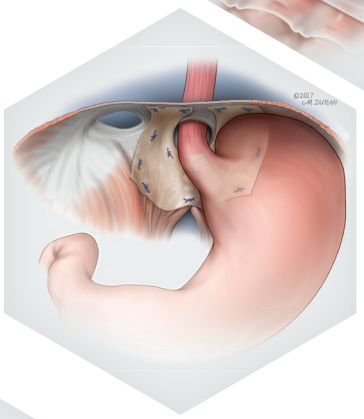
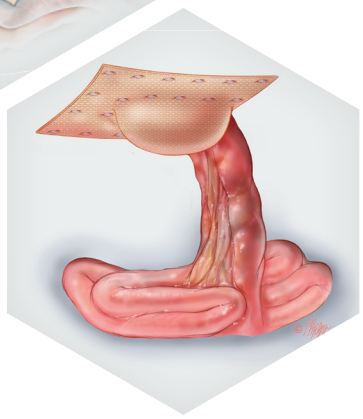
Gentrix®

Value Analysis Committee - Product Information Kit

Hernia Repair & Soft Tissue Reinforcement





ACell®

Gentrix®

ACell® is a leading regenerative medicine company dedicated to helping patients return to their normal lives through solutions in complex wounds and surgical soft tissue repair. ACell's surgical portfolio, Gentrix® Surgical Matrix, is manufactured using our patented MatriStem UBM™ technology, the only commercially available form of Urinary Bladder Matrix. **The devices are fully resorbable, non-crosslinked, and biologically-derived, making them suitable for a wide range of surgical procedures, including hernia repair.**

Ventral hernia repair is one of the most common surgical procedures performed in the United States with approximately 350,000 repairs performed annually[1].There are many factors to consider in choosing the right solution for reinforcement. Different patient populations require different solutions in order to make a repair as cost-effective and risk-averse as possible. While permanent synthetic meshes perform well in simple, clean hernias, they may not be ideal in the complex hernia setting due to the increased risks of surgical site occurrences (SSOs) and recurrences[2-5]. **These complications can prove costly with each hernia recurrence and wound event, estimated to cost an additional $44,000 and $85,000 respectively[6,7].**

As clinicians and hospitals evaluate options for cost-effective hernia repairs, it is important to weigh the initial savings with the potential costs of future complications, particularly in complex patient populations. Gentrix Surgical Matrix devices provide the optimal strength over time for a lasting repair while minimizing the risk of costly complications such as product migration, contraction, erosion, and infection that can occur with synthetic alternatives[8-12]. **Gentrix devices are well-established and consistently maintain a low complication rate[13]. For approximately 10 years, they have continued to be a reliable option in complex ventral hernia reinforcement.**

ACell is committed to being a trusted partner. Our consultative representatives provide support in the OR, as well as post-operatively to ensure your medical staff is fully trained on our devices. ACell looks forward to a collaborative partnership, providing you with innovative solutions so your organization can focus on providing the best care possible to your patients.

Note: References 8, 17, 18, 20, 21, and 26 are pre-clinical publications and cited throughout this book. Pre-clinical data may not reflect clinical results.

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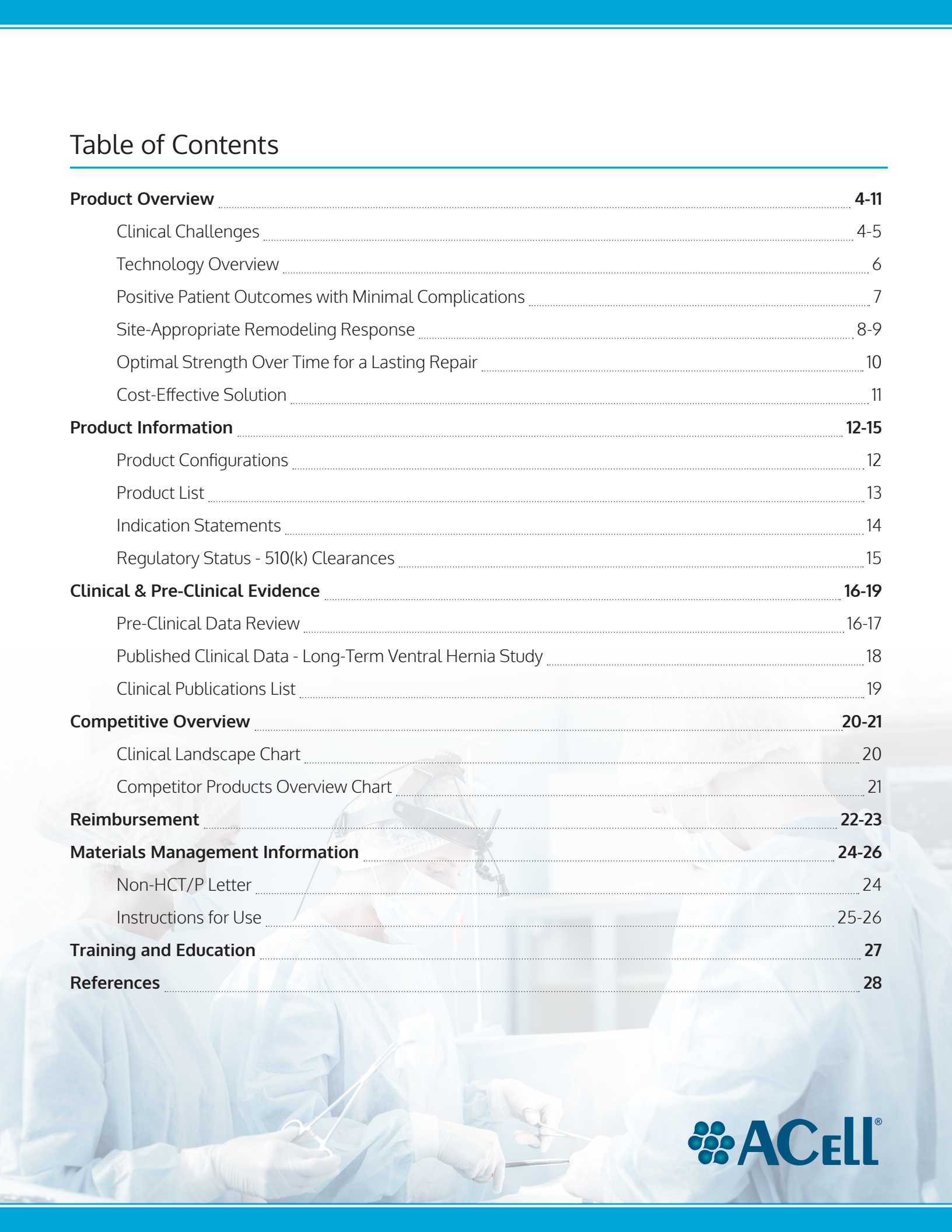

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Complex Ventral Hernias...

Studies have shown certain variables may pre-dispose patients to hernia recurrence and surgical site occurrences (SSOs) after ventral hernia repair[14,15]. **Some of these variables include:**

Comorbidities[14]

- Smoking
- Diabetes
- Obesity
- Advanced Age
- Immunosuppression
- Chronic Obstructive Pulmonary Disease (COPD)
- Coronary Artery Disease (CAD)
- Chronic Corticosteroid Use
- Low Serum Albumin
- Nutritional Status

Other Characteristics[14,15]

- Loss of Abdominal Domain
- Mesh Removal
- Previous Mesh Infection
- Prior Hernia Repairs
- Incarcerated or Strangulated Bowel
- Large Defects (>10 cm)

One study confirmed that the higher a hernia is graded on the Ventral Hernia Working Group's (VHWG) grading scale, the higher the risk for surgical site occurrences (SSOs) and recurrence after open ventral hernia repair[16].

GRADE 1 **Low Risk**	GRADE 2 **Co-Morbid**	GRADE 3 **Potentially Contaminated**	GRADE 4 **Infected**
• Low risk of complications • No history of wound infection	• Smoker • Obese • Diabetic • Immunosuppressed • COPD	• Previous wound infection • Stoma present • Violation of the gastrointestinal tract	• Infected mesh • Septic dehiscence
SSO: 14% **Recurrence: 11.5%**	**SSO: 29%** **Recurrence: 13.4%**	**SSO: 38%** **Recurrence: 32.5%**	**SSO: 49%** **Recurrence: 52.5%**

...Present a Complex Problem

While permanent synthetic meshes perform well in simple, clean hernias, several drawbacks have precluded them from being used in the complex setting. Human (allograft) and animal (xenograft) dermal products were developed to overcome these challenges[2-5].

