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REMODELING CHARACTERISTICS AND COLLAGEN DISTRIBUTION IN BIOLOGICAL SCAFFOLD MATERIALS EXPLANTED FROM HUMAN SUBJECTS AFTER ABDOMINAL SOFT TISSUE RECONSTRUCTION: AN ANALYSIS OF SCAFFOLD REMODELING CHARACTERISTICS BY PATIENT RISK FACTORS AND SURGICAL SITE CLASSIFICATIONS

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Abstract

OBJECTIVE—The study purpose was to evaluate the associations between patient characteristics or surgical site classifications and the histologic remodeling scores of biologic meshes biopsied from abdominal soft tissue repair sites in the first attempt to generate a multivariable risk prediction model of non-constructive remodeling.

INTRODUCTION—Host characteristics and surgical site assessments may predict remodeling degree for biologic meshes used to reinforce abdominal tissue repair sites.

METHODS—Biologic meshes were biopsied from the abdominal tissue repair sites of n=40 patients during an abdominal re-exploration, stained with hematoxylin and eosin, and evaluated according to a semi-quantitative scoring system for remodeling characteristics [cell types (CT), cell infiltration (CI), extracellular matrix (ECM) deposition, scaffold degradation (SD), fibrous encapsulation (FE), and neovascularization (NEO)] and a mean composite score (CR). Biopsies were stained with Sirius Red & Fast Green, and analyzed to determine the collagen I:III ratio. Based on univariate analyses between subject clinical characteristics or surgical site classification and the histologic remodeling scores, cohort variables were selected for multivariable regression models using a p-value < 0.200.

RESULTS—The model selection process for CI score yielded 2 variables: age at mesh implantation and mesh classification (c-statistic=0.989). For CR score, the model selection process yielded 2 variables: age at mesh implantation and mesh classification ($r^2=0.449$).

CONCLUSION—These preliminary results constitute the first steps in generating a risk prediction model that predicts the patients and clinical circumstances most likely to experience non-constructive remodeling of abdominal tissue repair sites with biologic mesh reinforcement.

Keywords

hernia repair; abdominal wall reconstruction; soft tissue repair; biologic scaffold; human dermis; remodeling; type I collagen; type III collagen; Sirius Red/Fast Green; contamination; surgical site infection; CDC wound class

INTRODUCTION

The U.S. Markets for Soft Tissue Repair Report prepared by the Millennium Research Group states that a staggering 305,900 ventral hernia repairs were performed in 2006, the vast majority of which were repaired with reinforcement materials¹. Level A/B evidence supports reinforcement with synthetic or biologic repair materials for all incisional ventral hernias to reduce recurrence²⁻³. Given the aging patient population, the rapid rise in the incidence of obesity, and the prevalence of co-morbidities contributing to the loss of soft tissue integrity, analyses by the Millennium Research Group predict a 7% annual growth rate in the current \$1 billion United States soft tissue repair device market, largely driven by costly biologic scaffold materials for ventral hernia repair.

Although synthetic materials provide strong tissue repairs, these materials have been found to induce polymer-dependent inflammatory responses^{4–5}, likely leading to greater associated rates of postoperative seroma formation, adhesion formation, erosion into surrounding tissue, intestinal complications, and chronic pain⁶. Furthermore, bacteria avidly adhere to synthetic polymers and synthesize biofilms. These biofilms provide resistance to host immunologic defenses and hematogenous delivery of antibiotics, leading to chronic infection of the tissue repair site.

Biologic scaffolds provide a viable alternative to primary closure, absorbable mesh reinforcement, and autologous tissue transfer in contaminated or infected soft tissue repair sites⁷. Biologic scaffolds composed of mammalian extracellular matrices possess favorable characteristics for cell attachment, proliferation, and differentiation. For these reasons, biologic scaffolds may potentially serve as ideal substrates for tissue repair. Extracellular matrices from diverse species and tissue sources have been used as biologic scaffolds in a variety of experimental and therapeutic applications^{8–9}. In abdominal soft tissue repair applications, these scaffolds are predominantly extracellular matrix constructs derived from dermal, fascial, pericardial, or intestinal submucosal tissue of human, porcine, or bovine origin. Demand for these biologic scaffold materials is expected to expand based on pre-clinical evidence that biologic materials enable revascularization of soft tissue repair sites and improve pathogen clearance in contaminated and infected surgical sites^{10–11}.

The host tissue response to these materials plays a critical role in the constructive tissue remodeling of biologic scaffolds. Mononuclear cells, including both proinflammatory (M1) and immunomodulatory and remodeling (M2) macrophages, are pivotal in the host response to biological scaffolds. A high M2:M1 ratio favors constructive tissue remodeling over chronic inflammatory response¹². The gradual degradation of the biologic scaffold by M2 macrophages and matrix metalloproteinases (MMPs) allows for simultaneous tissue remodeling through cellular infiltration, host deposition of collagen and other extracellular matrix components, and neoangiogenesis. Conversely, elicitation of a strong M1 macrophage inflammatory response can lead to fibrous encapsulation of the scaffold and restricted cellular infiltration and neovascularization¹². Studies have demonstrated that even the scaffold degradation products are chemotactic and mitogenic for multipotent progenitor cells¹³. Host fibroblasts that successfully infiltrate the scaffold will proliferate and secrete components of the extracellular matrix, such as collagen and elastin. Low soft tissue distribution ratios of collagen I:collagen III have been shown to be associated with the failure of initial and repeat soft tissue repairs^{14–15}, as collagen III confers less mechanical strength to tissue than collagen I. Despite the critical role of the host tissue response to the constructive remodeling of biologic scaffolds, the potential influence of host comorbidities and wound characteristics on the scaffold remodeling has not previously been described.

Biologic grafts are biodegradable and susceptible to enzymatic degradation by bacteria. These materials are therefore associated with high long-term hernia recurrence rates in closed-space infections where the rate of scaffold degradation exceeds the rate of leukocyte infiltration, neovascularization, and tissue remodeling^{16–22}. In addition to the duration of time for which the biologic scaffold is *in vivo*, host characteristics such as age, sex, body mass index (BMI), body mass category, diabetes mellitus, and smoking status are well-

described risk factors for poor wound healing and may play a significant role in this perturbation of scaffold remodeling. As previously described, pathogen burden of the surgical site can further inhibit constructive tissue remodeling and contribute to high rates of repair failure. Contaminated or infected hernia repair sites reinforced with biologic scaffolds are associated with recurrence rates as high as 50%²². Wound classification systems, such as the Center for Disease Control (CDC) adaptation of the Centers for Disease Control and Prevention (CDC) wound classification, are ordinal scales that incorporate the degree of pathogen burden (CDC wound class) in their scores. Given the relatively high recurrence rate for abdominal wall hernias and hiatal hernias reinforced with biologic mesh in contaminated or infected surgical sites, repeat surgical repair of the abdominal wall or hiatal hernia presents the potential opportunity to procure biopsies of biologic scaffold materials. A wealth of information about the previously undescribed influence of host comorbidities and wound characteristics on biologic scaffold remodeling can therefore be obtained from explants of materials that have been utilized in abdominal soft tissue repair applications.

