Acellular Dermal Matrices: Applications in Plastic Surgery

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Semin Plast Surg 2019;33:173–184.

Abstract

Modern advances in tissue engineering have transformed the plastic surgeon's management strategies across a wide variety of applications. Comprehension of the fundamentals of biologic constructs is critical to navigating the available armamentarium. It is essential that plastic surgeons become familiar with some of the existing methods for utilizing biologics as well as the advantages and limitations to their use. In this article, the authors describe the basic science of biologics with a focus on acellular dermal matrices (ADMs), and review the recent evidence behind their use for a variety of reconstructive and aesthetic purposes. The review is organized by system and examines the common indications, techniques, and outcomes pertaining to the application of ADMs in select anatomic areas. The final section briefly considers possible future directions for using biologics in plastic and reconstructive surgery.

Keywords
- Biologics
- acellular dermal matrix
- plastic surgery
- reconstructive surgery

The terms *biomaterials*, *biologic scaffolds*, *bioprosthetics*, and *biologic matrices* are used interchangeably and represent a diverse continuum of engineered products that serve as scaffolds which interact with native tissue, promoting vascular and cytologic ingrowth, cell propagation, migration, and differentiation.[1,2] Given the enormous breadth of this topic, we will focus on the use of a specific subset of biomaterials known as acellular dermal matrices (ADMs). These are materials comprised of nonliving dermal components from an allogenic (human cadaveric) or xenogenic (animal) donor.

Scaffold denotes the presence of a specialized three-dimensional structure with unique properties based on its chemical and physical composition, while *matrix* corresponds to the actual substance within that space. Biologic scaffolds can be subdivided into cellular and acellular matrices. Within the former, living cells are retained and some degree of antigenicity may be expected. For this reason, cellular grafts can only be obtained from an allogenic (human cadaveric) donor while acellular grafts can be derived from an allogenic or xenogenic (animal) source. Although naturally occurring extracellular matrix (ECM) can be found in all types of tissues, the amount of ECM relative to the tissue's cellular component and the type of collagen in the ECM is location specific. Submucosal and dermal forms of ECM are abundant and tend to be well vascularized. They contain primarily type I collagen, elastin, laminin, site-specific glycosaminoglycans, and an array of growth factors. These are the core building blocks common to all ADMs. Their acellular constitution lends to their reduced antigenicity, to the point that they may be immunologically inert. While xenografts are almost entirely derived from bovine or porcine donors, the composition of either xenogenic or allogenic scaffolds can be augmented by unique proteins harvested from additional species, as well.[3–5]

Although ADMs can be used as both temporary and permanent biologic dressings, they are not designed to be complete skin substitutes as they lack an epidermal component. There is a category of acellular bilayered matrices that feature an additional synthetic "epidermal" layer which provides a semipermeable barrier to microbes and evaporation. Integra is an example of a bilayered ADM, and is primarily used as a tissue regeneration matrix or temporary

Issue Theme Biologics in Plastic Surgery; Guest Editor: Edward M. Reece, MD, MBA

DOI https://doi.org/10.1055/s-0039-1693019.
ISSN 1535-2188.

wound dressing.[6] Bilayered matrices are not examined in this article, but deserve mention for their well-demonstrated value in the management of skin and soft-tissue deficits. Many studies describe the application for ADMs across an immense spectrum of conditions and diseases processes affecting the skin and soft tissue—and more specifically, there is a growing body of evidence to support their use in the management of acute and chronic wounds of the extremities. A review of the approaches for using ADM in the treatment of the integumentary system requires considerably more space for the sheer amount of information available, and goes beyond the scope of our discussion. Nonetheless, clinicians should critically examine potential roles for ADMs in such relevant settings.

Acellular dermal matrices generally refer to matrices that are used to reinforce soft-tissue repairs and support wound healing; applications largely aided by their dermal collagen component and the presence of some source growth factors. On the whole, ADMs incorporate into host tissues and revascularization can be appreciated at 1 to 2 weeks after implantation, as shown by DeGeorge and colleagues using advanced imaging techniques based on photon and photoacoustic microscope.[7] Endothelial cells and subsequent fibroblasts that enter the scaffold release additional chemoattractants that signal the migration of other structural cells. The cycle of remodeling consists of degradation of the biomaterial and rebuilding of the collagen scaffold with host tissue; the balance of, and rate at which this process occurs influences the ultimate strength and integrity of the repair.

The processing of ADMs is a proprietary procedure particular to each manufacturer, yet highly consequential to the surgeon and patient, insofar that the chemical and physical steps taken to achieve durability and diminish antigenicity can heavily influence the behavior of the matrix in vivo. The chemical and physical processes allow for the provision of a durable construct by alternation of native collagen molecules via enhancement of intra- and intermolecular chemical bonds, or "crosslinks"; the degree of cross-linking determines the tissue regeneration patterns of ADMs. Durability may be improved with crosslinking processes but at the expense of decreasing the rate of integration, which can have a potentially detrimental effect depending on the clinical application. Conversely, noncrosslinked ADMs exhibit rapid tissue integration, which can also be problematic by abbreviating the degree and duration of soft-tissue support. The variable crosslinking concept has become an important paradigm in ADM design by lending itself to a balanced pattern of biointegration.[8] Moreover, physical modifications to an already processed ADM, for example, making perforations in the material, has been shown to increase the rate of cellular invasion without diminishing tensile strength. In fact, the decreased time for incorporation coupled with improved egress of fluid may be associated with decreased risk for infection and seroma.[9]