Risks of Synthetics[14]

- Increased risk for visceral adhesions
- Erosion into the bowel leading to formation of enterocutaneous fistula and/or bowel obstruction
- Extrusion of the repair material
- Infection most likely resulting in reoperation to remove material

Drawbacks of Dermal Products

- Can be difficult to handle and fixate, especially laparoscopically
- Pre-clinical studies have evidenced host inflammatory response, encapsulation, and a lack of implant remodeling[17,18]
- A long-term single-study of these materials demonstrated a 31.8% recurrence rate and 36.6% wound infection rate at 18.2 months follow up, indicating dermal products may not be overcoming the challenges of synthetics[19].

Gentrix Surgical Matrix is a versatile, biologically-derived, non-dermal ECM that provides:

- ✔ Positive Patient Outcomes with Minimal Complications[9]
- ✔ A Site-Appropriate Remodeling Response[8,9,20]
- ✔ Optimal Strength Over Time for a Lasting Repair[8,9,21]
- ✔ A Cost-Effective Solution[6,7,9,13,19,22,24,25]

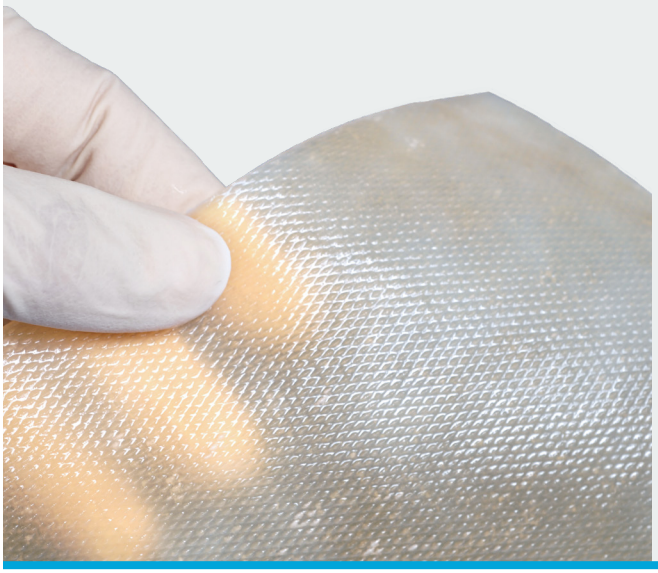
Gentrix®

A Different Option

While multiple variables can affect outcomes in complex ventral hernia repair, the choice of graft matters.

Complex Ventral Hernias: Gentrix Offers a Unique Solution

ACell's Gentrix Surgical Matrix devices are fully resorbable, biologically-derived extracellular matrix scaffolds composed of porcine urinary bladder. The devices are specifically designed for the repair and reinforcement of complex ventral hernias. In a pre-clinical model, it has been found to facilitate a host tissue remodeling response that leads to the formation of biomechanically functional, site-appropriate tissue[8,21]. Our product has demonstrated a lasting repair with positive patient outcomes and minimal complications in complex patients[9] (84% classified as "major" in the Slater severity classification system[15]).



Key Characteristics

- Maintains a mechanical strength and stiffness similar to native fascia for a lasting repair[8]*
- Minimizes the risk of costly complications such as product migration, contraction, erosion, and infection that can occur with synthetic alternatives[8-12]*
- Facilitates host tissue remodeling while minimizing the foreign body response[8,9,20]*
- Offers ease in handling and securing in both open and laparoscopic procedures

* Pre-clinical data cited may not reflect clinical results.

Product Composition

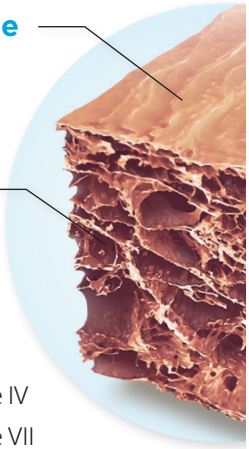
Gentrix Surgical Matrix products are engineered using ACell's proprietary MatriStem UBM (Urinary Bladder Matrix) technology and are intended to reinforce soft tissue where weakness exists. Gentrix devices are minimally processed and do not incorporate detergents or other harsh chemicals that could damage the product. This process allows for a naturally-derived scaffold that contains multiple types of carbohydrates, collagens, proteins, and other components.

Epithelial Basement Membrane

The epithelial basement membrane can contribute to cell attachment and proliferation.

Lamina Propria

The lamina propria surface is conducive for integration of host connective tissue into the scaffold.



Contains

- Glycosaminoglycans
- Collagen Type I
- Collagen Type III
- Collagen Type IV
- Collagen Type VII
- Laminin

Positive Patient Outcomes with Minimal Complications

Complex Patient Population

In a recent study, 64 patients underwent complex incisional hernia repair utilizing Gentrix as a reinforcement graft. The patient population was complex, with 84% classified as "major" (Slater severity classification system[15]).

Slater Scale	
Minor (Low Risk)	0 (0%)
Moderate (Comorbid)	10 (16%)
Major (Potentially Contaminated)	54 (84%)

Patient Complexity	
Previously Failed Repair	38 (59%)
Stoma Present	16 (25%)
Bowel Fistula at Time of Repair	3 (5%)
Incarcerated Bowel or Omentum	30 (47%)
Diabetes	18 (28%)
Old Mesh Excised	9 (14%)
Concomitant Procedures	42 (66%)

Results

At a median follow up of 36 months, **the total recurrence rate was 15.6%[9]**. The same study demonstrates long-term clinical results with a low rate of complications, despite the severity of the patient population. There were no cases of erosion, fistulization, or bowel obstruction observed in any of the 64 patients in this study.

This study compares favorably to other recently published studies utilizing biologically derived ECMs in hernia repair with similar patient populations and shorter follow up periods. Two of the most comparable studies had recurrence rates of **23%** and **31.8%** at **24 months** and **18 months**, respectively[19,22].

Results (Long-Term Clinical Follow Up After Complex Ventral Incisional Hernia Repair[9])	
Median Follow Up Time	36 mos (12-70 mos)
Total Recurrences	10 (15.6%)
Median Time to Hernia Recurrence	32 mos (4-51 mos)
Surgery for Repair of Hernia Recurrence	9 (14%)
Seroma	12 (19%)
Major Wound Care	13 (20%)
Median Carolinas Comfort Scale (CCS)	16 (115 max. points)

A **4% recurrence rate** was displayed at **24 months[9]***

* Kaplan-Meier freedom from recurrence statistical analysis.

