Endoform™ Dermal Template - Authentic Complexity

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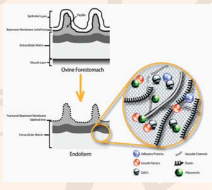
Abstact: We have generated a new biologically-derived extracellular matrix (ECM) termed 'Endoform', to meet existing needs within wound care and emerging needs for tissue regeneration sca olds. A novel tissue processing procedure has been developed to render the ECM of ovine forestomachs acellular, while conserving its inherent biological and physical properties. As such, Endoform retains a biologically rich collagen matrix, and importantly, a host of co-factors that are critical for cellular growth and tissue regeneration. An analysis of the microstructure of Endoform con rmed removal of the epithelial and muscle layers, partial retention of the basement membrane and the native 3-dimensional collagenaceous matrix. A biochemical comparison of Endoform and the commercial ECM-based product OaSIS™revealed that the two products were grossly similar. However, an important distinction was Endoform's elevated concentrations of bronection , an important cell adhesion molecule. Endoform was shown to be non-toxic towards mammalian cell lines ***in vitro***, and was well tolerated in a porcine full thickness excisional wound model. In a porcine model cells penetrated into the Endoform matrix via open micro-architecture, and the matrix underwent a natural process of remodelling. Importantly, Endoform induced signi cantly higher levels of cell di erientation and vasculatization relative to OaSIS™. A biophysical study demonstrated that Endoform had excellent performance characteristics for clinical applications. In some instances, Endoform outperformed leading commercial products.

Summary: Endoform is a promising new material for clinical applications in wound care and tissue regeneration. Studies ***in vitro*** and ***in vivo*** have demonstrated its applicability and outstanding performance characteristics. Endoform's properties can be attributed to its complimentary biochemical, architectural and biophysical properties, termed 'authentic complexity', which make this a unique and robust matrix material for immediate clinical applications.



Macroscopic Characterization

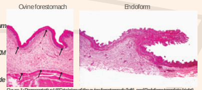


Figure 1: Representative H&E staining of the ovine forestomach (left), and Endoform template (right). 10x Magni cation. The muscle:ECM junction and epithelium:ECM junction are indicated by black arrows in the left panel.

Endoform is prepared using a proprietory processing method to decellularize and delaminate ovine forestomach tissue. Histology was used to demonstrate e ective removal of the epithelial and muscle layers (**Figure 1**). Immunohistochemistry staining for collagen IV and laminin demonstrated the existence of a partially intact basement membrane (**Figure 2**), which would be expected to have important implications to cell adhesion to Endoform.

Nuclear staining (**Figure 3**) demonstrated Endoform was essentially acellular, and retained the complex collagenaceous matrix (**Figure 4**)

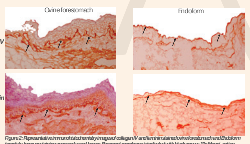


Figure 2: Representative immunohistochemistry images of collagen IV and laminin stained ovine forestomach and Endoform template. Immunostaining appeared as red-brown. Basement membrane is indicated with black arrows. 10x Magni cation.

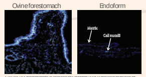


Figure 3: Representative images of Hoescht 33258 stained sections of ovine forestomach and Endoform template. Cells appear as intense blue uorescence while the matrix and connective tissues appear more di use. 20x Magni cation.

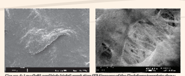


Figure 4: Low (left) and high (right) resolution SEM images of the Endoform template showing the relatively smooth luminal surface (left) and the complex collagenaceous matrix underlying the basement membrane (right).