Despite the well-described role of the host tissue response to the constructive remodeling of biologic meshes^{23–27}, statistical modeling of the influence of host comorbidities and wound characteristics on the remodeling has not previously been described. Needed is a risk prediction model that reliably predicts the patients and clinical circumstances for which non-constructive remodeling of an abdominal soft tissue repair site with biologic mesh reinforcement is most likely to occur. Thus, the purpose of this study was to evaluate the multivariable associations of patient characteristics and surgical site classifications to the histologic remodeling scores of biologic meshes biopsied from the abdominal soft tissue repair sites of the patients in the first attempt to generate a risk prediction model of non-constructive remodeling. We hypothesized that higher collagen type I:III ratios and more favorable histologic remodeling scores of explanted meshes would directly correlate with indwelling duration of mesh, and inversely correlate with subject age at the time of mesh implantation, diabetes status, tobacco use, chemotherapy treatment, abdominopelvic radiation therapy, and body mass index (BMI) and Centers for Disease Control and Prevention (CDC) wound classification assessed at the time of both scaffold implantation (T1) and explantation (T2). Furthermore, we hypothesized that higher collagen type I:III ratios and more favorable histologic remodeling scores of explanted meshes would demonstrate greater association with allograft biologic meshes compared to xenograft biologic meshes.

MATERIALS & METHODS

Patient Selection & Specimen Collection

The study protocol was approved by the Human Research Protection Office (HRPO) at Washington University in St. Louis (Institutional Review Board # 201101959), and meets the corresponding ethical guidelines for human research conduct. The study was also registered with clinicaltrials.gov (identification # NCT01060046). Forty subjects (n=40) with biologic mesh implanted during a previous abdominal soft tissue reconstruction and subsequently scheduled for a clinically-indicated abdominal re-exploration were identified and consented for the study between August 2007 and February 2013. Specimens of the

biologic meshes were harvested during the clinically-indicated abdominal re-exploration. Specimens were preserved in 10% formalin, embedded in paraffin, sectioned to 5 μm , and stained with Hematoxylin & Eosin (H&E) and Sirius Red/Fast Green (SR/FG).

Remodeling Characteristics

Hematoxylin & Eosin (H&E) stained slides were evaluated for the degree of six remodeling characteristics, including: cellular infiltration, cell types, host extracellular matrix deposition, scaffold degradation, fibrous encapsulation, and neovascularization. A single slide of each specimen was evaluated under light microscopy at 100x magnification by a pathologist using a semi-quantitative scoring system adapted from Valentin et al²⁸ for biologic mesh implants and presented previously^{29–32}. Assigned to each specimen was a single score for each remodeling characteristic ranging in value from 0 to 3, with higher scores representing more favorable remodeling characteristics (Figure 1). A composite remodeling score was then calculated as the mean of the six component remodeling scores for each specimen.

Collagen Distribution

Sirius Red/Fast Green (SR/FG) stained slides were prepared and evaluated according to methods presented previously³³. In brief, Sirius Red stains collagen fibers, whereas Fast Green stains non-collagenous proteins for contrast. When the sulphonic groups of the Sirius Red molecules interact with the basic groups of the collagen protein in an acidic environment, the long axes of the Sirius Red molecules and the collagen fibers align in parallel orientation thereby enhancing the natural birefringency of the collagen fibers. Under polarized light, the types of collagen present may be determined by the hue of the Sirius Red-stained collagen fibers. The hues of the collagen fibers under polarized light indicate the fiber diameters, a property by which the collagen types may be distinguished. Under polarized light, Sirius Red-stained type I collagen fibers appear bright red while Sirius Red-stained type III collagen fibers appear pale green.

Each slide was photographed under cross-polarized light using an Axioskop 40® microscope (Carl Zeiss®, Thornwood, NY) equipped with a Zeiss Axiocam® at a magnification of 400x (n=10 photographs per specimen). Axiovision 4.7® (Zeiss®) software was utilized to semi-quantitatively evaluate both the areas (μm^2) that appear red under cross-polarized light (for type I collagen) and the areas that appear green under cross-polarized light (for type III collagen) on each slide. A collagen I:III ratio was then calculated. To obtain baseline values of collagen I and III, the collagen I area, collagen III area, and collagen I:III ratio were also calculated from a single biologic scaffold of each commercially-available manufacturer type that had never been implanted (de novo scaffold). These baseline values were then subtracted from each outcome value obtained from an explanted specimen of the same manufacturer type.

Variables

The dependent variables selected for this study are histologic scores for the assessment of constructive biologic mesh remodeling. The composite histologic remodeling score, and its six component scores describe the degree of cellular infiltration, cell types, extracellular

matrix deposition, scaffold degradation, fibrous encapsulation, and neovascularization of the specimens^{29–32}. The SR-stained area evaluated under polarized light further quantifies the type I collagen surface area, the type III collagen surface area, and collagen I:III ratio of the specimens³³.

The independent variables selected for investigation were as follows, with some data ascribed at the time of scaffold implantation (T1) to assess the potential contribution of baseline host and surgical site characteristics, and at the time of scaffold explantation (T2) to assess the potential contribution of host and surgical site characteristics acquired during the period of scaffold indwelling: mesh classification (human dermis scaffold, porcine dermis scaffold, bovine dermis scaffold); sex (male or female); race (Caucasian or Black); mean age at T1 (years); median duration of *in vivo* scaffold dwelling (days); diabetes mellitus diagnosis status (diabetic or non-diabetic); smoking history (positive or negative history of ever being a tobacco smoker); smoking status (never smoked, quit 30 days before T2 without resumption, or current smoker); pack-year history (median pack-years); chemotherapy (positive or negative history of ever having chemotherapy); abdominopelvic radiation therapy (positive or negative history of ever having radiation therapy to the abdomen or pelvis); mean body mass index (BMI, kg/m²) at T1 and T2; CDC wound class at T1 and T2 (clean or clean-contaminated/contaminated/infected)^{34–35}. Note that the race variable was dichotomized to Caucasian or Black because the small sample size and the racial homogeneity of the subject population did not allow for further distinction. Similarly, the CDC wound class variable was dichotomized to clean or “not clean” (clean-contaminated/contaminated/infected) because the small sample size and the data distribution for the wound class variable did not allow for further distinction.

Independent variable data for the following variables were abstracted from the medical record by several trained co-investigators (JAC, JO, JC, SB): mesh type; sex; race; age at T1; duration of *in vivo* scaffold dwelling; diabetes mellitus diagnosis status; smoking history; smoking status; pack-year history; chemotherapy; abdominopelvic radiation therapy; and BMI at T1 and T2. Subjects were presumed to be non-diabetic if the medical record did not assign a diagnosis of diabetes mellitus type 1 or type 2. Similarly, subjects were presumed to have never smoked tobacco, never have undergone chemotherapy, or never have undergone abdominopelvic radiation therapy if the medical record reported neither previous nor current use of tobacco, chemotherapy, or abdominopelvic radiation therapy, respectively. If the medical record reported a previous history of tobacco smoking, chemotherapy, or abdominopelvic radiation therapy but did not report discontinuation, the subject was assumed to be a current tobacco smoker, currently undergoing chemotherapy, or currently undergoing abdominopelvic radiation therapy, respectively. Using surgical site descriptions and data abstracted from the medical record, two trained co-investigators (JAC and BDM) independently assessed the surgical site environment according to previously-established definitions^{34–35}, then reached consensus by discussion of any discrepant assessments before assigning the final CDC wound class at T1 and T2 for each subject.