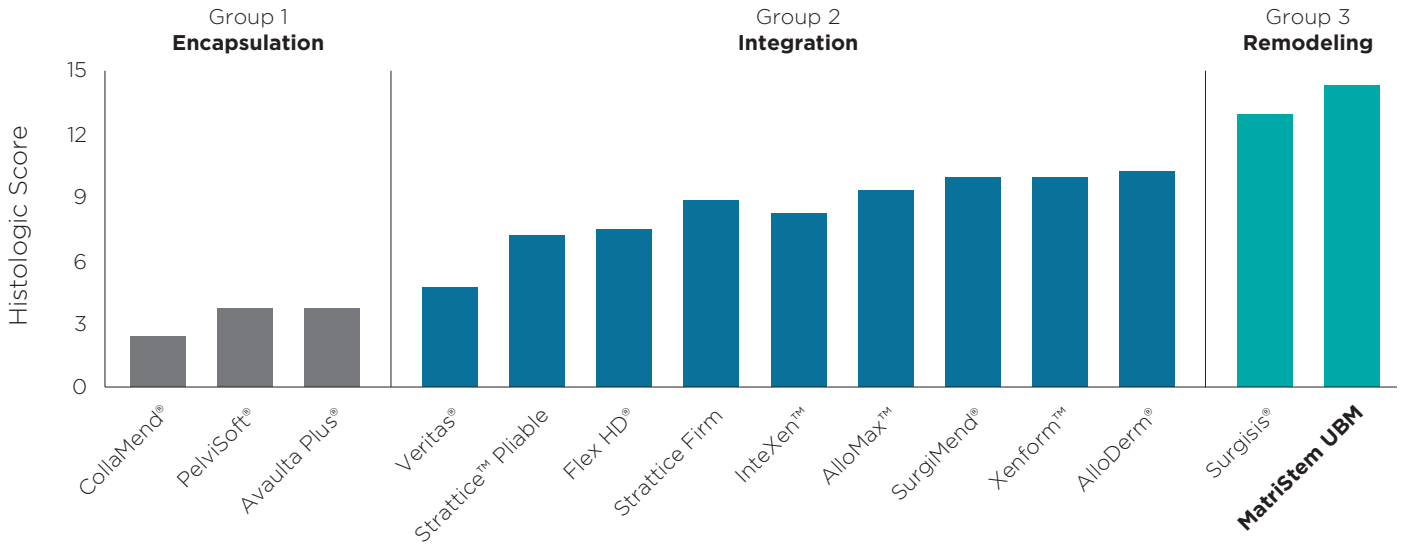
Site-Appropriate Remodeling Response

Gentrix Surgical Matrix devices can be rapidly repopulated and revascularized by the host, leading to a more favorable remodeling response. Reinforcement with Gentrix devices has been shown to facilitate a host tissue remodeling response that leads to the formation of biomechanically functional, site-appropriate host tissue[8,21,].

Evidence of Tissue Remodeling

Brown et al.[20] described the tissue remodeling response of 14 different commercially available biologic surgical mesh devices in a rat model of abdominal wall repair. Higher scores are more indicative of a site-appropriate tissue remodeling response, while low scores are more indicative of an encapsulation or foreign body response. Of the 14 different commercially available ECMs tested, MatriStem UBM technology had a favorable host remodeling response at both 14 and 35 days post-implantation.

Histological Score - 35 Days Post-Implantation*



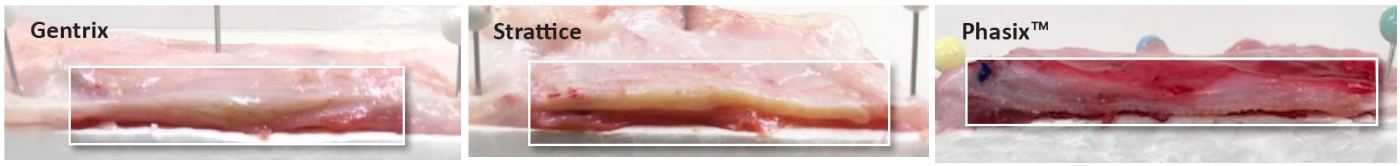
GROUP 1 Encapsulation	GROUP 2 Integration	GROUP 3 Site-Appropriate Tissue Remodeling
Chronic inflammation and foreign body response.	Early immune cell infiltration with decreased cellularity and little evidence of site-specific cells at later time points.	Early infiltration by immune cells and signs of site-specific cells at later time points.

* Some products in graph are not currently commercially available.

Site-Appropriate Remodeling Response

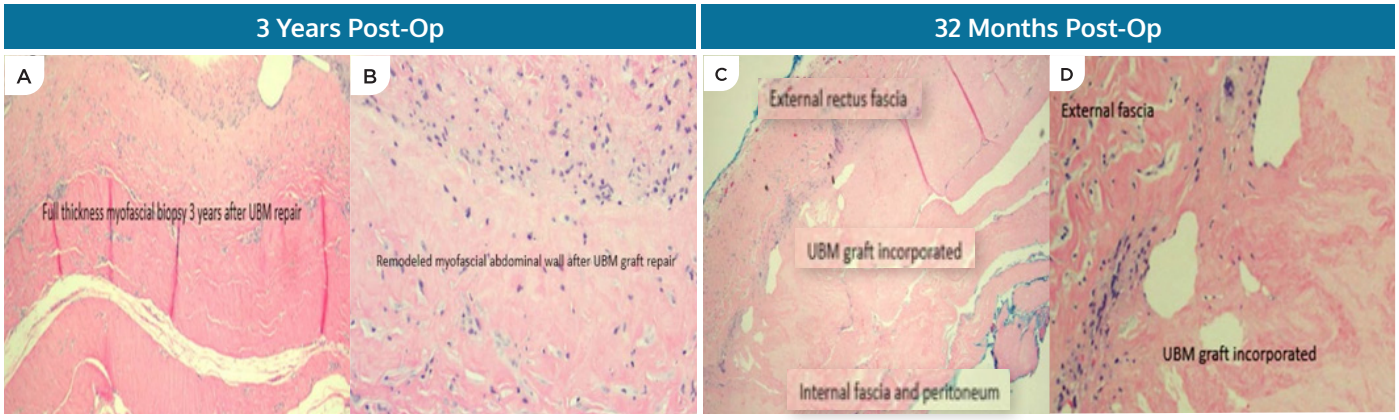
Site-appropriate remodeling has been observed in both pre-clinical and clinical models, with resulting biomechanically functional host tissue analyzed and demonstrated pre-clinically[8,9,21].

Pre-Clinical Model



In a pre-clinical ovine study, the remodeling response of Gentrix was compared to that of Strattice and Phasix. At three months, the Gentrix device was fully remodeled into site-appropriate connective tissue, while the Strattice and Phasix devices were easily identifiable from surrounding tissue[8,23].

Clinical Results



(A) Full-thickness myofascial biopsy after Gentrix repair of ventral hernia at 4x power. **(B)** 10x power full-thickness myofascial biopsy following intraperitoneal repair. **(C)** 4x power myofascial biopsy after retrorectus repair of incisional hernia. **(D)** 4x power myofascial biopsy after retrorectus repair of incisional hernia at interface of external native fascia and remodeled Gentrix.

In a clinical study of 64 patients undergoing complex ventral hernia repair with Gentrix reinforcement, histological analysis of the repaired fascia was obtained from three patients during the course of the study.

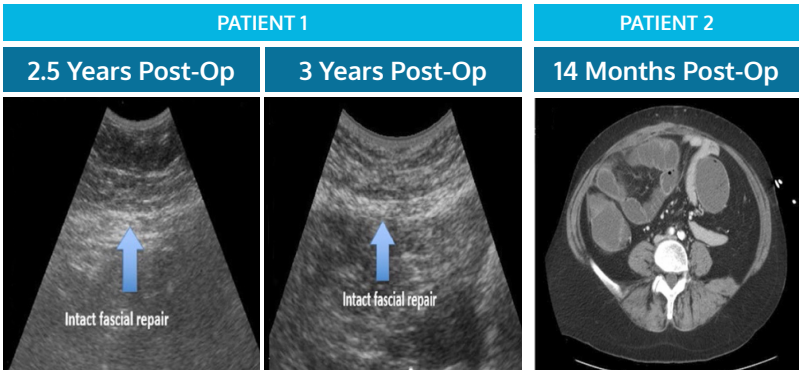
In each case where a full-thickness fascial biopsy was obtained, closer examination revealed an intact repair with a visual and tactile sense of strength equivalent to native fascia. Histologically, each case showed that the UBM implant region exhibited site-appropriate remodeling of connective tissue[9].

Optimal Strength Over Time for a Lasting Repair

Gentrix Surgical Matrix devices are intentionally designed to match the strength and stiffness of native fascia. The out-of-the-package strength of the device is sufficient to reinforce and hold the repair until the body remodels biomechanically functional, site-appropriate host tissue capable of sustaining the physiologic mechanical loading on its own[8]. Pre-clinical and clinical data have shown that Gentrix devices facilitate a lasting repair[8,9,21].

In a clinical study of 64 patients undergoing complex ventral hernia repair with Gentrix reinforcement, radiographic evidence of fascia was obtained in a subset of 28 patients.

In the patients evaluated with ultrasound, all cases without clinical hernia recurrence showed an intact, defined fascial layer without reherniation (Figures 1 & 2). CT scans also demonstrated an intact fascia of the abdominal wall (Figure 3).



