Use of Biologics in Abdominal Wall Reconstruction

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Disclosures

• No Financial Conflicts of Interest
Common and Significant Problem

• Half of all people are born with or will acquire a ventral hernia in their lifetime

• Problem with ventral hernias
  – Adversely impact function
  – Cause pain
  – Cause disfigurement
  – Incarceration, strangulation
How Have We Been Doing?

• Three institutions (Ventral Hernia Outcomes Collaborative)

• 794 elective ventral hernia repairs with at least 6 months of follow-up

• Divided patients into four groups:
  – Primary Ventral Hernia Repair (PVHR)
  – First time Incisional Hernia Repair (IHR1)
  – Second time Incisional Hernia Repair (IHR2)
  – Third or more time Repair (IHR3)
The Vicious Cycle

- **PVHR vs IHR1 vs IHR 2 vs IHR 3**
- More Complex Repairs
  - Operative duration (102 vs 180 min)
  - Biologic mesh (0% vs 39%)
  - Component separation (1.5% vs 35.7%)
The Vicious Cycle

- **PVHR vs IHR1 vs IHR 2 vs IHR 3**
- More Likely to Have a Poor Outcome
  - Reoperations (7.5% vs 32.1%)
  - SSI (13.5% vs 39.3%)
  - Hernia Recurrences (8.9% vs 28.6%)
<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI</td>
<td>2.03 (1.12-3.56)</td>
<td>4.57 (2.58-8.09)</td>
</tr>
<tr>
<td>History SSI</td>
<td>-</td>
<td>2.81 (1.35-5.83)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.08 (1.04-1.13)</td>
<td>-</td>
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<tr>
<td>Prior Repairs</td>
<td></td>
<td></td>
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<tr>
<td>PVHR</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>IHR1</td>
<td>3.04 (1.58-5.87)</td>
<td>3.13 (1.66-5.91)</td>
</tr>
<tr>
<td>IHR2</td>
<td>3.74 (1.61-8.67)</td>
<td>1.34 (0.63-4.26)</td>
</tr>
<tr>
<td>IHR3</td>
<td>9.01 (2.91-27.9)</td>
<td>4.86 (1.62-14.6)</td>
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<tr>
<td>Concomitant</td>
<td>4.15 (2.13-8.07)</td>
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<tr>
<td>Mesh Type</td>
<td></td>
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<tr>
<td>None</td>
<td>Reference</td>
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<tr>
<td>Biologic</td>
<td>0.47 (0.21-1.08)</td>
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</tr>
<tr>
<td>Synthetic</td>
<td>0.52 (0.27-1.00)</td>
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</table>
Vicious Cycle of Cost and Complications

- Ventral Hernia Repair
- Reoperation
- Recurrence
- SSI

Holihan 2015
Long-term results are poor. Multiple studies demonstrate 50% long-term recurrence.
Topics

• Current evidence

• Controversies: Mesh

• Controversies: Conflict of interest (COI)
Topics

• Current evidence

• Controversies: Mesh

• Controversies: Conflict of interest (COI)
Oxford Centre Levels of Evidence

- Confounders
- Selection bias
- Recall bias
- Etc.

* RCT = RANDOMIZED CLINICAL TRIAL
Ventral hernia publications by level of evidence

- Level 1 (n=100)
- Level 2/3 (n=459)
- Level 4 (n=757)

Number of Publications

Year

1980 1990 2000 2010
What Questions Do We Have Answers To?

• 39 published randomized controlled trials on ventral hernias

• Topics of these RCTs:
  – lap versus open
  – mesh versus suture
  – mesh type
  – mesh location
  – mesh fixation
  – pain control
Questions

• Mesh:
  – When to use it?
  – How to use it?
  – What kind to use?
Questions

• Mesh:
  – When to use it?
  – How to use it?
  – What kind to use?
When to use it?