Study data were managed through a customized electronic database using Research Electronic Data Capture® (REDCap®) tools hosted at Washington University in Saint Louis³⁶. REDCap® is a secure, web-based application designed to support electronic data

capture for research studies. REDCap provided an intuitive interface for validated data entry, audit trails for tracking data manipulation, and automated export procedures for data downloads to statistical packages.

Statistical Analysis

Data from the REDCap® study database were securely exported to Statistical Analysis System® version 9.3 (SAS Institute, Inc.®; Cary, North Carolina) to perform all statistical analyses. The following dependent variables were analyzed as continuous variables: composite remodeling score, collagen I area, collagen III area, collagen I:III ratio. Collagen I area, collagen III area, and collagen I:III ratio were analyzed as difference scores, with the outcome value of a single de novo scaffold subtracted from each value obtained from an explanted specimen of the same manufacturer type. Given the low sample size and sparseness of the data, the following dependent variables with greater than 2 ordinal categories were collapsed based on the data distribution and analyzed as dichotomous variables: cell infiltration score (≤ 2 or >2), cell type score (≤ 3 or >3), extracellular matrix deposition score (≤ 2 or >2), scaffold degradation score (≤ 2 or >2), fibrous encapsulation score (≤ 2 or >2), and neovascularization score (≤ 2 or >2). As for the independent variables, sex, race, diabetes mellitus diagnosis status, smoking history, chemotherapy, abdominopelvic radiation therapy, and CDC wound class at both T1 and T2 were treated as dichotomous variables; mesh classification and smoking status were treated as categorical variables; and host age at T1, BMI at T1 and T2, pack-year smoking history, and duration of *in vivo* scaffold dwelling were treated as continuous variables.

Data for all continuous variables were assessed for approximate symmetry of distribution before univariate analyses ensued. Continuous cohort characteristics were summarized as mean (standard deviation (SD)) or median (25th percentile (q1), 75th percentile (q3)) in the case of skewed distributions. In the univariate analyses, the continuous characteristics were compared by the dichotomous outcomes with t-tests or Wilcoxon rank-sum tests. For continuous outcomes, Pearson (r) or Spearman (rho) correlations were utilized to assess the relationship between the cohort characteristics. Categorical cohort characteristics were summarized as column percent N (%) and compared by the dichotomous outcomes with chi-square tests or Fisher's exact tests, in case of small cell sizes. The relationship between categorical characteristics, with more than two categories and an ordinal structure, and dichotomous outcomes was assessed via exact Cochran-Armitage trend tests. The relationship between categorical characteristics and continuous outcomes was determined with t-tests or Wilcoxon rank-sum tests while, for characteristics with more than two categories, Kruskal-Wallis tests were used.

Multivariable associations with dichotomous outcomes were evaluated via logistic regression models using Firth's penalized likelihood approach³⁷, to address issues of small sample sizes and data sparseness. Based on the univariate analyses, cohort characteristics were selected for multivariable models using a liberal cut-off of p-value ≤ 0.200 . The multivariable models were then reduced via backward elimination using a cut-off of p-value ≤ 0.100 . P-values were based on penalized likelihood ratio tests^{38–39}. Multivariable associations with continuous outcomes were assessed via linear regression models. As with

dichotomous outcomes, cohort characteristics were selected for multivariable models using a liberal cut-off of p-value 0.200. Based on the selected characteristics, all possible combinations of models were fit and discriminated between using corrected Akaike Information Criterion (AICC)⁴⁰. Residual analyses were performed for the final linear models selected and, where the homogeneity of the errors assumption was questionable, standard errors and p-values were computed using heteroscedasticity robust standard errors⁴¹. Categorical cohort characteristics with more than two categories were treated as a single entity in the model selection processes for both dichotomous and continuous outcomes and tested with an overall F-test or penalized likelihood ratio test.

RESULTS

Patient Characteristics

Under an IRB-approved protocol, biologic mesh specimens were biopsied from 40 subjects at the time of a subsequent clinically-indicated abdominal surgery. As shown in Table 1, the subjects (12M:28F) had a mean age at T1 of 55.4 ± 10.9 years (range: 32.5–75.0 years), and a racial distribution of 38 Caucasian:2 Black. Median (quartile 1, quartile 3) duration of biologic mesh implantation was 457 days (308 days, 674 days; range: 25–2210 days), and the onlay:inlay:sublay locations of mesh were 2:10:19 (9 not reported). Indications for biologic mesh implantation were: ventral hernia repair (n=36), and hiatal or paraesophageal hernia repair (n=4). Of the initial ventral hernia repairs, the surgical sites were clean (n=14), clean-contaminated (n=8), contaminated (n=15), or infected (n=2) (1 not reported). Indications for abdominal re-exploration at the time of specimen collection were: repeat ventral hernia repair or parastomal hernia repair (n=34), repeat hiatal or paraesophageal hernia repair (n=4), exploratory laparotomy with adhesiolysis (n=1), and debridement of abdominal wall sinus tracts (n=1). Of the abdominal re-explorations, the surgical sites were clean (n=29), clean-contaminated (n=2), contaminated (n=8), or infected (n=0) (1 not reported). At the time of abdominal re-exploration, clinical evidence of persistent surgical site contamination was present in only 9 of the 25 subjects for whom surgical site contamination or infection was present at the time of original biologic mesh implantation.

Remodeling Characteristics

Cell Type Score—The cohort variables whose associations with Cell Type Score were evaluated in multivariable models were sex (univariate p-value= 0.143), mesh indwelling duration (univariate p-value=0.060), and BMI at T2 (univariate p-value=0.110). Of these three variables, none remained in the logistic regression model for cell type scores after the backward elimination process.

Cell Infiltration Score—The cohort variables whose associations with Cell Infiltration Score were evaluated in multivariable models were age at T1 (univariate p-value=0.022), mesh indwelling duration (univariate p-value=0.008), and mesh classification (univariate p-value=0.002). Of these three variables, age at T1 and mesh classification remained in the logistic regression model for cell infiltration scores after the backward elimination process (Table 2). Compared to mesh specimens composed of human dermis, mesh specimens composed of porcine dermis were estimated to have 0.0021 times the odds of having a Cell

Infiltration Score > 2, controlling for subject age at T1 (p-value<0.001). Compared to mesh specimens composed of human dermis, mesh specimens composed of bovine dermis were estimated to have 0.0010 times the odds of having a Cell Infiltration Score > 2, controlling for subject age at T1 (p-value=0.007). Compared to mesh specimens composed of porcine dermis, mesh specimens composed of bovine dermis were estimated to have 0.486 times the odds of having a Cell Infiltration Score > 2, controlling for subject age at T1 (p-value=0.633) (2 df penalized likelihood ratio test p-value=0.001). Controlling for mesh classification, a one-year increase in the subject age at T1 was associated with a 1.3216 times greater odds of having a Cell Infiltration Score > 2 (p-value=0.004; n=36). The multivariable model's area under the receiver operating curve (ROC) was 0.989, suggesting excellent predictive capacity in this sample.

Extracellular Matrix Deposition Score—The cohort variables whose associations with Extracellular Matrix Deposition Score were evaluated in multivariable models were age at T1 (univariate p-value=0.118), mesh indwelling duration (univariate p-value=0.025), and mesh classification (univariate p-value=0.002). Of these three variables, mesh classification remained in the logistic regression model for extracellular matrix deposition scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have 0.0739 times the odds of having an Extracellular Matrix Deposition Score > 2 (p-value=0.001). Compared to specimens composed of human dermis, specimens composed of bovine dermis had 0.2992 times the odds of having Extracellular Matrix Deposition Scores > 2 (p-value=0.326). Compared to specimens composed of porcine dermis, specimens composed of bovine dermis had 4.0477 times the odds of having Extracellular Matrix Deposition Scores > 2 (p-value=0.238) (2 df penalized likelihood ratio test p-value=0.004; n=36). The area under the receiver operating curve (ROC) for the single predictor model was 0.793, indicating moderate predictive capacity in this sample.