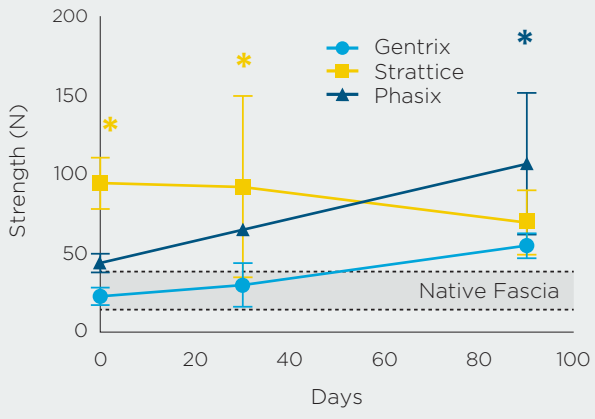
Figures 1 & 2. Abdominal wall ultrasound imaging depicting repaired fascia demonstrating a recognizable, robust, intact fascial layer without recurrent herniation.

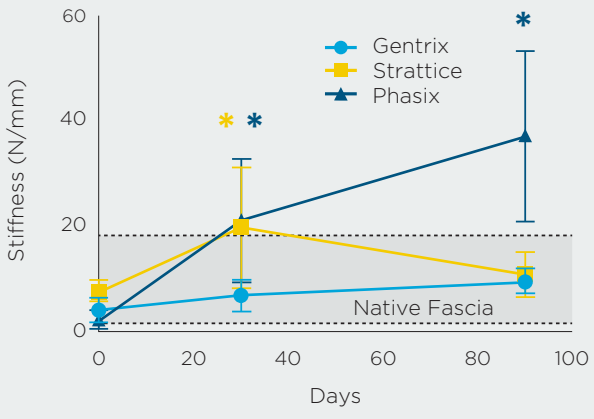
Figure 3. Axial CT scan demonstrates intact fascia post-retrorectus repair prior to exploration for bowel obstruction. Thickening of right and mid-abdominal wall noted from repair.

Reinforces While it Remodels

When Gentrix devices were implanted into an ovine fascia lata defect, the devices showed full remodeling at three months. The devices had been replaced with vascularized tissue. When mechanically studied at time of implantation, 30 days, and 90 days, **the strength of the remodeled fascia displayed an increasing trend[8].**

The Gentrix group maintained a mechanical strength and stiffness that was similar to native, uninjured fascia even when the implanted device had resorbed. In contrast, the acellular dermal matrix (ADM) device (Strattice) showed a decreasing trend in strength over time and the resorbable synthetic mesh (Phasix) showed an increasing stiffness over time that was twice as stiff as native tissue by the end of the study[8,23].





Mechanical behavior of different reinforcement materials over time in a pre-clinical model indicates $p<0.05$ compared to native fascia.

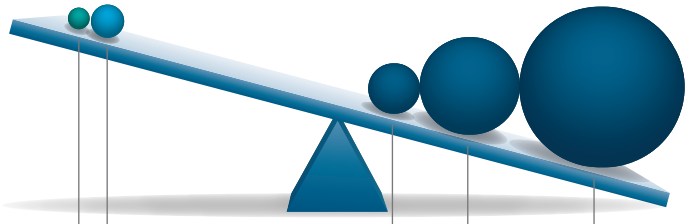
Cost-Effective Solution

$3.2 BILLION

The annual cost of hernia repair procedures in the U.S.[1]

Weighing the Cost of Complex Hernia Repair

As clinicians and hospitals evaluate options for cost-effective hernia repairs, they must weigh the initial savings when selecting a reinforcement mesh with the potential costs of future complications, particularly in complex patient populations.



UPFRONT COSTS

AVERAGE COST OF INITIAL OPERATION[24]

- SYNTHETIC | **$19,000**
- BIOLOGIC | **$29,000**

LONG-TERM COSTS

- MESH INFECTION
- WOUND COMPLICATION
- RECURRENCE

LONG-TERM COSTS

Gentrix[13]	<0.5%	MESH INFECTION | $140,000[7]
Acellular Dermis[19,22,25]	1-2%	
Synthetic Mesh[24]	23%	
Gentrix[9]	20%	WOUND COMPLICATION | $85,000[7]
Acellular Dermis[19,22,25]	35-39%	
Synthetic Mesh[24]	21%	
Gentrix[9]	4%	RECURRENCE | $44,000[6]
Acellular Dermis[19,22,25]	7-32%	
Synthetic Mesh[24]	15%	

Product Configurations

The Gentrix product line is available in five configurations with a large variety of sizes to suit a range of surgical procedures in both open and laparoscopic settings.

GENTRIX SURGICAL MATRIX THIN

- 3-layer
- **Minimum hydration time:** 5 minutes
- Cases could include anastomotic wraps, urethral reconstruction, and small hernias
- Suitable for laparoscopic or open repair

GENTRIX SURGICAL MATRIX

- 6-layer
- **Minimum hydration time:** 10 minutes
- Cases could include reinforcement of hiatal hernias, parastomal hernias and small ventral hernias
- Suitable for laparoscopic or open repair

GENTRIX HIATAL

- 6-layer
- **Minimum hydration time:** 10 minutes
- Designed for hiatal hernia reinforcement, featuring a pre-cut shape with smooth, rounded edges
- Designed to be easily handled and secured in laparoscopic surgery

GENTRIX SURGICAL MATRIX PLUS

- 8-layer
- **Minimum hydration time:** 20 minutes
- Cases could include reinforcement of small to midsize complex ventral hernias, inguinal hernias, hiatal hernias, parastomal hernias, and rectal prolapse repair
- Suitable for laparoscopic or open repair

GENTRIX SURGICAL MATRIX THICK

- 8-layer
- **Minimum hydration time:** 20 minutes
- Cases could include reinforcement of large complex ventral hernias and abdominal wall reconstruction
- Suitable for open repair

Product List

Gentrix Surgical Matrix Thin

Item Number	Size	Description	Quantity
PSM0505	5 x 5 cm	Gentrix Surgical Matrix Thin	1/box
PSM0412	4 x 12 cm	Gentrix Surgical Matrix Thin	1/box
PSM0710	7 x 10 cm	Gentrix Surgical Matrix Thin	1/box
PSM0615	6 x 15 cm	Gentrix Surgical Matrix Thin	1/box
PSM0715	7 x 15 cm	Gentrix Surgical Matrix Thin	1/box
PSM1015	10 x 15 cm	Gentrix Surgical Matrix Thin	1/box

Gentrix Surgical Matrix

Item Number	Size	Description	Quantity
PSMX0505	5 x 5 cm	Gentrix Surgical Matrix	1/box
PSMX0710	7 x 10 cm	Gentrix Surgical Matrix	1/box
PSMX1015	10 x 15 cm	Gentrix Surgical Matrix	1/box

Gentrix Hiatal

Item Number	Size	Description	Quantity
HIAT0706	6 x 7.5 cm	Gentrix Hiatal	1/box

Gentrix Surgical Matrix Plus

Item Number	Size	Description	Quantity
MSPL0507	5 x 7 cm	Gentrix Surgical Matrix Plus	1/box
MSPL0710	7 x 10 cm	Gentrix Surgical Matrix Plus	1/box
MSPL1010	10 x 10 cm	Gentrix Surgical Matrix Plus	1/box
MSPL1015	10 x 15 cm	Gentrix Surgical Matrix Plus	1/box

Gentrix Surgical Matrix Thick

Item Number	Size	Description	Quantity
PSMT1020	10 x 20 cm	Gentrix Surgical Matrix Thick	1/box
PSMT1620	16 x 20 cm	Gentrix Surgical Matrix Thick	1/box
PSMT2020	20 x 20 cm	Gentrix Surgical Matrix Thick	1/box
PSMT2025	20 x 25 cm	Gentrix Surgical Matrix Thick	1/box
PSMT2030	20 x 30 cm	Gentrix Surgical Matrix Thick	1/box
PSMT3030	30 x 30 cm	Gentrix Surgical Matrix Thick	1/box
PSMT3040	30 x 40 cm	Gentrix Surgical Matrix Thick	1/box

Indication Statements

Gentrix Surgical Matrix Thin (3-Layer) is intended for implantation to reinforce soft tissue where weakness exists in patients requiring urological, gastroenterological, or plastic & reconstructive surgery. Reinforcement of soft tissue within urological, gastroenterological, and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Surgical Matrix Thin minimizes tissue attachment to the device in case of direct contact with viscera.

