surgical settings. Patients who benefit from PBA use range from healthy patients, such as those in elective surgical procedures, to patients with a range of comorbid conditions, to athletes with injuries that require surgical interventions. Examples of surgical procedures in the practice areas mentioned are described here with specific case examples provided alongside the corresponding surgical specialty.

### *Foot and Ankle Procedures*

Numerous foot and ankle procedures conducive to the use of PBAs are discussed here. The procedures incorporated PBAs with outcomes that provide evidence of efficacy, reduced healing time, and reduced postsurgical complications. Examples of surgical procedures involving the foot and ankle include tendon lengthening, peroneus brevis repair, Achilles tendon rupture, hallux rigidus, hallux limitus, lower leg mass identified as a pigmented neurofibroma, lipoma found to be attached to the tibia bone, plantar fibroma resection, and tarsal tunnel release.

Tendon lengthening is performed to correct cases involving contracted or ruptured Achilles tendon, a multifaceted condition found in the general population. Complications that emerge from surgeries involving tendon repair include adhesions. Integrating PBAs into the procedure has successfully resulted in a lack of adhesion formation and a superior healing profile. Dehydrated amnion chorion membrane products (eg, AmnioFix) have been integrated effectively in elective surgeries for peroneus brevis repair. The procedure involves applying an amniotic sheet product over dissected peroneus brevis and then tucking it underneath and alongside the tendon. The closure is done in layers over the tendon while simultaneously applying additional product in the tissue planes, ensuring that fibrosis does not occur. The tendon is fully exposed during the repair procedure resulting in natural healing with no impairment in the natural sliding of the tendon within the tendon sheath.

PBAs are also versatile enough to be used on bone. Patients with hallux rigidus often present with severely compromised range of motion (ROM) and developed spurs on the first metatarsophalangeal joint. Instead of performing a joint implant or joint fusion, it is possible to remodel the joint to allow for a greater range of motion. The technique involves a modified Valenti procedure, in which portions of the first metatarsal head and the base of the proximal phalanx are resected dorsally. The goal of the Valenti procedure is to significantly improve dorsiflexion. If a patient undergoing a repeat procedure for their metatarsophalangeal joint has preexisting fibrosis, the use of an umbilical cord product (after the fibrosis has been dissected alongside the Valenti procedure) will serve to reduce the likelihood of fibrosis. Umbilical cord is advantageous because it can be directly sewed into place with an absorbable suture, and once hydrated, resembles normal tissue. The umbilical cord material is sewed to the base of the proximal phalanx, to the soft tissue around the first metatarsal, then to the bottom of the plantar aspect of the metatarsophalangeal joint. In general, using as little absorbable material as possible decreases the likelihood of developing fibrosis. Postoperative results have

## Case Vignette 1

This case illustrates the effective application of PBA over bone and tendon. The patient presented with a magnetic resonance image that showed a slowly growing mass on the lower leg enveloping the tibia. During surgery, the mass was found to be a pigmented neurofibroma. The procedure involved incision and dissection of the benign pigmented neurofibroma, albeit a rare lesion, with complete extraction from the wound. The excision of the pigmented neurofibroma left behind a rather prominent gaping hole in the lower leg. To fill the deficit, layers of amnion/chorion membrane were placed on the exposed bone. Despite the nature of the wound at the surgical site, the patient exhibited no pain, edema, or pooling of blood. The patient was evaluated 2 weeks later with no complications, and both the surgeon and patient were happy with the positive outcomes of the procedure.

## Case Vignette 2

Another case illustrating successful PBA application on bone involved a 64-year-old man presenting with a slow mass growing on the lower right leg positioned anteriorly over the tibia and 6 cm above the ankle. During surgery it was discovered that the depth of the mass reached the tibia. The excision procedure resulted in a deficit with exposed bone, and dHACM was used to fill the defect and cover the exposed bone to prevent the development of fibrosis or scarring around the bone. Closure occurred in layers with further insertion of amnion/chorion product. The patient was evaluated 2 weeks later with an impressive positive outcome, minimal postoperative pain, and very mild swelling.

been overwhelmingly positive, with increased range of motion devoid of complications. **Case Vignettes 1 and 2** provide additional insights into the use of PBA over bone.

