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## Contemporary concepts in hernia prevention: Selected proceedings from the 2017 International Symposium on Prevention of Incisional Hernias

Hobart W. Harris<sup>a,\*</sup>, William H. Hope<sup>b</sup>, Gina Adrales<sup>c</sup>, Dana K. Andersen<sup>d</sup>,  
Eva B. Deerenberg<sup>e</sup>, Holger Diener<sup>f</sup>, Gregory Dumanian<sup>g</sup>, Barbora East<sup>h</sup>, John P. Fischer<sup>i</sup>,  
Miguel A. Garcia Ureña<sup>j</sup>, George J. Gibeily<sup>k</sup>, Birgitta M. Hansson<sup>l</sup>, Pilar Hernández-  
Granados<sup>m</sup>, Michael C. Hiles<sup>n</sup>, Johannes Jeekel<sup>e</sup>, Howard Levinson<sup>o</sup>, Manuel Lopez-Cano<sup>p</sup>,  
Filip Muysoms<sup>q</sup>, José Antonio Pereira<sup>r</sup>, Michel Prudhomme<sup>s</sup>, Archana Ramaswamy<sup>t</sup>,  
Cesare Stabilini<sup>u</sup>, Jared Torkington<sup>v</sup>, Silvia Valverde<sup>w</sup>, David M. Young<sup>a</sup>

<sup>a</sup> Department of Surgery, University of California, San Francisco, San Francisco, CA

<sup>b</sup> Department of Surgery, New Hanover Regional Medical Center, Wilmington, NC

<sup>c</sup> Department of Surgery, Johns Hopkins University, Baltimore, MD

<sup>d</sup> Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

<sup>e</sup> Department of Surgery, Erasmus University Medical Center, Rotterdam, Netherlands

<sup>f</sup> Department of Vascular Medicine, University of Hamburg, Hamburg, Germany

<sup>g</sup> Department of Surgery, Northwestern School of Medicine, Chicago, IL

<sup>h</sup> Department of Surgery, Charles University, Prague, Czech Republic

<sup>i</sup> Department of Surgery, University of Pennsylvania, Philadelphia, PA

<sup>j</sup> Department of Surgery, Francisco de Vitoria University, Madrid, Spain

<sup>k</sup> Division of Surgical Devices, Center for Devices and Radiologic Health, US Food and Drug Administration, Silver Spring, MD

<sup>l</sup> Department of Surgery, University of Nijmegen, Nijmegen, Netherlands

<sup>m</sup> General and Digestive Surgery Unit, Fundación Alcorcón University Hospital, Madrid, Spain

<sup>n</sup> Cook Biotech, Inc., West Lafayette, IN

<sup>o</sup> Department of Surgery, Duke University, Durham, North Carolina

<sup>p</sup> Department of Surgery, Universidad Autonoma de Barcelona, Barcelona, Spain

<sup>q</sup> Department of Surgery, Maria Middelaers Hospital, Ghent, Belgium

<sup>r</sup> Departments of Experimental and Health Sciences, University Pompeu Fabra, Barcelona, Spain

<sup>s</sup> Department of Surgery, University of Nîmes, Nîmes, France

<sup>t</sup> Department of Surgery, University of Minnesota, Minneapolis, MN

<sup>u</sup> Department of Integrated Surgical and Diagnostic Sciences, University of Genoa, Genoa, Italy

<sup>v</sup> Department of Surgery, Cardiff University, Cardiff, Wales

<sup>w</sup> Department of Surgery, Instituto Quirúrgico Lacy, Barcelona, Spain

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## ABSTRACT

Incisional hernia is a frequent complication of midline laparotomy and enterostomal creation and is associated with high morbidity, decreased quality of life, and high costs. The International Symposium on Incisional Hernia Prevention was held October 19–20, 2017, at the InterContinental Hotel in San Francisco, CA, hosted by the Department of Surgery, University of California, San Francisco. One hundred and three attendees included general and plastic surgeons from 9 countries, including principal participants for several of the seminal studies in the field. Over the course of the 2-day meeting, there were 38 oral presentations, 3 keynote lectures, and 2 panel discussions. The Symposium was a combination of new information but also a comprehensive review of the existing data so as to assess the current state of the

\* Corresponding author: 513 Parnassus Avenue, Room S-301, San Francisco, CA 94143-0104.

E-mail address: [hobart.harris@ucsf.edu](mailto:hobart.harris@ucsf.edu) (H.W. Harris).

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field and to set the stage for future research. Further, the Symposium sought to increase awareness and thus emphasize the importance of preventing the formation of incisional and enterostomal hernias.

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## Epidemiology, pathogenesis & economics of incisional hernias

Although the overall epidemiology of incisional hernias has been well delineated, the fundamental pathogenesis of this post-operative complication and how to identify patients at increased risk remain topics of active interest and research. Furthermore, the substantial economic impact of the condition, estimated to be >\$3 billion annually in the US, is garnering more attention.