The ability for ADM to become vascularized and remodeled by autologous cells is an impetus behind its increasing use in contaminated fields. The perceived resistance of ADM to infection is a consequence of its biointegration, not sterility. ADMs can be categorically unsterile if they are of the "aseptically processed" variant. Aseptic processing refers to washing of the allograft with detergents, antibiotics, and mechanical forces. Until recent years, terminal sterilization was not feasible due to risk of damage to the matrix from contemporaneous techniques. The development of advanced processes, such as the use of an electron beam, gamma radiation, ethylene oxide, or hydrogen peroxide, that could permit sterilization without compromising collagen composition, was in part driven by earlier literature on implant based breast reconstruction that suggested there was an increased risk for infection and seroma with the use of aseptically processed ADMs as compared with terminally sterilized ADMs. More recent evidence has offered mixed results, including a meta-analysis that failed to show a significant difference in outcomes between the two types.[10]

Plastic surgeons have realized a wealth of applications for ADMs, with techniques tailored to the specific requirements of an operation. There are many ADMs available today and they are distinguished by subtle differences in their processing, properties and hence indications. Considerations for each product include how it is stored, whether it requires a period of rehydration prior to implantation, how it might stretch in vitro, or whether there is an "up" and "down" side—characteristics that invariably influence selection and positioning. The attributes of commonly available ADMs are summarized in ►**Table 1**.

Acellular dermal matrices are being used from head to toe—from the visible to the visceral. Most evidence lies in descriptive and nonrandomized studies; however, an increasing number of large randomized clinical trials are on the horizon.[11,12] The following sections discuss the various landscapes in plastic surgery that have been reshaped by the use of ADMs. Descriptions include a brief overview of the indications, techniques, and outcomes that are commonly encountered. The proposed parameters for the application of ADMs are not absolute, but meant to provide a backdrop for the surgeon's discretion.

Head and Neck

There is growing literature validating the use of ADM in head and neck surgery for both aesthetic and reconstructive purposes. From elective lip augmentation to complex reconstruction of the oropharynx after oncologic resection, ADMs have afforded surgeons a readily available material with a wide assortment of clinical applications. In a systematic review by Shridharani et al, the authors identified 30 studies with quantifiable, objective results pertaining to the use of ADM in reconstructing nasal soft tissue and skeletal support, tympanic membrane, soft-tissue deficits from parotidectomy, extraoral and intraoral defects, oropharyngeal defects, periorbital soft tissue, and dura mater.[13]

In primary and revisional rhinoplasties, ADM can be used to correct external contour deformities of the nose by covering its osseocartilaginous frame. Bony irregularities and adhesions of the dorsal skin to the nasal bones can be corrected by placing ADM as a dorsal onlay via intercartilagenous incisions.

Table 1 Overview of commonly used ADMs and their properties

Allografts	Source	Processor	Prep time	Cross-linked	Sterility: processing	Refrigeration/ shelf life	Hydration	Orientation	Additional features
Alloderm (LifeCell Corp.)	Human cadaveric dermis	LifeCell	RT/warm NS/ LR: 10–40 min	No	No: aseptic processing	Yes/2 yr	Dehydrated	Yes	Freeze dried
Alloderm Ready to Use (LifeCell Corp.)	Human cadaveric dermis	LifeCell	RT NS/LR: 2 min	No	Yes: ebeam radiation	No/2 yr	Hydrated	Yes	Terminal sterilization
Allomax (Bard)	Human cadaveric dermis	CR Bard	RT NS: 3 min	No	Yes: gamma radiation	No/5 yr	Dehydrated	No	Not freeze dried; previously Neoform
DermaCELL (LifeNet Health)	Human cadaveric dermis	Arthrex	None	No	Yes: terminal	No/2 yr	Hydrated	Yes	>97% DNA removal
DermaMatrix (Synthes, Inc.)	Human cadaveric dermis	MTF	RT NS/LR: < 3 min	No	No: aseptic processing	No/3 yr	Dehydrated	Yes	Freeze dried; high tensile strength
DermaSpan (Zimmer Biomet)	Human cadaveric dermis	Biomet	RT NS: 15–45 min	No	Yes: gamma radiation	No/not specified	Dehydrated	Yes	Freeze dried; high tensile strength
FlexHD (MTF Biologics)	Human cadaveric dermis	MTF	None	No	No: aseptic processing	No/3 yr	Hydrated	Yes	Stretch resistant
GraftJacket (LifeCell Corp.)	Human cadaveric dermis	Wright Medical	RT NS/LR: 10 min	No	No: aseptic processing	Yes/2 yr	Dehydrated	Yes	Freeze dried; high tensile strength; premeshed
Repriza (Promethean)	Human cadaveric dermis	SSP	None	No	No: unspecified	No/2 yr	Hydrated	No	Available in custom sizes
Xenograft									
CollaMend (Bard)	Porcine dermis	CR Bard	RT NS: 3 min	Yes	Yes: ethylene oxide	No/9.5 months	Dehydrated	No	Heavily crosslinked; fenestrated
Enduragen (Stryker Corp.)	Porcine Dermis	Stryker	None	Yes	Yes: unspecified	No/unspecified	Hydrated	No	May be used as a scaffold for regeneration
Permacol (Covidien)	Porcine dermis	Covidien	None	No	Yes: gamma radiation	No/5 yr	Hydrated	No	Durable
SurgiMend (Integra LifeSciences)	Fetal bovine dermis	TEI Biosciences	RT NS: 1 min	No	Yes: ethylene oxide	No/3 yr	Dehydrated	No	Type III collagen
Strattice (LifeCell Corp.)	Porcine dermis	LifeCell	RT NS/LR: 2 min	No	Yes: ebeam radiation	No/18 months	Hydrated	No	No sidedness
Tecnoss (OsteoBiol)	Porcine dermis	AFS Medical	RT NS: 15–20 min	No	Yes: low temperature deantigenization	Unspecified	Hydrated	No	N/A
XenMatrix (Bard)	Porcine dermis	CR Bard	None	No	Yes: ebeam radiation	No/unspecified	Hydrated	No	Open collagen structure

Source: Table Adapted from *Essentials of Plastic Surgery,* 2nd ed. Saint Louis: QMP/CRC Press; 2014: 95–9.

