Anthem

Medical Policy

Subject: Allogeneic, Xenographic, Synthetic, Bioengineered, and Composite Products for Wound Healing and Soft Tissue Grafting
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Description/Scope

This document addresses the use of soft tissue (e.g., skin, ligament, cartilage, etc.) substitutes in wound healing and surgical procedures. There is a wide array of uses for such products, including use as a cover for wounds related to disease processes (e.g., diabetes, peripheral artery and venous disease, recessive dystrophic epidermolysis bullosa), coverage or support of surgical and other wounds (e.g., complex abdominal wall repair, breast, and other types of reconstructive procedures), use as a surgical reconstructive material during surgical procedures (e.g., ligament augmentation or substitution, slings for internal organs, trauma, fistula repair, congenital defects), structural support of soft tissues (e.g., injection laryngoplasty, cosmetic augmentation), treatment for dermal and other burns, use in nerve grafting procedures, and many others. Tissue-engineered skin is a significant advance in the field of wound healing and was developed due to limitations associated with the use of autografts.

For the purposes of this document the following terms are defined as below:

- *Autologous:* A product derived from the individual's own body or body products.
- *Allogeneic:* A product derived from humans, other than the individual being treated.
- *Xenographic:* A product derived from non-human organisms (e.g., cows, pigs, horses, etc.).
- *Synthetic:* A product derived from man-made materials.
- *Composite:* A product derived from a mix of materials of various origins.
- *Bioengineered*: A product derived from cultured and processed cells.

Note: The use of fresh, unfrozen, unprocessed allogeneic cadaver-derived skin grafts is not addressed in this document.

Note: This document does not address the use of meshes or patches of when used for standard hernia repair procedures.

Note: This document does not address products used to treat osteochondral defects. For information on such products, please refer to the applicable guidelines used by the plan.

Note: For additional information please see:

- ANC.00007 Cosmetic and Reconstructive Services: Skin Related
- ANC.00008 Cosmetic and Reconstructive Services of the Head and Neck
- MED.00110 Silver-based Products for Wound and Soft Tissue Applications
- MED.00132 Adipose-derived Regenerative Cell Therapy and Soft Tissue Augmentation Procedures
- SURG.00023 Breast Procedures; including Reconstructive Surgery, Implants and Other Breast Procedures
- TRANS.00035 Therapeutic use of Stem Cells, Blood and Bone Marrow Products

Position Statement

Medically Necessary:

I. *Breast reconstruction surgery*

The following products are considered **medically necessary** when used for breast reconstruction surgery:

A. AlloDerm Regenerative Tissue Matrix (aseptic or sterile);**or**
B. Cortiva®; **or**
C. DermACELL™; **or**
D. DermaMatrix®; **or**
E. FlexHD®; **or**
F. SimpliDerm™; **or**
G. Strattice™; **or**
H. SurgiMend®.

II. *Burns*

The following products are considered **medically necessary** when used for the treatment of full-thickness or deep partial-thickness burns:

A. Biobrane; **or**
B. Epicel®; **or**
C. EZ Derm™; **or**
D. Fresh frozen unprocessed allograft skin products (for example, AlloSkin™*, TheraSkin®); **or**
E. Integra™ Bilayer Matrix Wound Dressing; **or**
F. Integra® Omnigraft Dermal Regeneration Template; **or**
G. ReCell™ Autologous Harvesting Device; **or**
H. StrataGraft®.

***Note:** "AlloSkin", "AlloSkin RT™", and "Alloskin™ AC" are different products. AlloSkin is a fresh-frozen product, AlloSkin RT is a

fresh irradiated product (not frozen) and Alloskin AC is an acellular dermal matrix product. Please see the investigational and not medically necessary section below for the position on AlloSkin RT™ and Alloskin™ AC.

III. *Complex abdominal wall wounds*

The following products are considered **medically necessary** for the surgical repair of complex abdominal wall wounds:

A. AlloDerm Regenerative Tissue Matrix (aseptic or sterile); **or**
B. Strattice; **or**
C. OviTex™.

IV. *Diabetic foot ulcers*

The following products are considered **medically necessary** for the treatment of diabetic foot ulcers when the clinical criteria below have been met:

A. Products:
   1. AmnioBand®, sheet or membrane form; **or**
   2. Apligraf®; **or**
   3. Biovance®; **or**
   4. DermACELL™; **or**
   5. Dermagraft®; **or**
   6. EpiCord; **or**
   7. EpiFix™; **or**
   8. Grafix® PRIME; **or**
   9. Kerecis®; **or**
   10. mVASC; **or**
   11. Oasis™; **or**
   12. TheraSkin®;
   and
B. Clinical Criteria:
   1. Ulcers that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, and standard dressing changes) attempted for at least 1 month but not greater than 52 weeks.

V. Dystrophic epidermolysis bullosa

The following products are considered **medically necessary** for the treatment dystrophic epidermolysis bullosa:

A. Dermagraft®; **or**
B. OrCel™.

VI. *Lower extremity dermal wounds*

The following products are considered **medically necessary** for the treatment of lower extremity dermal wounds when the clinical criteria below have been met:

A. Products:
   1. GraftJacket™, sheet or membrane form; **or**
   2. Oasis™; **or**
   3. PriMatrix™; **or**
   4. TheraSkin;
   and
B. Clinical Criteria:
   1. Wounds that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, standard dressing changes, and compression therapy) attempted for at least 1 month but not greater than 52 weeks.

VII. Ocular indications

Allogeneic amniotic membrane-derived grafts or wound coverings, including, but not limited to the following, are considered **medically necessary** when the clinical criteria below have been met:

A. Products:
   1. AmbioDisk™; **or**
   2. AmnioGraft®; **or**
   3. Artacent® Ocular; **or**
   4. Prokera®; **or**
   5. Vendaje Optic™*; **and**
B. Clinical Criteria:
   1. Reconstruction of large conjunctival resections; **or**
   2. Treatment of corneal injuries; **or**
   3. As an adjunct to surgical procedures involving the cornea.

*See Investigational and Not Medically necessary section for the use of other Vendaje products.

VIII. Venous stasis ulcers

The following products are considered **medically necessary** for the treatment of chronic venous stasis ulcers when the clinical criteria are met:

A. Products:

1. AmnioBand, sheet or membrane form; **or**
2. Apligraf®; **or**
3. EpiFix™;
   and

B. Clinical Criteria:
1. Wound has been present for at least 1 month; **and**
2. Has been unsuccessfully treated with compression therapy for at least 14 days.

Not Medically Necessary:

The following products are considered **not medically necessary** when criteria above are not met and for any use not listed above:

1. AlloDerm Regenerative Tissue Matrix (aseptic or sterile)
2. Allogeneic amniotic membrane-derived grafts or wound coverings when used for ocular indications
3. AlloSkin
4. AmbioDisk
5. AmnioBand, sheet or membrane form
6. AmnioGraft
7. Apligraf
8. Artacent Ocular
9. Biobrane
10. Biovance
11. Cortiva
12. DermACELL
13. Dermagraft
14. DermaMatrix
15. Epicel
16. EpiCord
17. EpiFix, sheet or membrane form
18. EZ Derm
19. FlexHD
20. Fresh frozen unprocessed allograft skin products (for example, AlloSkin*, TheraSkin)
21. Grafix PRIME
22. GraftJacket, sheet or membrane form
23. Integra Bilayer Matrix Wound Dressing
24. Integra® Omnigraft Dermal Regeneration Template
25. Kerecis™
26. mVASC
27. Oasis™
28. Omnigraft (also see Integra Omnigraft Dermal Regeneration Template)
29. OrCel
30. OviTex
31. PriMatrix
32. Prokera
33. ReCell™ Autologous Harvesting Device
34. SimpliDerm
35. StrataGraft
36. Strattice
37. SurgiMend®
38. TheraSkin
39. Vendaje Optic

Investigational and Not Medically Necessary

The use of **all** other allogeneic, xenographic, synthetic, and composite products for wound healing or soft tissue grafting, including but not limited to the following products, is considered **investigational and not medically necessary** for all uses:

1. Ac5 advanced wound system
2. Acesso DL
3. Acesso TL
4. ACM Extra Surgical Collagen
5. ACM Extra Surgical Collagen Powder
6. ACM Surgical Collagen
7. Actishield™
8. ActiveBarrier®
9. ActiveMatrix®
10. Affinity™
11. AlloGen-LI™
12. AlloGen™
13. AlloMax™
14. AlloMend™
15. Allopatch HD™
16. AlloPatch® Pliable
17. Alloskin AC
18. AlloSkin RT
19. AlloWrap®
20. AlloWrap™ Dry

21. AlloWrap™ DS
22. Alphaplex™ with MariGen Omega3™
23. AltiPly™
24. AmbientFactor™
25. Ambio5®
26. AmniCore Pro+
27. Amnio FRT™
28. Amnio F™
29. Amnio Quad-Core
30. Amnio Restore™
31. Amnio Tri-Core amniotic
32. Amnio wound
33. AmnioAMP-MP
34. AmnioAMP-PF
35. AmnioAMP-X
36. AmnioArmor®
37. AmnioBand, particulate or injectable form
38. AmnioBind
39. AmnioCare®
40. AmnioClear®
41. AmnioCord®
42. AmnioCore
43. AmnioCore Pro
44. AmnioCyte
45. AMNIOEXCEL™
46. Amniofill®
47. AmnioFix™
48. Amnioflex™
49. AmnioGuard®
50. AmnioHeal®
51. AmnioMatrix™
52. AmnioMTM™
53. Amniopro™
54. AMNIOREPAIR™
55. Amnios®
56. Amnios® RT
57. AmnioShield®
58. Amniostrip™
59. Amniotext
60. Amniovo™ (Solo, Dual, and Matrix)
61. Amniovo™ Max
62. Amniowrap2™
63. Amniply
64. AmnyoFactor™
65. AmnyoFluid™
66. Anu RHEO™
67. Aongen™ Collagen Matrix
68. Apis®
69. Architect Extracellular Matrix™
70. AROA ECM™
71. Artacent® AC Powder
72. Artacent® cord
73. Artacent® Flex
74. Artacent® Wound
75. Artelon®
76. Arthrex® Amnion matrix
77. ArthroFlex™
78. ARTIA™ Reconstructive Tissue Matrix
79. Ascent®
80. Atlas Wound Matrix
81. Avance® Nerve Graft
82. Avaulta Plus™
83. Avive®
84. AxoBioMembrane
85. Axograft™
86. AxoGuard® nerve connector
87. AxoGuard® nerve protector

88. Axolotl Ambient™
89. Axolotl Cryo™
90. Axolotl DualGraft™
91. Axolotl Graft™
92. Axolotl Shot™
93. BEAR® (Bridge-Enhanced ACL Repair) Implant
94. BellaCell HD
95. Belladerm®
96. BellaGen™
97. Bio-ConneKt®
98. BioDDryFlex® Resorbable Adhesion Barrier
99. Biodesign Nipple Reconstruction Cylinder
100. BioDExCel™
101. BioDFactor™
102. BioDFence™
103. BioDOptix™
104. Bioengineered autologous skin-derived products (for example, SkinTE™, MyOwn Skin™)
105. BioFiber™
106. BioFix
107. BioSkin® Flow Amniotic Wound Matrix
108. Biotape XM Tissue Matrix
109. BioWound
110. BioWound plus
111. BioWound Xplus
112. Cardiamend™
113. CardioCel®
114. CardioGRAFT®
115. Celera Dual Layer™
116. Celera Dual Membrane™
117. CellerateRX®
118. Cellesta amnion granulate
119. Cellesta amniotic membrane
120. Cellesta cord
121. Cellesta flowable amnion
122. Cellesta™ Amniotic Membrane
123. CG CryoDerm™
124. CLARIX™ 100 Quick-Peel Wound Matrix
125. CLARIX™ 1k
126. CLARIX™ FLO
127. Cocoon Membrane
128. Cogenex Amniotic Membrane
129. Cogenex Flowable Amnion
130. CollaFilm®
131. CollaFix™
132. CollaGUARD®
133. CollaMend™
134. COLLARX®
135. CollaSorb™
136. CollaWound™
137. Coll-e-Derm™
138. Collexa®
139. Collieva®
140. Complete AA
141. Complete ACA
142. Complete FT
143. Complete SL
144. Conexa™
145. Connext™ Surgical Matrix
146. CoreCyte™
147. Coreleader Colla-Pad
148. Coretext™
149. CorMatrix®
150. Corova
151. Corplex™
152. C-QUR™
153. CRXa™
154. Cryo-Cord™

155. CryoMatrix®
156. CryoSkin®
157. Cuffpatch™
158. CYGNUS Matrix™
159. CYGNUS Max™
160. CYGNUS Solo™
161. Cymetra®
162. Cytal® Burn Matrix (formerly MatriStem)
163. Cytal® Multilayer Matrix (formerly MatriStem)
164. Cytal® Wound Matrix (formerly MatriStem)
165. Cytoflex®
166. Cytoplast™
167. DeNovo® NT Graft
168. DermaBind CH
169. DermaBind SL
170. Dermacyte
171. DermADAPT™ Wound Dressing
172. Derma-Gide®
173. DermaPure™
174. DermaSpan™
175. Dermavest 2™
176. Dermavest™
177. DermMatrix
178. Derm-Maxx
179. DressSkin™
180. DuraForm™
181. Duragen® XS
182. Duragen™ Plus
183. DuraMatrix™
184. Durepair® Regeneration Matrix
185. Emerge Matrix
186. Endobon® Xenograft Granules
187. Endoform® Antimicrobial
188. Endoform® Natural Dermal Template
189. ENDURAgen™
190. Enverse®
191. EpiBurn
192. EpiDex®
193. EpiFix™, particulate or injectable form
194. EpiFlex®
195. Excellagen®
196. Fibro-Gide®
197. FloGraft™
198. FlowerDerm™
199. FlowerFlo™ (FlowerAmnioFlo)
200. FlowerPatch™ (FlowerAMINOPatch)
201. Fluid flow™
202. Fluid GF™
203. FortaDerm™ Wound Dressing (see PuraPly™)
204. Fortiva™ Porcine Dermis
205. GalaFLEX®
206. GalaFORM®
207. GalaSHAPE® 3D
208. Gammagraft™
209. Genesis amniotic membrane
210. Gentrix® Surgical Matrix
211. GENTRIX™
212. GORE BIO-A® Fistula Plug
213. Gore® Acuseal Cardiovascular Patch
214. Grafix plus
215. Grafix® CORE
216. GrafixPL PRIME®
217. Graftjacket™ Xpress injectable
218. GraftJacket™, injectable form

219. GraftRope™
220. HA Absorbent Wound Dressing
221. Helicoll
222. HeliMEND
223. Helisorb®
224. hMatrix®
225. Human health factor 10™ amniotic patch (hhf10-p)
226. Hyalomatrix®
227. Impax Dual Layer
228. Inforce®
229. InnovaBurn®
230. InnovaMatrix® PD
231. InnovaMatrix® AC
232. InnovaMatrix® FS
233. Integra® Flow
234. InteguPly™
235. Interfy
236. Jaloskin®
237. Keramatrix®
238. Kerasorb®
239. KeraSys™
240. Keroxx Flowable Wound Matrix
241. Lamellas
242. Lamellas XT
243. LiquidGen™
244. Lyoplant® (See Tutopatch)
245. MariGen Shield
246. MatrACELL®
247. MatriDerm®
248. Matrion
249. MatriStem®
250. Matrix HD™
251. MatrixDerm™ (see Cytal)
252. Medeor™
253. MediHoney®
254. Mediskin®
255. Membrane Graft™
256. Membrane Patch™
257. Membrane Wrap ™
258. Membrane Wrap-Hydro
259. Memoderm™
260. Menaflex™ Collagen Meniscus Implant
261. Meso BioMatrix™
262. MIAMNION®
263. Microlyte matrix®
264. Miro3D
265. MIRODERM™
266. Miromatrix Biological Mesh
267. Miromesh®
268. MLG-Complete
269. MyOwn Skin
270. Myriad Matrix™
271. Myriad Morcells™
272. Nanofactor™ Flow
273. Nanofactor™ Membrane
274. Neoform Dermis™
275. NeoMatriX
276. Neopatch
277. Neostim DL
278. Neostim membrane
279. Neostim TL
280. Neox RT®
281. NEOX® 100 Quick-Peel Wound Matrix
282. NEOX® 1k Wound Matrix
283. NEOX® FLO
284. Neuragen® Nerve Guide
285. Neuragen® Nerve Wrap

286. NeuraWrap™
287. Neuroflex™
288. NeuroMatrix™
289. NeuroMend™
290. NEVELIA® bi-layer matrix
291. Novachor
292. Novafix™
293. Novomaix Rebound Matrix
294. Novosorb™ Biodegradable Temporizing Matrix (BMT)
295. NuCel®
296. NuDyn™
297. NuShield®
298. Ologen™ Collagen Matrix
299. Omeza Collagen Matrix
300. OrthADAPT™
301. Orthoflow
302. OsseoGuard®
303. Ovation®
304. PalinGen Flow™
305. PalinGen SportFlow™
306. PalinGen® Xplus Hydromembrane
307. PalinGen® Xplus Membrane
308. Pelvicol®
309. PelviSoft®
310. Pericol®
311. Peri-Guard® Repair Patch
312. Peri-Strips Dry®
313. Permacol™
314. PermeaDerm B
315. PermeaDerm C
316. PermeaDerm Glove
317. Phasix Mesh™
318. Phoenix™ Wound Matrix
319. PhotoFix® Decellularized Bovine Pericardium
320. Plurivest®
321. PolyCyte™
322. Preclude® Pericardial Membrane
323. Preclude® Vessel Guard
324. Procenta®
325. ProgenaMatrix™
326. ProLayer
327. ProMatrX ACF
328. Promogran™
329. Protext™
330. PTFE felt
331. Puracol®
332. PuraPly™ (see Fortaderm)
333. Puros® Dermis
334. PX50® and X50® Plus
335. RegenePro™
336. REGENETEN™
337. REGUaRD
338. ReNu®
339. Renuva®
340. Repliform®
341. Repriza™
342. Resolve Matrix™
343. Restore® Orthobiologic Soft Tissue Implant
344. Restorigin
345. Restrata®
346. REVITA®
347. Revita®
348. Revitalon™
349. RevoShield + Amniotic Barrier
350. Rx Flow
351. Rx Membrane

352. Seamguard®
353. SERAGYN® BR
354. SERASYNTH® MESH
355. SERI® Surgical Scaffold
356. Signature A Patch
357. SIS Wound Dressing II
358. SJM™ Pericardial Patch
359. SkinTE
360. SportMatrix
361. SportMesh™
362. SS Matrix™
363. SteriGraft™
364. SteriMatrix™
365. SteriShield™
366. Stimulen™ Collagen
367. Stravix™
368. SUPRA SDRM®
369. Suprathel®
370. SureDerm®
371. SurFactor®
372. SurGraft®
373. SurGraft FT
374. SurGraftXL
375. SurgiCord™
376. surgiGRAFT™
377. surgiGRAFT™ nano
378. surgiGRAFT™-Dual
379. Surgisis® (including Surgisis® AFP™ Anal Fistula Plug, Surgisis® Gold™ Hernia Repair Grafts, and Surgisis® Biodesign™)
380. Symphony™
381. Talymed™
382. tarSys™
383. TenoGlide™
384. TenSIX™
385. TheraForm™ Standard/Sheet
386. TheraGenesis®
387. TIGR Matrix Surgical Mesh
388. TiLOOP® Bra
389. TissueMend®
390. Tornier® BioFiber Absorbable Biological Scaffold
391. TranzGraft®
392. TruSkin™
393. Tutomesh™ Fenestrated Bovine Pericardium
394. Tutopatch™ Bovine Pericardium
395. Unite™
396. Vascu-Guard®
397. Vendaje (Other than for ocular indications. See medically necessary section for use for ocular indications)
398. Veritas® Collagen Matrix
399. VersaShield™
400. VersaWrap®
401. VIA DERMIS™
402. Via Disc® NP
403. Viable Allograft Supplemental Disc Regeneration (VAST)
404. Viaflow
405. VIAGENEX®
406. VIM® human amniotic membrane
407. WoundEx®
408. Woundfix Plus
409. Woundfix Xplus
410. Woundfix,
411. WoundFix™
412. Xceed™
413. Xcellistem®
414. XCM Biologic™
415. Xelma®
416. XenMatrix™ Surgical Graft

417. XenoSure® Biologic Patch
418. X-Repair
419. Xwrap™ (Hydro, DRY, and ECM)
420. Zenith™ human amniotic membrane.

Rationale

General considerations

There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products differ in species source (e.g., human cadaveric, synthetic, bovine, porcine, equine, a combination of several types, etc.), tissue source (e.g., dermis, pericardium, intestinal mucosa, etc.), bioburden reduction (e.g., nonsterile, sterile), additives (e.g., antibiotics, surfactants), delivery formats (e.g., wet packaged, freeze-dried), and preparation requirements (e.g., multiple rinses, rehydration). Additionally, they are procured, produced, manufactured, or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products. This is made evident not only in the wide range of shelf-life recommendations for these types of products, but also in the descriptions of their physical properties. Additionally, there are a limited number of comparative studies available addressing the clinical outcomes for allographic, xenographic, and composite products, and the results are heterogeneous. What comparative data is available demonstrates a wide range of outcomes, with some studies reporting no differences and others indicating significant differences in the rate of healing, incidence of seroma and infection, surgical failure, and other outcomes. Therefore, each product is assessed on the basis of the available scientific evidence specific to that product rather than considering groups of products as belonging to a class (for example, acellular dermal matrix products) and then evaluating all members of that class as though they were therapeutically equivalent. While this approach has certain merits, within each possible class that could be constructed there are products that have no full-text, peer-reviewed, published studies available to evaluate the clinical utility or draw a conclusion as to whether that particular product is therapeutically equivalent to another similar but studied product. Products for which there is a lack of quality published and peer-reviewed evidence to consider are considered investigational and not medically necessary. For other products, there may be one or more published studies of varying quality. The use of blinding in studies for these types of products may pose a challenge due to the nature of the products compared to standard therapies, as well as other factors. However, investigators should strive to design and apply rigorous study methodologies to minimize possible sources of bias within their trials.

Below, we summarize the findings of the most recent or most rigorous studies available. Please note that the discussion below is not meant to be an exhaustive review of the evidence available, but to address the most significant studies available for each product. Many studies have been omitted because they were considered poorly designed or underpowered to adequately demonstrate efficacy for a more general population.

Non-Product Specific Acellular Dermal Matrix (ADM) Studies, Multiple Product Studies, Meta-analyses, and Systematic Reviews

The use of ADM products of various origins has been proposed for both immediate and two-stage breast reconstruction surgeries and has become widely used and accepted. However, the current evidence of these techniques has been understudied and the data that has been made available is not from rigorously designed and conducted randomized controlled trials (RCTs).

To properly address the question of both safety and efficacy, the MultiCentre Canadian Acellular Dermal Matrix trial (MCCAT) has begun recruitment in a two-arm parallel superiority trial that will compare one-stage ADM facilitated implant breast reconstruction with two-stage tissue expander and implant breast reconstruction (Zhong, 2013). The results addressing this pressing issue are eagerly anticipated.

In 2012, two well-designed meta-analysis studies were published that evaluated the available peer-reviewed published evidence addressing the use of ADMs for use in breast reconstruction procedures. Ho and colleagues conducted their meta-analysis using 16 studies that met their inclusion criteria. They noted that analysis of complication rates was limited by the small number of studies and the small sample size of study participants. Additionally, they commented that the overall quality of the evidence was low. Five studies were included that had data for both participants who received ADM and those who did not. Overall, they found that the ADM group had significantly higher complication rates for seroma, infection, and reconstructive failure when compared with the non-ADM group. ADM-assisted breast reconstructions were found to be almost 4 times as likely to be complicated by seroma, nearly 3 times as likely to become infected, and 3 times as likely to have a reconstructive failure as breast reconstructions performed without the use of ADM. After exclusion of outlier data, they found that the pooled odds ratio (OR) of developing skin flap necrosis in ADM reconstructions was three-fold higher than non-ADM reconstructions.

Kim and others conducted a meta-analysis on 44 studies that met their inclusion criteria. The results found that there was an increased rate of total complications with ADM use when compared to non-ADM reconstructions (15.4% vs. 14.0%). For specific complications, this finding continued to apply; specifically for seroma (4.8% vs. 3.5%), infections (5.3% vs. 4.7%), and flap necrosis (6.9% vs. 4.9%). However, the rate of hematoma was greater in the control cohort (1.5% vs. 1.0%). The rate of reconstructive failure was very similar in both cohorts, 3.8% vs. 3.8%. When looking at the studies that provided comparative data between ADM and non-ADM groups in the same study, the authors noted that there was an increase in the risk of total complications (relative risk [RR], 2.05; 95% confidence interval [CI], 1.55 to 2.70), seroma (RR, 2.73; 95% CI, 1.67 to 4.46), infection (RR, 2.47; 95% CI, 1.71 to 3.57), and reconstructive failure (RR, 2.80; 95% CI, 1.76 to 4.45) in the ADM group vs. the non-ADM group. These findings call into question the practice of using ADM for breast reconstruction surgery.

A systematic review of ADM use for abdominal wall reconstruction was published by Zhong and others (2011). They report on a total of 30 articles that met inclusion criteria, specifically mentioning that they did not identify any level I or II studies addressing this issue. They included 4 level III and 26 level IV studies. Among their findings they report wide variation in indications for ADM use and poorly defined terminology used to define participant populations (e.g., abdominal wall reconstruction, high-risk/recurrent/complex/large ventral hernia and high-risk/contaminated wound). The incidence of postoperative hernia varied widely, with some studies reporting 0% and others reporting 80%. Out of the 30 studies reviewed, three used porcine ADM, one a synthetic composite mesh, and one a bovine-derived ADM. No separate data was provided for these studies. The remainder of the studies used allogeneic ADMs. Within the literature, there was significant variation with regard to placement of ADMs within the surgical field, with ADM used as underlay/inlay, interposition, overlay/onlay or sandwiched (underlay and overlay) repairs. The type of fascial repair (bridged vs. reinforced) also had significant impact on outcomes. They state that in cases where fascial re-approximation was achieved, ADM used in a reinforced repair with fascial re-approximation was significantly better than that used in a bridged repair without fascial re-approximation. With the significant variation in selection criteria, ADM types, and surgical techniques, this pool of evidence should not be used to evaluate the use of ADM for abdominal reconstructions in a global manner, and each study should be weighed on its own merits.

Ibrahim and colleagues (2013) conducted a large retrospective study using data from the American College of Surgeon's (ACS)

National Surgical Quality Improvement Program (NSQP) database. The study investigated 30-day outcomes in 19,100 cases that involved tissue expander implant-based breast reconstruction surgeries. A subset of 3301 (17.3%) cases involved the use of ADMs as part of the surgical procedure. It was reported that, overall, the rate of complications was not statistically different between cases that used ADMs (n=175, 5.3%) and those that did not (n=776, 4.9%) (p=0.396). This rate is much lower than the rate of complications reported in previous studies. It should be noted that there are several major limitations of this study, including the fact that the data was derived retrospectively from a large database with no randomization, no blinding, and no concurrent comparison groups. Additionally, the ACS does not use a standardized definition for the term “complications.” This presents a major problem, considering that there may be significant heterogeneity in the major study endpoint data. Also of import is that the data in the NQSP database is derived from academic medical centers, and no data from community hospitals and private clinics is included. It is unclear whether or not this had an impact on complication rates. Finally, there were significant differences between groups at baseline with regard to age, race, and type of reconstruction, which may have introduced significant bias into the analysis.

In 2017, Lee and others published a meta-analysis investigating the use of ADMs for implant-based breast reconstruction. A total of 17 studies were included, with only one being a prospective RCT and the others having retrospective nonrandomized designs. There were 12 studies available involving comparisons with FlexHD, DermaMatrix, and aseptic or sterile AlloDerm products. In the meta-analysis comparing FlexHD and aseptic AlloDerm, involving a total of six studies, both products showed similar pooled risks for all complications. For comparisons between DermaMatrix and aseptic AlloDerm, the results from four studies likewise found no differences between the pooled risks of complications. Finally, the meta-analysis of four studies comparing the aseptic or sterile forms of AlloDerm demonstrated that the pooled risks for the complications did not differ. The authors concluded that these products have similar risks of complications.

Sorkin (2017) reported the results of a retrospective controlled study involving 1297 participants who underwent expander/implant-based breast reconstruction procedures with either ADM (n=655) or no ADM (n=642). At 2 years post-procedure, no significant differences were seen between groups with regard to overall complications (OR, 1.21; p=0.263), major complications (OR, 1.43; p=0.052), wound infections (OR, 1.49; p=0.118), or reconstructive failures (OR, 1.55; p=0.089). No significant differences were reported in participant-reported outcome scores, including satisfaction with breasts, psychosocial well-being, sexual well-being, physical well-being, and postoperative pain.

Schnarrs (2016) reported the results of a retrospective non-randomized controlled trial involving 126 participants who underwent 170 breast reconstruction procedures involving the use of aseptic AlloDerm (n=143), sterile AlloDerm (n=19), FlexHD (n=18), and hMatrix (n=32). The authors reported no significant differences between groups with regard to complication rates (p>0.05). They also reported that both smokers and large-breasted participants (≥ 500 g) were at significantly higher risk for complications vs. nonsmokers and non-obese participants (p<0.01 and p<0.03, respectively). The conclusion was that there were no significant differences between products with regard to complications. However, the study design, including disparate group sizes, limits the generalizability of these findings. Results from more rigorously designed and conducted trials would be helpful in better understanding the comparability of various soft tissue grafting products used in breast reconstruction procedures.

Products addressed in the Medically Necessary statement

Allogeneic amniotic membrane-derived grafts or wound coverings used for ophthalmologic indications.

Allogeneic amniotic membrane-derived products have a history of longstanding use for the management of select ophthalmologic wounds and reconstruction of large conjunctival resections where there is limited access to autologous tissue for transplant, or when allogeneic transplant is not appropriate. These types of products come in a wide array of forms, including cryopreserved, fresh-frozen, lyophilized, irradiated, stored in mineral oil, and others. Most products used are obtained directly from tissue banks and not marked by any particular manufacturer. However, several products are commercially marketed, including AmnioGraft and Prokera.

Reconstruction of large conjunctival resections

The treatment of large conjunctival resections, commonly needed for the surgical treatment of cancerous lesions of the eye, is a challenge due to the finite amount of conjunctival tissue available for local conjunctivoplasty or rotational flaps. In such cases, the use of amniotic membrane-derived products have become the standard-of-care option to provide adequate grafting materials to successfully complete these types of procedures, and multiple weak case series studies have been published to support this use (Asoklis, 2011; Dalla Pozza, 2005; Gündüz, 2006; Hanada, 2017; Paridaens, 2001; Tanaka, 2016, Tseng, 1997).

Bullous keratopathy in individuals who are not candidates for curative endothelial or penetrating keratoplasty

Amniotic membrane-derived products are one of several modalities used for treatment of bullous keratopathy due to corneal endothelial dysfunction. Given that amniotic membrane-derived products do not address the underlying endothelial disease, their role in treating bullous keratopathy is palliative rather than curative; for this reason, it is a reasonable alternative for individuals who are not candidates for curative endothelial or penetrating keratoplasty. Supporting evidence includes a prospective RCT of 40 participants treated with amniotic membrane transplantation or anterior stromal puncture (Paris F dos S, 2013). At 90- and 180-days post-procedure, the presence of a regular epithelial surface was higher in the amnion group than in the control group (60% vs. 16.7% at 90 days, p=0.006; and 50% vs. 6. 3% at 180 days, p=0.008). At 180 days follow-up there was no statistical difference between the two groups in pain severity (p=0.391) or duration (p=0.715). Georgiadis (2008) published the results of a prospective case series study involving 81 participants with bullous keratopathy treated with cryopreserved amniotic grafts. They reported that 71 (87.6%) eyes became asymptomatic with healed epithelium at a mean of 21 months follow-up. Repeated amniotic transplantation was needed for 7 participants and 3 underwent penetrating keratoplasty. Visual acuity improved in 64 (79%) participants and remained unchanged in 14. No complications were recorded. Multiple other weak case series studies describe positive results from the use of amniotic graft products for bullous keratopathy (Chansanti O, 2005; Espana EM, 2003; Pires RT, 1999; Siu, 2015; Srinivas, 2007; Stefaniu, 2014).

Acute chemical burns of the ocular surface

Acute chemical burns of the ocular surface can be challenging to treat due to the lack of transplantable or resectionable autologous tissue. Use of amniotic membrane-derived products has been shown to reduce inflammation and promote healing. The use of this type of graft has been described in two prospective RCTs. The first involved participants (44 eyes) with acute moderate grade ocular burns treated with amniotic graft (n=20) or standard medical care (n=24) (Tamhane, 2005). Standard medical care involved the use of topical prednisolone acetate (1%), ofloxacin, sodium ascorbate (10%), sodium citrate (10%), preservative-free lubricants, homatropine (2%), oral vitamin C (500 mg) and antiglaucoma therapy including timolol maleate 0.5% drops and/or oral acetazolamide if required. The authors reported that the log mean percentage reduction in size of epithelial defect by day 7 was 7.43 ± 0.89 after amnion treatment vs. 6.23 ± 1.10 with control treatment (p=0.01). However, there was no difference between the two groups in eyes with severe burns. Additionally, no difference between groups was noted in the final visual acuity, symblepharon formation, corneal vascularization, and tear function tests at 3 months. The second RCT involved 100 participants with moderate to severe ocular burns treated with amniotic graft (n=50) or standard medical care (n=50) (Tandon, 2011). The rate of epithelial healing was reported to have been significantly better in the amnion group vs. controls (p=0.0004). No other differences between groups were reported with regard

to final visual outcome, symblepharon formation, corneal clarity and vascularization with or without amniotic membrane transplantation. In addition to these RCTS, multiple underpowered case series studies have been reported demonstrating beneficial results with amniotic grafts for ocular chemical burns (Arora, 2005; Kheirkhah, 2008; Prabhasawat. 2007; Tejwani, 2007; Uçakhan, 2002; Westekemper, 2000).

Persistent corneal epithelial defects that do not respond to conservative therapy

The prompt treatment of persistent corneal epithelial defects that do not respond to conservative therapy is critical due to the risk of the development of corneal ulcers, corneal melt, and perforation. While first-line treatment of corneal defects include topical lubricants, antibiotics, therapeutic contact lenses and patching, when these methods fail, the use of amniotic membrane-derived products has become the standard of care. In severe cases, the option of corneal transplantation is available, but that procedure entails its own significant risks, and less invasive methods are often tried first. One prospective RCT evaluated 19 participants with corneal thinning treated with amnion (n=9) or allograft cornea (n=10) (de Farias, 2016). All participants showed significant increase in final thickness in the area of thinning at 180 days postoperatively, but those who received corneal transplant had a slight but significantly higher final thickness (p=0.48). Regardless of the surgical technique, all participants showed epithelialization. No difference between groups was noted for post-op corneal opacity. Participants undergoing amnion grafting showed an 89% decrease in neovascularization, whereas none was reported in the corneal transplant group. Final corrected distance visual acuity was better in participants submitted to AMT. In addition to this study, additional weak case series studies have been published demonstrating beneficial outcomes (Dekaris, 2010; Gris, 2002; Lee, 1997; Letko, 2001; Prabhasawat, 2001; Seitz, 2009).

Corneal perforation when corneal tissue is not immediately available or as adjunct to corneal transplantation in individuals with active inflammation

As noted above, the use of corneal transplant is the preferred method of treatment for corneal perforation. However, the temporary use of amniotic membrane-derived products has been a standard temporary option when transplant tissue is not immediately available or if there is ongoing active inflammation. Multiple weak case series studies have described the successful use of amnion-derived grafting products for this purpose (Hick, 2005; Prabhasawat, 2001; Rodríguez-Ares, 2004; Solomon, 2002).

Corneal ulcers or corneal melts that do not respond to conservative therapy

Similar to the treatment of persistent corneal epithelial defects, treatment of corneal ulcers or corneal melts (also known as keratolysis) that do not respond to conservative therapy is critical to avoid the development of corneal perforation. While corneal ulcers and corneal melts may result from a wide range of etiologies, a common characteristic is underlying inflammation. The use of amniotic membrane-derived products is accepted as an adjunctive treatment along with treatment of the primary cause of the condition when use of topical lubricants, antibiotics, or therapeutic contact lenses fails. Multiple weak case series studies have been published supporting this approach (Chen, 2006; Hanada, 2001; Kruse, 1999; Prabhasawat, 2001; Sheha, 2009; Solomon, 2002; Tok, 2015).

Neurotrophic keratitis that does not respond to conservative therapy

Neurotrophic keratitis, similar to persistent corneal epithelial defects, corneal ulcers, and corneal melts, presents a significant risk of corneal perforation when unresponsive to conservative therapy such as topical lubricants, antibiotics, therapeutic contact lenses and patching. As with those other conditions, treatment of refractory neurotrophic keratitis with amniotic membrane-derived products has become widely accepted as standard of care and described in several underpowered case series studies (Chen, 2000; Iveković, 2002; Khokhar, 2005; Suri, 2013; Uhlig, 2015).

Partial limbal stem cell deficiency in conjunction with superficial keratectomy

Limbal stem cell deficiency is characterized by a loss or deficiency of the stem cells in the limbus that are vital for re-population of the corneal epithelium. Total limbal stem cell deficiency is commonly treated with limbal cell transplantation; partial limbal stem cell deficiency is commonly treated with an approach which includes grafting with amniotic membrane-derived products in conjunction with superficial keratectomy to remove the diseased tissue (Kheirkhah, 2008; Sangwan, 2004).

Extensive, double, or recurrent pterygium in which there is insufficient healthy tissue to create a conjunctival autograft

A pterygium is a triangular, fleshy fold of tissue that extends from the conjunctiva and encroaches onto the cornea. The size and growth rate of pterygia vary, and when vision is affected, surgery is often indicated. Treatment of pterygium is most commonly done with autograft or bare scleral techniques. Multiple RCTs have demonstrated that for both primary and recurrent pterygium, treatment with autograft was superior to treatment with amniotic membrane-derived products (Küçükerdönmez, 2007; Luanratanakorn, 2006; Prabhasawat, 1997; Tananuvat, 2004). This is supported by the American Academy of Ophthalmology in their 2013 report titled Options and Adjuvants in Surgery for Pterygium (Kaufma, 2013), as well as Cochrane review (Clearfield, 2016). However, when there is extensive, double, or recurrent pterygium in individuals who have insufficient healthy tissue to create a conjunctival autograft, the amniotic membrane-derived products may be used.

Moderate or severe Stevens-Johnson syndrome involving the cornea and/or conjunctiva

For moderate or severe Stevens-Johnson syndrome (SJS), there are few treatment options, and the use of amniotic membrane-derived products has been widely accepted as the standard of care. A prospective RCT published by Sharma (2016) involved 50 participants with acute SJS who were assigned to treatment with either amnion (n=25) or medical therapy (n=25). The authors reported that best-corrected visual acuity at 6 months was significantly better in the amnion group vs. controls (p=0.042). Mean tear film breakup time and Schirmer test results were also significantly better in the amnion group vs. controls (p=0.015 and p=0.001, respectively). Conjunctival congestion persisted in 44% of control participants vs. 4% in the amnion group at 6 months (p=0.03). Corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications were not reported in the amnion group, but the control group experienced corneal haze (44%, p=0.001), corneal vascularization and conjunctivalization (24%, p=0.03), symblepharon (16%, p=0.12), ankyloblepharon (4%, p=1.00), ectropion and entropion (8%, p=0.47), and trichiasis and metaplastic lashes (24%, p=0.03). Several weak case series studies have also demonstrated favorable outcomes (Gregory, 2011; Honavar, 2000; John, 2002; Shammas, 2010; Tomlins, 2013).

Other ocular conditions

Amniotic membrane-derived products have been investigated for the treatment of other conditions, including glaucoma and dry eye. The treatment of glaucoma has been studied in two controlled trials. The first, published by Mahdy (2010), was a nonrandomized controlled trial involving 30 pediatric participants with glaucoma treated with either trabeculectomy with mitomycin C or trabeculectomy with mitomycin C plus lyophilized amniotic membrane. The authors reported that operative success occurred in 80% of amnion group participants and 60% of control participants. Mean postoperative intraocular pressure was significantly decreased in both groups. However, the intraocular pressure gradually increased throughout the follow-up visits, with significantly higher intraocular

pressure in the amnion group vs. controls up to 18 months ($p<0.05$). Complications such as inflammation, choroidal detachment, or toxic keratopathy were not noted in the amnion group but were noted in the control group. The authors concluded that trabeculectomy with amniotic membrane transplantation and mitomycin C can effectively control the elevated intraocular pressure in pediatric patients with glaucoma without significant postoperative complications. The other study by Sheha and others (2008) was a prospective RCT of 37 eyes with glaucoma undergoing trabeculectomy with mitomycin C and amnion (n=19 eyes) or trabeculectomy with mitomycin C alone (n=18). Complete success, defined as intraocular pressure < 22 mm Hg without glaucoma medications, was reported in 93.7% of amnion-treated eyes and 60% control eyes at 6 months ($p=0.03$), and 80% and 40% at 12 months ($p=0.03$). Intraocular pressure decreased significantly in both groups at 12 months ($p<0.0001$). Early postoperative hypotony developed in 16.7% of control eyes owing to excessive filtration but none of the amnion group eyes ($p=0.1$). Encapsulated bleb occurred in 38.9% of control eyes but in 5.3% of amnion-treated eyes ($p=0.02$). While these studies have demonstrated significant benefits, the use of amniotic membrane-derived products has not yet become widely accepted as standard practice. A wide array of other less invasive treatment options are currently available which provide significant relief to this population.

Short term treatment of dry eye has also been a proposed use for amniotic membrane-derived products. One RCT has been published addressing this treatment option (John, 2017). The underpowered prospective RCT involved 17 participants with dry eye disease treated with either cryopreserved amnion (n=8) or standard care (n=9). The authors stated that pain and visual disturbances decreased significantly in the amnion group but not in the control group (no p values provided). No differences between groups were reported for visual acuity. Dry Eye Work Shop (DEWS) measures were significantly improved vs. controls (no p values provided). No differences between groups were reported for corneal topography measures. Central corneal nerve density, dendritiform cell density and corneal sensitivity was greater in the amnion group (no p values provided). While these reported findings seem beneficial, the small sample size and lack of proper statistical data do not allow reliable conclusions. Two case series studies have also demonstrated beneficial outcomes (Cheng, 2016; McDonald, 2018, described below). Use of amniotic membrane-derived products also limits visual acuity. However, this treatment has not been widely accepted as a standard treatment approach in the clinical setting. Many effective less invasive treatments are available for dry eye.

Several branded amniotic-membrane derived products have been the subject of published peer-reviewed studies. These are described below.

Prokera

Prokera is a composite product consisting of amniotic membrane tissue in between two rings of clear, flexible material. It was cleared through the FDA's 510K process and is intended for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred. The device is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions.

To date, the largest study published addressing the use of Prokera was a retrospective case series study involving 97 eyes of 84 participants with severe dry eye refractory to maximal medical management (McDonald, 2018). Participants had superficial punctate keratitis (86%), filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). After treatment with Prokera for a mean of 5.4 days, 74 (88%) of participants demonstrated an improved ocular surface. Dry eye workshop score (DEWS) was reduced significantly from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months ($p<0.001$ for all). A total of 10 eyes (10%) required repeated treatment to complete healing. Apart from discomfort during CAM placement, there were no adverse events.

Another underpowered retrospective case series study involved placement of Prokera in 58 participants undergoing penetrating keratoplasties (PKP) in high-risk recipients (Nguyen, 2014). Twelve participants underwent their first PKP and 46 had repeat PKP. The authors reported that risk factors for graft failure included repeat PKP (79.3%), corneal neovascularization (51.7%), preexisting glaucoma (46.6%), and presence of anterior synechiae (37.9%). Both first and repeat PKP groups had similar survival rates until 6 months (75% vs 74%, OR, 1.06, $p=1.00$). At 12 months, the first PKP group showed a better survival rate (67% vs 43%, OR, 2.60, $p=0.20$). Eyes with > 3 risk factors had a higher graft failure rate (OR, 5.81, $p=0.003$).

Vlasov (2016) reported on the use of Prokera in 80 participants undergoing photorefractive keratectomy. Participants were treated with either Prokera (n=40) or high-oxygen-transmissible bandage contact lens (Acuvue Oasys, n=40). No significant differences between groups were reported with regard to visual outcomes, corneal clarity, and optical quality of the cornea. The Prokera group experienced 1 case of spontaneous extrusion, 1 case of delayed epithelial healing, 2 cases of persistent defect, 4 cases of corneal infiltrates, and 1 case of nongranulomatous uveitis. Four cases of corneal infiltrates were reported in the control group. The authors concluded that the use of Prokera for post- photorefractive keratectomy wound healing remains speculative.

McDonald (2023) reported a study addressing the use of Prokera for the treatment of dry eye disease. This multi-center, retrospective study involved 77 participants (89 eyes) with moderate-to-severe dry eye disease (DEWS severity score 3.24 ± 0.56) treated with Prokera. Treatment duration varied, with participants having treatment of 2 days (n=10), 3 days (n=15), 4 days (n=12), 5 days (n=19), 6 days (n=6), or 7 days (n=27) (average of 4.9 days). The authors reported significant improvement in DEWS scores at 1 week, 1 month, and 3 months for all treatment duration groups (1.45 at 1 week, 1.45 at 1 month, and 1.47 at 3 months, $p<0.0001$ for all), with no significant differences observed between treatment duration groups at any timepoint. Visual acuity significantly improved from logMAR 0.30 at baseline to logMAR 0.22 at 1 and 3 months ($p=0.001$). Ocular discomfort significantly improved at all time points ($p=0.004$), as were visual symptoms ($p=0.04$). Only one participant (10%) required re-treatment. The authors concluded that a single placement of Prokera for 2 days can significantly improve signs and symptoms of dry eye disease with a lasting benefit observed for up to 3 months. These results warrant further investigation in a prospective controlled trial to establish more generalizable data.

Allogeneic amniotic membrane-derived grafts or wound coverings used for other than ophthalmologic indications.

The use of amniotic-membrane derived products has been proposed for a wide variety of other indications, which may be addressed further in this document. These types of products may be used for a large number of other non-ocular indications. However, except where otherwise indicated, such use has not been widely accepted by the practicing community.

AlloDerm Regenerative Tissue Matrix (Aseptic)

AlloDerm Regenerative Tissue Matrix, also known as AlloDerm RTM, is an aseptic human-derived decellularized grafting product which is regulated through the U.S. Food and Drug Administration (FDA) Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) process as human tissue for transplantation. This aseptic product is being phased out of the market by the manufacturer beginning in 2021. This is due to the increasing use of the sterile version of this product, also known as AlloDerm Regenerative Tissue Matrix, AlloDerm Ready to Use (RTU) and AlloDerm SELECT RTM.