### *A systematic review of factors affecting midline incisional hernia rates*

A comprehensive review of the literature, including the largest meta-regression analysis published to date on the subject, identified several factors that independently increased the risk of midline incisional hernia. The factors included increasing age, obesity (or upper midline incision alone), abdominal aortic aneurysm surgery, previous laparotomy, and previous incisional hernia repair.<sup>1</sup> Notably, there was no evidence that suture type (absorbable vs nonabsorbable) affects the rate of hernia formation. The overall pooled incidence of incisional hernias of midline wounds at 2 years was 12.8% with a wide range (0%–36%).

### *Incisional hernias represent a failure of early wound healing*

Whereas most incisional hernias are not clinically apparent for 12–18 months after abdominal surgery, compelling evidence from a few studies indicates that the hernias develop within a few weeks after surgery due to a failure of early wound healing. Normal wound healing involves an orderly sequence of well-coordinated interactions between various forms of cells in the inflammatory response and the extracellular matrix consisting of 4 phases: coagulation, inflammation, proliferation, and remodeling. Collagen deposition and maturation occurs during the proliferation and remodeling phases, respectively, with a progressive increase in the ratio of collagen type 1:type 3 signifying a more organized extracellular matrix. In most causes of deficient early wound healing, such as seen in diabetic patients, recent evidence implicates altered inflammation due to the decreased recruitment of bone-marrow-derived circulating cells.<sup>2</sup> Clinical evidence that failed early wound healing causes incisional hernias includes studies wherein metallic clips placed as markers of the opposed fascial edges were shown to have separated >1 cm within 30 days after operation in patients who went on to develop incisional hernias.<sup>3</sup> The radiographic detection of separation of these metal clips in the early phase of wound healing after operation was both sensitive and specific for the eventual formation of an incisional hernia. A close association of fascial separation detected by computed tomography (CT) within 1 month after laparotomy with later formation of ventral hernias provided further evidence that incisional hernia formation represents a failure of early wound healing.<sup>4</sup> The forces on the abdominal wall are greater than the sum of the strength of biologic healing and the physical construct of the repair, leading frequently to failure at the suture-tissue interface with suture pull-through. Therefore, the prevention of incisional hernias should target methods that support the early inflammatory phase of wound healing.

### *Economic perspectives on incisional hernia prevention*

Hernia prevention can come in many forms, including decreased infection, less open surgery, patient “prehabilitation,” optimal suture technique, and mesh-reinforced closures. Prehabilitation relevant to preventing incisional hernias would include steps taken to optimize a patient’s wound healing, including control of diabetes, smoking cessation, weight loss, and good overall nutritional status. Several key stakeholders have been identified, including patients, hospitals, payers, industry, and providers. Analysis of the nationwide inpatient sample demonstrates that approximately 1.9 million patients underwent open surgery in 2013, and this population exhibited a relevant and substantial comorbidity burden as evidenced by the high prevalence of obesity, pulmonary disease, and diabetes. Based on a simple calculation, approximately 600,000 patients per year undergoing open surgery are at a markedly increased risk for developing an incisional hernia. Recent work has demonstrated the cost utility of the mesh-reinforced closure, establishing that adding mesh to abdominal wound closure to prevent hernia could add benefit to society and decrease overall costs.<sup>5</sup> This work has also been validated as it relates to the payers’ perspective. From the hospitals’ perspective, strong consideration is paid toward the cost of an effective preventative technique and its impact on Medicare Severity Diagnosis Related Group payments. Currently, there is a category III CPT code (0437T) available for use, with current efforts under way to convert this research code to a reimbursable, category I code in the near future.

### **Suture closure of the abdomen**

Nonclinical data published in 2001<sup>6</sup> heralded the increased bursting strength of an abdominal incision when small (3–6 mm) bites of the fascia were taken as compared to 1-cm bites. Over 15 years later, the body of clinical data demonstrating a decrease in rate of incisional hernia formation when laparotomies are closed using the small bites technique continues to grow. Yet, widespread adoption remains a challenge. In addition, other suturing methods and suture types are under investigation.

### *Small bites versus large bites: The STITCH Trial*

In 1993, Israelsson and Jonsson published a landmark, prospective clinical study introducing the importance of a suture length to wound length ratio of >4 in preventing incisional hernias after midline laparotomy.<sup>7</sup> Subsequent studies have corroborated this seminal observation. Most recently, a prospective, multicenter, double-blind, randomized controlled trial (RCT) was conducted in surgical and gynecologic departments in 10 hospitals located throughout the Netherlands comparing the traditional, large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.<sup>8</sup> Adult patients were equally assigned to closure of the incision using large bites (1-cm bites every 1 cm) versus small bites (5-mm bites every 5 mm). The primary outcome was the occurrence of incisional hernia; the hypothesis was that the incidence would be less in the small bites group. Over approximately 29 months, 560 patients were randomized to the large bites group ( $n=284$ ) or the small bites group ( $n=276$ ). Patients in the small bites group had fascial closures sutured with