Potential drawbacks may include mildly prolonged edema and partial resorption of the biologic implant over time, the latter of which is believed to be secondary to continuous mechanical stress or pressure. The thickness of the ADM can vary and stacking sheets atop one another to correct larger defects without compromising integration has been reported.[14] In addition to external contouring, ADM can be used internally for repairs of nasal septal perforations by interposing the graft between mucoperichondrial flaps; this application has been shown to enhance the success rate with repairs of medium to large septal defects by achieving a watertight seal that would otherwise be challenging with an autologous tissue repair method alone.[14–16]

Although to date there have been no reported cases of using ADM to reconstruct the soft-tissue framework of the external ear, several studies have validated the use of ADM in repairing perforations of the tympanic membrane and in preventing the infra-auricular depressed deformities often seen after parotidectomies. The use of ADM after parotidectomy has also been shown to decrease the incidence of Frey syndrome, as demonstrated by Govindaraj et al, by placing a 1-mm thick sheet of AlloDerm over the parotid bed and deep to the dermal flap.[17] It is postulated that by providing an interpositional barrier between the severed postganglionic autonomic fibers of the parotid gland and the overlying sweat glands, ADM may curtail aberrant innervation.[18]

Acellular dermal matrices alone, or in combination with fat grafting, have been well described in elective lip augmentation. In their series of 47 patients (94 grafts), Rohrich et al demonstrated excellent cosmetic results with minimal complications using AlloDerm for soft-tissue enhancement of both the upper and lower lips. Their technique involved tunneling of the graft material in a submucosal plane beneath the vermillion and superficial to the orbicularis using counterincisions located 1 cm from the commissures along the wet–dry junction. The implants were not fixed and gentle digital manipulation was used to facilitate contouring. Significant resorption of the graft was observed in three patients at 12 months, while malpositioning was observed in one case. They did not experience any hematomas, infections, or graft exposures.[19] In a series of six patients, Castor et al demonstrated increased vermillion show using AlloDerm with fat grafting compared with fat grafting alone.[20] Evidence from case series, suggests that the use of ADM for lip augmentation is a safe and effective option for adding both fullness to the lip and elevation at the vermillion.

Acellular dermal matrices can be used for intraoral reconstruction and have proven to be a particularly valuable tool in the treatment algorithm for patients with mucosal defects of the oral cavity (tongue, floor of mouth, maxilla, mandible, hard and/or soft palate, lip, and tonsil) following resection of primary intraoral tumors. ADM can provide an alternative to split-thickness skin grafting (STSG) for mucosal resurfacing and has demonstrated excellent take with complete epithelialization within 4 weeks. In their prospective analysis of 34 patients undergoing intraoral reconstruction with AlloDerm versus STSG, Girod et al noted that graft thickness of 0.009 to 0.013 inches was the optimal thickness of AlloDerm to use in their procedures. The use of thicker grafts in the setting of prior radiation was associated with lower graft survival rates.[21] ADM has also been proven to be beneficial in reconstructing oropharyngeal defects following oncologic resections and can provide a reliable barrier between the pharyngeal cavity and the neck. This application can be especially helpful in complex patients at risk for vascular catastrophes from prior radiation therapy and fistula formation. When used in conjunction with local muscle flaps, ADMs of varying thickness can provide protective coverage when primary closure is not possible.[22]

Several authors have substantiated the utility of ADM in various phases of palatoplasty, specifically as a strategy to augment repairs, minimize postoperative fistula formation, and also to repair fistulas when they do occur. One of earliest studies that examined the safety and efficacy of ADM in the primary repair of wide cleft palates was a retrospective review by Clark and colleagues, which consisted of 7 consecutive patients with clefts of the hard and soft palate wider than 15 mm.[23] Palates were repaired in the standard 2-flap approach with intravelar veloplasty and placement of AlloDerm immediately deep to the oral mucosal closure. Patients were then assessed for dehiscence, fistula, infection, rejection, scarring, and contracture. There were no fistulas and in all cases, the decellularized dermal graft mucosalized. In two patients, the oral mucosa dehisced, exposing the dermal graft; however, there were no cases of local inflammation or infection and the degree of scarring and contracture was indistinguishable from the adjacent scar. In their experience with 26 patients using AlloDerm (thicknesses of 0.33–0.76 mm) as an interpositional graft placed between nasal and mucoperiosteal flaps versus traditional repair methods, Steele and Seagle reported a fistula repair rate of 100 and 83.3% in the ADM and historical control groups, respectively.[24] In another small comparative analysis, Cassi and Massei noted less dehiscence and no recurrences following repair of oronasal fistulae with local mucoperiosteal flaps and ADM.[25] A growing body of evidence suggests that ADM is an effective adjunct in the repair of cleft palates and oronasal fistulas, and that the benefits of its judicious placement outweigh potential drawbacks.[24–29]