Biochemical Characterization

	Ovine Forestomach		Endoform		OaSIS™	
	(mg/g ± SE)¹	% composition	(mg/g ± SE)²	% composition	(mg/g ± SE)¹	% composition ³
Total Collagen	142.7 ± 9.7	40.5	821.0 ± 9.0	86.4	629.7 ± 39.7	80.6
Soluble Collagen	55.3 ± 3.21	-³	71.2 ± 16.3	-³	48.7 ± 5.3	-³
Collagen III	61.3 ± 0.7	-³	196.8 ± 6.9	-³	171.5 ± 11.1	-³
Collagen IV	46.6 ± 1.5	-³	9.7 ± 2.1	-³	6.6 ± 1.1	-³
Soluble Elastin	112.0 ± 15.0	32.0	36.6 ± 5.7	4.2	54.0 ± 6.1	6.9
Insoluble Elastin	30.9 ± 6.4	8.8	27.5 ± 4.5	3.2	41.4 ± 5.0	5.3
Total GAG's	3.9 ± 0.1	1.1	1.5 ± 0.3	0.2	7.3 ± 0.4	0.9
Hyaluronic Acid	1.95 ± 0.02	0.6	0.4 ± 0.1	0.1	1.58 ± 0.11	0.2
Heparin Sulphate	N.D.⁴	-	N.D.⁴	-	2.1 ± 0.1	-⁵
DNA	9.0 ± 0.5	2.6	2.2 ± 0.5	0.3	2.7 ± 0.2	0.4
Lipid	50.2 ± 2.9	14.4	59.0 ± 5.2	5.7	44.7 ± 4.0	5.7

Table 1: Major biochemical components of the ovine forestomach, and the matrices, Endoform and OaSIS™. ¹Errors represent standard error from triplicate experiments. ²Errors represent standard errors from three independent production lots, tested in triplicate. ³Percentage composition based on total collagen from the hydroxyproline analysis only, excludes collagen III, collagen IV and soluble collagen. ⁴N.D. = Not detected. ⁵Percentage composition excludes heparin sulphate as this is included in total GAG's.

The major and minor biochemical components of Endoform and OaSIS™ were quanti ed using established techniques.

Endoform was shown to be a 'rich' biological matrix containing connective, adhesion and signaling proteins, all of which play critical roles in cell adhesion, di erientation and proliferation. The matrix was mainly composed of collagen, including types III and IV. Elastin was present in high concentrations as well as GAGs and bronectin. On the whole Endoform had comparable biochemistry to OaSIS™ apart from elevated bronectin concentrations.

Importantly, the basement membrane proteins laminin and collagen IV were present, a nding that parallels IHC studies (**Figure 2**). Further studies are being conducted to understand the biological signi cance of these ndings, as well as identify additional matrix components.

	¹Ovine Forestomach (mg/g ± SE)	²Endoform (mg/g ± SE)	¹OaSIS™ (mg/g ± SE)
Fibronectin	15.30 ± 1.17	13.67 ± 1.64	5.00 ± 0.50
Laminin	6.30 ± 0.24	9.65 ± 4.54	6.80 ± 0.30
FGF2	1.70 ± 1.38	1.47 ± 0.32	4.85 ± 0.84

Table 2: Minor biochemical components of the ovine forestomach, Endoform and OaSIS™. ¹Errors represent standard error from triplicate experiments. ²Errors represent standard errors from three independent production lots, tested in triplicate.

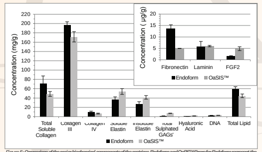


Figure 5: Comparison of the major biochemical components of the matrices, Endoform and OaSIS™. Errors for Endoform represent the standard error from three independent production lots, tested in triplicate. Errors for ovine forestomach and OaSIS™ represent standard errors from triplicate experiments. Figure 6: (insert) Comparison of the minor biochemical components of the matrices, Endoform and OaSIS™. Errors for Endoform represent the standard error from three independent production lots, tested in triplicate. Errors for ovine forestomach and OaSIS™ represent standard errors from triplicate experiments.

