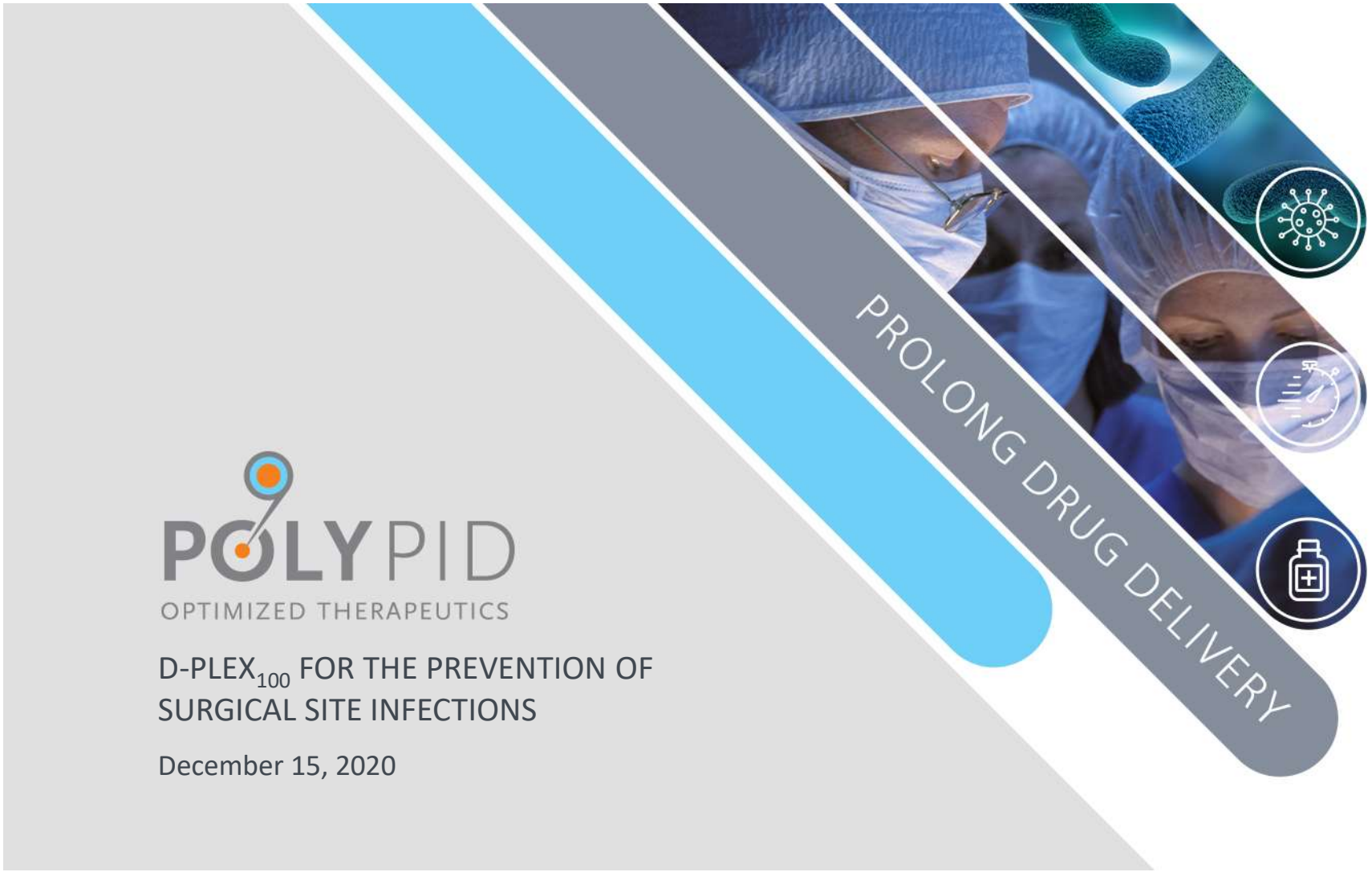

POLYPID

OPTIMIZED THERAPEUTICS

D-PLEX$_{100}$ FOR THE PREVENTION OF SURGICAL SITE INFECTIONS

December 15, 2020

Disclaimer

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Agenda

01	**The Burden of Surgical Site Infections** – Dr. Anthony Senagore
02	**The Impact of Prevention of SSI in Heart Surgery** – Dr. Hartzell Schaff
03	**Surgical Site Infections in Colorectal Surgery** – Dr. Oded Zmora
04	**Results From D-PLEX$_{100}$ Phase 2 Trials** - Dr. Anthony Senagore
05	**The Future of D-PLEX$_{100}$** – Dr. Noam Emanuel
06	**Q&A**

Today's Moderator: Anthony Senagore, MD

Anthony
Senagore, MD

Anthony J. Senagore, MD, is a colorectal surgeon with a long track record of academic surgery practice. He has served as Professor of Surgery at a number of prestigious academic medical centers including most recently UTMB at Galveston. He has served as Chair of the Colorectal Surgery Residency Review Committee for the ACGME, President of the Board of Colon and Rectal Surgery and he a Past President of the ASCRS and Midwest Surgical Association. He also served on the Relative Value Update Committee for 16 years and as Chair of the Practicing Physicians Advisory Committee for the Centers for Medicaid Services. He has significant experience in revenue cycle and capacity management for healthcare. In addition, during his career he was involved in the development of many innovations in laparoscopic colorectal surgery and the field of enhanced recovery.

Dr. Senagore earned his medical degree from Michigan State University (MSU), East Lansing, MI. He completed his residency in General Surgery at the Butterworth Hospital/MSU program. Dr. Senagore then completed a research fellowship and colon and rectal surgery residency at Ferguson Hospital on the Grand Rapids and East Lansing campuses of MSU. He continued his education and later received his Master of Science degree in physiology from MSU and a Master of Business Administration from the University of Phoenix, San Francisco, CA campus. He has edited 5 textbooks in colon and rectal surgery, authored over 230 peer-reviewed publications and 25 textbook chapters

Today's Presenters

Hartzell V. Schaff, MD
Dr. Schaff is the Stuart W. Harrington Professor of Surgery and a consultant in the Division of Cardiovascular Surgery at Mayo Clinic, Rochester, Minnesota. He is a member of major international societies, including the American Association for Thoracic Surgery (2012-2013 President). He has authored or co-authored 784 papers, 94 book chapters, edited or written nine textbooks, and delivered over 500 lectures. He has served or is serving on the editorial boards of 11 journals, including Circulation and the Journal of Thoracic and Cardiovascular Surgery, where he is currently the Associate Editor. Dr. Schaff received his medical degree and training at the University of Oklahoma School of Medicine, where he also completed an NIH Research Fellowship. His surgical training was completed at Johns Hopkins Hospital.