more stitches than those in the large bites group (mean  $\pm$  SD number of stitches  $45 \pm 12$  vs  $25 \pm 10$ ;  $P < .0001$ ), a greater ratio of suture length to wound length ( $5.0 \pm 1.5$  vs  $4.3 \pm 1.4$ ;  $P < .0001$ ), and a greater closure time ( $14 \pm 6$  min vs  $10 \pm 4$  min;  $P < .0001$ ). The rates of adverse events did not differ significantly between groups. There were significantly more incisional hernias in the large bites group (21% vs 13%;  $P = .022$ , covariate adjusted odds ratio 0.52, 95% confidence interval 0.31–0.87;  $P = .0131$ ) at 1-year follow-up. These findings indicate that the small bites suture technique is more effective than the traditional large bites technique for prevention of incisional hernia in midline incisions and is not associated with a greater rate of adverse events. This study provides further evidence that the small bites technique should become the standard technique for closing midline incisions.

#### *Hughes abdominal repair (HART) trial*

The “Hughes repair,” also known as the “Cardiff repair,” is a standard mass closure combined with a series of horizontal and 2 vertical mattress sutures within a continuous suture. The closure technique is thought to distribute the load both along and across the incision length and thus, theoretically, avoids ischemia and suture pull-through. Although there is evidence that the technique is as effective as mesh for repairing incisional hernias,<sup>9,10</sup> no trials have compared the Hughes repair to the standard mass closure for preventing incisional hernias after a midline incision. The HART Trial is a prospective, randomized controlled trial at 28 centers throughout the United Kingdom that will compare the “Hughes closure” to the surgeons’ customary suture techniques.<sup>11</sup> The investigators have almost finished recruiting the planned 800 patients, which includes those with colorectal cancer undergoing a midline incision of more than 5 cm and both emergency and elective patients. Results are expected to be reported within the next 2 years.

Of note, all published randomized clinical trials and meta-analyses indicate that the best way to decrease the risk of incisional hernia when closing the abdominal wall with suture after elective, midline laparotomy is a small bites, continuous technique using slowly absorbable, monofilament suture, eg, 2-0 polydioxanone or polyglyconate. This technique has been shown repeatedly to yield a suture length:wound length ratio of  $\geq 4$ . Consequently, this method should become the standard closure technique for midline incisions. Notably, there is little evidence on how to best close the abdomen after emergency surgery, in morbidly obese patients, or when using other types of abdominal incisions.

#### **Prophylactic mesh augmentation: Laparotomies**

Another strategy to decrease the incidence of incisional hernias involves prophylactic reinforcement of the fascial closure with prosthetic mesh, especially in patients at increased risk for this complication. Early reports on the use of mesh to prevent incisional hernias after weight-loss surgery date back over 2 decades and were initially disappointing<sup>12</sup>; however, substituting prosthetics made from permanent rather than absorbable materials has yielded considerably better results. The current challenges include where best to position the mesh and how to more accurately identify high-risk patients who stand to most benefit from this intervention.

#### *Onlay mesh reinforcement after midline and subcostal incisions*

Incisional hernias are a problem for all patients undergoing abdominal surgery, including gastrointestinal, vascular, urologic, and gynecologic procedures. Recently, investigators reported hernia rates of 30%, 53%, and 56% in urologic, gynecologic, colorectal, and

all other patients with cancer undergoing abdominal surgery.<sup>13</sup> Importantly, an expanding body of evidence demonstrates the safety and efficacy of prosthetic mesh when placed in an onlay position to prevent the development of an incisional hernia. Results of a recent review of 172 patients in whom a prophylactic, lightweight polypropylene mesh was placed during the index operation yielded an incisional hernia rate of 7.6% with a mean follow-up of 5 years (unpublished). Although 2 of the 172 patients needed their mesh prosthetic explanted, there were no chronic seromas, no foreign body reactions, and no complaints of chronic pain. Similarly, the use of prophylactic mesh augmentation to prevent incisional hernias after bilateral subcostal incisions has been reported in a case-control study using a lightweight, macroporous, self-gripping polypropylene mesh placed in a retromuscular position.<sup>14</sup> Both groups had comparable rates of local and systemic complications, but the incisional hernia rate was markedly less in the mesh group than in the historical control group (1.7% vs 17.5%;  $P = .0006$ ) with a mean follow-up of 2 years.

#### *Mesh augmentation after emergency surgery*

Whereas prophylactic mesh augmentation appears safe and effective in preventing incisional hernias after elective abdominal surgery, there is scant data regarding this approach under emergency surgical conditions. However, Argudo et al hypothesized that prophylactic mesh could be used to prevent incisional hernias in patients undergoing emergency abdominal surgery without increased postoperative complications.<sup>15</sup> Accordingly, they compared patients retrospectively whose incisions were closed with a running, slowly absorbable suture ( $n = 190$ ) versus those ( $n = 76$ ) with the addition of a partially absorbable lightweight mesh (Ultrapro; Ethicon, Inc, Somerville, NJ) placed in an onlay position. Median follow-up was 16.7 months. Addition of the mesh onlay decreased the incisional hernia rate by  $>80\%$  (5.9% vs 33.3%;  $P = .0001$ ) without an impact on surgical site infections or mortality. Thus, albeit a retrospective study with all its limitations in patient comparability, these data suggest that the use of prophylactic mesh augmentation in emergency laparotomy effectively prevents incisional hernias without increasing the procedure’s overall morbidity, even in the presence of wound contamination.