In Vivo E cacy - Porcine Model of Wound Healing

In order to evaluate the ***in vivo*** tolerance of Endoform and determine its e ectiveness in stimulating tissue regeneration and to undergo remodelling, we conducted a comprehensive wound healing study in pigs. The porcine wound healing model is generally considered to be the best of the animal models with which to study the wound healing process and to evaluate the e ectiveness of clinical or therapeutic interventions. Numerous studies have been published describing the use of exogenous extracellular matrix (ECM) products in wound healing studies in rodent and pig models, so this current study was well bench-marked in the literature (Hodde, 2002).

On day 0 of the study, a total of 20 full thickness 20 mm diameter wounds were surgically created on the back of a 6 week old anaesthetised female pig (approx. 18-20 kg) using a dermal punch. The wounds were created in four columns of 5 rows, spaced 3 cm apart, according to **Figure 16**. A total of ve animals were used in the study (100 wound sites).

Each of the wounds is either untreated, or treated with sterile Endoform template (termed 'FM'), 2-ply laminated Endoform (termed 'LFM') or the established wound matrix product, OaSIS™. In each case, a circular piece of wound matrix (20 mm diameter) was applied to the wound and rehydrated in situ by the application of sterile saline. In order to average any positional bias, the location of the four treatments was changed between each animal, such that the no two animals received the same treatment layout. Treated and untreated wounds were dressed identically.

On days 0, 3, 7, 14, 28 and 42 all wounds were digitally imaged and the wound area and depth (height, if appropriate) were recorded. Additionally, a single row of wounds from each animal was biopsied. While under anaesthesia the wound, as well as, a portion of normal tissue from the wound margins was surgically excised. All biopsies were formalin xed, mounted, sectioned and stained for analysis.

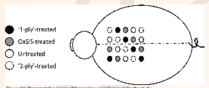


Figure 16: Representative image of the porcine wound map used in the study.

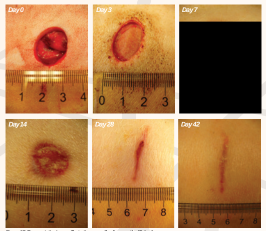


Figure 17: Representative images illustrating wound healing over the 42 day time course

Endoform Persistence and Remodeling

An examination of xed tissue biopsies taken during the course of the study provided evidence that Endoform was in ltrated by cells during the healing process (**Figure 18**). ECM's (FM, LFM or OaSIS™) appeared as green ribbons in Gomori's trichrome stained sections, and ECM's were especially prominent at day 7 (indicated by black arrows, Figure 10). Cells were clearly visible within the exogenous ECM collagen sca old at day 7. Both the Endoform matrices and the commercial product OaSIS™ were visible for approximately 14-28 days, after which time the matrices were fully degraded and mature collagen laid-down in a process of remodelling. No matrix was visible in wounds on day 42.

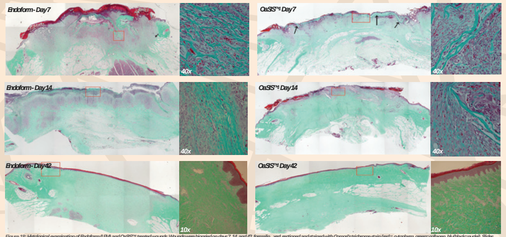


Figure 18: Histological examination of Endoform (LFM) and OaSIS™ treated wounds. Wounds were biopsied on days 7, 14 and 42, formalin xed, sectioned and stained with Gomori's trichrome stain [illegible] Sections were imaged at 4x, 10x (days 42) and 40x (days 7 and 14). Higher magni cations were taken [illegible]

Endoform Increases Cell Di erentiation and Vascularization

Cell Di erientation: In order to quantify cell proliferation, immunohistochemistry of biopsied tissue was conducted using the cell marker Ki67. Ki67 is a protein that is expressed during all active phases of the cell cycle, and is therefore a useful marker of cell proliferation and cellular activity. Ki67 is not expressed in resting cells.