Plantar fibromas, or a fibrous nodule in the arch of the foot, represent another type of benign lesion that is amenable to the use of an umbilical cord as an implant. It is customary to resect a portion of the plantar fascia along with the fibroma to prevent the possibility of reoccurrence, which can be high in these procedures. A typical problem with resecting the plantar fascia is that a major deficit is produced in the supporting structure of the foot. Optimizing the use of PBAs in plantar fibroma cases have led to the expectation of no further reoccurrence of the plantar fibroma or complications resulting from the PBA use (**Case Vignette 3**).

Clinical cases of tarsal tunnel releases have demonstrated positive outcomes with the use of PBAs. Physicians remain cautious in performing tarsal tunnel releases due to the possibility of fibrosis or scarring following the release of the entrapped nerve, necessitating a repeat procedure. To avoid this complication, amnion/chorion membrane, known to alter the scarring profile, can be applied into the tarsal canal immediately before closure. The PBA product is broken up into bits and evenly distributed. Umbilical cord can be implemented in tandem with the amnion/chorion membrane to decrease the likelihood of fibrosis, the occurrence of dehiscence, swelling at the site, and other complications while facilitating the overall healing process of the underlying structures.

*Obstetrics and Gynecology*

The utility of PBAs can be applied to laparoscopic procedures. Peritoneal resections are often necessary in the treatment of endometriosis. Due to the nature of the operation, there is tremendous potential for omentum scarring in places like the anterior abdominal wall. Leveraging stem cell recruitment aids in regulating fibrosis and minimizing pelvic adhesion formation by promoting healthy healing. A PBA may be placed in the cavity to augment the healing process after proceeding with peritoneal stripping, perhaps along the cul-de-sac in an endometriosis patient undergoing hormonal suppression.

PBAs may be used in tandem with other procedures, such as injections into the pelvic floor for hypertonicity, to improve previous loss of urinary function and to provide support to underlying structures. As fertility is a significant cause of concern for patients, PBAs can also be used to prevent adhesion formation. The use of PBAs, in general, has been noted to reduce the incidence of postoperative pain. For example, in several instances, patients have been noted to take less pain control medication than expected for the procedures involved, including elective surgeries, perineal wound repair, and others.

*Colorectal*

Colorectal surgery is performed in a difficult-to-control environment subject to both a mechanical and a bacterial pressure gradient with the potential for inflammation and fibrosis. These factors affect the scaffolding, cells, and signals necessary for precision healing and authentic remodeling. The concept of regenerative healing remains comparatively foreign to noncolorectal and nongeneral surgeons and is an area of foreseeable opportunity and growth. For several years, general and colorectal surgery fields have been relatively void regarding the use of biological allografts, a relatively untapped source of regenerative healing.

The scope of colorectal disorders that require surgical interventions ranges from benign constipation to aggressive advanced Crohn disease, a high prevalence of colorectal cancer cases reaching stage IV burden, and serious problems such as anastomotic leaks. Smaller problems include cases of highly recurrent and difficult-to-close pilonidal disease, persistent fistula-in-ano, and complex perineal wounds. Such cases require attention to incorporate treatments involving cells, signals, and scaffolds. The scope of colorectal surgeries involves patients who are strong candidates for the use of biologic allografts, such as PBAs.

In the domain of colorectal surgery, extremely dangerous complications exist, such as an anastomotic leak. Gastrointestinal (GI) anastomosis has an alarmingly high mortality rate and severe economic repercussions for health care payors. For example, costs can reach almost a quarter of a million dollars in intensive care unit (ICU), rehabilitation care, and critical, life-preserving measures, and the need for repeat procedures.[18] A number of these issues can be addressed by incorporating PBAs into clinical surgical practice. A circumferential leak, for example, can be sealed without additional intervention or drain. Data from retrospective studies that support the efficacy of using allografts in colorectal anastomosis showed a 25% reduction in the leakage rate as compared to the initial rates. Specifically, rates dropped from the original 4% to 5% rate to around 1.2% to 1.3%.[18] While these results are reproducible, future research may benefit from increasing the overall power of the studies.