Oded Zmora, MD
Dr. Zmora is a Colon and Rectal Surgeon and Chair of the Department of Surgery, Shamir Medical Center, Israel. He is also an associate professor of surgery at the Tel Aviv University School of Medicine. Dr. Zmora's education and training include residency in general surgery at the Sheba Medical Center in Israel and the Mount Sinai Medical Center in New York, followed by two years of clinical and research fellowships at the Cleveland Clinic, Florida. Dr. Zmora is a past president of the Israel Society of Colon and Rectal Surgeons, immediate past chair of the S-ECCO (Surgeons' European Crohn and Colitis Organization), and past co-editor of Techniques in Coloproctology. His main research interests focus on colorectal surgery, including surgical infectious complications, prevention of colorectal cancer metastases, treatment of perineal fistulas, and clinical research in colon and rectal surgery.

The Burden of SSI

Anthony Senagore, MD

SSI is Globally Recognized as a Problem With Human and Financial Cost

Up to 30%

Estimated SSI rate of patients undergoing colorectal surgery[1,2]

7-11 days

Additional post-operative hospital days for patients with SSIs[3]

20%

SSI rate of all health care-associated infections in US hospitals[3]

2-11x

Increased risk of death for SSI patient (up to 40% mortality after deep sternal infection)[1]

$11k-26k

Cost of treatment per infection directly attributable to SSIs

US $10bn **EU ~€11bn**

Estimated SSI-related incremental annual hospital costs in the US and EU[4, 5]

SSI GUIDELINES: *What's New and What's Not*

CDC Centers for Disease Control and Prevention

*"**The human and financial costs of treating surgical site infections (SSIs) are increasing**. The number of **surgical procedures performed in the United States continues to rise**, and surgical patients are initially seen with **increasingly complex comorbidities**."*

World Health Organization

*"The **prevention of SSIs is complex and requires** the integration of a **range of preventive measures before, during, and after surgery**. No international guidelines are available…the **prevention of SSIs is a priority for patient safety**." [6]*

[1] DeverickJ et al, Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2014 Update, Infection Control and Hospital Epidemiology, 2014. [2] Estimated figures likely underestimated as ~50% of SSIs become evident only after a patient has been discharged. [3] Financial Impact of Surgical Site Infections on Hospitals. John Shepard and al. JAMA Surg. 2013;148(10):907-914. https://www.cagesideseats.com/wwe/2018/2/6/16980406/big-show-reveals-hip-surgery-complications ; [4]Surgical site infection - a European perspective of incidence and economic burden. Leaper DJ et al. Int Wound J. 2004 Dec;1(4):247-73. [5] ~€11bn represents the midpoint of the range discussed in WHO Global guidelines on the prevention of surgical site infection. Nov 2016: 29 ; [6]New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Benedetta Allegranzi et al. Lancet Infect Dis. 2016 Dec;16(12):e288-e303.

The Financial Impact of SSI is Felt in Hospitals Big and Small

In 2019, Medicare cash penalties for 7 of the 21 hospitals on the U.S. News Best Hospitals Honor Roll[1]

Hospital	Hospital-acquired condition penalty [2]	Readmission penalty [2]
UPMC Shadyside in Pittsburgh	$2,720,780	$977,439
Ronald Reagan UCLA Medical Center in L.A.	$2,400,390	$347,034
Keck Hospital of USC	$1,553,190	$92,152
Stanford Health Care's main hospital in Northern California	$3,704,170	$88,052
UCSF Medical Center in San Francisco	$3,388,430	$397,376
New York-Presbyterian/Weill Cornell Medical Center in Manhattan	$7,441,260	$1,677,600
Mayo Clinic's hospital in Phoenix	$1,787,440	$233,798

*In fiscal 2020, **CMS will withhold an estimated $394 million in Medicare payments** to hospitals under the Hospital-Acquired Condition Reduction Program[2]*

Source: 1) Preeminent Hospitals Penalized Over Rates Of Patients' Injuries, Kaiser Health News, https://tinyurl.com/y5863xtl 2)The advisory Board, www.advisory.com/daily-briefing/2020/02/03/hac-penalties

The Impact of Prevention of SSI in Heart Surgery

Hartzell V. Schaff, MD

Professor of Surgery, Division of Cardiovascular Surgery

Mayo Clinic

MAYO CLINIC

Eliminating the risk of infection can have a profound change on how CABG surgery is performed

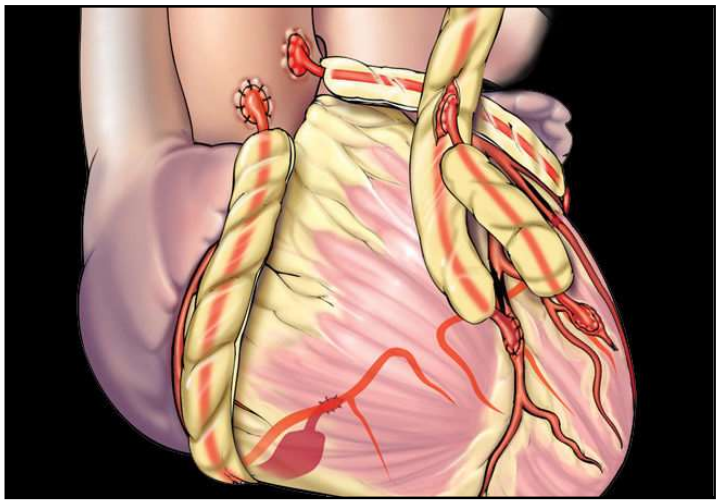
- Current **SSI rate of about 6-8%**[1] in high-risk cardiac surgery patients
- **One of the most devastating complications** following cardiac surgery is Deep Sternal Wound infection (DSWI)
  - **Mortality rates of up to 40%** in case of deep Infections[2]
  - Additional costs of up to **$130K and 30 additional hospital days**[3]
- SSI following CABG surgery is **considered a "Never Event" by CMS** and therefore not reimbursed

MAYO CLINIC

1 Effect of an Implantable Gentamicin-Collagen Sponge on Sternal Wound Infections Following Cardiac Surgery - JAMA. 2010;304(7):755-762; 2 *Guide for the Prevention of Mediastinitis Surgical Site Infections Following Cardiac Surgery, APCI, 2008.* [4] *Raja, Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection following cardiac surgery, International Journal of Surgery, 2012; 3 Sears, E.D., Wu, L., Waljee, J.F. et al. The Impact of Deep Sternal Wound Infection on Mortality and Resource Utilization: A Population-based Study. World J Surg 40, 2673–2680 (2016). https://doi.org/10.1007/s00268-016-3598-7*

Bilateral internal mammary artery (BITA) has shown better outcomes than single internal mammary artery (SITA) but usage is low