Formalin xed biopsy tissues were mounted, sectioned and active cells were then detected using a Ki67 primary antibody and staining developed using HRP-conjugated secondary antibody and DAB via an automated Bond Max™ Automated IHC/ISH Staining System (Leica Microsystems Instruments). Using ImageJ (National Institute of Health) images were processed to quantify the number of Ki67-positive cells per frame (**Figure 19**).

Generally, cell proliferation spiked on days 7 and 14 for all four treatment groups. On both days 7 and 14, Endoform-based treatments had signi cantly greater cell proliferation than OaSIS™ treated and untreated groups (P<0.01 one-way ANOVA using GraphPad Prism). This proliferative phase resolved over time with Ki67-positive cells returning to 'baseline' on day 42 in all treatment groups.

Vascularization: In order to quantify the extent of endotheliazation and the development of vasculature in the healing wounds we used immunohistochemistry coupled with digital quanti cation methods. Fixed biopsy tissues were sectioned, mounted and stained with an anti-CD34 antibody at 1:100 dilution and visualised using an HRP-conjugated secondary antibody and DAB staining, before light counterstaining with Mayer's Haemotoxylin (**Figure 20**). Tissue biopsies taken at day 3 were excluded from this analysis given the absence of a clearly de ned dermal layer. Stained slides were digitally imaged at 40x magni cation and the number of vessels quanti ed using ImageJ.

The average total number of vessels count per frame is given in **Figure 20**, for each of the four treatment groups over the course of the experiment (day 3 excluded). There was a statistically signi cant increase in the number of blood vessels in wounds treated with either of the Endoform templates, relative to untreated wounds. The increase in total blood vessels relative to untreated wounds was evident on days 14 (P<0.01 FM and LFM), 28 (P<0.01 FM and LFM) and 42 (P<0.01 FM and P<0.05 LFM). In comparison, OaSIS™ treatment did not increase the total number of blood vessels relative to the untreated control.

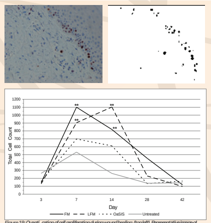


Figure 19: Quanti cation of cell proliferation during wound healing. Ki67-stained tissue sections [illegible] ated using ImageJ [illegible] Ki67-positive cells in [illegible] regenerating dermal [illegible] were sampled at the [illegible] ANOVA.

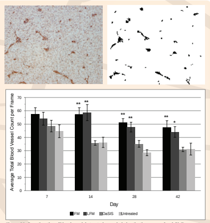
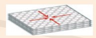


Figure 20: Quanti cation of blood vessels in treated wounds during the time course. [illegible]

Biophysical Characterization

Biaxial Strength - Ball Burst Strength

Ball burst strength provides a measure of a biomaterials resistance to load when biaxial force is applied. As expected there was a dramatic increase in the strength of the Endoform products as additional sheets were laminated to generate the series of multi-ply devices (2-, 3-, and 4-ply) (**Figure 21**).



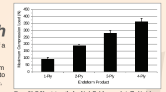


Figure 21. Ball burst strength of multi-ply Endoform products. The biaxial strength of single or multi-ply Endoform products was determined using a Ball Burst Test according to ASTM D3797-89 "Standard Test Method for Bursting Strength of Knitted Goods, Constant-Rate-of-Traverse (CRT) Ball-burst Test", using an Instron 5800 series electromechanical tester, tted with a ball-burst compression cage, whereby a 25.4 mm stainless steel ball was pushed against the test material at a feed-rate of 305 +/- 13 mm/min, until failure. A 1 kN load cell was used to record maximum compression load at failure (N). Error bars represent the standard error of at least ve samples

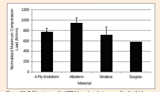


Figure 22. Ball burst strength of ECM-based products, normalized to thickness. Data taken from Table 3. Errors represent standard errors from at least ve samples, or from published data. No thickness error reported for Surgisis™.