Gentrix Surgical Matrix (6-Layer) is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia (e.g. hiatal/diaphragmatic) and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Surgical Matrix minimizes tissue attachment to the device in case of direct contact with viscera.

Gentrix Hiatal (6-Layer) is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia (e.g. hiatal/diaphragmatic) and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Hiatal minimizes tissue attachment to the device in case of direct contact with viscera.

Gentrix Surgical Matrix Plus (8-Layer) is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia (e.g. hiatal/diaphragmatic) and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Surgical Matrix Plus minimizes tissue attachment to the device in case of direct contact with viscera.

Gentrix Surgical Matrix Thick (8-Layer) is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following procedures: hernia and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair.

Regulatory Status - 510(k) Clearances

The following table lists the brand names of all Gentrix Surgical Matrix devices utilizing MatriStem UBM technology and the corresponding 510(k) premarket submission numbers* under which the devices are legally marketed in the United States:

ACell Device Brand Names	510(k) Numbers
Gentrix Surgical Matrix Thin Gentrix Surgical Matrix Gentrix Hiatal Gentrix Surgical Matrix Plus	K182259
Gentrix Surgical Matrix Thick	K170763

* FDA premarket submission number means the number assigned by FDA to a premarket device submission (21 CFR807.3(w)). A 510(k) is a premarket device submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.92(a)(3)) that is not subject to premarket approval and does not, in any way, denote official approval of the device.

Pre-Clinical Data Review

UBM has a considerable breadth of research supporting its value in surgical settings. The extensive body of research on MatriStem UBM technology includes more than 100 pre-clinical and 50 clinical peer-reviewed articles. The following highlights several of the pre-clinical studies performed to date.

Study	Outcome	Publication
Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials[20]* (2012) Study evaluating the tissue remodeling response to 14 different commercially available biologic surgical mesh devices in a rat model of abdominal wall repair	• Remodeling of the ECMs was measured using a histologic assessment, and scoring was then correlated to the macrophage phenotype. • MatriStem UBM technology showed evidence of a favorable host remodeling response at both 14 and 35 days, including islands of skeletal muscle at the surgical site at 35 days. • Of the devices evaluated, MatriStem UBM technology had the highest histologic score and highest M2:M1 ratio at both 14 and 35 days which may be a predictor for site-appropriate tissue formation by the host.	
Retrorectus repair of incisional ventral hernia with urinary bladder matrix reinforcement in a long-term porcine model[21] (2018) Study evaluating the mechanical and tissue remodeling characteristics of the abdominal wall following reinforcement with UBM in a large animal ventral hernia model	• An acute midline abdominal defect was created in adult Yucatan mini pigs and then repaired using a retromuscular approach. Repairs were reinforced with either Gentrix Surgical Matrix Plus, Gentrix Surgical Matrix Thick, or left as a primary suture control. Animals were survived to either three or eight months, with four animals per treatment group per time point. • At eight months post-op, reinforcement of hernias with Gentrix devices prevented recurrence throughout the course of observation compared to 50% of recurrence in non-reinforced controls. • Furthermore, all UBM devices showed full remodeling at eight months, evidenced by the deposition of vascularized tissue mimicking the appearance and strength of natural, uninjured posterior fascia.	

* Some products in study are not currently commercially available.

Pre-Clinical Data Review

Study	Outcome	Publication
Comparison of in vivo remodeling of urinary bladder matrix and acellular dermal matrix in an ovine model[8] (2018) Study evaluating the host response and mechanical performance of two extracellular matrix-derived materials in a sheep model of fascial repair	• Bilateral defects were created in the fascia lata on both sides of the sheep. One side was repaired with Gentrix Surgical Matrix Plus, and the contralateral side was repaired with Strattice® Firm (AbbVie®/Allergan®). Animals were sacrificed at one month (n=3) and three months (n=4). • At three months, Gentrix devices were completely remodeled and replaced with organized, vascularized tissue. In contrast, the Strattice devices could be identified with a clear boundary between the device and the surrounding fascial tissue. • Throughout the study, the Gentrix group maintained a mechanical strength and stiffness that was similar to native, uninjured fascia. Strattice demonstrated significantly higher strength than Gentrix and native fascia pre-implantation, but steadily decreased throughout the study. By the end, there was no difference in the strength between the two devices.	
Biomechanical features of reinforced esophageal hiatus repair in a porcine model[26] (2019) Study comparing the biomechanical characteristics and histologic remodeling of nonabsorbable synthetic, absorbable synthetic, and resorbable biologic materials in a porcine laparoscopic hiatal hernia model	• A hiatal defect was created in Landrace pigs and then the repair was reinforced with either Prolene® (Polypropylene; Ethicon®), Gore® BIO-A® (Polyglycolic Acid: Trimethylene Carbonate mesh; Gore®), Gentrix Surgical Matrix Plus (Urinary Bladder Matrix; ACell) or left as a primary suture control. There were five animals in each test group and they were survived to three months. • Histological analysis of the Prolene and Gore BIO-A groups showed mononuclear infiltrates and a large foreign body reaction characterized by fibroencapsulation, necrosis, remnants of mesh, and disorganized tissue. The Gentrix group, however, showed well-organized tissue with aligned collagen fibers resembling native tissue. • Biomechanically, pigs in the groups reinforced with Prolene or Gore BIO-A showed more signs of stiffness and fibrosis compared to the Gentrix group.	

Additional Pre-Clinical Research

Title	Author
Mechanical strength vs. degradation of a biologically-derived surgical mesh over time in a rodent full-thickness abdominal wall defect.	Costa et al.
Urinary bladder matrix scaffolds strengthen esophageal hiatus repair.	Riganti‡ et al.

Backed by Published Clinical Data

Long-term clinical, radiological, and histological follow-up after complex ventral incisional hernia repair using urinary bladder matrix graft reinforcement: a retrospective cohort study[9]

Sasse KC[¶], Lambin JH, Gevorkian J, Elliott C, Afshar R, Gardner A, Mehta A, Lambin R, Peraza L. Hernia. 2018; doi: 10.1007/s10029-018-1830-0

Overview

This peer-reviewed, retrospective clinical study evaluated the use of Gentrix Surgical Matrix Thick, an extracellular matrix (ECM) scaffold derived from urinary bladder matrix (UBM) when used to reinforce complex ventral hernia repairs. Sixty-four patients underwent repair of complex incisional hernias with UBM reinforcement by a single treating surgeon. Post-operative follow up ranged from 12-70 months, with a median follow-up time of 36 months. A 24-month statistical analysis displayed a 4% recurrence rate, while the overall recurrence rate was 15.6%. Radiographic and histological imaging displayed a long-term, durable, biomechanically functional repair. Study results provide clinical evidence of safety and efficacy when utilizing UBM for reinforcement following a complex ventral hernia repair.

Results

Sixty-four patients had complex ventral incisional hernia repair with UBM reinforcement, where 35 patients (55%) had the UBM graft placed in the retrorectus position after component separation and 28 patients (44%) had the UBM graft placed in the intraperitoneal position. One graft placement was not specified. Average graft size was 610 cm^2. Overall, the patient population was complex, with 84% classified as "major" (Slater severity classification system). Thirty-eight patients (59%) had a failed previous hernia repair, including eleven cases involving excision of prior synthetic mesh. Forty-two patients (66%) had concomitant procedures performed.

The median follow up time was 36 months (range 12-70 months) from the time of surgery. The total recurrence rate was 15.6%, with a median time to recurrence of 32 months. Ten patients developed a recurrent ventral hernia, with nine patients repaired surgically and one patient managed nonoperatively. A 4% recurrence rate was displayed at 24 months (Kaplan-Meier freedom from recurrence statistical analysis). Overall patient demographics and results are detailed in Tables 1-3 (right).

Conclusions

In this retrospective case series, with a 36-month median follow up, the utilization of Gentrix Surgical Matrix Thick in challenging and complex hernia repair resulted in successful resolution with a 15.6% recurrence rate. This compares favorably to other recently published studies utilizing biologically-derived ECMs in hernia repair with similar patient populations and shorter follow up periods. Two of the most comparable studies had recurrence rates of 23.4% and 31.8% at 24 months and 18 months respectively[19,22]. In this study, there were no cases of erosion, fistulization, or bowel obstruction. There was also no graft-related infection or UBM graft explantation. Uniquely, this study also included histological analysis at extended time points, highlighting the site-appropriate remodeling of Gentrix devices by the body.