- Use of **BITA has been associated with improved long-term survival** and freedom from repeat revascularization[1]
- **Surgeons continue to avoid using BITA** grafting because of proven increased risk of DSWI, especially in high-risk patients
- In 2016, **BITA grafting was used in only 5.5% of CABG** procedures in the US, and in more than 20% outside the US in CABG patients



MAYO CLINIC

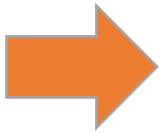
1. D.P. Taggart, R. D'Amico, D.G. Altman; Effect of arterial revascularization on survival: a systematic review of studies comparing bilateral and single internal mammary arteries; Lancet, 358 (2001), pp. 870-875

D-PLEX$_{100}$ could be a game changer in the CABG world

The Society of Thoracic Surgeons: "Although graft patency and **survival appears superior with BITA** grafting, the main concern for surgeons is the potential **increased risk of sternal wound infections** compared with SITA" [1]

Apply **D-PLEX$_{100}$** in high-risk cardiac surgery patients

Reduce the risk for SSI



Better outcome for patients & lower healthcare costs

Increase use of BITA- The **"gold standard"** for CABG procedures

MAYO CLINIC

1. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting

Surgical Site Infections In Colorectal Surgery

Oded Zmora, MD

Chair, Department of Surgery

Associate Professor of Surgery

Shamir Medical Center

Israel

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Common Indications for Colorectal Surgery

- Colon / rectal cancer
- Colon and rectal polyps
- Inflammatory bowel diseases (IBD)
- Diverticular disease

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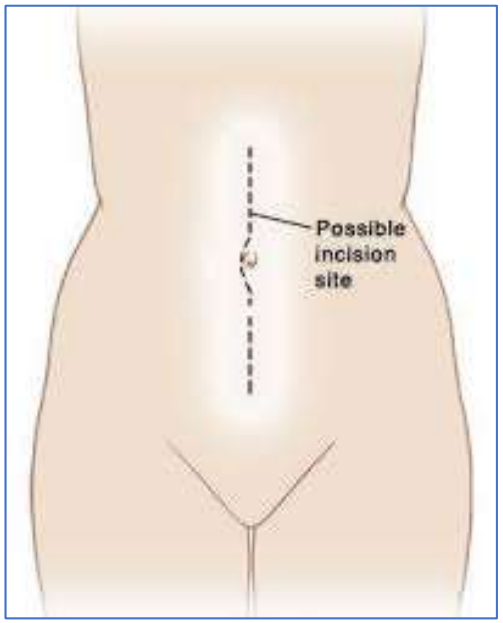
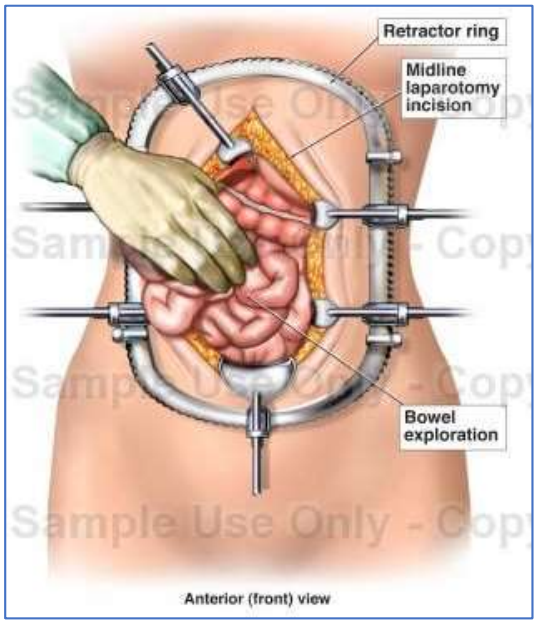
Approaches to Colorectal Surgery: Open Surgery





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Approaches to Colorectal Surgery: Endoscopic Surgery (Laparoscopy/ Robot)

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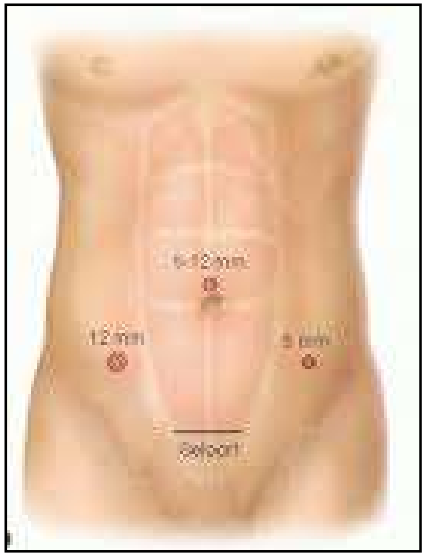
Approaches to Colorectal Surgery: Laparoscopic Colectomy

One wound needs to be extended to allow removal or the resected bowel



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Approaches to Colorectal Surgery: Robotic Colectomy

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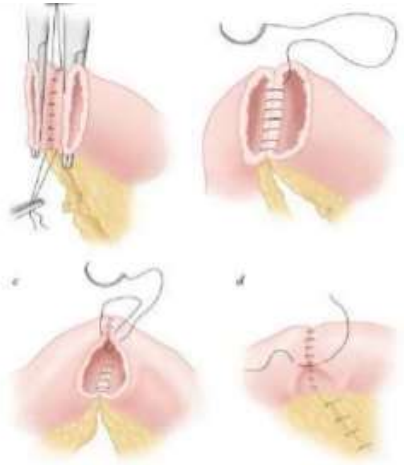
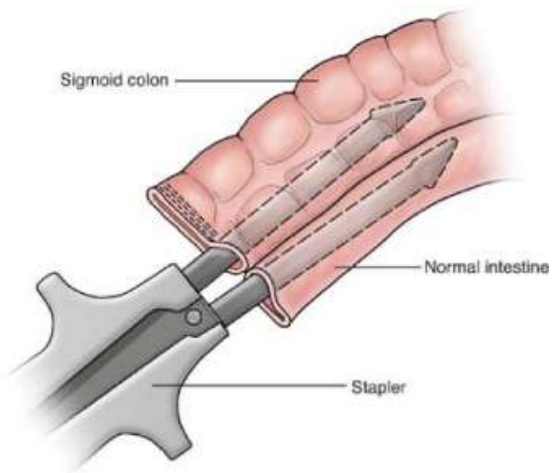
Following Resection the Proximal And Distal Stumps Need To Be Joined (Anastomosis)

Anastomosis can be performed in two ways:

Hand sewn



Stapled



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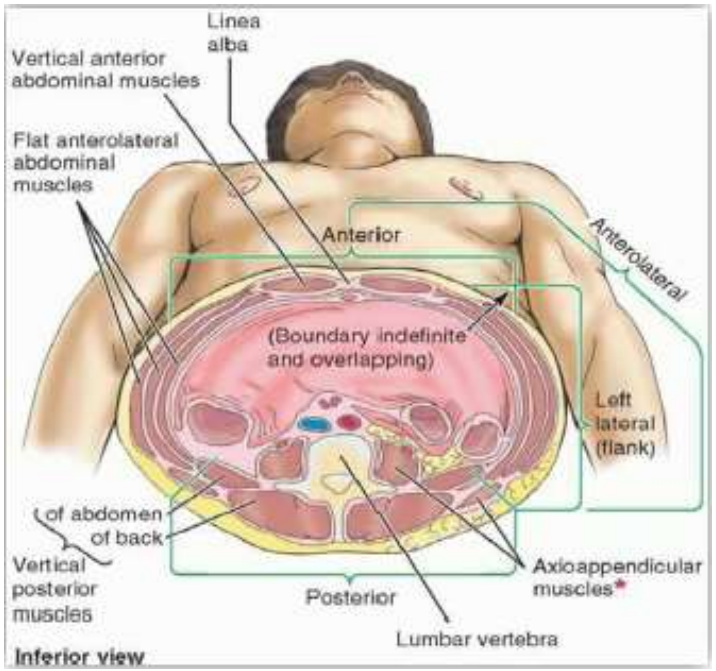
At the Conclusion of Surgery, the Abdominal Wall and the Skin Are Closed

The layers that need to be closed depends on type and site of the incision:

- **Abdominal wall**: muscles, facia
- **External to the abdominal wall**: subcutaneous fat, skin



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Postoperative Complications Occur in Close to One-third of Patients Undergoing Colorectal Procedures[1]

Complications related to the surgical procedure include:

- Anastomotic leak
- Abdominal abscess
- Surgical Site Infection (SSI)

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1. Longo W E, Virgo K S, Johnson F E. et al. Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum. 2000;43(1):83–91

SSI is a Major Issue in Colorectal Surgery

- The bowel is loaded with bacteria
- The risk for SSI increases due to endogenic bacteria (comes from the inside)
- May also be caused by skin bacteria

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SSI Rate Differs by Surgery Type and Personal Risk Factors

Rate of SSI infection by surgery type:

- Open surgery: 10-30%
- Laparoscopic colectomy: <10%

Personal risk factors include:

- Obesity
- Diabetes
- Smoking and COPD
- Immunosuppression
- Nutritional status

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.JournalofSurgicalResearch.com
ELSEVIER
JSR

Risk factors for superficial surgical site infection after elective rectal cancer resection: a multivariate analysis of 8880 patients from the American College of Surgeons National Surgical Quality Improvement Program database

Elie Sutton, MD,[a,b] Hiromichi Miyagaki, MD, PhD,[a,c] Geoffrey Bellini, MD,[a] H.M.C. Shantha Kumara, PhD,[a] Xiaohong Yan, PhD,[a] Brett Howe, MD,[a] Amanda Feigel, MD,[a] and Richard L. Whelan, MD[a,]*

[a] *Department of Colon and Rectal Surgery, Mount Sinai West Hospital, New York, New York*
[b] *Department of Surgery, Maimonides Medical Center, Brooklyn, New York*
[c] *Department of Surgery, Saiseikai Senri Hospital, Suita, Osaka, Japan*

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Prevention Measures Are a Part of the Standard of Care…

- Perioperative intravenous antibiotics
- Bowel mechanical cleansing
- Oral antibiotics
- Wound irrigation with water
- Closure technique

… but the risk of SSI in colorectal surgery remains high

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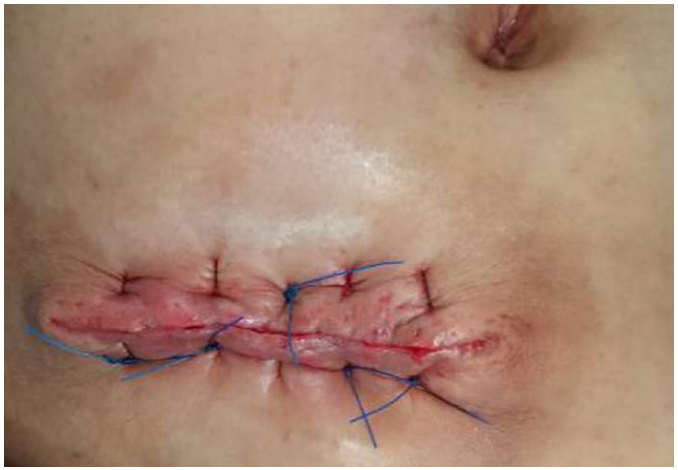
Symptoms, Signs and Treatment of SSI Can Vary Depending on the Severity of the Infection

Symptoms & Signs:

Pain, fever, redness, purulent discharge, dehiscence



Escalating Measures for treating SSI may include:

- Open the wound for drainage
- Frequent change of wound dressing
- Post-operative antibiotic treatment
- Readmission
- Additional surgery and debridement

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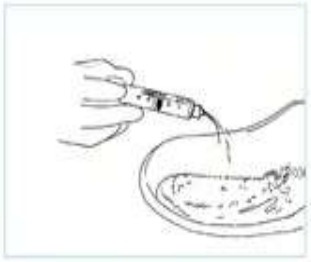
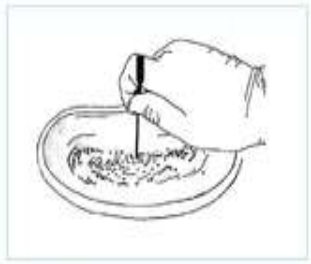
Video: Application of D-PLEX$_{100}$ in Colorectal surgery