	Maximum Compression Load (N±SE)	Thickness (mm)	Normalized Maximum Compression Load (N/mm±SE)
4-ply Endoform™	361.5±24.9	0.47±0.01	773.7±68.6
Alloderm™ (Boguszewski, Dyment et al. 2008)	1781.5±80.2	1.9±0.1	937±106.0
Strattice™ (Boguszewski, Dyment et al. 2008)	1059.7±181.8	1.49±0.07	711.2±155.4
Surgisis™ (package insert)	440±81	0.76	578.9

Table 3. Comparison of ball-burst properties the 4-ply Endiform and commercial implant products. Errors represent standard errors from at least ve samples, or from published data. No thickness error reported for Surgisis™.

We compared the biaxial strength of the 4-ply Endoform laminate with published ball burst data for the commercial products, Alloderm™ (LifeCell Corporation), Strattice™ (LifeCell Corporation), and Surgisis™ (Cook Biotechnology) (**Table 3** and **Figure 22**). Using this analysis, we demonstrated that the relative biaxial strengths of the four products were statistically similar.

Uniaxial Strength

Uniaxial strength measures the one-dimensional force tolerance of a biomaterial whereby a strip of material is clamped at either end and opposing forces are applied. The maximum load of a sample is dependent on the inherent strength of the test material, as well as, the size and thickness of the test sample. We tested single and multi-ply Endoform products and determined the maximum load (**Figure 23**) for each Endoform product, as well as, the maximum tangential sti ness (N/mm) (data not shown), elongation at failure (mm) (data not shown), the modulus of elasticity (GPa) (**Figure 24**) and yield stress (MPa) (**Figure 25**). The yield stress is a term normalized to the dimensions of the test sample and can be used to compare similar products of di erent thicknesses. As expected, increasing the lamination state of the product signi cantly improved the uniaxial strength . However, lamination did not statistically alter the maximum elongation, or modulus of elasticity. This suggests that the process of lamination increases the strength of the product, but does not alter its pliability, suggesting the handling of 1- and 4-ply products would be similar.

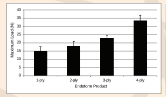


Figure 23. Comparison of the uniaxial strength of Endoform single and multi-ply products. A. Maximum load at failure (N); . Modulus of elasticity (Young's) (GPa). Maximum load at failure of single and multi-ply products was determined using an Instron 5800 series electromechanical tester. Various materials were cut to dog-bone shaped samples with a 0.6 cm width. Samples were clamped with a gauge length of 7.5 cm. and elongated at a rate of 25.4 mm/min until failure. Load (N) was recorded using a 500 N load cell. Sti ness was calculated from the slope of the load (N) versus elongation (mm) curve. The load versus elongation curve was transformed to a stress (N/m2) versus strain curve, using a cross-sectional area of calculated from the thickness of the product. The slope of this latter curve was used to calculate the modulus of elasticity, or Young's modulus (GPa) (Figure 24). Error bars represent the standard error of at least ve samples

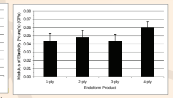
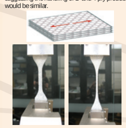


Figure 24. Comparison of the Modulus of elasticity (Young's) (GPa) of Endoform single and multi-ply products, calculated according from Figure 9. Error bars represent the standard error of at least ve samples

	Modulus of Elasticity (Youngs') (GPa±SE)	Yield Stress (MPa)	Thickness (mm±SE)
4-ply Endoform™	0.06±0.01	11.97±1.16	0.47±0.01
Alloderm™ (Lemer, Chaikin et al. 1999)	ND	16.79±2.10	ND
Alloderm™ (Morgan, McI et al. 2004)	ND	10.55±2.37	0.9±0.1
Alloderm™ (Choe, Kothandapani et al. 2001)	ND	7.20±2.56	1.00±0.05
Alloderm™ (Vural, McLaughlin et al. 2006)	ND	15.25±7.13	1.34±0.05
Alloderm™ (Gouk, Lim et al. 2008)	0.014±0.0015	7±1	0.45±0.05
Alloderm™ (Sclafani, McCormick et al. 2002)	0.001±0.002	8.64±3.31	1.89±0.30

Table 4. Comparison of uniaxial strength properties of 4-ply Endoform and Alloderm™. ND = no data. Errors represent standard errors from at least ve samples, or published values.