To best envision the GI environment as it relates to the dynamic characteristics of PBAs in the wound healing process, a basic grasp of cells, signals, and scaffolds is necessary. By leveraging the power of cells, signals, and scaffolds, colorectal surgeons may be able to tackle cases such as a fistula-in-ano that currently have no consensus on treatment algorithms. A proctectomy patient with a history of extensive fibrotic fistulas may also benefit from the regenerative properties of a PBA. PBAs can be used to buttress a closure for fistula-in-ano and improve the overall success rate to 80% to 90%. To achieve this high success rate in a fistula-in-ano procedure, the placental-based product is integrated into the tract in a powdered form and serve as an additional plug. The biologic products are versatile enough to be used in powdered form or parachuted into the area using folded sheets for increased tensile strength. PBAs can fill a large abscess cavity, restoring some of the cells, signals, and scaffolding for chronic wound healing.

Patients with pilonidal disease tend to be from a younger patient population and are excellent candidates for PBA use. A space-filling technique coupled with a nonocclusive, nonshearing dressing can be applied to a shaved area. Patients generally heal faster without negative pressure therapy and can resume normal activities of interest. Patients with prostate radiation often present with failed reconstruction, even with chronic vacuum-assisted closure, and are likely to have long-term packing for gaping, open wounds. These patients can benefit from primary closure supported by placental allografts, which may mitigate issues concerning asymmetry and allow for improved healing without dehiscence.

Patients with Crohn disease represent another population with recurrent, fistulizing disease and extensive fibrotic tissue, hindering the overall wound healing process. They, too, can benefit from the application of PBA to help modulate scaffolds from chronic fibrosis and promote cell signaling. Patients who develop diverticulitis present with complex incisional wounds described as one of the most challenging situations to resolve as the wound environment has disturbances in cell signaling, ECM scaffolding, and cell types. This type of procedure is an optimal time to gather assistance in wound healing from the implantation of biological allografts. In the operating room, the colon is transected twice to create an anastomosis.

## Case Vignette 3

The surgical procedure involving a patient who presented with a plantar fibroma involved the use of hydrated umbilical cord. The umbilical cord product, described as suitably hefty, was implanted then sewed in the four corners and the center of the deficit and effectively served as an analogous structure that replicated the inherent support function of the plantar fascia. Follow-up with this patient revealed complete healing along the incision site with no scarring. Palpation from the lateral to the medial side yielded the presence of normal fascia with uniform tension, even across the incision line. The deficit was remedied, and a follow-up computed tomography scan confirmed no deficit or fibrotic areas with homogenous planes. The patient did well with no reoccurrence of the plantar fibroma.

Anastomotic leaks, a significant source of morbidity and mortality, may be prevented by using PBAs. These patients are expected to make a dramatic recovery. PBAs are a cost-effective adjunctive therapy and an excellent option for colorectal surgical patients with comorbidities and suboptimal wound healing environments.

*Reconstructive*

Reconstructive surgeons work within the construct of the "reconstructive ladder," which is a strategy that guides decisions in determining optimal approaches in reconstructive surgical procedures.[19,20] The experiences of the surgeon with progressively challenging wound types as they proceed up the ladder aid in decisions regarding procedural approaches. Decisions concerning the treatment plan will integrate patient-specific conditions, such as occupational role, donor compatibility and morbidity, functional status, and prognosis.[19,20] Patients presenting for reconstructive surgeries who have comorbidities are candidates for the use of PBAs.