- **Suture versus mesh**
  - 10 randomized controlled trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Hernia type</th>
<th>N</th>
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<tbody>
<tr>
<td>Arroyo</td>
<td>2001</td>
<td>Primary</td>
<td>200</td>
</tr>
<tr>
<td>Polat</td>
<td>2005</td>
<td>Primary</td>
<td>50</td>
</tr>
<tr>
<td>Ammar</td>
<td>2010</td>
<td>Primary</td>
<td>80</td>
</tr>
<tr>
<td>Luijendijk/Burger</td>
<td>2000/2004</td>
<td>Incisional</td>
<td>181</td>
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<tr>
<td>Korenkov</td>
<td>2002</td>
<td>Incisional</td>
<td>100</td>
</tr>
<tr>
<td>de Vries Reilingh</td>
<td>2007</td>
<td>Incisional</td>
<td>37</td>
</tr>
<tr>
<td>Venclauskas</td>
<td>2010</td>
<td>Incisional</td>
<td>161</td>
</tr>
<tr>
<td>Lal</td>
<td>2012</td>
<td>Incisional</td>
<td>62</td>
</tr>
<tr>
<td>Weber</td>
<td>2002/2010</td>
<td>Mixed</td>
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</tr>
<tr>
<td>Abdel-Baki</td>
<td>2007</td>
<td>Mixed</td>
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## Recurrence: Suture vs Mesh

<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence (Mesh)</th>
<th>Recurrence (Suture)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Baki</td>
<td>0</td>
<td>4</td>
<td>0.000</td>
</tr>
<tr>
<td>Ammar</td>
<td>1</td>
<td>5</td>
<td>0.167</td>
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<tr>
<td>Arroyo</td>
<td>1</td>
<td>11</td>
<td>0.082</td>
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<tr>
<td>de Vries</td>
<td>11</td>
<td>10</td>
<td>1.414</td>
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<tr>
<td>Korenkov</td>
<td>7</td>
<td>4</td>
<td>0.846</td>
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<tr>
<td>Lal</td>
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<td>3</td>
<td>0.000</td>
</tr>
<tr>
<td>Luijendijk</td>
<td>17</td>
<td>39</td>
<td>0.377</td>
</tr>
<tr>
<td>Polat</td>
<td>0</td>
<td>2</td>
<td>0.000</td>
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<tr>
<td>Venclauskas</td>
<td>13</td>
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<td>0.484</td>
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<tr>
<td>Weber</td>
<td>15</td>
<td>50</td>
<td>0.255</td>
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<tr>
<td><strong>Summary</strong></td>
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<td>0.33</td>
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</table>

Favors Mesh
## SSI: Suture vs Mesh

<table>
<thead>
<tr>
<th>Study</th>
<th>SSI (Mesh)</th>
<th>SSI (Suture)</th>
<th>OR</th>
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<tbody>
<tr>
<td>Abdel-Baki</td>
<td>2</td>
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<td>0.63</td>
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<tr>
<td>Ammar</td>
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<td>3</td>
<td>2.06</td>
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<td>Arroyo</td>
<td>2</td>
<td>3</td>
<td>0.66</td>
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<tr>
<td>de Vries</td>
<td>9</td>
<td>3</td>
<td>5.33</td>
</tr>
<tr>
<td>Korenkov</td>
<td>6</td>
<td>0</td>
<td>Inf</td>
</tr>
<tr>
<td>Lal</td>
<td>2</td>
<td>5</td>
<td>0.33</td>
</tr>
<tr>
<td>Luijendijk</td>
<td>3</td>
<td>0</td>
<td>Inf</td>
</tr>
<tr>
<td>Polat</td>
<td>2</td>
<td>1</td>
<td>1.03</td>
</tr>
<tr>
<td>Venclauskas</td>
<td>9</td>
<td>2</td>
<td>2.39</td>
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**Summary**

<table>
<thead>
<tr>
<th>Favors Mesh</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Favors Suture</td>
</tr>
</tbody>
</table>