To evaluate the suitability of the Endoform product line for implantation we compared the biophysical properties, as derived from uniaxial strength testing, with similar published data relating to the commercially available product Alloderm™ (**Table 4**). It is apparent from the spread of reported data that the consensus about the true strength, and elastic potential of Alloderm™ has not been reached in the literature. Reported yield stress of Alloderm™ range from 7.00±1.00 to 16.79±2.10 MPa. In order to make a meaningful comparison we calculated the mid-point of the data spread as 11.90 MPa, which is comparable to the yield stress of the 4-ply laminate (11.97±1.16 MPa). The two reported modulus of elasticity for Alloderm™ are an order of magnitude di erent from each other making a comparison with the 4-ply product di cult.



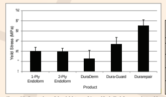


Figure 25. Comparison of the yield stress of 1- and 2-ply Endoform products with commercial dural repair products. Errors represent standard errors from at least ve samples, or published data. Data taken from Table 4.

	Modulus of Elasticity (Youngs') (GPa±SE)	Yield Stress (MPa)	Thickness (mm±SE)
1-ply Endoform™	0.04±0.01	10.15±1.81	0.25±0.01
2-ply Endoform™	0.05±0.01	9.77±1.68	0.31±0.01
DuraDerm™ (Sclafani, McCormick et al. 2002)	0.002±0.009	6.27±4.20	1.4±0.2
Dura-Guard™ (Zerris, James et al. 2007)	0.08±0.02	13.5±3.3	0.400±0.001
Durarepair™ (Zerris, James et al. 2007)	0.07±0.01	22.7±2.8	0.50±0.02

Table 5. Comparison of uniaxial strength properties of 1-ply and 2-ply Endoform products with commercial dural repair products. Errors represent standard errors from at least ve samples, or published values

The uniaxial strength properties and thicknesses of the 1- and 2-ply Endoform products, were compared with published data for the dural repair products DuraGuard™ and Durarepair™ (**Table 5** and **Figure 25**). The 1- and 2-ply Endoform products had a similar yield stress to Dura-Guard™ (13.5±3.34 MPa) and all three products out performed Dura-Derm™ (6.27±4.20 MPa). The strongest of the products, Durarepair had a yield stress of 22.7±2.83 MPa. The 1- and 2-ply Endoform products (Young's modulus of 0.04±0.01 and 0.05±0.01 GPa, respectively) had better elastic properties than Dura-Guard™ and Durarepair™ (0.08±0.02 and 0.07±0.01 MPa, respectively). DuraDerm™ demonstrated the best elastic potential (modulus 0.002±0.009 GPa), but as noted above, was the weakest of the products surveyed.

Suture Retention Strength

Sutute retention testing is a practical clinical consideration that determines the resistance of a biomaterial to suture 'pull-out'. The test protocol is similar to uniaxial strength, however in this instance one edge of the test material is clamped, while the other is secured to the opposing clamp via a suture placed through the test material. Lamination of the Endoform increased the resistant of the product to suture pull-out (**Figure 26**). A comparative analysis of Endoform products and the dural repair products Durarepair™ and Dura-Guard™ is shown in **Table 6** and **Figure 27**. Taking into account the relative thicknesses of the four products via normalized suture retention the four products had equivalent potential to resist suture pull-out.