Foundational wound care practices are essential to ensuring positive surgical outcomes across surgical specialties, including reconstructive procedures. In the absence of infection, traumatic wounds are generally subjected to a debridement and extensive irrigation protocol before attempting to close.[19] During the debridement process, contaminated and necrotic tissue are duly eliminated.[19] However, if there is an underlying infection, the physician may attempt a delayed closure.[19] In cases with sufficient granulation tissue, the wound site in question may heal via secondary intention.[19] Even from a reconstructive surgery perspective, there are cases in which the appropriate procedure is simply not available or an improvement in patient outcome can be better realized by using adjunctive PBAs (**Case Vignettes 4 and 5**). **Case Vignette 6** highlights the importance of attention to wound care and infection control due to the presence of MRSA cultures in the wound, and **Case Vignette 7** involves a patient with infection, poor vascular flow, and at risk for amputation.

## Case Vignette 4

A 57-year-old male triathlete following Mohs resection of a basal cell carcinoma presented with a 3.5 x 4.5 cm defect on the forehead and displayed negative margins around the wound. In the operating room, the surgeon proceeded to debride fibrinous exudate. A base was produced with healthy granulation tissue but healing via secondary intention would otherwise produce cosmetic issues, namely the undesirable appearance of distorted brows with central-circular scarring. The surgeon proceeded to minimize the scar circumferentially via purse-string suturing, then the glabellar scar was allowed to heal by primary intention while leveraging the properties of mechanical creep over the next few weeks. At follow up, AmnioCord™, a dehydrated cellular umbilical cord allograft with high hyaluronic acid content, was introduced to allow for seamless approximation of the wound edges. The product is a thick graft, ideal for suturing, and can be fastened within deeper surgical sites. The AmnioCord™ measured 3 x 5 cm and a temporary bolster dressing was placed on top. Over the course of several weeks, occlusive dressings and wet-to-dry dressings changes were performed while the vertical scar continued to diminish until it was no longer readily apparent.

## Case Vignette 5

A Mohs patient presented with a complicated picture that included comorbid issues involving a past and current smoking history, poor diet, and ongoing problems with wound healing. The patient initially refused a skin graft, including reconstruction in the form of adjacent tissue transfers or local flaps. The patient's squamous cell carcinoma was excised 10 weeks prior. EpiFix™, a variant of dHAC allografts available in the sheet configuration, was presently applied at the base with the goal of creating granulation tissue where there was denuded bone without any periosteum and the wound site was desiccated. The patient was placed on a high-protein diet and asked to refrain from the use of nicotine. A week later, the patient returned with more granulation tissue centrally but not enough healthy bone to work with. He was brought to the operating room to undergo further debridement of the base, but care was made to leave the granulating and epithelialized tissue intact. While some healthy bone was revealed by the procedure as evidenced by a nutmeg appearance with punctate bleeding, the contour was far from desirable. In this case, umbilical cord graft was used again, applied over the bone and granulation tissue, and suitably tucked under the edges wherever possible. A temporary bolster dressing was used followed by a few rounds of occlusive dressing. Despite the lack of a skin graft or any advanced maneuvers, the patient made a complete recovery with regular wound care management and his deficit epithelialized over the next few weeks.

Allografts can be applied over many different types of wounds, including muscle, tendon, and bone with great success. Attention to wound care and vascular flow are essential aspects in promoting tissue healing using PBAs. The joint and bone/spine literature is replete with examples concerning the transformative framework of regenerative healing, namely, moving away from fibrosis and inflammation in pursuit of leveraging the body's regenerative properties.

*Vascular*

Patients may undergo amputations due to trauma such as farm equipment accidents or comorbid vascular and diabetic conditions. In extreme cases, a patient can present with no inflow or a lack of a pulse, necessitating an adjunctive inflow procedure. **Case Vignettes 8 and 9** highlight the role of PBAs in limb salvage following revascularization procedures for patients who were previously considered candidates for major limb amputations.

*Limb Salvage*

The global diabetic population is of chief concern to the field of limb salvage as these patients constitute the primary source of leg amputations, noting that an amputation procedure occurs approximately every 30 seconds in a diabetic patient.[22] Different types of wounds accompany the diabetic patient, including neuropathic and pressure wounds. A Charcot foot is a severe presentation that can develop from diabetic neuropathy with progressive degeneration of a weight-bearing joint. Without early intervention, an increased likelihood of amputation exists.