Scaffold Degradation Score—The cohort variables whose associations with Scaffold Degradation Score were evaluated in multivariable models were mesh indwelling duration (univariate p-value=0.028), mesh classification (univariate p-value<0.001), and BMI at T2 (univariate p-value=0.087). Of these three variables, mesh classification remained in the logistic regression model for scaffold degradation scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have 0.0640 times the odds of having a Scaffold Degradation Score ≥ 2 (p-value<0.001). Compared to specimens composed of human dermis, specimens composed of bovine dermis had 0.1459 times the odds of having a Scaffold Degradation Score ≥ 2 (p-value=0.090). Compared to specimens composed of porcine dermis, specimens composed of bovine dermis had 2.2799 times the odds of having a Scaffold Degradation Score ≥ 2 (p-value=0.517) (2 df penalized likelihood ratio test p-value=0.002; n=36). The area under the receiver operating curve (ROC) for the single predictor model was 0.803, indicating moderate predictive capacity in this sample.

Fibrous Encapsulation Score—The only cohort variable with a significant association at the alpha=0.200 level for the Fibrous Encapsulation Score was mesh classification

(univariate p-value=0.108). In a logistic regression model, the 2 df penalized likelihood ratio test for this variable had a p-value=0.161, resulting in no predictors selected for the Fibrous Encapsulation Score.

Neovascularization Score—The cohort variables whose associations with Neovascularization Score were evaluated in multivariable models were mesh indwelling duration (univariate p-value=0.111), and mesh classification (univariate p-value=0.005). Of these two variables, mesh classification remained in the logistic regression model for neovascularization scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have 0.1077 times the odds of having a Neovascularization Score > 2 (p-value=0.005). Compared to specimens composed of human dermis, specimens composed of bovine dermis were estimated to have 0.1077 times the odds of having a Neovascularization Score > 2 (p-value=0.055, 2 df penalized likelihood ratio test p-value=0.009; n=36). The area under the receiver operating curve (ROC) for the single predictor model was 0.771, indicating moderate predictive capacity in this sample.

Composite Remodeling Score—The cohort variables whose associations with Composite Remodeling Score were evaluated in multivariable models were age at T1 (univariate p-value=0.153), mesh indwelling duration (univariate p-value=0.009), and mesh classification (univariate p-value=0.005). Of these three variables, the model selection process for Composite Remodeling Scores yielded a linear regression model with age at T1 and mesh classification (Table 3). Controlling for mesh classification, a one-year increase in subject age at T1 was associated with a 0.017 unit increase in the mean Composite Remodeling Score (p-value=0.111). Controlling for subject age at T1, specimens composed of porcine dermis were estimated to have a mean Composite Remodeling Score 0.898 units lower than specimens composed of human dermis (p-value=0.001), whereas specimens composed of bovine dermis were estimated to have a mean Composite Remodeling Score 0.805 units lower than specimens composed of human dermis (p-value=0.255). Specimens composed of porcine dermis were estimated to have a mean Composite Remodeling Score 0.093 units lower than specimens composed of bovine dermis (p-value=0.805) (2 df F-test p-value<0.001; n=36). As indicated by the r^2 value, the model explained approximately 44.9% of the variability in the Composite Remodeling Scores.

Mean Collagen I Area—The cohort variables whose associations with mean collagen I area were evaluated in multivariable models were age at T1 (univariate p-value=0.157), race (univariate p-value=0.091), wound class at T1 (univariate p-value=0.077), chemotherapy (univariate p-value=0.078), and abdominopelvic radiation therapy (univariate p-value=0.078). Of these five variables, wound class at T1 remained in the linear regression model for mean collagen I area after the backward elimination process. A wound class of “not clean” (clean-contaminated/contaminated/infected) was associated with a mean collagen I area 2857.7 units lower relative to a wound class of clean (p-value=0.077; n=35). As indicated by the r^2 value, the model explained approximately 9.2% of the variability in the mean collagen I area.

Mean Collagen III Area—The cohort variables whose associations with mean collagen III area were evaluated in multivariable models were age at T1 (univariate p-value=0.137), and mesh classification (univariate p-value<0.001). Of these two variables, mesh classification remained in the linear regression model for mean collagen III area after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have a mean collagen III area 2464.8 units lower (p-value<0.001), whereas specimens composed of bovine dermis were estimated to have a mean collagen III area 1965.9 units higher (p-value=0.074). Compared to specimens composed of porcine dermis, specimens composed of bovine dermis were estimated to have a mean collagen III area 4430.7 units higher (p-value<0.001) (2 df F-test p-value<0.001; n=35). As indicated by the r^2 value, this single predictor model explained approximately 40.8% of the variability in the mean collagen III area.

Mean Collagen I:Collagen III Ratio—The cohort variables whose associations with mean collagen I:III ratio were evaluated in multivariable models were race (univariate p-value=0.061), chemotherapy (univariate p-value=0.133), and abdominopelvic radiation therapy (univariate p-value=0.133). Of these three variables, race remained in the linear regression model after the backward elimination process. Compared to specimens explanted from Caucasian subjects, specimens explanted from Black subjects were estimated to have a mean collagen I:III ratio 3359.1 units lower (p-value=0.061). However, due to the racial homogeneity of the subset sample (n=35, 33 Caucasian: 2 Black), the dataset is not conducive to reliable estimations of the effect of race. As indicated by the r^2 value, this single predictor model explained approximately 10.3% of the variability in the mean collagen I:III ratio.

DISCUSSION

Biologic scaffolds have been evaluated in multiple animal models for a variety of applications^{23, 29–33}. However, the results of these preclinical trials are limited in their generalizability to clinical practice due to biases introduced into the study design by industry sponsorship, and the limited translative potential inherent to animal models. Reports of the constructive remodeling of these materials in the human body have thus far been limited to a few small case series documenting histologic analyses of explanted biological scaffolds following periodontal^{24–25} and breast reconstruction^{26–27}. The literature is currently lacking a risk prediction model that reliably predicts the patients and clinical circumstances for which non-constructive remodeling of an abdominal soft tissue repair site with biologic mesh reinforcement is most likely to occur. Thus, the purpose of this study was to evaluate the multivariable associations of patient characteristics and surgical site classifications to the histologic remodeling scores of biologic meshes biopsied from the abdominal soft tissue repair sites of the patients in the first attempt to generate a risk prediction model of non-constructive remodeling. Forty subjects (n=40) with biologic mesh implanted during a previous abdominal soft tissue repair were identified and consented for the study, and specimens of the biologic meshes were procured during a subsequent clinically-indicated abdominal surgery.