PLEX candidate

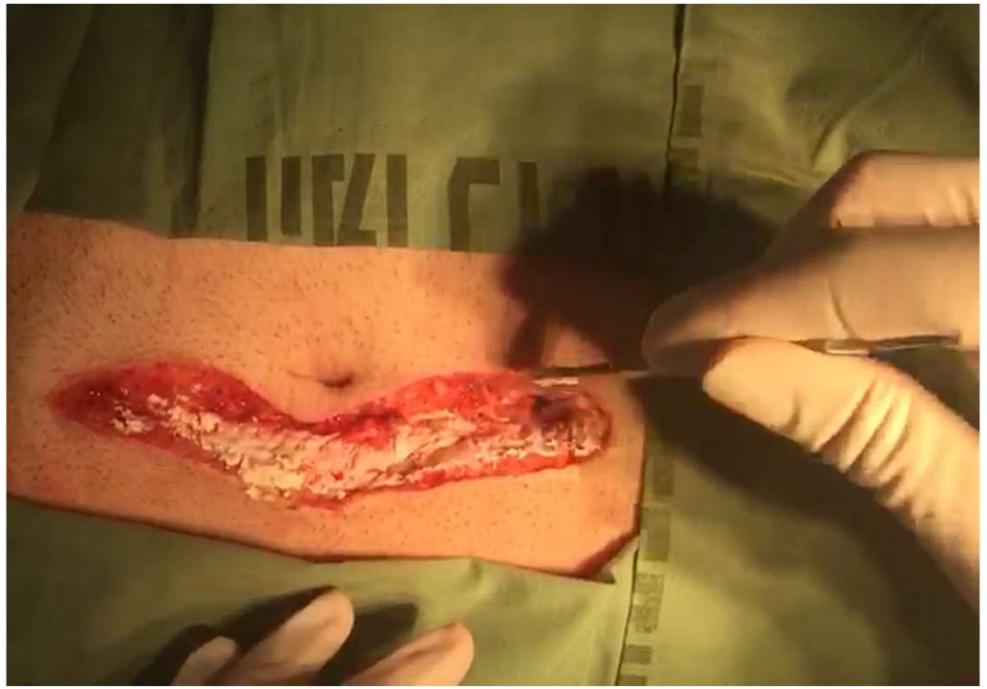
1) Pour



2) Hydrate



3) Mix



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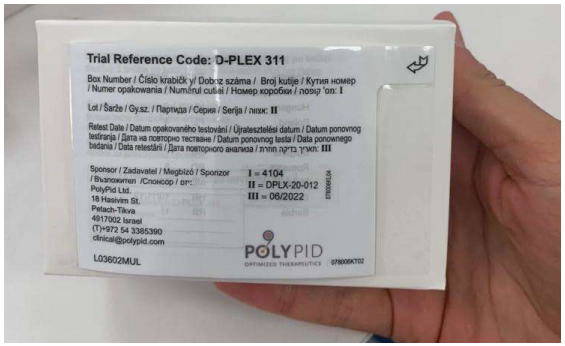
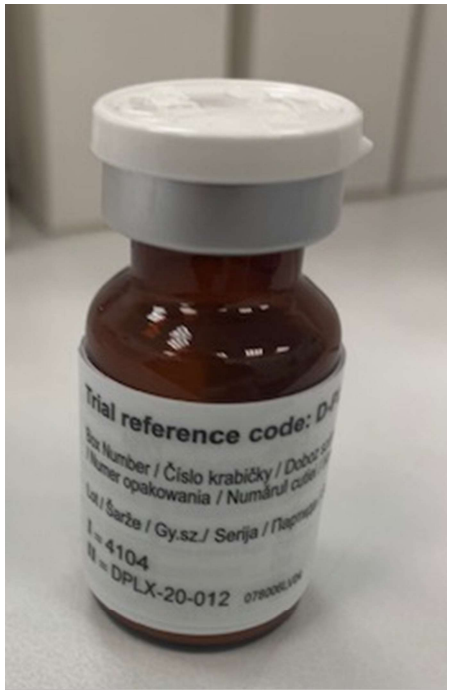
My Experience with D-PLEX$_{100}$ in Phases 2 and 3 Studies

- Easy to use
- Requires minimal training
- No patient's discomfort





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Results From DPLEX$_{100}$ Phase 2 Trials

Anthony Senagore, MD

D-PLEX$_{100}$ – Localized Drug Delivery System Optimized for the Prevention of SSI

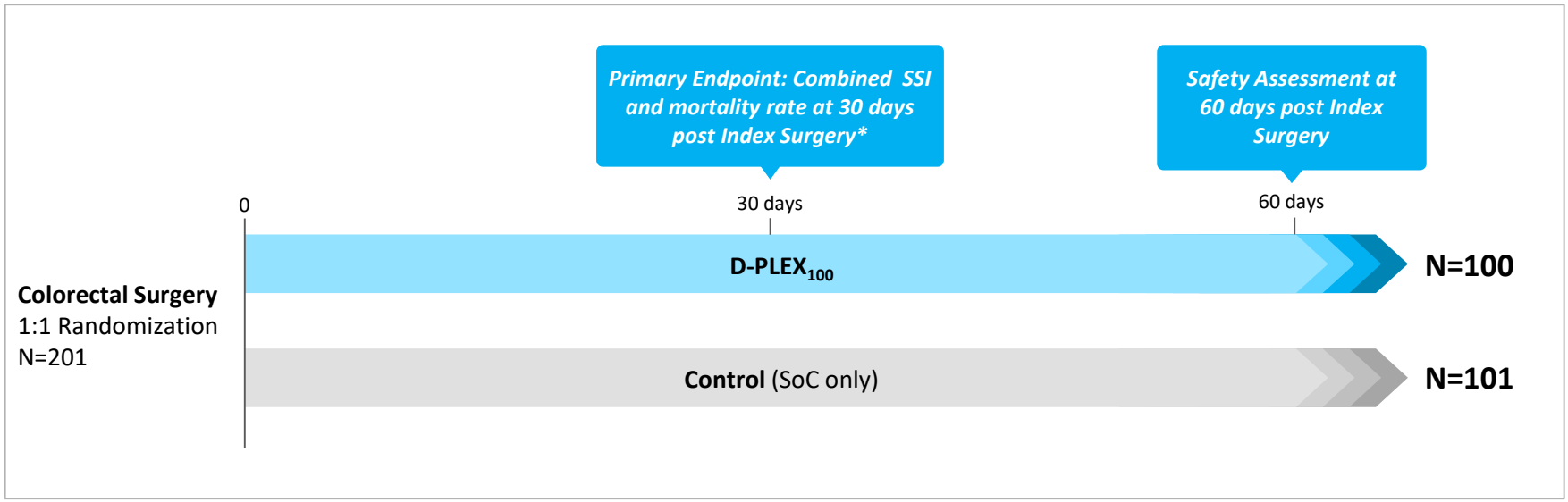
D-PLEX for prophylaxis of SSI:

- **Active Ingredient:** **Doxycycline**; broad spectrum antibiotic
- **Release Profile:** **Constant & linear release** regardless the tissue: bone & soft tissues
- **Release Rate:** Generating the optimal local concentration and extending the therapeutic window
- **Release Duration:** **Prolonged therapeutic effect** - 4 weeks

Local Exposure that is Effective against **Resistant Bacteria**

D-PLEX$_{100}$ Phase 2 Study Design in Abdominal Surgeries (soft tissues)