A patient may present with either glycemic control, offloading shoes, or medication management for wound healing, but none of these factors in isolation will effectively prevent an amputation. A combination of factors contributes toward successful limb salvage, including good perfusion, appropriate offloading shoes, and antibiotic therapy.

Three essential areas that require attention include an evaluation for adequate blood supply, attention to wound care, and pressure offloading.

- First, the blood supply evaluation is necessary to ensure adequate blood flow that encompasses the need to deliver infection control medications to the area if needed.
- Second, issues concerning wound care must be addressed. The wound must be thoroughly cleaned and appropriately debrided, and a healthy wound bed with good granulation tissue must be prepared. Placental products serve as an effective bridge to allow the wound bed to prepare for possible grafting in the diabetic and comorbid patient.
- Third, the clinician must assess for consistent offloading protocols. A weight-bearing surface, coupled with infection and an open wound, will ultimately make the healing process very difficult, resulting in the possibility of limb amputation.

## Case Vignette 6

A 62-year-old former wound care nurse with diabetes mellitus and obesity was referred by her orthopedic surgeon for reconstruction for a refractory case of patellar tendon injury. The referring orthopedic surgeon had repaired with a braided permanent suture and then primarily closed after a washout for dehiscence. The tendon was exposed at the base of the wound, and the patient was brought to the operating room to have it covered with healthy tissue. The sutures were opened, and a 4-cm squared deficit was uncovered. Medially based adjacent tissue was transferred over to the site of the defect, followed with an incisional wound vacuum-assisted closure. However, after 3 weeks, the patient's dehiscence had returned, necessitating more investigative procedures. Even though the patient did not exhibit any tangible signs of infection, there was erythema over her kneecap. She was immediately brought to the operating room and started on intravenous antibiotics due to confirmed MRSA cultures discovered growing in the wound. The patient underwent weekly washouts in addition to VERAFLO™ for wound perfusion and debridement. Permanent sutures from the previous orthopedic surgery were removed after consultation and the wound was closed upon confirmation of negative cultures. A laterally based flap was designed to give support to the original medially-based flap and umbilical cord was placed squarely on the tendon for an extra layer of protection. Despite the lateral and medial sites not closing primarily, the patient was able to ambulate without assistance at 2-months postoperatively and exhibited full range of motion of the knee.

## Case Vignette 7

A 68-year-old man with a history of poorly controlled type 2 diabetes and significant malnutrition with poor prealbumin levels and a sustained Gustilo IIIA tibial fracture while attempting to cut branches from a tree. The orthopedic surgeon washed out the wound site, placed an amnion membrane, and closed it. The patient was sent to a rehab facility where the dressing was not changed for 2 weeks. At that point, the patient returned to his orthopedic surgeon with a foul odor, purulent drainage, and gross infection with dehiscence of closure and necrosis of some soft tissue. He was taken to the operating room by his orthopedic surgeon again, and his wound had evolved to a Gustilo IIIB status with exposed fracture distally. The patient was then referred to the reconstructive surgeon. The patient had severe vascular disease with 70% tibioperoneal trunk blockage and was therefore not a suitable candidate for free muscle flap reconstruction or antibiotic therapy due to a lack of perfusion to the wound. An umbilical graft was sewed in place with vacuum-assisted closure. A discussion regarding possible amputation was planned for the follow-up appointment. After a period of observation, physical therapy, and lymphatic massage, the patient was re-evaluated. There were no signs of active infection (no leukocytosis or erythema), the fracture line was not visible, good granulation tissue had developed, and the deficit was diminishing with time. Umbilical allograft was reapplied, and a full-thickness skin graft was placed at 12 weeks. Six months later, this patient, once considered for amputation, was actively engaged in recreational activities, including dance competitions.