Table 1.

Patient Characteristics

Number of Patients	64
Median Age	59 years (25-98)
Avg. BMI	33 kg/m^2 (21-72)
Avg. Graft Size	610 cm^2 (70-1200 cm^2)
Median Follow Up	36 months (12-70 months)

Table 2.

Patient Comorbidities

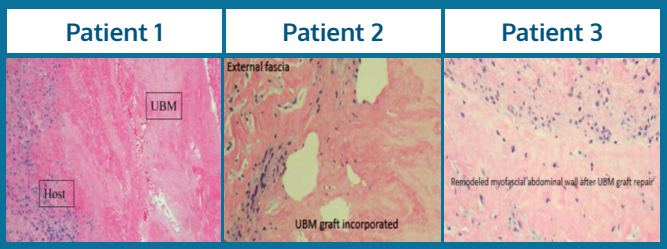
Previously Failed Repair	38 (59%)
Stoma Present	16 (25%)
Bowel Fistula at Time of Repair	3 (5%)
Incarcerated Bowel or Omentum	30 (47%)
Diabetes	18 (28%)
Old Mesh Excised	9 (14%)
Concomitant Procedures	42 (66%)

Table 3.

Overall Results

Parameter	Total (64)	Retrorectus (35)	Other (29)
Median Follow Up Time (months)	36 (12–70)	34 (15–70)	44 (12–69)
Total Recurrences	10 (15.6%)	8 (23%)	2 (7%)
Median Time to Hernia Recurrence (months)	32 (4–51)	32 (5–51)	25 (4–45)
Surgery for Repair of Hernia Recurrence	9 (14%)	7 (20%)	2 (7%)
Seroma	12 (19%)	9 (26%)	3 (10%)
Major Wound Care	13 (20%)	7 (20%)	6 (21%)
Median CCS Score (out of 115 possible)	16 (1–106)	18 (1–106)	12 (1–96)

Histology Images



H&E stains at 14 months post-retrorectus Gentrix placement (patient 1), at three years post-intraperitoneal repair with Gentrix (patient 2) and at 32 months post-retrorectus Gentrix repair (patient 3) showed incorporation of the graft and a remodeling response at the interface between the host and the graft.

Full-thickness fascial biopsies at the UBM graft repair were obtained from the three patients who underwent surgery for unrelated reasons. Biopsies of the repaired fascia (retrorectus and intraperitoneal placement) were histologically analyzed. In all cases, a remodeling response characterized by cell infiltration and absence of inflammatory response was observed.

Clinical Publications

Title	Author
Esophageal reinforcement with an extracellular scaffold during total gastrectomy for gastric cancer.	Afaneh et al.
Paraesophageal hiatal hernia repair with urinary bladder matrix graft.	Howell et al.
Endoscopic deployment of MatriStem for treatment of a colorectal anastomotic leak.	Iorio et al.
Laparoscopic rectopexy with urinary bladder xenograft reinforcement.	Mehta et al.
Use of scaffolding tissue biografts to bolster vesicourethral anastomosis during salvage robot-assisted prostatectomy reduces leak rates and catheter times.	Ogaya-Pinies et al.
Different biologic grafts for diaphragmatic crura reinforcement during laparoscopic repair of large hiatal hernia: a 6-year single surgeon experience.	Reznichenko
Long-term clinical, radiological, and histological follow-up after complex ventral incisional hernia repair using urinary bladder matrix graft reinforcement: a retrospective cohort study.	Sasse[¶] et al.
Parastomal hernia repair with urinary bladder matrix grafts: case series with 2-year follow-up and discussion.	Sasse[¶] et al.

Clinical Landscape

	Itani et al.[22] April 2012 (The RICH Study)	Rosen et al.[27] June 2013	Huntington et al.[19] Dec 2016	Sasse[1] et al.[9] June 2018
Study Type	Prospective, Multicenter Observational	Retrospective Analysis of a Prospectively Maintained Database, Single-Center	Prospectively Enrolled Operative Outcomes Database, Single-Center	Retrospective, Single-Center, Observational
Product Used	Strattice™	80% Strattice 13% AlloDerm® 3% Biodesign® 3% Xenmatrix™ 3% Bio-A®	18% AlloDerm 10% AlloMax™ 31% FlexHD® 31% Strattice 10% XenMatrix	Gentrix®
# of Patients	80	128	223	64
Comorbidities/ Patient Characteristics	Previous Infection: 34% Prior VIHR: 64% Infected Mesh Excision: 19% Diabetes: 21% Obesity: 23% Smoking: 18%	Avg. # of Previous Hernia Repairs: 2.5 Infected Mesh: 35% Diabetes: 51% Smoking: 23%	Prev. Abdominal Operation: 96% Infected Mesh: 28% Diabetes: 36% Obesity: 30% Smoking: 31%	Previously Failed Repair: 59% Incarcerated Bowel: 47% Concomitant Procedures: 66% Old Mesh Excision: 14% Diabetes: 28%
Average BMI	75% < 30.0 kg/m^2	34.1 kg/m^2	34.8 kg/m^2	33 kg/m^2
Average Defect Size	236 cm^2	431 cm^2	257 cm^2	Not Available
Average Mesh Size	86%: 20 cm x 20 cm	Not Available	384 cm^2	610 cm^2
Mesh Placement	Intraperitoneal Underlay: 60% Retrorectus: 36% Onlay: 4%	Intraperitoneal Underlay: 31% Retrorectus: 66% Onlay or Sandwiched: 3%	Preperitoneal Space: 38%	Retrorectus: 55% Intraperitoneal Underlay: 44% Undetermined: 2%
Component Separation or Bridging	Component Separation: 65% Bridging: 20%	Component Separation: 70% Bridging: 6%	Component Separation: 48% Bridging: 20%	Component Separation: 55% Bridging: 0%
Average Follow Up	24.0 Months	21.7 months	18.2 months	36.0 months
Complexity	VHWG Grade I: 0% Grade II: 0% Grade III: 75% Grade IV: 25%	CDC Class I: 0% Class II: 34% Class III: 39% Class IV: 27%	ASA Stage I & II: 36% Stage III: 55% Stage IV: 10%	Slater Mild: 0% Moderate: 16% Major: 84%
Recurrence	Overall: 28% Excluding Bridged Patients: 23%	31.3%	31.8%	15.6%
Wound Events	Overall Wound Events: 66% Infection: 35% Seroma: 29% Wound Edge Separation: 18% Fistula: 3%	Overall Wound Morbidity: 48% • Major: 46% • Minor: 54%	Wound Infection: 37% Seroma: 25% Wound Dehiscence: 13%	Major Wound Care: 20% Seroma: 19%

Note: Data from studies is organized for efficiency. The studies above are completely independent of each other, and therefore cannot be directly compared.

Competitor Products Overview

	Gentrix	XenMatrix	Strattice	SurgiMend®	BioDesign	Ovitex®	Permacol™	XCM Biologic®
Manufacturer/ Distributor	ACell®	BD®	AbbVie®	Integra®	Cook®	TelaBio®	Medtronic®	Ethicon® (J&J®)
Material	Porcine Urinary Bladder Matrix	Porcine Dermis	Porcine Dermis	Bovine Dermis	Porcine Small Intestine Submucosa	Ovine Rumen with Polypropylene or Polyglycolic Acid	Porcine Dermis	Porcine Dermis
Crosslinked	No	No	No	No	No	No	Yes	No
Smallest Size	5 x 5 cm	6 x 6 cm	6 x 6 cm	0.3 x 25 cm	2 x 3 cm	4 x 8 cm	1 x 4 cm	6 x 12 cm
Largest Size	30 x 40 cm	30 x 45 cm	25 x 40 cm	25 x 40 cm	20 x 30 cm	25 x 40 cm	28 x 40 cm	25 x 35 cm
Multiple Thicknesses/ Layering	3-Layer 6-Layer 8-Layer	No	Strattice RTM Strattice RTM Extra Thick	1.0 mm 2.0 mm 3.0 mm 4.0 mm	4-Layer 8-Layer	4-Layer 6-Layer 8-Layer	0.5 mm 1.0 mm 1.5 mm	Not Specified
Open & Laparoscopic Options	Yes	Yes	Yes	Laparoscopic Not Stated in IFU	Yes	Yes	Laparoscopic Not Stated in IFU	Yes
Pre-Cut Hiatal Option	Yes	No	No	No	Yes	No	No	No

Note: All information procured from active product websites and accurate to the best of our knowledge as of December 2020. Information is subject to change without notice.