There are over a dozen weak case series studies and nonrandomized controlled trials published in the peer-reviewed medical literature describing the use of aseptic AlloDerm to partially or completely enclose an implanted breast prosthesis during post-mastectomy breast reconstruction (Becker, 2009; Bindingnavele, 2007; Breuing, 2005, 2007; Gamboa-Bobadilla, 2006; Preminger, 2008; Salzberg, 2006, 2011; Spear, 2008; Woo, 2017). The goal of using aseptic AlloDerm for this type of procedure is to reduce

complications related to contracture, periprosthetic atrophy, and development of thin capsules. The results provided in these case series studies indicate good symmetry, increased soft tissue padding, and decreased rippling and implant visibility. While the available data is limited regarding the long-term benefits and outcomes of this procedure, it has become a widely used and accepted method of breast reconstruction. Expert opinion of breast surgeons supports the use of aseptic AlloDerm for this indication.

However, care must be taken when selecting aseptic AlloDerm for use in breast reconstruction. A retrospective, nonrandomized controlled study by Weichman and others published in 2012 found significant complication rates with its use. In their study, 407 consecutive participants underwent 628 immediate 2-stage breast reconstructions either with aseptic AlloDerm (n=442, 70.3%) or without aseptic AlloDerm (n=186, 29.6%). The authors reported that major complications were significantly increased in the aseptic AlloDerm group (15.3% vs. 5.4%, p=0.001). Complications included infection requiring intravenous antibiotics (8.6% vs. 2.7%, p=0.001), flap necrosis requiring excision (6.7% vs. 2.7%, p=0.015), and explantation of the tissue expander (7.7% vs. 2.7%, p=0.004).

The treatment of infected or contaminated abdominal wall wounds and defects is difficult. Standard fascial prostheses such as polypropylene and polyester mesh, which are routinely used for non-complex cases, may exacerbate wound infection, fistula and adhesion formation, and erosion, leaving few real options for such individuals. The use of aseptic AlloDerm for the treatment of complex abdominal wall wounds has been reported in over 30 peer-reviewed journal articles (Espinosa-de-los-Monteros 2007; Glasberg, 2006; Lee, 2009; Lin, 2009; Maurice, 2009; Patton, 2007; Vertrees, 2009). These studies demonstrate a high rate of successful wound healing with relatively low numbers of complications. As with the use of aseptic AlloDerm for breast reconstruction, aseptic AlloDerm for complex abdominal wall wounds has been widely used and is an accepted treatment method, although data is limited regarding the long-term benefits and outcomes of this use. Expert opinion of surgeons who routinely treat these types of wounds supports the use of aseptic AlloDerm for this indication.

At this time, there is limited data addressing the use of aseptic AlloDerm in treating chronic wounds. There is very limited evidence available regarding the use of aseptic AlloDerm in the treatment of burns or for surgical reconstruction procedures such as in the treatment of lid retraction in individuals with Graves' disease or in the prevention of Frey's Syndrome. Additionally, aseptic AlloDerm has been proposed for use in a wide variety of other surgical applications.

The use of aseptic AlloDerm has been proposed for the treatment of various nasal and oral surgeries, including palatal fistula. At this time, there are only a limited number of underpowered studies addressing this use in clinical trials (Helling, 2006; Steele, 2006). These studies show promising results but are underpowered and use weak study designs. Additional studies are needed to demonstrate the efficacy of this use of aseptic AlloDerm.

In the one available clinical trial of aseptic AlloDerm in people with lid retraction due to Graves' disease, only 14 participants were studied in a non-blinded fashion (Sullivan, 2003).

A retrospective non-randomized case series involving 54 participants (95 eyes) with Grave's orbitopathy who underwent swinging eyelid orbital decompression was reported by Kim (2017). The participants were divided into 3 groups: 1) conjunctival lengthening using AlloDerm (36 eyes), 2) inferior retractor recession (33 eyes), and 3) decompression only (26 eyes). Participants in groups 1 and 2 showed correction of eyelid retraction at 4 to 6 months (2.7 mm and 1.8 mm, respectively). Mean improvement in margin reflex distance-2 at 4 to 6 months was significantly better in the AlloDerm group vs. the other two groups ($p<0.001$). Similarly, the mean reduction in inferior scleral show at baseline to 4 to 6 months after surgery was also significantly better in group 1 vs. group 2 and group 3 ($p<0.001$). All 3 groups achieved good surgical results. The author concluded that the use of AlloDerm resulted in better outcomes when compared to inferior retraction recession or decompression only. While promising, further controlled studies with larger numbers of participants are needed to confirm these findings.

There are currently two studies available in the peer-reviewed literature addressing the use of aseptic AlloDerm for treatment of burns. The first study involved 19 participants randomized to aseptic AlloDerm with an *autograft* overgraft vs. aseptic AlloDerm with an *allograft* overgraft which was replaced with an autograft overgraft after 1 week (Munster, 2001). Graft uptake was not different between groups. Immediate use of aseptic AlloDerm with thin autograft was associated with more healing than spilt thickness grafts. The second study involved 52 nonrandomized participants all of whom received aseptic AlloDerm covering to radial arm free flap donor sites (Sinha, 2003). The results of this study indicated that there were minimal contractures or restrictions to the healed graft. While these studies suggest some benefit from the use of aseptic AlloDerm for burns, larger randomized trials are needed to confirm efficacy of this procedure.

At this time, there are two available studies in the peer-reviewed literature regarding the use of aseptic AlloDerm to treat Frey's syndrome. The first involved 64 participants randomly assigned to the use of aseptic AlloDerm placement in the parotid bed following removal of the parotid gland vs. no aseptic AlloDerm (Govindaraj, 2001). While the rate of gustatory sweating in the aseptic AlloDerm group was found to be statistically lower than the control group, the aseptic AlloDerm group also had an almost three-fold increase in complications, including both a higher frequency of seroma as well as one wound infection. In a second study, 30 participants were randomized into 3 groups; (1) superficial parotidectomy with placement of aseptic AlloDerm, (2) superficial parotidectomy without placement, and (3) deep-plane rhytidectomy (Sinha, 2003). The incidence of both subjective and objective Frey's syndrome was significantly higher in group 2 when compared to both groups 1 and 3. However, given the small numbers of participants in each group, the results of this study do not allow strong conclusions to be drawn as to the effectiveness of this procedure.

Overall, the available evidence addressing the use of aseptic AlloDerm for breast and complex abdominal reconstruction procedures demonstrates significant benefits in relation to health outcomes. While AlloDerm has been used for a wide variety of other indications, as discussed above, such uses have been poorly studied and have not been widely accepted by the practicing community.

AlloDerm Regenerative Tissue Matrix (also known as AlloDerm SELECT RTM and AlloDerm Ready To Use [RTU]) (Sterile)

Another AlloDerm product, also known as AlloDerm Regenerative Tissue Matrixand formerly known as AlloDerm SELECT RTM, AlloDerm Ready To Use, and AlloDerm RTU, is a sterile product that is reportedly easier to use. The manufacturer of the AlloDerm products, Allergan, is phasing out use of the aseptic AlloDerm product in favor of the sterile version of this product.

The sterile product is similar to the aseptic AlloDerm product in origin and processing and is treated as human tissue for transplantation under the FDA's HCT/P process. Both products are derived from donated cadaveric dermis and undergo the same aseptic tissue processing. However, the sterile AlloDerm product undergoes additional sterilizing with electron beam radiation. Additionally, whereas aseptic AlloDerm is freeze-dried prior to packaging and requires rehydration prior to use, sterile AlloDerm is not freeze-dried and requires no rehydration.

Weichman (2013) conducted a nonrandomized controlled, consecutive series study of participants undergoing either immediate breast reconstruction with tissue expander or permanent implants. For the first year of the study, all participants requiring reconstruction with acellular dermal matrix received aseptic AlloDerm (n=58; 90 breasts). At the 1-year point, participants meeting the same criteria were all treated with sterile AlloDerm (n=64; 105 breasts). Concurrently, the investigators followed all individuals undergoing breast reconstruction without the need for acellular dermal matrix, and who underwent submuscular coverage (n=223; 351

breasts). For the most part, the two AlloDerm groups were equivalent with the exception that the aseptic group was noted to have statistically significantly larger mean specimen weight and higher body mass index (BMI) vs. the sterile group (p=0.0485 and p=0.0376, respectively). The sterile group also had a higher incidence of nipple-sparing surgeries (p=0.0021). With regard to complications, the sterile group had significantly fewer overall infections vs. the aseptic group (8.5% vs. 20%, p=0.0088). However, there were no significant differences between groups with regard to explantations (sterile=2 vs. aseptic=6, p=0.147) or major infections requiring antibiotics (sterile=4.7% vs. aseptic=12.2%, p=0.069). The incidence of seroma, hematoma, and skin flap necrosis were not different between groups. When comparing the sterile group vs. the submuscular coverage group, the sterile group had significantly higher incidence of immediate permanent implantations (p=0.0001) and nipple-sparing surgeries (p=0.0012), as well as greater tissue expander size, initial tissue expander fill and percentage tissue expander fill. Both groups were found to have similar outcomes with regard to skin flap necrosis, overall infection, need for explantation and the incidence of seroma and hematoma. Univariate analysis found that risk factors for increased infectious complications included breast with flap necrosis (p=0.0003), those in which aseptic was used (p=0.0004), and those with seroma (p=0.0012). In addition, diabetes was an independent risk factor, and individuals with diabetes were 2.9 times more likely to suffer complications (p=0.037). The authors identified the differences between the sterile and tissue expander groups to be possible confounding factors in this study. The authors conclude that the use of sterile AlloDerm is acceptable and mitigates the risk of infectious complications compared to aseptic AlloDerm.

In 2015, Lewis and others published the results of a retrospective case series study of participants receiving aseptic AlloDerm (n=93) or sterile AlloDerm (n=74) as part of either breast reconstruction or breast augmentation procedures to investigate the incidence of complications and “red breast syndrome” (RBS). While the decrease in individual complications, including seroma, necrosis, and RBS were not significant between groups, the overall complication rate was significantly in favor of the sterile group (p=0.046). Based on aggregate complication rate on a per-breast basis, the absolute risk reduction with sterile AlloDerm was reported to be 14.9%. The authors concluded that the use of the sterile AlloDerm product resulted in fewer complications when compared to aseptic AlloDerm.

Parikh (2018) reported the results of a retrospective cohort study involving 1285 consecutive participants undergoing 2039 immediate prosthetic breast reconstructions. Participants underwent treatment with either aseptic (n=612, 910 breasts) or sterile (n=673, 1129 breasts) AlloDerm. The authors reported that the aseptic group experienced a significantly higher rate of explantation compared to the sterile group (18.0% vs. 12.0%, p=0.0036). No significant differences were reported with regard to the between-group rates of surgical site infection, wound dehiscence, mastectomy flap necrosis, seroma, or hematoma. Multivariate regression analysis indicated that participants in the aseptic group did have higher odds of explantation vs. the sterile group (OR, 1.570, p=0.0161).The results of these studies, in conjunction with the previously reported evidence from aseptic AlloDerm, have demonstrated a significant outcome benefit of the sterile AlloDerm product. This product is accepted as substantially equivalent to the aseptic AlloDerm product. These products are sourced and processed in an identical manner, with the addition of a sterilization process in the case of the sterile product. This addition has not been demonstrated to have any negative impact on the performance of the product, and there is building evidence that there is some benefit derived from its sterilized nature.

Overall, the available evidence addressing the use of sterile AlloDerm for breast and complex abdominal reconstruction procedures demonstrates significant benefits in relation to health outcomes. While AlloDerm has been used for a wide variety of other indications, including insufficient conjunctiva (Park, 2017), such uses have been poorly studied and are not widely accepted by the practicing community.

Fishel Bartal and colleagues (2022) published the results of a prospective, single center study of 102 fetuses with open in utero spina bifida repair. When primary skin approximation was not feasible due to deficit size, the decision whether to use a patch for closure was made by the pediatric neurosurgeon. Patch types were; acellular bovine skin matrix (Durepair®; n=31) and human acellular dermal matrix (Alloderm; n=1). Neonatal outcomes at birth and 1 year were compared between the two groups. Seventy (68.6%) fetuses had primary skin closure and 32 (31.4%) had patch-based closure. Fetuses with myeloschisis were more likely to require a patch than those with a myelomeningocele. The median surgical time of repair was 4 minutes greater for patch-based technique compared to primary skin closure (37 vs 33 min; p=0.001). After patch-based repair, neonates had a longer length of stay in the neonatal intensive care unit (NICU) by 24 days (adjusted risk ratio, 2.40 [95% CI, 1.41–4.29]) compared to primary skin closure. Outcomes at 1 year of age was available for 90 infants. Wound revisions within the first year after birth were more common in infants who had a patch compared to primary skin closure (19.4% and 5.1%; p=0.05 respectively). There were no differences between the groups in other 1-year outcomes, including the need for ventriculoperitoneal shunt placement and surgery for tethered cord. The authors concluded that patch-based closure during spina bifida repair is associated with a prolonged fetal surgery time, long NICU stay, and the need for wound revision within the first year after birth. Additional large cohort studies are needed to understand the impact of these unfavorable outcomes, identify optimal patches for repair, and alternative methods to improve clinical outcomes.

AmnioBand

AmnioBand is a dehydrated human placental membrane comprised of amnion and chorion. It is treated as human tissue for transplantation under the FDA’s HCT/P process. This product is available in both sheet or membrane form and particulate or injectable form.

There are currently a few weak studies published on the use of the sheet/membrane from in human participants. DiDomenico (2016) described an RCT involving 40 participants with chronic nonhealing diabetic foot ulcers (DFUs) assigned to receive continued standard of care or treatment with the membrane form of AmnioBand plus standard care. Participants were followed until wound closure or 12 weeks, whichever came first. The authors reported that at 6 weeks, 70% (14/20) of the AmnioBand group was completely healed vs. 15% (3/20) of the controls. At 12 weeks, 85% (17/20) of the AmnioBand group were completely healed vs. 25% (5/20) of controls (mean time to healing 36 days vs. 70 days, respectively). Only one adverse event and one serious adverse event were reported in the AmnioBand group, although neither was deemed graft related by the authors.

This same group published a retrospective crossover study to evaluate the effectiveness of the membrane form of AmnioBand in participants that failed to respond to the standard care treatment in the above mentioned RCT (DiDomenico, 2017). This report involved 11 participants, and 9 (82%) wounds healed with AmnioBand. The mean wound area decreased from 1.7 cm^2 to 0.2 cm^2 (p=0.0005), with a corresponding mean percentage area reduction of 92%. Of the 2 wounds that failed to meet the definition of healed in this study, 1 DFU decreased in area by 91% and the other by 26%.

An evaluator blinded RCT was published involving 80 participants with DFUs assigned to treatment with the membrane form of AmnioBand (n=40) vs. continued standard care (n=40) (DiDomenico, 2018). Participants failed a minimum of 4 weeks of standard care prior to entry into the study. At 6 weeks, 12 participants in the control group (30%) and 2 from the AmnioBand group (5%) were withdrawn from the study due to failure to have their wounds decrease at least 50%. These participants were considered treatment failures. Complete wound healing at 6 weeks, the primary endpoint, was reported in 68% of the AmnioBand group vs. 20% of the control group participants (p<0.0001). At 12 weeks, complete healing was reported in 85% of AmnioBand participants vs. 33% of control participants (p<0.0001). Mean time to heal at 6 weeks was 29.2 days vs. 39.5 days, respectively (p<0.0001). At 12 weeks, mean time to heal was 37 days vs. 67.3 days (p<0.0001), respectively. The HR for treatment with AmnioBand vs. standard care was 4.25. There were 11 adverse events (AEs) reported, with 3 in the AmnioBand group and 8 in the control group. All involved localized pedal infections initially treated with antibiotics. A total of 4 serious adverse events were also reported, with 1 in the AmnioBand group

and 3 in the control group. All were related to foot infections requiring hospitalization, with the majority progressing to osteomyelitis and IV antibiotic treatment and debridement, as necessary. No adverse events were found to be graft related.

Glat (2019) reported on an RCT involving a group of 60 participants with DFUs comparing the membrane form of AmnioBand to Apligraf (n=30 each). All participants had failed at least 4 weeks of standard care. Time to heal within 6 weeks was 24 days in the AmnioBand group vs. 39 days in the Apligraf group ($p=8.0x10^{-6}$, hazard ratio (HR), 5.8). The proportion of wounds closed within 6 weeks was 77% in the AmnioBand group vs. 23% in the Apligraf group (no p-value reported), and at 12 weeks the data indicated 90% and 40%, respectively ($p=4.9x10^{-5}$). Mean time to heal at 12 weeks was 32 days and 63 days, respectively, ($p=3.2x10^{5}$). Percentage area reduction (PAR) at 12 weeks was 98% for the AmnioBand group vs. 44% in the Apligraf group (no p-value reported). Serious adverse events occurred in 3 AmnioBand participants and 4 Apligraf participants, all of which were severe infections (between group comparison p=0.52).

The results of these studies demonstrate that DFUs failing standard care subsequently treated with the membrane form of AmnioBand have significantly better results with regard to complete wound closure and time to heal when compared to standard care and to at least one other product available on the US market. The use of the membrane form of AmnioBand for other conditions is not widely supported by the practicing community.

Serena and colleagues (2022) completed a multi-center prospective open-label RCT that evaluated the impact of weekly and biweekly applications of AmnioBand with SOC compared to SOC alone for adults (n=60) with chronic venous stasis ulcers (VSUs) at 8 wound care centers. Participants were randomized into 1 of 3 study groups: 1) SOC alone, 2) weekly AmnioBand plus SOC, or 3) biweekly AmnioBand plus SOC. At 12 weeks, a significantly greater number of VSUs healed in the 2 AmnioBand groups (30/40, 75%) compared to the SOC group (6/20, 30%) (p=0.001). Six VSUs (30%) healed in the SOC group at 12 weeks compared to 15 VSUs (75%) in the weekly application group (p=0.02) and 15 VSUs (75%) in the biweekly application group (p=0.02). The adverse event rate in the SOC group was 75% vs. 57.5% in the combined AmnioBand groups. The reported adverse events included wound-related infections and new ulcer formation, none of which were determined to be related to AmnioBand or the procedure. An important finding of the study was no demonstrable differences in outcomes in weekly versus biweekly application of the AmnioBand. Therefore, regardless of treatment frequency, the AmnioBand was more effective than SOC alone.

At this time there are no studies available addressing the use of the particulate or injectable form of AmnioBand. Further investigation is needed to assess the safety and efficacy of this form of the product.

Apligraf

Apligraf is a composite grafting product composed of agarose, L-glutamine, hydrocortisone/bovine serum albumin, bovine insulin, human transferrin, triiodothyronine, ethanolamine, O-phosphoryl-ethanolamine, adenine, selenious acid, DMEM powder, and HAM's F-12 powder. It has been approved through the FDA's Premarket Approval (PMA) process. It has been considered for a wide variety of uses, but primarily for treatment of diabetic ulcers and burn wounds.

Veves and others published the results of a RCT addressing the use of Apligraf for the treatment of neuropathic diabetic ulcers (2001). In this trial, 208 participants were randomly assigned to be treated with either Apligraf (n=112) or standard care (n=96). At the 12-week follow-up, 63 (56%) participants in the Apligraf group achieved complete wound healing vs. 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two groups, with the exception of individuals with osteomyelitis or lower-limb amputations, both of which were less frequent in the Apligraf group. Steinberg and colleagues conducted an RCT following the methodology used by Veves et al (2010). This study involved 72 participants, 33 of whom received treatment with Apligraf and 39 control participants who received standard care. However, this study was discontinued early, due to non-safety-related reasons. The authors do not elaborate on this further. Because this study was stopped before full enrollment, results from this study are underpowered for demonstrating statistically significant differences. However, even though the study was halted prematurely, the results are similar to those reported by Veves; in particular, the Steinberg study showed significant (p=0.049) superiority of Apligraf to achieve complete healing at 12 weeks follow-up in comparison to the control group. These results, taken together, support the use of Apligraf for the treatment of foot ulcers.

Apligraf has been investigated for the treatment of other indications, including burns. Only one peer-reviewed published study has been published at this time addressing burns (Waymack, 2000). In this randomized controlled trial, 40 participants with burn injuries were treated with either meshed autograft covered by meshed allograft or meshed autograft covered by Apligraf. There was no difference in take rate or the median days to 75% graft take. The unblinded investigators rated 22 (58%) of the Apligraf sites as superior to controls, 10 (26%) equivalent to controls, and 6 (16%) worse than controls (p=0.0037). Pigmentation of the Apligraf sites was also rated as superior to control sites at 2 years (p=0.0005), and normal vascularity was seen in 18 (47%) of Apligraf sites vs. 6 (16%) of controls for the same time period (p value not provided).

The use of Apligraf for the treatment of DFUs and VSUs is well established and supported by both the published literature. Its use for other indications has not yet been established or accepted by the practicing community.

Biobrane

Biobrane, a synthetic product composed of a silicone film bonded to a nylon fabric base, has been approved through the FDA's PMA process. Data regarding the use of synthetic Silicone/Nylon Membrane wound dressing (e.g., Biobrane) has been described in four separate randomized controlled trials (RCTs) in peer-reviewed published medical journals (Barret, 2000; Feldman, 1991; Gerding, 1990; Lal, 2000). All of these studies found that in comparison to their various control groups the use of Biobrane significantly improved pain scores and healing times.

Additionally, the use of Biobrane has been reported in an underpowered case series study of 18 participants with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS-TEN) (Rogers, 2017). The authors reported that there were no complications, infections, premature removals, or Biobrane-associated sepsis in 24/25 applications (96%). Time to healing was 13 (12-16) days, and mean burn center length of stay was 34 days. This weak study demonstrates promising data regarding the safety and efficacy of Biobrane for SJS and other conditions.

Based on clinical practice standards, relevant expert opinions, the above-mentioned evidence, and the overall clinical experience with Biobrane, an acceptable level of safety and efficacy has been established for the use of this product in the treatment of burns and Stevens-Johnson Syndrome. The evidence for use of this product for other indications is unestablished and not widely accepted by the practicing community.

BioVance/Biovance 3L

BioVance Human Amniotic Membrane Allograft is a decellularized dehydrated human amniotic membrane, regulated as an HCT/P by the FDA.

Smiel (2015) and colleagues reported an observational, non-randomized, non-blinded, evaluation of Biovance in the treatment of uninfected, full-thickness or partial-thickness wounds in 165 participants (179 wounds), at 15 wound treatment centers. Clinicians provided the routine number of visits, applications, concomitant therapies, and changes in wound-care regimens. Heterogeneous wound types included; VSU (n=98, 49.7%), DFU (n=47, 26.3%), pressure ulcers (n=20, 11.2%), and arterial ulcers (n=15, 8.4%). The results showed that 60 participants (49.6%) with chronic wounds, complicated comorbidities, and an average wound baseline size of 3.1 cm^2, including those that failed previous therapy with advanced biologics, achieved complete closure within a median of 6.3 weeks with no product-related adverse reactions. The authors concluded that despite the many factors affecting healing, Biovance is safe and efficacious in a variety of chronic wound types.

Based on relevant expert opinions, and the above-mentioned study, BioVance has an acceptable level of safety and efficacy and has been established for the use, in the treatment of chronic wounds, including DFUs that have not healed with standard conservative therapy.

Cortiva

Cortiva allograft dermis is a product composed of acellular human dermis and is treated as human tissue for transplantation under the FDA's HCT/P process.

Keifer and colleagues (2016) described a retrospective comparative trial involving 166 participants who underwent 198 breast reconstruction procedures with either aseptic AlloDerm (n=98, 174 breasts) or Cortiva (n=68, 124 breasts). Follow-up data was limited to 60 days post-procedure. The authors noted that participants in the Cortiva group were significantly older (p=0.002), heavier (p=0.008) and had a higher rate of hypertension (p=0.01) compared to the AlloDerm group. The results indicated that the Cortiva group had a significantly higher rate of mastectomy flap necrosis (p=0.02). However, a multiple linear regression model analysis did not identify matrix type as a predictive factor in developing mastectomy flap necrosis, only BMI was identified as a predictive factor (p=0.036). The authors addressed the limitations of this study, noting the retrospective, unblinded methodology, limited geographical scope of the study, and short follow-up period. They concluded by stating further work should involve larger sample sizes, wider geographical scope, and longer follow-up time.

Moyer and colleagues (2017) reported the results of a prospective histological study of 17 participants (20 breasts) following prosthetic reconstruction with AlloDerm (n=7) compared to Cortiva (n=13). Biopsies were taken from the dermal matrix and the natural capsules surrounding the expander/implant during the second surgery. The transforming growth factor (TGF-1) staining demonstrated lower levels in the Cortiva capsules (p=0.0139). The percentage of elastin and collagen were similar in all groups. The native capsules showed a greater number of blood vessels when compared with Cortiva and AlloDerm (p=0.0371 and p=0.0347, respectively), there was no difference in vascular pattern between the two products. The authors concluded that Cortiva demonstrates equal vascularity with less TGF-1 activation compared with AlloDerm. However, given that the trial was underpowered, confirmation in adequately powered studies is needed.

Parikh (2018) published the interim results from an ongoing prospective single-blind RCT comparing Cortiva vs. sterile AlloDerm for submuscular breast reconstruction. The report involved data from 59 breasts (Cortiva, n=31; AlloDerm, n=28). The authors reported no statistically significant differences with respect to time to drain removal, complications, fill volumes, patient-reported outcomes, or narcotic consumption. While these results are promising, the final analysis from this trial-which will provide a more complete picture of the safety and efficacy of Cortiva.

Urquia (2020) reported the results of a retrospective case series study involving 118 participants (183 breasts) who underwent prepectoral breast reconstruction procedures using Cortiva. One or more major complications were observed in 21.19% of participants (32 breasts, 17.49%). No statistical differences with regard to major complication rate was found between immediate vs 2-stage reconstruction procedures (p=0.824). Infection was the most common reason for reoperation (7.65% of all breasts). Prepectoral reconstruction procedures were successful in 89.62% of cases. Infection was the most frequent complication responsible for failure (52.63% of cases). A total of 10 breasts (5.4%) had Baker III/IV capsular contractures. Participants with implants > 450 mL were statistically more likely to experience implant failure (p=0.018). Concerns regarding the high rate of adverse events are difficult to assess in comparison to active competitors, given the absence of an appropriate control group.

Keane and colleagues (2023) reported the final results of the study previously described by Parikh (2018). This prospective, single-blinded, RCT involved 302 individuals comparing Cortiva (n=277 breasts) to AlloDerm RTU (n=280 breasts) in immediate prepectoral and subpectoral post-mastectomy prosthetic breast reconstruction performed at two academic medical centers. Participants who underwent procedures with tissue expanders were followed until planned secondary reconstructive procedure or reconstructive failure. Direct-to-implant reconstructions were followed for a minimum of 3 months postoperatively or until reconstructive failure. There were no significant differences between groups with regard to in age, race, BMI, diabetes, or smoking status. However, hypertension was more prevalent in the AlloDerm group (25% vs. 15% in the Cortiva group, p=0.04). Utilization of radiation, chemotherapy, immunotherapy, and sentinel lymph node biopsy did not differ between groups and resected mastectomy weights were similar. The primary outcome measure was reconstructive failure, defined as unplanned, premature tissue expander explantation for any reason. Secondary outcomes measured were adverse events including as infection that required oral or intravenous antibiotics, and/or reoperation, as well as any of the following that required intervention; seroma or hematoma identified by imaging, necrosis, or incisional dehiscence. Participant-reported outcomes were reported as Q-scores generated by the Breast-Q tool. Reconstructions in both groups were majority tissue expander (62%) compared to direct-to-implant (38%), smooth device (68%) compared to textured (32%), and prepectoral (80%) compared to subpectoral (20%). No differences in reconstructive failure was identified between groups (AlloDerm 9.3% vs. Cortiva 8.3%, p=0.68), or for complications or participant reported outcomes. Seromas occurred less often in Cortiva group vs. the AlloDerm group (7.6% vs. 12 %, p=0.09). The AlloDerm RTU odds of seroma formation were two-fold higher (OR, 1.93, 95% CI, 1.01-3.67, p=0.047). The authors concluded that the safety, clinical efficacy, participant reported and outcomes of Cortiva is non-inferior to AlloDerm in immediate prosthetic breast reconstruction with a lower risk of seroma formation. The results of this study demonstrate supportive findings for the use of Cortiva in prosthetic breast reconstruction.

The use of Cortiva for abdominal wall reconstruction was reported by Lindsey in 2020. This retrospective chart review involved 82 participants who underwent abdominal wall reconstruction with either AlloDerm (n=53) or Cortiva (n=29). The overall complication rate was found to be not significantly different between groups (51.92% in the AlloDerm group vs. 72.41% in the Cortiva group, p=0.099). No explantations were reported. This was the first peer-reviewed, published description of Cortiva for the treatment of abdominal wall reconstruction procedures. Additional data is needed to fully evaluate the clinical utility of this technique.

DermACELL

DermACELL, a product composed of acellular human dermis, has been studied for a limited number of indications, including chronic lower extremity wounds in individuals with diabetes and breast reconstruction. It is treated as human tissue for transplantation under the FDA's HCT/P process.

The most rigorous study to date was a prospective non-blind RCT involving 168 participants with DFUs assigned in a 2:2:1 fashion to treatment with DermACELL (n=71), conventional care (n=69), or Graftjacket (n=28) (Walters, 2016). At 16 weeks post intimal

treatment, participants in the DermACELL group were reported to have a significantly higher proportion of completely healed ulcers vs. the conventional care group (67.9% vs 48.1%; p=0.0385) but no significant differences vs. the Graftjacket group (67.9% vs 47.8%; p=0.1149). The DermACELL group also did not exhibit a greater average percent reduction in wound area vs. either comparison group (conventional care=91.4% vs 80.3%; p=0.0791; Graftjacket group=91.4% vs 73.5%; p=0.0762). No differences between groups were reported with regard to severe adverse events (p≥0.05).

Another large study was a retrospective consecutive case series study involving 140 participants undergoing breast reconstruction treated with either sterile AlloDerm or DermACELL (n=70, each group) (Zenn, 2016). Participants were selected on either side of the time point when the investigators switched from using sterile AlloDerm to DermACELL. No statistical differences were reported between groups with regard to complications, including the incidence of seroma, infection, implant loss, and unplanned return to the operating room.

Pittman and others (2017) published the results of a retrospective review of 58 participants who underwent breast reconstruction with either DermACELL (n=30) or sterile AlloDerm (n=28). The authors reported that 74% of the AlloDerm participants underwent immediate reconstruction with tissue expanders vs. 56% of the DermACELL group. Mean initial expansion volumes were 193 ml and 188 ml, respectively. In those participants having direct-to-implant procedures, the mean implant size was 463 cc and 443 cc, respectively. Unfortunately, no p-values were provided for these comparisons, but the authors stated that no statistical differences were found. Likewise, no differences between groups were noted with regard to unilateral vs. bilateral reconstruction and breast irradiation. The DermACELL group had significantly shorter time to drain removal (15.8 vs. 20.6 days, p=0.017). A significantly higher rate of “red breast,” defined as self-limiting erythema in the absence of skin edema or induration in an otherwise asymptomatic participant isolated to the lower pole of the breast in the distribution of the acellular matrix graft, was reported in the AlloDerm group (13 vs. 0, p=0.0001). No differences between groups was noted with regard to hematoma, seroma, flap necrosis, or cellulitis requiring oral antibiotics. Delayed wound healing was reported as occurring more frequently in the AlloDerm group (20% vs. 8%); however, the significance of this is unclear as no p-values were provided. While these findings are promising, the small sample size, retrospective and unblinded nature of the methodology impairs the strength of this study.

Cazzell (2017) conducted an RCT involving 132 participants with chronic DFUs undergoing treatment in a 2:2:1 fashion with either DermACELL (n=53), conventional care (n=56), or GraftJacket (n=23). Participants were followed through 24 weeks, with endpoint measurement at 12, 16, and 24 weeks. A single application of DermACELL resulted in significantly greater wound closure rates vs. conventional care at all three endpoints (p=0.0123, p=0.0003, and p=0.0008, respectively), and significantly higher healing rate vs. conventional care at week 16 and week 24 (p=0.028 and p=0.489, respectively). GraftJacket did not show a significantly greater healing rate over conventional care at any of these time points, but small numbers of participants may have impacted that finding. Closed ulcers in the DermACELL group remained healed at a significantly greater rate vs. the conventional care arm at 4 weeks post study termination (100% vs. 86.7%; p=0.0435). No significant difference was noted between the GraftJacket group vs. the conventional care group for healed wounds remaining closed. Again, small numbers of participants introduce significant potential bias into this observation.

Chang (2017) reported a retrospective comparative series study of 47 participants who underwent breast reconstruction using FlexHD Pliable (n=18), aseptic AlloDerm (n=15), or DermACELL (n=14). The authors reported that there were no differences in the rates of seroma, infection, or skin flap necrosis. Additionally, there were no cases of red breast, expander explanation, or failed reconstruction in any group. Time to drain removal was significantly shorter in FlexHD and DermACELL participants compared to aseptic AlloDerm (20 days vs. 15 days vs. 26 days, respectively; p=0.01).

Another retrospective comparative series study comparing the use of DermACell vs. sterile AlloDerm was reported by Powers in 2021. In this study, 79 participants undergoing prepectoral breast reconstruction received treatment with either DermACell (n=41) or sterile AlloDerm (n=38). The DermACell group had a higher rate of bilateral (p=0.03) and direct-to-implant (p=0.001) reconstructions, higher average initial fill volume (p<0.001), and longer average drain duration (p=0.006). Additionally, the follow up time in the AlloDerm group was significantly longer (p<0.001). The authors reported that the postoperative infection rate was significantly higher in the AlloDerm group (26.8% vs. 5.3%; p=0.014). Infections were reported in 11 AlloDerm participants, all of which were considered major and treated with either intravenous antibiotics or return to the operating room. Infections were reported in 2 DermACell participants, 1 which was treated orally and the other treated with IV antibiotic therapy. No p-values were provided for the between-group differences. Two of the 11 AlloDerm participants were treated with IV antibiotics. The remaining 9 participants required operative intervention for either explantation (n=-3) to expedite chemotherapy/radiotherapy or attempt at salvage with implant replacement and quantitative polymerase chain reaction-tailored antibiotic beads (n=6). This report is supportive of the use of DermACell vs. AlloDerm. However, the methodological weakness inherent in this study limits the generalizability of the findings.

Other weak non-comparative studies have also been published describing significant benefits due to DermACELL (Bullocks, 2014; Ortiz, 2017; Yonehiro, 2013).

While relatively new to the market, DermACELL has been subject to multiple published clinical trials, including several RCTs and reasonably sized case series studies. The clinical experience with this product had demonstrated an acceptable level of safety and efficacy for use in the treatment of diabetic foot ulcers and during breast reconstruction procedures. The evidence for use of this product in other procedures or for other indications is still unclear and further investigation is warranted.

Use of DermACELL for the treatment of large, complex DFUs with exposed probed tendon or bone was described by Cazzell (2019). This case series study involved 61 participants with Wagner grade 3 or 4 DFUs between 4 to 52 weeks in duration. The authors reported that the entire per-protocol population (n=47) achieved 100% granulation with a mean time to 100% granulation of 4.0 weeks. The mean percent wound area reduction was 80.3% at 16 weeks. DFUs 15 cm or smaller were substantially more likely to close compared to DFUs larger than 29 cm (p=0.0008) over a 16-week duration. No complications related to the use of DermACELL were reported. These findings are promising, but the small population and poor study methodology make it difficult to generalize these findings to a wider population.

The use of DermACELL for use in breast reconstruction procedures and treatment of DFUs has been well established. However, the use of this product for other indications has not been, and is not widely accepted by the practicing community.

DermACELL AWM and DermACELL AWM Porous are two products also available on the market. They are not substantially different from the original DermACELL product, having the same tissue origin and processing. They are just different formats of the original DermACELL and are considered equivalent for the purposes of this document.

Dermagraft

Dermagraft is a composite grafting product composed of cryopreserved human fibroblastin and allograft collagen scaffold that has been approved through the FDA’s PMA process. The use of Dermagraft has been described in several peer-reviewed studies (Gentzkow, 1996; Marston, 2003; Warriner, 2011). The largest and most rigorous of these was a RCT involving 355 participants with VSUs randomized to receive compression therapy plus Dermagraft (n=186) vs. compression therapy alone (n=180) (Harding, 2013). The endpoint was the proportion of participants healed by 12 weeks. No differences were found between groups, with 34% (64/186)

of participants in the Dermagraft group experiencing healing by week 12 vs. 31% (56/180) in the control group (p=0.235). However, a significant difference was reported for participants with ulcers ≤ 12 months duration, with 52% (49/94) of the participants in the Dermagraft group healed at 12 weeks vs. 37% (36 /97) of the control participants (p=0.029). For ulcers ≤ 10 cm^2, no differences were identified in complete healing at week 12 (p=0.223). The most common adverse events (AEs) were wound infection, cellulitis, and skin ulcer. The frequency of AEs did not markedly differ between the treatment and control groups.

The results of another RCT were reported by Marston and colleagues (2003). This study involved 314 participants with diabetic foot ulcers (DFUs) present for at least 2 weeks; 245 of these were considered chronic ulcers (> 6 weeks). Of the 245 chronic ulcer participants, 19% (46) did not complete the 12-week study period. All participants were randomized to receive treatment with Dermagraft (n=130) or standard care (n=115). The final analysis showed that among participants with chronic ulcers, the Dermagraft group healed significantly better at 12 weeks than standard care (30% vs. 18%, p=0.023). Additionally, for participants with forefoot or toe ulcers, 29.5% of the Dermagraft-treated ulcers were closed compared to 19.6% of the controls (p=0.065). Similar findings were reported for heel ulcers, with 33% vs. 8% of ulcers healed, respectively (p=0.01). Dermagraft-treated participants were significantly faster to heal (p=0.04), and at 12 weeks, the median percent with closure was 91% for the Dermagraft group compared to 78% for the control group (p=0.044).

Another RCT using Dermagraft was published by Gentzkow et al (1996). This study involved 50 participants with DFUs randomized to receive treatment with either standard of care (n=13) or one of three Dermagraft regimens plus standard care: (1) one piece of Dermagraft applied weekly for a total of 8 pieces and 8 applications (n=12); (2) two pieces of Dermagraft applied every 2 weeks for a total of 8 pieces and 4 applications (n=14); and (3) one piece of Dermagraft applied every 2 weeks for a total of 4 pieces and 4 applications (n=11). At 12 weeks, the percentage of participants who achieved complete wound closure was significantly higher in the high frequency Dermagraft (Group 1) than in the control group (50.0% vs. 7.7%, p=0.03), and the percentage that achieved at least 50% closure was 75% in Group 1 vs. 23.1% in controls. No recurrences were reported at the 14-month follow-up period.

Label warnings and precautions indicate that Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts.

Dermagraft was granted an FDA Humanitarian Device Exemption (HDE) (2002) for the treatment of dystrophic epidermolysis bullosa.

The use of Dermagraft for the treatment of DFUs and dystrophic epidermolysis bullosa is well established. However, use of this product for other indications has not, and is not widely accepted by the practicing community.

DermaMatrix

DermaMatrix, a product composed of acellular human dermis, has been studied for a variety of indications. It is treated as human tissue for transplantation under the FDA's HCT/P process. Below are discussions of several of the most recent controlled studies.

The use of DermaMatrix was evaluated in a retrospective, nonrandomized controlled trial involving 50 participants who were assigned to undergo breast reconstruction with DermaMatrix (n=25) or aseptic AlloDerm (n=25) (Becker, 2009). The authors reported that there were no significant differences between groups with regard to complication rates. Both groups exhibited good incorporation, with evidence of neovascularization. A larger retrospective non-controlled study was done which involved 173 participants receiving breast reconstruction and implantation of either aseptic AlloDerm (n=49), DermaMatrix (n=110), FlexHD (n=62), or no implantation (n=64) (Brooke, 2012). The authors reported no significant differences between groups with regard to overall complication rates between the implanted and control groups (p=0.48) or between implant groups (p=0.47).

Athavale and colleagues published the results of a retrospective, non-controlled study of the complication rate for parotid reconstruction surgery involving 100 participants who received treatment with either aseptic AlloDerm (n=69) or DermaMatrix (n=31) (2012). Sixty-nine AlloDerm implants were associated with a total of 5 complications (7%), whereas 31 DermaMatrix implants were associated with a total of 8 complications (26%) (p=0.0107). Subgroup analyses found that for subtotal parotidectomies, the incidence of complications was found to be 8% for the AlloDerm group and 37% for the DermaMatrix group (p=0.004). The authors conclude that:

> …this study suggests that DermaMatrix was associated with increased postoperative complications compared with AlloDerm when used for reconstruction of parotidectomy defects. To better define the complication profile of AlloDerm versus DermaMatrix in the postoperative parotid bed, a prospective study should be considered to determine implant performance following parotidectomy reconstruction.

Michelotti (2013) conducted a retrospective, nonrandomized controlled study of 73 participants with breast cancer who underwent 284 tissue expander reconstructions. Participants had received treatment with no ADM use (n=64 reconstructions), or with the use of aseptic AlloDerm (n=49 reconstructions), DermaMatrix (n=110 reconstructions), or FlexHD (n=64 reconstructions). Overall, there were 18 (6.3%) seromas reported in all 284 reconstructions. In the participants who received treatment with ADMs (n=220 reconstructions), there were 17 (7.7%) seromas reported; 2 in the AlloDerm group, (11.76%), 6 in the DermaMatrix group (35.29%), and 9 in the FlexHD group (52.94%) (p=0.016). Within the limited scope of this underpowered nonrandomized or blinded study, the results of this study demonstrate that the use of DermaMatrix appears to be similar to AlloDerm with regard to the occurrence of postoperative seromas, and significantly better than FlexHD. This study highlights that there are significant differences in the clinical performance of different ADMs, and further investigation into this issue is warranted.

The design and methods of a moderately sized RCT were reported by Argarwal in early 2015. This trial, known as the BREASTrial, was designed to compare aseptic AlloDerm to DermaMatrix for immediate breast reconstruction procedures. The planned follow-up time was 2.5 years. Argarwal and others randomized 128 participants to undergo reconstruction with either AlloDerm (n=64, 101 breasts) or DermaMatrix (n=64, 98 breasts) at the beginning of the study. The protocol describes three phases of the study. Phase I is from time of mastectomy and tissue expander placement to the definitive reconstruction procedure. Phase II is from definitive reconstruction to 3 months postoperatively. Finally, Phase III is from 3 months to 2 years postoperative. The primary outcome is the incidence of complications and secondary outcomes include: expander dynamics; degree of biointegration; impact of radiation therapy, chemotherapy, smoking, obesity and diabetes; duration of drains; and patient satisfaction. While the surgeons and participants were aware of group assignment, the pathologist who evaluated the implant for biointegration was blinded to assignment. Results from Phase I of the BREASTrial have been reported by Mendenhall (2015). In the AlloDerm group, 5 participants lost their tissue expander vs. 11 losses in the DermaMatrix group (p=0.11). The overall complication rate was 36.2%; for the AlloDerm group it was 33.6% vs. 38.8% in the DermaMatrix group (p=0.52). The only complications that were significantly different between groups were early loss of the implant defined as less than 45 days (1.0% for AlloDerm vs. 6.1% for DermaMatrix; p=0.049) and loss due to skin necrosis (1.0% for AlloDerm vs. 47.1% for DermaMatrix; p=0.027). The authors also reported that less time was needed in the AlloDerm group for complete expansion vs. DermaMatrix (42 days vs. 70 days; p<0.001). The results of Phase II, from the time of definitive reconstruction to 3 months post-operative were published in 2017 by Mendenhall and colleagues. The authors reported an overall complication rate of 16.6%, with under half of them (7.5%) being classified as "major" complications requiring inpatient or operative management. The most common complications were infection (4.6%), wound dehiscence (3.5%), skin necrosis (2.9%), and hematoma (0.6%). Overall implant loss rate was 2.9%. No differences were reported between the AlloDerm and DermaMatrix groups

with regard to complications. Only obesity was reported as an independent predictor of complications. The results from Phase III are pending.

Finally, as mentioned above, Lee and colleagues (2017) published a meta-analysis investigating the use of ADMs for implant-based breast reconstruction. A total of 17 studies were included, with only one being a prospective RCT and the others having retrospective non-randomized designs. There were 12 studies available involving a comparison with FlexHD, DermaMatrix, and aseptic AlloDerm or sterile AlloDerm. For comparisons between DermaMatrix and aseptic AlloDerm, the results from four studies likewise found no differences between the pooled risks of complications. Finally, the meta-analysis of four studies comparing aseptic AlloDerm or sterile AlloDerm demonstrated that the pooled risks for the complications did not differ. The authors concluded that these products have similar risks of complications compared to aseptic AlloDerm.

Mendenhall and colleagues (2023) conducted a Stage III RCT (n=108 participants [167 breasts]) of individuals undergoing mastectomy and immediate tissue expander reconstruction with AlloDerm (n=56 /89 breasts) or DermaMatrix (n=52 /78 breasts). The outcome and satisfaction data from 3 months postoperatively to 2 years were reported from 70 participants (n=33 AlloDerm participants and n=37 DermaMatrix participants). The data showed no differences between groups in the overall number of complications (6% vs. 13.2%, respectively; p=0.3) or the severity of those complications (p=0.7). Obesity was a positive predictor for complications, regardless of group (p=0.02). Satisfaction was also positive overall and did not vary between ADM groups. The authors concluded that AlloDerm and DermaMatrix demonstrate similar histologic and clinical outcomes, that obesity is a primary predictor of complications, and that ADM should be used with caution in these obese individuals.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with DermaMatrix, an acceptable level of safety and efficacy has been established for the use of this product in breast reconstruction procedures. However, use of this product for other indications has not been widely accepted by the practicing community.

Epicel cultured epidermal autograft (CEA)

Epicel CEA was approved by the FDA as an HDE in 2007. It is authorized for use in adult and pediatric individuals who have deep dermal or full thickness burns with a total body surface area (TBSA) greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in individuals for whom split-thickness autografts may not be an option due to the severity and extent of their burns. Epicel is contraindicated in individuals with a history of anaphylaxis to vancomycin, amikacin, and amphotericin, or with known sensitivities to bovine or murine materials. Epicel is also contraindicated in clinically infected wounds.

Hickerson (2016) reported a retrospective database analysis and summary of 954 burn wounds treated with Epicel over 25 years; 325 burn survivors (34%) were pediatric and 628 (66%) were adults, the age of 1 individual was unknown. The mean TBSA burned was 67%, median graft take was 75%, and overall survival was 84% (804/954). Survival rates were similar for both Epicel groups, 89% pediatric compared to 82% adult. The survival rates reported by the National Burn Repository were higher in the Epicel group than a similar population that received standard of care without Epicel treatment. The median graft take at discharge was also similar for both Epicel groups compared to those that received standard of care, 80% and 73% respectively. The only adverse events were infections, and the rate of infection was comparable in both pediatric and adult survivors. The authors concluded that as an adjunctive treatment to conventional split-thickness skin graft (STSG) for large burns Epicel demonstrated an increased survival rate and a parallel rate of graft take in individuals with similar burn injuries.