The efficacy of ADM in the reconstruction of periorbital defects has been well described by several authors (5 studies with AlloDerm and 1 with ENDURAGen).[30–35] First reported by Rubin and colleagues in their retrospective, noncomparative case series of 23 patients, the use of AlloDerm demonstrated promising results as a soft-tissue replacement for a variety of oculoplastic applications (primary and secondary implant coverage, lid spacer graft, and periorbital volume augmentation). Overall, the grafts were well tolerated, with no cases of infection or explantation. Barrier grafts were applied as single sheets and stacked sheets or rolled grafts were used for volume augmentation. As a soft-tissue scaffolding and barrier implant, the ADM persisted sufficiently to permit repopulation with native tissue, while rolled/stacked implants demonstrated unpredictable resorption, particularly in the upper eyelid.[30] The efficacy of AlloDerm was further supported by Shorr et al in a retrospective,

noncomparative case series consisting of 63 patients. The authors demonstrated successful use of AlloDerm (mean thickness of 1 mm) as a posterior lamellar conjunctival spacer graft in the upper and lower eyelid, a conjunctival spacer graft in an ophthalmic socket reconstruction, a soft-tissue interpositional graft for subcutaneous and orbital volume deficiency, and as a hydroxyapatite wrapping material. They noticed clinical improvement in all cases, without any complications attributable to the use of ADM.[31] McCord and colleagues also reported promising results with the use of ENDURAGen as a spacer graft in upper and lower eyelid reconstruction, based on a retrospective chart review of 69 patients with a total of 129 eyelids. They encountered a 10% complication rate that included nine cases requiring surgical revision and four cases of infection successfully treated with topical and oral antibiotics.[32] ADM appears to be a reliable alternative to autologous tissue in an assortment of oculoplastic applications.

The utility of ADM in the reconstruction of scalp and dural defects has been well demonstrated. One of the earliest described clinical applications for ADM in head and neck reconstruction was for a calvarial burn involving the brain (class IV). Barret and colleagues successfully treated a 6-week-old infant who underwent debridement of the bone, dura, and superficial brain, by covering the full thickness defect with AlloDerm and split thickness skin graft (STSG). The area engrafted completely without complication.[36] The favorable biocompatibility profile of ADM has since proven to be an advantageous component for its use in dural reconstruction. While synthetic materials have been used for many years, their application has been fraught with adhesion formation to the underlying brain parenchyma, inflammation, and acute and chronic infections. Achieving a watertight seal with an immunological inert material that is resistant to infection and adhesion formation is paramount in dural reconstruction, and has been made possible by the application of ADMs.[13] In a retrospective review of 200 patients who underwent craniotomy with resultant need for duraplasty, Warren et al demonstrated promising results using AlloDerm with varying thicknesses. There were no cases of cerebrospinal fluid (CSF) leakage or adhesion formation. Only four patients developed superficial wound infections, but none had involvement of the AlloDerm.[37] Endoscopic reconstruction of large anterior skull base defects ($>$ 2 cm) using AlloDerm has also been described with little or no morbidity.[38] Results from several retrospective reviews, suggest that ADM is a reliable adjunct in the reconstruction of the neuro- and viscerocranium. Its application can range from the correction of full thickness defects involving bone and dura to subtle contour deformities of the scalp secondary to loss of skin and soft tissue alone.[36–40]

Chest

Chest wall reconstruction, like abdominal wall reconstruction, is tempered by dynamic physical forces that are constantly at play. Exposure of vital thoracic structures and interference with chest wall mechanics are potential sequelae of differing pathologic conditions and in select cases the use of ADM can enhance reconstructive efforts.[41] Additionally, ADM has been successfully used to correct contour deformities of the bony chest for purely aesthetics reasons.[42]

The majority of chest wall defects result from oncologic resections and depending on the size and/or location of the defect, patient comorbidities, and condition of local tissues, these defects can compromise the rigid framework that protects the underlying viscera, supports the upper extremities, and facilitates ventilation. Although there are no strict guidelines that prescribe the need for skeletal reconstruction after chest wall resection, the goal of reconstruction with ADM is the same as with synthetic mesh—to mitigate alterations to the chest wall and their potential complications, that is, lung hernia, paradoxical chest wall motion, shrinkage of the hemithorax, and scapular entrapment.[41]

Smaller and/or more posterior defects are better tolerated than larger and/or more anterior defects. Anterior and lateral defects of up to three ribs with a resultant total defect less than 5 cm in size, or posterior defects up to 10 cm in size with support from the overlying scapula or adjacent back musculature, can typically go without skeletal reconstruction. In patients with a history of radiation or prior surgery, dense pleural adhesions, scarring of the lung, or soft-tissue fibrosis with resultant decreased tissue compliance can obviate the need for reconstruction as there may be no change in ventilation, even with larger defects. Conversely, a small defect in a patient with an already tenuous baseline pulmonary status may warrant reconstruction to reduce complications.[41] Ultimately, it's the surgeon's judgment that mandates reconstruction of the thoracic skeleton, and given the paucity of literature to support the use of ADM over the more cost-effective prosthetic grafts, the addition of biologic mesh to a reconstructive strategy is left to the surgeon's critical vantage point.