Cell type scores were dichotomized to scores < 3 and scores ≥ 3 . The distinguishing histologic feature therefore became the presence of inflammatory cells versus the absence of inflammatory cells in the specimens (Figure 1). At a liberal significance threshold of $p = 0.200$ for the univariate analyses, sex (p -value= 0.143), mesh indwelling duration (p -value=0.060), and BMI at the time of mesh explantation (p -value=0.110) were found to significantly correlate with the cell type scores from the histologic analysis. Specifically, female sex of the subject was more highly associated with the absence of inflammatory cells in the scaffold specimens, whereas male sex of the subject was more highly associated with the presence of inflammatory cells in the scaffold specimens. As expected, longer mesh indwelling durations were more highly associated with the absence of inflammatory cells in the mesh specimens. These data are consistent with the minimal inflammatory response to biologic scaffolds as the scaffold degrades over time. A greater mean BMI at the time of mesh explantation was associated with the absence of inflammatory cells in the mesh specimens. None of these variables remained in the multivariable logistic regression model for cell type scores after the backward elimination process.

Cellular infiltration scores were dichotomized to scores ≤ 2 and scores > 2 . The distinguishing histologic feature therefore became the lack of cellular penetrance to the center of the mesh specimens versus cellular penetrance to the center of the scaffold specimens (Figure 1). Note that references to the center pertain to the center of the scaffold biopsy specimen, and not necessarily the center of the entire piece of scaffold implanted into the subject. At a liberal significance threshold of $p = 0.200$ for the univariate analyses, subject age at the time of mesh implantation (p -value=0.022), mesh indwelling duration (p -value=0.008), and mesh classification (p -value=0.002) were found to significantly correlate with the cell infiltration scores from the histologic analysis. Specifically, specimens from subjects with a greater age at the time of scaffold implantation were more highly associated with cellular penetrance to the center of the scaffold specimen. As expected, longer mesh indwelling durations were more highly associated with cellular penetrance to the center of the scaffold specimen. Human dermis scaffolds, porcine dermis scaffolds, and bovine dermis scaffolds were more highly associated with cellular penetrance to the center of the scaffold specimen, indicating constructive remodeling for each of the biologic mesh types.

Of these three variables, subject age at the time of mesh implantation and mesh classification remained in the logistic regression model for cell infiltration scores after the backward elimination process. Compared to mesh specimens composed of human dermis, mesh specimens composed of porcine dermis were estimated to have significantly lower odds of demonstrating cellular penetrance to the center of the scaffold specimen on histologic analysis, controlling for subject age at the time of mesh implantation (OR=0.0021; p -value<0.001). Compared to mesh specimens composed of human dermis, mesh specimens composed of bovine dermis were estimated to have significantly lower odds of demonstrating cellular penetrance to the center of the scaffold specimen on histologic analysis, controlling for subject age at the time of mesh implantation (OR=0.0010; p -value=0.007). When compared to mesh specimens composed of porcine dermis, mesh specimens composed of bovine dermis were estimated to have lower odds of demonstrating cellular penetrance to the center of the scaffold specimen on histologic analysis, controlling for subject age at the time of mesh implantation; however, a statistically

significant difference was not detected (OR= 0.486; p-value=0.633; 2 df penalized likelihood ratio test p-value=0.001). These data indicate more favorable cellular infiltration for human dermis scaffolds compared to porcine dermis scaffolds and bovine dermis scaffolds. Furthermore, although a statistically significant difference was not detected, a trend toward more favorable cellular infiltration for porcine dermis scaffolds compared to bovine dermis scaffolds was noted. Controlling for mesh classification, a one-year increase in the subject age at the time of mesh implantation was significantly associated with a 1.3216 times greater odds of demonstrating cellular penetrance to the center of the scaffold (p-value=0.004). The c-statistic or area under the ROC for this multivariable model was 0.989, suggesting excellent predictive capacity in this sample.

Extracellular matrix deposition scores were dichotomized to scores ≤ 2 and scores > 2 . The distinguishing histologic feature therefore became the absence of extracellular matrix protein deposition at the center of the scaffold specimen versus the presence of extracellular matrix protein deposition at the center of the scaffold specimen (Figure 1). At a liberal significance threshold of $p = 0.200$ for the univariate analyses, subject age at the time of mesh implantation (p-value=0.118), mesh indwelling duration (p-value=0.025), and mesh classification (univariate p-value=0.002) were found to significantly correlate with the extracellular matrix deposition scores from the histologic analysis. Specifically, specimens from subjects with a greater age at the time of scaffold implantation were more highly associated with extracellular matrix deposition at the center of the scaffold specimen. As expected, longer mesh indwelling durations were more highly associated with extracellular matrix deposition at the center of the scaffold specimen. Human dermis scaffolds and bovine dermis scaffolds were more highly associated with extracellular matrix deposition at the center of the scaffold specimen, whereas porcine dermis scaffolds were more highly associated with the absence of extracellular matrix deposition at the center of the scaffold specimen. These data indicate that constructive remodeling by the host cells is more pervasive with human dermis and bovine dermis biologic mesh types compared to porcine dermis scaffolds in this sample.

Mesh classification remained in the logistic regression model for extracellular matrix deposition scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have significantly lower odds of demonstrating extracellular matrix deposition at the center of the scaffold specimen (OR=0.0739; p-value=0.001). Specimens composed of bovine dermis had 0.2992 lower odds of demonstrating extracellular matrix deposition at the center of the scaffold specimen compared to human dermis scaffolds, and 4.0477 greater odds of demonstrating extracellular matrix deposition at the center of the scaffold specimen compared to porcine dermis scaffolds, although statistically significant differences were not detected (p-value=0.326 and p-value=0.238, respectively; 2 df penalized likelihood ratio test p-value=0.004). These data indicate significantly more favorable extracellular matrix deposition for human dermis biologic mesh compared to porcine dermis biologic mesh. Furthermore, although statistically significant differences were not detected, trends toward more favorable extracellular matrix deposition for human dermis scaffolds compared to bovine dermis scaffolds, and for bovine dermis scaffolds compared to porcine dermis

scaffolds were noted. The c-statistic or area under the ROC for this single predictor model was 0.793, indicating moderate predictive capacity in this sample.

Scaffold degradation scores were dichotomized to scores < 2 and scores ≥ 2 . The distinguishing histologic feature therefore became the partial degradation of the original scaffold versus the near-complete degradation of the original scaffold (Figure 1). At a liberal significance threshold of $p = 0.200$ for the univariate analyses, mesh indwelling duration (p -value=0.028), mesh classification (p -value <0.001), and BMI at the time of mesh explantation (p -value=0.087) were found to significantly correlate with the scaffold degradation scores from the histologic analysis. As expected, longer mesh indwelling durations were more highly associated with near-complete degradation of the original scaffold. Human dermis scaffolds were more highly associated with near-complete scaffold degradation, whereas porcine dermis scaffolds and bovine dermis scaffolds were more highly associated with partial degradation of the original scaffold. Greater subject BMI at the time of mesh explantation was more highly associated with near-complete scaffold degradation.

Of these three variables, mesh classification remained in the logistic regression model for scaffold degradation scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have significantly lower odds of demonstrating near-complete scaffold degradation on histologic analysis (OR=0.0640; p -value <0.001). Specimens composed of bovine dermis had 0.1459 lower odds of demonstrating near-complete scaffold degradation on histologic analysis compared to human dermis scaffolds, and 2.2799 higher odds of demonstrating near-complete scaffold degradation on histologic analysis compared to porcine dermis scaffolds, although statistically significant differences were not detected (p -value=0.090 and p -value=0.517, respectively; 2 df penalized likelihood ratio test p -value=0.002). These data indicate that scaffold degradation by the host is more extensive with human dermis scaffolds compared to porcine dermis scaffolds in this sample. Furthermore, although statistically significant differences were not detected, the data indicate trends toward more extensive scaffold degradation for human dermis scaffolds compared to bovine dermis scaffolds, and for bovine dermis scaffolds compared to porcine dermis scaffolds. The c-statistic or area under the ROC for this single predictor model was 0.803, indicating moderate predictive capacity in this sample.