Based on clinical practice standards, and the above mentioned study, Epicel has an acceptable level of safety and efficacy and is established for clinical use in the treatment of large partial and deep thickness burn injuries.

EpiCord

EpiCord, a dehydrated umbilical cord allograft, is treated as human tissue for transplantation under the FDA's HCT/P process. A double-blind RCT published by Tettelbach (2018) addressed the safety and efficacy of the EpiCord product and involved 155 participants with DFUs assigned in a 2:1 fashion to treatment with either EpiCord (n=101) or standard care with alginate wound covering (n=54). The per-protocol analysis included 134 participants who completed the 12-week study period (n=86 EpiCord [85%], n=48 controls [89%]). All participants had type 1 or 2 diabetes-related foot ulcers 1-15 cm^2 present for at least 30 days and non-healing despite 2 weeks of optimal conservative therapy. The intent-to-treat (ITT) analysis showed that the EpiCord group was more likely to heal within 12 weeks vs. control participants (70% vs. 48%, p=0.0089). This finding was upheld in the per-protocol analysis, with healing rates at 12 weeks being 81% in the EpiCord group and 54% in the control group (p=0.0013). Additionally, of those wounds that were deemed to have had adequate debridement (n=107, ITT population), 96% of the EpiCord-treated wounds healed completely within 12 weeks, vs. 65% of the control treated wounds (p<0.0001). At the 16-week follow-up, 73% of the EpiCord and 54% of the control participants had complete healing (p=0.0199). In the per-protocol population, 85% vs. 60% of wounds were healed, respectively (no p-values provided). Of the wounds healed in the 12-week trial period, 96% of EpiCord-treated wounds and 85% of the control-treated wounds remained healed at 16 weeks (no p-values provided). Adverse events were recorded in 75 participants, with a total of 160 adverse events recorded, however none were attributed to the treatment dressings.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with EpiCord, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of DFUs. However, use of this product for other indications has not been widely accepted by the practicing community.

EpiFix

EpiFix is a product composed of allographic amniotic membrane and is regulated by the FDA's HCT/P process as human tissue for transplantation. The use of EpiFix has been proposed for the treatment of various conditions including burns and corneal injuries. There are several peer-reviewed published studies available describing the use of materials derived from allographic amniotic membrane. However, the available evidence addressing EpiFix has been very limited. Three underpowered case series studies describing the use of EpiFix have been published (Forbes, 2012; Sheik, 2013; Zelen, 2013a). These studies involved very small numbers of participants; 5, 4, and 11, respectively. Such evidence provides limited data demonstrating the safety and efficacy of this product.

A non-blinded RCT involving 25 participants with DFUs assigned to either standard care (n=12) or treatment with EpiFix (n=13) was reported by Zelen and others (2013c). The authors report significantly reduced ulcer surface area at both week 4 and at week 6 (p<0.001). The mean reduction in ulcer size was most marked at the end of week 1, when the mean reduction in wound size was noted to be 20% for the control group and over 80% in the EpiFix group. At 4 weeks, none of the participants from the control group (0%) were healed, whereas 10 of the 13 participants in the EpiFix group (77%) had wounds that had completely epithelialized (p<0.01). At 6 weeks, 1 of the 12 participants from the control group (8%) was healed and 12 of the 13 participants in the EpiFix group (92%) were healed (p<0.001). For those participants that healed, mean time to complete healing was 5 weeks in the control group (n=1) versus 2.5 ± 1.9 weeks in the EpiFix group (n=12). At the 6-week evaluation, 12 of the 13 participants in the EpiFix group had healed completely. In early 2014, follow-up data from this trial was published (Zelen, 2014a). The authors reported that 11 of the 12 participants from the initial RCT control group who had failed treatment were subsequently treated with EpiFix. The report included

data from 18 of the total 24 participants treated with EpiFix from both cohorts who had complete follow-up data to 12 months. The authors reported that 17 of the 18 participants (94.4%) continued to have fully healed wounds at 12 months of follow-up.

Serena (2014) reported the results of an unblinded RCT involving 84 participants with VSUs assigned to receive treatment with either EpiFix plus multi-layer compression therapy (n=53) or multi-layer compression therapy alone (n=31). The primary study outcome was the proportion of participants achieving 40% wound closure at 4 weeks. The authors reported that 62% in the Epifix group vs. 32% in the control group met the primary endpoint (p=0.005). Furthermore, after 4 weeks, in wounds treated with Epifix, the mean size of the wound decreased 48.1% vs. 19.0% for controls.

Zelen (2014b) published the interim results of a second unblinded RCT involving 60 participants with DFUs randomized in a 1:1:1 fashion to receive treatment with either EpiFix, Apligraf, or standard wound care (n=20 per group). At the 4- and 6-week endpoints, the proportion of EpiFix participants achieving complete wound closure was 85% and 95%, significantly higher (all adjusted p-values ≤ 0.003) than for the participants receiving Apligraf (35% and 45%) or control treatment (30% and 35%). After 1 week, wounds treated with EpiFix had reduced in area by 83.5% vs. 53.1% for Apligraf participants. The median time to healing was significantly faster (all adjusted p-values ≤ 0.001) with EpiFix (13 days) vs. 49 days for the Apligraf group and 49 days for control participants. A follow-up publication to that study with a total of 100 participants was published in 2015 (Zelen, 2015). The final participant distribution for this study was 35 participants in the EpiFix group, 33 participants in the Apligraf group, and 35 participants in the standard wound care group. The reported 12 week compete closure rate was reported to be 97%, 73% and 51%, respectively (p=0.00019). Compared to standard care, participants treated with EpiFix had a significantly higher probability of healing (HR=5.66, adjusted $p=1.3x10^{-7}$), while no difference in probability was reported between the Apligraf and standard care groups. Participants treated with Apligraf were less likely to heal than those treated with EpiFix [HR=0.30, unadjusted $p=5.8x10^{-5}$]. The mean time-to-heal within 12 weeks was 23.6 days in the EpiFix group, 47.9 days in the Apligraf group, and 57.4 days in the standard care group (adjusted $p=3.2x10^{-7}$). The results of this additional paper confirm the findings originally reported, that EpiFix provides significant healing benefits for individuals with diabetic foot ulcers.

Another RCT involved 109 participants with VSUs who were treated with either EpiFix combined with multilayer compression dressing (n=52) or multilayer compression dressings alone (n=57) (Bianchi, 2017). The investigators reported that participants receiving weekly application of EpiFix and compression were significantly more likely to experience complete wound healing than those receiving control treatment (60% vs. 35% at 12 weeks, p=0.0128, and 71% vs. 44% at 16 weeks, p=0.0065). Both the time-to-heal and higher probability of complete healing within 12 weeks were significantly improved in the EpiFix group vs. controls (p=0.0110 and p=0.01, respectively).

Based on this evidence, specifically the data provided in the Bianchi (2017), Serena (2014) and Zelen (2014b) studies, the use of EpiFix appears to provide significant clinical benefit when compared to standard compression therapy alone in the treatment of VSUs and DFUs. Furthermore, the criteria presented in the medically necessary statement for EpiFix in the Position Statement section above is based on the participant inclusion criteria of these two studies.

Tettelbach (2018) reported the results of an RCT involving 110 participants with DFUs treated with either EpiFix (n=54) or standard care (n=56). Of these, 98 participants successfully completed the study, 47 in the EpiFix group and 51 in the control group. The authors reported that both the ITT and per-protocol analysis revealed that EpiFix participants were significantly more likely to have complete healing vs. control participants (ITT: 70% vs. 50%, p=0.0338, per-protocol: 81% vs. 55%, p=0.0093). A Kaplan-Meier analysis comparing time-to-heal demonstrated significantly improved time to heal in the EpiFix group vs. controls (log-rank p<0.0187). Additionally, Cox regression analysis showed that EpiFix participants were more than twice as likely to heal completely within 12 weeks vs. control participants (HR, 2.15; p=0.003). At the final follow-up at 16 weeks, 95% of EpiFix-healed ulcers and 86% of control group healed ulcers remained closed. The authors concluded that their results confirmed that EpiFix is an efficacious treatment for lower extremity ulcers in a heterogeneous patient population.

In 2015, Patel and others published the first study to address the use of EpiFix as a protective measure for the prostatic neurovascular bundle during nerve-sparing robot-assisted prostatectomy. This prospective study involved 58 potent and continent participants who underwent the procedure compared to 58 propensity-matched participants who underwent the same procedure without the use of EpiFix. It was reported that continence at 8 weeks returned in 81.0% of the EpiFix participants vs 74.1% of the control participants (p=0.373). Mean time to continence was enhanced in the EpiFix participants vs. controls (1.21 months vs. 1.83 months; p=0.033). Potency at 8 weeks returned in 65.5% of the EpiFix participants vs. 51.7% of the controls (p=0.132). Mean time to potency was enhanced in the EpiFix group vs. controls (1.34 months vs. 3.39 months; p=0.007). The authors concluded that the use of EpiFix appeared to hasten the early return of continence and potency in participants following nerve-sparing robot-assisted prostatectomy. However, the results of this weak unblinded nonrandomized study need to be further investigated and a large well-controlled blinded trial is warranted.

Toman (2021) published the results of a retrospective case-control study involving 286 participants who underwent Mohs micrographic surgery of the face, head, or neck with the use of EpiFix or autologous tissue-based procedures, including full-thickness skin grafts (FTSG) and flaps (n=143, respectively). In univariate analysis, the authors reported that participants in the EpiFix group had no postoperative complications vs. the autologous tissue group participants (97.9% vs. 71.3%, p=<0.0001, RR=13.67). The EpiFix group also experienced significantly fewer infections (p=0.004), better scar cosmesis (p<0.0001), fewer scar revisions (p<0.0001), and fewer surgical reinterventions at the index site (p=0.0007). The autologous tissue group required fewer mean (SD) follow-up visits (2.5 vs. 3.4, p<0.0001). In a multivariate analysis controlling for defect surface area, operation time, age, medical history, and gender, use of autologous tissue remained an independent significant risk factor for infection or additional operation (OR, 11.71, p<0.0001). The authors also reported the results of an analysis that included cosmetic outcomes. The results indicated that the odds of infection, additional operation, poor scar cosmesis, or scar revision were 19-times higher in autologous group (OR,18.76, p<0.0001). Finally, they found that being a natal female was also associated with 3-times greater odds of having a cosmetic complication (OR, 2.84, p=0.010).

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with EpiFix, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of DFUs and VSUs. However, use of this product for other indications has not been widely accepted by the practicing community.

EZ Derm

EZ Derm is a product composed of porcine acellular dermis and cleared through the FDA's 510K process. The available evidence addressing the use of the EZ Derm brand porcine derived decellularized fetal skin is limited. Data from two moderately sized retrospective case series studies have been published. The first involved 157 participants with partial-thickness burns treated with EZ Derm (Troy, 2014). The authors reported 19 complications, including premature separation of graft (n=9, 16%), infection (n=4, 3%), and need for excision (n=6, 4.5%). The other study involved 164 participants, also with burns (Burkey, 2016). The authors reported a significant decrease in average narcotic dose following treatment (p<0.001) and fewer dressing changes needed (p<0.001). Only 4 (2.4%) participants developed infections, although only one of these infections was at the site of the study graft.

Additionally, two trials from over a decade ago addressing the use of EZ Derm for the treatment of burns have been published (Healy, 1989; Vanstraelen, 1992). The Vanstraelen study concluded that hypertrophic scarring occurred in 25% of xenograft-dressed sites, but none was seen in the comparison group. Several allergic reactions were reported to the porcine xenograft. The conclusions of the Healy study found, in comparison to burned participants treated with Jelonet®, individuals treated with EZ Derm did not vary significantly in terms of bacterial colonization rate, need for surgical treatment, time for spontaneous healing, analgesic requirements or frequency of dressing changes.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with DermaMatrix, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of burns. However, use of this product for other indications has not been widely accepted by the practicing community.

FlexHD

FlexHD is an acellular hydrated dermis product and is treated as human tissue for transplantation under the FDA's HCT/P process. For the most part, the data addressing the use of FlexHD is from retrospective, nonrandomized controlled studies. The largest of these was published by Palaia and colleagues in 2015. This study involved 450 participants undergoing immediate two-stage implant breast reconstructions who received treatment with either AlloDerm (n=134) or FlexHD (n=316). It is unclear which form of AlloDerm, aseptic or sterile, was used in this study. Demographics between the two groups were similar, with the exception that the FlexHD group had a significantly greater mean expander fill volume (p=0.0134). The authors reported no significant differences between groups with regard to seroma formation, incidence of infection, or explantation. There was a significant difference between groups with regard to rate of extrusion, with 6.2% reported for the AlloDerm group vs. 1.9% for the FlexHD group (p=0.0062). Another large retrospective nonrandomized controlled study involved 417 participants (592 breasts) who received breast reconstruction following radiation therapy for breast cancer (Seth, 2012). In this study, 137 participants received reconstruction with FlexHD and 280 underwent standard reconstruction without implantation. The authors noted significant differences in the baseline characteristics between groups, with the FlexHD group having a larger body mass (p=0.0001) and more nipple-sparing mastectomies (p=0.04). Postoperatively, the FlexHD group was noted to have received larger intraoperative fill volumes (p<0.0001). No significant differences were noted between groups with relation to complications (p=0.19). However, it was reported that when stratified for radiation exposure, the FlexHD group had a lower risk of complications (p=0.003). The control group was seen to have a higher rate of extrusion (p=0.01) and pain and tightness (p=0.0005). Liu (2014) reported the results of a retrospective, nonrandomized controlled study of 382 participants (547 reconstructions) who underwent immediate implant-based breast reconstruction with the use of FlexHD (n=97), aseptic AlloDerm (n=165), or either immediate or two-stage reconstruction with no ADM (n=120). The authors reported that participants who received treatment with ADMs were significantly more likely to have delayed healing (20.2% vs. 10.3%, p=0.009). Furthermore, a multivariate analysis identified that FlexHD posed a significantly greater risk of implant failure compared to AlloDerm (p=0.042). This study provides more data demonstrating that not all ADMs are equivalent, and that significant differences in clinical results may be seen between products. Another large retrospective case series involved 255 participants (369 breasts) who underwent breast reconstruction (Seth, 2013). This study compared the use of FlexHD (n=159; 233 breasts) to aseptic AlloDerm (n=96; 136 breasts). This study found no significant differences between groups with regard to total complication rate including flap necrosis (p=0.849), IV antibiotic use (p=0.09), hematoma (p=0.431), seroma (p=1.0), and dehiscence (p=1.0).

In 2016, Sobti described a study involving 233 participants undergoing breast reconstruction with FlexHD (n=101) or AlloDerm (n=132). The study involved the use of either aseptic or sterile AlloDerm (31.1% vs. 68.9%) as well as a mix of FlexHD Pliable/Perforated, FlexHD Pliable, or FlexHD Structural (80.2%, 18.8%, and 0.9%, respectively). No significant differences were reported with regard to infection rate (p=0.92), rates of seroma (p=0.25), hematoma (p=0.96), explantation (p=0.38), or delayed wound healing (p=0.70). Another retrospective non-controlled study, also discussed in the DermaMatrix section below, involved 173 participants receiving breast reconstruction and implantation with aseptic AlloDerm (n=49), DermaMatrix (n=110), FlexHD (n=62), or no implantation (n=64) (Brooke, 2012). The authors reported no significant differences between groups with regard to overall complication rates between the implanted and control groups (p=0.48) or between implant groups (p=0.47). Finally, Rawlani and others (2011) conducted a large case series study describing the use of FlexHD during tissue expander breast reconstruction. During a mean follow-up time of 44 weeks, 121 participants underwent several expansions prior to expander-to-implant exchange. Complications occurred in 20 (16.5%) of the participants including nine soft tissue infections, eight partial flap necroses, and two seromas. Eleven participants ultimately required explantation. Participants undergoing radiation therapy (n=26) were significantly more likely to have complications (30.8% vs. 13.7%).

Michelotti (2013) conducted a retrospective, nonrandomized controlled study of 73 participants with breast cancer who underwent 284 tissue expander reconstructions. Participants had received treatment with no ADM use (n=64 reconstructions), or with the use of aseptic AlloDerm (n=49 reconstructions), DermaMatrix (n=110 reconstructions), or FlexHD (n=64 reconstructions). Overall, there were 18 (6.3%) seromas reported in all 284 reconstructions. In the participants who received treatment with ADMs (n=220 reconstructions), there were 17 (7.7%) seromas reported; 2 in the AlloDerm group, (11.76%), 6 in the DermaMatrix group (35.29%), and 9 in the FlexHD group (52.94%) (p=0.016). Within the limited scope of this underpowered nonrandomized or blinded study, the results of this study demonstrate that the use of FlexHD appears to be inferior to AlloDerm or DermaMatrix with regard to the occurrence of postoperative seromas. This study highlights that there are significant differences in the clinical performance of different ADMs, and further investigation into this issue is warranted.

In 2013, Bochicchio and colleagues published the results of a prospective, consecutive case series study involving participants undergoing complicated hernia surgery. Between January 2005 and December 2007, 55 consecutive participants were treated with aseptic AlloDerm. From February 2008 to January 2010, 40 participants received treatment with FlexHD. The authors reported that at 1 year follow-up, all (100%) of the AlloDerm participants and 11 (31%) FlexHD participants were diagnosed with a recurrence requiring surgical revision. This difference is quite startling, but is mitigated by the fact that, as the authors point out, there were significant differences between groups in the operative technique used. As such, the results reported are of little use in helping to understand the differences between FlexHD and AlloDerm with regard to safety and efficacy since there is significant bias in the study design.

Cahan and colleagues (2011), evaluated a new surgical approach to breast reconstruction. This study involved 98 participants undergoing 159 mastectomies using either FlexHD or aseptic AlloDerm. The authors report that successful reconstruction was achieved in 93% of cases. Complications were seen in 23% of participants, including dehiscence, seroma, full-thickness necrosis and infection. Removal of the implant was needed in 5 cases as a result of persistent infection (5%). Unfortunately, no data was provided enumerating the number of participants receiving each product nor was any data provided comparing outcomes between product groups. The relative performance of FlexHD in this setting is unclear.

A case series study involving the use of FlexHD for post-mastectomy breast reconstruction was published by Vu (2015). This prospective study reported on the outcomes of 41 participants who underwent 72 procedures conducted by a single surgeon. The surgical complication rate was 12.5% (9 of 72 breasts) and included hematoma (n=2) and skin flap necrosis (n=7). Resolution of six of these complications occurred with surgical interventions. The seventh participant experienced complete failure of reconstruction. The authors noted a complete lack of infections or seromas in this study. Responses to the self-administered BREAST-Q questionnaire

were received from 97.6% of participants and demonstrated satisfaction with breasts and psychosocial and sexual well-being had all returned to baseline values at 6 months postoperatively (p=0.903, p=0.321, p=0.479, respectively). Interestingly participants who underwent postoperative radiation therapy reported lower satisfaction with their breasts as well as lower sexual satisfaction (p=0.004 and 0.006, respectively). These results are interesting, especially the lack of seroma and infections.

Broyles (2021) published the results of a prospective unblinded RCT involving 230 participants who had undergone 387 breast reconstruction procedures with either FlexHD Pliable (113 participants, 187 breasts) or sterile AlloDerm (117 participants, 197 breasts). The authors reported no statistical difference between groups was found with regard to overall graft-related complications (4.3% vs. 7.1%, p=0.233). They did report the rate of complications was significantly higher for obese participants (OR, 1.14, p=0.001) as well as for those receiving prepectoral graft placement (OR, 4.53, p=0.001).

The body of evidence addressing the use of FlexHD is predominantly retrospective nonrandomized controlled studies, with a few case series also available. While this methodology is not particularly robust, the data from studies are consistent in identifying lower or equivalent complication rates when compared to aseptic AlloDerm and other ADMs. Based on this evidence, expert opinion supports the use of FlexHD as an adjunct to breast reconstruction surgical procedures, and such use has become the standard of care. However, use of this product for other indications has not been widely accepted by the practicing community.

Fresh Frozen Unprocessed Allograft Skin for Burns (including AlloSkin and TheraSkin. Please see TheraSkin section below regarding for treatment of wounds)

The use of fresh, unfrozen, unprocessed skin allograft has been used as a treatment of serious burn injuries since the First World War and it has become an accepted standard therapy. The current process for the collection and preparation of these allografts involves several steps, starting with the harvesting of the skin sample from carefully selected cadaver donors. Following harvesting, initial serological and microbial testing takes place to screen for communicable diseases, including HIV and hepatitis. Next, the sample is bathed in a solution of various chemicals, including antibiotics, for several hours to several days to kill or inactivate possible pathogens. The tissue is then packaged aseptically for shipping and clinical use. The shelf life of this type of product is approximately 3 days from the time of harvesting, and it must be used within this time. One complexity in the use of this type of product is that, in urgent clinical situations, the results of final, definitive pathological tests are not usually available until approximately 10-14 days after harvesting. This means that, in urgent clinical situations, the clinician using the product is expected to use it prior to being assured of absolute clearance of pathogens. This concern, as well as other issues such as shelf life, etc., has led to the use of fresh frozen (cryopreserved) skin allograft as an acceptable alternative product for the treatment of burns for over 40 years. This product is processed in a similar manner to the fresh unfrozen products, but it is frozen once the initial screening is completed, and it is not released for use until after the definitive pathology reports have been completed. This additional step of freezing also allows for a shelf life of up to 5 years, which makes it more easily accessible for use in urgent medical situations. However, there is some evidence that indicates that this type of product loses some degree of viability due to the cryopreservation process, which may have an impact on its clinical effectiveness. However, this issue has not been well studied.

There are several brands of fresh, frozen, unprocessed allograft, including AlloSkin and TheraSkin. These products are treated as human tissue for transplantation under the FDA's HCT/P process.

A small number of studies have been published in the peer-reviewed literature addressing the use of TheraSkin. Landsman and colleagues (2010) conducted a single-center, retrospective, uncontrolled case series study of 188 participants with VSUs and diabetic foot ulcers. The authors used historical controls for comparison, many of which were derived from previously published RCTs. The follow-up time was 20 weeks. The authors reported that at the 12-week follow-up, 60.4% of diabetic ulcers and 60.7% of venous ulcers were closed. At 20 weeks, those numbers increased to 74.1% and 74.6%, respectively. Neither of these differences was statistically significant. The authors conclude that TheraSkin is "highly effective" for the treatment of both VSUs and diabetic foot ulcers. No superiority was found, and in the absence of the desired outcome, the authors proffer that TheraSkin is equivalent to the control treatment. However, such conclusions reflect an inappropriate interpretation of the data from this effectiveness trial, which was not initially designed to test for equivalency, but superiority. To answer the question of equivalency, the authors would have had to have used an equivalency or non-inferiority study design, which would have utilized a different initial hypothesis and different set of assumptions.

DiDomenico and others (2011) conducted a non-controlled comparative trial of TheraSkin compared to Apligraf involving 28 participants with diabetic foot ulcers, 16 of whom received TheraSkin and 12 received Apligraf. At 12 weeks, 66.7% of the TheraSkin participants and 41.3% of the Apligraf participants had closed wounds. These numbers changed only slightly at 20 weeks, to 66.7% and 47.14% respectively. The authors concluded that TheraSkin was more efficacious in healing diabetic foot ulcers. However, it should be noted that randomization problems in this study resulted in uneven blocks of participant enrollment in the two cohorts, and the small sample size was not sufficiently powered to conclude whether TheraSkin was more effective than Apligraf.

Sanders (2014) reported the results of an underpowered RCT involving 23 participants with DFUs randomized to receive treatment with either Dermagraft (n=12) or TheraSkin (n=11). At 12 weeks follow-up, 7 (63.6%) participants in the TheraSkin group and 4 (33.3%) in the Dermagraft group were healed (p=0.0498). At the end of the 20-week evaluation period, 90.91% of TheraSkin participants vs. 66.67% of the Dermagraft participants were healed (p=0.4282). Time to healing in the TheraSkin group was significantly shorter (8.9 weeks) than in the Dermagraft group (12.5 weeks) (log-rank test, p=0.0323). The authors noted that the results of this study are similar to previous outcomes reported using these treatment modalities (see above studies) and suggest that, after 12 weeks of care, DFUs managed with TheraSkin are approximately twice as likely to heal as DFUs managed with Dermagraft, with approximately half the number of grafts required. However, they are careful to comment that, "Research confirming these results with a larger sample size and in individuals with different types of wounds is warranted."

Towler (2018) reported the results of a prospective RCT comparing Apligraf (n=12) to TheraSkin (n=15) for the treatment of VSUs. The authors reported no statistical differences between groups with regard to time to complete healing at 12 or 20 weeks (p=0.294 and p=0.569, respectively). Additionally, no differences were noted between groups with regard to the number of grafts needed (p=0.119). No adverse events were reported for either group. The authors concluded that both products are safe and effective to treat VSUs. However, the study was limited by small sample size, lack of blinding and other methodological issues.

In 2018, Choi reported on the use of cadaver allograft (n=698) vs. conventional treatment (n=584) in participants with burns involving > 30% body surface area. In both unmatched and propensity-matched participant groups, 90-day in-hospital mortality was significantly better in the allograft group vs. controls (31.7 vs. 39.7% for unmatched comparisons and 37.8 vs. 47.3% for propensity matched comparisons). Logistic regression analyses showed a significant association between cadaver skin allograft and lower 90-day in-hospital mortality in the propensity-matched groups (OR, 0.42).

Armstrong (2021) conducted a randomized, prospective, evaluator-blinded study which compared the response of 100 participants with non-healing DFU's, 50 of which were treated with TheraSkin and 50 treated with SOC. A total of 23 participants withdrew from the trial, 4 in the TheraSkin group and 19 in the control group. In the TheraSkin group 1 was removed for not achieving > 50% area reduction by 6 weeks, 1 for wound worsening, and 2 due to adverse events, 1 potentially related to the study treatment and the other not related. In the control group, 11 participants were removed for not achieving > 50% area reduction by 6 weeks, 1 due to reopened

wound, 3 due to serious adverse events, 2 which were potentially treatment related, and 4 due to adverse events, 1 of which was possibly related to study treatment. In the ITT analysis the results at 12 weeks showed that 76% (38/50) of the TheraSkin-treated DFUs healed compared to 36% (18/50) of controls treated with SOC (adjusted p=0.00056). The mean percent area reduction at 12 weeks was 77.8% in the TheraSkin group vs. 49.6% in the SOC group (adjusted p=0.0019). The average time for closure within the 12-week period was 46.9 days for the TheraSkin group vs. 65.3 days for controls (p=0.0019). The authors concluded that wounds treated with TheraSkin in addition to SOC improved wound healing compared to SOC alone.

The use of fresh, unfrozen, unprocessed skin allograft products has been a part of standard medical practice for the treatment of burns for almost a century. However, concerns regarding the risk of disease transmission and shelf life continue to be an issue, and other products have been proposed as an alternative. One of the most commonly used alternative products is fresh frozen skin allograft. Unfortunately, the current level of evidence addressing the safety and efficacy of fresh frozen skin allograft is weak. No solid conclusions can be made regarding the superiority, equivalency, or inferiority of these types of products in relation to other treatment options. However, despite this lack of evidence, a decades-long anecdotal track record for these products, easy access and availability, and a higher degree of certainty that the product is free from communicable pathogens has led to their acceptance as the standard of care in the burn treatment community. The use of fresh frozen skin allograft beyond the treatment of burns has not been established and is not widely accepted by the practicing community.

Grafix PRIME (see below for other Grafix products, including GrafixPL PRIME and Grafix CORE)

Grafix PRIME is a grafting product derived from allogeneic amniotic membrane. It is treated as human tissue for transplantation under the FDA's HCT/P process. A similar product, GrafixPL Prime, is also available. The difference between these products is that Grafix Prime is cryopreserved, and GrafixPL Prime is lyopreserved (a method of dehydration).

Lavery and others (2014) conducted an RCT involving 97 participants with DFUs who were randomized to receive treatment with either Grafix PRIME (n=50) or standard care (n=47). The proportion of participants achieving complete wound closure was reported to be significantly higher in the Grafix group (62%) vs. the control group (21%, p=0.0001). Median time to healing was 42 days in the Grafix group vs. 69.5 days in the control group (p=0.019). Fewer Grafix-treated participants experienced adverse events (44% vs. 66%, p=0.031) and wound-related infections (18% vs. 36.2%, p=0.044). Among the study participants that healed, ulcers remained closed in 23 of 28 participants (82.1%) in the Grafix group vs. 7 of 10 participants (70%) in the control group (p=0.419). The authors concluded that treatment with Grafix significantly improved DFU healing compared with standard wound therapy and reduced DFU-related complications.

In 2018, a follow-up study was published by this group reporting on the results of 24 participants who had failed treatment in the control group and crossed over to treatment with Grafix Prime (Lavery, 2018). The authors reported a 65.4% complete healing rate at a median of 34 days of treatment. These participants also experienced fewer adverse events and wound-related infections than participants followed in the initial study period reported above (adverse events, p=0.019; infections, p=0.116).

In 2016, Johnson and others published a report of a retrospective nonrandomized study comparing the outcomes from two separate cohort studies involving Grafix PRIME (n=40) or Epifix (n=39) for the treatment of a variety of wounds including VSUs, surgical wounds, DFUs, arterial ulcers, pressure ulcers, and 'other' wounds. The authors reported that the proportion of wounds achieving complete wound closure was 63.0% (29/46) for the Grafix group and 18.2% (10/55) for the Epifix group (OR=7.5, p<0.0001) for all treated wounds combined. When analyzed by wound type, the results indicated that treatment with Grafix group had a significantly higher rate of completely closed VSUs (70% vs. 7%, p=0.0024) and surgical wounds (81.9 vs. 18.2%, p=0.009). The small number of participants, and retrospective, non-random, and unblinded methodology used in this study impair the generalizability of the results.

Another published case series study addressed the use of Grafix PRIME and included 67 wounds in 66 participants with either DFUs (n=27), VSUs (n=34), or other chronic wounds (n=6) (Regulski, 2013). At 12 weeks, 51 of 67 wounds (76.1%) were healed. By wound type, 23 of 34 (67.6%) VSUs and 23 of 27 (85.2%) DFUs were healed at 12 weeks. The average time to closure in these wounds was 5.8 (± 2.5) weeks. No significant differences were reported between the two wound type groups, and no adverse events or recurrences were reported.

Raspovic (2018) reported a retrospective case series analysis of 360 participants with 441 DFUs treated with Grafix PRIME or Grafix CORE using data from Net Health's Wound Expert electronic health records database. The mean size of the index wound was 5.1 cm^2 with 3.9 mm depth. Mean wound duration prior to study treatment was 102 days. The mean duration of treatment with a Grafix product was 89.3 days (median 56.0). Complete wound closure at the end of treatment occurred in 59.4% of participants. Median time to closure was 42.0 days with a median of 4 graft applications. The proportion of closure decreased as wound size increased, with 72.3% of wounds between 0.25 cm^2 to 2 cm^2 having complete healing at a median of 21 days and 4 applications. For wounds larger than 25 cm^2, only 27.8% achieved complete healing at a median of 105 days and 11 applications. The authors did not provide any data regarding the percentage of participants receiving treatment with Grafix PRIME vs. those receiving Grafix CORE.

Ananian (2018) reported the results of a single-blind non-inferiority RCT comparing Grafix PRIME vs. Dermagraft in 62 participants (31 in each group) with chronic DFUs. At the end of the 9-week study period, 100% reepithelialization occurred in 48.7% of Grafix participants and 38.7% of Dermagraft participants, meeting the endpoint of non-inferiority, defined for this study as a treatment effect difference of 20% (p=NS). At 28 days post-initial study application, a 50% or greater reduction in wound area was reported in 70.8% of Grafix participants and 67.7% of Dermagraft participants. The percent average reduction in wound size at the end of the study period was 86.3% in the Grafix group vs. 78.1% for the Dermagraft group (p=NS). The Grafix group had a mean of 5.3 applications vs. 4.4 applications to achieve 100% reepithelialization (p=NS).

Based on clinical practice standards, relevant expert opinion, the above-mentioned studies, and the overall clinical experience with Grafix PRIME, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of DFUs. However, use of this product for other indications has not been widely accepted by the practicing community.

GraftJacket

GraftJacket is an acellularized human skin-derived product and is treated as human tissue for transplantation under the FDA's HCT/P process.

One randomized controlled trial compared the use of standard surgical debridement followed by GraftJacket placement vs. standard surgical debridement alone (20 participants in each group) (Brigido, 2004). The findings of the study demonstrated significant differences between the two groups, with the experimental group demonstrating much faster healing progression. While the results of this study are promising, the small sample size, as well as its single-blind design, limits its utility. The same authors conducted a second RCT with 28 participants with chronic DFUs who were assigned to receive either GraftJacket (n=14) or standard care (n=14) (Brigido, 2006). At 16 weeks, 12 of 14 (85.7%) of the GraftJacket participants demonstrated complete wound closure, compared with 4 of 14 (28.6%) in the control group (p value not provided). Participants treated with GraftJacket demonstrated a statistically significant higher percentage of wound healing with respect to wound area, and clinically significant differences in wound depth and

wound volume (p<0.001).

Reyzelman (2009) reported the results of an RCT involving 85 participants with diabetic foot ulcers assigned to receive treatment with either GraftJacket (n=46) or standard care (n=39). The authors reported significantly better complete and mean healing times in the GraftJacket group (69.6% and 5.7 weeks) compared to the controls (46.2% and 6.8 weeks) who received standard care (p=0.029). Furthermore, there was a significantly higher non-healing rate for the control group (53.9%) compared with the study group (30.4%) at 12 weeks (p=0.015). Neither the participants nor the investigators were blind to group assignment.

A prospective non-blind RCT involving 168 participants with DFUs assigned in a 2:2:1 fashion to treatment with DermACELL (n=71), conventional care (n=69), or Graftjacket (n=28) (Walters, 2016). At 16 weeks post intimal treatment, no significant differences in the proportion of completely healed ulcers vs. the conventional care group was found (67.9% vs 47.8%; p=0.1149). No differences between groups were reported with regard to severe adverse events (p≥0.05).

Cazzell (2017) conducted an RCT involving 132 participants with chronic DFUs undergoing treatment in 2:2:1 fashion with either DermACELL (n=53), conventional care (n=56), or GraftJacket (n=23). Participants were followed through 24 weeks, with endpoint measurement at 12, 16, and 24 weeks. GraftJacket did not show a significantly greater healing rate over conventional care at any of these time points. No significant difference was noted between the GraftJacket group vs. the conventional care group for healed wounds remaining closed. However, as noted above, the results of this comparison for GraftJacket are significantly hampered by small numbers of participants, and the results should be viewed with that in mind.

GraftJacket has also been proposed for use in shoulder surgery to repair soft tissue injuries. Barber and colleagues (2012) reported on an RCT involving 42 participants with rotator cuff injuries randomized to undergo repair with GraftJacket (n=20) or standard surgical procedures (n=22). At the 2-year follow-up period, significant benefits were noted on several scales, including the American Shoulder and Elbow Surgeons (ASES) (p=0.035) and Constant (p=0.008) assessment tools. No significant difference was seen on the University of California, Los Angeles (UCLA) tool (p=0.43). Imaging studies found that at 2 years, 85% of the GraftJacket group had intact grafts, compared to only 40% in the standard care group (p<0.01). A prospective case series study by Gupta and others (2012) involved 24 participants with rotator cuff tears treated with GraftJacket and followed for 3 years postoperatively. The authors report significant improvements with regard to pain, (p=0.002), mean active forward flexion and external rotation (p=0.002), mean shoulder abduction (p=0.0001), supraspinus strength (p=0.0003), and ASES scores (p=0.0003). Ultrasonography showed 76% of repairs were fully intact, with the remainder of participants with partially intact repairs.

Marks and colleagues (2017) reported on a study involving the use of GraftJacket for the treatment of 60 participants with osteoarthritis at the first carpometacarpal (CMC I) joint who underwent treatment with either trapeziectomy with suspension-interposition arthroplasty using the flexor carpi radialis (FCR) tendon (n=29) or GraftJacket (n=31). They reported that baseline Michigan Hand Outcomes Questionnaire (MHQ) total scores significantly increased from 51 to 83 in the FCR group and 53 to 76 in the GraftJacket group by 12 months (p<0.05 for both). No differences between groups were reported (p>0.05). Complications were reported in 5 FCR-related participants, and 10 in the GraftJacket group (p=0.24). Revision surgery was required for 1 allograft subject. They concluded that the use of the FCR tendon or GraftJacket for trapeziectomy with suspension-interposition arthroplasty leads to similar outcomes, but with more complications, mainly tendon irritations, associated with GraftJacket. They noted that they “only use the allograft in cases of severe instability requiring a larger amount of suspension-interposition material or for revision procedures after failed suspension-interposition with the FCR tendon.”

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with GraftJacket, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremity dermal wounds. However, use of this product for other indications has not been widely accepted by the practicing community.

Integra Bilayer Matrix Wound Dressing

Integra Bilayer Matrix Wound Dressing is a composite grafting material made from cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. It has been cleared through the FDA’s 510K Premarket Notification process. The use of this product has been found to be efficacious in the post-excisional treatment of full-thickness or deep partial-thickness burns when autografting is not feasible. This conclusion is supported by well-designed randomized studies (Branski, 2007; Heimbach, 2003).

Othman (2021) reported the results of a retrospective case series study involving the use of Integra Bilayer Matrix Wound Dressing for the treatment of cutaneous scalp defects in 127 participants older than 60 years of age. The reconstructive procedures were conducted in a 2-stage fashion, with the wound first being treated with Integra followed by STSG between 3-4 weeks afterwards. A total of 107 (84%) participants were successfully reconstructed. The 20 participants who had treatment failure were more likely to have a history of radiotherapy (30% in the failure group vs. 12% in the success group, p<0.04). Place of service was noted as a significant factor in treatment failure, with 25% of participants treated in the inpatient setting having failure vs. 8% of participants treated in the outpatient setting (p<0.034). The authors noted that postoperative wound infection was significantly associated with reconstructive failure (30% vs. 6.5%, respectively; OR, 6.4, p<0.006). The results of this study are promising, but the weak methodology used does not allow generalization of these findings to a wider population.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with Integra Bilayer Matrix Wound, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of burns. However, use of this product for other indications has not been widely accepted by the practicing community.

Integra OmniGraft Dermal Regeneration Template

Integra Dermal Regeneration Template is a composite graft material made from bovine collagen, chondroitin-6-sulfate (C6S), and a semi-permeable polysiloxane (silicone) layer. It is a skin substitute used for dermal reconstruction in the post excisional treatment of life-threatening full-thickness or deep partial-thickness burns where sufficient autograft is not available at the time of excision, or is not desirable due to the physiological condition of the individual. It has been cleared through the FDA’s 510K Premarket Notification process.

Ryan and colleagues (2002) completed a single-center retrospective review of 270 individuals with acute burns 20% of TBSA or greater who received treatment with Integra (n=43) or standard care (n=227). Integra was placed on 43 individuals during 59 operative procedures. No difference in mortality was found between individuals who received Integra (30%; n=43) and individuals who did not (30%; n=227). Integra mortality rates were not different from the control group. Burn survivors treated with Integra (n=30) had a longer length of stay, however, they were more extensively burned than survivors who did not receive Integra, thus longer hospitalizations were expected. In a subgroup analysis, the mean length of stay of an Integra-treated individual with two or more mortality risk factors (age > 60 years, burn size > 40% TBSA, or inhalation injury; n=15) was 63 days compared with 107 days in individuals with two or more risk factors (n=29) who did not receive Integra (p=0.014); therefore, Integra use was associated with a marked decrease in LOS.

Heimbach and colleagues (2003) evaluated the use of Integra Dermal Regeneration Template at 13 burn care facilities in 216 individuals with full-thickness or deep partial-thickness burns with a mean TBSA of 36.5%. Integra Regeneration Template was applied exclusively to fresh, clean, surgically excised burn wounds after the complete removal of residual eschar, and upon hemostasis. Once the Integra was fully vascularized and the neodermis had formed, the silicone layer was removed and an ultrathin meshed epidermal autograft was placed to allow healing. Participants were followed until either the burn wounds healed or the participant was discharged from acute care. The primary outcome measured was the incidence of invasive infection at Integra-treated sites and the participant mortality associated with such infections; secondary outcomes were graft take. A total of 841 sites were treated; 589 sites subsequently had thin epidermal autografting. In 252 sites epidermal autograft was not placed due to participant death (n=30 partcipants,139 wound sites). Spontaneous epidermal regeneration occurred and did not require autograft at 27 sites. Substitution of cultured skin for epidermal autograft occurred at 26 sites. Deficient take and removal occurred at 15 sites, and amputation occurred at 4 sites. The results demonstrated an invasive infection rate of 3.1% (95% CI, 2.0–4.5%), and superficial infection rate of 13.2% (95% CI, 11.0–15.7%) at Integra treated sites. The median take rate was 95%. The mean take rate of epidermal autograft was 87.7%; the median take rate was 98%. The authors concluded that neither type of infection was associated with increased mortality risk (p=0.05). These findings support the use of Integra in the treatment of burn wounds.

In 2015, Driver and colleagues reported the results of an RCT involving 307 participants with DFUs assigned to treatment with either standard care (n=153) or treatment with Omnigraft (n=154) and followed initially for 16 weeks or until confirmation of complete wound closure, and then for a further 12 weeks. The investigators reported that complete DFU closure during the treatment phase was significantly greater with Omnigraft vs. control treatment (51% vs. 32%; p=0.001). The median time to complete DFU closure was 43 days for Omnigraft participants vs. 78 days for controls, in wounds that healed. The rate of wound size reduction was significantly better in the Omnigraft participants (7.2% per week vs. 4.8% per week, p=0.012). They concluded that for the treatment of chronic DFUs, Omnigraft treatment decreased the time to complete wound closure, increased the rate of wound closure, improved components of quality of life and had less adverse events compared with the standard of care treatment.

Hicks and others (2020) reported the results of a case series study that included 85 participants treated with Omnigraft who underwent surgical procedures for debridement of a DFU or gangrene resulting in complex post-surgical DFUs. Overall, 107 wounds were treated, with 45.8% involving the forefoot, 23.4% the heel, 19.6% the midfoot, 5.6% the ankle, and 5.6% the lower leg/Achilles tendon. Bone involvement due to acute or chronic osteomyelitis occurred in 71.7%. Most participants were at high risk for amputation based on Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification score (6.4% were WIfI classification score 4). Overall success rate for all initial dermal regeneration template applications was 66.7%, with the majority of wounds (81.3%) receiving one dermal regeneration template application. Two applications were reported in 15.9% of cases and three applications in 2.8%. Mean time to complete healing was 198 ± 18 days. Location of the wound on the forefoot was associated with significantly better healing (hazard ration [HR], 5.2) as was the presence of bone involvement (HR, 1.86). While these results are promising, the lack of a comparison group and other methodological weaknesses limit their generalizability.

In 2021 Mogedas-Vergara described a retrospective cohort study involving 70 participants with skin cancer undergoing scalp reconstruction procedures. All participants were over 65 years or age. Each participant underwent 2-stage procedures involving a first stage where Integra Derma Regeneration Template was used followed by the application of a STSG after 3-4 weeks. The mean surface area treated was 23 cm^2 and the mean interval between stages was 30.6 days. Seven participants (10%) did not undergo a second-phase procedure due to rapid wound epithelialization. The Integra and skin graft success rates were 87.1% and 100% respectively. A total of 13 participants (18.6%) developed infections. In 4 participants (5.7%) the infection caused partial Integra loss, which was treated via debridement and antibiotics and no need to reconsider placement of the graft. Infection resulted in total loss of the Integra graft in in 9 participants (12.9%) and healing was completed by second intention without major complications. Mean wound epithelization in this subgroup of 13 participants was 60.33 days and no other complications were recorded. The results of this study are promising, but the weak methodology used does not allow generalization of these findings to a wider population.

Falcone (2023) reported on the results of a retrospective comparative study involving the use of single-layer Integra to treat allogenic radial artery forearm free-flap skin donor site sites during total phallic construction. A total of 34 participants were included, 18 who received FTSG alone and 16 who received Integra covered by a STSG. The authors reported significantly better healing time in the Integra group vs. the FTSG group (24 days vs. 30 days, p=0.003). Similarly, the Integra group had significantly better complete graft take (93.8% vs. 27.8%, p=0.001), shorter operative times (310 min vs. 447 min, p=0.001), and median hospital stay (8 days vs. 10 days, p=0.001). This was the first study of its kind to be published. The results are promising, but additional data from more robustly designed and conducted trials is warranted to better understand the role of Integra for the treatment of free-flap donor sites.

Kerecis™ Omega3

Kerecis Omega3 is an acellular dermal matrix derived from fish skin and cleared through the FDA's 510K process.

The available evidence addressing the clinical safety and efficacy of Kerecis is limited. A double-blind, parallel-group non-inferiority RCT involving 81 participants with 162 full-thickness surgical wounds was reported by Baldursson in 2015. Each participant underwent the creation of two 4 mm full thickness wounds made on the proximal anteriolateral aspect of their non-dominant arm, 2 cm apart. Each participant had one wound treated with Kerecis and the other wound with Oasis porcine-derived graft product and were followed for 28 days. At the study endpoint, 95% (76/80) of wounds in the Kerecis group and 96.3% (79/82) of wounds in the Oasis group were healed. The authors reported that this result was within the 95% two-sided confidence interval for non-inferiority margin of 0.1. They also noted that the OR of a Kerecis-treated wound being healed vs. an Oasis-treated wound was 4.75 (p=0.041), indicating that Kerecis added significantly faster wound healing vs. Oasis. No significant immunological responses were noted in the Kerecis group. While the findings of this study are interesting, they do not provide data regarding performance of the product in the populations for which they are proposed, specifically, those with impaired healing and chronic wounds. The results involving experimentally created wounds are not useful in informing the discussion of the clinical utility of Kerecis Omega3 in the real-world setting for the treatment of individuals with impaired healing function.

Michael et al. (2019) published the results of a retrospective case series study involving 51 participants with 58 DFUs treated with Kerecis. Offloading methods were described in 34 wounds. At 16 weeks, the mean reduction in wound surface area was 87.57%, with 60.35% (35/58) healed completely. In the same time frame, > 90% reduction in wound surface area was achieved in 74.14% (45/58) of wounds. Only 2 wounds were reported to not have any healing in 16 weeks, but both healed eventually at 24 and 36 weeks, respectively, the former following additional Kerecis Omega3 applications, and the latter with no additional applications. The lack of a control group, blinding and other methods of bias control significantly hamper the generalizability of these findings.