OR: Odds Ratio
Pooled Outcomes: Suture vs Mesh

Recurrence
- Suture 30%
- Mesh 12%

SSI
- Suture 3%
- Mesh 9%
## Subgroup Analysis: Suture vs Mesh

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td></td>
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<tr>
<td>Studies at Low Risk for Bias</td>
<td>0.37</td>
<td>0.24-0.57</td>
<td>2.93</td>
<td>1.17-6.32</td>
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<tr>
<td>Polypropylene Mesh</td>
<td>0.32</td>
<td>0.21-0.49</td>
<td>1.54</td>
<td>0.84-2.84</td>
<td></td>
<td></td>
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<tr>
<td>Primary Ventral Hernias</td>
<td>0.09</td>
<td>0.02-0.39</td>
<td>1.29</td>
<td>0.48-3.49</td>
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<tr>
<td>Ventral Incisional Hernias</td>
<td>0.45</td>
<td>0.29-0.68</td>
<td>1.11</td>
<td>2.32-4.86</td>
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<td></td>
</tr>
</tbody>
</table>

Questions

• Mesh:
  – When to use it?
  – How to use it?
  – What kind to use?
How to use mesh?

• Mesh location
  A. Onlay
  B. Inlay
  C. Sublay
  D. Underlay
How to use it?

• Mesh location
  – 20 randomized controlled trials
  – Compare:
    • Suture- (reference)
    • Laparoscopic
    • Open
      – Onlay
      – Sublay
      – Underlay
Network Meta-Analysis

Suture

Suture

Sublay

Onlay

Direct

Indirect

Direct
## Mesh Location

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Odds Ratio</th>
<th>95% Credible Interval</th>
<th>Probability of being the best</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublay</td>
<td>0.74</td>
<td>0.1-0.4</td>
<td>0.565</td>
<td>1</td>
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<tr>
<td>Onlay</td>
<td>Ref (1.00)</td>
<td>-</td>
<td>0.238</td>
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<tr>
<td>Laparoscopic</td>
<td>1.88</td>
<td>0.1-12.3</td>
<td>0.151</td>
<td>3</td>
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<tr>
<td>Underlay</td>
<td>5.11</td>
<td>0.1-60.0</td>
<td>0.045</td>
<td>4</td>
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<tr>
<td>Suture</td>
<td>7.0</td>
<td>1.1-33.4</td>
<td>0.001</td>
<td>5</td>
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</table>

## SSI

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Credible Interval</th>
<th>Probability of being the best</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublay</td>
<td>1.39</td>
<td>0.01-6.4</td>
<td>0.238</td>
<td>3</td>
</tr>
<tr>
<td>Onlay</td>
<td>Ref (1.00)</td>
<td>-</td>
<td>0.126</td>
<td>4</td>
</tr>
<tr>
<td>Underlay</td>
<td>25.6</td>
<td>0.01-193</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>
Areas of controversy
Mesh Location

- Other outcomes
  - Reoperation
  - Adhesions
  - Off midline defects

Guideline:
(1) When safe and feasible, laparoscopic repair is preferred
(1) Use sublay in open cases when safe and feasible
Entering the retrorectus space
Entering the retrorectus space
Entering the retrorectus space
Entering the retrorectus space
Questions

• Mesh:
  – When to use it?
  – How to use it?
  – What kind to use?
What kind of mesh to use?

- Synthetic
- Biologic
  - Bio-absorbable
- Porosity
- Weight
- Cross-linked
- Non-cross-linked
- Material
- Biologic
- Tissue source
What kind to use?