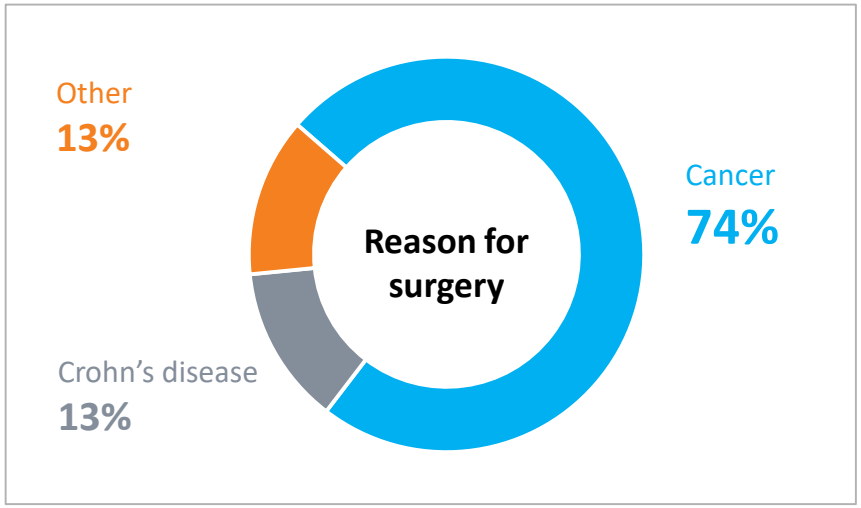
- Prospective, multicenter, randomized, controlled, two arm, single blind, study
- Assess safety and efficacy of D-PLEX administered prophylactically concomitantly with the standard of care (SoC) to prevention incisional surgical site infection

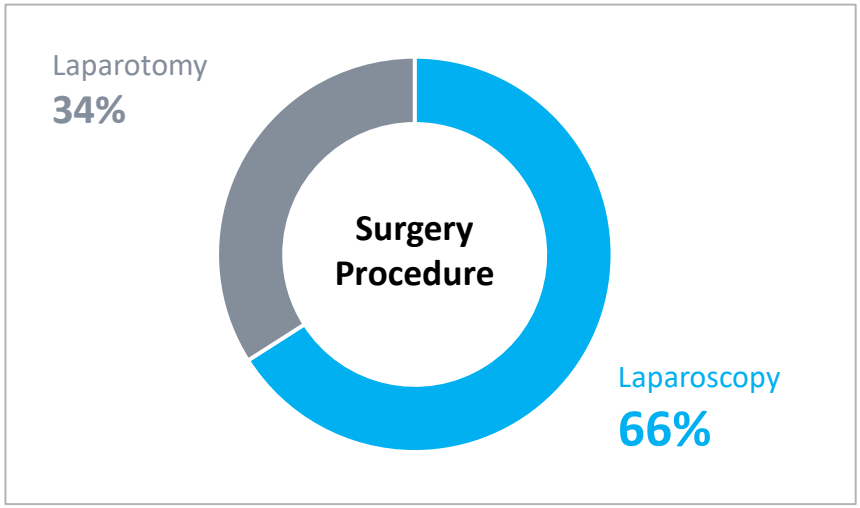


** As confirmed by a blinded and independent adjudication committee*

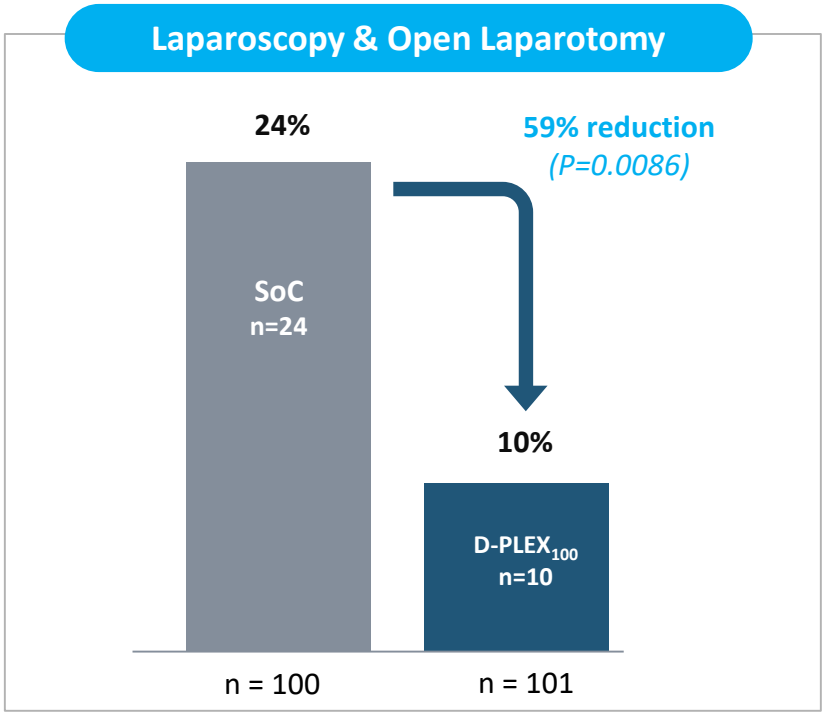
Demographics and Baseline Data Summary Statistics

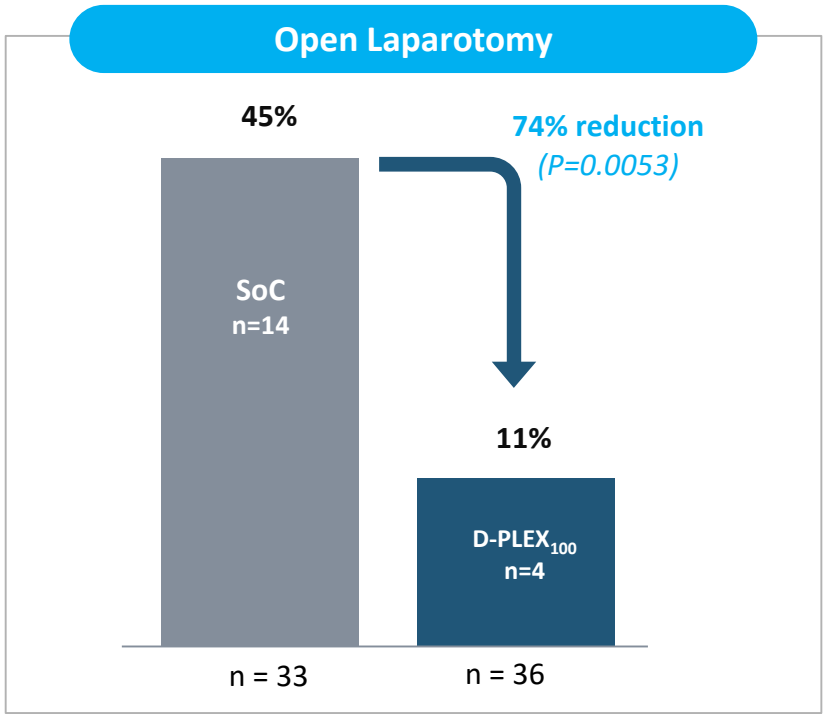
- **Elective abdominal colon surgery involving resection** and ileocolonic, ileorectal, colocolonic or colorectal anastomosis or with a stoma. In laparoscopic or open surgery, an abdominal wall incision ≥ 5 cm.
- Baseline demographic (Age, BMI, etc.) and surgical characteristics were balanced between the groups