Fibrous encapsulation scores were dichotomized to scores < 2 and scores ≥ 2 . The distinguishing histologic feature therefore became the presence of $\geq 25\%$ fibrous encapsulation versus the presence of $<25\%$ fibrous encapsulation (Figure 1). The only cohort variable with a significant association at the $\alpha=0.200$ level to the fibrous encapsulation scores was mesh classification (p -value=0.108). In a logistic regression model for fibrous encapsulation scores, the 2 df penalized likelihood ratio test for this variable had a p -value=0.161, resulting in no predictors selected for the model in this sample.

Neovascularization scores were dichotomized to scores ≥ 2 and scores < 2 . The distinguishing histologic feature therefore became the absence of blood vessels penetrating the center of the scaffold specimen versus the presence of blood vessels penetrating the

center of the scaffold specimen (Figure 1). At a liberal significance threshold of $p = 0.200$ for the univariate analyses, mesh indwelling duration (p -value=0.111), and mesh classification (p -value=0.005) were found to significantly correlate with the neovascularization scores from the histologic analysis. As expected, longer mesh indwelling durations were more highly associated with neovascularization at the center of the scaffold specimen. Human dermis scaffolds were more highly associated with neovascularization at the center of the scaffold specimen, whereas porcine dermis scaffolds and bovine dermis scaffolds were more highly associated with the absence of neovascularization at the center of the scaffold specimen.

Mesh classification remained in the logistic regression model for neovascularization scores after the backward elimination process. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have significantly reduced odds of demonstrating neovascularization at the center of the scaffold specimen on histologic analysis (OR=0.1077; p -value=0.005). Compared to specimens composed of human dermis, specimens composed of bovine dermis were estimated to have reduced odds of demonstrating neovascularization at the center of the scaffold specimen, although a statistically significant difference was not detected (OR=0.1077; p -value=0.055). Specimens composed of porcine dermis and specimens composed of bovine dermis were estimated to have identical odds of demonstrating neovascularization at the center of the scaffold specimen (OR=1.0000; p -value=1.000; 2 df penalized likelihood ratio test p -value=0.009). These data indicate that human dermis scaffolds demonstrated more extensive neovascularization compared to porcine dermis scaffolds, and trended toward more extensive neovascularization compared to bovine dermis scaffolds although a significant difference was not detected. Furthermore, these data indicate that neovascularization appeared to be equally as extensive in porcine dermis scaffolds and bovine dermis scaffolds in this sample. The c-statistic or area under the ROC for this single predictor model was 0.771, indicating moderate predictive capacity in this sample.

The composite remodeling score, calculated as the mean of the six component remodeling scores, was found to be significantly correlated with subject age at the time of mesh implantation (p -value=0.153), mesh indwelling duration (p -value=0.009), and mesh classification (p -value=0.005) at a liberal significance threshold of $p = 0.200$. As one might expect, more favorable composite scores for constructive remodeling directly correlated with mesh indwelling duration (ρ =0.417). However, as the antithesis of what one might expect, more favorable composite scores for constructive remodeling were directly correlated with subject age at the time of mesh implantation (ρ =0.237). Furthermore, the mean composite remodeling score was 2.71 ± 0.37 SD for specimens composed of human dermis, 1.75 ± 0.83 SD for specimens composed of porcine dermis, and 1.90 ± 0.97 SD for specimens composed of bovine dermis, indicating significantly more favorable scores for constructive remodeling for the human dermis specimens. Of these three variables, the model selection process for mean composite remodeling score yielded a linear regression model with subject age at the time of mesh implantation and mesh classification. Controlling for mesh classification, a one-year increase in subject age at the time of mesh implantation was associated with a 0.017 unit increase in the mean composite remodeling score, although a significant difference was not detected (p -value=0.111). Controlling for subject age at the

time of mesh implantation, specimens composed of porcine dermis were estimated to have a mean composite remodeling score 0.898 units significantly lower than specimens composed of human dermis (p -value=0.001). Controlling for subject age at the time of mesh implantation, specimens composed of bovine dermis were estimated to have a mean composite remodeling score 0.805 units lower than specimens composed of human dermis, and a mean composite remodeling score 0.093 units higher than specimens composed of porcine dermis, although statistically significant differences were not detected (p -value=0.255 and p -value=0.805, respectively; 2 df F-test p -value<0.001). These data are consistent with the minimal fibrotic response; the near-complete original scaffold degradation; and the more extensive host cell infiltration, extracellular matrix deposition, and neovascularization of the human dermis scaffolds compared to the porcine dermis scaffolds and bovine dermis scaffolds in this sample. This multivariable model explained approximately 44.9% of the variability in the composite remodeling scores.

The mean collagen I area was found to be significantly correlated with subject age at the time of mesh implantation (p -value=0.157), race (p -value=0.091), wound class at the time of mesh implantation (p -value=0.077), chemotherapy (p -value=0.078), and abdominopelvic radiation therapy (p -value=0.078) at a liberal significance threshold of $p = 0.200$. As one might expect, the mean quantity of type I collagen was inversely correlated with subject age at the time of mesh implantation (ρ =-0.244). That is, the stronger type I collagen fibers decrease with advanced subject age. Interestingly, the mean quantity of type I collagen was -26.8 ± 4514.2 SD for scaffolds explanted from Caucasian subjects, and -5177.6 ± 23.0 SD for scaffolds explanted from Black subjects. Note that a negative value denotes a mean quantity of type I collagen from the explanted specimens that is less than the mean quantity of type I collagen from a single de novo scaffold of the same manufacturer type. These data seem to indicate more favorable quantities of type I collagen from scaffolds explanted from Caucasian subjects compared to scaffolds explanted from Black subjects; however, due to the small number of Black subjects, this result must be interpreted with caution. Furthermore, the large standard deviation for the mean quantity of type I collagen from the Caucasian subjects indicates a large degree of variation in this value among the subjects in the sample. As one might expect, the mean quantity of type I collagen was significantly decreased in specimens from subjects who underwent abdominopelvic radiation therapy compared to specimens from subjects who did not (-3417.8 ± 2794.1 SD versus 194.9 ± 4605.0 , respectively; $p=0.078$), and was significantly decreased in specimens from subjects who underwent chemotherapy treatment compared to specimens from subjects who did not (-3417.8 ± 2794.1 SD versus 194.9 ± 4605.0 SD, respectively; $p=0.078$). Note that the mean quantities of collagen I and the p -values are identical for the abdominopelvic radiation therapy variable and the chemotherapy variable because the same individuals in the study sample who underwent abdominopelvic radiation therapy also underwent chemotherapy treatment and therefore the data are dependent. These data indicate less favorable quantities of the stronger type I collagen fibers for specimens explanted from subjects who underwent abdominopelvic radiation therapy and chemotherapy treatment. As expected, the mean quantity of type I collagen was significantly decreased in specimens implanted into surgical sites that were "not clean" (clean-contaminated, contaminated, or infected) compared to specimens implanted into surgical sites that were clean (-1300.9 ± 4614.1 SD versus 1556.7

± 3923.8 SD, respectively; p -value=0.077). The multivariable model selection process for type I collagen quantity yielded a linear regression model with wound class at the time of mesh implantation. A wound class of “not clean” was associated with an estimated mean quantity of type I collagen 2857.7 units lower relative to a wound class of clean (p -value=0.077). These data indicate that a surgical site that is “not clean” at the time of mesh implantation is associated with less deposition of the stronger type I collagen fibers by the host during the constructive remodeling process, although a statistically significant difference was not detected. This single-predictor model explained approximately 9.2% of the variability in the mean quantity of type I collagen. With greater sample sizes, this multivariable model may be expanded to predict more of the variability in the mean quantity of type I collagen.