Reimbursement

Hospital Inpatient Codes and Payments

The following code list has examples of potential ICD-10 procedure codes that are available for hospitals when reporting inpatient hernia procedures.

Hernia Procedures	Operating Room Procedures
0DV40ZZ	Restriction of Esophagogastric Junction, Open Approach
0BQT0ZZ	Repair Diaphragm, Open Approach
0BQT4ZZ	Repair Diaphragm, Percutaneous Endoscopic Approach
0BUT0KZ	Supplement Diaphragm with Nonautologous Tissue Substitute, Open Approach
0D1K0Z4	Bypass Ascending Colon to Cutaneous, Open Approach
0D1L0Z4	Bypass Transverse Colon to Cutaneous, Open Approach
0D1M0Z4	Bypass Descending Colon to Cutaneous, Open Approach
0D1N0Z4	Bypass Sigmoid Colon to Cutaneous, Open Approach
0DQ54ZZ	Repair Esophagus, Percutaneous Endoscopic Approach
0DU64KZ	Supplement Stomach with Nonautologous Substitute, Percutaneous Endoscopic Approach
0DV44ZZ	Restriction of Esophagogastric Junction, Percutaneous Endoscopic Approach
0VB50ZZ	Excision of Scrotum, Open Approach
0WBFXZ2	Excision of Abdominal Wall, Stoma, External Approach
0WQF0ZZ	Repair Abdominal Wall, Open Approach
0WQF3ZZ	Repair Abdominal Wall, Percutaneous Approach
0WQF4ZZ	Repair Abdominal Wall, Percutaneous Endoscopic Approach
0WQFXZ2	Repair Abdominal Wall, Stoma, External Approach
0WQFXZZ	Repair Abdominal Wall, External Approach
0WUF0KZ	Supplement Abdominal Wall with Nonautologous Tissue Substitute, Open Approach
0WUF4KZ	Supplement Abdominal Wall with Nonautologous Tissue Substitute, Percutaneous Endoscopic Approach
0YQ50ZZ	Repair Right Inguinal Region, Open Approach
0YQ54ZZ	Repair Right Inguinal Region, Percutaneous Endoscopic Approach
0YQ60ZZ	Repair Left Inguinal Region, Open Approach
0YQ64ZZ	Repair Left Inguinal Region, Percutaneous Endoscopic Approach
0YQA0ZZ	Repair Bilateral Inguinal Region, Open Approach
0YQA4ZZ	Repair Bilateral Inguinal Region, Percutaneous Endoscopic Approach
0YU50KZ	Supplement Right Inguinal Region with Nonautologous Substitute, Open Approach
0YU54KZ	Supplement Right Inguinal Region with Nonautologous Substitute, Percutaneous Endoscopic Approach
0YU60KZ	Supplement Left Inguinal Region with Nonautologous Substitute, Open Approach
0YU64KZ	Supplement Left Inguinal Region with Nonautologous Substitute, Percutaneous Endoscopic Approach
0YUA0KZ	Supplement Left Bilateral Region with Nonautologous Substitute, Open Approach
0YUA4KZ	Supplement Bilateral Inguinal Region with Nonautologous Substitute, Percutaneous Endoscopic Approach

Reimbursement

Full reimbursement guides available at
www.acell.com/reimbursement

MS-DRGs - Hospital Inpatients

The 2020 Medicare payment rates, listed in the table below, are national unadjusted payment rates. Check with your MAC for payment rates specific to your region.

MS-DRG	MS-DRG Description*	National Average MS-DRG Rate Payment**
Inguinal, Lumbar, Ventral, Umbilical, Spigelian & Epigastric Hernia Repair		
350	Inguinal and femoral hernia procedures with mcc	$15,591.26
351	Inguinal and femoral hernia procedures with cc	$9,475.29
352	Inguinal and femoral hernia procedures without cc/mcc	$7,012.38
353	Hernia procedures except inguinal and femoral with mcc	$19,125.32
354	Hernia procedures except inguinal and femoral with cc	$11,335.51
355	Hernia procedures except inguinal and femoral without cc/mcc	$8,641.18
Hiatal Hernia Repair		
326	Stomach, esophageal and duodenal procedures with mcc	$34,189.00
327	Stomach, esophageal and duodenal procedures with cc	$16,590.66
328	Stomach, esophageal and duodenal procedures without cc/mcc	$10,588.50
Parastomal Hernia Repair		
347	Anal and stomal procedures with mcc	$15,649.75
348	Anal and stomal procedures with cc	$8,534.38
349	Anal and stomal procedures without cc/mcc	$6225.95

* Comorbidities and Complications/Major Comorbidities and Complications (cc/mcc)

** DRG values calculated using a base rate of $5,891.33 and Capital Standard Payment of $466.22. The national average hospital Medicare base rate is an average of the sum of four categories: Hospital Submitted Quality Data and is a Meaningful EHR User, Hospital Did NOT Submit Quality Data and is a Meaningful EHR User, Hospital Submitted Quality Data and is NOT a Meaningful EHR User, Hospital Did NOT Submit Quality Data and is NOT a Meaningful EHR User. This information is provided as a benchmark reference only. There is no official publication of the average hospital base rate; therefore, the national average payments provided are approximate. Actual reimbursement will vary by geographic region, status as a teaching facility, share of low-income patients, status of submitting quality data, status as a meaningful electronic health user, participation in the Hospital Value-Based Purchasing (VBP), and Hospital Readmissions Reduction Program (HRRP). Calculations were based on data provided in FY 2021 IPPS Final Rule CN (Tables 1A, 1D, and 5CN). It is always the provider's responsibility to determine and submit appropriate codes, charges, and modifiers for services rendered.

Non-HCT/P Letter

ACell®
Healing Through Regenerative Medicine

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Website: www.acell.com

July 10, 2019

Re: ACell, Inc. MicroMatrix®, Cytal®, and Gentrix® Devices

To Whom It May Concern:

This letter is written on behalf of ACell, Inc. ("ACell"). ACell manufactures and provides for distribution all commercially available MicroMatrix®, Cytal®, and Gentrix® medical devices. Each of these devices incorporates ACell's patented MatriStem UBM™ technology (hereinafter these devices will be referred to collectively as "MatriStem UBM Devices"). ACell maintains current medical device establishment registrations and medical device listings with the United States Food and Drug Administration ("FDA") for all of its MatriStem UBM Devices.

Specifically, ACell markets its MatriStem UBM Devices pursuant to the 510(k) clearance notification numbers noted in parentheses below, which are issued to ACell by FDA's Center for Devices and Radiological Health ("CDRH"):

- MicroMatrix® (K172399)
- Cytal® Wound Matrix 1-Layer (K152721)
- Cytal Wound Matrix 2-Layer (K152721)
- Cytal Wound Matrix 3-Layer (K152721)
- Cytal Wound Matrix 6-Layer (K152721)
- Cytal Burn Matrix (K152721)
- Gentrix® Surgical Matrix Thin (K182259)
- Gentrix Surgical Matrix (K182259)
- Gentrix Surgical Matrix Plus (K182259)
- Gentrix Surgical Matrix Thick (K170763)
- Gentrix Incisional (K040621)
- Gentrix Surgical Matrix Hiatal (K182259)

MatriStem UBM Devices are acellular xenografts derived from porcine urinary bladder. This material does **not** contain human tissue or human cells, nor any type of dermal derivative of any kind. Consequently, none of ACell's MatriStem UBM Devices are regulated by Center for Biologics Evaluation and Research ("CBER") as "human cells, tissues, and cellular and tissue-based products" ("HCT/Ps") or as "biologics". Therefore, the following documentation does not apply to ACell's current product line:

- CLIA License – ACell does not process human tissue; therefore donor testing by a CLIA licensed laboratory is not a requirement for our current product line
- FDA Form 3356 – ACell does not manufacture nor do its medical devices contain any human cells, tissues, and/or human cellular elements. Therefore, ACell is not regulated by the FDA as an HCT/P
- AATB Certificate – ACell medical devices are not human tissue products, and therefore do not qualify to receive certification issued by the American Association of Tissue Banks.