D-PLEX$_{100}$ Effective in Reduction of SSI & Mortality in Soft Tissue Colorectal Surgical Model within 30 days (Primary End-Point, ITT population)





Same Rate of Serious Treatment Emergent Adverse Events – With Significant Reduction in Mortality

No significant variance in number of subjects with **Serious Treatment Emergent Adverse Events**

Injury, poisoning and procedural complications	D-PLEX (N=99)	CONTROL (N=100)
Anastomotic hemorrhage	1 (1.0%)	0 (0.0%)
Anastomotic leak	2 (2.0%)	3 (3.0%)
Injury	0 (0.0%)	1 (1.0%)
Procedural complication	1 (1.0%)	0 (0.0%)
Ureteric injury	1 (1.0%)	0 (0.0%)
Stoma site hemorrhage	1 (1.0%)	1 (1.0%)
Overall	**5 (5.0%)**	**5 (5.0%)**

Significant reduction in **subjects who Experience Death** within 60 Days Post-Surgery by Treatment

Fatal Event	D-PLEX (N=101)	CONTROL (N=100)	P-value
Septic Shock	0 (0.0%)	2 (2.0%)	
Cardio-respiratory arrest	0 (0.0%)	1 (1.0%)	
Lower gastrointestinal hemorrhage	0 (0.0%)	1 (1.0%)	
Death (unknown)	0 (0.0%)	1 (1.0%)	
Overall	**0 (0.0%)**	**5 (5.0%)**	*0.0290*

More than 70% of the infected bacteria within the surgical wounds were resistant to +2 antibiotics

D-PLEX$_{100}$ demonstrated efficacy in surgeries were Multidrug-resistant bacteria (MDR) strains are very common

Type of bacteria isolated from surgical wounds following the Ph2 abdominal study:

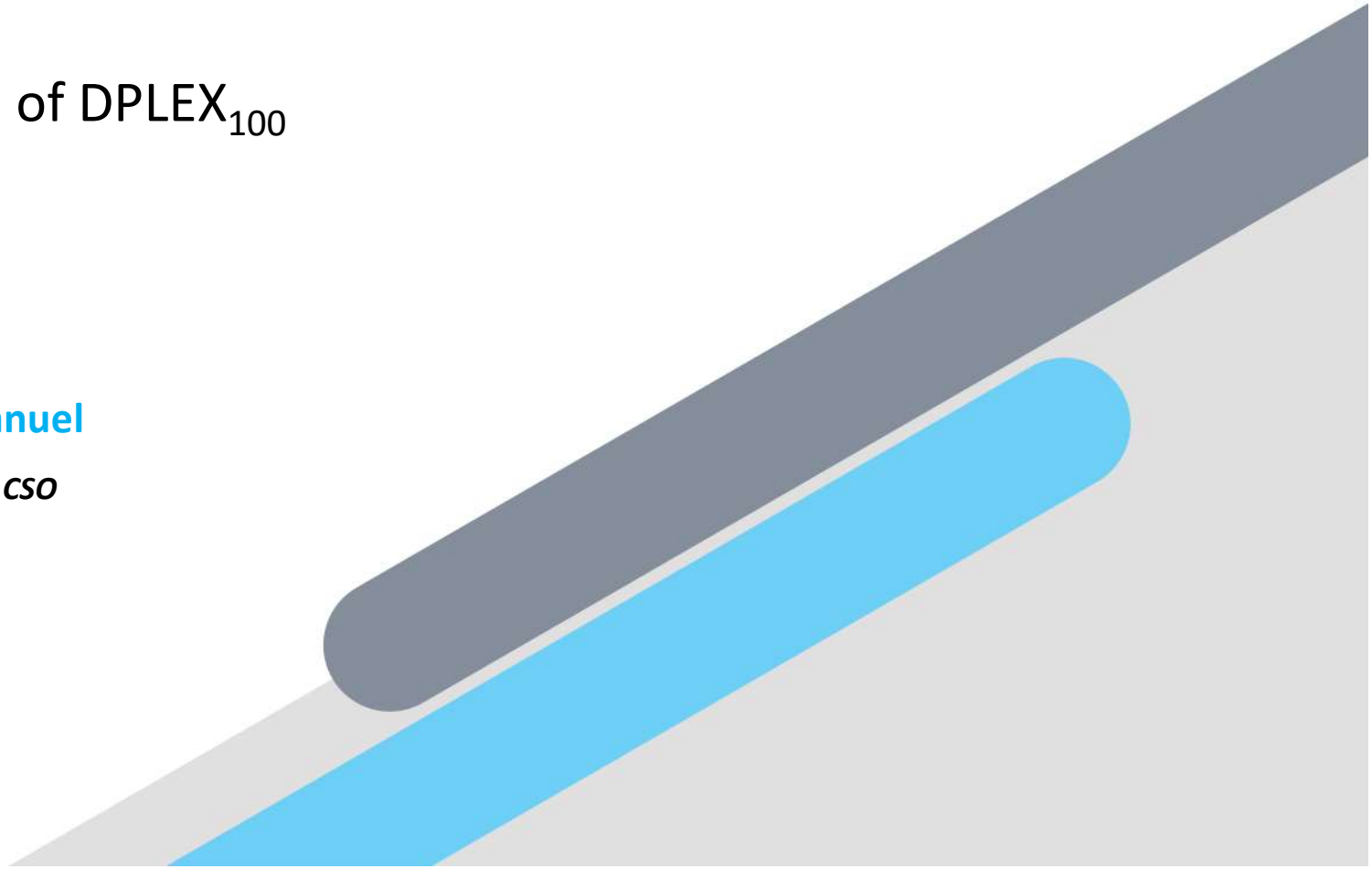
- *Staphylococcus epidermidis (Coagulase Negative SA)*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Escherichia coli*
- *Enterococcus faecalis*
- *Serratia marcescens*
- *Enterobacter cloacae* complex
- Staphylococcus aureus (MRSA)