#### *PRImary Mesh Closure of Abdominal Midline Wound (PRIMA) trial: Prevention of incisional hernia with mesh augmentation in midline laparotomies*

The PRImary Mesh Closure of Abdominal Midline Wound trial was a multicenter, double-blind RCT involving high-risk patients with either an abdominal aortic aneurysm or a BMI  $\geq 27$  who were undergoing an elective midline laparotomy.<sup>16</sup> The trial investigated both the benefit of augmentation with prophylactic mesh and the best location for placing the mesh. Specifically, patients were assigned randomly to primary suture closure, onlay mesh augmentation, or sublay (retrorectus) mesh augmentation. The primary endpoint of the study was the incidence of incisional hernia at 2 years. Whereas both mesh augmentation techniques significantly decreased the rate of incisional hernia formation compared to primary suture closure (13% or 18% vs 30%;  $P \leq .05$ ), the proportion of patients with an incisional hernia was not different between the mesh augmentation groups. Onlay mesh augmentation was associated with more frequent seromas (18%) than in the suture closure or sublay mesh groups but without an increase in surgical site infections, reinterventions, or hospital readmissions. In conclusion, prevention of incisional hernias was achieved with both onlay and sublay mesh augmentation, supporting the use of this approach as a standard treatment in high-risk patients.

### *PREventive midline laparotomy closure with a BIOabsorbable mesh (PREBIOUS) trial: Absorbable mesh augmentation*

Incisional hernia after midline laparotomy is a complication detectable within the first 30 days after abdominal surgery. Several different methods for selectively reinforcing the incised linea alba have been described. The PREBIOUS (PREventive midline laparotomy closure with a BIOabsorbable mesh) trial is an active, randomized, control trial examining the potentially beneficial effects of reinforcing a midline laparotomy incision with a bioabsorbable (GORE BIO-A; W. L. Gore & Associates, Inc, Flagstaff, AZ) prosthetic.<sup>17</sup> The prophylactic strategy of inserting a bioabsorbable prosthetic between the healing edges of the midline fascia has been successfully demonstrated in a preclinical study in rodents.<sup>18</sup> At present, the PREBIOUS trial has recruited approximately 250 patients undergoing both elective and emergency abdominal surgery. No comparative data is yet available. As expected, however, approximately 30% of patients who have completed the planned 2-year follow-up period have developed an incisional hernia. We await the results of this interesting approach toward prevention of incisional hernias.

### **Prophylactic only mesh implantation after abdominal aortic aneurysm repair: 2-year results**

The incidence of incisional hernias after an open repair of an abdominal aortic aneurysm through a midline approach has been reported to be as high as 38% at 2 years of follow-up and 69% at 5 years. In 2016, a multicenter, RCT demonstrated that prophylactic mesh augmentation prevents incisional hernias after the repair of aortic aneurysms via a midline laparotomy.<sup>19</sup> The Amsterdam Investigator-initiated Absorb Strategy All-comers (AIDA) trial, also a multicenter RCT, examined the hypothesis that a lightweight, large-pore polypropylene mesh onlay would decrease incisional hernia formation compared to suture closure alone using 1 of 2 different types of suture. A total of 108 patients (mean age 69.8 ± 7.7 years) were randomized between February 2011 and July 2013. After 24 months, the mesh onlay decreased the rate of incisional hernias by 5-fold and 8-fold, respectively (onlay mesh: 4.1 % vs suture A: 23.1% or suture B: 31.8%;  $P = .026$ ). After 24 months, the number of hernias was decreased after prophylactic mesh onlay compared to a running line suture closure ( $P = .026$ ). There was a significant difference in wound seromas, which were exclusively found in the mesh-treated patients (18%), but there were no significant differences in pain measured by the Visual Analog Scale or quality of life measured by the EQ-5D questionnaire between the groups. Consequently, the investigators concluded that onlay mesh after median laparotomy for repair of an abdominal aortic aneurysm decreased the rate of incisional hernias.