The readily apparent advantages to using ADM include the lack of donor-site morbidity, wide availability, and sizing options. Although such benefits are not exclusive to the application of ADM in chest wall reconstruction, they can be particularly consequential when managing large, complex defects of the thoracic skeleton, where autologous options are limited by tissue availability and/or patient comorbidities. The inherent comorbidities often encountered in patients with chest wall defects make the use of ADM in high-risk patients an attractive option. Unlike synthetic meshes, if the postoperative course is plagued by a wound infection, ADM may be salvageable whereas synthetic mesh, once exposed or infected, typically mandates implant removal; a particularly morbid scenario in chest wall reconstruction.[41]

Neoadjuvant and adjuvant radiation therapy are common components of the multimodal treatment of patients with chest wall tumors and introduce additional variables into the calculated efforts of the reconstructive surgeon. Irradiated tissue is more prone to local wound complications; so compared with synthetic mesh, ADM may be better suited for such potentially hostile environments. Likewise, if the need for postoperative radiotherapy is anticipated, there is

evidence to suggest that ADM can impart a protective effect against local tissue changes, specifically radiation-related inflammation.[43–45]

In regards to product selection and technique, no evidence-based guidelines or standardized approaches exist. At least four different types of ADM have demonstrated promising results following their application in chest wall reconstruction, including AlloDerm, FlexHD, Strattice, and Permacol. Across nine separate studies, consisting entirely of case reports and small retrospective reviews, there were 24 total applications of ADM (AlloDerm = 8, FlexHD = 5, Permacol = 8, and Strattice = 3).[46–54] Descriptions include using the ADM in the following ways: as an adjunct to local soft-tissue coverage for small defects, for stabilizing the chest wall by spanning across large musculoskeletal defects, for correcting congenital and acquired contour deformities, and in combination with autologous flaps. Of the studies that provided follow-up data, which ranged from 2 to 36 months, the overall results appear promising, with little to no morbidity associated with the use of the ADM. Three patients developed wound seromas within 30 days, one with AlloDerm and two with FlexHD, one of whom was infected. Schmidt and colleagues demonstrated no apparent complications in their six patients who underwent sarcoma resection followed by chest wall reconstruction using Permacol (mean defect size was 149 cm^2), with a mean follow-up of 27.6 months. In all six cases, no change in chest wall stability was observed at follow-up visits beyond 3 months; and, on routine follow-up computed tomography (CT) scans, all implants were identified as intact without bulging, herniation, rupture, loss of structural integrity, excessive encapsulation, or seroma formation.[52]

The use of ADM for the correction of acquired cosmetic deformities has been explored on a limited scale but with very encouraging results. Uflacker and Janis demonstrated the successful use of parasternally placed extra-thick AlloDerm to correct prominent rib deformities in implant based breast reconstruction following bilateral skin sparing mastectomies without radiation therapy.[42]

The reconstructive strategy for chest wall defects should include careful consideration of the local tissue environment (specifically the availability of well vascularized tissue planes that can support biointegration) and the mechanical stresses that correspond to the location and size of the defect. The margins of any resected ribs should be checked for sharp ends and smoothed over to avoid injury to the mesh or underlying viscera. To prevent migration or bulge, the ADM should be well secured to either bone or fascia while factoring in patient positioning. The surface of the ADM can be placed directly against visceral or parietal pleura. The use of permanent anchoring sutures is advisable and the mesh implant should be devoid of any laxity when it is completely secured.[41] Following placement, the mesh should exhibit a tense, drum-like feel that is maintained when the patient is returned to a more neutral position. Seroma formation can be mitigated with the use of drains and efforts should be made to reduce any dead space, the latter may involve progressive tension sutures or layered closure.

Synthetic materials have been around longer and continue to offer excellent results at a fraction of the cost compared with ADM, but there is ample basic science evidence to suggest increased resistance to infection with the use ADMs, a point that deserves attention when caring for patients at high risk for wound complications following chest wall reconstruction. Additionally, the durability and customizability of ADM may lend itself to the correction of cosmetic deformities resulting from an imbalance between the amount of overlying soft tissue and the underlying skeletal framework.

Pelvis

The use of ADM in pelvic surgery has been well examined, specifically in the management of common urogynecologic problems such as stress incontinence, cystocele, rectocele, and pelvic organ prolapse. Based on a review of level I evidence behind biologic graft use in urogynecologic reconstruction as compared with native tissue and synthetic mesh repairs, Yurteri-Kaplan and Gutman concluded that there was no benefit to the use of biological materials for prolapse and incontinence surgery.[55] The following section focuses on the application of ADM as an adjunct in the reconstruction of acquired pelvic defects following abdominoperineal resections (APR) or pelvic exenterations for the treatment of colorectal, gynecologic, and urologic malignancies—a topic that has been reported on a much smaller scale. Although beyond the scope of this review, it is worth mentioning that the use of ADM has demonstrated promising results in urethral reconstruction, creation of a neovagina, and penile girth augmentation.[55]

Authors have described effective algorithms for the autologous reconstruction of pelvic defects with regional flaps based on individual attributes that make each flap most appropriate for each pelvic subunit.[56] In contrast, no templates exist to guide the use of ADM despite promising results from a variety of applications that have been described in pelvic reconstruction. In one of the earliest reported cases, Brizendine and colleagues used AlloDerm with a gluteus maximus muscle advancement flap overlay to repair a large parasacral hernia in a patient 1 year after a radical coccygectomy and partial sacrectomy for a chordoma. There were no apparent complications and at 8 months follow-up; there was no evidence of recurrence or bulge.[57] In the last decade several more authors have reported on the successful application of ADMs in the reconstruction of parasacral hernias and pelvic floor defects that result from extensive oncologic resections. The types of mesh that have been used include AlloDerm, Strattice, SurgiMend, and Permacol.[57–63] In the largest reported series of sacral reconstructions using a combination of HADM and gluteus maximus myocutaneous flaps, Dasenbrock and colleagues demonstrated that this approach may have rates of wound dehiscence comparable to other techniques and low rates of parasacral herniation.[58] In a total of 34 patients with a mean follow-up of 45.7 months, seven patients (20.6%) developed a postoperative wound dehiscence and only 1 patient

developed an asymptomatic parasacral hernia. In reconstructions of large pelvic floor defects following sacrectomies and/or coccygectomies the remaining adjacent bony structures can provide reliable anchor points for securing the mesh. The application of ADM in combination with thigh-based flaps to reconstruct the pelvic floor and perineum following pelvic exenteration and radical vulvectomy, when wound conditions are unfavorable for the use of permanent prosthetic meshes, has also demonstrated promising results.[59] The placement of ADM between well-vascularized tissues planes remains essential to the process of biointegration—this principle cannot be overstated.