Please do not hesitate to contact me with any questions regarding this letter.

Best,

Michelle Huettner
Director of Regulatory Affairs

cc: Chris Branch, General Counsel

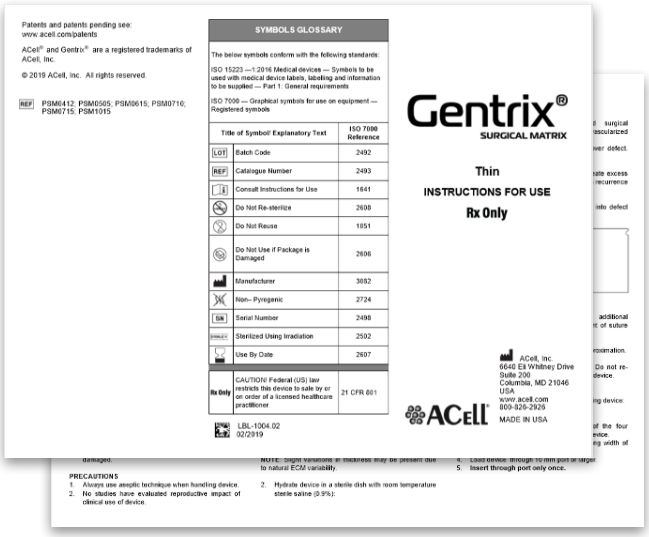
6640 Eli Whitney Dr. Suite 200 Columbia, MD 21046

MK-0517.3
2019

Instructions For Use

Full IFUs available at
www.acell.com/instructions-for-use

Gentrix Surgical Matrix Thin



Gentrix®
SURGICAL MATRIX
Thin
INSTRUCTIONS FOR USE
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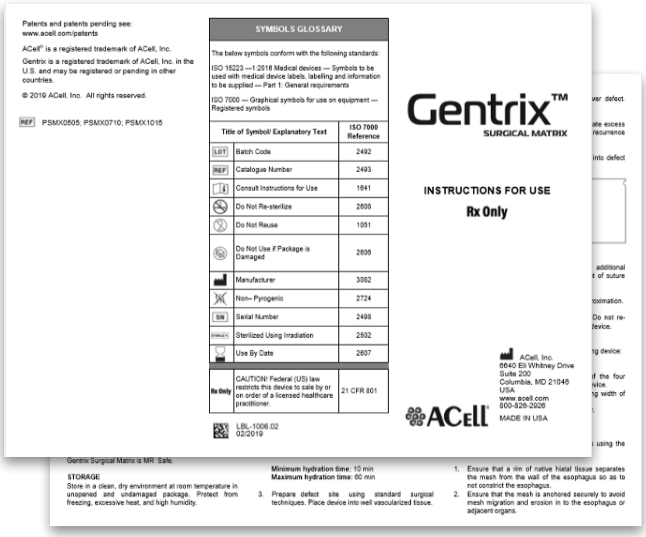
Gentrix Surgical Matrix



Gentrix™
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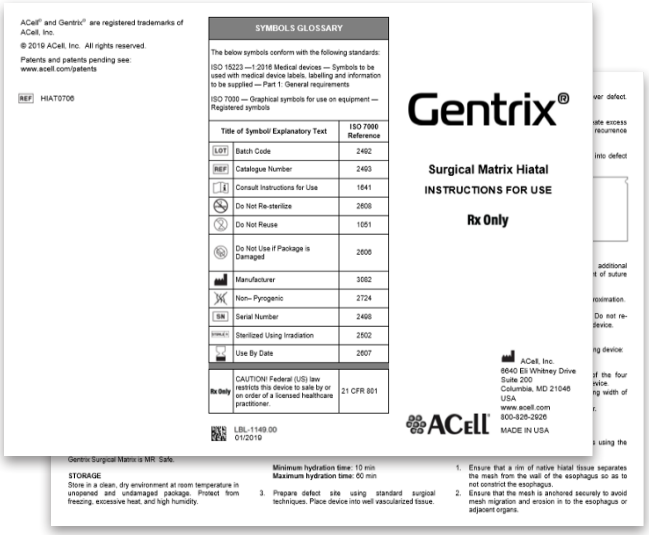
Gentrix Hiatal



Gentrix®
Surgical Matrix Hiatal
INSTRUCTIONS FOR USE
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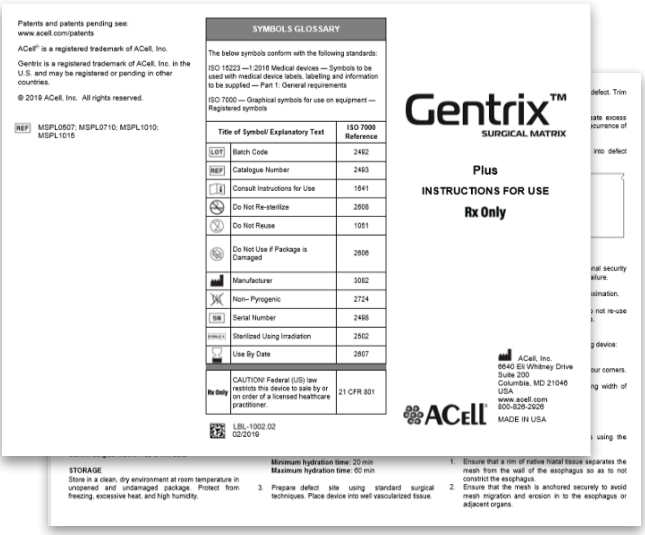
Gentrix Surgical Matrix Plus



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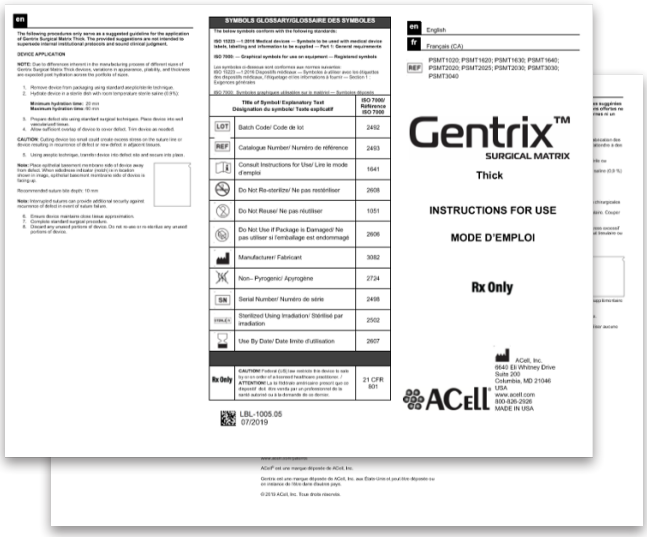
Gentrix Surgical Matrix Thick



Gentrix™
SURGICAL MATRIX
Thick

INSTRUCTIONS FOR USE

MODE D'EMPLOI

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8640 Bl Whitney Drive
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USA
www.acell.com
800-926-2926
MADE IN USA

LBL-1005.05
07/2019

MATERIALS MANAGEMENT INFORMATION

Training and Education

In addition to online resources, ACell offers training events for healthcare professionals throughout the year. These educational resources provide opportunities for clinicians to learn about the safe and effective use of Gentrix Surgical Matrix devices.

Under the direction of course faculty, program attendees may participate in didactic sessions and cadaver labs highlighting the use of Gentrix devices for abdominal wall reconstruction and other hernia repair procedures. Upon completion of these courses, attendees will be able to:

- Identify patient selection criteria when utilizing Gentrix Surgical Matrix devices
- Confidently handle and implant Gentrix devices
- Apply surgical techniques to implant Gentrix Surgical Matrix devices

ACell is committed to providing physicians with as many educational resources as possible, including a team of knowledgeable product specialists, videos, and technique guides, to ensure Gentrix Surgical Matrix device users feel confident while using the devices.

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