### **Prevention of parastomal hernias**

Parastomal hernias are a common, frequently debilitating condition that affects an estimated 50% to 80% of patients with a stoma, depending on the sensitivity of the diagnostic method.<sup>20</sup> Furthermore, operative repair can be difficult, with recurrence rates of up to 17%, even when prosthetic mesh is used to reinforce the surrounding abdominal wall.<sup>21</sup> Recently, as more effective treatments have increased the survival of colorectal cancer patients, more attention has been focused on dysfunctional stomas and their impact on patient overall quality of life. In 2004, Israelsson et al published the results of a randomized trial demonstrating that placement of mesh prophylactically at the time of creation of the stoma significantly and markedly decreased the formation of parastomal hernias without leading to infective complications.<sup>22</sup> Yet, despite positive RCTs, conclusive meta-analyses, and a strong recommendation

from the European Hernia Society, fear of mesh-related complications and some contradictory reports prevent many surgeons from prophylactically reinforcing the stoma site with mesh to prevent parastomal hernias.<sup>23,24</sup>

### *GRECCAR 7: A study in primary prevention of parastomal hernias*

GRECCAR 7, a multicenter, randomized trial involving 199 patients, was designed to determine whether insertion of a prophylactic mesh at the time of creation of a colostomy would decrease the incidence of formation of a parastomal hernia. During the Symposium, one of the investigators presented that there was no statistical difference in pain, healing of the stoma, quality of life (Stoma-QOL test), or frequency of stomal complications between the intervention group and the control group after 3 months of follow-up. The early data indicate that inserting a synthetic mesh when creating an end colostomy via an open or laparoscopic approach is a safe and easy procedure. We await the results of long-term follow-up to determine the impact of mesh placement on formation of a parastomal hernia.

### *PREVENT-trial for prevention of parastomal hernias*

The PREVENTion of parastomal hernia trial is an RCT that examined whether the use of a lightweight polypropylene mesh placed in a sublay (retromuscular) location decreased the incidence of parastomal hernia as compared to the conventional method of creating an end colostomy. The incidence of parastomal hernia, morbidity, mortality, quality of life, pain, and cost-effectiveness was measured after 1 year of follow-up. Although the operative time was 26 minutes greater, patients treated with mesh had no infections, strictures, fistulas, or cases where the mesh needed to be removed.<sup>25</sup> Sublay mesh markedly decreased the incidence of parastomal hernias as compared to control patients after 1 year of follow-up (4.5% vs 24.2%;  $P = .0011$ ). Interestingly, the study demonstrated no statistically significant difference in quality of life, pain, or cost-effectiveness. Therefore, whereas prophylactic mesh reinforcement during colostomy creation effectively decreased parastomal hernia formation, it had no impact on other important patient-centered measures, including postoperative complications, quality of life, or costs.

Of note, data derived from meta-analyses provide compelling evidence in support of the PREVENT-trial and how to prevent parastomal hernia formation after open surgery,<sup>26</sup> but data are inconclusive regarding the best method of preventing parastomal hernia when a laparoscopic approach is used.<sup>27,28</sup>

### *Stapled mesh reinforcement technique*

First reported in 2011, SMART (Stapled Mesh stoma Reinforcement Technique) is a novel method of constructing a reinforced, end ostomy.<sup>29</sup> In brief, the procedure begins with using a circular (EEA) stapler and a 7-cm circular piece of lightweight polypropylene mesh to create a 28-cm to 31-cm funnel-shaped opening in the posterior rectus sheath, and ends by suturing the outer border of the mesh circle to the anterior rectus sheath. In this manner, a precise, mesh-reinforced fascial opening is cut through which the intestine can be delivered and a stoma matured. Recent reports indicate that the SMART method for stoma creation is safe and effective, with few wound complications and a significantly decreased rate of formation of parastomal hernias.<sup>29,30</sup> During the Symposium, a series of 16 patients whose stomas were created via the SMART method between January 2015 and September 2017 in San Camillo Hospital, Trento, Italy was presented. The average age of the cohort was 71 ± 10 years, with a mean BMI = 25 ± 4, and median follow-up was 16 ± 8 months. Notably, although there was

no stoma-related morbidity, there were 3 (19%) small (EHS type I), “clinically insignificant” parastomal hernias that developed that were only detected by CT; although they were “clinically insignificant,” and have not yet required reoperation, the future of these small hernias is as yet undetermined but concerning.

#### *Non-mesh techniques of stoma creation*

Mesh prophylaxis for prevention of parastomal hernias has been shown to be quite successful, but the adoption rate for this technique in the United States has been disappointingly low. Surgeons and patients alike have voiced concerns regarding the placement of prosthetic material during stoma creation and the use of mesh in general, especially given the abundant and well-publicized lawsuits in America involving complications connected to these prosthetics. Therefore, methods of preventing parastomal hernias without the use of mesh are worth examining. The basic dogma of stoma creation includes steps that have little scientific support and demonstrate considerable variability in practice. These controversies include the optimal size of the ellipse of skin excised, the size and shape of the incision in the anterior rectus sheath (cruciate vs elliptical), the location (through vs adjacent to the rectus abdominis muscle), and an intraperitoneal versus an extraperitoneal pathway through the abdominal wall. Ongoing studies are examining some of these questions,<sup>31</sup> and a systematic analysis identified creation of an extraperitoneal stoma as being associated with a significantly lesser rate of parastomal hernia formation (18% vs 6%).<sup>32</sup>