Perineal wound complications frequently occur after APR with neoadjuvant radiotherapy for rectal cancer. Despite cohort studies suggesting that biological mesh closure of the pelvic floor improves perineal wound healing, the level of evidence is limited. To date, there has been only one multicenter randomized control trial investigating the use of ADM in pelvic floor reconstruction following APR. In a double arm trial with 104 patients, Musters and colleagues showed that perineal wound healing after APR was not improved when using a biological mesh; however, a secondary finding revealed a significantly lower 1-year perineal hernia rate after biological mesh closure.[60] When reconstructing a perineal defect following APR, omentum, if available, can be draped over-top the peritoneal facing side of the mesh and the undersurface should similarly be well covered with healthy tissue. Alternatively the ADM can be used as the innermost layer in direct apposition with the viscera while a pedicled muscle flap is brought over the exterior side. The key is to provide a reliable flux of host cells into the graft material from all sides, as free-floating or lax segments of ADM are not destined for biointegration. The mesh is an adjunct to autologous tissue reconstruction, not a standalone replacement for missing tissue. The application of ADM without the addition of local flaps (i.e., gluteal fasciocutaneous flaps) may result in higher rates of recurrence of perineal hernias. Barring unique circumstances, when performing large reconstructions using ADM, the placement of drains remains essential to mitigating fluid collections.[61–65]

As a counterpoint, a recently published large cohort study with 260 patients undergoing oncologic spine surgery with subsequent plastic surgery soft-tissue reconstruction, demonstrated an increased risk of infection and seroma with the use of biological tissue matrices (Strattice, SurgiMend, and AlloDerm) in posterior trunk reconstruction.[66]

In conclusion, based on our review of several case series, cohort studies, and a single multicenter, randomized control trial, it appears that ADMs can serve as valuable adjunct in the management of complex pelvic defects by providing a barrier between the intra-abdominal contents and outer flaps, preventing bowel adhesions/obstruction and fistulas as well as preventing sacroperineal hernias. The paucity of large randomized trials precludes any definitive recommendations.

Breast

To date, the most studied application of ADM is in the realm of breast surgery. With breast reconstruction on the rise, the push is made to maximize outcomes and minimize complications. ADMs have shown hope of offering a trifecta of technical simplicity, improved results, and decreased complications; but there is a paucity of high-quality prospective data to definitively confirm this aspiration.

As in other applications, the indications for ADM in breast reconstruction are yet to be clearly defined. Much less, the most optimal scenarios for use are more elusive still. Majority opinion states that any candidate for prosthetic based reconstruction is a candidate for ADM.[67] Soft indications proposed by experienced authors are based around the unique advantages ADM can provide. These can be divided into technical considerations and postoperative performance. On the technical side, use of ADM can facilitate partial muscle coverage techniques by extending a deficient pectoralis major in submuscular implant placement. For most surgeons, ADM is used as a sling to support the implant pocket, thus extending the lower border of the pectoralis to cover the inferior pole of the implant. This offers soft-tissue support as well as a stable inferolateral breast margin.[68] This additional prosthetic coverage allows tailoring of the pocket in a way that would otherwise not be possible. Thus, the surgeon can have greater control over projection, lower pole fullness, intraoperative filling volumes, and placement of the inframammary fold.[67] Likewise, the extension of the pocket offers the option of one-stage implant-based reconstruction for patients in which this would otherwise be impossible.[69] The benefits of ADM have also been shown in revision reconstruction for secondary conditions such as rippling, malposition, and symmastia.[70,71] The postoperative benefits center around a drastically decreased rate of capsular contracture, (with rates approaching zero, even in some studies of revision reconstruction) and improved performance in irradiated fields.[72–75] These results can be attributed to the biologic properties discussed in the basic science section. It is important to keep in mind that the superiority of one ADM product over others in breast reconstruction has not been yet illustrated. Becker et al have performed one of the few head to head comparisons (Alloderm vs. Dermamatrix) in a retrospective fashion, but were unable to illustrate an advantage of one over the other.[76] More investigation into this point is warranted. ADMs have begun to percolate into the aesthetic world as well. Its use has been advocated mostly for correction of secondary deformities, such as capsular contracture, rippling, and malposition after primary breast augmentation. However, it has also been used in prohibitively small series for primary augmentation to preemptively address rippling, stretch, mismatch, and hyperanimation deformities.[71] It has also anecdotally been described as both a sling for the pedicle in reduction mammoplasty, and as a primary onlay to address contour defects of the thorax.[70]

Despite promising reports, ADM is not without its drawbacks in the breast. Many studies have shown ADM to result in significantly increased risk of certain complications. Ho et al examined this in a meta-analysis which showed an odds ratio (OR) of four for seroma and three for both infection and reconstructive failure in cases in which ADM was utilized.[75]