Bacteria strains responsible to more than 50% of SSI cases across all surgeries

The Future of DPLEX$_{100}$

Dr. Noam Emanuel

Polypid Founder & CSO

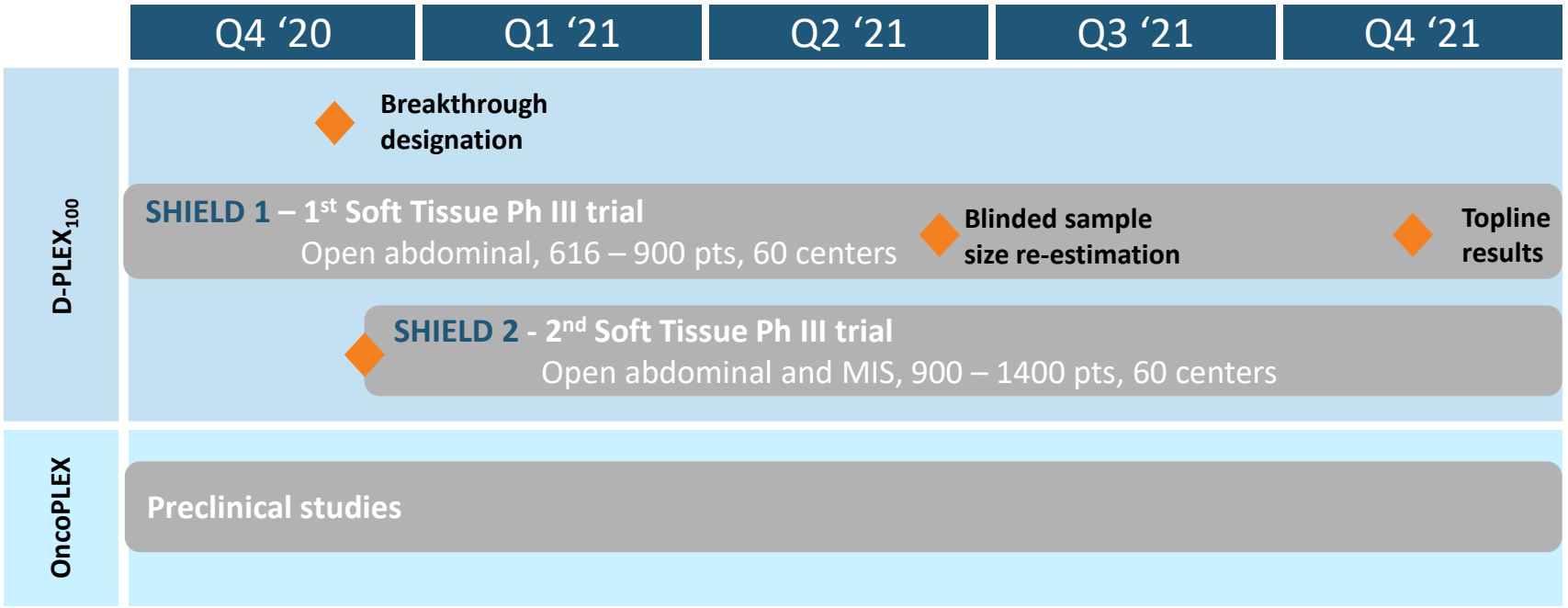


We Imagine a World Without the Fear of SSIs…

We believe that intraoperative use of D-PLEX$_{100}$ can have a profound change in the way we operate and treat patients

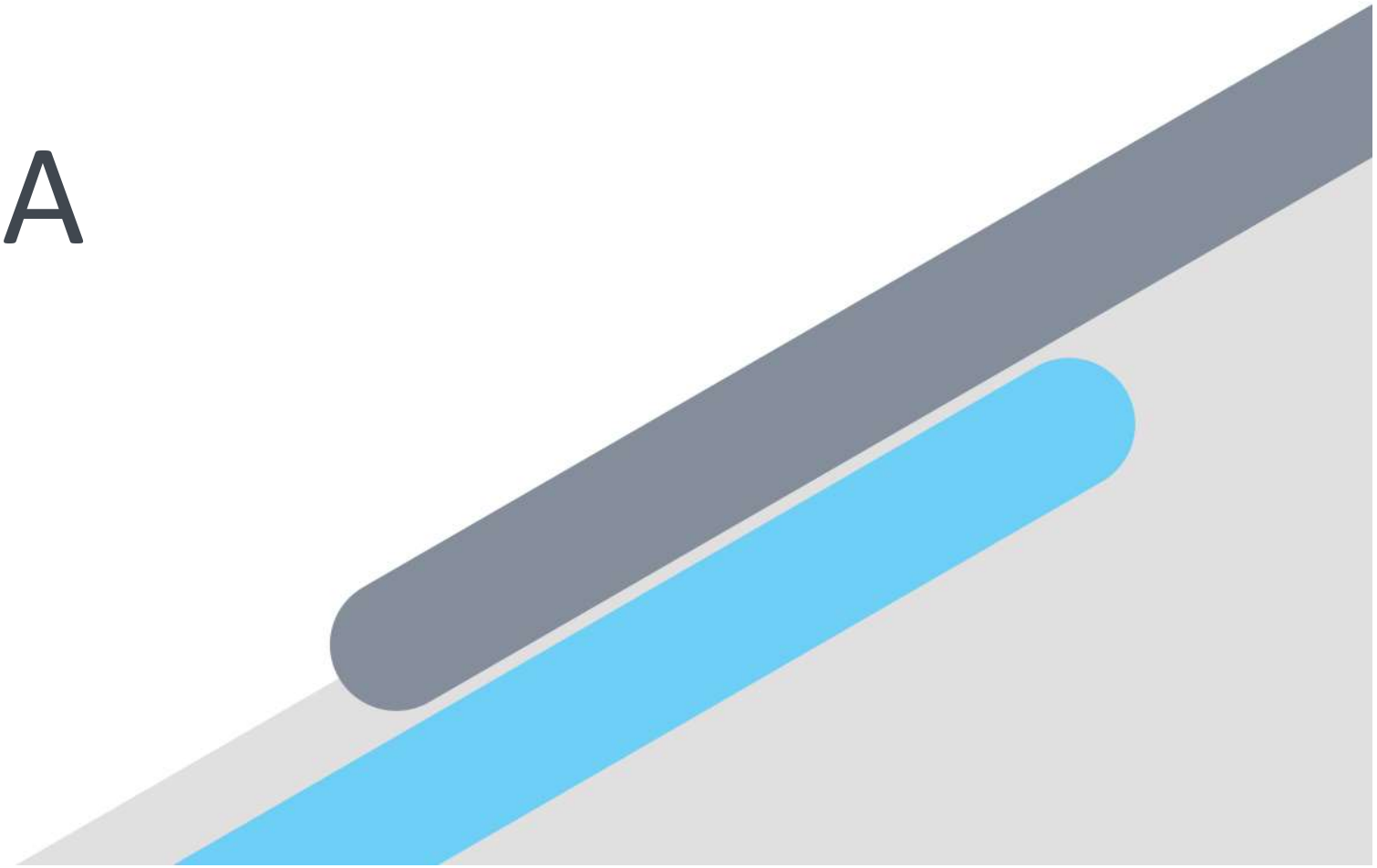
- **Change** the **prophylactic** Standard of Care, e.g., eliminate/reduce post - and even pre-surgery prophylactic antibiotics
- **Change** the way we **operate** to achieve better outcomes, e.g., BITA vs. SITA cardiac surgery
- **Change** the **post operative procedures**, e.g., Immediate wound closer in contaminated patients allowing reduced hospitalization

Milestones for the Next 12 Months



MIS = Minimally Invasive Surgery, Laparoscopic

Q&A



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