#### **Hernia prevention: Science, education & reimbursement**

##### *Extracellular matrix (Surgisis Gold) in hernia prevention surgery*

Early in the product life cycle of Surgisis Gold, Cook Medical (West Lafayette, IN) undertook a 400-patient, randomized, controlled clinical trial to determine whether an extracellular-matrix-based graft could dramatically decrease the rate of primary midline hernia formation in the clean-contaminated population of patients undergoing an open Roux-en-Y gastric bypass, the results of which were presented during the Symposium.<sup>33</sup> Overall, the implant group had more adverse events than the suture-only control group, but the hernia rate at 2 years of follow-up was not significantly different. This lack of significance was attributed potentially to patients lost to follow-up, failures of the surgical technique, and the challenge of healing in this complex patient population. Interestingly, the pattern of hernia development over time appeared to differ between the 2 groups. Whereas early failures were more frequent in the Surgisis Gold group, failures in the suture-only group appeared at a more constant rate over time. Hernia prevention, as a treatment modality, may have very different objectives than traditional hernia repair, but the principles of good wound healing, patient selection, and proper procedures for the types of implant likely affect the outcomes.

##### *Trocar hernia incidence and prophylaxis*

The incidence of hernias at the trocar site after laparoscopic operations is likely underreported. Whereas short-term, retrospective series note rates of 1% to 6%, greater follow-up of patients undergoing a laparoscopic cholecystectomy has noted hernias in up to 26% of patients at 3 years.<sup>34</sup> Older patients and those with a high BMI, an existing umbilical hernia, or superficial surgical site infection are at greater risk for trocar site herniation. There are a number of different trocar types, and it is unclear if the type of trocar used has an impact on the rate of herniation. A 2015 Cochrane

review included a comparative analysis of radially expanded versus cutting trocars and reported no trocar site herniation among 462 patients in 4 studies with follow-up of 6–48 months<sup>35</sup>; however, this study was considered to be of low quality evidence. It does appear, however, that the risk of herniation increases with the size of the trocar used. Although the rate of herniation at 5-mm trocar sites appears to be very low, it is significantly greater for trocars with diameters larger than 10 mm, for which port site fascial closure is recommended. In an RCT of sutured versus prosthetic mesh closure of umbilical port sites ( $\geq 10$  mm), mesh placement dramatically decreased the rate of trocar site hernias (31.9% vs 4.4%;  $P < .001$ ).<sup>36</sup> Although the advocates of robotic surgery tout decreased trauma at robotic port sites, the rates of port site hernias after robotic surgery appear statistically no different than that of traditional laparoscopic ports. Whereas meticulous closure is recommended for all port sites  $>5$  mm, prophylactic mesh reinforcement is probably best reserved for the larger diameter trocar sites in high-risk patients.

##### *Implementing a program to improve abdominal wall closure*

During the Symposium, a program to implement the small bites (5-mm bites every 5 mm) technique for closing laparotomies in all of the surgical departments in a public, general hospital was presented. The program consists of 3 phases: (1) Information, (2) Certification, and (3) Audit. In the period between July 2016 and April 2017, a total of 460 laparotomies were performed in 416 patients. Review of the program revealed that in only 36% of the operations did the surgeons adhere to the complete protocol. But, after a 6-month follow-up period, patients whose abdominal walls were closed according to the complete protocol experienced a lesser incidence of burst abdomen and incisional hernias than patients where the closure protocol was incomplete. Whereas the small bites technique is easy to teach and learn, implementation of the closure method is difficult, thought to be due in part to surgeon resistance to change and the known delay getting research evidence into clinical practice.<sup>37</sup>

##### *Predicting the risk of incisional hernia*

In considering any prophylactic intervention, it is critically important to weigh the relative risks of the condition against those of the intervention. Therefore, in the case of attempts to prevent incisional hernia formation, preoperative risk stratification and decision algorithms will be of potentially important value. Published studies have identified many common preoperative risk factors, including obesity, open surgery, smoking, prior surgery, abdominal aortic aneurysm, and wound contamination as predictors of formation of incisional hernias. Recently, several investigators identified a multitude of risk factors and created risk models for predicting incisional hernias after surgery.<sup>5,38</sup> An important next step will be to translate these risk models into practice through decision-support interfaces that allow real-time calculation of risk at point of care to further personalize an individual patient's operative management. Specific interventions of preoperative and operative risk reduction could include weight loss, smoking cessation, improved glucose management, optimal fascial closure method, and prophylactic soft tissue reinforcement.