The mean collagen III area was found to be significantly correlated with subject age at the time of mesh implantation (p -value=0.137), and mesh classification (p -value<0.001) at a liberal significance threshold of $p = 0.200$. As one might expect, the mean quantity of type III collagen was directly correlated with subject age at the time of mesh implantation ($\rho = -0.256$). That is, the type III collagen fibers with less tensile strength compared to type I collagen, increase in quantity with advanced subject age at the time of mesh implantation. Interestingly, the mean quantity of type III collagen was significantly decreased in scaffold specimens of porcine dermis origin compared to scaffold specimens of human dermis origin, and was significantly decreased in scaffold specimens of human dermis origin compared to scaffold specimens of bovine origin (-1178.6 ± 1714.3 SD versus 1286.2 ± 1439.6 SD versus 3252.1 ± 3488.2 SD, respectively; $p < 0.001$). The only variable that remained in the linear regression model for mean quantity of type III collagen after the backward elimination process was mesh classification. Compared to specimens composed of human dermis, specimens composed of porcine dermis were estimated to have a mean quantity of type III collagen that was 2464.8 units significantly lower (p -value<0.001). When compared to specimens composed of porcine dermis, specimens composed of bovine dermis were estimated to have a mean quantity of type III collagen that was 4430.7 units significantly higher (p -value<0.001). Compared to specimens composed of human dermis scaffolds, specimens composed of bovine dermis were estimated to have a mean quantity of type III collagen that was 1965.9 units higher, although a significant difference was not detected (p -value=0.074; 2 df F-test p -value<0.001). These data indicate that the type III collagen with less tensile strength is deposited in least quantity in the porcine dermis scaffolds, in intermediate quantity in the human dermis scaffolds, and trended toward deposition in greatest quantity in the bovine dermis scaffolds in this sample. This single predictor model explained approximately 40.8% of the variability in the mean quantity of type III collagen in this sample.

The mean collagen I:III ratio was found to be significantly correlated with race (p -value=0.061), chemotherapy (p -value=0.133), and abdominopelvic radiation therapy (p -value=0.133) at a liberal significance threshold of $p = 0.200$. Interestingly, the mean collagen I:III ratio was 371.4 ± 2406.8 SD for scaffolds explanted from Caucasian subjects, and -2987.7 ± 814.8 SD for scaffolds explanted from Black subjects. Note that a negative value denotes a mean collagen I:III ratio from the explanted specimens that is less than the mean collagen I:III ratio from a single de novo scaffold of the same manufacturer type. These data

seem to indicate more favorable mean collagen I:III ratios from scaffolds explanted from Caucasian subjects compared to scaffolds explanted from Black subjects; however, due to the small number of Black subjects, this result must be interpreted with caution. Furthermore, the large standard deviation for the mean quantity of type I collagen from the Caucasian subjects indicates a large degree of variation in this value among the subjects in the sample. As one might expect, the mean collagen I:III ratio was significantly decreased in specimens from subjects who underwent abdominopelvic radiation therapy compared to specimens from subjects who did not (-1363.2 ± 1384.8 SD versus 436.6 ± 2530.8 , respectively; $p=0.133$), and was significantly decreased in specimens from subjects who underwent chemotherapy treatment compared to specimens from subjects who did not (-1363.2 ± 1384.8 SD versus 436.6 ± 2530.8 , respectively; $p=0.133$). Note that the mean collagen I:III ratios and the p-values are identical for the abdominopelvic radiation therapy variable and the chemotherapy variable because the same individuals in the study sample who underwent abdominopelvic radiation therapy also underwent chemotherapy treatment and therefore the data are dependent. These data indicate less favorable mean collagen I:III ratios for specimens explanted from subjects who underwent abdominopelvic radiation therapy and chemotherapy treatment. Of these three variables, race remained in the linear regression model for the mean collagen I:III ratio after the backward elimination process. Compared to specimens explanted from Caucasian subjects, specimens explanted from Black subjects were estimated to have a mean collagen I:III ratio that was 3359.1 units lower, although a significant difference was not detected ($p\text{-value}=0.061$). Furthermore, due to the limited number of Black subjects in this sample, this dataset is not conducive to reliable estimations of the effect of race.

The combination of Sirius Red staining and visualization under polarized light microscopy is considered highly sensitive and specific for collagen types I, II, and III⁴²⁻⁴⁴. There are, however, other oriented basic proteins that have their birefringency enhanced by Sirius Red staining, including keratin, fibrin, component C1q of the complement cascade, and amyloid⁴³⁻⁴⁴. Since amyloid does not have the characteristic fibrous configuration of collagen, it can easily be distinguished from collagen proteins⁴³. Keratin is not likely to have been present in the tissues studied. There remains the possibility, however, that the presence of fibrin and C1q, both of which are fibrous in configuration and appear pale green under polarized light⁴³⁻⁴⁴, may potentially have led to an overestimation of collagen III and an underestimation of the collagen I:III ratio in the tissues evaluated. Furthermore, while the combination of Sirius Red staining and visualization under polarized light microscopy causes collagen type II to appear yellow or blue in hue, this type of collagen exists in cartilage and chondrosarcoma⁴², neither of which is likely to have been present in the tissues studied. It is reasonable to conclude, therefore, that the collagen that appeared red and green in the tissues studied were collagen I and III, respectively. Future studies will attempt to verify these findings using additional methodologies, including immunohistochemistry. Further note that it is not possible to visualize all of the collagen present under linearly-polarized light microscopy⁴⁴. When aligned parallel to the transmission axes of the crossed polarizing filters, collagen fibers will appear dark. The use of circular polarized light microscopy, in which a rotating microscope stage changes the orientation of the tissue section with respect to the transmission axes to minimize underestimations of the collagen

types⁴⁴, will be explored in future studies. However, even with circular polarized light microscopy, collagen fibers that enter or exit the two-dimensional plane of the tissue section may appear in various hues of the spectrum and lead to inaccurate estimations of the collagen types present⁴⁴.