Pooled complication rates also showed an increased occurrence of skin flap necrosis, the most common complication, most likely due to overaggressive filling allowed by the extended pocket. These complications, however, were juxtaposed against a 0.58% rate of capsular contracture; a rate so low that it may alone justify the increased rate of short-term complications. This increase in complications, however, was not demonstrated in a recent multicenter, prospective, large-volume study by Sorkin et al who found no significant differences between ADM and non-ADM immediate breast reconstruction in regard to total complications, infections, or reconstructive failures. Interestingly, there was also no significant improvement in positive outcomes as well, such as time to permanent implant exchange, subjective outcome scores, or patient satisfaction.[77] Despite unclear rates of complications, most authors agree that many of the predictable complications can be mitigated by simple considerations such as judicious intraoperative filling, sterile technique, use of perioperative antibiotics, and the addition of closed suction drains.[78] Another consideration is that of cost. Jordan et al address this issue with a resource-sensitive algorithm selecting patients who would be unlikely to benefit from ADM. Using both preoperative and intraoperative criteria, their algorithm decreased widespread use of ADM from 84% to 36% with tremendous savings to the system. Most importantly, aesthetic outcomes and complication rates did not suffer when compared with controls.[79]

An important point that continually shows up in the literature is that, despite great promise, there is an absence of high-quality data in regard to ADM in breast reconstruction. Thus, there are currently no best practice guidelines or reproducible indications for use. Much of the expertise surrounding ADM is derived from case series from a small number of surgeons who regularly use ADM, and in many cases there is great contradiction among commonly cited articles in regard to success rates and complication rates. While many results are promising, and at times very impressive, they lack the generalizability and broad applicability sought by many skeptics. Many questions are yet to be answered regarding ADM in breast surgery, and hopefully the design of high-quality studies will begin to define a very promising topic.

Abdomen

Abdominal wall reconstruction (AWR) remains a complex problem for both plastic and general surgeons alike. Even with the diverse array of meshes on the market, the ideal mesh is yet to be developed.[80] With synthetic meshes failing to meet the needs of the patient in certain circumstances, ADM has become an interesting consideration in AWR in select patients. When reviewing the available literature, it is important to recognize its limitations. Diverse defects, patient comorbidities, and a vast buffet of products and techniques make drawing reliable, consistent, and generalizable conclusions a daunting task. In 2012, Janis et al performed a systematic review of the existing literature with a few key conclusions that provided a benchmark of understanding of ADM in AWR that will be used as the foundation of this discussion.[81]

Acellular dermal matrices have drawn attention in AWR mainly due to their advanced biocompatibility. Theoretically, the increased integration seen in ADM should confer protection against some of the most common complications seen in AWR, including infection, extrusion, adhesions, and erosion. Perhaps the most significant advantage is the opportunity for use in contaminated fields where synthetic meshes are contraindicated; typically, these are Ventral Hernia Working Group class 3 and 4 hernias.[82] While no formal indications have been validated, Baumann and Butler proposed scenarios in which to consider the use of ADM that have since been investigated further.[80] First, ADM should be considered in grossly contaminated fields where synthetic mesh repair is contraindicated.[81,83–85] Second and third are patients at high risk for wound healing complications and for planned exposure of the mesh where the increased resistance to infection is important.[81,83,86] Lastly, ADM should be considered when placement is directly over viscera and/or if there is high likelihood for subsequent reoperation through the mesh.[80,81,86]

More so than other applications, the AWR literature includes a wide array of ADM products. These include different offerings of HADM, BADM, and PADM, each with their own unique characteristics. An important contextual point in the literature is that ADM in AWR was initially heavily focused on HADM. However, the course of this application showed extremely high recurrence and bulge rates.[81,82,87–89] Thus, the focus and application shifted almost entirely to XADM, where it currently remains. Among the most studied are Strattice (porcine), Permacol (Porcine), Alloderm (human), Allomax (human), FlexHD (human), and XenMatrix (porcine), but few studies offer head-to-head comparison directly between products. In one prospective study by Huntington et al, Strattice was found to have a hernia recurrence rate of 14.7 % at 18.2 months; less than half that of Alloderm, Allomax, FlexHD, and XenMatrix.[87] Strattice has also shown a lower rate of short-term complications compared with Permacol, although longer-term recurrence rates were not significantly different.[90] Additionally, Permacol has shown a lower hernia recurrence rate compared with Alloderm, despite an increase in early and late complications.[88] Flex HD has also been demonstrated to be superior to Alloderm by a study that compared 31% and 100% recurrence rates at one year, respectively.[89] While these types of comparisons are important to continue, currently they lack broad applicability across the vast landscape of available ADMs and more investigation is warranted into determining the best product for a given application.

After ADM has been chosen, thoughtful operative placement and technique become of equal importance. Those familiar with AWR understand that there is no standard hernia and the surgical approach cannot be "one size fits all." Even within most studies there are variances in regard to ADM position, method of fixation, use of adjunctive techniques, and patient characteristics. Thus, when analyzing outcomes, it becomes complicated to elucidate the relative

contributions of the ADM versus the integrity of the repair performed using the ADM in question. In most studies reviewed, these decisions were made at the discretion of the surgeon, with variable degrees of explanation. Despite this limitation, an increasing volume of literature has begun to show superiority and inferiority of certain techniques.