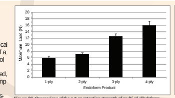


Figure 26. Comparison of the suture retention strength of multi-ply Endoform products. Samples of multi-ply Endoform products were tested for suture retention according to ANSI/AAMI VP20-1994 Guidelines for Cardiovascular Implants Vascular Prostheses Measured in Newton's. Sutures were made in 4 cm x 2.5 cm samples, using suture with a bite-depth of 2 mm. Load at failure was recorded using a Instron 5800 series electromechanical tester, tted with a 100 N load cell using an advance rate of 100 mm/min. Load at failure was de ned as a 90% reduction in the observed load. The free end of the sample was held in a 25 mm vice grip, while the suture was attached to the opposing clamp via a stainless hook. Error bars represent the standard error of at least six samples

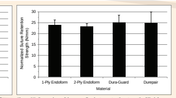
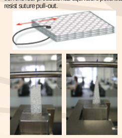


Figure 27. Comparison of the normalized suture retention strength of Endoform products and dural repair products. Errors represent standard errors from ve independant samples, or from published data.

	Suture Retention - Maximum Load (N±SE)	Thickness (mm±SE)	Normalized Suture Retention (N/mm)
1-ply Endoform™	4.7±0.4	0.25±0.01	18.9±1.5
2-ply Endoform™	7.1±0.5	0.31±0.01	23.2±1.6
Dura-Guard™ (Zerris, James et al. 2007)	10.02±1.35	0.40±0.01	25.1±3.4
Durarepair™ (Zerris, James et al. 2007)	12.38±2.10	0.50±0.02	24.76±5.19

Table 6. Comparison of the suture retention strength of Endoform products and commercially available dural repair matrices. Errors represent the standard error of ve samples, or published data.



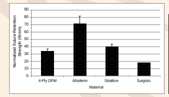


Figure 28. Comparison of the normalized suture retention strength of 4-ply Endoform product and commercially available implant matrices. Errors represent standard errors from at least ve samples, or from published data. No error reported for Surgisis™. Alloderm™ and Strattice™ tested with a bite depth of 10 mm, 4-ply Endoform and Surgisis™ tested with a bite depth of 2 mm.

	Suture Retention - Maximum Load (N±SE)	Thickness (mm±SE)	Normalized Suture Retention (N/mm)	Bite Depth (mm)
4-ply Endoform™	16.0±1.3	0.47±0.01	34.2±2.8	2
Alloderm™ (Boguszewski, Dyment et al. 2008)	135.2±11.1	1.9±0.13	71.2±10.71	10
Strattice™ (Boguszewski, Dyment et al. 2008)	59.9±2.3	1.49±0.07	40.2±3.43	10
Surgisis™ (Oasis Product Insert)	13.7±3.2	0.76	18.0	2

Table 7. Comparison of the suture retention strength of Endoform products and commercially available implant matrices. Errors represent standard errors from at least ve samples, or from published data. No error reported for Surgisis™.

The comparative study was extended to determine the performance of Endoform products relative to commercially available implant products, Alloderm™, Strattice™ and Surgisis™. The analysis is summarized in **Table 7** and **Figure 28**. The 4-ply Endoform laminate product was signi cantly more resistant to suture pull-out than the Surgisis™ product (normalized suture retention strengths, 34.2±2.8 and 18.0 N/mm, respectively). The reported suture retention strengths of both Alloderm™ and Strattice™ have employed a modi cation to the ASTM standard, using a bite-depth of 10 mm (Table 5). The normalized suture retention strengths of these products was 71.2±10.71 and 40.2±3.43 N/mm, respectively. In comparison, the normalized suture retention strength of the 4-ply Endoform product was 34.2±2.8 N/mm, using a bite-depth of 2 mm. We suspect that the suture retention strength of the 4-ply product would equivalent to both Alloderm™ and Strattice™ if all three products were tested in side-by-side experiments using equivalent bite-depths. This notion is supported by the observation that the 4-ply Endoform has similar yield stress under uniaxial testing (see **Table 5**), and that the three products have similar normalized ball-burst strengths (**Table 3**).

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