#### **Hernia prevention: Research & novel approaches**

##### *The federal agenda toward research*

Complex ventral hernias can present unique clinical and technical challenges to the health-care team. Frequently, the operating surgeon must innovate and craft customized solutions for a specific

patient under circumstances where the best repair technique or prosthetic device to use is uncertain. As such, what distinguishes innovation versus research? *Innovation* is a process undertaken for the sole benefit of a single patient.<sup>39</sup> When an innovative technique is used in 3 or more patients, it becomes clinical research whether or not the surgeon plans to report it and as such, this innovative procedure requires approval by the Institutional Review Board beforehand. If the surgeon reports his or her Institutional Review Board-approved experience with a new technique or device, it is an anecdotal (case) report, and if the results are compared with historic controls, it is a retrospective series. Innovation is often a process whereby knowledge is used to create a new technique or application that may have commercial value. *Research* is a process whereby resources (eg, money) are used to create new knowledge. Research and innovation are synergistic and mutually dependent.

The federal government (eg, National Institutes of Health) provides research grants to enable clinical research that is not related to commercial interests. Examples of clinical research opportunities at the National Institute of Diabetes and Digestive and Kidney Diseases include the R21 (Pilot Project) grants, R01 (single center) grants, U34/U01 (multicenter) grants, and K awards (career development grants) for young investigators. Examples of clinical research projects currently funded by the National Institute of Diabetes and Digestive and Kidney Diseases in the areas of surgical research include projects on hepatic and hepatobiliary surgery, the treatment of acute appendicitis with antibiotics versus surgery, postoperative ileus, and the treatment of abdominal wall defects (hernias). There is currently little federally funded research regarding abdominal wall hernias, but resources are potentially available and can be allocated to the study of this clinically important condition through increased awareness, education, and well-crafted applications for funding.

#### *Prevention of hernia formation: Role of growth factors, and wound healing*

To prevent the formation of incisional hernias, many methods to alter the local expression of growth factors and the subsequent effects on wound healing have been tried. To date, however, no method has proven to be clinically relevant. Deficient recruitment of inflammatory cells from the bone marrow has been implicated as the common pathway for delayed and deficient wound healing in a variety of diseases. Specifically, recruitment of macrophages and differentiation from an M1 to an M2 phenotype results in collagen deposition during normal wound healing. In contrast, a deficient or delayed induction of M2 macrophages leads to poor healing and is likely to be associated with formation of incisional hernias. Maintaining a normal core body temperature in patients during operations leads to more collagen deposition and fewer surgical site infections.<sup>40</sup> Better nutritional support and control of serum glucose, and maintaining adequate blood flow to surgical sites, also produce better healing. But none of these factors have been well studied in clinical settings to prevent the formation of incisional hernias. Instead, methods such as closure with small bites of suture and placement of prosthetic mesh have been shown in multiple randomized clinical trials to decrease the risk of developing an incisional hernia. These techniques probably increase collagen deposition and fibrosis, thus augmenting the healing process. Hopefully, better understanding of the inflammatory response and macrophage function in wound healing will lead to better methods to manipulate the healing of laparotomies and thus prevent incisional hernias.

#### *Closure of the abdominal wall with mesh-derived sutures*

A frequent observation with incisional hernias is the presence of suture pull-through, ie, sutures having torn through the fascia and soft tissue around which they were placed. When the forces applied to the abdominal wall closure exceed the repair strength, early failure and gap formation between the fascial borders occur, resulting later in an incisional hernia. This process implies that the cause of incisional hernia can include a problem with the “physics” of the repair, in addition to a problem with the biology of wound healing. Dumanian created a new mesh suture that is almost 10 times larger in diameter than a standard suture, but was designed to limit acute suture pull-through due to an improved distribution of forces at the suture-tissue interface.<sup>41,42</sup> Because much of the diameter of the mesh sutures is air between the filaments of the mesh, these filaments collapse at the knot to become smaller and more biocompatible. The walls of the suture are an open mesh so that tissue can grow into and surround the woven filaments as early as 8 days after placement. This “tissue integration” into the actual suture may limit or possibly eliminate chronic suture pull-through and hernia formation. Preclinical studies have shown increased resistance to suture pull-through in rat and porcine abdominal walls, dog shoulders, and human finger tendons. To use the concepts of force distribution in patients now, an off-label use of PROLENE Soft Mesh was devised. Cutting along the blue lines, 20-mm-wide strips were fashioned from a single piece of mesh and used as sutures for both simple and complex abdominal wall defects. Forty-eight patients with some form of minimal potential wound contamination during repair of incisional hernias averaging 10 cm in width were closed with this “mesh sutured repair.”<sup>43</sup> The recurrence rate of hernia formation was 13% with a mean follow-up of 12 months. Therefore, mesh sutured repairs may represent a new era of high surface area/low filament size closures that distribute forces and lay down a magnified foreign-body response at the site of suture closure. An FDA-cleared mesh suture product should be available for clinical use in 2018.