While potential complications can be varied, of deepest interest are recurrence and laxity, as these represent subjective reconstructive failure for the patient. In the articles included, recurrence rates with ADM range from 6.2% to as high as 100%.[89,91] While the ADM certainly contributes to this variability, this extremely broad range is largely representative of factors outside of the ADM product chosen. Depending on the above-mentioned factors, including type of ADM, position, fixation, patient factors, and so forth, one can expect recurrence rates to increase or decrease in a largely predictable fashion. Likewise, secondarily tracked outcomes, such as seroma, hematoma, and surgical site infections, have shown similar variability.[82,85,86,88,91,92] Perhaps the best study to date is from Garvey et al from 2017. This was a large-volume study of AWR with ADM with 3- and 5-year follow-up. This single center study also followed patients with surveillance CT scans, the gold standard in detecting recurrence.[93] This study found a recurrence rate of 11.5 and 14.6% at 3 and 5 years, respectively. They illustrated inferiority of bridged repair, but also confirmed worse outcomes with HADM. When these two variables were excluded, their recurrence rates were reduced almost by half to 6.4 and 8.3% at 3 and 5 years respectively. They experienced a 25.1% rate of surgical site occurrence in their study.

While exact rates of complications, laxity, and recurrence attributable to the ADM itself can be hard to define within the literature, certain recommendations can be confidently made to decrease their occurrence. As shown in the non-ADM literature, primary fascial closure with the use of ADM as reinforcement has repeatedly been shown to be superior to bridged repair in both surgical site occurrence and hernia recurrence.[83,91–93] This has been redemonstrated with multiple ADMs, and consensus can be made that bridged repair should be avoided when possible. To facilitate primary fascial closure, component separation is recommended by many authors and been shown to be protective against both recurrence and overall complication rates when specifically studied in conjunction with ADM.[83,92,93] Reference is made in multiple studies to further details about the ADM placement, including method of fixation, choice of suture, tension across the ADM, and amount of fascial overlap. While these factors are undoubtedly important, their lack of standardization and inconsistent reporting limits the conclusions that can be drawn based on their use, and further investigation is warranted.[81]

As with other ADM applications, paucity of controlled studies with long-term outcomes limits the opportunity to draw specific therapeutic conclusions about ADM in AWR. In the systematic review by Janis et al in 2012 there were zero studies that met the benchmark for level one or two evidence, and this has continued to be the trend.[81] Additionally, much of the current literature lacks focus, analyzing diverse populations at short endpoints, thus allowing only broad generalizations to be inferred about specific products or applications. While intuitively and mechanistically these inferences make sense, and have been shown in the available data, larger prospective studies are needed to further elucidate the role of ADM in AWR.

Extremity

The discussion of the use of ADM in extremity reconstruction in this presentation will be intentionally incomplete. Many of the most up-to-date applications for ADM in extremity reconstruction utilize a specific subtype of ADM that is bilaminate, such as Integra. These ADM products have diverse applications and their own specific characteristics, indications, technical considerations, and outcomes that warrant a distinct discussion beyond what is possible in this review. Despite this omission, there are descriptions of the use of ADM in the extremities that are worthy of consideration.

Where ADM has found the most utility has been in the distal upper extremity. The paucity of available local tissue in conjunction with the abundance of important nerves, tendons, and joints presents a difficult reconstructive challenge for the plastic surgeon. While there have been assorted case reports of the use of ADM in the upper extremity for a variety of indications, the best-quality data regards the donor sites following the harvest of a radial forearm free flap (RFFF). Rarely are these defects amenable to primary closure, and in the past skin grafting has been the modality of choice for closure. Despite its widespread acceptance, skin grafting is not without its issues which include contracture, unacceptable cosmesis, temperature sensitivity, and donor site morbidity. Additionally, in circumstances of exposed tendon, nerve, or bone (more common in trauma or oncologic resections), skin grafting is unlikely to be successful due to poor "take" or functionally unacceptable secondary contracture.[94] In a prospective trial by Sinha et al, AlloDerm showed acceptable cosmesis, but a much prolonged healing time of up to 12 weeks.[95] Future studies focused on comparison with skin grafting alone, or in conjunction with ADM. These studies in aggregate demonstrate aesthetic noninferiority and potential functional superiority when ADM is used in underneath a skin graft.[96–99] Given the modest improvements demonstrated in these studies, it becomes important to weigh the cost/benefit analysis for each individual patient.

While there are some studies investigating and showing benefit of the use of ADM for other upper extremity applications, such as burn contracture release, carpometacarpal arthroplasty, or congenital malformations, these are limited studies or small case series. Further investigation into these proposed uses is warranted.

Conclusion and Future Applications

In conclusion, ADMs represent an intriguing tool in the reconstructive arsenal. Falling somewhere between synthetic and autologous, these products attempt to provide

the best aspects of both, without their respective downsides. While the current data are encouraging, much remains to be proven before their role is cemented across all applications discussed in this article. As mentioned previously, the need for more rigorous, high-quality, prospective data remains to be an area of need, and will be what ultimately defines the role of ADM in the realm of plastic surgery and medicine as a whole.[100]

The future outlook appears promising at this time, with novel applications imagined frequently. Much interest currently lies in the use of ADM as a scaffold in regenerative medicine and tissue engineering. There is data to suggest that ADM can be impregnated and used as a scaffold or vehicle for delivery of a variety of both endogenous and exogenous substances ranging from growth factors to stem cells.[101–104] This idea has even been taken a step further, to the point of prefabricating an off-the-shelf construct made from a fasciocutaneous flap design and ADM.[105] While many of these ideas are still in proof-of-concept phase, the future looks bright for these exciting applications with some early successes in patient trials.[104,106,107]

Conflicts of Interest
Dr. Janis has been a consultant for LifeCell, Bard, Daiichi Sankyo, Allergan, and Pacira in the last 12 months but has no active relationships currently. He also receives royalties from Thieme Publishing. RJ and ST have no disclosures.

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