In some patients, vascular flow requires procedural interventions. Deep venous arterialization is a technique used in limb salvage patients. The procedure involves connecting an artery from the lower leg to the veins in the foot within a circuit that allows the veins to deliver arterialized blood to the distal aspect of the foot.[23] Deep venous arterialization is increasing in clinical practice as the procedure helps to revascularize patients who would otherwise undergo amputations.[23] Diabetic patients also tend to lack a pedal loop, which is the circuit that forms between the posterior and anterior tibial artery. Diabetic patients with extensive tibial disease may benefit from pedal artery revascularization procedures to produce an environment conducive to optimal healing.[23,24] This is of relevance as recent research supports the notion of improved healing in patients who have been effectively treated for concurrent tibial and pedal artery disease. [24] Still, even diabetic patients with good blood flow to the ankle may demonstrate positive surgical outcome from tibial recanalization, allowing for direct perfusion to the wound bed. These patients, especially when considering the relatively slower healing process, are excellent candidates for placental-based products.

According to the research literature, to ensure proper wound healing of the diabetic foot, a toe pressure of at least 55 mmHg must be maintained.[25] However, because calcium has a predilection for tibial vessels, measurement techniques for vascular diseases are rendered unreliable and meaningless. Furthermore, because diabetes affects the microvasculature of the feet, a toe pressure yielding less than 55 mmHg will indicate a wound that is unable to heal. Pressure offloading aids in allowing cells to grow as the wound is in a low-pressure position that provides the structure for healing. Offloading methods, such as casts or shoes, aid in reducing pressure on a foot wound. Overall, if a clinician has good patient selection and uses amniotic tissue early on a clean bed to promote wound healing, there is a marked increase in the chance of limb salvage with a simultaneous decrease in cost.[26] Considerable data have posited that there is something inherent to placental (or amniotic) tissue, influencing the direction of cytokines and growth factors in preparation for a healthy wound healing environment.[1]

## Case Vignette 8

A 61-year-old man with multiple comorbidities including hypertension, hyperlipidemia, diabetes mellitus, and tobacco use, presented for amputation due to the presence of substantial development of gangrene. The patient presented with poor flow, evidenced by an ankle-brachial index (ABI) of 0.27 on the ipsilateral side. It was suspected that the previously ambulatory patient sustained a distal embolization that affected his lower extremity. A right common femoral artery aneurism was discovered with surgical repair consisting of an inline bypass graft from the distal externa iliac to the profunda femoris and an in-situ bypass using the great saphenous vein to the below-knee tibial segment. To increase the likelihood of a successful outcome, it is of utmost importance to achieve satisfactory blood flow before addressing the wound itself. After completing the revascularization procedures, the next goal involved aggressive management of the wound. While the forefoot was unable to be salvaged despite extensive debridement of the dorsum of the foot, a conscious attempt was made to avoid major limb amputation. AmnioFix sheets were generously applied with sufficient coverage over the deficit that resulted from resection of subcutaneous tissue/skin. The patient achieved satisfactory glycemic control, which is an important factor in reducing the incidence of nosocomial infections.[21]

After the fourth week, a transmetatarsal amputation was performed, which produced a wound on the distal part of the foot and revealed an exposed tendon. While the metatarsal heads were present, the lack of a sufficient plantar flap rendered it difficult to manage the wound. AmnioFix sheets were applied liberally over the site to circumvent this issue, encouraging the growth of granulation tissue in preparation for a graft. Optimal granulation tissue conditions were achieved by applying a nonadherent dressing on top of that and then following up with vacuum-assisted closure of the wound. The patient was evaluated every 2 weeks, and, in a relatively short span of 10 weeks, coupled with adequate vascular flow, PBAs facilitated good coverage of the wound and secondary closure. Secondary coverage with a skin graft was not necessary in this case as there was already a positive outcome.