Another study addressing the clinical outcomes of Kerecis has been published (Yang, 2016). However, this study was very underpowered, involving only 5 participants, and did not involve any comparison group. The value of this publication in understanding the generalizable safety and efficacy of Kerecis is limited.

Kirsner (2020) published the results of a double blind RCT involving 85 healthy participants who had two investigator-created full thickness punch biopsy wounds randomly assigned to treatment with either Kerecis or EpiFix. A total of 170 wounds were treated. The authors stated that the Kerecis-treated wounds healed significantly faster than the EpiFix-treated wounds (HR, 2.37, p=0.0014). No

differences between groups were reported with regard to adverse or serious adverse events. These results indicate that Kerecis is similar to EpiFix in the treatment of acute surgical wounds. However, as with the Baldursson study previously discussed, this study did not adequately reflect the actual real-world use of these products, such as for the treatment of refractory DFUs.

Lullove (2021) reported the results of a prospective single-blind RCT involving 49 participants with chronic superficial DFUs treated weekly for 12 weeks with either Kerecis and standard care with moisture-retentive foam dressing and hydrogel as needed to retain adequate moisture balance (n=24) or standard care with collagen alginate dressing alone (n=25). At 12 weeks the Kerecis group included 21 (87.5%) and the control group had 13 (52.0%), for an overall loss to follow-up of 30.1%. At 12 weeks, 67% Kerecis wounds had fully closed vs. 32% in the control group (p=0.0152). At the same time point, the reduction of wound area was 97.3% in the Kerecis group vs. 76.8% in the control group (p<0.06). The loss to follow-up at 12 weeks, along with other methodological flaws hinder the generalizability of these findings.

Kim (2021) reported the results of a retrospective non-randomized controlled study involving of 56 participants with acute or chronic deep dermal wounds who were treated once with Kerecis (n=16) vs. daily standard dressings (n=41). Choice of group was at the participants preference. The control group had 9 participants convert to surgical treatment before the end of the trial, for a total of 32 participants (78%) completing the trial period. In the Kerecis group, 8 participants had acute burns, 5 had acute traumatic wounds, and 1 DFU, 1 VSU and 1 pressure ulcer. In the control group, 15 participants had acute burns, 11 had acute traumatic wounds, and 6 had other unspecified wounds. In the Kerecis group, it was reported that the graft was fully absorbed at an average of 5.56 ± 1.60 days following application, with an average healing rate of 77.7% at 2 weeks. There were no significant differences in wound healing rates between groups for participants with traumatic wounds. For burn participants, the mean healing rate was 86.5% in the Kerecis group vs. 61.1% in the control group (p=0.021). The overall average healing rate of all wound types treated with Kerecis was 77.7% vs. 53.3% for the control group (p<0.05). These results are promising in aggregate, but limited sample sizes limit generalizability, including how Kerecis preforms for certain wound types.

Lullove (2022) published an interim analysis of the aforementioned 2021 prospective, single-blind, multicenter, parallel-group, RCT assessing the efficacy of Kerecis graft on chronic nonresponsive diabetic foot ulcers in comparison with the standard of care (collagen alginate dressings). The endpoint of the trial was the proportion of index ulcers closed at 12 weeks. The secondary outcome measure is time to heal and wound area reduction by percentage at 12 weeks. Ninety-four participants completed the protocol. At the 12-week follow-up healing was achieved in 63.0% of index ulcers (29 of 46 participants) in the Kerecis group compared with 31.3% in the control group (15 of 48 participants) (p=0.0036). In both groups the mean healing time was 7 weeks. The median number of applications of Kerecis to achieve healing was 6. For wounds that did not heal, the mean wound area reduction at 6 weeks was 69.3% in the Kerecis group and 44.2% in the control group (p=0.015). This significant difference continued throughout the 12-week follow-up period, at which time the wound area reduction was 87.1% in the Kerecis group and 54.0% in the control group (p=0.0039). One limitation of this study is that long term follow-up is lacking.

Lullove and colleagues (2023) reported the findings of a prospective, multicenter, parallel-group, randomized controlled trial, with an independent single-blinded assessment of DFU wound healing outcomes. The overall study included 102 participants, 51 who received treatment with Kerecis and 51 treated with SOC using collagen alginate therapy. The per-protocol analysis included 77 participants who completed the study (n=43 in the Kerecis group and n=34 in the SOC group). The study compared wound closure rates, wound healing rates, and the mean wound percentage area of reduction in individuals receiving treatment over 12 weeks. The authors reported that DFU's in the Kerecis group were more likely to close, with 56.9% (29/51) of Kerecis group participants having wound closure at 12 weeks vs. 31.4% (16/51) in the SOC group (p=0.0163). At 12 weeks, the mean wound percent area reduction was 86.3% in the Kerecis group vs. 64% in the SOC group (p<0.05 for both the per-protocol and ITT analyses). The mean percentage area of reduction was 86.3% for the Kerecis group vs. 64.0% for the SOC group at 12 weeks (p=0.0282). Interestingly, the average number of applications in the Kerecis group was 5.9 vs. 17.1 in the SOC group (no p-values provided). A total of 8 serious adverse events were reported, 3 in the Kerecis group and 5 in the SOC group. Only 1 in the Kerecis group was deemed potentially treatment related and all 5 events were deemed potentially treatment related in the SOC group. A total of 45 participants were reported to have complete healing during the trial period, 27 in the Kerecis group and 15 in the SOC group. Ulcer recurrence was reported in 3 Kerecis participants and 1 SOC participant (no p-values provided). However, 3 of these 4 recurrences were deemed to be related to failure to use offloading footwear and not related to the treatment assignment. The results of this study demonstrate supportive findings for the use of Kerecis vs. SOC for DFUs.

In 2023 Lantis and colleagues reported the final results of the aforementioned prospective, multicenter, RCT (Lullove, 2022) evaluating the use of Kerecis compared with collagen alginate therapy in the management of DFUs. The primary outcome was the proportion of index ulcers healed at 12 weeks in each group. Wounds were classified as either healed or not healed. Secondary outcomes were time to healing and mean percentage wound area reduction at 6 and 12 weeks. The tertiary outcome was ulcer recurrence during the follow-up period. A total of 102 individuals with DFUs (n=51 Kerecis, n=51 collagen alginate therapy) participated in the trial as ITT candidates, 77 of those were included in the per protocol analysis (n=43 Kerecis, n=34 collagen alginate therapy). Six months after treatment, individuals with healed ulcers were followed for ulcer recurrence. The findings demonstrated that DFUs treated with Kerecis were more likely to achieve closure than those managed with collagen alginate therapy (ITT: 56.9% compared to 31.4%; p=0.0163). The mean percentage area wound reduction at 12 weeks was greater for Kerecis (86.3% vs. 64.0% for collagen alginate therapy, p=0.0282). The authors concluded that treatment of DFUs with Kerecis resulted in more wounds healed compared with standard of care collagen alginate therapy.

The published literature supports the use of Kerecis for treatment of diabetic foot ulcers that have not healed with standard conservative therapy. Additional studies that address long term follow-up will help elucidate the durability of these results.

mVASC

mVASC is a product derived from processed subcutaneous allogenic microvascular tissue and is treated as human tissue for transplantation under the FDA's HCT/P process. It is derived from the structural elements of microvascular tissue of human donors and includes inherent non-viable cells and signaling factors.

In 2021 Gould and colleagues reported on the results of a prospective single blind RCT involving 100 participants with DFUs who were treated with either standard care with collagen alginate dressing or standard of care with mVASC (n=50 per group). Participants were followed for 12 weeks. The authors reported that the percentage of wounds closed at 12 weeks was significantly better in the mVASC group vs. the control group (74% vs 38%, p=0.0003), and the odds of healing by 12 weeks in the mVASC group was 9-fold vs. the control group (OR, 9.0; p=0.00008). The change in percent of wound area reduction was similarly found to be significantly in favor of the mVASC group beginning at week 4, with the mVASC group having a mean percent wound area reduction of 76%, over 3-fold more than the mean percent wound area reduction seen in participants in the control group (p=0.009). Finally, the mean time to healing was significantly faster for the mVASC group vs. controls (54 days vs. 64 days, p=0.009). Measurement of a secondary endpoint, wound perfusion, indicated a consistent decrease in the mean ingress rate in the mVASC-treated wounds, corresponding to an increase in perfusion of 60%. The control group demonstrated a consistent increase in the mean ingress rate, indicating a significant decrease in perfusion (67%). Additionally, based on results of the Semmes-Weinstein monofilament (SWM) exam, mVASC group participants had a significant improvement in peripheral neuropathy at 12 weeks vs. control group participants (118% vs. 11%;

p=0.028). No adverse events (AEs) or serious adverse events (SAEs) related to the study treatment were reported.

While this is the only published clinical trial of the use of mVASC, it is a well-designed and conducted study and demonstrated significant benefits of the use of this product vs. standard care in the treatment of DFUs. Potential benefits from the use of mVASC for other indications are unclear and such use has not been widely accepted by the practicing community.

Oasis

Oasis® Matrix products (Smith+Nephew, Andover MA) are a suite of grafting products composed of decellularized porcine intestinal mucosa that are indicated for the management of acute and chronic wounds. Oasis has been cleared through the FDA's 510K process.

The first study addressing Oasis was published by Mostow and colleagues in 2005. They described a randomized controlled trial (RCT) involving 62 participants who received Oasis and compression therapy for VSUs vs. a control group of 58 participants who received compression therapy alone. The authors reported significantly better healing rate in the Oasis group over the control group at 12 weeks. Another publication described a RCT involving individuals with DFUs (Neizgoda, 2005). The experimental group included 37 participants who were treated with the Oasis graft and 36 who were treated with Regranex gel. As with the previously described trial, the authors reported significantly improved results with the Oasis graft.

Romanelli and colleagues describe a study comparing Oasis against a product not currently available in the U.S., Hyaloskin (2007). The result of this trial, while favorable to Oasis, is not particularly useful in the evaluation of Oasis. This is due to the fact that the comparison product is unknown here in the U.S. and there is no currently available scientific literature addressing its use in the clinical setting.

The same group published a second RCT involving 50 participants with either mixed venous/arterial ulcers (n=25) or venous ulcers (n=25) (Romanelli, 2010). Participants were randomized to receive treatment with either Oasis or standard petrolatum impregnated gauze and followed for 8 weeks. At the completion of the study, the authors reported that for all measures the Oasis group was significantly superior compared to the control group, including average healing (5.4 weeks vs. 8.3 weeks, p=0.02) and complete wound closure (80% vs. 65%, p<0.05). Granulation of tissues increased from 50% to 65% in the Oasis group and decreased in the control group (p<0.02). The Oasis group also required fewer dressing changes, more than doubling the time between dressing changes.

Cazzell (2015) reported the results of an unblinded RCT involving 82 participants with neuropathic ulcers treated with either Oasis (n=41) or standard care (n=41). Participants were followed for 12 weeks or complete ulcer closure. The Oasis group had a significantly greater proportion of wounds closed by 12 weeks vs. controls at all measurement times (54% vs. 32%, p=0.021). The time to closure for ulcers that achieved closure was 2 weeks earlier in the Oasis group vs. controls (9 vs. 11 weeks, respectively). The probability of wound closure at 12 weeks was 62% for the Oasis group vs. 40% for controls. Median reduction in ulcer area was significantly greater for Oasis at each weekly visit (p<0.05 for all). The most important predictor of wound closure in regression analysis was group assignment (HR, 2.005; p=0.049). No significant differences between groups with regard to adverse events were reported.

Martinson (2016) analyzed Medicare claims data from 2011-2014 to identify individuals with DFUs. Information regarding wound treatment products (Apligraf, Dermagraft, Oasis, and MatriStem), the episode length, amputation rate, and skin substitute utilization were compared. There were 13,193 overall treatment episodes. Apligraf was used in 4926 (37.3%), Dermagraft 5530 (41.9%), Oasis 2458 (18.6%), and MatriStem 279 (2.1%). The percentage of DFUs that healed at 90 days by product was reported: MatriStem 62%; Oasis 63%; Apilgraf 58%; and Dermagraft 58%. MatriStem was determined to be non-inferior to Oasis (p<0.001), and both were better than Apilgraf or Dermagraft (p<0.005). The authors concluded the analysis demonstrated that MatriStem and Oasis were associated with both shorter DFU episode lengths and lower payer reimbursements than the other products.

Brown-Etris and colleagues (2019) reported an open label RCT of 130 individuals at 12 treatment facilities to evaluate the clinical safety and efficacy of Oasis Wound Matrix (n=67) as a treatment for full-thickness pressure ulcers compared to standard of care (n=63). Participants' ulcer size was measured at enrollment and weekly at each visit for a period of up to 12 weeks. Complete healing in the Oasis group was 40% vs. 29% in the standard care group (p=0.111). The percentage of participants with a 90% reduction in ulcer surface area was 55% in the Oaisis group compared to 38% in the standard of care group (p=0.037).

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with Oasis, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremity dermal wounds and diabetic foot ulcers that have not healed with standard conservative therapy.

Additionally, several studies have been published addressing the use of Oasis products for the treatment of burns. The first (Salgado, 2014) involved a total of 5 participants treated with both Oasis and silver-containing cellulose hydrofiber (Aquacel AG) at different burn sites on the same subject. This study reported on the histomorphometric outcomes, which demonstrated favorable results in favor of the Oasis product. Measurement of epithelial maturation within the repair areas were considered significantly more phenotypically structured after 7 days of treatment with Oasis vs. the Aquacel-treated wounds at 7 days (6.2 vs. 3.2, p=0.029). No infections or "irritation" were reported. Both products were naturally expelled in all participants by 7 days. The Vancouver Scar Scale score for vascularity, pigmentation, and pliability indicated more favorable results in the Oasis group (3.6 vs. 7.2, p=0.025). The unblinded nature of the study, in addition to the low power and other methodological weaknesses do not allow generalization of the findings across larger populations.

A retrospective unblinded case-control study was reported published by Glik in 2017. This study involved 30 participants treated with either Oasis (n=6) or Suprathel (n=24). Histopathological specimens were harvested for evaluation from the participants at 14 and 21 days. The authors provide qualitative observations of the healing process, including comments regarding product adherence to the wound, progression of epithelialization, and pain levels. However, no quantitative data in these factors were reported. While the authors state that Oasis provides clinical benefit in the treatment of burn wounds, their report is of little value due to the lack of quantitative data to support their findings. Additionally, as with the Salgado study above, significant methodological weaknesses in this study do not allow generalization of the findings across larger populations.

While this evidence is promising, the use of Oasis for burns has not been widely accepted within the practicing community.

OrCel

OrCel is a living skin equivalent (composite cultured skin) composed of human allogeneic skin cells cultured in layers of Type I bovine collagen that has been approved through the FDA's PMA process. This product was granted an FDA HDE in 2001 for use in children with recessive dystrophic epidermolysis bullosa (RDEB), who are undergoing reconstructive hand surgery. However, there is still little clinical data to support the use of OrCel for other applications and such use has not been widely accepted by the practicing community.

OviTex

OviTex is a decellularized ovine forestomach extracellular matrix mesh reinforced with five percent polymer fiber. OviTex has both permanent and resorbable variations. The product was cleared through the FDA's 510k process in 2014.

Sivarajah and colleagues (2022) reported a retrospective analysis of 109 participants, 18 years of age and older, from 2002-2021 who underwent ventral hernia repair to assess the association of mesh type with complications and surgical site occurrence. Ventral hernia repair was performed with OviTex reinforced biologic ovine rumen (n=50) or synthetic polypropylene mesh (n=59). Synthetic products used included: Prolene (n=29), Parietex (n=15), and Physiomesh (n=15). A1l participants with OviTex had prior abdominal surgery compared to 86.4% of participants who received synthetic mesh (p=0.01). Participants who received OviTex had lower rates of adverse events (16.0 vs 30.5%, p=0.12), and similar hernia recurrence rates (4.0 vs. 6.78%, p=0.68) compared to participants with synthetic mesh. Synthetic mesh was associated with increased odds for overall complications (3.78, p<0.05) and adverse events (3.87, p<0.05). The authors concluded that OviTex had a superior profile to other mesh products due to comparable hernia recurrences and decreased rate of adverse events.

The same investigators (Sivaraj 2022) also reported a retrospective analysis of 141 participants who underwent ventral hernia repair with varying biologic mesh types which compared postoperative donor site complications and hernia recurrence rates amongst 1) Strattice (n=51), 2) Permacol (n=17), 3) OviTex (n=36), and 4) Surgimend (n=37). There were less complications in participants with OviTex (16.7%), compared to Permacol (52.9%), Strattice (47.1%), and Surgimend (43.2%) (p=0.015 for OviTex vs. all other products). Rates of hernia recurrence were also lower in participants that received OviTex (2.78%) and Strattice (13.7%) compared to Permacol (29.4%) and Surgimend (24.3%) (p=0.022). These results reiterated the authors' previous findings that OviTex decreased both abdominal complications and recurrence rates after ventral hernia repair compared to the other products.

OviTex is supported by sufficient evidence showing that it is at least commensurate with other accepted approaches for hernia repair and may provide a lower risk of adverse events.

PriMatrix

Primatrix is a product derived from acellular bovine dermis and has been cleared through the FDA's 510K process. To date, there are only a limited number of small studies addressing its use in humans. One retrospective, nonrandomized controlled series involved 68 participants with either diabetic foot wounds (n=40) or VSUs (n=28) who received treatment with either Apligraf (n=34) or PriMatrix (n=34) (Karr, 2011). The number of participants with each type of wound receiving treatment with Apligraf or PriMatrix was equal, with 20 diabetic foot wounds and 14 VSUs in each group. For diabetic foot ulcers, the Apligraf-treated group's time to complete healing was 87 days, the PriMatrix was 37 days. The average number of graft applications was 2 in the Apligraf group and 1.5 in the PriMatrix group. For VSUs, the time to complete healing was 63 days in the Apligraf group and 32 days in the PriMatrix group. The Apligraf group had 1.7 graft applications compared to 1.3 in the PriMatrix group.

Another retrospective, nonrandomized controlled series involved 20 participants with Charcot neuropathy and chronic non-healing ulceration treated with either PriMatrix (n=12) or standard wound care (n=8) (Kavros, 2012). The mean time to healing in the PriMatrix group (116 days) was significantly shorter than in the control group (180 days) (p<0.0001). A significantly faster rate of healing was observed with PriMatrix (87.9 mm^3/wk) compared with control (59.0 mm^3/wk) (p<0.0001). The authors conclude that, "The significantly faster rate of healing and steeper slope of volume reduction in the PriMatrix group warrants further investigation into its effects on healing of neuropathic ulcerations and potential limb salvage."

Lantis and others (2021) reported the results of an unblinded RCT involving 226 participants with treatment resistant DFUs treated with either PriMatrix plus standard care or standard care. The authors state that the study was terminated early due to the COVID-19 pandemic. They conducted a modified intent-to-treat analysis on a total of 207 participants, 103 in the PriMatrix group and 104 in the standard care group. Additionally, a total of 161 participants completed the study per modified protocol, with 79 receiving PriMatrix and 82 standard care. The modified intent-to-treat analysis found that PriMatrix treated participants had a significantly greater number of wounds achieve complete wound closure vs. those treated with standard care (45.6% vs. 27.9%, p=0.008). Similar findings were reported in the modified per-protocol analysis (59.5% vs. 35.4%, p=0.002). The odds of complete wound closure at 12 weeks were reported to be 2.2 times greater in the PriMatrix group (p=0.008). No significant differences were noted with regard to median time to closure within 12 weeks (43 days vs. 57, p=0.36). The mean and median number of PriMatrix applications to achieve closure per wound was 1.4 and 1. No adverse events or serious adverse events related to the use of PriMatrix or the procedure were reported. The authors concluded that a single application of PriMatrix plus standard care offers a safe, faster, and more effective treatment of DFUs than standard care alone.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with PriMatrix, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremity dermal wounds. However, use of this product for other indications has not been widely accepted by the practicing community.

ReCell Autologous Cell Harvesting Device

The ReCell Autologous Cell Harvesting Device (Avita Medical Americas, Valencia, CA) received FDA approval through the PMA process in June, 2021. It is indicated for treatment of acute partial thickness burns in adults 18 years and older. The device is used at point of care to prepare autologous skin cell suspension which is sprayed directly on second-degree burns or applied in combination with meshed autografts for third-degree burns.

Holmes and colleagues (2018) conducted a multicenter, prospective, within-subject, evaluator blinded RCT involving 30 participants with third-degree burns. Following burn excision, 2 comparable contiguous or non-contiguous areas were treated with ReCell plus STSG or STSG only. Participants were followed for 52-weeks. Results demonstrated at 8 weeks 85% of the STSG wounds were healed vs. 90% of the ReCell plus STSG treated wounds. Both groups' wounds were similar in size; however, the mean donor skin needed was reduced by 32% with the ReCell group (p<0.001). The same number of participants experienced adverse events in both groups (n=17, 57%). Mild or moderate adverse events were experienced by 27% and 37% of participants, respectively. One participant died during the study due to a complicated clinical course following a burn injury which was attributed to an underlying condition rather than the study. There were no differences between groups noted in the rate or severity of adverse events; including delayed healing, infection, allergic response to trypsin, wound durability, or scars requiring surgery. There were also no significant differences between groups observed in pain ratings or incidence of graft loss requiring surgery, (16.7% in the STSG group vs. 13.3% in the ReCell plus STSG group, p>0.05). The authors concluded that when used with widely meshed STSG, ReCell is a safe and effective treatment for mixed-depth burns with comparable healing outcomes to standard STSG while decreasing donor skin use.

Holmes and colleagues (2019) conducted another multicenter, prospective, RCT to evaluate the performance of ReCell compared to meshed STSG for treatment of deep partial thickness burns in 101 individuals. A total of 83 (83%) participants completed the 52-week follow-up. For each individual, 2 similar wound areas were randomly selected to be treated with either ReCell or skin graft in a 1:2 fashion. The 101 participants enrolled comprised the ITT population. The 83 participants who completed the follow-up without major

protocol deviations comprised the per-protocol population, which was used for definitive closure analysis. Definitive closure was reported to be 97.6% (81/83) for the ReCell treated sites and 100% (83/83) for the control sites at week 4. This difference, -2.4%, was deemed as noninferior with a 95% CI: -8.4%, 2.3%. This conclusion was based on predefined noninferiority (NI) margin lower bound of the CI of -10%. No significant differences in pain between the treatment sites was reported through the first 16 weeks of treatment. Based on the ITT population, the majority of adverse events, including treatment and donor sites, were deemed mild. The incidence of treatment site adverse events was greater in the ReCell group compared to the control group (35.6% vs. 21.8%, p=0.0013). The authors attributed the difference to the use of silver sulfadiazine in the 4 ReCell participants, as well as reinjury at the recipient site due to lack of protective dressings following re-epithelialization. Overall, 2 ReCell participants underwent subsequent intervention for graft loss; 1 regrafting procedure, and 1 debridement with redressing. Both cases healed at 4 weeks and remained healed. Long-term results showed no difference with appearance and scarring at the ReCell-treated sites compared with the control sites.

Wala and colleagues (2023) completed a single center, retrospective, chart review of 21 pediatric individuals with burns treated with ReCell. The median age was 5 years and ranged from 1 to 17 years old. African American, Hispanic, and multi-racial children made up 28.6%, 4.8%, and 4.8% of the population, respectively; the remainder were Caucasian. The mechanisms of injury included; flame (67%), scald (29%), and grease (5%). The median TBSA burn at initial visit was 31%. The majority (95.2%) had placement of a dermal substrate prior to ReCell; 4 children did not receive STSG with ReCell treatment. The median time between the date of burn and the first ReCell application was 18 days and the number of ReCell applications ranged from 1-4 per child. The median wound healing time was 81 days, median maximum Vancouver scar scale measurement per child at time healed was 8. Five children who received skin grafts had graft loss and 3 of these had graft loss from areas treated with ReCell. The authors concluded that ReCell provides an additional method for wound coverage, with or without STSG and is safe and effective. However, the authors also acknowledged limitations to the study including lack of data for the time healed and maximum Vancouver scar scale measurements due to variability in follow-up and documentation. It is also noted that the FDA PMA for ReCell is indicated for treatment of acute partial thickness burns in adults 18 years and older.

The results of these studies demonstrate supportive findings for the use of ReCell in mixed depth burns and reducing the need for donor skin.

SimpliDerm

SimpliDerm (Azyi Biologics Inc., Silver Spring, MD) is a pre-hydrated allograft composed of acellular dermal matrix (ADM) treated as human tissue for transplantation under the FDA's HCT/P process. The product is terminally sterilized via gamma irradiation to a sterility assurance level of 10−6.

Tierney (2021) completed a 30-day case series comparing SimpliDerm and AlloDerm RTU in ADM-assisted breast reconstruction. The outcomes of 59 participants (108 breasts) who underwent immediate 2-stage reconstruction with SimpliDerm (n=28) or AlloDerm RTU (n=31) following mastectomy were reported. There were no statistically significant differences between groups for age, race, ethnicity, body mass index, smoking status, medical history, or pretreatment medications, chemotherapy, or radiotherapy. Most of the of reconstructions performed used a prepectoral implant placement (103 breasts, 95%). Five participants in the AlloDerm RTU group and zero in the SimpliDerm group had subpectoral reconstructions (p=0.025). In both groups, most reconstructions were bilateral (87.3% AlloDerm RTU, 94.3% SimpliDerm). No participants in either group received post-surgical radiotherapy or radiotherapy combined chemotherapy during follow-up. Postprocedural complications occurred in 6 (19.4%) AlloDerm RTU participants and 7 (25.0%) SimpliDerm participants (p=NS), of which 5 (83.3%) and 4 (57.1%), respectively, required surgical intervention. One participant in each group had a complication that resulted in explantation. None of the reported adverse events were considered serious, and all were of mild or moderate severity. The adverse events identified in the AlloDerm RTU group were flap ischemia (n=4, 66.7%) and hematoma (n=2, 33.3%). Adverse events identified with SimpliDerm included infection (n=1, 14.3%), flap ischemia (n=4, 57.1%), seroma (n=1, 14.3%), and one small skin pinhole with surrounding redness (14.3%). There was no hematoma identified in the SimpliDerm group. The authors concluded the study demonstrates equivalent complication profile between SimpliDerm and AlloDerm RTU.

Additionally, a retrospective review from Tierney (2022) expanded upon the 2021 study, which included four sites between 2016-2021 where 107 participants who had immediate, two-stage reconstruction (181 breasts) with either SimpliDerm (n=38 participants/67 breasts) or AlloDerm RTU (n=69 participants/114 breasts) after mastectomy were followed for 133.5 days. The mean participant age was 51.4, mean BMI was 28.0, more participants in the SimpliDerm group were of Hispanic or Latino ethnicity (34.2% vs. 7.2%; p<0.001). Reconstructions were predominantly prepectoral (82.3%), and 35 adverse events occurred in 27 (25.2%) participants. There was no difference in the event type, classification, or rates between groups. None of the events were considered related to either product. The adverse events were also similar to those published for other ADMs in immediate breast reconstruction. This study reiterated the authors previous finding that SimpliDerm and AlloDerm are clinically equivalent for breast reconstruction.

StrataGraft

StrataGraft is an allograft product derived from human dermis with a layer composed of neonatal immortalized keratinocytes (NIKS) seeded on murine collagen embedded with allograft dermal fibroblasts. This product is treated as human tissue for transplantation under the FDA's HCT/P process. A small phase I/II comparative trial of StrataGraft to cryopreserved cadaver skin was conducted by Schurr (2009) to assess autograft take in 15 participants 2 weeks after coverage. At the 2-week time point the authors reported that the StrataGraft participants exhibited a fully stratified epidermis with multilamellar lipid sheets and barrier function as well as robust human β defensin-3 mRNA levels. Analysis revealed no differences in autograft take between wound sites pretreated with StrataGraft skin substitute or cadaver allograft. No StrataGraft-related adverse events or serious adverse events were observed.

Holmes (2019) reported on the results of an open-label, controlled, randomized study of StrataGraft vs. autograft for the treatment of deep partial-thickness burns (3%-43% total body surface area) in 30 participants who were assigned to treatment with ≤ 220 cm^2 autograft; ≤ 440 cm^2 of autograft; or ≤ 440 cm^2 of StrataGraft. Two comparable wounds on each participant were randomized to receive StrataGraft tissue or autograft. By Day 28, the authors reported that no StrataGraft tissue treatment sites had undergone additional autografting. At 3 months, 93% and 100% of the StrataGraft tissue and autograft treatment sites achieved complete wound closure, respectively. The most common adverse event was pruritus (17%).

Gibson (2021) reported the results of an open label RCT involving 71 participants with thermal burns on the torso or extremities. Two eligible wounds on each participant of comparable depth, severity, and size were randomly selected to be treated with either StrataGraft or autograft. Participants were followed for 3 months for the measurement of the primary endpoints of mean percent wound healing and percentage of participants achieving durable wound healing. The authors reported that 3 participants received subsequent autografting of their StrataGraft-treated wound. Of the wounds initially treated with autograft, 2 required repeat autografts. The mean percent wound area requiring autograft in participants who required autograft by 3 months was significantly in favor of the StrataGraft wounds (4.3% vs 102.1%, p<0.0001). At 3 months, 83.1% of participants (n=59) had achieved durable wound closure for wounds treated with StrataGraft. Of the wounds treated with autograft, 85.9% (n=61) had similar results. No p-values were reported for between-group comparisons. All wounds reported closed at 3 months remained closed at 6- and 12-months follow-up. The authors

reported that the StrataGraft group had a 92% durable wound closure rate at 3 months without a need for autografting. Mean donor-site pain intensity was observed through day 14 in StrataGraft donor sites compared with autograft donor sites, primarily due to the lack of autograft donor tissue use in the StrataGraft group (p<.0001). Similarly, mean donor-site cosmetic appearance was significantly better in the StrataGraft group, for the same reason (p<0.0001). At 12 months, no significant differences between groups were reported with regard to cosmetic appearance (p=0.43). Overall, these results demonstrate that the use of StrataGraft delivers similar healing rates for the treatment of burns while decreasing the need for autografts and the autograft-related complications.

Holmes (2022) reported on the pooled safety data from 2 clinical trials, including the data reported by Gibson (2021) and previously unpublished data from NCT01437852. The pooled results included a total of 101 participants thermal burns covering 3-49% of total body surface area who were followed for up to 1 year. Adverse events were reported for 87 participants who had a total of 397 events. Adverse reactions occurred in 37 participants, 16 experienced serious adverse events. The most frequent adverse events included pruritus (30.7%), blister, hypertension, and hypertrophic scar (10.9% for each). The most common adverse reaction was pruritus (12.9%). Serious adverse events occurred in 2 participants, but were deemed to be unrelated to StrataGraft. The authors concluded that StrataGraft was well tolerated and had a safety profile similar to autograft. However, that latter conclusion was not tested in this trial.

The available evidence has demonstrated the clinical utility of StrataGraft for the treatment of Burns. However, use of this product for other indications has not been widely accepted by the practicing community.

Strattice

Strattice is an acellular dermal collagen product of porcine origin and has been cleared under the FDA's 510k process. In 2012, three studies evaluating the use of Strattice were published. The largest was a retrospective, controlled study looking at the use of Strattice (n=96) vs. aseptic AlloDerm (n=90) for tissue expander breast reconstruction (Glasberg, 2012). The authors reported a significantly higher complication rate in the AlloDerm group (21.4% vs. 6.3%; p=0.0003), caused by the incidence of seromas (12.7% vs. 1.4%; p=0.0003). No other significant differences were reported, including capsule formation (2.4% for AlloDerm and 2.8% for Strattice). This study was not prospective, randomized, or blinded.

The second trial involved the use of Strattice for complex abdominal reconstruction (Itani, 2012). This case series study involved 80 participants undergoing contaminated ventral hernia repair that were prospectively enrolled and treated with Strattice. Sixty participants continued through the final 24-month follow-up (25% loss to follow-up). The authors reported that midline restoration was achieved with primary closure in 64 participants with defects bridged in 16 participants. At 24 months, 53 participants (66%) experienced 95 wound events including seroma (n=23, 29%), infection (n=28, 35%), dehiscence (n=14, 18%), hematoma (n=7, 9%), and abscess (n=7, 9%). No grafts required complete excision. Hernia recurrence was reported in 22 participants (28%) by month 24. There was no correlation between infection-related events and hernia recurrence.

The third study, by Patel and colleagues, was a retrospective case study also evaluating the use of Strattice for complex abdominal reconstruction (2012). This study involved 41 participants with complex ventral hernias undergoing component separation with Strattice underlayment. Concomitant panniculectomy was conducted in 9 participants (22%). The complication rate was 24.4% (10/41), with the majority of early complications being skin necrosis (n=9), but also included Strattice exposure (n=5). These participants required intervention in the operating room (OR). Wound dehiscence and seroma were noted in 3 participants, respectively. One participant required skin grafting for wound closure.

Rosen (2013) published a study investigating the use of acellular matrix for the reconstruction of infected and contaminated abdominal wall defects. The study involved 128 participants who received treatment with Strattice (n=102), aseptic AlloDerm (n=16), Biodesign (n=4), Xenmatrix (n=4), and BioA (n=4). Postoperative wound complications were identified in 61 (47.7%) participants. The report indicated that predictors of wound complications included American Society of Anesthesiologists (ASA) score, diabetes, smoking, number of previous abdominal surgeries or hernia repairs, hernia defect size, and operative time. Hernia recurrence was identified in 40 (31.3%) participants at a mean follow-up time of 21.7 months. The majority of recurrent hernias were asymptomatic, and 7 participants underwent repair.

Use of Strattice was reported in a study of 41 participants with complex abdominal wall defects at increased risk for perioperative complications (Patel, 2013). Reported comorbidities included coronary artery disease (63.4%), diabetes mellitus (36.6%), and chronic obstructive pulmonary disease (17.1%). The authors reported that fascial closure was achieved in 40 participants (97.6%). Recurrent/complex hernia was present in 78% participants. The overall complication rate was 22.0%, and included seroma (7.3%), wound dehiscence with Strattice exposure (4.9%), cellulitis (2.4%), and hematoma (2.4%). All participants achieved abdominal wall closure with no recurrent hernias or need for Strattice removal.

Maxwell and Gabriel (2014) reported the results of a case series study of 106 participants undergoing revision breast surgery with the use of Strattice. The mean follow-up time was 3.1 years, with 1 participant experiencing a complication, yielding an overall complication rate of 0.9%. All participants' presenting complaints resolved after revision surgery, with no recurrence of the presenting complaint during the follow-up period.

A retrospective case-control study of 80 participants undergoing ventral hernia repair with either Strattice (n=40) or conventional open repair (n=40) was reported by Richmond (2014). Mean follow-up was 33.1 months. The authors reported that the defect size was greater in the Strattice group (mean, 372.5 vs. 283.7 cm^2, p=0.01) as was the percentage Ventral Hernia Working Group Grade III/IV hernias (65.0% vs. 30.0%, p=0.03). Despite this, the number of recurrences were lower in the Strattice group (13.2% vs. 37.5%, p=0.02), and infection rates were lower as well (0% vs. 23%, respectively, p=0.002). Finally, the indications for reoperation, including recurrence or complications requiring reoperation, were also lower in the Strattice group (17.5% vs. 52.5%, p=0.002).

Huntington (2016) published the results of a retrospective nonrandomized comparative study involving 223 participants who underwent open ventral hernia repair with AlloDerm (n=40), AlloMax (n=23), FlexHD (n=70), Strattice (n=68), or Xenmatrix (n=22). The mean follow-up was 18.2 months. The authors reported the hernia recurrence rate varied significantly by product, with 35% for AlloDerm, 34.5% for AlloMax, 37.1% for FlexHD, 14.7% for Strattice, and 59.1% for Xenmatrix (p=0.001). After multivariate analysis with Strattice as the comparator, AlloMax had a 3.4 higher OR for recurrence, FlexHD a 2.9 OR, and Xenmatrix a 7.8 OR. They concluded that the choice of biologic mesh affects long-term postoperative outcomes in ventral hernia repair, and Strattice had significantly lower odds of hernia recurrence compared with AlloMax, FlexHD, and Xenmatrix.

In 2016, Dikmans and colleagues published the results of a retrospective case series study involving the use of Strattice during single-stage breast reconstruction procedures in 88 participants. Unilateral procedures were done in 60 participants and bilateral in 25 (n=110 breasts). Minor complications reported included seroma (20.9%), skin necrosis (20.0%), wound dehiscence (11.8%), erythema/inflammation (14.5%) and infection (11.8%). The authors observed that the total complication rate was very high (78%), and although most complications were minor, reoperation was performed in 22.7%, with explantation of the implant in 11.8% of breasts. They concluded, "The use of a Strattice sheet in single-stage implant-based breast reconstruction may be a promising technique, but more evidence from prospective, randomized studies is necessary to justify its use."

A retrospective review involving 41 participants who underwent 52 breast reconstructions using ADMs was reported by Paprottka (2017). Participants received treatment with either EpiFlex (n=15), Strattice (n=21), or Tutomesh (n=16). Follow-up was 36 months (range 12-54). Overall complication rate was 17%, with 7% for the EpiFlex group, 14% for the Strattice group, and 31% for the Tutomesh group. Capsular contracture occurred in 6%, more frequently in this study compared to the current literature. The authors recommended the use of human derived grafting materials (EpiFlex) over those from porcine of bovine sources.

Lohmander (2019) conducted a non-blinded RCT involving 135 participants undergoing immediate breast reconstructions assigned to treatment with either Strattice (n=64) or with no ADM (n=65). Overall, the outcomes were similar between groups, but 4 participants (6%) in each group had reconstructive failure with implant loss. However, the group treated with Strattice exhibited a trend of more overall complications and reoperations (p=0.070) and with higher risk of wound healing problems (p=0.013). The authors noted, “Further investigation of risk factors and patient selection in a long-term follow-up is warranted.”

Kalstrup (2021) reported the results of a retrospective case series study involving 154 participants undergoing direct to implant breast reconstruction with Strattice. A total of 232 breasts were included in the report, which focused on complications and explantations. They reported that per-participant complications within 6 months included hematoma (4%), seroma (8%), infection (9%), necrosis, wound dehiscence and delayed wound healing (19%). The total complication rate per participant was 34%. Explantation occurred in 20 participants (13%) of which 9 (6%) experienced implant loss. Significant predictors of explantation included preoperative radiotherapy (adjusted OR, 4.9; p=0.045). Smoking was also associated with risk of explantation, however, it was not found to be significant (adjusted OR, 4.0; p=0.050).

Wilson (2021) reported on a retrospective case series study of 166 participants who underwent breast reconstruction with either Strattice (n=117, 51 bilateral) or submuscular reconstruction (n=49, 6 bilateral). In the Strattice group, 17 (10.1%) participants had Baker 3/4 contractions vs. 6 (9.2%) in the submuscular group (p=0.85). Of the participants with Baker 1/2 contractions, 6 (3.6%) Strattice participants and 8 (13.6%) submuscular participants had previously undergone revision surgery for prior capsular contracture (p=0.01). The authors reported that combining both of these findings provided an estimated rate of capsular contracture of 13.6% in the Strattice group vs. 21.2% in the submuscular group (p=0.14).

Wilson (2023) reported the results of a retrospective comparative study involving 795 participants who underwent immediate implant-based breast reconstructions with a submuscular technique performed with (n=553) or without (n=242) Strattice. Median follow-up was 4.3 years and 5.7 years (range, 2 to 8.1 years), respectively. The data indicated no significant differences between groups with and without Strattice with regard to complication rates (36.9% vs. 31.8%; p=0.17). implant loss rate (8.5% vs. 5.4%, p=0.12) and revision rates were comparable (46.7% vs. 41.1%; p=0.2). The rates of infections and wound dehiscence were higher in the Strattice group (20.6% vs. 12.8%, p=0.009; and 16.3% vs. 10.4%, p=0.03, respectively). Significantly fewer Strattice reconstructions required revision surgery for capsular contracture (5.3% vs. 15.6%; p<0.001). The authors concluded that the risk of complications associated with Strattice is small and not statistically significant, and likely outweighed by reduced revision rates.

Also see Clemens, 2013 and Mazari, 2018 in the SurgiMend section below for an additional study involving Strattice.

The use for the treatment of other indications is still under investigation. Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with Strattice, an acceptable level of safety and efficacy has been established for the use of this product for the surgical repair of complex abdominal wall wounds and breast reconstruction surgery. However, use of this product for other indications has not been widely accepted by the practicing community.

SurgiMend

SurgiMend is a product made from acellular fetal bovine dermis and is cleared under the FDA’s 510k process. The available peer-reviewed published literature addressing its use in humans is limited to a few studies. The largest of these was a nonrandomized, retrospective case series reviewing a single surgeon’s 5-year experience of 440 consecutive, immediate breast reconstructions in 281 participants (Butterfield, 2013). In 222 participants, reconstructions were done using SurgiMend and the other 59 used aseptic AlloDerm. The investigators reported no significant differences in complication rates between the two products in the incidence of hematoma, infection, major skin necrosis, or breast implant removal. However, the incidence of seroma was significantly more common in the AlloDerm participants (15.7%) vs. the SurgiMend group (8.3%) (p<0.05). However, this finding must be considered in light of the fact that the AlloDerm group was followed, on average, for over twice the length of time (15.6 ± 8.79 months for SurgiMend vs. 32.8 ± 15.87 for AlloDerm; p<0.0001). The SurgiMend group had a significantly higher rate of any necrosis (11.0% vs. 3.4%; p<0.0265). In a multivariate analysis, it was found that both a BMI > 30 kg/m^2 and previous radiation therapy significantly increased the rate for complications and expander loss.

A retrospective, nonrandomized comparative trial involving 120 participants undergoing complex abdominal wall reconstruction was reported by Clemens in 2013. Participants received either SurgiMend (n=51) or Strattice (n=69) and were followed for a mean of 21 ± 9.9 months. Postoperative surgical complication rates between groups were not statistically different. However, intraoperative complications were significantly higher in the Strattice group vs. the SurgiMend group (7 vs. 0, p=0.02) and the overall complication rate for the SurgiMend group was reported as 25.5% vs. 36.6% for the Strattice group (p=0.04). The authors concluded that the two products appear to result in similar outcomes, but Strattice may result in higher rates of device failure.

Eichler (2015) reported on a retrospective, nonrandomized comparative trial involving 127 breasts undergoing reconstruction with either SurgiMend (n=63) or EpiFlex (n=64). All procedures were conducted by a single surgeon. The authors reported that gross complication rates were 11.1% for SurgiMend and 40.6% for EpiFlex (p=0.003). Red breast syndrome was reported in 3 SurgiMend and 9 EpiFlex participants (p=0.003). Seroma occurred in 1 SurgiMend participant and 6 EpiFlex participants (p=0.07). Revision surgery was needed in 3 SurgiMend and 8 EpiFlex participants (p=0.21). This study reports favorable benefits for SurgiMend over EpiFlex. However, given the lack of credible, robust evidence supporting the clinical utility of EpiFlex, as well as the lack of availability of that product in the US, it calls into question its use as a comparator and weakens the generalizability of these study findings.

The same group published another retrospective, nonrandomized comparative trial involving 54 participants undergoing breast reconstruction procedures with either SurgiMend (n=18) or Tutomesh (n=27) (Eichler, 2017). No difference was noted in the rate of complications, consistent with other previous reports.

Endress (2012) reported the results of a retrospective, nonrandomized case series study involving of 28 participants who underwent 49 breast reconstructions with SurgiMend compared to 91 participants who underwent 123 control breast reconstructions with no additional grafting materials. The mean immediate fill volume in the SurgiMend group was 181.2 ± 148.3 mL and 117.7 ± 6.3 mL in the control group (p<0.001). The results show that the duration of drainage was significantly shorter in the SurgiMend group vs. controls (8.51 ± 0.4 days vs. 11.07 ± 5.1 days; p<0.015). No significant differences in the overall complication rate were reported (20.8% in the SurgiMend group, 13.0% in the control group). The authors provided a subgroup analysis that indicates that the SurgiMend group with complications had significantly longer drain removal time (9.48 vs. 7.97 days), larger initial fill volumes (238.1 vs. 145.3 mL), and a higher BMI (25.8 vs. 22.6 kg/m^2) when compared with the complication-free subgroup. Unfortunately, these comparative findings are hampered by the small participant population of the SurgiMend group, as well as the significant difference between groups in fill

volume.

Mazari (2018) reported the results of a retrospective controlled study involving 82 participants (97 breasts) comparing Strattice (n=54 breasts) and SurgiMend (n=43 breasts) for implant-based immediate breast reconstruction. No differences were noted with regard to implant loss rate (p=0.077). The ADM loss rate was significantly higher in the Strattice group vs. the SurgiMend group (n=7 vs. n=0, p=0.014). Reoperation rates were significantly higher in the Strattice group vs. the SurgiMend group (n=17 vs. n=2, p=0.002). Incidence of red breast was significantly higher in the SurgiMend group (n=9 vs. n=3, p=0.022). No differences between groups were noted with regard to seroma, wound problems, or infection rates.

A retrospective case series study involving 111 participants (147 breasts) undergoing immediate breast reconstruction with SurgiMend was reported by Scheflan in 2018. Overall rates of minor and major complications after a median follow-up of 24.3 months, were 25.2 percent and 12.9 percent, respectively. Seroma was the most common major complication (8.2%), with necrosis (6.1 %) the second most common. The rate of capsular contracture was 2.7% and explantation occurred in 2.7%. In a univariate analysis, smokers had a greater risk of major complications (p=0.013), and postoperative radiation therapy and obesity were associated with an increased risk of capsular contracture (p=0.006) and explantation (p=0.006), respectively. Multivariate analysis identified several factors that were associated with complications or explantation, including obesity (p<0.05), preoperative chemotherapy (p<0.001), and mastectomy weight (p<0.05). However, the authors note that these associations agreed with the results of other ADM studies, and that they do not appear to be unique to SurgiMend.

Asaad (2021) reported the results of a prospective RCT involving 90 participants undergoing immediate tissue expander breast reconstruction receiving either SurgiMend or sterile AlloDerm (n=45 for each group). Only 68 participants have completed data (75%, n=36 SurgiMend [80%] and n=32 AlloDerm [71%]). The average follow-up was 38 months, with a large range of 8-62 months. Postoperative complications were reported in 14 breasts (25%) in the AlloDerm group vs. 13 breasts (27%) in the SurgiMed group (p=0.85). While infection was the most common complication, no differences between groups was reported (n=8 for SurgiMend vs. n=5 AlloDerm, p=0.25). Similarly, no differences between groups were noted for other major complications (p=0.17), complications requiring reoperation (p=0.27), and tissue expander loss (p=0.14). One case of capsular contracture was diagnosed clinically 1 year following tissue expander placement in the AlloDerm group. Implant loss was identified in 4 (7%) of the AlloDerm participants and 8 (17%) SurgiMend participants (p=0.14). This study is promising, but the significant loss to follow-up hampers generalization of the findings.