• Mesh type
  – 7 randomized controlled trials
  – Many are at high risk of bias

<table>
<thead>
<tr>
<th>Author</th>
<th>Hernia type</th>
<th>N</th>
<th>Control versus Intervention</th>
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<tbody>
<tr>
<td>Conze 2005</td>
<td>Incisional</td>
<td>165</td>
<td>High weight mesh vs low weight polypropylene</td>
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<tr>
<td>Rickert 2012</td>
<td>Incisional</td>
<td>80</td>
<td>Mid weight polypropylene vs low weight polypropylene</td>
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</tbody>
</table>
## Mesh type

<table>
<thead>
<tr>
<th>Control vs intervention</th>
<th>N</th>
<th>SSI</th>
<th>P-value</th>
<th>Recurrence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy weight vs light weight</td>
<td>165</td>
<td>13 (16%) vs 15 (18%)</td>
<td>0.653</td>
<td>6 (7%) vs 14 (17%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Mid weight vs light weight</td>
<td>80</td>
<td>0 (2%) vs 1 (2%)</td>
<td>0.326</td>
<td>0 vs 1 (2%)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>
Areas of controversy

Mesh type

• Role of biologic and bioabsorbable mesh

Guideline: Avoid light weight mesh

• Preferred mesh for laparoscopic, primary, and incisional ventral hernia repairs
Summary of Evidence

Suture versus mesh
• Mesh should be used in all non-contaminated cases
  – Strength of recommendation: strong

Mesh location/fixation
• When safe and feasible, repairs should be performed using a laparoscopic approach
  – Strength of recommendation: strong
• In open cases, mesh should be placed in a sublay
  – Strength of recommendation: moderate

Mesh type
• Light weight mesh should be avoided
  • Strength of recommendation: weak
Despite High Quality Data…

• Laparoscopy is only utilized
  – in 25% of ventral incisional hernias
• Mesh is not used in
  – 15% of elective ventral incisional hernia repairs
  – 50% of elective primary ventral hernia repairs
• “Substantial discrepancy exist among surgeons including areas of patient selection, surgical decision-making, and technique”

Funk 2014
Holihan 2015
Park 2015
Topics

• Current evidence

• Controversies: Mesh

• Controversies: Conflict of interest (COI)
THE ENTIRE PAST

OBSERVED

REMEMBERED

RECORDED

SURVIVED
Giant hernias, fistulas, adhesions

Polypropylene, NPWT, Polyglactin 910 (Vicryl), HADM

Giant hernia, fistulas

Better than everything else?
Experience with Porcine Acellular Dermal Collagen Implant in One-stage Tension-free Reconstruction of Acute and Chronic Abdominal Wall Defects

- 2007: “[Biologic mesh] has the potential for reconstruction of large acute and chronic abdominal wall defects. Medium-term recurrence rate is comparable to synthetic mesh and repairs”

- Case series, level of evidence IV
2010: “Grade 2: Increased risk for SSO suggests additive risk of permanent synthetic repair material, and potential advantage for appropriate biologic reinforcement. (Grade B)”

“Grade 3 and 4: Permanent synthetic material not recommended; biologic repair material should be considered. (Grade A, B)”

Expert opinion and cohort studies (Level of evidence II-V)
2013: “Despite the high rate of wound morbidity associated with single-staged reconstruction of contaminated fields, it can safely be performed with biologic mesh reinforcement. Although biologic mesh in these situations is safe, the long-term durability seems to be less favorable”

Case series, Level of evidence IV
FIGURE 1. Kaplan-Meier estimate for overall recurrence [with 95% confidence interval (CI)].
Hernia Defect Size
Synthetic vs Biologic
20 cm$^2$ vs 431cm$^2$

FIGURE 1. Kaplan-Meier estimate for overall recurrence [with 95% confidence interval (CI)].
Comparative Studies on Biologic

<table>
<thead>
<tr>
<th>Author</th>
<th>Biologic</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Bondre 2016</td>
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<td>15</td>
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<tr>
<td>Fischer 2014</td>
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<td>Sandvall 2014</td>
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<td>13</td>
</tr>
<tr>
<td>Brahmbhatt 2014</td>
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<td>15</td>
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<td>Liang 2014</td>
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<td>34</td>
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<td>Sailes 2010</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Ko 2009</td>
<td></td>
<td>18</td>
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</table>

- Mixed results and no definitive conclusions can be drawn due to significant selection bias for biologic mesh in more complicated cases (Level of evidence II-IV)
In this prospective longitudinal study, biosynthetic, absorbable mesh showed efficacy in terms of long-term recurrence and quality of life for complex ventral hernia repair patients and offers an alternative to biologic and permanent synthetic meshes in these complex situations.