## Case Vignette 9

Another challenging case involving a patient presenting for amputation involved a patient who required a right axillofemoral bypass to maintain satisfactory flow. She underwent serial debridement and washouts with removal of fibrinous exudate as the wound bed was being prepared. A large, exposed tendon to the lateral part of the wound on the anterolateral compartment of the leg, made it exceedingly difficult for the surgeon because of the mobile nature and shearing forces of the wound. AmnioFill™, a collagenous, placental tissue ECM derivative, was made into a paste from its native particulate form to provide more control over the wound application. It was then layered in the direction of the tendons with AmnioFix™ sheets to avoid shearing forces and given custom perforations. The arrangement provided good coverage and aided in the formulation of granulation tissue. The product was liberally applied over the wound with vacuum-assisted closure and evaluated every 7 to 10 days. After 6 weeks, a split-thickness graft was placed onto the wound. She was previously considered a candidate for amputation, but due to the application of amnion/chorion tissue resulting in the development of excellent granulation tissue, her limb was spared.

### Cost-Effectiveness of Placental-Based Allografts

Experts note that costs of using PBAs in the surgical setting generally range from $300 to $5000 per procedure, depending on procedure details and products needed. The positive outcomes seen with PBAs provide evidence of the cost-effectiveness of the PBAs as they significantly contribute to avoiding surgical complications. Typical complication rates experts note for surgical interventions range from 3% to 27%, with associated costs of complications that develop from surgical interventions ranging from hundreds to thousands of dollars, possibly even higher in some cases, and are further associated with increased morbidity and mortality.

The costs associated with surgical complications include hospitalizations and rehospitalizations, repeat surgical procedures, possible adjunctive procedures, possible need for ICU care, extended rehabilitation, and the possible need for emergency procedures. The financial costs of procedures with complications can be as high as five times the cost of the procedures or more, plus the increased morbidity and mortality rates. For example, from an economic aspect, a failed GI anastomosis is a catastrophe. An unsuccessful left-sided anastomosis intervention can lead to a quarter of a million dollars in costs of ICU and rehabilitation care, in addition to critical, lifesaving, rectifying procedures that are necessary to address the situation, and the emergence of adverse sequelae such as enterocutaneous fistula development. As a cost-effective, adjunctive procedure, PBAs have a substantial role in advancing the field of colorectal surgery by remedying costs that amount

to a quarter million dollars and the concomitant mortality rates of 10% to 15%.[27]

The immediate and extended costs associated with amputations can sometimes be avoided as these products have demonstrated efficacy in limb salvage efforts. If a clinician has good patient selection and uses amniotic tissue early on a clean bed to promote wound healing, there is a marked increase in the chance of limb salvage with a simultaneous decrease in extended cost.[26] Placental products serve as an effective bridge to allow the wound bed to prepare for possible grafting in the diabetic and comorbid patient. Moreover, wound care can be expensive. From a global perspective, the projected costs associated with wound care interventions are expected to increase from an average of roughly $2.1 billion as determined by data collected 7 years prior, to $3.5 billion in 2021.[28] Similar to the costs associated with surgical complications, the costs of wound care are not driven by wound care products but rather by repeat procedures and rehospitalizations.[26]

Amniotic products can reduce the economic burden of chronic wound management across various scenarios, including the surgical setting. The use of placental-based tissue products and their ability to mitigate risks associated with surgical complications, especially in patients with comorbidities, contribute to the cost-effectiveness of such products. The positive outcomes observed with PBA use, the improved outcomes specific to wound healing, and the decreased or negligible role in postsurgical complications further support the cost-effectiveness of placental-based tissue products in surgical applications.

## Discussion

This review of the consensus panel's presentations and their shared insights regarding the application of PBAs and related placental-based tissue products provides evidence of the benefits of incorporating adjunctive biological applications in the surgical setting. Proper patient selection, optimal attention to the wound, and proper application of PBAs are central to successful outcomes using these products. Introducing biological allografts across surgical settings significantly and positively impacts patient outcomes, even in compromised patients with comorbidities, as the use of PBAs has demonstrated positive impacts such as decreased healing time, reduced postoperative pain, fewer surgical complications, and decreased incidence of fibrosis. The cost-effectiveness of using PBAs in surgical procedures is substantial in reducing the costs associated with complications such as repeat hospitalizations, repeat procedures, ICU and extended care, limb salvage, morbidity, and mortality. This review includes essential information that advances knowledge regarding PBAs in the surgical setting and the significant positive outcomes associated with their use.

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