In 2023, Asaad and colleagues reported a retrospective review of 383 individuals (557 breasts) who had immediate prepectoral implant-based breast reconstruction comparing clinical outcomes and satisfaction data of three AMD types (78.6 % AlloDerm, 14% SurgiMend, 7.4 % Dermacell). Participants in the Dermacell group were older (p=0.001) and more likely to have diabetes (p=0.001) compared with the other groups participants, otherwise characteristics were similar among the three groups. Most of the individuals had a skin-sparing mastectomy (82% AlloDerm, 73% SurgiMend, and 81% Dermacell group) with immediate reconstruction (96% of the AlloDerm and SurgiMend groups, and 98% of the Dermacell group). The time from tissue expander insertion to permanent implant exchange was not significantly different between the groups. The authors reported that overall adverse events were equivalent among the three groups (AlloDerm 27% vs. SurgiMend 33% vs. Dermacell 39%; p=0.209). BMI was identified as the primary risk factor for overall complications, infection, major complications, and device explantation. A total of 127 individuals (33.2%) were included in the BREAST-Q analysis. Ten individuals who had implant explantation without device salvage were excluded; 117 individuals were included. The authors reported no significant differences in satisfaction with breasts, psychosocial well-being, or sexual well-being among the three groups (p=0.109, p=0.439, and p=0.152, respectively), and that the type of ADM used was not associated with overall complications or participant reported outcomes. However, it is noted that less than half the individuals treated responded to the survey, and those with explant were excluded in the results.

Chu (2023) reported the impact of ADM type on early complication rates in 2-stage alloplastic prepectoral breast reconstruction in a single-center cohort analysis. ADM types used were AlloDerm, FlexHD, and SurgiMend. Complication rates based on the number of tissue expanders lost (defined as a tissue expander that was removed due to a complication and not replaced), were determined for each ADM type. Secondary outcomes were reconstruction related complications, including seroma, mastectomy skin flap necrosis, hematoma, infection, cellulitis, tissue expander exposure, and tissue expander malposition/rotation. A total of 726 participants (1054 tissue expanders: 194 AlloDerm, 93 FlexHD, 767 SurgiMend) were included. The groups differed by mastectomy types, ADM perforation, and ADM size. No differences were reported between ADM types for seroma, infection, exposure, malposition, or tissue expander loss. The authors concluded that ADM type did not affect the risk of complications. They noted that their study demonstrated that SurgiMend is comparable to other ADM types used in prepectoral breast reconstruction.

Lampridis (2023) described the results of a non-randomized comparative study of 66 participants who underwent diaphragmatic and/or chest wall reconstruction for a malignant (74.2%) or benign (25.8%) disease with SurgiMend (n=26, 39.4%) or synthetic expanded polytetrafluoro ethylene mesh (Gore-Tex, n=40, 60.6%). The Gore-Tex group experienced a significantly higher rate of surgical site complications vs. the SurgiMend group (n=6 [37.5%] vs. 2 [11.5%]; p=0.025). Readmission rates were significantly higher in the Gore-Tex group (17.5% vs. 0%; p=0.037), with causes including pleural effusion (n=3), pneumothorax (n=2), empyema (n=1), and pneumonia (n=1). Among the study cohort, only 1 participant with a synthetic mesh underwent reoperation (p > 0.99). There were no differences between groups with regard to medical complications or 90-day mortality. This study demonstrates beneficial results with regard to the use of SurgiMend vs. Gore-Tex for diaphragmatic and/or chest wall reconstruction. However, the low power and other methodological issues impair the generalizability of these findings.

Please see the AlloDerm and Enduragen sections for additional studies involving SurgiMend.

TheraSkin (Please see the 'Fresh Frozen Unprocessed Allograft Skin for Burns' section above for discussion of evidence addressing TheraSkin for burns)

Barbul (2019) published the result of a retrospective non-randomized propensity-matched controlled trial involving 1556 participants with diabetic lower extremity wounds treated with either TheraSkin or standard of care (n=778 per group). Complete treatment data were available for only 376 TheraSkin group participants (48.3%) and the modified intent-to-treat (MITT) group included 459 participants (59%). In the MITT analysis, overall healing rates were 66.8% for the TheraSkin group vs. 55.9% for the control group (p=0.0045). Additionally, healing rates for Wagner grade 4 ulcers was significantly better in the TheraSkin group (66.7% vs. 40.0 %, p=0.04). A significant difference in healing rates was reported for wounds 90-179 days old, with TheraSkin demonstrating better results (65.1% vs. 46%, p=0.0073). No differences in healing rates were reported for wounds less than 90 days old. Additionally, no differences were reported in healing rates when stratified by wound location (lower leg, foot, or toe), or in the rate of amputations in the first 20 weeks post-treatment. With regard to percent area reduction (PAR), TheraSkin has significantly higher mean reduction vs. controls (63.6% vs. 57%, p=0.036). Interestingly, TheraSkin participants were significantly more likely to be treatment compliant through completion of treatment (59% vs. 48.3%, p<0.0001). Recidivism data at 1 year was available for 684 TheraSkin participants and 651 controls, indicating a high rate of treatment success in the TheraSkin group (40.2% vs. 35%, p=0.042). The odds of TheraSkin closure of a wound was calculated to be 1.59, indicating a 59% increase over standard of care.

Another retrospective non-randomized propensity-matched controlled trial was published looking at the use of TheraSkin plus

standard of care vs. standard of care for the treatment of lower extremity wounds of multiple etiologies including diabetic ulcers, lymphedema, pressure ulcers, radiation injury, surgical wounds, trauma, venous ulcers, and arterial ulcers was reported by Gurtner (2019). The study included 1997 participants in the TheraSkin group and 1997 control participants who received standard of care only. Overall healing rates were significantly better in the TheraSkin group (68.3% vs. 60.3%, p<0.001). Mean percent area reduction was also better in the TheraSkin group (78.73% vs. 68.85%, p<0.001). When stratified by wound duration, the TheraSkin group had significantly better healing times vs. controls for wounds greater than 90 days (p<0.0001), 90 to 179 days (p=0.0195), and 180 days or greater (p<0.0010). Arterial, diabetic, pressure, radiation and trauma wounds all healed significantly better in the TheraSkin group (p=0.0325, p<0.0001, p<0.0001, p=0.05, and p=0.0311, respectively). Recidivism was not significant between groups at 12 months, nor was the mortality rate (32.6% vs. 34.4%, p=0.296; 4.6% vs. 5.4%, p=0.25, respectively). Amputation rates were 2.75 times higher in the control group vs. TheraSkin group (1.9% vs. 0.5%, respectively).

The results of these trials demonstrate significant benefits from treatment of chronic lower extremity dermal wounds with TheraSkin, including improvements in healing time and a healing rates, while not negatively impacting adverse event rates. However, other than for this indication and burns, the use of this product for other indications has not been widely accepted by the practicing community.

Products addressed in the Investigational and Not Medically Necessary statement

Affinity

Affinity is a cryopreserved human amnion-derived tissue allograft and is treated as human tissue for transplantation under the FDA's HCT/P process. There is currently only one available study published on its use in human participants.

Serena (2020) reported on the results of an unblinded prospective RCT involving 76 participants with DFUs treated with either Affinity plus standard care (n=38) or standard care alone (n=38). Wound closure for the Affinity group was significantly greater than the control group at both 12 weeks (55% vs. 29%, p=0.02) and 16 weeks (58% vs 29%, p=0.01). At 16 weeks, wound closure was reported in 60% of Affinity participants vs. 48% of control participants (p=0.04). The authors reported that the probability of wound closure with Affinity vs. standard care increased by 75% (HR, 1.75). The authors concluded that the use of Affinity increased the frequency and probability of DFU wound closure. Additional data from well-designed trials are warranted to support these conclusions.

AlloMax

AlloMax is an acellular, non-cross-linked allograft dermis product and is treated as human tissue for transplantation under the FDA's HCT/P process. The currently available evidence in the peer-reviewed published literature addressing the use of AlloMax is sparse. A case series study involving 65 participants undergoing tissue expander breast reconstruction was described by Venturi (2013). The results of this study are limited but include a complication rate of 4.6% (3 participants). These included one case of cellulitis and two cases of partial mastectomy flap necrosis requiring debridement. No seromas or explantations were reported. Histological verification of full graft incorporation was demonstrated in the first 20 biopsies. A second retrospective case series involving 203 participants (348 breasts) undergoing mastectomy with immediate breast reconstruction was reported by Rundell in 2014. The authors reported that infection occurred in 6.6% of participants, with 3.7% being major infections requiring intravenous antibiotics and 2.9% being minor infections requiring oral antibiotics only. Seromas occurred in 3.4% of cases and reconstruction failure occurred in 0.6% of cases. The authors stated that the analysis suggested that the complication prevalence was significantly higher in individuals with a BMI > 30 (p=0.03).

AlloPatch

AlloPatch is a product composed of acellular human dermis treated as human tissue for transplantation under the FDA's HCT/P process.

At this time, there is limited evidence published in the peer-reviewed literature addressing the use of this product. The most rigorous study to date involved 45 participants with chronic refractory DFUs (Zelen, 2016b). A total of 40 participants in this investigator blinded RCT were assigned in a 1:1 fashion to either standard care alone (n=20) or AlloPatch plus standard care (n=20). AlloPatch grafts were applied weekly for up to 12 weeks. Initial ulcer size at baseline was greater in the AlloPatch group vs, controls (4.7 cm^2 vs. 2.7 cm^2). At 6 weeks, the authors reported that 65% of the AlloPatch group participants were completely healed (13/20) vs. 5% in the control group (1/20). At 12 weeks, the proportions of DFUs healed were 80% and 20%, respectively. The mean time to heal within 12 weeks was 40 days in the AlloPatch group vs. 77 days for controls. No differences between groups were reported with regard to adverse or serious adverse events. The authors reported that, "Weekly application of HR-ADM is an effective intervention for promoting closure of non-healing DFUs."

This group published a continuation study with an additional 40 participants (n=20 per group) and results of the total 80 participant population were reported by Zelen in 2018. In the continuation population, the AlloPatch group had more smokers (7 vs. 1, p=0.044) and the control group was older (67 years vs. 55 years, p=0.008). At 6 weeks, 85% of the AlloPatch group vs. 15% of the controls were completely healed ($p=2.7 \times 10^{-6}$). The mean PAR in wounds was greater in the AlloPatch group (62% vs. 50%, $p=2.7 \times 10^{-6}$). Mean time to healing at the 6-week time point was 27 days for the AlloPatch group vs. 41 days for controls ($p=9.9 \times 10^{-7}$). At 6 weeks, 2 AlloPatch participants (5%) and 19 control participants (48%) were withdrawn from the study due to failure to have a 50% reduction in wound area. At 12 weeks, 80% of AlloPatch participants and 30% of the control participants had complete wound healing ($p=8.4 \times 10^{-6}$). At 12 weeks, mean time to heal was 38 days in the AlloPatch group vs. 72 days in the control group ($p=3.9 \times 10^{-7}$). After adjusting for age and baseline wound area, the HR for the AlloPatch vs. the control group was 8 ($p=3.7 \times 10^{-7}$). No adverse events related to the study treatment were reported.

Further investigation is warranted to fully evaluate the safety and efficacy of AlloPatch treatment for DFUs.

AMNIOEXCEL

AMNIOEXCEL is a dehydrated human amnion-derived tissue allograft and is treated as human tissue for transplantation under the FDA's HCT/P process. There is currently only one available study published on its use in human participants. Snyder (2016) reported on the results of a prospective, open label, randomized, parallel group trial involving 29 adults with type 1 or type 2 diabetes mellitus who have one or more ulcers presenting for more than 1 month with no signs of infection/osteomyelitis. Participants were randomized in a 1:1 fashion to receive treatment with either standard care (SOC, n=14) or AMNIOEXCEL plus SOC (n=15) until wound closure or 6 weeks. The authors reported that 35% of participants in the experimental group achieved complete wound closure at or before week 6 vs. 0% in the SOC group (p=0.017). They observed that there was a more robust response noted in the per protocol population, with 45.5% of participants in the experimental group achieving complete wound closure, while 0% of SOC alone participants achieved complete closure (p=0.0083).

Amniofix

Amniofix is a product that consists of an injectable form of processed allogeneic amniotic tissue and is treated as human tissue for transplantation under the FDA's HCT/P process. Only one RCT regarding its use has been published in the peer-reviewed published literature. Zelen and colleagues (2013b) report on 45 participants with plantar fasciitis randomized in a single-blind fashion to receive one of three treatments: (1) standard care plus injection with 1.25 cc of sterile 0.9% saline (control group); (2) standard care plus injection with 0.5 cc Amniofix (0.5 cc group), and (3) standard care plus injection with 1.25 cc Amniofix (1.25 cc group). All participants also received injection with 2 cc of 0.5% Marcaine plain, and the use of tramadol for pain was allowed as needed throughout the study. There were 15 participants in each group. A total of 41 participants (91.1%) completed the 8-week follow-up period. All 4 participants who failed to complete the study were in the control group. The authors report that significant benefits were seen in all groups throughout the study compared to baseline on the American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Scale ($p<0.01$). Additionally, the AOFAS scale outcomes were significantly higher for both Amniofix groups vs. controls ($p<0.001$). No differences were noted between the two Amniofix groups. At the end of week 1, the median reduction in pain was 3 points for controls and 6 points and 5 points for those receiving 0.5 cc and 1.25 cc of Amniofix, respectively ($p<0.001$; $p=0.004$). Using the Wong–Baker FACES Pain Rating Scale, a visual analog pain scale (VAS), controls reported moderate to severe pain throughout the 8-week study period. Both Amniofix groups reported a significant reduction of pain from very severe at baseline to within the mild to moderate range at 1 week and reported continuing reduction in pain over the study period ($p<0.001$), with no statistically significant difference between groups. Based upon the physical and mental scales on the SF-36v2 quality of life tool, it was reported that both Amniofix groups had significant improvements from baseline compared to controls. No difference between Amniofix groups was reported. At the end of the first follow-up week, significantly more participants in both Amniofix groups vs. controls needed additional treatment with tramadol (57.1% of controls, 73.3% of the 0.5 cc group, and 100% of the 1.25 cc group). This was not significant for the 0.5 cc group vs. controls but was for the 1.25 cc group vs. controls ($p=0.004$) as well as the 1.25 cc group vs. the 0.5 cc group ($p=0.032$). At the second follow-up visit, rates of tramadol use were significantly lower in all groups ($p>0.05$ for all groups). No adverse events related to treatment were observed in any study participants. This weak study indicates some benefit from the use of Amniofix for individuals with plantar fasciitis. However, due to the small study population and lack of investigator blinding, further research is warranted to fully understand the efficacy of this treatment method. **Amniotic Allografts – Not specified**

There is an increasing body of evidence in the available peer-reviewed published literature addressing the use of allogeneic amniotic tissues for the treatment of a variety of uses, including ophthalmologic, obstetric, and burn conditions. A small number of these publications address branded products, which are addressed elsewhere in this document. However, the vast majority of the published studies involve the use of amniotic-derived products that are: (1) not specified by the authors, (2) branded products not commercially available in the U.S, or (3) materials that are locally sourced. Many of these studies are randomized controlled trials, but with small study populations (Abdulhalim, 2015; Amer, 2010; Andonovska, 2008; de Farias, 2016; Harvinder, 2005; Küçükerdönmez, 2007; Luanratanakorn, 2006; Paris, 2013; Sharma, 2016; Sheha, 2008; Tamhane, 2005; Tandon, 2011). These studies are heterogenous with regard to the type of amniotic graft used, including lyophilized, cryopreserved and glycerin preserved products. Furthermore, there is a wide array of indications addressed across these studies, with a critical mass of evidence not established for any particular one. Finally, due to the differences in the harvesting and processing procedures these materials undergo that may impact the physical properties of the materials, the findings of such studies cannot be used to support the use of amniotic-derived products as a group.

Artacent Wound

Artacent is a product composed of dehydrated acellular human amniotic membrane and is treated as human tissue for transplantation under the FDA's HCT/P process.

Sledge (2020) reported on a study involving 26 participants who were participants in an RCT that was discontinued due to logistical issues. All participants had non-infected DFUs that had failed previous standard care and were treated weekly or biweekly with Artacent Wound. The primary endpoint of 100% healing at 12 weeks was reported in 17 participants (65%). The incidence of adverse events potentially related to the grafting product was 12% (4/34) and serious adverse events were reported in 6% (2/34).

This data is interesting but does not provide data that is reasonably generalizable to a wider population of individuals with DFUs. Further investigation is warranted.

Artelon (Including CMC and TMC)

Artelon is a synthetic grafting material made from degradable polyurethaneurea cleared through the FDA's 510K process. - Nilsson, (2010) published the results of an RCT consisting of 109 participants with osteoarthritis of the carpometacarpal joint of the thumb. In this study, 72 participants were treated with Artelon and 37 were treated with standard tendon interposition arthroplasty. There was a significant loss to follow-up, with less than 50% of participants having available data at the 1-year follow-up time point. The authors report that swelling and pain were more common in the Artelon group, and 6 implants were removed because of such symptoms. Interestingly, 5 of these participants did not receive antibiotics preoperatively according to the study protocol. In the intention-to-treat analysis but not in the per-protocol analysis, significantly better pain relief (VAS) was obtained in the control group. Self-perceived disability evaluated by the DASH (disability of arm-shoulder-hand) questionnaire improved in both groups. However, these findings are not particularly useful, given the significant loss to follow-up reported.

At this time, the available peer-reviewed published articles addressing Artelon TMC are underpowered case series studies involving 13 and 15 participants each (Jörheim, 2009; Nilsson, 2005; respectively). This level of evidence is inadequate to fully evaluate the safety and efficacy of this product. Further investigation is warranted.

Cuttica (2023) reported the results of a retrospective case series study involving 18 participants undergoing surgical treatment for insertional Achilles tendinosis with tendon repair augmentation using Artelon. The study reported on pain score, strength, and ankle motion. The Wilcoxon signed-rank test was used to compare baseline and final follow-up VAS scores. One participant had 2 suture anchor pull-out from the calcaneus. Final strength was obtained for 17 participants, with 15 (83.24%) reported as being 5/5 and 2 (11.76%) being 4/5. Final active dorsiflexion was measured in all participants, with 17 (94.44%) reaching at least 10°. No participants had evidence of foreign body reaction or neritic complications, required return to the operating room, developed deep vein thromboses, or developed other major complications. The authors concluded that Achilles tendon augmentation with Artelon is a viable option in the treatment and that its use has minimal morbidity and can be an alternative to other forms of augmentation. However, the results of this study are not generalizable due to the low power, lack of a comparison group, and other methodological concerns. Further investigation in the form of rigorously designed and conducted trials is warranted.

Artia

Artia™ reconstructive tissue mesh is a product derived from porcine acellular dermal matrix and cleared through the FDA's 510K process. King (2023) reported a retrospective non-randomized comparative trial involving the use of Artia for implant-based breast reconstruction in 63 participants vs. 181 participants who received treatment with AlloDerm ADM. Bilateral procedures were done in 95 participants for a total of 276 breasts (n=98 Artia and n=178 AlloDerm). Significantly more participants in the Artia group received prepectoral reconstruction (69.4% vs. 46.6%, $p<0.01$). Eleven underwent delayed reconstruction, while 265 underwent immediate reconstruction, with no significant difference between groups ($p=0.34$). Two stage reconstruction with tissue expanders was utilized in the majority of cases (243 breasts), with no difference in reconstruction technique between groups ($p=0.2$). The authors reported no

significant differences between groups with regards to major complications (28.6% vs 31.2%, p=0.69) or minor complications (9.1% vs 14.0%, p=0.24), including hematoma, infection, seroma, dehiscence, necrosis, capsular contracture, and explantation. The results of this study appear to indicate equivalent outcomes between Artia and the standard of care product. However, the small sample size and other methodological issues impair the generalizability if these findings. Further investigation with more robust trials is warranted to establish the clinical utility of this product.

Avance Nerve Graft

Avance nerve graft is a decellularized allogeneic product derived from donated peripheral nerve tissue and is treated as human tissue for transplantation under the FDA's HCT/P process. The currently available evidence addressing the clinical use of Avance is limited.

The only currently available comparative trial involving this product was published by Means in 2016. This double-blind RCT involved 23 participants with 31 digital nerve injuries treated with hollow conduit (n=9) or Avance processed nerve allograft (n=14). The authors reported that the Avance group demonstrated significantly greater recovery vs. conduit participants as measured by results by static 2-point discrimination (5 ± 1 mm vs. 8 ± 5 mm, p<0.5). Among participants with 6-month data available, all participants in the Avance group returned to S3+ (8 of 8 digits) vs. 75% (9 of 12 digits) in the conduit group. A return to S4 was not statistically significant between groups. At 12 months, results of Semmes-Weinstein Monofilament (SWMF) assessment testing found that the Avance group had a significant improvement vs. controls (mean of 3.6 ± 0.7 vs. 4.4 ± 1.4, p<0.05) and recovery of protective sensation, equivalent to SWMF score of 4.31 or better, was reported in 100% of Avance-treated participants vs. 75% of control participants. No differences between groups were found with regard to results on the Disability of the Arm, Shoulder and Hand (DASH) questionnaire or assessment of thermal discretion or pain assessment at 12 months. While this study had a rigorous methodology, the small numbers of participants and significant loss to follow-up (> 70%) hinder the utility of the results.

Brooks and others (2011) reported a case series study involving 108 participants with nerve injuries. Outcomes were only available for 59 participants (56%). The authors report "meaningful recovery" in 87% of participants available for evaluation. A post hoc subgroup analysis demonstrated no significant differences with regard to nerve type, gap length, participant age, time to repair, age of injury, or mechanism of injury (p>0.05). No graft related adverse experiences were reported and a 5% revision rate was observed. The data presented is insufficient to allow full assessment of the safety and efficacy of the Avance nerve graft.

Safa (2019) reported a case series study involving data from the RANGER® registry involving 385 participants who underwent 624 nerve repair procedures using Avance and were compared to historical data from participants undergoing hollow tube conduit and/or autografts. Follow-up was 12 months for sensory nerves and 18 months for mixed/motor nerves. Overall response rate was reported to be 87%, with response being defined as "any improvement after repair based on either qualitative and/or quantitative assessments". Meaningful recovery, defined as S3 or M3 or greater improvement as measured by the Mackinnon-Dellon Modification of the Medical Research Council Classification (MRCC) sensory and motor scale, was reported as 82% of participants. By body region, meaningful recovery was reported as 83%, 53% and 100% for the upper and lower extremity and head/neck, respectively. The difference between upper and lower extremity was significantly different (n=0.01). Compared to historical comparisons, the author's findings were not significantly different. For upper extremities, nerve gap lengths < 15 mm had significantly better meaningful recovery than those 50-70 mm (p=0.011). No differences in meaningful recovery stratified by gap length were reported for the lower extremities.

The results of these studies are promising. Further data from more rigorously designed and executed studies is warranted.

Avaulta

Avaulta is a composite product composed of polypropylene mesh with acellular cross-linked collagen of bovine origin and has been cleared through the FDA's 510K process. The use of Avaulta Plus and Avaulta Biosynthetic Support System for the treatment of vaginal prolapse has been described in one prospective case series study involving 40 participants (Bondili, 2012). Participants were followed for up to 3 years (median 27 months (range 20-36). The primary outcome was quality of life (QoL) and satisfaction as measured by the International Consultation on Incontinence Modular Questionnaire–Vaginal Symptoms (ICIQ-VS) tool. Twelve participants (30%) were undergoing a second procedure to address prolapse. Of the 40 participants, 19 (47%) underwent anterior repair, 20 (5%) posterior repair, and 1 (2.5%) underwent both anterior and posterior procedures. Vaginal laxness improved significantly, with 67.25% of participants reporting preoperative laxness which improved to 5% of participants with laxness at follow-up (p<0.0001). Decreased vaginal sensation also improved, from 30% to 7.5% (p<0.01). Sexual activity was reported to improve from only 32% to 100% postoperatively. The authors report that 1 participant continued to have prolapse symptoms (2.5%), resulting in a 97.5% success rate (p<0.0025). Only 2 participants (5%) needed to digitate the vagina to vacate their bowels, a significant decrease from 12 (57%) preoperatively (p<0.001). Vaginal pain decreased from 55% preoperatively to 2.5% postoperatively (p<0.0001). No surgical complications were mentioned.

A retrospective case series study by Oliveira and colleagues (2020) involved 97 participants with ≥ stage II genital wall prolapse repair with Avaulta. Mean follow-up was 2.9 years with 12 participants lost. Postoperative complications were experienced by 29.1% (n=23) of participants, with one removal due to hematoma. Other complications included voiding dysfunction (n=10), urinary infection (n=7), vesicovaginal fistula (n=1), pelvic abscess linked to hysterectomy (n=2), and mesh exposure (n=6). For participants with voiding dysfunction and bladder injury, a prolonged bladder drainage by a Foley catheter was required for a mean duration of 11.2 days. Four of the participants with vaginal mesh exposure required additional surgery to partially remove the mesh in 3 cases and a colpoplasty procedure to cover the mesh in the remaining case. Self-reported improvements were reported with regard to vaginal discomfort (n=79 at baseline vs. 4 at last follow-up, p>0.01), pelvic heaviness (n=46 at baseline vs. 3 at last follow-up, p>0.01), and voiding dysfunction (n=16 at baseline vs. 2 at last follow-up, p>0.01). No anterior wall prolapse was present in 79.1% of participants at last follow-up and stage I and II prolapse was reported in 19% and 3%, respectively. No apical and posterior prolapse was reported in 98.5% and 83.6%, respectively. Eight participants (12 %) had recurrence at 3 years.

The results of these weak uncontrolled case series are promising. Further data from more rigorously designed and executed studies is warranted.

Avive

Avive Soft Tissue Membrane is a product derived from allograft amnion and umbilical cord membrane, which is regulated through the U.S. FDA's HCT/P process as human tissue for transplantation.

Cox (2023) reported the first use of Avive in a prospective propensity-matched cohort study involving 77 participants (97 nerves) who underwent revision nerve decompression. Mean follow-up was 9.0 months. Avive was applied to the median nerve in 47.4% of cases, ulnar nerve in 39.2% of cases, and radial nerve in 13.4% of cases. In the Avive cohort, S4 sensory recovery was achieved in 58% of participants, S3+ in 33%, S3 in 7%, S0 in 2%, and improvement from baseline in 87%, strength was improved in 92%. Mean total active motion was 94.8%. Mean Quick Disability of Arm, Shoulder & Hand (QuickDASH) score was 36.1, and 96% reported improved or resolved symptoms. For between-group comparisons, postoperative pain was significantly lower in Avive group participants (p=0.001). Improved or resolved symptoms were more frequently reported in the Avive group (p<0.0001). Finally, clinically important

improvement in pain was reported in 64.9% in the Avive group vs. 40.8% the control group (p=0.002). This initial pilot study indicates some benefit to the use of Avive in revisions nerve surgery. Further investigation is needed to fully understand the benefits and harms of such use.

BEAR (Bridge-Enhanced ACL Repair) Implant

In December 2020, the FDA granted De Novo approval of the BEAR Implant (Miach Orthopaedics Inc. Westborough, MA). BEAR is a decellularized xenograft derived from bovine collagen and is indicated for repair of anterior cruciate ligament tear (ACL). The graft implant is combined with autologous whole blood to form a clot that replaces the ACL and functions as a bridge between the torn ends of the ligament.

Murray (2020) and Barnett (2021) both reported the results of the BEAR II trial, a double-blind RCT involving 100 participants aged 13-35 years with a complete midsubstance ACL injury treated with BEAR (n=65) or autograft ACL (n=35). Participants underwent surgery within 45 days of the index injury. Participant outcomes were assessed at 2 years by an independent examiner blinded to the procedure. Murray reported that the results on the International Knee Documentation Committee (IKDC) Subjective Score were 88.9 points for the BEAR group and 84.8 points for the control group (no p-value reported). The side-to-side difference in AP knee laxity in the BEAR group was 1.61 mm vs 1.77 mm in the control group (no p-values reported). The BEAR group had a significantly higher mean hamstring muscle strength index than the control group at 2 years (98.2% vs 63.2%; p<0.001). The report by Barnett stated that repeated-measures testing revealed a significant effect of group on the IKDC Subjective Score (p=0.015), most pronounced at 6 months after surgery (86 points in the BEAR group vs. 78 points in the control group; p=0.001). Results on the Knee Injury and Osteoarthritis Outcome Score-Symptoms subscale scores were significantly in favor of the BEAR group (p=0.010) attributable to higher BEAR scores at 1 year (88 vs 82; p=0.009). Hamstring strength was significantly better in the BEAR group vs. controls (p<0.001). Clearance for return to sports at 1 year after surgery was granted to approximately 88% of BEAR group participants and 76% of control group participants (p=0.261). The authors concluded participants undergoing the BEAR procedure had earlier resolution of symptoms as well as increased satisfaction with knee function and hamstring muscle strength.

Another study by Barnett (2020) also compared sex-specific outcomes following ACL reconstruction within 45 days of injury in 65 participants with complete ACL tear treated with BEAR. The results demonstrated no significant sex difference on the postoperative IKDC Subjective Score or any of the five Knee Injury and Osteoarthritis Outcome (KOOS) scores at 12 and 24 months. Additionally, AP laxity testing demonstrated differences that were similar in the two sexes at 2 years (1.7 mm and 1.5 mm in females and males, respectively; p=0.72). At 6 months postoperatively, males had a larger deficit in hamstring strength on the operated leg (14.0% vs. 1.7%; p=0.03) and a larger deficit in quadriceps strength on the operated leg (11.3% vs. 2.0%; p=0.004); however, no differences were noted at 12 or 24 months. Interestingly, females demonstrated superior single leg hop testing at both 6 and 12 months (91.3% vs. 78.1%, p=0.001 and 96.9% vs. 87.0%, p=0.01, respectively). No significant differences were reported with regard to ipsilateral ACL reinjury rates.

Menghini and others (2022) completed a cohort study using data from the above-mentioned BEAR II trial, examining the cross-sectional area (CSA) of the treated vs. contralateral native ACLs (n=65 in the BEAR group, n=35 in the autograft group, n=100 in the native group). CSA is a known predictor of strength and knee function. The authors reported that at 24 months, CSA in the autologous group peaked at 69%, 61% in the BEAR group, and 42% in the native group, with significant between-group differences (p<0.001). They concluded that while the BEAR ACLs remained significantly larger, the autograft ACL had a CSA profile comparable with that of the contralateral native ACL.

Flannery and colleagues (2023) reported the results of a retrospective analysis of 65 individuals from the BEAR II RCT, that compared BEAR graft to traditional ACL reconstruction using non-contemporaneous quantitative MRI to predict positive functional outcomes from 6-24 months post-ACL surgery. The study images were obtained at 6 months post-surgery, additionally single-leg hop test ratios, arthrometric knee laxity values, and IKDC subjective scores were measured at 6 and 24 months. The results demonstrated that CSA (r=0.44, p=0.01), volume (r=0.44, p=0.01), and estimated failure load (r=0.48, p= 0.01) measures at 6 months were predictive of the change in single-leg hop ratio from 6 to 24 months in bivariate analysis. The authors concluded that using qualitative MRI at 6 months post-surgery may be a predictor of longer term functional outcomes. This information may be useful in rehabilitation planning, return to sport decisions, and injury risk reduction.

The use of BEAR Implant for the treatment of ACL injury in the published literature is promising. However, the totality of evidence does not yet support a durable equivalent to standard of care ACL reconstruction. Further investigation is needed in the form or rigorous, well-designed comparative trials.

Belladerm

BellaDerm is a product composed of acellular human dermis and is treated as human tissue for transplantation under the FDA's HCT/P process.

Solomon and others (2013) published the results of a retrospective case series study involving 47 participants who underwent penis girth enhancement utilizing circumferential grafting with allograft material. The participants received either aseptic AlloDerm (n=9), Belladerm (n=20), and Repriza (n=21). Mean follow-up was 11.25 months (range 1 to 120 months). The rate of infection, which the authors defined as an open wound with graft exposure, occurred in 20 (42%) of 47 participants. Of these, 17 (36%) participants had graft exposure only and 3 (6%) participants sustained graft exposure and total graft loss. Graft exposure or loss occurred in 3 AlloDerm participants, 9 Belladerm participants, and 8 Repriza participants. No AlloDerm participants sustained graft loss, whereas 2 with Belladerm and 1 with Repriza did. No statistical differences between groups with regard to infection or graft loss was reported.

This study is too underpowered and the methodology too weak to sufficiently assess the safety or efficacy of any of these products for this procedure.

Biodesign

Please see 'Surgisis' section below.

CardioCel

CardioCel is a product produced from bovine pericardial tissue and has been cleared through the FDA's 510K process. At this time, the available published in the peer-reviewed literature addressing this product is limited. Pavy (2017) published the results of a retrospective series of 102 participants who underwent procedures addressing variety of congenital heart diseases, including septal defects to pulmonary outflow disorders. No infections, intraoperative implantation difficulties or postoperative mortality were reported to be associated with CardioCel. Graft failure reoperations occurred in 5 participants (5%), 4 of whom had the patch implanted for aortic angioplasty (2 in the ascending aorta and 2 in the aortic arch), and 1 participant had a monocusp replacement. The median time between the first and the second operation for graft failure was 245 (range 5-480) days. The authors concluded that, "Our experience shows that the patch is well tolerated in the septal, valvar and pulmonary artery positions. However, we experienced graft failures in infants in the aortic position."

Bell and colleagues (2019) reported on the results of another series study involving 377 participants with congenital heart defects who received surgical treatment with 501 CardioCel patches. Median follow-up was 31 months (1-60 months), and 11 deaths (2.9%) were reported, with 1 reportedly related to Cardiocel. The authors reported no echocardiographic or radiological evidence of patch calcification in any subject. The overall freedom from reintervention at 3- and 5-years post-implantation was 96%. A total of 14 (2.8%) implants required 18 reinterventions (3.6%) at the site of implantation. No differences in performance of CardioCel in neonates (0-28 days), infants (29-365 days) or children older than 1 year (p=0.22) were reported. Patukale (2023) reported on the mid-term performance of CardioCel for the repair of congenital heart defects. The retrospective study included a total of 1184 CardioCel patches implanted in 752 pediatric participants. Median age at implant was 12 months with median follow-up of 2.1 years. The authors reported the probability of freedom from CardioCel-related reintervention as 93% at 1 year, 91% at 3 years, and 88% at 5 years, respectively. A multivariable regression analysis indicated that participants undergoing aortic valve repair had a higher incidence of reintervention vs. other sites (HR, 7.15, p=0.008). They also stated that the probability of reintervention was higher in neonates (HR, 6.71, p=0.0007), especially when used for augmentation of the pulmonary arteries (HR, 14.38, p=0.029). This study indicates that CardioCel may be used for the repair of a variety of congenital heart defects. However, reinterventions were higher when CardioCel was used to augment the pulmonary arteries in neonates and for aortic valve repair as compared to other sites. This outcome needs further elucidation before the use of CardioCel can be widely used.

These results are promising, but data from larger, well-designed studies is needed to fully understand the safety and efficacy of CardioCel use in the repair of congenital heart diseases.

Clarix

Clarix is a product composed of cryopreserved acellular human amniotic membrane and umbilical cord and is treated as human tissue for transplantation under the FDA's HCT/P process.

Bemenderfer (2019) provided the only currently available published peer-reviewed study on this product. The unblinded non-randomized study involved 104 participants undergoing total ankle arthroplasty who received skin closure with either Clarix (n=54) or standard care (n=50). The authors reported that use of Clarix significantly decreased the overall time to skin healing (28.5 days vs. 40 days; p=0.03). No differences between groups were reported with regard to reoperations, skin dehiscence, local wound care, or antibiotic prescriptions. These results are promising, but additional data from larger controlled studies is needed to understand the safety and efficacy of this product.

Ross and colleagues (2022) reported a single center, retrospective study of pain outcomes in 52 individuals with musculoskeletal spinal disorders who were treated with ClarixFLO via epidural and facet injections. Conditions treated included; spondylosis (n=44), intervertebral disc (n=31), radiculopathy (n=18), stenosis (n=2), and other conditions. Pain was rated by participants on a scale of 0-10 where 0 indicated no pain and 10 indicated the worst imaginable pain. The average baseline pain score was 4.9, the mean duration of symptoms was 54.2 months. After ClarixFLO treatment, pain ratings decreased to 3.4 at 2 weeks (p< 0.0001) and 3.5 at 3-4 weeks (p=0.0023). During the follow-up period (average 10.6 weeks), pain was reduced to 2.8 (p< 0.0001) compared to baseline. There were no adverse events reported, and the authors concluded that additional larger studies are needed to confirm the safety and efficacy of ClarixFLO in epidural and facet injections.

Madan (2023) published a study that analyzed the use of ClarixFLO in the treatment of cystitis and bladder pain. In the first study, 5 natal females average age 64.4 (± 20.1 years) who had a median chronic radiation cystitis (CRC) duration of 10 years that was refractory to previous treatment modalities, received amniotic bladder therapy with ClarixFLO. The therapy was comprised of intra-detrusor injections of 100 mg micronized ClarixFLO diluted in 0.9% preservative-free sodium chloride. Outcomes measured were the Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), Overactive Bladder (OAB) Assessment Tool, and SF-12 Health Survey prior to surgery and 2, 4, 8 and 12 weeks post-injection. After treatment with ClarixFLO the BPIC-SS scores improved from baseline to 12 weeks (36.6 compared to 12.6); this was also associated with an improvement in ICSI, ICPI, OAB, and SF-12 scores. Additionally, uroflow assessments showed increases in voided volumes for all individuals. One individual was diagnosed with an acute urinary tract infection at 2 weeks which was treated successfully with oral antibiotics. No other adverse events were observed. The authors concluded that the results provide proof of the potential benefits of ClarixFLO in treating CRC.

A study by Radoiu (2023) involved 10 natal females aged 47.4 (± 14.4 years) with interstitial cystitis/bladder pain syndrome (IC/BPS) that had been refractory to previous treatment modalities for an average 7.8 years who received intra-detrusor injections of 100 mg ClarixFLO diluted in 0.9% preservative-free sodium chloride. Again, the outcomes measured were the ICSI, ICPI, BPIC-SS, Overactive Bladder Assessment Tool, and the SF-12 Health Survey prior to surgery and 2, 4, 8 and 12 weeks post-operatively. After treatment with ClarixFLO, voiding symptoms and bladder pain improved from pre-injection to 3 months. BPIC-SS decreased from 37.4 at baseline to 12.2 at 3 months (p< 0.001). There were no adverse events reported. The authors concluded that ClarixFLO may be a treatment option for individuals with IC/BPS symptoms based on the preliminary results. While these 2 small studies are promising, additional larger studies with longer endpoints are needed to confirm the clinical efficacy and durability of ClarixFLO in treating cystitis and BPS.

While these results are promising, further investigation in the form of more robust, well-designed and executed studies is needed to fully elucidate the clinical utility of ClarixFlo.

Conexa

Conexa is a product produced from acellular porcine dermis and has been cleared through the FDA's 510K process. At this time, the only comparative trial published in the peer reviewed literature addressing the use of this product was reported by Maillot and others in 2018. This prospective non-randomized trial involved 32 consecutive participants with large-to-massive rotator cuff tears assigned to treatment with 1) arthroscopic complete repair (repair group), 2) open repair and xenograft patch augmentation (patch group), or 3) arthroscopic debridement and tenotomy of the long head of the biceps (debridement group). Participants were evaluated preoperatively and postoperatively at 3, 6, 12 and 24 months. The authors reported that the mean improvement in the Constant-Murley score was +29.1, significant for all groups at the final follow-up examination (p<0.01 for all). No differences were reported between the repair and patch groups. However, comparison between the debridement group and the patch group at 12 months and the final follow-up was significant (p<0.001), as was the comparison between the debridement group and the repair group (p<0.002). Complications occurred in 5 of 11 participants in the patch group and only 1 in the repair group and none in the debridement group. The authors concluded that "the use of porcine dermis patches to augment repairs of massive and irreparable rotator cuff tears is not recommended because there is no benefit compared with repair without augmentation and patches result in more complications."

CorMatrix

CorMatrix is a product produced from acellular porcine small intestinal submucosa and has been cleared through the FDA's 510K process. At this time, there is very limited peer-reviewed published evidence addressing the use of CorMatrix. The data that is available addresses its use in cardiovascular surgical procedures. The largest of these studies is a retrospective, nonrandomized control study involving 111 participants undergoing coronary artery bypass surgery (CABG) who had pericardial reconstruction with

CorMatrix, compared to 111 control participants who underwent a standard CABG procedure without pericardial reconstruction (Boyd, 2010). The authors reported that postoperative atrial fibrillation occurred in 39% of controls vs. 18% of CorMatrix participants. No other results were significantly different. The safety and value of CorMatrix is difficult to interpret in this study, as it is the pericardial reconstruction procedure that seems to be the significant variable. Another publication by Quarti and colleagues (2011) describes the use of CorMatrix in a wide variety of cardiovascular surgeries, with no comparison groups provided. While the authors report no significant complications due to the use of CorMatrix, this study provides little in the way of helpful data to determine the safety and efficacy of this product. Similarly, Kelley and others (2017) reported the results of a retrospective case series study of 25 participants who underwent anterior leaflet augmentation. They reported a 32% recurrence rate of mitral regurgitation and concluded that further research is needed. Finally, Ashfaq (2017) reported good results from the use of CorMatrix in an underpowered case series of 15 pediatric participants undergoing atrioventricular (AV) septal defect repair. They reported 12 (80%) participants either improved or had stable left AV valve performance remaining at "mild" or less insufficiency, two (13%) declined from "none" to mild, and one (7%) from declined from mild to "severe," No residual shunting or left ventricular outflow tract (LVOT) obstruction was noted at follow-up. Only one (7%) reoperation was performed after 3 years due to left AV valve zone of apposition dehiscence. No permanent pacemakers were needed, and no deaths were reported.

Hu and others (2021) reported the results of a retrospective cohort study of 38 pediatric participants undergoing aortic valve repair with the aortic cusp extension procedures with either autologous pericardium (n=30) or CorMatrix (n=8). The authors reported that for the entire cohort the peak trans-valvular gradient significantly decreased immediately postoperatively (p=0.0017). No significant changes were observed at the 5-year follow-up timepoint (p=0.36). In the autologous group participants with aortic stenosis at baseline the peak trans-valvular gradient did not significantly change at follow-up (p=0.12). The CorMatrix group had only 4 participants with aortic stenosis at baseline, which did not allow for sufficient data for between-group tests. Moderate-to-severe aortic regurgitation was reported in 28 (93%) of autologous group participants at baseline, which improved to 11 (37%) postoperatively, but increased to 21 (70%) at follow-up. Eight (100%) CorMatrix group participants had moderate-to-severe aortic regurgitation, which improved to 3 (38%) postoperatively and increased to 7 (88%) at time of follow-up. Between-group data indicated a significant difference in favor of the autologous group (p=0.017). Freedom from reoperation at 5 years was significantly poorer in the CorMatrix group (12.5%) vs. the autologous group (62.5%, p=0.01). The most common reason for reoperation in the autologous group was for repair of moderate to severe aortic regurgitation and severe aortic regurgitation in the CorMatrix participants. While no CorMatrix participants had severe aortic regurgitation postoperatively, 88% developed it at 5 years follow-up. The authors concluded that autologous pericardium may outperform CorMatrix for aortic valve repair using the cusp extension method. However, several methodological weaknesses of this study limit the generalizability of these findings and further study is warranted.

Overall, the data regarding the safety and efficacy of CorMatrix is incomplete and conflicting. Further investigation with larger well-designed trials is needed.

Cymetra

Cymetra, an injectable micronized particulate form of aseptic AlloDerm (decellularized human dermis), has been proposed as a minimally invasive tissue graft product. It is treated as human tissue for transplantation under the FDA's HCT/P process. At this time, there are only three peer-reviewed published articles addressing the use of this product. All of these studies involve participants with vocal cord paralysis. One study by Morgan and colleagues (2007) was a retrospective, nonrandomized controlled trial involving 19 participants undergoing injection laryngoplasty with Cymetra or medialization laryngoplasty. The authors reported no significant difference between groups at 3 months follow-up. No long-term comparison data was provided. Another report of a retrospective case series study involving 10 participants who all received injection laryngoplasty was reported by Milstein et al (2005). The authors of this study reported significant improvement in voice quality, glottal closure, and vocal fold bowing. Of the study population, only 8 participants (40%) were found to have lasting benefit. Finally, Karpenko and others (2003) reported the results of a case series study (n=10). The results indicated that there were no significant quantitative or subjective voice quality improvements. They also stated that significant improvements were identified in maximum phonation time, relative glottal area, and subjective judgment of glottal competency. However, these results were not maintained at the 3-month study interval.

Cytal™

Cytal Matrix™ Wound Matrix is a product derived from porcine bladder epithelial basement membrane and tunica propria and has been cleared through the FDA's 510K process.

Huen (2022) published a retrospective case series study involving 10 pediatric participants undergoing corporal graft and correction of ventral curvature in proximal hypospadias repair. Median follow up was 14.1 months. Mean ventral curvature after degloving was 80 ± 50 degrees. All participants had straight erections at baseline and 9 had straight erections verified at a subsequent artificial erection test at least 6 months from the corporoplasty (90%). The remaining participant underwent a further procedure and had straight erections per parental history. No participants developed corporal diverticulum or demonstrated induration at site of corporoplasty on physical exam. There were no parental reports of atypical adverse systemic effects. This unique use of a graft product may provide some clinical benefit. However, the clinical utility should be established in larger, more robust trials.

DuraGen

DuraGen is made from bovine Achilles tendon collagen and is treated with a proprietary process to remove antigenic components. The graft is a porous scaffold that is purported to promote rapid fibrin clot formation while promoting natural dural growth it is contours to surfaces of the brain and spinal cord forming a biological seal to protect against CSF leakage.

Hamrick and colleagues (2023) performed a retrospective, single-center study of 106 individuals who had Chiari decompression surgery by a single surgeon. The study compared the incidence of graft-related complications after posterior fossa surgery using AlloDerm alone compared to AlloDerm with a DuraGen underlay. The inclusion criteria were ≥ 18 years of age, radiographic and clinical findings of Chiari 1 malformation. The exclusion criteria were individuals younger than 18 years, had a previous Chiari decompression, or had Chiari type 2 with associated spina bifida. The AlloDerm-only group had a percutaneous cerebrospinal fluid (CSF) leak rate of 8.6% versus a 0% rate in the dual graft group (p=0.037). At initial follow-up, there was a 15.5% combined rate of pseudomeningocele formation plus CSF leak in the AlloDerm-only group, and 18.8% in the AlloDerm plus DuraGen group (p=0.659). However, the pseudomeningoceles were larger in the AlloDerm-only group (p=0.004) and 5 individuals in the group required surgical repair (56%). All pseudomeningoceles resolved without the need for surgery in the AlloDerm plus DuraGen group (p=0.003). The authors concluded that DuraGen underlay with a sutured AlloDerm dural patch resulted in fewer CSF-related complications and eliminated the need for reoperation compared with AlloDerm alone. This single-center study provides promising evidence that dural grafts with a DuraGen may decrease the risk of complications, however larger RCT's are needed to analyze the efficacy of DuraGen in reducing rates of postoperative pseudomeningoceles and cerebrospinal fluid leak following Chiari decompression surgery.