#### *Advances in mesh technology: T-line hernia mesh*

Mesh functions to prevent ventral hernia formation by enhancing wound healing and distributing tension to the lateral abdominal wall. But mesh often fails at the suture-mesh-tissue interface; this failure may be because the suture “cheese wires” or slices through mesh or tissue because the tensile stress of the abdominal wall exceeds the tensile strength of the anchor points of the suture-mesh-tissue interface. To overcome this cheese wiring caused by tensile stress, Levinson and colleagues have developed a novel mesh prosthetic. The T-line hernia mesh contains seamless, uninterrupted extensions continuous with the mesh body that are 15-fold the surface area of standard suture. The extensions are sewn into fascia, just as sutures would be, and the T-line hernia mesh remains anchored to fascia at forces 300% greater than the maximum force exerted on the abdominal wall (16 N/cm). By comparison, the anchor points of standard suture repairs fail at 6–12 N/cm. In bench-top studies, the T-line mesh meets all federal performance and safety standards, and in pig studies, the mesh is safe and 275% stronger than standard mesh. In summary, one strategy for decreasing the risk of hernia formation is to develop a mesh that overcomes tensile stress and failure of the mesh-suture-tissue interface. T-line mesh appears to achieve this strategy by maintaining a broader surface area of anchor point contact with the fascia and by distributing tension from the midline to the lateral abdominal wall. Clinical trials are planned.

### Nanofiber electrospun technology for prevention of incisional hernias

A device able to support and accelerate the healing of injured abdominal wall tissue postoperatively would likely decrease the incidence of incisional hernia formation. Currently, the prosthetic materials used for soft tissue reinforcement are primarily polypropylene or polyesters, some with a special layer to enhance specific properties of the implant and suppress other disadvantageous properties. Yet, all permanent prosthetics pose a lifelong risk for material-related complications, including infection, seroma, adhesions, and pain. Electrospun nanofibers made from soluble polyesters are used widely as scaffolds for tissue engineering. Their production is cost-effective and fast. It is possible to make fibers with specific mechanical properties and enrich them with controlled released of growth factors, antibiotics, or other drugs.<sup>44</sup> Although in vitro testing indicates excellent biocompatibility, how these materials perform in vivo is unknown. In an established rabbit model, the nanofiber material appears to support the growth of fibrous tissue and mature collagen. The resulting scar is more elastic, contains less fat, and exhibited less shrinkage compared to the use of polypropylene nanofibers. Further studies are focused on more complete characterization of the host response to this novel material.

### MYOSEAL: Enhanced myofascial wound healing

Incisional hernias, the most frequent long-term complication of abdominal surgery, result from inadequate early wound healing. In 1894, Phelps reported the use of small silver coils during hernia repairs, exploiting the observation that as the implanted silver metal slowly disintegrated, it induced a local inflammatory response and wound fibrosis.<sup>45</sup> Despite impressive clinical results with hernia recurrence rates of <0.5%,<sup>45,46</sup> the disuse of silver wire prosthetics coincided with advances in polymer chemistry that produced new prosthetic materials, especially polypropylene (PROLENE), which was viewed as a superior alternative. Recently, investigators postulated that using microparticles of silver (MYOSEAL; Vitruvian, San Francisco, CA, USA) rather than fine silver wire would effectively accentuate the therapeutic benefits of this unique prosthetic material, including wound fibrosis. Through extensive preclinical experiments, this fascinating property of implanted metallic silver has been applied in an innovative way for a novel indication. Animal studies have demonstrated that MYOSEAL, when mixed in the wound with a commercial fibrin tissue sealant, enhances myofascial wound healing, resulting in decreased incisional hernia formation. Specifically, the MYOSEAL significantly decreased the incidence and size of incisional hernias in a dose-dependent and selective manner in an established rodent model. These data support the evaluation of silver microparticles as an innovative, safe, and highly feasible strategy to increase early wound healing and thus prevent incisional hernias in patients. Clinical studies are planned for 2018.

### Hernia prevention: Perspectives of the Food and Drug Administration

The Food and Drug Administration (FDA) is currently seeking methods of acquiring postmarket clinical data for the purpose of using these data to expand indications for use of novel applications, facilitating surgeon choices on the appropriate mesh for their hernia patients, improving device labeling to better inform surgeons and patients, and providing a stronger postmarket signal on delayed surgical device problems than is currently available through Medical Device Reports. The agency has recently issued regulatory guidance concerning the use of real-world evidence (RWE) (<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>).

RWE can provide a snapshot of a new device as it performs in the marketplace ecosystem at any time point in its total life cycle. The FDA is establishing the National Evaluation System for Health Technology (NEST), which will use data from many sources, thereby linking registries (domestic and global), large administrative databases, insurance claims, and electronic medical records. The clinical data generated through NEST can then be used to provide a more complete picture of the risks and benefits of any new device throughout its life cycle and may be used for future regulatory decisions. Implicit in the use of RWE is that the data must meet a reliability threshold, also discussed in the guidance of the Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Whereas the FDA remains understandably focused on existing hernia mesh prosthetics, building the infrastructure necessary to use RWE and establish NEST may indicate the agency's desire for a more comprehensive and nimble means of evaluating the performance and expanding the indication of medical devices, including those that will define the future of incisional hernia repair and prevention.

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