Since all but 2 specimens were procured during the repair of a hernia recurrence, note that these specimens were biased toward selection of biologic mesh explants following soft tissue repair failure. Therefore, the data contributed by these specimens may have been biased toward non-constructive remodeling. This study design was necessary to introduce minimal health risk to the consenting subjects. Of the 40 specimens, 36 were procured from a ventral hernia repair site, and 4 were procured from a hiatal or paraesophageal hernia repair site. It is possible that biomechanical force loading on the soft tissue in various anatomic locations within the abdomen may differentially affect the collagen distribution and tissue remodeling characteristics of the biologic scaffolds. However, the potential associations between either abdominal soft tissue location (anterior abdominal wall versus esophageal hiatus) or abdominal soft tissue repair location (onlay versus inlay versus underlay) and the remodeling outcomes were not examined in this study due to data sparseness. As all except 14 specimens were procured from previously contaminated or infected surgical sites, these specimens contributed data that may have been additionally biased toward non-constructive remodeling by the local inflammatory response to the pathogens present at the time of biologic mesh implantation. Of the 25 specimens for which surgical site contamination or infection was present at the time of mesh implantation, 9 specimens were procured from surgical sites with evidence of persistent contamination on clinical examination. For these 9 specimens, the persistence of contamination during the period of biologic mesh indwelling may have further biased the histologic results toward non-constructive remodeling⁴⁵. Note, however, that despite data indicating high rates of repair failure and wound morbidity^{46–48}, the off-label use of biologic meshes in clean-contaminated, contaminated, and infected surgical sites is representative of current clinical practice in the U.S. Therefore, the results of this study are reflective of current clinical practice.

Several significant findings were discovered in the univariate analyses and multivariable model estimations. It should be noted, however, that the absence of other significant univariate associations does not necessarily imply that these associations do not exist. The study may instead have been insufficiently powered to detect them and include them in the multivariable models. Dichotomization of the remodeling characteristic outcome variables, and exclusion of subjects with incomplete independent variable data were necessary for the statistical analyses due to the limited sample size and sparseness of the data. The results would be further informed by studies validating the expected distribution of the component scores for the remodeling characteristic histologic scoring system. With greater sample sizes, these multivariable models may be expanded to predict more of the variability in the histologic remodeling scores and the relative quantities of collagen types I and III for biologic meshes used to reinforce abdominal soft tissue repair sites.

These preliminary results are the first steps in generating a risk prediction model that reliably predicts the patients and clinical circumstances for which non-constructive

remodeling of an abdominal soft tissue repair site with biologic mesh reinforcement is most likely to occur. Ultimately, this risk prediction model will be further developed, validated, and applied to predict the patients most likely to experience abdominal soft tissue repair failure and the mean time to postoperative failure. This information is critical to surgical decision-making for patients with complex abdominal soft tissue defects, and will be instrumental to improvements in the quality of their care. The risk prediction model will provide useful data about modifiable patient risk factors that may be addressed with the patient to improve the likelihood of abdominal soft tissue reconstruction success. With larger sample sizes and diversity of mesh type data, the risk prediction model can be further developed to aid surgeon selection of the most appropriate reinforcement material for an individual patient given the clinical characteristics of the patient and the classification of the surgical site. By guiding appropriate utilization of these expensive biologic reinforcement materials and addressing modifiable patient risk factors to optimize patient outcomes, the risk prediction model has the potential to significantly improve quality of care for patients with complex abdominal soft tissue defects.

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Score	0	1	2	3
Cell Type	Inflammatory cells present, no fibroblasts present	Primarily inflammatory cells, few fibroblasts present	Primarily fibroblasts, few inflammatory cells present	Fibroblasts only, no inflammatory cells present
Cellular Infiltration (inflammatory cells include neutrophils, macrophages, and foreign body giant cells)	Zero cells in contact with scaffold	Cells contact periphery, but do not infiltrate the scaffold	Cells infiltrate scaffold, but none reach scaffold center	Cells penetrate into the scaffold center
Extracellular Matrix (ECM) Deposition	No host ECM deposition	Host ECM deposited at scaffold periphery	Host ECM deposited inside scaffold, but not the scaffold center	Host ECM deposited into scaffold center
Scaffold Degradation	Original scaffold intact; borders remain clearly demarcated	Scaffold partially degraded; layers separated by cells, blood vessels, host tissue, etc.	Scaffold extremely degraded; difficult to distinguish scaffold from host tissue	Scaffold completely degraded; no evidence of original scaffold
Fibrous Encapsulation (measurement of thickness in mm rather than a score)	Extensive fibrous encapsulation (50-100% of scaffold periphery)	Moderate fibrous encapsulation (25-49% of scaffold periphery)	Mild fibrous encapsulation (0<x<25% of scaffold periphery)	No fibrous encapsulation (0% of scaffold periphery)
Neovascularization	Zero blood vessels present	Vessels present to mesh periphery only, no penetration into scaffold	Vessels infiltrate scaffold, but none reach the scaffold center	Vessels penetrate into scaffold center

Figure 1.
Histologic Semi-Quantitative Scoring System for Biologic Mesh Remodeling

Table 1

Overall Cohort Variables.

	Descriptive Statistic
N	40
Cell Type Score 3, N (%) [subset n=40]	17 (42.5)
Cell Infiltration Score >2, N (%) [subset n=39]	31 (79.5)
Extracellular Matrix Deposition Score >2, N (%) [subset n=39]	25 (64.1)
Scaffold Degradation Score 2, N (%) [subset n=39]	22 (56.4)
Fibrous Encapsulation Score 2, N (%) [subset n=40]	28 (70.0)
Neovascularization Score >2, N (%) [subset n=39]	25 (64.1)
Composite Remodeling Score, mean (SD) [subset n=39]	2.3 (0.8)
Mean Collagen I Area - Control, mean (SD) [subset n=35]	-321.2 (4544.3)
Mean Collagen III Area - Control, mean (SD) [subset n=35]	680.1 (2174.3)
Mean Collagen I:III Ratio - Control, mean (SD) [subset n=35]	179.5 (2469.3)
Female, N (%) [subset n=40]	28 (70.0)
Caucasian, N (%) [subset n=40]	38 (95.0)
Age at T1, years, mean (SD) [subset n=39]	55.4 (10.9)
Mesh indwelling duration, days, median (q1, q3) [subset n=39]	457 (308, 674)
Mesh classification, N (%) [subset n=37]	
Human dermis	23 (62.2)
Porcine dermis	11 (29.7)
Bovine dermis	3 (8.1)
Wound class at T1, Not clean, N (%) [subset n=39]	25 (64.1)
Wound class at T2, Not clean, N (%) [subset n=40]	11 (27.5)
BMI at T1, mean (SD) [subset n=34]	33.9 (5.2)
BMI at T2, mean (SD) [subset n=40]	33.9 (5.9)
Diabetes, N (%) [subset n=40]	13 (32.5)
Smoking status, N (%) [subset n=40]	25 (62.5)
Pack-year history, median (q1, q3) [subset n=40]	12.0 (0, 40)
Smoking history, N (%) [subset n=38]	
Never smoked	17 (44.7)
Quit 30 days before T2 and never resumed	13 (34.2)
Current smoker	8 (21.1)
Abdominopelvic radiation therapy, N (%) [subset n=40]	5 (12.5)
Chemotherapy, N (%) [subset n=40]	5 (12.5)

Table 2

Multivariable Associations Between Cohort Variables and Cell Infiltration Score (n=36).

Effect	OR Estimate	95% CI	P-value
Age at T1, years	1.3216	(1.0626, 2.1974)	0.004
Mesh classification			
Human dermis	(reference)	-	-
Porcine dermis	0.0021	(0.0001, 0.1482)	<0.001
Bovine dermis	0.0010	(0.0001, 0.2095)	0.007

Table 3

Multivariable Associations Between Cohort Characteristics and Composite Remodeling Score (n=36).

Effect	Estimate	Standard Error	P-value
Age at T1, years	0.017	0.010	0.111
Mesh classification			
Human dermis (reference)		-	-
Porcine dermis	-0.898	0.249	0.001
Bovine dermis	-0.805	0.694	0.255