Case series, Level of evidence IV
Probability of recurrence-free survival

Hernia Recurrence
17% (n=16 patients)

Follow-up (Months)
Hernia Defect Size
Absorbable Synthetic vs Biologic
137 cm² vs 431 cm²

FIGURE 1. Kaplan-Meier estimate for overall recurrence [with 95% confidence interval (CI)].
2018: Still no consensus!!! Still no randomized controlled trial(s)
Pending Randomized Controlled Trials

- **Case Western**: Enrolling in 2011. Study Completed 2012. (NCT01295125)
  - Never published
  - COI from Bard
- **Carolinanas Healthcare system**: Enrolling since 2013. (NCT01794338)
  - Not completed enrollment yet (estimated 2019)
  - COI from Lifecell
- **UCSF**: Enrolling since 2014 (NCT02041494)
  - Not completed enrollment yet (estimated 2019)
  - Funding from NIH
Pending Randomized Controlled Trials

- Cleveland Clinic/Case Western: Enrolling since 2015, (NCT02451176)
  - Not completed enrollment yet (estimated 2019)
  - No listed COI
- University Calgary: Enrolling 2016, (NCT02703662)
  - Paid by Medtronic
- UT Houston: Enrolling since 2017, (NCT03091790)
  - Anticipate completing enrollment in 2018
  - No COI
Topics

• Current evidence

• Controversies: Mesh

• Controversies: Conflict of interest (COI)
2010-Patient Protection and Affordable Care Act

Centers for Medicare and Medicaid Services-Open Payments Database (OPD)

Providers + Hospitals

Financial interests and relationships

COI

Healthcare companies

Study results, opinions, practice patterns

Cherla et al, JACS 2018
Financial Conflict of Interest

- 70% of ventral hernia manuscripts are written by authors with a financial conflict of interest
- 90% of conflict of interest are relevant to the paper written
- 50% of financial conflicts of interests are not reported by authors

Cherla et al, JACS 2018
Financial Conflict of Interest

- Authors with undisclosed conflicts of interest are paid on average $42,600/year.
- The vast majority of paid authors are not receiving payments for research.
- Authors with any financial conflict of interest are 200% more likely to write a study favorable to industry.

Cherla et al, JACS 2018
Terrible Triad of Research

Lack of Blinding  Conflict of Interest  Lack of Randomization
Conclusions

- Ventral hernias are a common and clinically significant problem
- Current care of ventral hernias is limited by poor-quality evidence and poor long-term results
Ventral Hernia Outcomes Collaborative

- Started as: Bob Martindale, Scott Roth, Me
- Currently 20 surgeons across the world
- Published (printed or in press) over a dozen group manuscripts
- First US group to write an evidence-based consensus statement (clinical guide): Annals of Surgery
Ventral Hernia Outcomes Collaborative

• Surgeons invested in unbiased comparative effectiveness research

• Databases cannot answer questions of comparative effectiveness: they are subject to enormous bias and are hypothesis generating only

• Answer important questions by performing comparative effectiveness randomized controlled trials
Ventral Hernia Outcomes Collaborative

- RCT: Prehabilitation versus current care (presented at 2018 ASA)
- RCT: Laparoscopic primary fascial closure versus current care (completed enrollment, submit to 2019 ASC)
- Prospective trial: Non-operative management versus operative repair (completed enrollment, presented 3 year results at 2018 ASC)
- RCT: Biologic versus synthetic mesh (complete enrollment 2018)
- RCT: Hernia prevention (complete enrollment 2019)
- RCT: Laparoscopic versus Robotic VHR (start enrollment next month)
Use of Biologics in Abdominal Wall Reconstruction

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