Xu (2023) completed a retrospective case series review of 1011 individuals who had an open surgical procedure for microvascular decompression using a retrosigmoid approach. The study objective was to identify factors that may lead to CSF leak after a microvascular decompression procedure. Of the individuals who had the procedure, 37 (3.7%) presented with postoperative CSF leaks. Individuals with and without CSF leaks were not statistically different in age, sex, BMI, diagnoses, prior treatment, or

comorbidities. In both groups most individuals presented with Type I trigeminal neuralgia. The results demonstrated that CSF leak after a craniotomy occurred more frequently compared with a craniectomy (13.5% compared to 3.0%), p=0.001. Individuals were more likely to develop a CSF leak with closure of air cells with bone wax, (p=0.002) and compared to the use of Cranios/Norian bone cement, (p=0.01), CSF leak rates were higher with the use of both Durepair (dural substitute) or DuraGen (dural onlay), p=0.04. The authors concluded that the results showed an increased risk for postoperative CSF leak when primary dural closure was not established. Creating a water-tight closure of the dura, regardless of dural substitutes and other dural overlays may be critical to decrease the risk of CSF leaks and postoperative outcomes. Due to the small sample size additional studies are needed to confirm the findings.

DuraMatrix-Onlay

DuraMatrix Onlay (Collagen Matrix Inc, Oakland, NJ) is a product derived from acellular bovine Achilles tendon and has been cleared through the FDA's 510K process. Mekonnen (2023) described a retrospective case series study involving 33 participants who underwent a duraplasty procedures using DuraMatrix-Onlay® Plus collagen dura membrane. The majority of procedures were elective operations for the resection of a lesion (n=19, 58%). Average graft size was 17.69±4.73 cm^2. At an mean follow-up of 3 months, no postoperative CSF leaks were reported. The rates of infection, dural substitute complication, and removal were 6%, 6%, and 3%, respectively. The clinical utility of this product warrants further investigation in more robust trials.

Enduragen

Enduragen is a product composed of porcine acellular dermal matrix and has been cleared through the FDA's 510K process. McCord and others (2008) have published the only available study addressing the use of Enduragen. Their retrospective case series involved 69 participants who underwent 192 reconstructive or cosmetic eyelid procedures with Enduragen grafts. Eight procedures were for spacers in the upper lid, 104 were for spacers in the lower lid, and 17 were for lateral canthal reinforcement. There were 13 eyelid complications, for a complication rate of 10%. Nine cases required surgical revision, and there were four cases of infection, all of which were successfully treated with oral and topical antibiotics. The results of this study are insufficient to adequately evaluate the safety and efficacy of Enduragen. Further research is needed.

Barmettler (2018) published the results of a prospective, randomized clinical trial involving 39 participants (42 eyelids) undergoing lower eyelid retraction repair with spacer graft. Participants were assigned to undergo their procedure with autologous auricular cartilage (n=19 eyelids), SurgiMend (n=11 eyelids), or Enduragen (n=12 eyelids). The authors reported no significant differences between groups with regard to 6-month measures including MRD2, conjunctival injection, tearing, discomfort, itching, corneal abrasions, or repeat procedures.

Fortiva

Fortiva is a product composed of porcine acellular dermal matrix and has been cleared through the FDA's 510K process. The only currently available published peer-reviewed study addressing its use in a clinical setting was published by Maxwell in 2019, who reported on the results of a retrospective non-randomized controlled study investigating the use of Fortiva (n=72) compared to Strattice (n=98) and AlloDerm (n=59) in 229 participants undergoing abdominal wall reconstruction. The incidence of recurrence of abdominal wall defect was significantly higher in the AlloDerm group (20.3%) compared with the Fortiva (10.2%) and Strattice groups (6.9%) (p=0.040). The 1-, 3-, and 5-year survival rates for the repair with Fortiva were 1.4% and 6.9%, and 0%. For Strattice, the results were 5.1%, 9.2%, and 10.2%, and for AlloDerm, 6.8%, 18.5%, and 20.3%. Although participants in the AlloDerm group had the longest median hernia-free interval, 26.8 months (2-60 months), this was not found to be significantly different from Fortiva and Strattice (data not provided). The most common complication was surgical site infection (26.2%), followed by delayed healing (24.0%). Seroma formation was reported to have been significantly lower in the Fortiva group vs. the Strattice and AlloDerm groups (1.4% vs 13.3% vs 11.9%; p=0.021). This study indicates promising results; however, this data is limited and not methodologically robust. Additional investigation into the safety and efficacy of Fortiva is needed.

GalaFLEX

GalaFLEX is a synthetic bioabsorbable product composed of poly-4-hydroxybutyrate and was cleared through the FDA's 510K process. In reconstructive surgery GalaFLEX has been used as an alternative to ADM or in combination with ADM both in delayed and immediate reconstruction.

Adams (2018) published a case series report involving 62 participants undergoing mastopexy procedures. The authors reported that 89.7% of participants had successful ptosis correction and maintenance at 1 year. Both participant and surgeon satisfaction for breast shape, droop/sag of the breast, and maintenance of results at 1 year was reported as high. Adverse events deemed to be related to the device occurred in 5 participants (8.0%), including nerve pain, breast swelling, ptosis, and 2 instances of asymmetry. It is not clear how the safety and efficacy of this product compares to other products, including those considered the standard of care for breast procedures. Additional comparative trials are warranted.

Sigalove and colleagues (2023) reported a retrospective case series of 263 individuals (499 breasts) who had immediate, two-stage expander-implant, prepectoral breast reconstruction that compared GalaFLEX plus AlloDerm combination (n=135/250 breasts) to AlloDerm only (n=128/249 breasts). In the GalaFLEX plus AlloDerm group the lower third of the expander was covered by the AlloDerm and the rest of the expander was covered by GalaFLEX Complications after reconstruction were compared between the groups. Mean BMI, preoperative chemotherapy use, skin reducing mastectomy, and bilateral reconstructions were higher in the AlloDerm only group, whereas nipple-sparing mastectomy and unilateral reconstructions were higher in the GalaFLEX plus AlloDerm group. Individuals in the AlloDerm-only group were followed up for an average of 41.9 months, whereas those in the GalaFLEX plus AlloDerm group were followed for an average of 15 months from the date of initial surgery (p<0.0001). Complications occurred in 19 breasts that received AlloDerm-only and 16 breasts that received GalaFLEX plus AlloDerm; overall complication rates were 7.6% and 6.4%, respectively. All complications occurred within the first year after initial surgery; 61% of individuals in the GalaFLEX plus AlloDerm group had at least 1 year of follow-up, and 17% had at least 2 years of follow-up. The rate of complication was 7.6% in the AlloDerm-only group and 6.4% in the GalaFLEX plus AlloDerm group. The rate of infection, major skin necrosis, seroma, capsular contracture, prosthesis exposure/extrusion, and prosthesis loss were less than or equal to 3.0% in the GalaFLEX plus AlloDerm group and did not differ significantly from those in the AlloDerm-only group. There were no significant differences in complications between the two groups with the exception of skin necrosis (5.2% for the AlloDerm-only group vs. 1.2% for the GalaFLEX plus AlloDerm group), which the authors noted was driven by a higher rate of intermediate skin necrosis. However, the rate of major skin necrosis did not differ significantly between the groups. The study is limited by its retrospective nature and the relatively short follow-up duration. The authors concluded that the GalaFLEX has a comparable safety profile, however additional long-term data and clinical experience are needed to comprehensively understand the safety profile of GalaFLEX bioabsorbable matrix for use in breast reconstruction.

Gentrix

Gentrix is a product composed of porcine acellular urinary bladder and has been cleared through the FDA's 510K process. The only

currently available published peer-reviewed study addressing its use in a clinical setting was published by Wang and others in 2018. They reported on an underpowered unrandomized controlled trial involving 65 participants who underwent paraesophageal hernia (PEH) repair with (n=32) or without (n=33) reinforcement with Gentrix. There was no difference reported between groups with regard to recurrence rates, size of recurrence, postoperative symptomatic or quality of life improvement. The authors noted that participants in the unreinforced group who suffered recurrence had more severe symptoms and a higher rate of dissatisfaction. Of the 3 participants with recurrences after Gentrix placement, reoperation demonstrated anterior failure where no reinforcement had occurred because of the posteriorly placed U-shaped graft. It is not clear how the safety and efficacy of this product compares to other products, including those considered the standard of care. Additional comparative trials are warranted.

Gore BioA

Gore BioA is a completely synthetic, bioabsorbable product composed of 67% polyglycolic acid and 33% trimethyl chitosan and was cleared through the FDA's 510K process. Ommer and others published the results of a case series study involving 50 participants with trans-sphincteric (n=28) or supra-sphincteric (n=12) anal fistula who were treated with Gore BioA (2012). Postoperatively, 1 participant developed an abscess which had to be managed surgically. In 2 participants, the plug had fallen out within 2 weeks after surgery. Six months after surgery, the fistula had been healed in 20 participants (50.0%). Three additional fistulas healed after an additional 7 to 12 months. The authors reported that the overall healing rate was 57.5% (23/40). However, they noted that healing rates differ significantly between the surgeons (from 0 to 75%), and also varied depending on the number of previous interventions. In individuals having had only drainage of the abscess, success occurred in 63.6% (14/22) whereas, in those having had one or more flap fistula reconstructions, the healing rate decreased slightly to 50% (9/18). Further study is warranted to better understand the impact of surgeon experience as well as optimal selection criteria for individuals requiring treatment for anal fistulas. Heydari (2013) described the results of a retrospective case series study involving 48 participants with 49 anal fistulas treated with the Gore BioA. The overall healing rate was reported to be 69.3% (34/49 fistulas, 33/48 participants). Eight participants (24.2%) had complete healing by 3 months after surgery, 21 participants (63.6%) had healed by 6 months, and 4 participants (12.1%) had healed by 12 months. At 3 months, there were no reports of perineal pain or fecal incontinence. The authors reported no incidents of dislodged devices, anal stenosis, bleeding, or local infection.

In 2018 Jordan and others published the results of a retrospective comparative study involving 87 participants undergoing breast reconstruction with mesh underlay reinforcement at 123 sites with either polypropylene mesh (n=58) or Gore BioA (n=65). The overall incidence of bulge or hernia was 11.4%. The Gore BioA group experienced significantly more bulges/hernias than the polypropylene mesh group (20% vs. 1.7%). They concluded that use of Gore BioA was associated with a 13.3-fold risk of bulge/hernia (p=0.016) and was not appropriate for anterior rectus fascia reinforcement following abdominal tissue transfer.

While these reports are promising, the lack of larger comparative trials impedes a full assessment of the efficacy of the GORE BioA device. Further investigation is warranted.

In 2017, the American Society of Colon and Rectal surgeons published a new Practice guideline for the management of anal fissures (Stewart, 2017). Their recommendations do not mention the use of grafts or plugs of any kind.

Gore® Acuseal Cardiovascular Patch

Gore® Acuseal Cardiovascular Patch is an expanded polytetrafluoroethylene (ePTFE) separated by an elastomeric layer and may be available both with and without covalently bound bioactive heparin. It has been cleared through the FDA's 510K process. Stone (2014) published the results of a prospective randomized study comparing clinical outcomes of Acuseal vs. bovine pericardium patching (Vascu-Guard) when used for primary closure for carotid endarterectomy. This study involved 200 participants assigned in a 1:1 fashion and the mean follow-up period was 15 months. They reported that mean hemostasis time was 4.90 min for Acuseal vs. 3.09 min for Vascu-Guard (p=0.027). The mean operative times were similar for both groups (2.09 hr vs. 2.16 hr, p=0.669). The incidence of reexploration for neck hematoma was higher in the Vascu-Guard group; 6.12% vs. 1.03% (p=0.1183). The incidence of perioperative ipsilateral neurologic events was 3.09% for Acuseal patching vs. 1.02% for Vascu-Guard patching (p=0.368). The respective freedom from ≥ 70% carotid restenosis at 1, 2, and 3 years were 100%, 100%, and 100% for ACUSEAL patching vs. 100%, 98%, and 98% for Vascu-Guard patching (p=0.2478).

AbuRahma (2023) reported on the 10-year results of the study previously published by Stone et al. (2016). Mean follow-up time was 81 months (range 0-149 months). No significant differences were reported between groups for rates of long-term death, 47% in the Acuseal group vs. 48% in the Vascu-Guard group p=0.9402). Similarly, the incidence of late strokes was reported to be 5% in both groups (p=1.0). One patch complication was noted in the Acuseal group (infection) vs. the Vascu-Guard group (aneurysmal dilatation and rupture, no p-values provided). No significant differences in the rate of reintervention was reported (5% in the Acuseal group vs. 4% in the Vascu-Guard group, no p-values provided). The rate of ≥50% restenosis was 9% for the Acuseal group vs. 22% for Vascu-Guard group (p=0.0186). The rates of ≥80% restenosis, freedom from stroke, freedom from stroke/death, freedom from ≥80% restenosis, and overall survival rates were all not significantly different between groups for any time point (p=0.564, p=0.1112, p=0.8591, p=0.9407, p=0.9123, respectively). The authors concluded that both product are durable and have similar clinical outcomes at 10 years, except that ACUSEAL patching has significantly better rates of freedom from ≥50% restenosis.

While this data is promising, it compares does not compare outcomes to standard care, which is the critical question with regard to these products. Further investigation is needed to elucidate that issue.

Grafix CORE

Grafix CORE is a grafting product derived from allogeneic chorion membrane. It is treated as human tissue for transplantation under the FDA's HCT/P process.

Frykberg (2016) reported the results of a prospective case series study involving participants with complex DFUs ≤ 15 cm in their longest dimension and extending through the dermis with exposed muscle, tendon, fascia, bone, or joint capsule. All were treated with weekly applications of Grafix CORE. The intent-to-treat (ITT) population included 31 participants and the per-protocol population included 27 participants. The ITT participant population had significant co-morbidities, with 80% having hypertension, 60% current or former smokers, 55% having heart disease, and 45% having a previous partial foot amputation. Prior advanced treatment (for example, negative pressure wound therapy) for the index wound had occurred in 67.7% of participants. At 16 weeks, 96.3% of the per-protocol group had 100% granulation of the index wound and complete closure occurred in 59.3%. The mean area reduction of the index wound at day 28 was 54.3% and 72.8% at 8 weeks. At the end of the 16-week study period the mean wound area reduction was 92.3%. No Grafix-related adverse events were reported. This study demonstrated the use of Grafix CORE in the healing of complex DFUs. However, the small study population and lack of controls hampers the generalizability of these results.

Raspovic (2018) reported a retrospective case series analysis of 360 participants with 441 DFUs treated with Grafix PRIME or Grafix CORE using data from Net Health's Wound Expert electronic health records database. The mean size of the index wound was 5.1 cm^2 with 3.9 mm depth. Mean wound duration prior to study treatment was 102 days. The mean duration of treatment with a Grafix

product was 89.3 days (median 56.0). Complete wound closure at the end of treatment occurred in 59.4% of participants. Median time to closure was 42.0 days with a median of 4 graft applications. The proportion of closure decreased as wound size increased, with 72.3% of wounds between 0.25 cm^2 to 2 cm^2 having complete healing at a median of 21 days and 4 applications. For wounds larger than 25 cm^2, only 27.8% achieved complete healing at a median of 105 days and 11 applications. The authors did not provide any data regarding the percentage of participants receiving treatment with Grafix PRIME vs. those receiving Grafix CORE.

At this time, the safety and efficacy of Grafix CORE, is uncertain. Additional well designed and conducted trials are warranted.

GrafixPL Prime

GrafixPL Prime is a grafting product derived from allogeneic amnion membrane. It is treated as human tissue for transplantation under the FDA's HCT/P process. A similar product, Grafix Prime, is also available. The difference between these products is that Grafix Prime is cryopreserved, and GrafixPL Prime is lyopreserved (a method of dehydration).

Davis (2020) published the results of a prospective cohort study involving 40 participants with foot ulcers treated with GrafixPL Prime once a week for 12 weeks. After 12 weeks of treatment, closure was achieved in 48% of participants (n=19) with an average time to closure of 40.0 days. A total of 60% of participants had a 50% wound area reduction, and significantly more participants who achieved closure reached a 50% wound area reduction in 4 weeks compared with those who did not (73.7% vs 47.6%, p=0.093). Five participants were identified to have no response to treatment, defined as a percent wound area reduction of < 30% by the end of the study. Participants that did not achieve wound closure tended to be older (63 vs 59 years, p=0.011), have larger ulcers at baseline (7.8 vs 1.6 cm^2, p=0.012), and have ulcers of longer duration (60.0 vs 130.0 days, p=0.062). Fifty-eight percent of participants had at least one adverse event during treatment including infection (n=10), infection requiring hospitalization (n=2), hospitalization for non-foot related issues (n=4), and amputation (n=1). In addition to the clinical study, the authors reported a bench study assessing cellular viability of cryopreserved Grafix Prime vs. the lyopreserved GrafixPL Prime. The reported that cellular viability was equivalent between cryo- and lyopreserved amniotic tissues.

While these results are helpful in beginning to understand the clinical utility of GrafixPL Prime, additional data is needed for an adequate evaluation.

Hyalomatrix

Hyalomatrix is a synthetic wound covering product composed of a benzyl ester of hyaluronic acid. This product has been approved through the FDA's PMA process. The currently available evidence addressing the use of Hyalomatrix is limited mostly to weak, uncontrolled, unblinded case series studies. Only one RCT has been published to date involving 16 participants with VSUs, 9 of which were treated with Hylaomatrix and 7 treated with standard wound care (Alvarez, 2017). The authors reported that the incidence of wound healing at 12 weeks was 66.6% for the Hyalomatrix group vs. 14.2% for controls (p=0.066). At 16 weeks, the incidence of wound healing was 87.5% of participants in the Hyalomatrix group vs. 42.8% in the control group (p=0.059). The mean time to healing in the Hyalomatrix group was 41 days compared with 104 days in the control (p=0.029). The largest studies available involve 300, 262, 79, and 57 participants (Gravante, 2007; Caravaggi, 2003 and 2011; Gravante 2010, respectively). The Carravaggi study addresses chronic wounds while the Gravante studies address burns. The rest of the studies published involve significantly fewer than 30 participants and encompass a variety of indications including various surgically created wounds (Faga, 2013; Landi, 2014; Onesti, 2014), traumatic wounds (Kozusko, 2023; Onesti, 2014; Vaienti, 2013), and chronic ulcers (Motolese, 2013).

In summary, the body of literature addressing Hyalomatrix is limited to predominantly weak case series studies involving a heterogeneous collection of indications. While most of these studies demonstrate promising results, the uncontrolled, unblinded nature of these studies does not allow proper assessment of the safety and efficacy this product.

Integra Flowable Wound Matrix

In 2017, Campitiello and colleagues published an RCT comparing Integra Flowable Wound Matrix vs. standard care for the treatment of 46 participants with DFUs with irregular geometries. There were 23 participants in each group who were evaluated once a week for 6 weeks. The authors reported that the overall complete healing rate was 69.56%, with the rate in the Integra group being 86.95% vs. 52.17% in the control group (OR=1.67, p=0.001). Mean time to healing was 29.73 days in the Integra group vs. 42.78 in the control group (p<0.000). The amputation and rehospitalization rates in the Integra group were 4.34% vs. 30.43% in controls (RR=0.16, p=0.028). The authors concluded that Integra Flowable Wound Matrix was significantly superior to the wet dressing, but that additional research will shed more light on the promising advantages of this material in healing diabetic foot ulcers.

Keramatrix

This product is composed of freeze-dried acellular animal-derived keratin and has been approved through the FDA's 510K process. At this time, the most rigorous evidence is an underpowered nonrandomized controlled study involving 40 participants with superficial or partial thickness burn injuries treated with Keramatrix, compared to 40 historical controls who received standard of care treatment (Loan, 2016). The results indicated a significantly faster mean healing time in the Keramatrix group vs. controls (8.7 days vs. 14.4 days, p<0.05), hospital inpatient days (0 days vs. 2.6 days, p<0.05), and number of outpatient appointments following initial therapy (1.2 vs. 3.3, p<0.05). No differences in complications were reported.

KeraSys

Kerasys is composed of decellularized xenogeneic porcine small intestinal submucosa and has been approved through the FDA's 510K process. The only available study described in the published peer-reviewed literature addressing the use of this product was published by Nagi and others in 2013. Their study was a retrospective, noncomparative, consecutive case series of 42 eyes with tube-related exposure complications due to glaucoma drainage device surgery. KeraSys was used to cover the defect. The authors reported that 4 (10%) eyes experienced patch-related complications. Two had exposure at 8 months postoperatively, 1 had exposure at 13 months postoperatively, and 1 with exposure at 4 weeks postoperatively. They concluded that, "The effectiveness of the KeraSys patch graft is limited by the higher than expected early exposure rate found in this case series."

MatrACELL

MatrACELL is a decellularized allograft product composed of human cardiovascular tissue treated as human tissue for transplantation under the FDA's HCT/P process.

Currently the only study published regarding the use of this product was published by Hopkins (2014). This nonrandomized controlled study involved 108 consecutive participants undergoing cardiovascular reconstructive procedures using MatrACELL pulmonary artery patches during pulmonary arterioplasty. A second retrospective cohort of 100 participants who received arterioplasty patches using classical cryopreserved pulmonary artery allografts (n=59 participants) or synthetic materials (n=41 participants) was used for comparison. The reported results included that 106 participants with 118 decellularized patches had no device-related serious adverse events, no device failures, and no evidence of calcifications on chest roentgenograms. In contrast, the control participants

experienced an overall 14.0% patch failure rate requiring device-related reoperations (p<0.0001) at mean duration of 194 ± 104 days (range, 25 to 477 days). The authors concluded that the intermediate-term data obtained in this study suggest favorable performance by decellularized pulmonary artery patches, with no material failures or reoperations provoked by device failure.

Additional study is warranted to fully evaluate the safety and efficacy of this product.

MatriDerm

MatriDerm is a decellularized dermis allograft product treated as human tissue for transplantation under the FDA's HCT/P process. Riml (2011) reported a study of 30 participants undergoing nasal tip skin grafts non-randomly assigned to receive either conventional FTSG, retroauricular perichondrodermal composite grafts, or skin transplantation supplemented with MatriDerm. Ten participants were assigned to each group. This retrospective study was conducted in a randomized and blinded manner by assigned reviewers using the Manchester scale. The authors report that 2 (20%) of the MatriDerm participants developed fistulae and concluded that MatriDerm was not suitable for nasal tip reconstruction.

Another study by Haslik and colleagues evaluated the use of MatriDerm for the management of FTSG (2010). This underpowered case series study involved 17 participants with upper extremity skin wounds, all of whom received MatriDerm in conjunction with unmeshed skin grafts. The reported take rate was 96%. A 12-month follow-up Vancouver scale score of 1.7 and DASH (disability of arm-shoulder-hand) score showed excellent hand function in participants with burn injury and participants with a defect due to the harvest of a radial forearm flap achieved satisfying hand function.

Wallner and colleagues (2023) published a retrospective study that compared the use of single autologous STSG alone or in combination with MatriDerm ADM in 147 cases of severe traumatic soft tissue defects of the leg with exposed structures, such as tendons, ligaments, vessels, or bone of the lower extremities. Severe soft tissue defects consisted of 18 open fractures with extensive decollement, 43 thermic and chemical burns, 78 severe soft tissue lesions, and 8 ulcers. Overall, soft tissue defects were more severe in the MatriDerm plus STSG group. The healing rate, defined as the number of individuals with take rate ≥ 75%, was 88/147 (60%) and no significant differences between the groups was reported (p=0.15). Despite variable wound complexity between the groups there were no differences in scar tissue quality 12 months postoperatively. Overall complication rate was approximately 25%. In 15% of the cases, a surgical revision was required. The number of cases with at least one necessary surgical revision was 4 in the STSG-only group compared to 18 in the MatriDerm plus STSG group (p=0.02). The number of individuals with documented adverse events (33%) or necessary revision surgery (21%) was higher in the STSG plus MatriDerm group. The complications reported after more than 100 days included scar instability, fistula formation, and swelling. Additionally, the use of negative pressure wound therapy may have impacted the STSG take rate. The authors concluded that surgical treatment with STSG and additional MatriDerm application is a satisfactory alternative for dermis replacement in individuals with severe skin defects, independent of age. Due to the higher rate of adverse events, complications, and surgical revision, further studies with larger, well designed trials are needed to fully evaluate the safety and efficacy of MatriDerm..

MediHoney

The use of honey has been proposed for the treatment of various skin conditions including burns, chronic ulcers, and superficial abrasions. It has been hypothesized that honey, with its antibacterial properties, can significantly improve skin healing when applied topically to skin wounds. Several randomized controlled trials have been published involving MediHoney, a product cleared through the FDA's 510K process, most addressing the treatment of venous leg and foot ulcers. Jull and colleagues published the largest of these trials, which included 368 participants randomized to receive treatment with either calcium alginate dressing impregnated with manuka honey or standard care with whatever dressings were appropriate for the individual at that time (2008). After following the participants for a total of 12 weeks of follow-up, the authors concluded that there was no significant difference in outcomes between the two groups. It was noted that the honey-treated group experienced significantly greater numbers of adverse events (p=0.013). Contradicting these findings is a study by Gethin and Cowman (2008). In this study, 108 participants with venous ulcers were randomized to receive treatment with either honey dressing or standard hydrogel therapy. The findings were that the honey-treated group had significantly better results in terms of median reduction in wound size at 12 weeks (44% vs. 33%, p=0.037), but no significant differences between groups in other primary endpoints were reported.

The other most studied condition addressed in the literature is the treatment of burns. The largest study currently available addressing burns involved 150 participants randomized to receive treatment with either silver sulphadiazine (SSD) or honey (Malik, 2010). Each participant acted as his or her own control, with one burn site randomly treated with SSD and the other with honey. The authors report that the honey-treated sites had significantly faster re-epithelialization and healing of superficial and partial thickness burns than the SSD sites (13.47 days vs. 15.62 days, p<0.0001). Additionally, the honey-treated sites achieved complete healing significantly faster than SSD sites (21 days vs. 24 days, p<0.0001).

Lund and colleagues compared the use of honey-coated dressing for breast malignant wounds. In this study, 67 participants, 79% of whom had breast cancer, were randomized to receive treatment with either honey-coated dressing (n=34) or silver dressing (n=33). The authors report no significant differences between groups, and they concluded that the possible antibacterial effect of either treatment "could not be confirmed in these malignant wounds."

At this time, the evidence addressing the use of honey for skin wounds is lacking. The current studies are mostly unblinded, controlled studies, and a large variety of controls have been used. These factors make comparison study outcomes difficult to interpret. Further investigation with large well-done blinded trials using standardized controls is warranted.

Menaflex (formerly "Collagen meniscus implant" or CMI)

Collagen meniscus implants (e.g., Menaflex) have been proposed as a treatment method for individuals with a damaged knee meniscus. Menaflex is a human-derived acellular collagen product treated as human tissue for transplantation under the FDA's HCT/P process. At this time, there is only one large trial for this type of procedure (Rodkey, 2008). This study involved 311 participants with irreparable injury of the medial meniscus or a previous partial medial meniscectomy. The study population was divided into two groups, those with prior meniscal surgery (chronic group) and those with no prior surgery (acute group). These populations were further randomized to receive either treatment with a collagen meniscus implant or a partial meniscectomy only. The mean duration of follow-up was 59 months (range, 16 to 92 months). Repeat arthroscopies done in the experimental group at 1 year showed significantly (p=0.001) increased meniscal tissue compared with that seen after the original index surgery. In the chronic group, participants who had received the collagen implant regained a significantly higher degree of pre-surgery activity than did the controls (p=0.02). This group also underwent significantly fewer non-protocol reoperations (p=0.04). The authors reported no significant differences between the two treatment groups in the acute arm of the study.

Zaffahnini and colleagues conducted a long-term trial of the performance of the Menaflex implant in 33 participants. This nonrandomized controlled trial allowed participants to choose treatment with either Menaflex (n=17) or partial medial meniscectomy (n=16). Participants were evaluated at baseline, 5 years and then 10 years after surgery. At 10 years, the authors report that the Menaflex group showed significant improvement compared to meniscectomy with regard to visual analog scale for pain (p=0.004),

International Knee Documentation Committee knee form (p=0.0001), Teger index (p=0.026), SF-36 Physical Health Index (p=0.026), and SF-36 Mental Health Index (p=0.004). Radiographic evaluation showed significantly less medial joint space narrowing in the Menaflex group than in controls (p=0.0003). There were no significant differences reported between groups regarding Lysholm score (p=0.062) and Yulish score (p=0.122). Genovese score remained constant between 5 and 10 years after surgery (p=0.5).

Another case series study of 22 participants followed for 10 years was reported by Monllau and colleagues (2011). The results of this study demonstrated that several measures improved, including the visual analog pain scale and radiographic joint line narrowing. The Lysholm score was significantly improved, from 59.9 at baseline, 89.6 at 1 year (p<0.001), and 87.5 at 10 years (p<0.001). Failure rate was only reported to be 8% in the 25 participants initially implanted.

Van Der Straeten published the results of a cohort study of 313 participants who received treatment with the collagen meniscal implant and were followed for a mean follow-up of 6.8 years (2016). A total of 56.5% of the implants were still intact and in place; 27.4% had been removed. This included 63 implants converted to a knee arthroplasty (19.2%). The overall cumulative allograft survivorship was 15.1% at 24.0 years. Simultaneous osteotomy significantly deteriorated survival (0% at 24.0 years) (p=0.010). The authors stated that 61% of participants underwent at least one additional surgery (range 1-11) for clinical symptoms after implantation. They concluded that the collagen meniscal implant did not delay or prevent tibiofemoral OA progression.

Another large cohort study was reported by Waterman (2016). This study involved 230 active-duty military personnel who underwent treatment with the collagen meniscal implant. A total of 51 complications occurred in 46 (21.1%) participants, including a secondary tear or extrusion (9%). The authors reported that 10 participants (4.4%) required secondary meniscal debridement at a mean of 2.14 years. Revision was done in 1 participant (0.4%) and 20 participants (0.9%) subsequently underwent total knee arthroplasty. After implantation, 50 participants (22%) underwent knee-related military discharge at a mean of 2.49 years postoperatively. They concluded that while there were low reoperation and revision rates, their investigation indicated that 22% of participants who received implants were unable to return to military duty due to persistent knee limitations at short-term follow-up.

While these studies show that there is some potential benefit to the use of meniscal collagen implants in some populations, further data from rigorously designed and conducted trials is warranted to further understand the clinical implications of this technology.

Menaflex was originally cleared by the FDA in the 510K process. Subsequent to further review by the FDA, this clearance was revoked. The manufacturer, ReGen Biologics, Inc. went bankrupt shortly thereafter. The Menaflex device is currently not marketed in the U.S.

Myriad Matrix ™ and Myriad Morcells™

Myriad Matrix is a product composed of processed ovine forestomach matrix and cleared through the FDA's 510K process. Two studies published in 2023 are the first to address the clinical utility of Myriad Matrix and Myriad Morcells.

Cormican (2023) reported the results of a retrospective pilot case series involving 10 participants with 13 contaminated lower-extremity defects undergoing surgical reconstruction with Myriad Matrix (n=3), Myriad Morcells (n=4), or both (n=6). All participants had at least 1 significant comorbidity with the potential to complicate their healing trajectory. Mean defect age was 3.5±5.6 weeks and mean area was 217.3±77.9 cm^2. Most defects had exposed structures (85%), and all defects were Centers for Disease Control and Prevention grade 2 or higher. Mean time to 100% granulation tissue formation was 23.4±9.2 days, with a median product application of 1.0. Staged reconstruction was used in 7 of 13 defects, with the remainder (6 of 13) left to heal via secondary intention using standard wound care protocols. Mean follow-up was 7.4±2.4 weeks, with 4 wounds (30%) lost to follow up ≤5 weeks. No major postoperative infections or adverse events were reported. The small sample size, an d high loss to follow-up do not allow reasonable, generalizable conclusions regarding the clinical utility of these products

Bosque (2023) described the results of a similar retrospective case series study involving 50 participants with complex lower-extremity defects undergoing surgical reconstruction with Myriad Matrix (n=41), Myriad Morcells (n=3), or both (n=6). The participants had heterogenous etiologies, including diabetic foot ulcers (DFUs) (48%), half of which were complicated by a necrotizing soft-tissue infection (50%). Additionally, in the total population, 34% of participants had exposed bone, 10% had exposed tendon, 18% had both exposed tendon and bone, and 4% had exposed capsule. Ten participants (20%) were lost to follow-up before complete closure of the defect, but after 100% granulation tissue had formed. Where Myriad products were used for dermal regeneration (n=47), the median time to 100% granulation tissue was 17 days (mean, 26±22.2 days; range, 7–120 days). A total of 38 participants (76%) were closed by secondary intention, with an overall median time to close of 14 weeks (mean, 14.0±5.9 weeks; range, 1–27 weeks). The overall time to closure from the initial surgical procedure to closure across defects (n=40) was 13 weeks (mean, 13.7±6.9 days; range, 2–29 weeks). This study involving these two Myriad products is promising, but the results are limited by multiple factors, including significant loss to follow-up, heterogeneity of wound etiologies, and use of multiple versions of the product used.

Overall, additional data from well designed and conducted trials is needed to establish the clinical utility of Myriad Matrix and Myriad Morcells.

Neuragen

Neuragen collagen tube conduits are composed of bovine-derived acellular collagen and have been cleared through the FDA's 510K process. This product is proposed for use in peripheral nerve repair.

At this time, the most rigorous published trial of Neuragen was an unblinded RCT involving 44 participants with ulnar or median nerve lacerations assigned to treatment with Neuragen (n=23) vs. direct fascicular repair or nerve grafting (n=21) (Boeckstyns, 2013). The authors reported that data for only 36 participants (81%) were available at the 24-month follow-up visit. However, they do not provide information regarding which groups the dropouts were from. At 24 months no significant differences between groups were reported with regard to amplitudes, latencies and conduction velocities. With regard to comparison to the contralateral hand, both groups remained significantly deficient on all electrophysiological measures. No surgical complications were reported. These results may indicate some benefit from the use of Neuragen, but the generalizability is hampered by missing information regarding participants at 24 months, as well as methodological flaws such small study population and lack of blinding.

In addition to this study, several unblinded non-randomized controlled trials and multiple case series studies addressing the use of Neuragen have been published, with most involving small numbers of participants (Ashley, 2006; Bushnell; Distinct, 2013; Erakat 2013; Farole, 2008; Haug 2013; Huber 2017; Karup, 2017; Lohmeyer, 2014; Rbia, 2019; Schmauss 2014; Taras, 2011; Wangensteen, 2010; Wilson, 2016). These studies involve weak methodologies and low power to control for bias. The clinical utility and generalizability of their conclusions is limited, and further study is needed in the form of larger, well-designed trials to fully evaluate the safety and efficacy of this product.

NeuraWrap

NeuraWrap nerve wrap is a product composed of bovine-derived acellular collagen and glycosaminoglycan and has been cleared through the FDA's 510K process. This product is proposed for use in peripheral nerve repair.

At this time, the available peer-reviewed published data addressing the clinical utility of NeuraWrap is limited to a small number of studies involving weak methodology and low numbers of participants (Hibner, 2012; Kokkalis, 2016; Soltani, 2014). Additional evidence addressing the clinical utility of this product from large, well-designed, and conducted trials is needed to fully assess the clinical utility of this product.

Novosorb Biodegradable Temporizing Matrix (BMT)

Novosorb Biodegradable Temporizing Matrix (BMT) product is composed of porous biodegradable polyurethane foam and has been cleared through the FDA's 510K process. This product has been proposed for the treatment of various dermal conditions including burns, ulcers, chronic wounds, etc.

At this time there is a reasonable number of studies published in the medical literature addressing the use of Novosorb for a variety of conditions including burns, treatment of necrotizing fasciitis, DFUs, and chronic complex wounds (Solanki, 2020; Schlottmann, 2022; Li, 2021; Lo, 2022; Austin, 2023; Kidd, 2023; Lo, 2023; Betar, 2023; and Guerrico, 2023). However due to the small sample size and weak methodologies the results cannot be generalized to the wider population. Larger studies in the form of well-designed and conducted trials are needed to assess the clinical utility and efficacy of Novosorb..

Ologen Collagen Matrix

Ologen Collagen Matrix product is composed of acellular porcine intestine and has been cleared through the FDA's 510K process. The use of this product has been proposed for a variety of ophthalmological indications; however, the published literature has been limited. The most rigorous trial to date was an open label, non-randomized, prospective study involving 93 participants undergoing phacotrabeculectomy assigned to receive treatment with mitomycin C (n=53) or Ologen (n=40). The authors reported that after 12 months follow-up there were no significant differences between groups with regard to best corrected visual acuity (p=0.151), intraocular pressure (p=0.254), mean number of medications used (p=0.91) or overall procedure success (p=0.745). No reported repeat procedures, blebitis or endophthalmitis were reported. This study indicates equal outcomes from the use of mitmycin C vs. Ologen during phacotrabeculectomy. However, the study was not designed as a non-inferiority trial and contained several methodological flaws that limit the generalizability of the reported findings. Further investigation in the form of well-designed and conducted studies is needed.

Park (2022) published a retrospective analysis of 72 individuals with glaucoma who underwent XEN gel stent implantation with (n=42) and without (n=30) Ologen col lagen matrix augmentation. Surgical success, defined as intraocular pressure (IOP) reduction greater than 20% than preoperative IOP, and the percentage of postoperative complications were compared between the Ologen implant augmented group and the non-augmented group. The surgical success rate at 6 months postoperatively was not different between the groups (56.4% compared to 43.3%, p>0.05). Neither was the prevalence of postoperative hypotony, 5-fluorouracil injections, use of anti-glaucoma medications, bleb needling, and additional glaucoma surgeries different between the groups at 6 months. The authors concluded that all groups showed IOP reduction after XEN gel stent implantation, however there was no significant difference between the Ologen implant augmented and non-augmented groups in surgical outcomes.

Bhatkoti (2023) and Khairy (2023) also published small studies that assessed the use of Ologen implant in place of or in combination with trabeculotomy. Bhatoki (n=43) demonstrated a similar success rate between trabeculectomy and Ologen implant in treating primary open angle glaucoma. However, there was a lower complication rate and faster visual recovery in the trabeculectomy-only group compared to the Ologen group. Khairy (n=21) compared the use of Mitomycin C or Ologen implant as an adjunct to combined trabeculotomy-trabeculectomy in the treatment of primary congenital glaucoma. Complete success was achieved in 17 eyes (81.0%) in combined trabeculotomy-trabeculectomy group, 18 eyes (85.7%) in Mitomycin-C group, and 17 eyes (81.0%) in the Ologen group. Qualified success, defined as IOP < 21 with or without antiglaucoma medications, was achieved in 85.7% in both the combined trabeculotomy-trabeculectomy and the Ologen groups, and 90.5% in the Mitomycin C group. The Ologen group had the lowest success probability at 3 months (85.7%). The authors concluded that combined trabeculotomy-trabeculectomy is a safe and effective primary surgical treatment in individuals with primary congenital glaucoma without the need for implant augmentation, and that the use of Ologen implant should be preserved for use in recurrent cases.

Additional larger studies are needed to assess the safety and clinical efficacy of Ologen in ophthalmic applications.

Pelvicol

Pelvicol is a porcine-derived acellular dermal collagen product cleared through the FDA's 510K process. The use of Pelvicol was evaluated in 132 participants with pelvic organ prolapse. This RCT involved 64 participants who underwent anterior and posterior colporrhaphy and 68 who received colporrhaphy with Pelvicol. At 3 months follow-up, there were significantly more surgical failures and recurrences in the Pelvicol group, but by the 3-year follow-up period recurrence rates were similar. No significant differences were noted with regard to symptom resolution, sexual activity, or complications rates. The authors conclude that, "Pelvicol did not provide advantages over conventional colporrhaphy in recurrent pelvic organ prolapse concerning anatomical and subjective outcomes."

Kahn (2015) published the results of an RCT involving 201 participants undergoing surgical treatment for stress urinary incontinence. Participants received treatment with either tension-free vaginal tape (TVT), autologous fascial sling (AFS), or Pelvicol. The authors reported that 162 (80.6%) participants were available for follow-up at a median follow-up of 10 years. They reported the 1 year "success rates", defined as being completely dry or improved, as 93% in the TVT group, 90% in the AFS group and 61% in the Pelvicol group. There were no significant differences between groups at 10 years. Comparing the 1- and 10-year success rates, there were significant reductions in the TVT and AFS groups (p<0.05 for both), but not for the Pelvicol group (p=1.0). Similar results were reported with the rates of "dry" participants at 1 and 10 years, with rates for TVT reported as being 55% and 31.7%, 48% and 50.8% for AFS, and 22% and 15.7% for Pelvicol. These rates significantly favored AFS (p<0.001 vs. Pelvicol and p=0.001 vs. TVT). The Pelvicol arm of the study was discontinued by the data monitoring group after it was clear that the Pelvicol group had significantly poorer results vs. TVT and AFS. The results of this study indicate that the use of Pelvicol for the treatment of stress urinary incontinence may present a significant risk of harm compared to other available treatments, and further investigation may be warranted.

Peri-Strips Dry

Peri-Strips Dry is a product derived from decellularized bovine pericardium and cleared through the FDA's 510K process. At this time there are only a limited number of peer-reviewed published article addressing the use of this product. Stamou and colleagues compared the use of Peri-Strips Dry (n=96) to standard care (n=91) in staple line reinforcement during sleeve gastrectomy procedures (2011). The authors reported that the use of Peri-Strips Dry significantly reduced the incidence of staple line bleeding (p=0.012) and intra-abdominal collections (p=0.026). Leak rate was not significantly reduced.

A similar study was conducted by Shah and others (2014) involving 100 participants undergoing sleeve gastrectomy procedures and assigned to surgery with either Peri-Strips Dry staple line reinforcement (n=51) or standard care (n=49). Participants were followed up for 30 days post procedure. No intra- or postoperative leaks were reported in either group. Staple line bleeds were reported to occur

less in the Peri-Strips group vs. controls (45.1% vs. 79.6%, p=0.0005). Overall BMI did not impact staple line bleeds ($p_{interaction}$=0.072). However, participants with BMI < 43 were significantly more likely to have staple line bleeds compared to participants with BMI ≥ 43 (79.3% vs. 33%, p=0.0015). Participants in the Peri-Strips group had less severe staple line bleeding vs controls, with moderate to severe bleeding occurring in 2 Peri-Strips group participants vs. 6 controls (p=0.0002). Peri-Strips participants also had shorter procedure times (58.8 minutes vs. 72.8 minutes, p=0.0153) as well as fewer hemostatic clips or sutures (19.6% vs. 67.3%, p<0.0001).

The results of these underpowered studies are promising. Further data from more rigorously designed and executed studies is warranted.

Permacol

Permacol is an acellular dermal collagen product derived from porcine pericardium that has been cleared through the FDA's 510K process. Currently, the peer-reviewed published data addressing the use of Permacol is limited. A retrospective, nonrandomized controlled study of 37 participants undergoing congenital diaphragmatic hernia repair was reported by Mitchell (2008). Participants received treatment with either Permacol (n=29) or synthetic Gore-Tex (n=8), with a median follow-up of 57 months for Gore-Tex and 20 months for Permacol. Overall recurrences were reported in 8 (28%) Gore-Tex participants with a median time to recurrence of 12 months. There were no recurrences reported in the Permacol group. These results are interesting, but due to the small sample size, retrospective nature and lack of randomization, it is not possible to generalize the results to other populations.

Kalaiselvan and colleagues (2020) performed a retrospective analysis of 13 participants who had abdominal wall defect repair with bridging Permacol over a 5-year period. Twelve of these (92%) participants developed abdominal wall defects (AWD) and enterocutaneous fistulation following complications of previous surgery. Six participants underwent fistula takedown and abdominal wall repair with Permacol, of which 5 (83%) recurred. Seven participants had already undergone similar procedures in their referring hospitals and had also recurred. Median time to fistulation after Permacol treatment was 17 days. In all cases, Permacol was used to bridge the defect and placed in direct contact with bowel. At reconstructive surgery for refistulation, it was inseparable from multiple segments of small intestine, necessitating extensive bowel resection. Histological examination confirmed that Permacol almost completely integrated with the seromuscular layer of the small intestine. The study raised concerns regarding intraperitoneal use due to the fact that Permacol may become inseparable from the serosa of the small intestine and was associated with recurrent intestinal fistula formation and treatment failure.

Rashid and colleagues (2020) examined rotator cuff repair augmented with either GraftJacket (n=4), Permacol (n=3) or SOC (n=3). The study addressed histological and proinflammatory changes in the native supraspinatus tendon in both Permacol groups. The authors reported increased friability of the matrix, and lack of parallel oriented collagen fibers. In the SOC group, which was a conventional repair without patch augmentation, the tissue resembled normal tendon. The Permacol-treated sections, however, demonstrated more disruption of the extracellular matrix when compared to sections treated with GraftJacket. They reported that one participant in the Permacol group experienced adverse tissue reaction characterized by extensive infiltration of pro-inflammatory cells. The authors concluded use of Permacol augmentation in rotator cuff repair lacks clinical efficacy and may potentially cause harm.

While the studies discussed above are underpowered, they raise concerns about the broader use of Permacol in both abdominal wall reconstruction and rotator cuff repair. More robust studies are warranted to investigate these findings.

Roman (2021) reported the results of a retrospective case-control study of 209 participants undergoing complete excision of large rectovaginal endometriotic nodules treated with (n=167) or without Permacol (n=42) mesh. No significant differences were reported in the rate of postoperative rectovaginal fistula formation (OR, 1.6) and the authors concluded that the use of Permacol mesh may not impact the rate of rectovaginal fistula formation compared to no mesh.

Vahtsevanos (2021) reported the results of a retrospective case-control study of 73 participants who had undergone 76 parotidectomy procedures with (n=32) and without Permacol (n=44) to evaluate the impact on the incidence of Frey's syndrome. At a mean follow-up of 26.3 months the incidence of Frey's syndrome was significantly lower in the Permacol group (6.7% vs. 31.8%, respectively, p=0.031). The incidence of severe Frey's syndrome was 3.12% in the Permacol group vs. 31.82% in the control group (p=0.002). The results of this study should be confirmed in a prospective trial.

Ball and colleagues (2022) conducted a parallel, dual-arm, double-blind randomized controlled trial involving adults (n=94) undergoing complex abdominal wall reconstruction with a biologic mesh (2017–2020). Participants were randomized in a 1:1 ratio to receive either Strattice or Permacol biologic meshes. The incidence of complications between groups was not statistically significant (46.0% v. 64.6%; p=0.06). A total of 14 (14.9%) participants experienced a hernia recurrence, with no differences between groups (n=6 in the Permacol group and n=8 in the Strattice group).

Further investigation into the clinical utility of Permacol is needed.

Phasix Mesh™ and Phasix-ST

Phasix-ST is a synthetic mesh product composed of poly-4-hydroxybutyrate cleared through the FDA's 510K process.

Abdelmoaty (2019) reported a retrospective case series of 50 participants undergoing PEH repair.Participant data was collected from a prospective database of Phasix-ST-treated participants who had elective, first-time laparoscopic PEH repair with 1-year follow-up. PEH repair combined with fundoplication was done in 29 participants and PEH repair, fundoplication, and Collis gastroplasty in 21 participants. Phasix-ST mesh was used for crural reinforcement in all participants. The authors report no intraoperative complications with the mesh placement, and a diaphragm relaxing incision was performed in 2 participants. The mean length of hospital stay was 2.8 days, and there was no major morbidity or mortality reported. At 1 year post procedure, recurrent hernia was found in 4 participants. No participants with Collis gastroplasty or a relaxing incision had a recurrent hernia, no reoperations were conducted, and no mesh infection or mesh erosion was reported. These results are promising but provide only limited short-term data from a weak non-comparative trial. Further investigation into the safety and efficacy of Phasix -ST is needed.

Several studies have assessed the use of Phasix and Phasix-ST for complex abdominal wall reconstruction of ventral and incisional hernias. Most are retrospective or prospective, single center, case series, that are underpowered, non-comparative, with short term follow-up (Bueno-Lledo, 2020, 2021; Christopher, 2021; Mesa, 2019; Pakula, 2020; Schecter, 2022; van Rooijen, 2020, 2021, and Vauclair, 2021).

Buell (2021) reported a comparative, retrospective, single center study (n=72) involving the use of Strattice (n=42) vs. Phasix (n=31) for complex abdominal wall reconstruction. The outcomes measured at 60 months included recurrence (38.1% Stratttice vs. 12.9% Phasix; p=0.017), surgical site infection (31% Strattice vs. 12.9% Phasix, p=0.071), and repeat repair (48% Strattice vs. 52% Phasix, (p=0.0736). There was no difference in the length of stay between groups. Phasix demonstrated decreased time to drain removal and lower rates of complications. These results are promising. However, additional larger studies are needed to permit reasonable conclusions about the effect of Phasix on net health outcomes.

Roth (2021 and 2022) reported the results of a prospective, multicenter, open label study of 121 participants with CDC class I wounds that underwent retrorectus or Phasix onlay repair of ventral inguinal hernias. Results were assessed at 30 and 60 months. At the 36-month endpoint 82 participants (67.8%) completed follow up. Recurrence was reported in 17 participants and surgical site infection occurred in 11 participants. At the 60-month endpoint, recurrence rate increased to 22%, surgical site infection rate increased to 10.1%, reoperation rate increased to 14.9%, and only 54 participants (44.6%) completed follow up. There was significant loss to follow up, and the increased adverse outcomes overtime requires further investigation.

Levy (2021) published a prospective, single center case series study of 105 individuals with prior hernia repair and multiple comorbidities that assessed the outcomes of Phasix mesh in complex abdominal wall reconstruction. Thirty percent of the participants had CDC Class II or greater wounds. Eighteen individuals (17%) developed recurrence between 2-36 months, 5 (5%) developed localized superficial infection, 3 (2.8%) required reoperation for non-healing wounds, 6 (6%) developed seroma, and none required mesh removal even when placed into a contaminated or infected field. The lack of comparison group and other methodological weaknesses limit the generalizability of these findings.

Classen (2021) reported a retrospectivea analysis of 2 prospective studies (n=70) using either Phasix or Bio-A in open single stage complex abdominal wall reconstruction. The median follow up time was 20 months. The surgical site infection rate was 45.7% overall, 25.0% in the Phasix group vs. 23.3% in the Bio A group, salvage rate was 58.8%, removal for persistent infection occurred in 10% (7/70), all of which were in the Phasix group, there were no difference in recurrence rates between groups. The need for explantation due to persistent infection exclusively in the Phasix group requires further investigation over a longer follow up period.

Based upon the literature review, the adverse outcomes in the setting of significant loss to follow up requires further analyses to determine whether this is attributed to the Phasix mesh product or the complexity of the wounds requiring complex abdominal wall reconstruction. More robust studies, with well-designed methodologies, and long term follow up are needed to permit reasonable conclusions concerning the effect of Phasix and Phasix-ST for use in CAWR on net health outcomes.

Promogran

Promogran is an acellular dermal collagen product of bovine origin cleared through the FDA's 510K process. The use of Promogran has been evaluated in two RCTs. The first, by Veves and others, involved 276 participants with DFUs randomized to receive treatment with either Promogran (n=138) or moistened gauze (control group; n=138) (2002). At 12 weeks of treatment, there was no statistically significant difference between groups with regard to complete wound closure (p=0.12), in healing for either the subgroup of participants with wounds of less than 6 months duration (p=0.056), or the group with wounds of at least 6 months duration (p=0.83). No differences were seen in the safety measurements between groups. The other study by Vin involved 73 participants with VSUs randomly allocated to receive either Promogran (n=37) or a non-adherent dressing (Adaptic) (n=36). Only 29 participants completed the 12-week study period (39.7%). No intent-to-treat analysis was provided. Because of this, the data reported is not particularly useful.

Further study is required to fully assess the safety and efficacy of Promogran.

PuraPly

PuraPly AM antimicrobial wound matrix is an acellular dermal collagen product composed of a purified collagen matrix of bovine origin containing polyhexamethylenebiguanide (PHMB) cleared through the FDA's 510K process.

Lintzeris (2018) published a case series involving 8 participants with chronic wounds with a variety of etiologies including trauma (n=1), DFUs (n=1), pressure ulcers (n=3), VSUs(n=1), surgical wounds (n=1), and calciphylaxis ulcers (n=1). PuraPly AM was applied once weekly after debridement. The authors reported a mean of 5.8 PuraPly applications were used. A total of 6 wounds had complete healing at an average time to closure of 10 weeks. The 3 wounds that did not completely heal demonstrated improved wound appearance with 100% granulation with an average area reduction 61.4%.

Bain (2020) published the results of the Real-World Effectiveness Study of PuraPly AM on Wounds (RESPOND) registry, a prospective cohort study involving 307 participants with wounds with a variety of etiologies including VSUs (n=67), DFUs (n=62), pressure ulcers (n=45), surgical wounds (n=54), and other wounds (n=79) treated with PuraPly AM. Participants were followed for 32 weeks. The authors reported the mean number of PuraPly AM applications as 5.2. Full wound closure was 52% at 20 weeks, 62% at 26 weeks, and 73% at 32 weeks. Complete wound closure for VSUs was 73%, for DFUs was 51%, for pressure ulcers 62%, for surgical wounds 96% and 67% for other wounds. No adverse events or serious adverse events attributable to PuraPly were reported.

Koullias and others (2022) completed a secondary analysis of the RESPOND registry examining the effects of PuraPly AM treatment in the subgroup of participants with VSUs (n=67) over 32 weeks. The use of PuraPly AM resulted in successful healing defined as > 60% reduction from baseline in wound area and depth, as well as the incidence of wounds demonstrating > 75% reduction from baseline in wound volume. This resulted in successful healing in 73% of participants as demonstrated by reduction in area, depth, and volume. A limitation of the study was the participants included were predominantly white (87%) females (58%).

Menack and colleagues (2022) also completed a secondary analysis of the RESPOND registry in a subgroup of participants with pressure injuries (PI) (n=45). The participants were primarily elderly, with large deep wounds of long duration. The use of PHMB in the management of PI resulted in 91% PAR and 62% rate of healing. While the evidence supports the PuraPly AM as a useful adjunct to SOC for treatment of chronic PIs larger randomized controlled trials are needed to further investigate the comparative effectiveness of this treatment to a wider population and to fully understand the clinical utility of PuraPly AM.

Regeneten

Regeneten is an acellular dermal collagen product of composed of bovine collagen. It has been cleared through the FDA's 510K process.

Clinical use of the Regeneten graft has been described in several studies. The first, published by Bokor and others (2016) described a case series study of 13 participants with intermediate- to high-grade partial thickness rotator cuff tears who were followed for 2 years. At the end of the study 10 participants with evaluable tears had demonstrable improvement in tear appearance on MRI, with 7 completely healed. The remaining 3 participants had continued tears, but with continued improvement. No evidence of tear progression was reported. Clinical symptoms were shown to improve significantly in overall Constant-Murley shoulder scores ($p \leq 0.01$) and Constant-Murley pain score, ($p \leq 0.001$), as well as American Shoulder and Elbow Society (ASES) total score ($p \leq 0.001$), and ASES pain score ($p \leq 0.001$). No postoperative infections and no adverse events associated with the product were reported.

Schlegel reported the results of a prospective case series study involving 33 participants with intermediate-grade or high-grade partial-thickness tears of the supraspinatus tendon treated with Regeneten and followed for 1 year. Intermediate-grade tears were reported in 12 participants and or high-grade tears in 21. Of these, 11 were articular, 10 were bursal, 4 were intrasubstance, and 8 were hybrid). At 12 months, a total of 8 participants (24%) had no visible defect on MRI, 23 participants (70%) had a decrease in tear size by at least 1 grade. Only 1 participant (3%) had a tear that remained unchanged. No tears progressed to full-thickness tears in

the participants who followed the postoperative rehabilitation protocol. No revision procedures were reported. Overall, tendon thickness increased significantly ($p<0.0001$) based upon MRI evidence of new tissue growth over the bursal surface of the supraspinatus tendon. The ASES pain score improved significantly at 1 year, as did the ASES shoulder function score and ASES shoulder index score ($p<0.001$ for all). No device-related significant adverse events were reported.

McIntyre (2019) published the results of a retrospective case series study involving data from participants with partial- and full-thickness cuff tears treated with Regeneten reported in the REBUILD registry. The registry included 203 participants and 173 (85%) had complete 1 year follow-up data. Overall, 90 participants had partial-thickness tears and 83 had full-thickness tears. Of the partial tear group, 16.7% were grade I tears, 37.8% grade II, and 45.5% grade III. Of the full-thickness tears, 4.8% were small, 50.6% medium, 30.1% large, and 14.5% massive. Other surgical procedures were conducted in conjunction with the graft placement, including acromioplasty (89.0%), acromioclavicular joint resection (39.9%), capsular release (12.1%), and biceps surgery (55.6%). At 12 months, the partial-thickness group has a statistically significant improvement with regard to outcomes on the single-assessment numeric evaluation (SANE), Veterans RAND 12-Item (VR-12) physical component, ASES, and Western Ontario Rotator Cuff (WORC) measures ($p<0.05$ for all). For the VAS pain and ASES scores, improvement was 84% and 83%, respectively, which met or exceeded each measure's minimal clinically important difference (MCID). In the full-thickness group, a statistically significant improvement was reported at the 12 month point on the VAS, SANE, VR12 physical component, ASES, and WORC measures ($p<0.05$ for all). MCIDs were met or exceeded on the VAS and ASES tools in 72% and 77% of participants, respectively. Revision surgery for complications was required in 8 participants (4.6%). Indications included progression of a partial thickness tear to a full thickness tear, deep vein thrombosis and adhesive capsulitis, loose mobile graft remnant in the joint, recurrent effusions, and failure to heal. In the partial thickness group, 29 participants (32.2%) required corticosteroid injections in the postoperative period for pain control, and 9 participants (10.8%) in the full-thickness group required injections. The majority of post-operative steroid injections administered in the study were done in 2 centers accounting for 76% of injections. Nine sites did not administer any steroid injections.

Thon (2019) reported on the results of a prospective case series study of 23 participants with large (n=11) or massive (n=12) full-thickness rotator cuff tears treated with Regeneten. In addition to complete rotator cuff repair, participants underwent subacromial decompression (n=19), distal clavicle excision (n=17), biceps tenodesis/tenotomy (n=12), and suprascapular nerve release (n=5). Mean time to postoperative MRI was 13 months, and final ultrasound evaluation was 24 months. Complete healing on both measurements was reported to be 96%, with 2 treatment failures. No difference was found between the two tear groups with regard to final ASES scores ($p=0.69$). There were no postoperative infections or adverse events associated with the device.

The results of these studies are all promising, but the weak methodology and other flaws limit the generalizability of this data to larger populations. Additional studies are warranted to better understand the clinical utility of Regeneten for rotator cuff repair surgery.

Seamguard

Seamguard is a synthetic product composed of polyglycolic acid and trimethylene carbonate cleared through the FDA's 510K process. It has been evaluated in only a few peer-reviewed published articles. The first, by Salgado and others, was a randomized controlled trial evaluating the use of Seamguard vs. extraluminal suturing or fibrin glue for open bariatric surgical procedures (2011). Twenty participants were assigned to each group; however, enrollment in the fibrin glue group was stopped due to serious complications, including leaks requiring surgical intervention. The authors report that no significant differences were found between the Seamguard group and the suturing group. This study was not designed or powered to be a non-inferiority study, so these findings are not particularly useful in understanding the safety and efficacy of Seamguard.

In another study by Albanopoulos and colleagues, Seamguard was compared to staple line suturing in laparoscopic sleeve gastrectomy procedures (2012). This study enrolled 90 participants, 48 who were assigned to the Seamguard group and 42 to the suturing group. As with the Salgado study, the authors reported no significant differences in measured outcomes. One exception to this was a 6.2% complication rate in the Seamguard group vs. no complications in the suturing group.

In 2013, Wallace published the results of a nonrandomized controlled study of 36 participants undergoing pancreatectomy with the addition of Seamguard to the stapled stump closure. This group was compared to 18 historical controls undergoing the same procedure without Seamguard. Postoperative leak rate was reported in 8% in the experimental group vs. 39% in the control group. This study is limited due to its small population, use of historical controls and other methodological issues. The available data addressing the use of Seamguard is limited to weak studies with significant methodological flaws. Further investigation with robust trials is warranted.

Guerrier and others (2018) published the results of a retrospective review of 256 participants undergoing laparoscopic sleeve gastrectomy. Participants received treatment with staple line reinforcement with oversewing (n=28), reinforcement with Seamguard (n=115), or no staple line reinforcement (n=111). Intraoperative staple line bleeding was significantly reduced in the reinforcement group (22.3 vs. 37.8%, $p=0.003$). Gastric leaks were reported in 9 participants (3.52%), with no difference between any reinforcement method (2.7 vs 2.1%, $p=0.54$). The authors did note that oversewing of the staple line was associated with higher incidence of stenosis, a serious complication with significant morbidity and mortality ($p<0.01$). The authors concluded that their study demonstrated that staple line reinforcement does not provide significant leak reduction but does reduce intraoperative staple line bleeding. However, this must be viewed in light of increased risk of stenosis development.

Suprathel

Suprathel is a synthetic copolymer consisting mainly of DL-lactide (>70%), trimethylenecarbonate, and e-caprolactone and was cleared under the FDA's 510k process. The available evidence addressing the use of Suprathel is limited. An RCT involving 22 participants with burn injuries treated with STSG was reported by Schwarze in 2007. Each donor site was randomly selected and was treated with Suprathel or Jelonet. There was no significant difference between the two materials tested regarding healing time and re-epithelization, but a significantly lower pain score was reported for the participants treated with Suprathel ($p=0.0002$). The same group reported the results of another RCT study involving 30 participants with burn injuries (Schwarze, 2008). Wounds from each participant were randomly selected and partly treated with Omniderm and partly treated with Suprathel. There was no significant difference between the two products regarding healing time and re-epithelization. There was a significantly lower pain score for participants treated with Suprathel ($p=0.0072$).

Rashaan (2017) reported the use of Suprathel in a population of 21 children with partial thickness burns. The authors reported a median reepithelialization time of 13 days (range 7-29), and 3 participants required treatment with split skin grafts. There were 7 (33%) participants with wound colonization before application of Suprathel, which increased to 12 (57%) during treatment. Only 1 participant developed a wound infection.

Nischwitz (2021) published the results of a prospective case series study involving 22 participants with chronic leg wounds treated with Suprathel and followed for 8 weeks. Out of the original participant pool, 19 participants completed the trial. No significant difference in average wound size was reported between baseline and 4 weeks ($p=0.074$). The wound size changed significantly between 4 and 8 weeks ($p=0.031$). Overall, the average wound size between baseline and 8 weeks decreased significantly ($p=0.006$). One wound was reported as healed at 4 weeks (5.3%) and two at 8 weeks (15.79%). When stratified by wound age < 12 months and

> 12 months, the overall wound size had a significant reduction for both old and young wounds (p=0.002 and 0.03, respectively). Similar findings were reported for both diabetic (p=0.014) and non-diabetic wounds (p=0.028). No adverse event associated to the intervention had occurred in the study period.

Heitzmann and colleagues (2023) published a prospective intra-individual clinical study in 23 individuals with burn injuries aged 18 to 85 years that compared Suprathel and Jelonet in the treatment of deep dermal burns after enzymatic debridement. Individuals had sustained partial-thickness-to-deep-thickness flame, scald, or contact burns of their hands or feet, with more than 0.3% of TBSA. The outcomes measured were wound healing, patient comfort, and pain. Wounds were divided in 2 areas, one treated with Suprathel and the other with Jelonet. Suprathel was placed on the wounds and gradually cut back as the re-epithelialization progressed until the dressings were completely detached. The Jelonet dressings were changed every 2 days. Wound closure was documented with a mean of 18.44 days for wounds treated with Suprathel, and 18.81 days with Jelonet (p=0.58), with no significant difference in final wound healing timeOnly 1 individual had a second debridement followed by skin grafting. Less pain was reported during the dressing changes with Suprathel compared to Jelonet on day 2 (p<0.001) and day 4 (p<0.0). Additionally, the wound areas treated with Suprathel showed less exudation and bleeding. The authors concluded that both dressings achieve safe and rapid healing after the enzymatic debridement of deep dermal burns of the hands and feet. However, the results of this study require further investigation in the form of more robust and well-designed trials.

Karlsson (2023) reported a retrospective, single center study of 58 pediatric individuals with burns comparing Suprathel (n=30) to Mepilex® Ag (n=28). The outcomes measured were healing time, burn wound infection, need for operations and number of dressing changes. The results showed that healing within 14 days occurred in 17 Suprathel group participants and 15 in Mepilex Ag group participants. A total of 10 participants from each group received antibiotics for suspected burn wound infection, and 2 from each group had skin grafting. The median number of dressing changes were 4 in each group. The authors concluded the results were similar with both Suprathel and Mepilex Ag dressings. However, they noted that these results to be interpreted with caution due to the retrospective study design, and the fact that burns were significantly larger in the Mepilex Ag group.

Overall, the evidence for the use of Suprathel is weak, consisting of small , poorly designed trials. Additional investigation in the form of well-designed and conducted trials is needed to understand the clinical utility of this product.

Surgisis (also known as Biodesign)

Surgisis, also known as BioDesign, is a product composed of decellularized intestinal mucosa of porcine origin and is cleared under the FDA's 510k process. Several forms of Surgisis/Biodesign are available, including Anal Fistula Plug (AFP), 4-Layer Tissue Graft, Dural Graft, Hernia Graft, and others. Cook Medical, the manufacturer of this product changed the name of Surgisis products to Biodesign in 2008. However, the medical literature continues to refer to these products by their former name.

At this time, there are a large number of case series studies published on the use of the Surgisis anal fistula plug (AFP) (Champagne, 2006; Cintron, 2013; Ellis, 2010; Ky, 2008; O'Connor, 2006; Schwandner, 2009; Thekkinkattil, 2009). The vast majority of these involve very small sample sizes and short follow-up times. The uncontrolled nature of these studies minimizes the scientific value of this data.

Several RCTs are currently available addressing the use of Surgisis for the treatment of anal fistulae. The first study, reported by Ortiz et al., involved 43 participants randomized to receive either endorectal advancement flap surgery or insertion of an anal fistula plug (2009). The drop-out rate was greater than 20% for each group. The authors reported that the relative risk for recurrence was 6.4 for those who received the plug intervention during the 1-year follow-up. Additionally, of the 16 who had previous fistula surgery, 9 had recurrence and 8 of these were from the plug group. Overall, the authors concluded that the anal fistula plug was associated with a low rate of fistula healing, especially in individuals with a history of fistula surgery. The second study included 60 participants with perianal fistulas who were randomly assigned to receive treatment with Surgisis (n=31) or a mucosal advancement flap (n=29) (van Koperen, 2011). Both participants and investigators were blinded to group assignment. At a follow-up of 11 months, the recurrence rates were 71% (n=22) in the Surgisis group vs. 52% (n=15) in the mucosal advancement flap group, which was not significantly different. Additionally, no significant differences were reported with regard to postoperative pain, pre- and postoperative incontinence scores, soiling, and quality of life. Senéjoux (2016) reported the results of an open-label, randomized controlled trial comparing seton removal alone (n=52) vs. Surgisis (n=54) in 106 participants with Crohn's disease and at least one ano-perineal fistula tract drained for more than 1 month. The authors reported that fistula closure at week 12 was achieved in 31.5% of participants in the Surgisis group vs. 23.1 % in the control group (p=0.19). No interaction in treatment effect was found when data was analyzed to control for case complexity (p=0.45). Adverse events at week 12 were reported in 17 participants in the Surgisis group vs. 8 controls (p=0.07). The authors concluded that the use of Surgisis was not more effective than seton removal alone. In 2017, Bondi and others published the results of an RCT involving 94 participants with cryptogenic trans-sphincteric anal fistulas assigned to treatment with either Surgisis (n=48) or mucosal advancement flap (n=46). The authors reported that the recurrence rate at 12 months was 66% in the Surgisis group and 38% in the flap group (p=0.006). While anal pain was reduced after operation in both groups, anal incontinence did not change in the follow-up period for either. No differences between the groups were reported with regard to pain, incontinence, or quality of life. The authors concluded that there was a considerably higher recurrence rate after the anal fistula plug procedure than following advancement flap repair.

Several studies have reported on the results from nonrandomized controlled, retrospective trials. Ellis and colleagues described the results of a study that involved 95 control participants who had trans-sphincteric or rectovaginal fistulas repaired via advancement flap repair (2007). The experimental group included only 18 participants who received treatment with Surgisis. The results indicated a significant benefit to the Surgisis procedure. Another study included 80 participants who received treatment with either anal fistula plug or endorectal advancement flap (Christoforidis, 2009). The results of this trial demonstrated that treatment success was close to over twice as likely with the flap procedure compared to treatment with a fistula plug after a mean follow-up period of 56 months. Chung and colleagues (2009) reported on the results of a retrospective study that involved 245 participants who underwent anal fistula repair surgery with either Surgisis (n=27), fibrin glue (n=23), Seton drain (n=86), or an endorectal advancement flap procedure (n=96). The results indicate that the rate of success was similar between the Surgisis group and the endorectal advancement flap group. Hyman and others conducted a study that involved 245 participants who received one of seven procedures, including the Surgisis plug (n=43), endorectal advancement flap (n=4), Seton drain (n=34), fibrin glue (n=5), fistulotomy (n=156), and other unspecified procedures (n=3) (2009). In contrast to the findings of the Chung study, the authors reported that the Surgisis plug demonstrated the lowest success rate, with only 32% healed at 3 months vs. 87% for the fistulotomy group. In 2014, Blom reported on a case series study involving 126 participants with anal fistulae treated in four different hospitals. After a median of 13 months, 30 (24%) of the fistulae had closed with no discomfort or secretion reported. The outcomes in the four hospitals varied from 13% to 33% with similar numbers of participants in each hospital. A success rate of 12% was observed for participants with anterior fistula compared with 32% for those with posterior tracks [HR for successful healing, 2.98] and 41% for those with a lateral internal opening (HR, 3.76). The authors concluded that their study demonstrated low success rates after the first plug-insertion procedure and that anterior fistulae were much less likely to heal compared with fistulae in other locations.

Jayne (2019) reported on the results of an RCT involving 304 participants with anal fistula treated with either Surgisis or 'surgeon's choice" (e.g., fistulotomy, cutting seton, advancement flap or ligation of intersphincteric fistula tract [LIFT] procedure). The authors

reported clinical evidence of fistula healing in 66 participants (54%) in the Surgisis group vs. 66 participants (55%) in the control group at 12 months. Furthermore, MRI data showed fistula healing in 54 participants (49%) in the Surgisis group vs. 63 participants in the control group. Overall, 12-month clinical healing rates were 55% in the Surgisis group vs. 64%, 75%, 53%, and 42% in the cutting seton, fistulotomy, advancement flap and LIFT procedure groups, respectively. The authors commented that overall, there was no significant difference between the use of Surgisis and other procedures.

A meta-analysis was reported by Lin (2019) that included 11 studies comparing the use of Surgisis to rectal advancement flap (RAF) for anal fistula repair in 810 participants. They reported that the pooled analysis indicated that there was no significant difference between the use of Surgisis and RAF in terms of healing rate, recurrence rate and incidence of fistula complications. However, the pooled results of the 4 RCTS and 1 series study with long-term follow-up revealed that the RAF group had a significantly higher healing rate (OR, 0.32; p=0.01) and lower recurrence rate (OR, 4.45; p=0.009) than the AFP group. These results appear to support the use of RAF over Surgisis for anal fistula repair.

Jayne (2021) published the results of an open-label RCT involving 304 participants undergoing anal fistula repair. Participants were assigned to treatment with either Surgisis anal fistula plug (n=152) or surgeon's preference (advancement flap, cutting seton, fistulotomy, Ligation of the Intersphincteric Fistula Tract procedure, n=152). At 12 months, the authors reported no significant differences between groups with regard to rate of clinical healing (54% in the Surgisis group vs. 55% in the surgeon's preference group, p=0.83). Similar findings were reported with regard to MRI-confirmed healing (49 vs. 57%, respectively, no p-value provided). Additionally, no significant differences between groups were reported at 12 months on the St. Mark's incontinence score (p=0.48), complication rate (23% vs. 20%, p=0.6), or rate of reintervention (23%. Vs. 22%, p=0.96). These results indicate that the use of Surgisis is equivalent to other surgical approaches to anal fistula repair.

Due to the conflicting evidence discussed above, further data is needed in the form of large, well-done, double-blind RCTs in order to properly understand the efficacy of Surgisis for the treatment of anal fistulas.

Unlike the anal fistula plug product discussed above, Surgisis Gold is provided in larger sheets. Sarr and others (2014) conducted an RCT involving 380 participants with body mass index (BMI) ≥ 35 kg/m^2 scheduled to undergo open Roux-en-Y gastric bypass surgery. Participants were randomized to receive standard suture closure alone or Surgisis Gold as a reinforcing adjunct. The authors reported that complications were more common in the Surgisis Gold group with significantly more wound events and seroma formation compared with the suture closure alone group. At final follow-up of 2 years post-procedure, 32 of 185 (17%) participants in the Surgisis Gold group and 38 of 195 (20%) in the control group developed an incisional hernia (p=0.6). Based on these findings, it would seem that the use of Surgisis Gold is not warranted, and further investigation is needed regarding the safety and efficacy of this product.

Korwar (2019) retrospectively reported the treatment of PEH in 154 consecutive participants who underwent standardized laparoscopic suture repair of the hiatus with Surgisis reinforcement. Follow-up barium swallow was performed in 122 participants (79.22%). Symptomatic recurrence was noted in 25 participants (28.73%), and recurrence on barium swallow was noted in 25 participants (20.4%). Both symptomatic and barium swallow recurrence were reported in 10 participants (12.98%). The reoperation rate was 3.25%. The authors concluded that use of Surgisis Biodesign for PEH repair is safe. They further commented that there was a high recurrence rate in long-term follow-up, but that the majority of recurrences are small, asymptomatic, and the reoperation rate is very low.

Surgisis Biodesign was also described in the repair of pelvic floor reconstruction following levator abdominoperitoneal excision of the rectum (Thomas, 2019). This retrospective case series study involved 100 participants, for whom 1-, 2-, and 5-year mortality rates were 3, 8 and 12%, respectively. The authors reported that 33 perineal wounds had not healed by 1 month, but no mesh was infected, and no mesh needed to be removed. Only 1 participant developed a symptomatic perineal hernia requiring repair. On review of imaging, an additional 7 asymptomatic perineal hernias were detected. At 4 years the cumulative radiologically detected perineal hernia rate was 8%.

Ravo (2019) described the results of a trial of 104 participants with inguinal hernia repair with a continuous suture of transversalis to transversalis fascia repair reinforced with Surgisis. Long term follow-up was scheduled at 1 week, 1 month, 1 year, 3 years, 7 years, and 10 years, and was achieved in 100%, 100%, 99%, 93%, 89% and 85% of the participants, respectively. The authors reported a recurrence rate of 1.9% (2 participants, one at 1 week in a participant with bilateral IH and one at 7 years). The mean recovery time was 1.2 days (range 1-5 days). Mortality was 0(0%).

In 2021 Alexandridis and others reported the results of a retrospective case series involving 155 participants with pelvic organ prolapse treated with Surgisis. A total of 138 (89.0%) participants completed the 3-month clinical visit, with 12 of the 17 participants not seen being contacted by telephone and included in the analysis of complications. At 3 months, 22 participants (15.9%) had Pelvic Organ Prolapse Qualification system (POP0Q) stage ≥ 2. The overall recurrence rate for Surgisis-treated defects was 11.6%. Reoperations were reported in 13 (8.4%) participants due to prolapse. Additionally, 7 participants experienced prolapse-related symptoms postoperatively, but had no record of reoperation. This data represents a subjective failure rate of 12.9%. Perioperative and postoperative complications occurred in 56% of participants. The most common complications were urinary (n=28) and pain (n=18). Major complications were reported in 8 participants (5.3%). Persistent complications at 3 months were reported in 28% of participants, including vaginal deformations, dyspareunia, stress urinary incontinence, urge urinary incontinence, and pain. Statistical analysis for recurrence identified a significant effect only for previous prolapse surgery at the same compartment as the Surgisis application (p=0.028). Other significant predictors for complications included lower age (p=0.034), smoking (p=0.022) and longer duration of surgery (p=0.003). The authors concluded, "The relatively high recurrence rates do not suggest a clear benefit from SIS graft use."

Additional evidence is needed from larger, well-designed trials to fully understand the safety and efficacy of Surgisis/Biodesign for conditions other than anal fistulas.

Talymed

Talymed is a synthetic product composed of poly-N-acetyl glucosamine (pGlcNAc) isolated from microalgae and is cleared under the FDA's 510k process. At this time, only a single RCT is available addressing the use of Talymed (Kelechi, 2011). In this reviewer-blinded trial, 82 participants with VSUs were randomized to receive either standard care (n=20) or to 1 of 3 groups that received standard treatment combined with different treatment frequencies with Talymed: (1) applied only once, (2) applied once every other week, or (3) applied once every third week. Seven participants were lost to follow-up, 5 from the 1 application group and 2 from the every 3-week group. Additionally, another 4 participants were withdrawn from the study, 3 from the 1 application group and 1 from the every 3 weeks group. This left 62 participants in the experimental group and 20 in the control group. At 20 weeks, the authors report that 45.0% (n=9 of 20) of participants receiving standard care alone had complete healing, while 45.0% (n=9 of 20), 86.4% (n=19 of 22), and 65.0% (n=13 of 20) of participants receiving Talymed only once, every other week, and every 3 weeks, respectively, had complete healing. This single study is insufficient to allow proper evaluation of the safety and efficacy of Talymed.

TIGR Matrix Surgical Mesh

TIGR Matrix Surgical Mesh is a synthetic polymer made of lactide, glycolide, and trimethylene carbonate and is cleared under the FDA's 510k process. It is indicated for use in the reinforcement of soft tissue plastic and reconstructive surgery, or for use in procedures involving soft tissue repair, such as for the repair of hernias or other fascial defects.

Hansson and colleagues (2020) reported a prospective, single-blind, clinical trial of 24 individuals (n=48 breasts) with bilateral mastectomy and immediate breast reconstruction. Participants were randomized to receive biological Veritas Collagen Matrix on one side and synthetic TIGR Matrix Surgical Mesh on the other side. During the 12-month follow-up the 2 meshes yielded significantly different esthetic results and asymmetry. Due to this finding, recruitment to the study was terminated. No participants were lost to follow-up at 12 months and 24 breasts in each group had an analysis of complications at 1 year postoperatively. All mastectomies were nipple-sparing. The most common complication was seroma formation (38% in the Veritas group vs. 3.8% in the TIGR group, p=0.011). All TIGR meshes were completely integrated during the exchange to a permanent implant, the Veritas meshes were poorly integrated in the participants with seroma. The frequency of total implant loss (stage I + II) in the Veritas mesh group was 8.5% vs. 2% in the TIRG group (p=0 .083). There were 2 implant losses and re-operations which were suspected to have been caused by penetration due to thin mastectomy flaps in the same participant. The authors concluded that there is a higher risk for complications, particularly seroma and implant loss, with Veritas vs. TIGR. However, more robust studies with larger sample sizes are needed to confirm these finding with a high degree of certainty.

Paganini and colleagues (2022) reported the results of a blinded, randomized, prospective trial that compared patient-reported outcomes after immediate breast reconstruction with TIGR mesh and Veritas mesh using the compared materials in the same participant. Twenty-four participants were recruited and all had a prophylactic bilateral mastectomy and a dual-plane reconstruction. There were no capsular contractures in either group at 5 years. No significant differences between groups were reported with regard to reported outcomes. The authors stated that the two products resulted in different types of reconstructed breasts, but concluded that the study was limited by its small sample size, varying surgical techniques, and variability in the meshes used, therefore more studies are needed to generalize the findings.

Additional larger studies with improved methodologies are needed to demonstrate the clinical efficacy and safety TIGR surgical mesh for use in breast reconstruction.

TiLoop Bra/TiLoop Bra Pocket®

TiLoop Bra (pfm medical; Cologne, Germany) is a synthetic titanised polypropylene ready to use mesh pocket indicated for breast reconstruction/augmentation. The product comes in two forms: TiLOOP Bra Pocket (pre-pectoral), and TiLOOP® Bra (sub-pectoral). It is purported to be superior to polypropylene because the hydrophilic and titanised surface carries a reduced risk of inflammation and thus a decreased tendency towards the formation of scars and shrinkage, resulting in permanent, stable tissue ingrowth and vascularized, flexible, optimal capsule quality.

There are multiple studies published addressing the use of TiLoop. However, this product is not currently available in the U.S and is under review by the FDA.

Tutomesh

Tutomesh is a product composed of decellularized bovine pericardium and is cleared under the FDA's 510k process. The literature addressing this product is sparse at this time. A retrospective review with 41 participants who underwent 52 breast reconstructions using ADMs was reported by Paprottka (2017). Participants received treatment with either EpiFlex (not available in the US, n=15), Strattice (n=21), or Tutomesh (n=16). Follow-up was 36 months (range 12-54). Overall complication rate was 17%, and 7% for the EpiFlex group, 14% for the Strattice group, and 31% for the Tutomesh group. Capsular contracture occurred in 6%, more frequently in this study compared to the current literature. The authors recommended the use of human derived grafting materials (EpiFlex) over those from porcine of bovine sources.

Eichler (2017) published a retrospective, nonrandomized comparative trial involving 54 participants undergoing breast reconstruction procedures using either SurgiMend (n=18) or Tutomesh (n=27) (Eichler, 2017). No difference in complications rates was noted, consistent with other previous reports.

Additional investigation into the safety and efficacy of this product is needed.

Vascu-Guard

Vascu-Guard is a decellularized product derived from bovine pericardium cleared under the FDA's 510k process. Please see the section for Gore® Acuseal Cardiovascular Patch above.

VIA Disc NP

VIA Disc is a processed human nucleus pulposus tissue allograft treated as human tissue for transplantation under the FDA's HCT/P process.

The currently available published literature addresing this product is limited. Beall (2021) reported the results of the VAST RCT involving 218 participants with single- or two-level degenerative disc disease assigned to treatment with either saline injection (n=39), conservative care (n=39), or VIA Disc (n=140). A total of 36 participants (17%) were lost to follow-up or had withdrawn from the study by the 12 month follow-up point (n=7 [18%] saline group, n=12 [30%] conservative group, and n=17 [12%] VIA Disc group), leaving 182 participants completing the trial. There were 58 participants treated at least one intravertebral level outside of the predefined levels of degeneration for inclusion. Younger participants were reported to have had a more favorable outcome vs. older participants in regard to improvement in Oswestry Disability Index (ODI) for participants less than the median age (32 years old, p=0.004). Clinically meaningful improvements were observed in the VIA Disc group, with a mean reduction in ODI of 27 at 12 months (no p-value provided). ODI-based function was noted to have worsened in the conservative care group during the first 3 months and all participants in this group crossed over to the VIA Disc group in an unblinded fashion. Results for both VIA Disc groups were similar at 12 months. Mean pain reduction as represented by change in Visual Analog Scale of Pain Intensity (VASPI) at 12 months was reported to be 30.5, 34.0, and 46.7 for the saline, VIA Disc, and conservative/crossover groups, respectively. Mean functional improvement per ODI was 23.9, 27.4, and 36.5 respectively (no p-values provided). No differences between participants treated at a single vs. two levels was noted. A modified intention-to-treat analysis indicated significant differences between the VIA Disc vs. saline groups, with a ≥ 15-point reduction in ODI measures (p=0.030). No significant differences were found between groups with regard to number of participants achieving a 50% reduction in pain at 12 months (p=0.467). In an ad hoc analysis of responders in all groups, participants in the VIA Disc and conservative/crossover groups achieved a statistically significant reduction in pain vs. saline group participants (p=0.022). There were 66 (29.8%) total adverse events in the VIA Disc group vs. 5 (13.2%) in the saline group (no p-value provided). Twenty-three potentially VIA Disc-related events were reported, vs. none in the saline or conservative treatment only groups. The conservative/crossover group experienced 7 VIA Disc-related events (8.6% of participants in the crossover group). Most events in the VIA Disc group were musculoskeletal and connective tissue related, with 41 total events (22.0%) and 14 VIA DISC-

related events (9.2%). The most common event was pain. In the saline group no adverse events were reported, while the conservative/crossover group reported back pain as a related event in 2.9% of participants.

A total of 11 serious adverse events were reported in the VIA Disc group (3.5%), with 6 considered possibly related to the treatment and/or procedure. Reported events included pain, back pain, bacteremia, and osteomyelitis. No serious events were reported in the saline group or conservative treatment only groups. One serious adverse event (2.6%) was reported in the conservative/crossover group (p=0.832). The 1 SAE in the crossover group was considered not related to treatment or procedure. The results of this trial indicate some potential benefit to the use of VIA Disc, but several methodological flaws limit the generalizability of this trial, including significant loss to follow-up, cross over of a large percentage of the control group to active treatment, loss of blinding, and others.

Hunter and colleagues (2021) published the results of a post hoc analysis of the VAST trial data exploring it stratified by age. They reported that participants younger than 42 years of age experienced significantly more improvement from treatment with VIS Disc than those older than 42 when compared to those in the saline treatment group. Furthermore, they noted that in participants older than 42 years of age, no differences between groups were seen with regard to functional benefit. As noted above, the VAST trial has several significant methodological flaws and additional investigation is warranted to assess the clinical utility of VIA Disc.

Veritas

Veritas is a decellularized product derived from bovine pericardium cleared under the FDA's 510k process. The available evidence addressing Veritas is currently limited to a single RCT of 94 participants assigned to treatment with either anterior colporrhaphy alone vs. colporrhaphy reinforced with Veritas bovine pericardium graft (Guerette, 2009). This study had significant loss to follow-up, with only 72 of 94 (76.6%) participants at the 1-year time point and 59 of 92 (64.1%) at the completion of the study at 2 years. The authors report no significant differences between groups.

Quah (2019) published the results of a retrospective, non-randomized controlled trial involving 215 participants undergoing mastectomy and implant-based reconstruction procedures with either Veritas (n=36) or TiLOOP® Bra (n=179), a product not currently approved for use in the U.S. In the Veritas group, 22 participants underwent unilateral procedures and 7 underwent bilateral procedures. In the TiLOOP group 61 participants underwent unilateral procedures and 59 participants underwent bilateral procedures. The authors reported that the Veritas group had a higher rate of postoperative complications when compared with the TiLOOP group (54% vs. 14%, respectively; p<0.01%). This included higher rates seroma (51.4% vs. 1.7%, p<0.01), nonintegration of mesh (51.4% vs. 1.6%, p<0.01), implant rotation (16.2% vs. 1.6%, p<0.01), infection (18.9% vs. 2.1%, p<0.01), and wound breakdown (10.8% vs. 0.5%, p<0.01). Additionally, when compared to the TiLOOP group, the Veritas group also had a higher rate of major interventions (35.1% vs. 7.8%, p<0.01), minor interventions (18.9% vs. 2.2%, p<0.01), implant loss (8.1 vs. 1.7%, p=0.05), and unplanned return to theater (27% vs. 6.1%, p<0.01). The results of this trial indicate that Veritas, at least when compared to TiLOOP Bra, results in significantly poorer outcomes.

Additional investigation into the clinical utility of Veritas is warranted.

Xelma

Xelma consists of amelogenin proteins purified from porcine teeth, propylene glycol alginate (PGA), and water. It has not yet received marketing approval or clearance by the FDA. Amelogenin is a cell adhesion protein, and when suspended in a gelatinous matrix has been proposed to promote cellular growth. The use of Xelma was reported in a single-blind randomized trial involving 123 participants with VSUs (Vowden, 2006). Participants were assigned to receive treatment with either Xelma plus compression therapy (n=62) vs. a mixture of PGA and water plus compression therapy (n=61) and were followed for 12 weeks. The authors of this study state that Xelma outperformed the control group in multiple factors, including percentage of wound size reduction. However, no statistical analysis is presented to support these claims. No data on complication rates was provided. Further investigation into the clinical safety and efficacy is warranted.

XenMatrix

XenMatrix is an acellular dermal collagen product of bovine origin cleared through the FDA's 510K process in May 2014. It is specifically indicated for the repair of colon, rectal, urethral, and vaginal prolapse; reconstruction of the pelvic floor; and procedures such as sacrocolposuspension and urethral sling.

Ilahi (2023) reported the results of a prospective case series study involving 75 participants undergoing ventral/incisional midline hernia repair using XenMatrix. The authors reported on surgical site occurrence in the first 45 days post-implantation and length of stay, return to work, hernia recurrence, reoperation, quality of life, and surgical site occurrence at 1, 3, 6, 12, 18, and 24 months. A total of 16 participants (21%) did not complete the study, resulting in complete data for 59 participants (79%). Overall, hernia recurrence was reported to be 5.8%. Device-related adverse events occurred in 4.0% of cases, and reoperation in 10.7%. Only one case of mesh infection was reported (1.3%) and no graft removal were needed. Surgical site occurrence requiring intervention within 45 days post-implantation was reported in 14.7% of participants, and 20.0% >45 days post-implantation. Surgical complications were evaluated according to the Clavien–Dindo system, with very few grade IVa, IVb, and V hernia-related complications (3%). Complications judged to be grade IIIa or IIIb occurred 37% of participants. The most common hernia-related complications seroma (n=14), bowel obstruction (n=9), pain (n=8), Ileus (n =4), incisional cellulitis (n=4), and surgical site infections (n=4). This study is impaired by weak methodology, including low power, lack of blinding and comparison groups, and others. Further, the significant loss of complete data makes these results difficult to interpret.

Other studies involving the use of XenMatrix are discussed elsewhere in this document for abdominal wall defect repair (Huntington, 2016; Rosen 2013). Those studies were weak and the results are not generalizable to a wider population.

Overall, the evidence addressing the use of XenMatrix in the clinical setting is limited and not generalizable to a wider population. Additional evidence addressing the clinical utility of this product from large, well-designed, and conducted trials is needed to fully assess the clinical utility of this product.

Recommendations from Authoritative Organizations

In 2020 the American Academy of Ophthalmology published a report titled *Bioengineered Acellular Dermal Matrix Spacer Grafts for Lower Eyelid Retraction Repair*. In this document they reviewed the available literature and provided recommendations for the use of such products. They observed that there is no level I evidence available on this issue, and that the existing level II and level III studies have variable primary end points, study design limitations, and only short-term follow-up. Their conclusions included "…the materials used may fill an important gap in care for patients for whom no acceptable alternatives exist, but long-term safety and efficacy remain unknown."

Background/Overview

Regulatory Processes for Grafting Materials

Soft tissue grafting materials find their way to U.S. market through several regulatory pathways. Oversight for all these pathways is provided by the U.S Food and Drug Administration (FDA).

The first and most rigorous regulatory path is the Premarket Approval (PMA) Process, which is detailed in the Code of Federal Regulations Title 21 Part 860. Devices required to undergo this process are those deemed to present the most risk of harm to the public. The PMA process involves several steps of pre-clinical and clinical trials (Phase 0 through III). Each step is reviewed by the FDA to evaluate safety and efficacy data. If the FDA finds the data presented acceptable, a larger and more robust study is authorized until Phase III trials have been completed. Devices which pass Phase III are deemed "Approved" by the FDA and may be marketed in the U.S. This path was used in only a small minority of products addressed in this document. More information regarding the PMA process can be found at: https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma.

The "510K" process, also referred to as the Premarket Notification (PMN) process, is named after Section 510(k) of the Food, Drug and Cosmetic Act. This section of the Act requires manufacturers of devices that qualify to notify the FDA of their intent to market a medical device at least 90 days in advance. This law applies to any device that: (1) is not required to undergo review under another pathway, (2) was not already in commercial distribution prior to May 28, 1976, and (3) is to be introduced into commercial distribution for the first time or reintroduced in a significantly changed or modified form that alters its safety or effectiveness. The regulations stipulate that devices applying for 510K clearance must demonstrate that they are substantially equivalent to a device with prior PMA approval or marketed prior to May 28, 1976. No significant new data addressing safety or efficacy is required g this process. Devices with this type of review may or may not have undergone rigorous clinical testing to establish the presence or absence of these attributes. Devices passing through this pathway are referred to as "cleared." More information regarding the 510K process can be found at: https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k.

A Humanitarian Device Exemption (HDE) is a regulatory path similar to a PMA but is exempt from the effectiveness requirements of sections 514 and 515 of the Code of Federal Regulations Title 21 Part 860, which details the PMA process. A device approved under an HDE is referred to as Humanitarian Use Device (HUD). An HUD is defined as a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year." The HDE process is intended to facilitate the development of devices that could benefit individuals with rare conditions for whom medical devices are unlikely to be developed through the PMA process. Devices covered under this regulation are exempt from many of the PMA requirements, but have certain restrictions placed on their use outside the investigational setting. More information regarding the HDE process can be found at: https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/hde-approvals.

There is a specific pathway available for biological tissue derived from human sources deemed as "minimally manipulated." The FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) is addressed in the Code of Federal Regulations Title 21, volume 8, Part 1271 "Human Cells, Tissues, And Cellular and Tissue-Based Products." These regulations detail the use of human autologous and allographic tissues for transplantation. They specify that "minimally manipulated" tissues undergo proper safeguards to prevent infection or other safety hazards. It should be made clear that products that reach the market through the HCT/P process do NOT require any testing to prove clinical safety or efficacy. Thus, their performance when used in the treatment of human participants may or may not have been tested in clinical trials. Human-derived tissues that are deemed to have been more than minimally manipulated are required to undergo one of the other regulatory pathways described above. HCT/Ps are regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act, which can be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271.

In the vast majority of cases, soft tissue grafting products are considered devices by the FDA. However, in some rare cases, based upon the composition, preparation, and method of delivery, some products may be considered drugs and reviewed under the FDA's drug regulatory process. Only one product addressed in this document has been so treated and is designated an Orphan Drug. This designation for drugs is similar to the HDE designation for devices. The Code of Federal Regulations Title 21, Part 316 details the "Orphan Drug" process and defines an Orphan Drug as a drug intended for use in a rare disease or condition as outlined in section 526 of the Act. As with HDEs, the Orphan Drug designation is intended to facilitate the development of drugs that could benefit individuals with rare conditions for whom drugs are unlikely to be developed through other regulatory processes. More information regarding the Orphan Drug designation can be found at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm.

Skin Wound Care

The skin is the largest organ of the body. It is composed of two layers, the epidermis, and the dermis, and provides functions critical to survival. The skin acts as a protective barrier to fluid losses and dehydration and it protects against infection and injury by providing a barrier to repel bacteria and other organisms. The skin provides sensory contact with our environment that tells us whether we are feeling light touch, pressure, pain, heat, or cold. Damage to the skin that is extensive or prolonged may interfere with these functions or with those of other body systems and may become life-threatening in some circumstances.

The treatment of burns and other wounds that have failed to heal despite conservative measures, referred to as chronic wounds, creates a significant burden on the population in terms of pain, disability, and decreased quality of life. Chronic wounds may be due to the effects of diabetes, venous insufficiency to the extremities, pressure due to prolonged periods in the same body position, and other types of skin injuries. They can be difficult to treat and may require treatment with various coverings, such as skin grafts or other materials to prevent infection, maintain an environment conducive to healing, or provide a medium for re-growth of new skin. Such coverings come in a wide array of types including synthetic materials, tissues from the individuals themselves (autologous), human donors (allogeneic), or from animals such as cows and pigs (xenographic), or any combination of these materials (composites).

In 2021the American Diabetes Association published Standards of Medical Care in Diabetes. The standards were updated in 2023 to include Foot Care standards with the following recommendation regarding DFUs:

> 12.32 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy.
>
> Level of evidence A: Defined as Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including:

- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in the analysis

Surgical Reinforcement Procedures

In a wide variety of surgical procedures, there may be a need for additional reinforcement of soft tissues to strengthen the structures being repaired, such as in abdominal wall repair or orthopedic reconstruction procedures. Traditionally this task is undertaken with the use of allogeneic cadaver-derived grafts or synthetic materials such as polypropylene and Gore-Tex®. However, in some cases such materials may not be appropriate, and other materials have been sought.

In other circumstances, the use of grafting materials has been suggested as substitute for surgery.

Product types:

Synthetic Products

Synthetic treatments include various forms of skin-like coverings, barriers, and devices to augment cartilage and other connective tissues. This category includes wound dressings, silicone/nylon membranes and material to augment or replace cartilage, tendons, and ligaments.

Completely synthetic wound dressings and other grafting products (e.g., Biobrane) are composed of man-made materials to form a covering for wounds. This type of product may consist of a wide array of materials including silicone, nylon, polypropylene, and polyester.

Allogeneic Products

There are currently several different types of allogeneic (human-derived) wound care products available. One type involves the use of donated human cadaver skin which is then treated with various methods to remove the cellular material and deactivate or kill pathogens (e.g., AlloDerm, GraftJacket, and Neoform Dermis). This process leaves only the collagen protein scaffold, which has been proposed as an acceptable medium for which new skin cells from the individual can populate and grow into when placed over a wound site.

Another type of allogeneic product includes composite products that may contain human skin cells, keratinocytes and/or fibroblasts (depending upon the product), which are imbedded into a decellularized collagen protein scaffold derived from a xenographic source (e.g., Apligraf, OrCel). Some of these products may also consist of layers of synthetic materials like silicone, nylon, or polyglactin (e.g., Dermagraft).

Xenographic and Xenographic-Related or Derived Products

Many wound care and reconstructive products are made from materials derived from various animal sources including cow, horse, and pig tissues. Most of these products are created by harvesting living tissues (e.g., skin, intestines, tendons, etc.) from a donor animal, which are then processed to remove the cellular content and leave only the collagen protein scaffold. As with such allogeneic products, this scaffold is intended to act as a welcoming environment into which new autologous cells (e.g., skin, tendon, and cartilage) may grow. Most xenographic products are composed of the decellularized collagen scaffold alone (e.g., Collamend, Cuffpatch, Mediskin, Oasis, OrthoADAPT, Pelvicol, Pelvisoft, PriMatrix, Surgisis, Unite).

Xenographic materials have been proposed for many applications including reconstruction procedures of the breast, pelvic floor, abdominal wall, tendons, and others. These products are sewn onto the soft tissues where they are needed to provide support and strengthen the underlying structures. This occurs by the xenograft acting as a bed for new growth of autologous tissue.

Another type of product is a substance made by or derived from xenographic sources. One such product is honey, which has been proposed as a topical treatment for a wide variety of skin conditions.

Composite Products

Composite products are created from a variety of materials of combined origins. Such products usually combine an allogeneic or xenographic collagen-based product with a synthetic one (for example, Avaulta Plus, Integra Matrix, and Integra Bilayer Matrix). Additionally, the development of advanced in vitro culturing techniques has allowed the development of new products which combine human dermal cellular materials with those derived from animals (e.g., Epicel). These products involve the harvesting of human epidermal cells (either from the individual being treated or from donor tissue) which are then cultured with animal cells to produce sheets of biosynthetic skin which have been proposed for use in treating human skin conditions.

Bioengineered autologous skin-derived products

Bioengineered autologous skin-derived products (for example, MyOwn Skin, SkinTE) involve the harvesting of skin from an individual, which is then processed in a lab where it is altered in a manner that has been proposed to enhance it as a healing vector for wounds.

In a 2022 Cochrane review, Thompson and colleagues compared licensed bioengineered nerve conduits or nerve wraps used in surgical repair of traumatic peripheral nerve injuries of the upper extremity, to the current gold standard surgical technique (microsurgical repair with use of nerve autografts). The authors concluded that the evidence does not support the use of nerve repair devices over standard repair. There was significant heterogeneity in study methodologies, participants, injury pattern, repair timing, and outcome measures across the studies of the bioengineered devices, this made comparisons unreliable. The studies were also small and at risk of bias which made the overall certainty of evidence low or very low. The data provided some evidence that more people may experience adverse events with the use of bioengineered devices than with standard repair and may also be at increased need for revision surgery. There was no data for a primary outcome measure (muscle strength) at 24 months and sensory recovery was uncertain. Additional trials with improved methodologies and a minimum of 12 months' follow-up are needed to analyze the safety and clinical efficacy of bioengineered nerve repair devices.

Definitions

Bullous keratopathy: A condition where small fluid-filled vesicles, or bullae, form within the cornea.

Complex Abdominal Wall Reconstruction: A surgical procedure to repair extensive or recurrent hernias, hernias resulting from previous surgeries, those affecting multiple areas of the abdominal wall, or associated with complicating factors like infections, compromised or damaged tissues, or contamination. The purpose of the procedure is to restore functional and structural integrity of the abdominal wall, it may involve moving muscles and skin flaps, implantation of synthetic, biologic, or composite mesh, and may require surgical component separation techniques to ensure a tension-free repair to reduce the risk of failure and recurrence.

Conjunctiva: A clear, thin membrane that covers part of the front of the eye and lines the inside of the eyelids.

Corneal melt: Keratolysis, or sterile melting of the cornea, is a condition characterized by a progressing thinning of the cornea, leading to perforation.

Diabetic foot ulcer (DFU): A potential complication of diabetes due to prolonged elevated blood sugar levels which can damage blood vessels and nerves throughout the body. A DFU is a slow healing full-thickness wound, through the dermis, below the ankle on a weight-bearing or exposed surface in an individual with diabetes. DFUs are categorized as being neuropathic, ischemic, or neuroischemic (mixed). The most common sites are the plantar surface of foot and the toes. DFUs are caused by repetitive injury to an insensate or vascularly compromised foot and may lead to amputation.

Epidermolysis bullosa (EB): A disease characterized by the presence of extremely fragile skin and recurrent blister formation, resulting from minor mechanical friction or trauma.

Equine-derived decellularized collagen products (e.g., OrthADAPT and Unite): This is a type of product derived from purified tissues which are derived from horses. It has been proposed that this type of technology may be used for the repair and reinforcement of soft tissues such as tendons and ligaments, as well as the treatment of skin wounds.

Frey's Syndrome: A condition occurring in some individuals after removal of the parotid salivary gland, in which nerve damage results in flushing and sweating on one side of the face when certain foods are consumed.

Hernia meshes of non-biologic origin: These products are either synthetic or biosynthetic:

> *Biosynthetic*: Mesh products are made from resorbable synthetically derived meshes with resorption profiles between 6 and 36 months. Theoretically, this allows native collagen deposition for wound strength and durability while reducing the risks of chronic mesh infection affiliated with permanent synthetic alternatives.
>
> *Synthetic*: Mesh products are made from either woven extruded monofilament (for example, polypropylene or polyester) or created from expanded polytetrafluoroethylene. They may be subcategorized by; weight/density, material, composition, pore characteristics, and mechanical parameters. Products in this category are permanent and are not absorbed by the body.

Limbal stem cell deficiency: A condition characterized by decreasing function of the stem cells within the epithelial layer of the cornea.

Nerve conduits: A bioengineered product used in the repair of traumatic peripheral nerve injuries. The product is used in the reconstruction of a gap defect by placing proximal and distal nerve stumps into a tubular construct. Conduits are intended to replace the need for nerve autograft harvest.

Nerve wraps: A bioengineered sheet of material used in the repair of traumatic peripheral nerve injuries. The product is formed into a tube around approximated nerve stumps, it's purpose is to minimize fibrosis and scarring, and provide a narrow gap to facilitate bridging across the repair site.

Neurotrophic keratitis: A degenerative disease of the eye due to a loss of corneal sensation leading to progressive damage to the top layer of the cornea.

Penetrating keratoplasty: A surgical procedure that is conducted during corneal transplantation.

Pterygium: A growth involving the conjunctiva of the eye that appears as a growth or bump on the side of the eye near the nose.

Standard hernia repair: A surgical procedure that is done to treat bulges of organ or intra-abdominal tissue through a weakness in the abdominal wall (hernias) when they are relatively small in size, technically simple to repair, and at low risk for complications. The procedure repairs the local defect and supports the weakened abdominal wall. The procedure can be done via laparoscopic approach and may use synthetic, biological or composite mesh to reinforce the abdominal wall.

Stevens-Johnson syndrome: Also known as toxic epidermal necrolysis, is a rare, serious disorder of the skin and mucous membranes that is characterized by painful rash in its mild form and severe blisters and skin peeling in its more advanced form.

Vancouver scar scale: An objective and validated method for describing burn scars that includes a summation of scar characteristics including pigmentation [0-2], vascularity [0-3], pliability [0-5], and height [0-3], normal skin is given a score of 0 for each category.

Wound infection: A wound with at least some clinical signs and symptoms of infections such as increased exudates, odor, redness, swelling, heat, pain, tenderness to touch, and purulent discharge; quantitative culture is not required.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Application of amniotic membrane-derived grafts or wound coverings for ophthalmologic conditions:

When services are Medically Necessary:

CPT	
65778	Placement of amniotic membrane on the ocular surface; without sutures
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
65780	Ocular surface reconstruction; amniotic membrane transplantation, multiple layers
HCPCS	
Q4290	Membrane Wrap-Hydro, per square centimeter
V2790	Amniotic membrane for surgical reconstruction, per procedure [vision services]
ICD-10 Diagnosis	
C69.00-C69.02	Malignant neoplasm of conjunctiva
C69.10-C69.12	Malignant neoplasm of cornea
H11.001-H11.069	Pterygium of eye
H16.001-H16.079	Corneal ulcer
H16.231-H16.239	Neurotrophic keratoconjunctivitis
H18.10-H18.13	Bullous keratopathy
H18.40-H18.599	Corneal degeneration, hereditary corneal dystrophies
H18.831-H18.839	Recurrent erosion of cornea
H59.091-H59.099	Other disorders of the eye following cataract surgery
L51.1	Stevens-Johnson syndrome

T26.10XA-T26.12XS	Burn of cornea and conjunctival sac
T26.60XA-T26.62XS	Corrosion of cornea and conjunctival sac

When services are Not Medically Necessary:
For the procedure codes listed above for all other diagnoses not listed.

Application of skin substitutes and soft tissue grafts:

When services may be Medically Necessary when product criteria are met:

CPT

15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk)
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when specified as implantation of biologic implants for soft tissue reinforcement in tissues other than breast and trunk]

HCPCS

C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof

ICD-10 Diagnosis

	All diagnoses

When services are Not Medically Necessary:
For the procedure codes listed above when product criteria are not met.

When services are Investigational and Not Medically Necessary:

For the procedure codes listed above when the code describes application of a product indicated in the Position Statement section as investigational and not medically necessary.

When Services are also Investigational and Not Medically Necessary:

CPT	
31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral [when specified as using a skin/tissue substitute such as Cymetra]
46707	Repair of anorectal fistula with plug (eg, porcine small intestine submucosa [SIS])
0627T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; first level [VAST, Via Disc]
0628T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; each additional level [VAST, Via Disc]
0629T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; first level [VAST, Via Disc]
0630T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; each additional level [VAST, Via Disc]

ICD-10 Diagnosis	
	All diagnoses

Products

When services may be Medically Necessary when criteria are met [for AmnioBand, Apligraf, BioVance, EpiCord, EpiFix (sheet or membrane form), Grafix PRIME, GraftJacket, Kerecis, mVASC, Oasis, OrCel, PriMatrix and Dermagraft]:

HCPCS	
A4100	Skin substitute, FDA cleared as a device, not otherwise specified [when specified as OrCel for epidermolysis bullosa only; or when specified as mVASC for diabetic foot ulcers only]
C9399	Unclassified drugs or biologicals [when specified as OrCel for epidermolysis bullosa only; or when specified as mVASC for diabetic foot ulcers only]
Q4100	Skin substitute, not otherwise classified [when specified as OrCel for epidermolysis bullosa only; or when specified as mVASC for diabetic foot ulcers only]
Q4101	Apligraf, per square centimeter
Q4102	Oasis Wound Matrix, per square centimeter
Q4106	Dermagraft, per square centimeter [for diabetic foot ulcers and epidermolysis bullosa only]
Q4107	GraftJacket, per square centimeter
Q4110	PriMatrix, per square centimeter
Q4124	Oasis Ultra Tri-Layer Wound Matrix, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter [when specified as Grafix PRIME, for diabetic foot ulcers only]
Q4151	AmnioBand or Guardian, per sq cm
Q4154	Biovance, per square centimeter [for diabetic foot ulcers only]
Q4158	Kerecis Omega3, per square centimeter [for diabetic foot ulcers only]
Q4186	EpiFix, per square centimeter
Q4187	EpiCord, per square centimeter [for diabetic foot ulcers only]
Q4283	Biovance Tri-layer or Biovance 3L, per square centimeter [for diabetic foot ulcers only]

ICD-10 Diagnosis	
E08.00-E13.9	Diabetes mellitus
I83.001-I83.029	Varicose veins of lower extremities with ulcer
I83.201-I83.229	Varicose veins of lower extremities with both ulcer and inflammation
I87.011-I87.019	Postthrombotic syndrome with ulcer
I87.031-I87.039	Postthrombotic syndrome with ulcer and inflammation
I87.2	Venous insufficiency (chronic) (peripheral)
I87.311-I87.319	Chronic venous hypertension (idiopathic) with ulcer
I87.331-I87.339	Chronic venous hypertension (idiopathic) with ulcer and inflammation
L12.30-L12.35	Acquired epidermolysis bullosa [Dermagraft, OrCel]
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified
L98.411-L98.499	Non-pressure chronic ulcer of skin, not elsewhere classified
Q81.0-Q81.9	Epidermolysis bullosa [Dermagraft, OrCel]

When services may be Medically Necessary when criteria are met [for AlloDerm Regenerative Tissue Matrix (aseptic or sterile), Cortiva, DermACELL, DermaMatrix, FlexHD, OviTex, SimpliDerm, Strattice, SurgiMend]:

HCPCS	
C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters [for breast reconstruction only]
C9399	Unclassified drugs or biologicals [when specified as Cortiva, DermaMatrix or SimpliDerm for breast reconstruction only, or OviTex for abdominal wall wounds only]
Q4100	Skin substitute, not otherwise specified [when specified as Cortiva, DermaMatrix or SimpliDerm for breast reconstruction only, or OviTex for abdominal wall wounds only]
Q4116	AlloDerm, per square centimeter [AlloDerm Regenerative Tissue Matrix (aseptic or sterile) for breast reconstruction and abdominal wall wounds]
Q4122	Dermacell, Dermacell AWM or Dermacell AWM porous, per square centimeter [for breast reconstruction or diabetic foot ulcers only]
Q4128	FlexHD, or Allopatch HD, per sq cm [when specified as FlexHD for breast reconstruction]
Q4130	Strattice, per square centimeter [for breast reconstruction and abdominal wall wounds]

ICD-10 Diagnosis	

	All diagnoses

When services may be Medically Necessary when criteria are met [for AlloSkin, Biobrane, EpiCel, EZ-Derm, Integra Bilayer Matrix Wound Dressing, Integra DRT/Omnigraft, ReCell, StrataGraft]:

HCPCS	
A4100	Skin substitute, FDA cleared as a device, not otherwise specified [when specified as Biobrane, EpiCel or StrataGraft]
C1832	Autograft suspension, including cell processing and application, and all system components [RECELL Autologous Cell Harvesting Device]
C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter
C9399	Unclassified drugs or biologicals [when specified as Biobrane, EpiCel or StrataGraft]
Q4100	Skin substitute, not otherwise specified [when specified as Biobrane, EpiCel or StrataGraft]
Q4104	Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter
Q4105	Integra Dermal Regeneration Template (DRT) or Integra Omnigraft dermal regeneration matrix, per square centimeter
Q4115	AlloSkin, per square centimeter
Q4136	EZ-derm, per square centimeter

ICD-10 Diagnosis	
T20.20XA-T20.39XS	Burn of second or third degree of head, face, and neck
T20.60XA-T20.79XS	Corrosion of second or third degree of head, face, and neck
T21.20XA-T21.39XS	Burn of second or third degree of trunk
T21.60XA-T21.79XS	Corrosion of second or third degree of trunk
T22.20XA-T22.399S	Burn of second or third degree of shoulder and upper limb, except wrist and hand]
T22.60XA-T22.799S	Corrosion of second or third degree of shoulder and upper limb, except wrist and hand
T23.201A-T23.399S	Burn of second or third degree of wrist and hand
T23.601A-T23.799S	Corrosion of second or third degree of wrist and hand
T24.201A-T24.399S	Burn of second or third degree of lower limb, except ankle and foot
T24.601A-T24.799S	Corrosion of second or third degree of lower limb, except ankle and foot
T25.211A-T25.399S	Burn of second or third degree of ankle and foot
T25.611A-T25.799S	Corrosion of second or third degree of ankle and foot
T31.0-T31.99	Burns classified according to extent of body surface involved
T32.0-T32.99	Corrosions classified according to extent of body surface involved

When services may be Medically Necessary when criteria are met [for TheraSkin]:

HCPCS	
Q4121	TheraSkin, per square centimeter

ICD-10 Diagnosis	
E08.00-E13.9	Diabetes mellitus
I83.001-I83.029	Varicose veins of lower extremities with ulcer
I83.201-I83.229	Varicose veins of lower extremities with both ulcer and inflammation
I87.011-I87.019	Postthrombotic syndrome with ulcer
I87.031-I87.039	Postthrombotic syndrome with ulcer and inflammation
I87.2	Venous insufficiency (chronic) (peripheral)
I87.311-I87.319	Chronic venous hypertension (idiopathic) with ulcer
I87.331-I87.339	Chronic venous hypertension (idiopathic) with ulcer and inflammation
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified
L98.411-L98.499	Non-pressure chronic ulcer of skin, not elsewhere classified
T20.20XA-T20.39XS	Burn of second or third degree of head, face, and neck
T20.60XA-T20.79XS	Corrosion of second or third degree of head, face, and neck
T21.20XA-T21.39XS	Burn of second or third degree of trunk
T21.60XA-T21.79XS	Corrosion of second or third degree of trunk
T22.20XA-T22.399S	Burn of second or third degree of shoulder and upper limb, except wrist and hand]
T22.60XA-T22.799S	Corrosion of second or third degree of shoulder and upper limb, except wrist and hand
T23.201A-T23.399S	Burn of second or third degree of wrist and hand
T23.601A-T23.799S	Corrosion of second or third degree of wrist and hand
T24.201A-T24.399S	Burn of second or third degree of lower limb, except ankle and foot
T24.601A-T24.799S	Corrosion of second or third degree of lower limb, except ankle and foot
T25.211A-T25.399S	Burn of second or third degree of ankle and foot
T25.611A-T25.799S	Corrosion of second or third degree of ankle and foot
T31.0-T31.99	Burns classified according to extent of body surface involved
T32.0-T32.99	Corrosions classified according to extent of body surface involved

When services are Not Medically Necessary:
For the product codes listed above when criteria are not met or for all other diagnoses not listed, or when the code describes a procedure indicated in the Position Statement section as not medically necessary.

When Services are Investigational and Not Medically Necessary:

HCPCS	
A2001	Innovamatrix AC, per square centimeter
A2002	Mirragen advanced wound matrix, per square centimeter
A2004	Xcellistem, 1mg
A2005	Microlyte matrix, per square centimeter
A2006	Novosorb synpath dermal matrix, per square centimeter
A2007	Restrata, per square centimeter
A2008	TheraGenesis, per square centimeter
A2009	Symphony, per square centimeter
A2010	Apis, per square centimeter
A2011	Supra SDRM, per square centimeter
A2012	Suprathel, per square centimeter

A2013	InnovaMatrix FS, per square centimeter
A2014	Omeza Collagen Matrix, per 100 mg
A2015	Phoenix Wound Matrix, per sq cm
A2016	PermeaDerm B, per sq cm
A2017	PermeaDerm Glove, each
A2018	PermeaDerm C, per sq cm
A2019	Kerecis omega3 MariGen Shield, per square centimeter
A2020	Ac5 advanced wound system (Ac5)
A2021	NeoMatriX, per square centimeter
A2022	InnovaBurn or InnovaMatrix XL, per square centimeter
A2023	InnovaMatrix PD 1 mg
A2024	Resolve Matrix, per square centimeter
A2025	Miro3D, per cubic centimeter
A2026	Restrata MiniMatrix, 5 mg
C9352	Microporous collagen implantable tube (NeuraGen Nerve Guide), per centimeter length
C9353	Microporous collagen implantable slit tube (NeuraWrap Nerve Protector), per centimeter length
C9354	Acellular pericardial tissue matrix of non-human origin (Veritas), per square centimeter
C9355	Collagen nerve cuff (NeuroMatrix), per 0.5 centimeter length
C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter
C9361	Collagen matrix nerve wrap (NeuroMend Collagen Nerve Wrap), per 0.5 centimeter length
C9364	Porcine implant, Permacol, per square centimeter
C9399	Unclassified drugs or biologicals [when describing a product with no specific code indicated as investigational and not medically necessary]
C9796	Repair of enterocutaneous fistula small intestine or colon (excluding anorectal fistula) with plug (e.g., porcine small intestine submucosa [sis])
G0428	Collagen meniscus implant procedure for filling meniscal defects (e.g., CMI, collagen scaffold, Menaflex)
Q4100	Skin substitute, not otherwise specified [when describing a product with no specific code indicated as investigational and not medically necessary]
Q4103	Oasis Burn Matrix, per square centimeter
Q4108	Integra Matrix, per square centimeter
Q4111	Gammagraft, per square centimeter
Q4112	Cymetra, injectable, 1 cc
Q4113	Graftjacket Xpress, injectable, 1 cc
Q4114	Integra Flowable Wound Matrix, injectable, 1 cc
Q4117	Hyalomatrix, per square centimeter
Q4118	Matristem micromatrix, 1 mg
Q4123	AlloSkin RT, per square centimeter
Q4125	ArthroFlex, per square centimeter
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter
Q4127	Talymed, per square centimeter
Q4128	FlexHD, or AlloPatch HD, per sq cm [when specified as AlloPatch HD]
Q4132	Grafix CORE and GrafixPL CORE, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter [when specified as GrafixPL PRIME, Stravix, StravixPL]
Q4134	hMatrix, per square centimeter
Q4135	Mediskin, per square centimeter
Q4137	AmnioExCel, AmnioExCel plus or BioDExCel, per square centimeter
Q4138	BioDfence Dryflex, per square centimeter
Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4140	BioDfence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	XCM Biologic Tissue Matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	TenSIX, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
Q4148	NEOX Cord 1k, NEOX Cord RT, or Clarix Cord 1k, per square centimeter
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap DS or Dry, per square centimeter
Q4152	DermaPure, per square centimeter
Q4153	Dermavest and Plurivest, per square centimeter
Q4155	NeoxFlo or ClarixFlo, 1 mg
Q4156	NEOX 100 or Clarix 100, per square centimeter
Q4157	Revitalon, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	NuShield, per square centimeter
Q4161	Bio-connekt wound matrix, per square centimeter
Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, BioSkin, per square centimeter
Q4164	Helicoll, per square centimeter
Q4165	Keramatrix or Kerasorb, per square centimeter
Q4166	Cytal, per square centimeter [formerly Matristem wound/burn matrix]
Q4167	TruSkin, per square centimeter
Q4168	AmnioBand, 1 mg [particulate]
Q4169	Artacent Wound, per square centimeter
Q4170	CYGNUS, per square centimeter
Q4171	Interfyl, 1 mg
Q4173	PalinGen or PalinGen Xplus, per square centimeter
Q4174	PalinGen or ProMatrX, 0.36 mg per 0.25 cc

Q4175	Miroderm, per square centimeter
Q4176	NeoPatch or Therion, per square centimeter
Q4177	FlowerAmnioflo, 0.1 cc
Q4178	FlowerAmniopatch, per square centimeter
Q4179	FlowerDerm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio Wound, per square centimeter
Q4183	Surgigraft, per square centimeter
Q4184	Cellesta or Cellesta Duo, per square centimeter
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4188	Amnioarmor, per square centimeter
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per square centimeter
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4194	Novachor, per square centimeter
Q4195	Puraply, per square centimeter
Q4196	PuraPly AM, per square centimeter
Q4197	PuraPly XT, per square centimeter
Q4198	Genesis amniotic membrane, per square centimeter
Q4199	Cygnus matrix, per square centimeter
Q4200	Skin TE, per square centimeter
Q4201	Matrion, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-gide, per square centimeter
Q4204	Xwrap, per square centimeter
Q4205	Membrane graft or Membrane wrap, per square centimeter
Q4206	Fluid flow or Fluid GF, 1 cc
Q4208	Novafix, per square centimeter
Q4209	SurGraft, per square centimeter
Q4210	Axolotl graft or Axolotl dualgraft, per square centimeter
Q4211	Amnion bio or AxoBioMembrane, per square centimeter
Q4212	AlloGen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter
Q4215	Axolotl Ambient or Axolotl Cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter
Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
Q4218	Surgicord, per square centimeter
Q4219	SurgiGRAFT-Dual, per square centimeter
Q4220	BellaCell HD or Surederm, per square centimeter
Q4221	Amniowrap2, per square centimeter
Q4222	Progenamatrix, per square centimeter
Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
Q4225	Amniobind or DermaBind TL, per square centimeter
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per square centimeter
Q4227	AmnioCore, per square centimeter
Q4229	Cogenex amniotic membrane, per square centimeter
Q4230	Cogenex flowable amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per square centimeter
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	Xcellerate, per square centimeter
Q4235	Amniorepair or AltiPly, per square centimeter
Q4236	CarePATCH, per square centimeter
Q4237	Cryo-cord, per square centimeter
Q4238	Derm-Maxx, per square centimeter
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per square centimeter
Q4240	CoreCyte, for topical use only, per 0.5 cc
Q4241	PolyCyte, for topical use only, per 0.5 cc
Q4242	AmnioCyte Plus, per 0.5 cc
Q4245	Amniotext, per cc
Q4246	Coretext or Protext, per cc
Q4247	Amniotext patch, per square centimeter
Q4248	Dermacyte Amniotic Membrane Allograft, per square centimeter
Q4249	Amniply, for topical use only, per square centimeter
Q4250	AmnioAMP-MP, per square centimeter
Q4251	Vim, per sq cm
Q4252	Vendaje, per sq cm
Q4253	Zenith Amniotic Membrane, per sq cm
Q4254	Novafix DL, per square centimeter
Q4255	REGUaRD, for topical use only, per square centimeter
Q4256	MLG-complete, per square centimeter
Q4257	Relese, per square centimeter
Q4258	Enverse, per square centimeter
Q4259	Celera dual layer or celera dual membrane, per square centimeter
Q4260	Signature Apatch, per square centimeter
Q4261	TAG, per square centimeter
Q4262	Dual Layer Impax Membrane, per square centimeter

Q4263	SurGraft TL, per square centimeter
Q4264	Cocoon membrane, per square centimeter
Q4265	NeoStim TL, per square centimeter
Q4266	NeoStim membrane, per square centimeter
Q4267	NeoStim DL, per square centimeter
Q4268	SurGraft FT, per square centimeter
Q4269	SurGraft XT, per square centimeter
Q4270	Complete SL, per square centimeter
Q4271	Complete FT, per square centimeter
Q4272	Esano A, per square centimeter
Q4273	Esano AAA, per square centimeter
Q4274	Esano AC, per square centimeter
Q4275	Esano ACA, per square centimeter
Q4276	Orion, per square centimeter
Q4277	WoundPlus membrane or E-graft, per square centimeter
Q4278	EPIEFFECT, per square centimeter
Q4279	Vendaje AC, per square centimeter
Q4280	Xcell amnio matrix, per square centimeter
Q4281	Barrera SL or Barrera DL, per square centimeter
Q4282	Cygnus Dual, per square centimeter
Q4284	DermaBind SL, per square centimeter
Q4285	NuDYN DL or NuDYN DL mesh, per square centimeter
Q4286	NuDYN SL or NuDYN SLW, per square centimeter
Q4287	DermaBind DL, per square centimeter
Q4288	DermaBind CH, per square centimeter
Q4289	RevoShield + Amniotic Barrier, per square centimeter
Q4291	Lamellas XT, per square centimeter
Q4292	Lamellas, per square centimeter
Q4293	Acesso DL, per square centimeter
Q4294	Amnio Quad-Core, per square centimeter
Q4295	Amnio Tri-Core amniotic, per square centimeter
Q4296	Rebound Matrix, per square centimeter
Q4297	Emerge Matrix, per square centimeter
Q4298	AmnioCore Pro, per square centimeter
Q4299	AmniCore Pro+, per square centimeter
Q4300	Acesso TL, per square centimeter
Q4301	Activate Matrix, per square centimeter
Q4302	Complete ACA, per square centimeter
Q4303	Complete AA, per square centimeter
Q4304	Grafix Plus, per square centimeter
Q4305	American amnion AC tri-layer, per square centimeter
Q4306	American amnion AC, per square centimeter
Q4307	American amnion, per square centimeter
Q4308	Sanopellis, per square centimeter
Q4309	VIA Matrix, per square centimeter
Q4310	Procenta, per 100 mg

ICD-10 Diagnosis

All diagnoses

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Peer Reviewed Publications:

Non-Product Specific Acellular Dermal Matrix (ADM) Studies, Multiple Product Studies, Meta-analyses, and Systematic Reviews

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Websites for Additional Information

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2. National Library of Medicine (NIH). Burns. Last updated April 18, 2016. Available at:https://medlineplus.gov/burns.html. Accessed on January 8, 2024.
3. National Library of Medicine (NIH). Diabetic Foot. Last updated May 31, 2018. Available at: https://medlineplus.gov/diabeticfoot.html. Accessed on January 8, 2024.
4. UpToDate. Hernia Mesh. Last updated April 24, 2023. Available at:https://www.uptodate.com/contents/hernia-mesh?search=hernia%20repair&topicRef=3687&source=related_link#H2646306443. Accessed on February 7, 2024.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised MN statement to include Cortiva and SurgiMend for breast reconstruction. Revised MN statement to include EPICEL, Integra Omnigraft Dermal Regeneration Template, and ReCell for the treatment of partial and deep thickness burns. Revised MN statement to include Biovance and Oasis for the treatment of diabetic foot ulcers. Revised NMN statement to align with revisions to MN statements. Added new products to the INV and NMN statement. Updated Definitions, Background, Discussion, References, and Websites sections. Updated Coding section to include 04/01/2024 HCPCS changes, added Q4310 replacing Q4244 deleted as of 04/01/2024, also added A2026, C9796, Q4305, Q4306, Q4307, Q4308, Q4309.
	12/28/2023	Updated Coding section with 01/01/2024 HCPCS changes, added Q4279, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, Q4304 and revised descriptor for Q4225.
	09/27/2023	Updated Coding section with 10/01/2023 HCPCS changes to add A2022, A2023, A2024, A2025, Q4285 and Q4286; also added HCPCS code C1832.
	06/28/2023	Updated Coding section with 07/01/2023 HCPCS changes, added Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283, Q4284. Updated URL for HCT/Ps information site.
Revised	02/16/2023	MPTAC review. Revised MN statement to include SimpliDerm for breast reconstruction. Revised MN statement to include Kerecis and TheraSkin for diabetic foot ulcers. Revised MN statement to include AmnioBand for venous stasis ulcers. Revised MN statement to include OviTex for complex abdominal wall wounds. Revised formatting in several MN statements. Revised NMN statement to align with revisions to MN statements. Added new products to the INV and NMN statement. Updated Rationale, Coding and References sections. Updated Coding section with 04/01/2023 HCPCS changes; added A2019, A2020, A2021, Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271.
	12/28/2022	Updated Coding section with 01/01/2023 HCPCS changes; added Q4262, Q4263, Q4264, and added Q4236 (code reactivated).
	09/28/2022	Updated Coding section with 10/01/2022 HCPCS changes; revised descriptor for Q4128 and added A2014, A2015, A2016, A2017, A2018.
Revised	05/12/2022	MPTAC review. Revised INV and NMN statement for products with MN indications. Updated Rationale and References sections. Updated Coding section, including 07/01/2022 HCPCS changes; added Q4259, Q4260, Q4261 and revised A2004 descriptor.

Revised	02/17/2022	MPTAC review. Moved StrataGraft from INV and NMN section to MN section for burns. Added mVASC to MN section for treatment of DUFs. Clarified product terminology regarding AlloDerm products. Added new products to INV and NMN statement. Updated Rationale and References sections. Updated Coding section to include MN indications for StrataGraft and mVASC (NOC codes) and 04/01/2022 HCPCS updates to add A2011, A2012, A2013, A4100, Q4224, Q4225, Q4256, Q4257, Q4258.
Revised	11/11/2021	MPTAC review. Updated title and scope to include bioengineered products. Reorganized MN section by indication. Simplified criteria for treatment of DFUs and venous stasis ulcers. Incorporated position statement addressing bioengineered autologous skin-derived products from MED.00110. Added new products to INV and NMN statement. Updated Description/Scope, Rationale, Background, and References sections. Updated Coding section with 01/01/2022 HCPCS changes to add A2001-A2002, A2004-A2010 and Q4199 effective 01/01/2022, also added Q4200, Q4226 previously addressed in MED.00110.
	10/01/2021	Updated Coding section with 10/01/2021 HCPCS changes; added Q4251, Q4252, Q4253 effective 10/01/2021 and removed Q4228, Q4236 deleted 09/30/2021.
Revised	11/05/2020	MPTAC review. Added new MN statement for TheraSkin for treatment of lower extremity dermal wounds. Revised note addressing fresh frozen unprocessed allograft skin products. Revised several statements to begin with the name of the product. Revised IVN and NMN statement for products which have MN indications. Added new products to INV and NMN statement. Updated Scope, Rationale, and References sections. Updated Coding section to include 01/01/2021 CPT changes adding 0627T-0630T.
	10/01/2020	Updated Coding section with 10/01/2020 HCPCS changes to add Q4249, Q4250, Q4254, Q4255, and also 10/01/2020 ICD-10-CM changes adding H18.599 replacing H18.59 deleted 09/30/2020.
	07/01/2020	Updated Coding section with 07/01/2020 HCPCS changes to add Q4227-Q4242, Q4244-Q4248 and revised descriptor for Q4176; also removed C1878, L8607 now addressed in MED.00132.
Revised	11/07/2019	MPTAC review. Moved AmbioDisk from INV and NMN statement to the MN statement addressing of allogeneic amniotic membrane-derived grafts or wound coverings. Added Artacent Ocular to MN statement addressing of allogeneic amniotic membrane-derived grafts or wound coverings. Added new products to INV and NMN statement. Updated Rationale and References sections.
	10/01/2019	Updated Coding section with 10/01/2019 HCPCS changes; added Q4205-Q4206, Q4208-Q4222, revised descriptors for Q4122, Q4165, Q4184; also added C1878.
	06/18/2019	Correction to MN statement addressing amniotic membrane-derived products for conjunctival and corneal indications made. Kerasys removed and replaced by AmnioGraft.
Revised	06/06/2019	MPTAC review. Added new MN and INV and NMN statements addressing amniotic membrane-derived products for conjunctival and corneal indications. Added new products to INV and NMN statement. Updated Rationale, Coding and References sections.
Revised	01/24/2019	MPTAC review. Added new MN statements for EpiCord, Grafix PRIME, and the sheet or membrane form of AmnioBand. Revised INV and NMN statements regarding those products. Added EpiBurn to INV and NMN statement. Updated Coding, Rationale, and References sections.
	12/27/2018	Updated Coding section with 01/01/2019 HCPCS changes; removed Q4131, Q4172 deleted 12/31/2018.
Revised	09/13/2018	MPTAC review. Added several products to the INV and NMN section. Updated Rationale, Coding and References sections.
Revised	01/25/2018	MPTAC review. Revised criteria for EpiFix and Integra Bilayer Matrix Wound Dressing. Deleted statement regarding TransCyte. Moved several products from the INV and NMN section to the MN section. Updated Rationale and References sections. Updated Coding section to include removing Q4182 no longer addressed.
	12/27/2017	The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Coding section with 01/01/2018 HCPCS changes; added codes Q4176-Q4182, descriptor revisions for Q4132, Q4133, Q4148, Q4156, Q4158, Q4162, Q4163.
Revised	08/03/2017	MPTAC review. Added new products to INV and NMN list. Removed Perlane and Restylane from Inv and NMN list. Updated Rationale, Coding and References sections.
Revised	02/02/2017	MPTAC review. Made minor typographical revisions to Position Statement. Added new products to INV and NMN list. Updated Rationale and References sections.
	01/01/2017	Updated Coding section with 01/01/2017 CPT and HCPCS changes; removed codes C9349, Q4119, Q4120, Q4129 deleted 12/31/2016.
Revised	05/05/2016	MPTAC review. Added AlloDerm Ready to Use as MN for the same indications as AlloDerm Regenerative Tissue Matrix. Added FlexHD as MN for breast reconstruction surgery. Clarified INV and NMN statement regarding fresh frozen allograft products. Added new products to the INV and NMN list. Updated Rationale, Coding, and References sections.
Revised	11/05/2015	MPTAC review. Added Restlyane and Perlane to investigational and not medically necessary list. Updated Rationale and References sections. Updated Coding section with 01/01/2016 HCPCS changes; also removed ICD-9 codes.
	07/01/2015	Updated Coding section with 07/01/2015 HCPCS change to descriptor for C9349.
Revised	05/07/2015	MPTAC review. Added new medically necessary position statement regarding the use of fresh, frozen, unprocessed skin allograft products for the treatment of full-thickness or deep partial-thickness burns when criteria are met. Added new products to investigational and not medically necessary section. Updated Rationale, Coding, and References sections.

Revised	02/05/2015	MPTAC review. Added new medically necessary position statement regarding the use the sheet or membrane form of EpiFix. Revised investigational and not medically necessary statement to differentiate between the sheet or membrane form of EpiFix and the particulate or injectable form of EpiFix. Added new products to investigational and not medically necessary section. Updated Rationale, Background, Coding, and References sections. Revised position statements were finalized in a follow-up vote on 03/04/2015.
	01/01/2015	Updated Coding section with 01/01/2015 HCPCS changes.
Revised	02/13/2014	MPTAC review. Clarified nomenclature of AlloDerm product in medically necessary section. Added new products to investigational and not medically necessary section. Updated Rationale, Background, and References sections.
	01/01/2014	Updated Coding section with 01/01/2014 CPT and HCPCS changes.
Revised	08/08/2013	MPTAC review. Added new products to Investigational and Not Medically Necessary list. Updated Rationale and References sections.
Revised	05/09/2013	MPTAC review. Added new products to Investigational and Not Medically Necessary list. Updated Rationale, Coding, and Reference sections.
	01/01/2013	Updated Coding section with 01/01/2013 HCPCS changes; removed C9366, C9368, C9369 deleted 12/31/2012.
Revised	05/10/2012	MPTAC review. Deleted “autologous” from title. Split off growth factors, silver-based products and autologous tissues for wound treatment and soft tissue to a new policy (MED.00110). Reorganized position statement section. Clarified Medically necessary statement for Apligraf regarding number of applications and deleted corresponding investigational and not medically necessary statement. Added new products to investigational and not medically necessary position statement. Revised Rationale, Background, References, and Index sections. Updated Coding section to include 07/01/2012 HCPCS changes.
	01/19/2012	Updated Coding section with correct diagnosis coding for Apligraf; removed HCPCS codes G0440, G0441 deleted 12/31/2011.
	01/01/2012	Updated Coding section with 01/01/2012 CPT and HCPCS changes; removed codes 15170, 15171, 15175, 15176, 15330, 15331, 15335, 15336, 15340, 15341, 15360, 15361, 15365, 15366, 15400, 15401, 15420, 15421, 15430, 15431, C9365 deleted 12/31/2011; also removed CPT 15150, 15151, 15152, 15155, 15156, 15157.
Revised	05/19/2011	MPTAC review. Added synthetic soft-tissue grafting materials as investigational and not medically necessary to Section I. Added xenographic-related or derived products as investigational and not medically necessary to Section IV. Updated Rationale, References, and Index sections. Updated Coding section with 07/01/2011 HCPCS changes.
Revised	02/17/2011	MPTAC review. Added use of cryopreserved allogeneic human skin to the Allogeneic section as investigational and not medically necessary. Updated Rationale, Coding, References, and Index sections.
	01/01/2011	Updated Coding section with 01/01/2011 HCPCS changes; removed Q4109 deleted 12/31/2010.
Revised	08/19/2010	MPTAC review. Added use of synthetic fistula plugs to synthetic products section as investigational and not medically necessary. Expanded investigational and not medically necessary statement for Dermagraft to cover all indications not listed as medically necessary. Revised language in xenographic investigational and not medically necessary statement. Updated list of xenographic products, including Menaflex™ Collagen Meniscus Implant. Added new section addressing composite autologous / allogeneic / xenographic products. Updated Rationale, Background, Coding, and References sections.
	07/01/2010	Updated Coding section with 07/01/2010 CPT and HCPCS changes.
	01/01/2010	Updated Coding section with 01/01/2010 CPT changes; removed CPT 0170T deleted 12/31/2009.
Revised	08/27/2009	MPTAC review. Added Platelet Rich Plasma as investigational and not medically necessary. Updated coding and Index sections.
Reviewed	05/21/2009	MPTAC review. Added note stating that this document does not address the use of meshes or patches of non-biologic origin when used for standard hernia repair procedures. Updated Index section. Updated coding section with 07/01/2009 HCPCS changes.
Revised	02/26/2009	MPTAC review. Added Investigational and Not Medically Necessary statements for C-QUR and Strattice.
Revised	11/20/2008	MPTAC review. Added AlloDerm as medically necessary for breast reconstruction and complex abdominal wall wound closure. Updated Rationale and Reference sections. Updated coding section with 01/01/2009 HCPCS changes; removed C9357, J7340, J7341, J7342, J7343, J7344, J7346, J7347, J7348, J7349 deleted 12/31/2008.
Revised	08/28/2008	MPTAC review. Added Vitagel to Investigational and Not Medically Necessary statement of Section II Autologous Products. Added Cymetra to Investigational and Not Medically Necessary statement of Section III Allogeneic Products. Updated Background. Coding section updated to include 10/01/2008 ICD-9 changes.
Revised	05/15/2008	MPTAC review. Changed title from “Wound Healing: Skin Substitutes and Blood-Derived Growth Factors” to “Autogous, Allogeneic, Xenographic, Synthetic and Composite Products for Wound Healing and Soft Tissue Grafting.” Reorganized Position Statement section. Added position statements regarding the following products: Actisorb, Avaulta Plus, Collamend, CuffPatch, Mediskin, Neoform Dermis, Pelcvicol, Pelvisoft, Silversorb, and Unite. Revised Rationale, Coding, Background, Definitions, References, and Index sections. Deleted information regarding Procuren®. Updated Coding section with 07/01/2008 HCPCS changes.

Revised	02/21/2008	MPTAC review. Added position statements for Integra™ Matrix Wound Dressing, Primatrix, and TissueMend. Expanded investigational and not medically necessary statement for Surgisis, Autogel and Safeblood to include all indications. Updated Rationale, Background, Definitions, and References sections.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS C9351, J7345 deleted 12/31/2007. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary.” This change was approved at the November 29, 2007 MPTAC meeting.
Revised	05/17/2007	MPTAC review. Added the use of AlloDerm for breast reconstruction or augmentation to investigational/not medically necessary statement. Updated Rationale and References sections.
	01/01/2007	Updated Coding section with 01/01/2007 CPT/HCPCS changes.
Revised	09/14/2006	MPTAC review. Added position statement for Surgisis®; updated rationale, background and reference sections. Coding updated; removed CPT 15342, 15343 deleted 12/31/05, HCPCS Q0182, Q0183 deleted 12/31/04.
Revised	03/23/2006	MPTAC review. Added position statement for AlloDerm® and GraftJacket™.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger Wellpoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	04/28/2005	SURG.00011	Wound Healing: Tissue Engineered Skin Substitutes and Growth Factors
WellPoint Health Networks, Inc.	04/28/2005	3.02.03	Human Skin Equivalent Grafts
	09/23/2004	8.01.08	Autologous Blood Derived Preparations for Wound Healing

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.